



Modelling the Preferential Solvation of Ferulic Acid in {2-Propanol (1) + Water (2)} Mixtures at 298.15 K

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ABSTRACT

Background: Recently Haq *et al.* reported the equilibrium solubility in {2-propanol (1) + water (2)} mixtures at several temperatures with some numerical correlation analysis. Nevertheless, no attempt was made to evaluate the preferential solvation of this compound by the solvents.

Methods: Preferential solvation of ferulic acid in the saturated mixtures at 298.15 K was analyzed based on the inverse Kirkwood-Buff integrals as described in the literature.

Results: Ferulic acid is preferentially solvated by water in water-rich mixtures ($0.00 < x_1 < 0.19$) but preferentially solvated by 2-propanol in mixtures with composition $0.19 < x_1 < 1.00$.

Conclusion: These results could be interpreted as a consequence of hydrophobic hydration around the non-polar groups of the solute in the former case ($0.00 < x_1 < 0.19$). Moreover, in the last case ($0.19 < x_1 < 1.00$), the observed trend could be a consequence of the acid behavior of ferulic acid in front to 2-propanol molecules because this cosolvent is more basic than water as described by the respective solvatochromic parameters.

Introduction

The experimental solubility of ferulic acid (IUPAC name: (*E*)-3-(4-hydroxy-3-methoxy-phenyl)prop-2-enoic acid, CAS number: 1135-24-6, C₁₀H₁₀O₄, molar mass: 194.18 g mol⁻¹) in aqueous mixtures of 2-propanol at different temperatures along with some numerical analyses has been reported.¹ The generated solubility data extends the available solubility database of pharmaceuticals in binary mixtures and could be used in the pharmaceutical/chemical industry.² Ferulic acid is a phenolic compound present in the seeds and cell-walls of several plants and it is widely used as precursor in the preparation of several other organic compounds.³ Moreover, some pharmaceutical dosage forms intended for dermatological care are developed including ferulic acid as active ingredient.⁴ As described earlier, the study of equilibrium solubility and the respective dissolution mechanisms is still a very important field in the pharmaceutical sciences.⁵ Thus, the common solubility models for mono and mixed solvents were correctly used for mathematical representation of the generated solubility data of ferulic acid in {2-propanol (1) + water (2)} mixtures at various

temperatures. A predictive version of the Jouyban-Acree-van't Hoff model was reported which provides accurate predictions in {2-propanol (1) + water (2)} mixtures at various temperatures without employing any further experimental data inputs¹. The aim of this communication is merely to expand the results of numerical analyses in term of the preferential solvation of ferulic acid by 2-propanol (1) and water (2) in the saturated mixtures based on the inverse Kirkwood-Buff integrals.^{6,7} These complementary analyses provide more information for better understanding of the dissolution process of ferulic acid in the investigated solutions.

Results and Discussion

The preferential solvation parameter of ferulic acid (compound 3) by 2-propanol (compound 1) in the {2-propanol (1) + water (2)} mixtures is defined as:^{6,7}

$$\delta x_{1,3} = x_{1,3}^L - x_1 = -\delta x_{2,3} \quad \text{Eq.(1)}$$

where $x_{1,3}^L$ is the local mole fraction of 2-propanol (1) in the environment near to ferulic acid (3) and x_1

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is the bulk mole fraction composition of 2-propanol (1) in the initial binary solvent. If $\delta x_{1,3} > 0$ then the solute is preferentially solvated by 2-propanol (1); on the contrary, if this parameter is < 0 the solute is preferentially solvated by water (2). Values of $\delta x_{1,3}$ are obtainable from the inverse Kirkwood-Buff integrals for the individual solvent components analyzed in terms of some thermodynamic quantities as shown in the following equations:^{6,7}

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{\text{cor}}} \quad \text{Eq.(2)}$$

With,

$$G_{1,3} = RT\kappa_T - \bar{V}_3 + x_2 \bar{V}_2 D / Q \quad \text{Eq.(3)}$$

$$G_{2,3} = RT\kappa_T - \bar{V}_3 + x_1 \bar{V}_1 D / Q \quad \text{Eq.(4)}$$

$$V_{\text{cor}} = 2522.5 \cdot$$

$$\left\{ r_3 + 0.1363 \cdot (x_{1,3}^L \bar{V}_1 + x_{2,3}^L \bar{V}_2)^{1/3} - 0.085 \right\}^3 \quad \text{Eq.(5)}$$

As has been previously described,^{6,7} in these equations κ_T is the isothermal compressibility of the {2-propanol (1) + water (2)} mixtures (which is calculated as an additive property by using the mixtures compositions and the reported values for neat solvents), \bar{V}_1 and \bar{V}_2 are the partial molar volumes of the solvents in the mixtures, similarly, \bar{V}_3 is the partial molar volume of ferulic acid in these mixtures. The function D (Eqn. (6)) is the derivative of the standard molar Gibbs energies of transfer of ferulic acid from neat water (2) to {2-propanol (1) + water (2)} mixtures with respect to

the solvent composition. The function Q (Eqn. (7)) involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents (G_{1+2}^{Exc}) with respect to the water proportion in the mixtures.^{6,7} V_{cor} is the correlation volume and r_3 is the molecular radius of ferulic acid calculated by means of Eqn. (8) with N_{Av} as the Avogadro's number.

$$D = \left(\frac{\partial \Delta_{\text{tr}} G_{3,2 \rightarrow 1+2}^0}{\partial x_1} \right)_{T,p} \quad \text{Eq.(6)}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1+2}^{\text{Exc}}}{\partial x_2^2} \right)_{T,p} \quad \text{Eq.(7)}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{\text{Av}}} \right)^{1/3} \quad \text{Eq.(8)}$$

Definitive correlation volume requires iteration because it depends on the local mole fractions around the solute. This iteration is done by replacing $\delta x_{1,3}$ and V_{cor} in the Eqns. (1), (2) and (5) to recalculate $x_{1,3}^L$ until a non-variant value of V_{cor} is obtained.

Figure 1 shows the Gibbs energy of transfer behavior of ferulic acid (3) from neat water (2) to {2-propanol (1) + water (2)} mixtures at 298.15 K. These values were calculated from the mole fraction drug solubility data reported by Haq *et al.*,¹ by using the following expression:

$$\Delta_{\text{tr}} G_{3,2 \rightarrow 1+2}^0 = RT \ln \left(\frac{x_{3,2}}{x_{3,1+2}} \right) \quad \text{Eq.(9)}$$

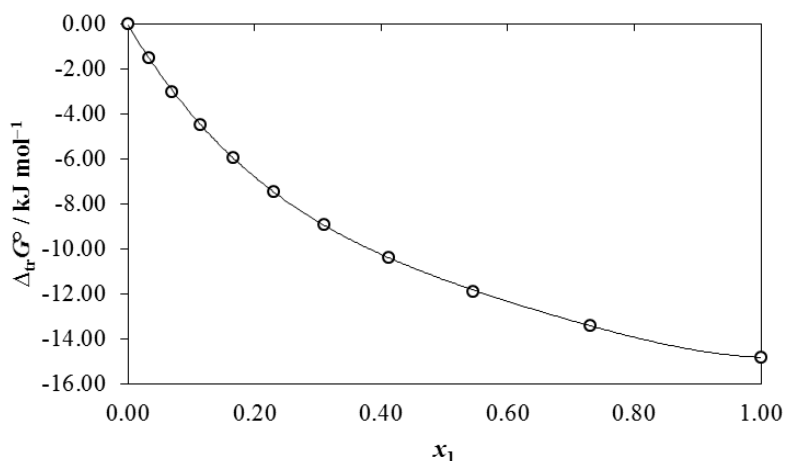


Figure 1. Gibbs energy of transfer of ferulic acid (3) from neat water (2) to {2-propanol (1) + water (2)} mixtures at 298.15 K. Line corresponds to the best regular polynomial correlating the data.

$\Delta_{tr} G_{3,2 \rightarrow 1+2}^o$ values were correlated according to polynomial presented as Eqn. (10). The obtained coefficients are as follows: $a = -0.05$, $b = -46.54$, $c = 77.76$; $d = -73.99$ and $e = 28.00$, with $r^2 = 0.9999$.

$$\Delta_{tr} G_{3,2 \rightarrow 1+2}^o = a + bx_1 + cx_1^2 + dx_1^3 + ex_1^4 \quad \text{Eq.(10)}$$

Thus, D values reported in Table 1 were calculated from the first derivative of the respective polynomial model and solved according to the cosolvent mixtures composition. For these {2-propanol (1) + water (2)} mixtures the Q , $RT\kappa_T$, \bar{V}_1 and \bar{V}_2 values were taken from the literature.⁸

Because no partial molar volumes of ferulic acid (3) in these mixtures are reported in the literature, in this research this property is considered as similar to that for the pure compound as a good approximation. In this way, the molar volume of ferulic acid (3) was calculated as $136.2 \text{ cm}^3 \text{ mol}^{-1}$ based on the Fedors' method (Table 2).⁹ $G_{1,3}$ and $G_{2,3}$ values shown in Table 1 are negative in all cases indicating that ferulic acid exhibits affinity for both solvents in all the mixtures. Solute radius value (r_3) was calculated as 0.378 nm. The correlation volume was iterated three times by using Eqns. (1), (2) and (5) to obtain the values reported in Table 1. This table also shows the preferential solvation parameters of ferulic acid (3) by 2-propanol (1), $\delta x_{1,3}$.

Table 1. Some properties associated to preferential solvation of ferulic acid (3) in {2-propanol (1) + water (2)} mixtures at 298.15 K.

x_1^a	$D / \text{kJ mol}^{-1}$	$G_{1,3} / \text{cm}^3 \text{ mol}^{-1}$	$G_{2,3} / \text{cm}^3 \text{ mol}^{-1}$	$V_{cor} / \text{cm}^3 \text{ mol}^{-1}$	100 $\delta x_{1,3}$
0.00	-46.54	-473	-135	693	0.00
0.05	-39.30	-414	-194	727	-2.01
0.10	-33.09	-371	-242	779	-2.21
0.15	-27.82	-338	-283	843	-1.27
0.20	-23.42	-313	-322	912	0.24
0.25	-19.78	-296	-364	982	2.02
0.30	-16.84	-285	-414	1053	4.01
0.35	-14.50	-280	-479	1126	6.34
0.40	-12.68	-281	-571	1203	9.32
0.45	-11.30	-288	-707	1288	13.46
0.50	-10.27	-302	-906	1383	19.42
0.55	-9.52	-316	-1176	1480	27.39
0.60	-8.95	-318	-1441	1560	34.00
0.65	-8.48	-290	-1513	1604	31.43
0.70	-8.03	-239	-1310	1593	21.78
0.75	-7.51	-193	-996	1566	12.84
0.80	-6.85	-164	-720	1559	6.93
0.85	-5.95	-147	-514	1573	3.42
0.90	-4.73	-138	-365	1600	1.42
0.95	-3.11	-134	-253	1635	0.38
1.00	-1.00	-133	-164	1676	0.00

^a x_1 is the mole fraction of 2-propanol (1) in the {2-propanol (1) + water (2)} mixtures free of ferulic acid (3).

Table 2. Application of the Fedors' method to estimate internal energy, molar volume, and Hildebrand solubility parameter of ferulic acid (3).

Group	Group number	$\Delta U^* / \text{kJ mol}^{-1}$	$V / \text{cm}^3 \text{ mol}^{-1}$
-CH ₃	1	4.71	33.5
-CH=	2	4.31 x 2 = 8.62	13.5 x 2 = 27.0
Phenyl ring trisubstituted	1	31.9	33.4
-O-	1	3.35	3.8
-OH	1	29.8	10.0
-COOH	1	27.6	28.5
		$\Sigma \Delta U^o = 105.98$	$\Sigma V = 136.2$
		$\delta_3 = (105,980/136.2)^{1/2} = 27.9 \text{ MPa}^{1/2}$	

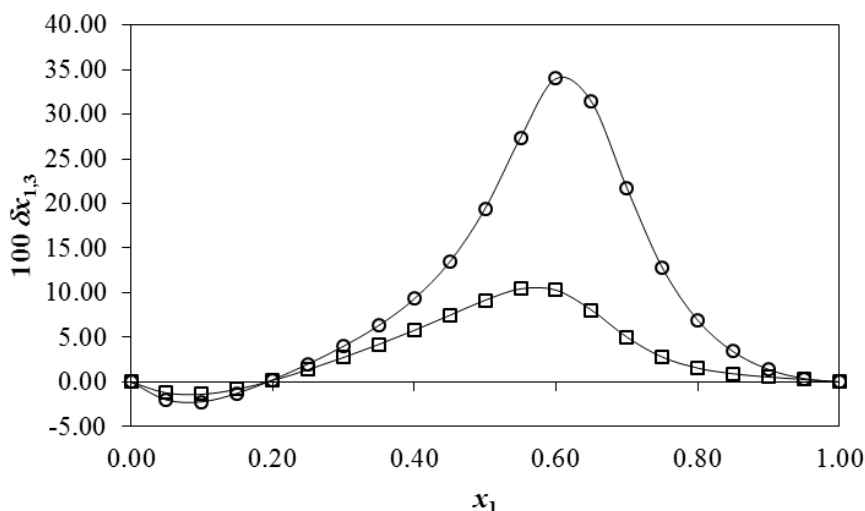


Figure 2. $\delta x_{1,3}$ values of some organic acids (3) in {2-propanol (1) + water (2)} mixtures at 298.15 K. \circ : ferulic acid; \square : gallic acid. Lines correspond to IKBI results according to Eq. (2).

Figure 2 shows that the values of $\delta x_{1,3}$ vary non-linearly with the 2-propanol (1) proportion in all the aqueous mixtures. Addition of 2-propanol (1) makes negative the $\delta x_{1,3}$ values of ferulic acid (3) from the pure water to the mixture $x_1 = 0.19$. Maximum negative value is obtained in the mixture $x_1 = 0.10$ (with $\delta x_{1,3} = -2.21 \times 10^{-2}$).

In mixtures with composition $0.19 < x_1 < 1.00$, the $\delta x_{1,3}$ values are positive indicating preferential solvation of ferulic acid by 2-propanol (1). The cosolvent action to increase the solute solubility could be associated to the breaking of the ordered structure of water around the non-polar moieties of ferulic acid which increases the solvation of this solute exhibiting maximum value in $x_1 = 0.60$ ($\delta x_{1,3} = 0.340$). It is conjecturable that in $0.19 < x_1 < 1.00$ region ferulic acid is acting as Lewis acid with 2-propanol molecules because this cosolvent is more basic than water as described by the respective Kamlet-Taft hydrogen bond acceptor parameters, as follows: $\beta = 0.84$ for 2-propanol and 0.47 for water.^{10,11}

A similar behavior has been reported in the literature for gallic acid in the same mixtures as can also be observed in Fig. 2,⁸ although the magnitudes in preferential solvation by water and 2-propanol are higher for ferulic acid. This could be a consequence of the lower polarity of ferulic acid regarding gallic acid as described by the Hildebrand solubility parameters calculated by Fedors' method, *i.e.* $27.9 \text{ MPa}^{1/2}$ for ferulic acid (Table 2) and $39.1 \text{ MPa}^{1/2}$ for gallic acid.⁹

In conclusion, further numerical analyses for modeling the solubility and preferential solvation of ferulic acid (3) in {2-propanol (1) + water (2)} mixtures were provided. As it is well known, all these sorts of correlations and predicting models are required in the pharmaceutical and chemical industries to save time and money in the

optimization of the solubilization and/or crystallization process designs.¹²⁻¹⁴

Conflict of interests

The authors claim that there is no conflict of interest.

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