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Original scientific paper

Determination of the pK_a for caffeic acid in mixed solvent using the net analyte signal method and the *ab initio* theory

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Abstract: Due to the biological effects of phenolic acid components, polyphenol-rich foods are a significant part of human and animal diets. In this study, the acidity constants of caffeic acid (3,4-dihydroxycinnamic acid) in binary mixtures of ethanol–water were determined spectrophotometrically using the introduced net analyte signal (NAS) algorithm and an *ab initio* quantum mechanical method. The NAS is an efficient chemometric algorithm for analysis of acid–base equilibrium systems by a spectrophotometric method. At different pH values, the distribution of acid species is obtained from an absorption data matrix and this procedure enabled the pK_a of caffeic acid to be obtained alternatively. The results showed that pK_{a1} (4.02, 4.26, 4.39, 4.57 and 5.11) and pK_{a2} (8.43, 8.68, 8.79, 9.00 and 9.34) were increased by increasing the percent ethanol in water (0, 10, 20, 30 and 40 vol. %) and these results were in agreement with the results of the Gaussian method. The *ab initio* calculated Gibbs energy change showed that *para*-hydroxy group is more acidic than *meta*-hydroxy group. The red shifts of different species of caffeic acid obtained using the *ab initio* quantum mechanical method are in good agreement with the results of UV–Vis spectroscopy.

Keywords: net analyte signal (NAS); caffeic acid; acidity constants; Gibbs energy change; *ab initio*; spectrophotometry.

INTRODUCTION

Foods and beverages derived of plants include considerable amounts of phenolic acids.[1–3] Phenolic compounds, one of the secondary metabolites of plants, are an essential part of both animal and human diets.[4] In addition, they have significant effects on color, flavor, stability, nutritional value and other food qualities.[5] They possess different effects, such as metal chelation, free-radical scavenging, and modulation of enzymatic activity. Due to their biological effects, dietary polyphenols are useful for human health. Researchers reported that there

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are relationships between consuming polyphenol-rich foods and some diseases, such as osteoporosis, cancer and coronary heart disease. These results led to more interest in the research of polyphenols.[6] Caffeic acid has been found to be pharmacologically active as an antioxidant, antimutagenic, anticarcinogenic agent, lipoxygenase inhibitor, and to have antimicrobial, anti-inflammatory and styptic activities.[1] Due to the biological effects of caffeic acid, it has been applied in supplement foods, as well as pharmaceutical formulations.[7] The structure of caffeic acid as a phenolc compound is shown in Fig. 1.

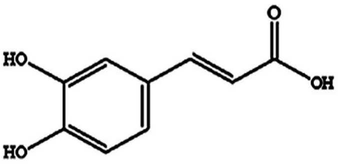

Fig. 1. The structure of caffeic acid.

As is known, the acidity constant, K_a, is a quantitative measurement of the strength of an acid in solution.[8] Thermodynamic information of K_a plays a key role in determining the endpoint of acid–base titrations, solvent extraction, complex formation, and medical properties of acid–base organic compounds.[9,10] The determination of the K_a values of polyphenolic acids is important because they can provide important information for the thorough understanding of some phenomena, such as reacting rates, biological uptake and receptor–ligand interaction at the molecular level.[11] Although the determination of K_a is very important, there is several problems in determining K_a of organic compounds, *e.g.*, low solubility in aqueous solutions and the low values of acidity constants. Solvent mixtures facilitate the determination of K_a.[12–15] Mixtures of two or more solvents are used to achieve appropriate solvent properties. Mixtures of water and organic solvents are most frequently used.[16] The acidity constants in various solvents are important in variety of fields, such as chemistry, medicine and the food industry.[17] Both theoretical (*ab initio* quantum mechanical methods[18]) and experimental methods (Fourier transform-infrared (FT-IR) spectrometry,[19] ultraviolet–visible (UV–Vis) absorption and fluorescence spectrophotometry[20,21]) have been introduced for the determination of acidity constants in different chemical environments. Among these methods, spectrophotometry (UV–Vis) is preferred due to its simplicity, low cost and high sensitivity. However, spectral overlapping of species and lack of selective wavelengths for all species are considered as great limitations in the use of the preferred method. Nowadays, with the development of mathematics in chemistry (chemometrics), some new techniques have been suggested to solve these limitations. The coupling of these inexpensive methods with UV–Vis spectroscopy, enabling the determination of a number of desired analytes in many signal (NAS), was defined by Lorber[22] based on spectroscopic complex samples, without the need of separation of interferences. In the present work, due to the high spectral overlap of caffeic acid species, the net analyte signal method was performed on the spectrophotometric data of caffeic acid in the ethanol–water solvent mixtures. Net analyte methods, as the part of the spectrum of a mixture that is unique for the analyte of interest, is orthogonal to the spectra of the interferences. Following a previous work for the determination of the acidity constant of TAR (4-(2′-hiazolylazo)resorcinol) in water–organic solvent binary mixtures by spectrophotometry using the Data Analysis (DATAN) program,[14] the acidity constant of TAR was determined by wavelet neural network (WNN).[10] The DATAN program, proposed by Momeni-Isfahani and Niazi,[23] calculates spectral profiles, concentrations and equilibrium constants. To the best of our knowledge, there is no report for determination of acidity constants of caffeic acid using NAS. Thus, in this work, a simple and non-expensive procedure is introduced for the determination of the acidity constants of caffeic acid by applying NAS to pH gradual change–UV–Vis spectral data (pH-spectra). In order to determine both the pK_{a1} and pK_{a2} values of caffeic acid in binary mixtures of ethanol–water, *ab initio* calculations were also employed in this study. The ability of the novel method of NAS and *ab initio* calculations was compared with well-known algorithms, such as DATAN. The Gibbs energy changes calculated by the *ab initio* method show red shifts of different species of caffeic acid. In addition, the theoretical calculations show that the *para*-hydroxyl group is more acidic than the *meta*-hydroxyl group.

Theoretical background of the net analyte signal

The net analyte signal (NAS) was defined by Lorber,[22] based on spectroscopic methods, as the part of the spectrum of a mixture that is unique for the analyte of interest, *i.e.*, it is orthogonal to the spectra of the interferences. The NAS method enables the separation of the net signal of each available species in acid–base equilibrium that have spectral overlapping with other species in each pH solution and it facilitates the ability to access the K_a value. In the present research, the introduced (NAS) algorithm was applied to determine the dissociation constant of caffeic acid. The electronic absorption spectrum was recorded in a range of acidic or basic pH. To achieve NAS, the mix vector or the mixture spectrum (m) is decomposed into the sum of the two vectors,[24] which can be described as:

$$m = r + p \tag{1}$$

where p is obtained by b multiples x ($p = bx$) where b equals any non-zero scalar, and r is orthogonal to x (Fig. 2). To calculate p, there are different methodologies. In this study, the proposed method by Gram and Schmidt[25] which involves Eq. (2) was used. r is orthogonal to x if and only if:

$$rx = 0 \tag{2}$$

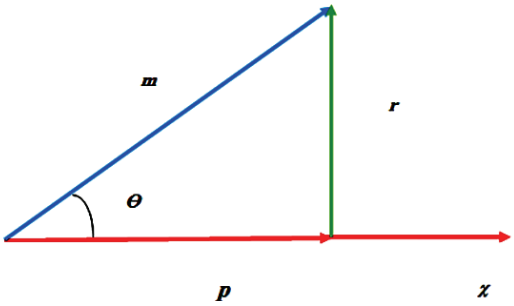

Fig. 2. Geometrical representation of the NAS vector. The orthogonal projection of *m* on the non-zero vector *x*.

The vector *p* (spectra of the interferences) is named orthogonal projection of *m* to *x* and the vector *r* is the fraction of *m* orthogonal to *x*, which *r* is named the NAS vector:[26]

$$p = \frac{x\,m}{|x|^2}x \tag{3}$$

Hence:

$$r = m - \frac{x\,m}{|x|^2}x \tag{4}$$

The norm NAS of the species of interest as a function of pH (||*r*||) has the same length as the concentration profiles of the favorite species of a (*i.e.*, c_a). The variation of the concentrations of the protogenic species of H_3A can be calculated according to the following equations:

$$c_{CA} = c_{H_3A} + c_{H_2A^-} + c_{HA^{2-}} + c_{A^{3-}} \tag{5}$$

$$c_{H_3A} = \frac{{c_H}^3 c_{CA}}{{c_H}^{+3} + K_{a1}{c_H}^{+2} + K_{a1}K_{a2}{c_H}^{+} + K_{a1}K_{a2}K_{a3}} \tag{6}$$

$$c_{H_2A^-} = \frac{{c_H}^2 K_{a1} c_{CA}}{{c_H}^{+3} + K_{a1}{c_H}^{+2} + K_{a1}K_{a2}{c_H}^{+} + K_{a1}K_{a2}K_{a3}} \tag{7}$$

$$c_{HA^{2-}} = \frac{c_H K_{a1}K_{a2} c_{CA}}{{c_H}^{+3} + K_{a1}{c_H}^{+2} + K_{a1}K_{a2}{c_H}^{+} + K_{a1}K_{a2}K_{a3}} \tag{8}$$

$$c_{A^{3-}} = \frac{K_{a1}K_{a2}K_{a3} c_{CA}}{{c_H}^{+3} + K_{a1}{c_H}^{+2} + K_{a1}K_{a2}{c_H}^{+} + K_{a1}K_{a2}K_{a3}} \tag{9}$$

where c_{H_3A} is the analytical concentration of caffeic acid. Caffeic acid is dissociated stepwise. H_3A is undissociated caffeic acid and $c_{H_2A^-}$, $c_{HA^{2-}}$, $c_{A^{3-}}$, are different equilibrium forms of the acid that are produced by stepwise dissociation of acid. The K_a values can be considered as being close to their true value when the correlation coefficient between the c_a and ||*r*|| achieves its maximum value.

Ab initio *calculations*

In this paper, all calculations were realized using the Gaussian 09 program. The solvation energies were calculated using the SMD model at the HF/6-31G* level in conjunction with G4MP2 gas-phase energies. Here, the pK_a values were calculated using Eq. (10) and the deprotonation energy is shown in Eq. (11).[27] Benzoic acid was used as reference species (RefH) for the calculation of the pK_a.[28] Based on Eq. (12), the pK_a for the dissociation of an acid (AH) in binary mixtures of ethanol–water can be given by Eq. (10), where R and T are gas constant and temperature, respectively. Ref$^-$ and A$^-$ are the conjugate base of a reference acid molecule (RefH) and the conjugate base of an acid (AH), respectively:

$$\mathrm{p}K_{\mathrm{aAH}} = \frac{\Delta_{\mathrm{r}} G_{\mathrm{soln}}}{RT\ \ln 10} + \mathrm{p}K_{\mathrm{a\ RefH}} \tag{10}$$

$$\Delta_{\mathrm{r}} G_{\mathrm{soln}} \Delta G_{\mathrm{soln}}\left(\mathrm{A}^{q-1}\right) + \Delta G_{\mathrm{soln}}\left(\mathrm{RefH}^{m}\right) - \Delta G_{\mathrm{soln}}\left(\mathrm{HA}^{q}\right) - \Delta G_{\mathrm{soln}}\left(\mathrm{Ref}^{\,m-1}\right) \tag{11}$$

The Gibbs energy change of the reaction ($\Delta_r G_{\mathrm{soln}}$) is calculated only with the Gibbs energy changes in the solution of the reactants and products (Eq. (11)). For calculating the acidity constant of hydroxycinnamic acid in mixed solvent solutions of water–ethanol, it is necessary to introduce a general equation for the Gibbs energy change of solvation in mixed solvents. The solvation Gibbs energy change of a binary solution at a specified temperature and pressure with ideal behavior is given by:

$$\Delta G_{\mathrm{solv,\ mix}} = x\Delta G_{\mathrm{solv,\ ethanol}} + \left(1-x\right)\Delta G_{\mathrm{solv,\ water}} \tag{12}$$

where x represents the mole fraction of ethanol. The $\Delta G_{\mathrm{solv,\ ethanol}}$ and $\Delta G_{\mathrm{solv,\ water}}$ are calculated using the SMD solvation model.[29] The ΔG_{soln} at a defined temperature can be calculated according to the following equation:[29]

$$\Delta G_{\mathrm{solv}} = \Delta G_{\mathrm{gas}} + \Delta G_{\mathrm{sov,\ mix}} \tag{13}$$

where ΔG_{gas}, ΔG_{soln} and ΔG_{solv} are the Gibbs energy changes in gas phase, in solution and of solvation, respectively.

EXPERIMENTAL

Chemicals

All the applied chemicals were purchased from Merck and used without further purification. The materials used in this work were caffeic acid, potassium chloride, ethanol, phosphoric acid and sodium hydroxide. Double distilled water was used for providing the experimental solutions.

Preparation of the samples

The absorbance spectra of the solution of 1.0×10^{-4} mol L^{-1} caffeic acid in various binary ethanol and water mixtures were recorded after each pH adjustment by the convenient phosphate buffer solution (0.10 mol L^{-1}) ranging from 2.0 to 10.0 in the wavelength range 200–400 nm. The ionic strength was adjusted to 0.10 mol L^{-1} by addition of an appropriate amount of KCl. All experiments were performed at a temperature of 25.0±0.5 °C.

Instrumentation and software

A Cintra 101 spectrometer GBC UV–Vis was used to record UV–Vis spectra and a Metrohm 692 pH-meter with a combined glass–saturated calomel electrode was used to measure pH values. Solutions of Metrohm buffers were employed to calibrate the pH meter in the various binary ethanol and water mixtures. However, when the pH-meter was standardized using aqueous buffers, the pH values in ethanol–water solvent mixtures were corrected using the equation pH* = pH(R) – δ, where pH* is the corrected reading, pH(R) is the pH meter reading obtained in a partially aqueous organic solvent, and δ is the correction parameter determined by Douheret.[9,10,14,30-33] MATLAB R2011A software was used for writing programs for the net analyte signal.

RESULTS AND DISCUSSION

The absorption spectra of the caffeic acid solution in ethanol/water mixture with different volume ratios of organic solvent (10–40 vol. %) were recorded in the wavelength range of 200–400 nm. Typical absorption spectra of caffeic acid at different pH values (from pH 2.0–10.0) in ethanol/water (10 vol. % of ethanol) are shown in Fig. 3A. This figure reveals that there is an intense overlap between the absorbance spectra of caffeic acid species and a high overlap between the absorbance spectra of caffeic acid species at various pH values. Hence, it is difficult to achieve the number of species in the equilibrium. Principal component analysis (PCA) is a powerful method to obtain the number of components in a mixture, which was used to obtain the number of components in this study. As can be seen in Fig. 3B, the estimated numbers of components were obtained as 3 in the pH range of 2.0 to 10.0. In Fig. 4, it is observed that the maximum wavelength for different species of caffeic acid slightly shifted to longer wavelengths (red shift) with increasing percent ethanol. This shift could be related to

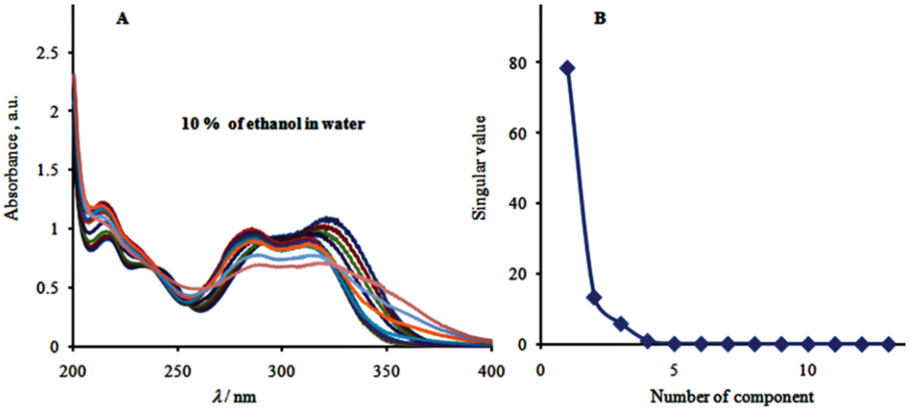

Fig. 3. A) Absorption spectra of caffeic acid at different pH values (from pH 2.0–10.0) in ethanol/water (10 vol. % of ethanol); B) Principal component analysis on the data matrix of caffeic acid in water solvent at different pH values.

the electrostatic properties of the hydrogen bond between caffeic acid and the solvent. The ground state of caffeic acid in ethanol is stabilized less than in water and thus, less energy is required to transfer electrons from the ground state to its excited state. As a result, longer wavelengths were observed in 40 percent ethanol in water.[14] The described red shifts of the different species of caffeic acid obtained using the *ab initio* quantum mechanical method are in good agreement with the results of UV–Vis spectroscopy.

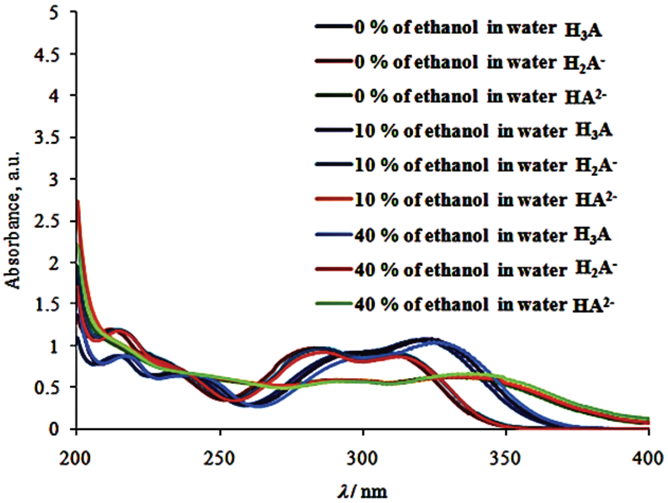

Fig. 4. Comparison of the obtained pure spectrum for species from the dissociation of caffeic acid in solution containing caffeic acid (1.0×10^{-4} mol L^{-1}) with 0, 10 and 40 vol. % of ethanol in water at pH 2.0–10.0.

The *ab initio* calculated Gibbs energy change shows red shifts of different species of caffeic acid. As can be seen from Table I, Gibbs free energy change for caffeic acid species in different percentages of ethanol–water increases by increasing the percentage of ethanol. By increasing the percentage ethanol in the binary mixture, the ground state of all species of caffeic acid is destabilized. The increased Gibbs free energy showed these changes. Caffeic acid (Fig. 1) has three acidity constants. One of them (K_{COOH}) is due to the dissociation of the carboxylic group (COOH) and two to the ionizable phenolic (OH) groups (K_{OH}). In this work, two acidity constants (pK_{a1} and pK_{a2}) of caffeic acid were determined. The values of the acidity constants for each mixture were obtained by applying NAS on the data matrix with 10, 20, 30 and 40 vol. % of ethanol. The acid dissociation constant is obtained, when correlation between c_a and $||r||$ reached its highest value. The concentration profiles of caffeic acid obtained in 10 vol. % mixed solvent of ethanol/water using NAS are shown in Fig. 5.

TABLE I. Gibbs energy changes (kJ mol^{-1}) of the different deprotonated forms of caffeic acid in binary mixtures of ethanol–water

Content of ethanol in water, vol. %	H_3A	H_2A^-	*meta*-Hydroxy HA^{2-}	*para*-Hydroxy HA^{2-}
0	–647.9264721	–647.4882156	–647.0094688	–647.0368731
10	–647.9264626	–647.4875721	–647.0078167	–647.0354099
20	–647.9264531	–647.4869286	–647.0061646	–647.0339468
30	–647.9264436	–647.4862851	–647.0045124	–647.0324836
40	–647.9264341	–647.4856416	–647.0028603	–647.0310205

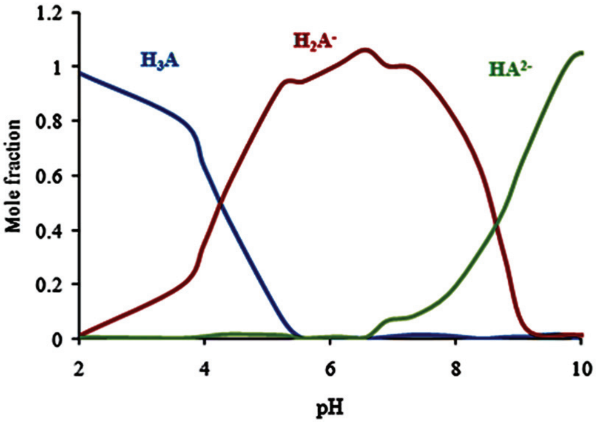

Fig. 5. Concentration profile of caffeic acid in binary mixtures of 10 vol. % of ethanol at different pH values by the NAS method.

With enhancement of pH, higher than 2, the concentration of H_3A decreases while the concentration of H_2A^- increases. At the point when $c_{H_3A} = c_{H_2A^-}$, the pH equals pK_{a1}. The value of pK_{a2} is obtained as the value when the concentrations of H_2A^- and HA^{2-} are equal. According to Fig. 5, the values of pK_{a1} and pK_{a2} were calculated as 4.28 and 8.77, respectively and these results are in agreement with the results of the NAS method in Table II (4.28 and 8.78). The obtained pK_{a1} values are summarized in Table II.

TABLE II. Comparison of net analyte signal, *ab initio* and DATAN for calculation of acidity constants of caffeic acid (1.0×10^{-4} mol L^{-1}) with various percentages of ethanol in water

Content of ethanol in water, vol. %	pK_{a1} by NAS	pK_{a2} by NAS	pK_{a1} by DATAN	pK_{a2} by DATAN	pK_{a1} by *ab initio* theory
0	4.02	8.43	4.27	8.76	4.69
10	4.26	8.68	4.32	8.75	4.72
20	4.39	8.79	4.55	8.92	4.84
30	4.57	9.00	4.62	9.02	5.07
40	5.11	9.34	5.19	9.38	5.33

The pK_{a2} values for caffeic acid were also predicted using the *ab initio* quantum mechanical method in binary mixtures of ethanol–water. In this process, the study of $\Delta_r G_{soln}$ accurately predicts pK_{a2} from Eq. (14):

$$\begin{gathered}\Delta_r G_{soln} = \Delta G_{soln}\left(HA^{2-}\right) + \Delta G_{soln}\left(RefH\right) - \\ -\Delta G_{soln}\left(H_2A^{-}\right) - \Delta G_{soln}\left(Ref^{-}\right)\end{gathered} \qquad (14)$$

As can be seen from Table III, $\Delta_r G_{soln}$ increases with increasing the percentage of ethanol in the binary solvent. By increasing the value of $\Delta_r G_{soln}$, HA^{2-} becomes unstable so pK_{a2} increases.

TABLE III. Gibbs energy changes of the deprotonated of caffeic acid anion (H_2A^-) in binary mixtures ethanol/water

Content of ethanol in water, vol. %	$\Delta_r G_{soln}$ / kJ mol^{-1}
0	2332.7
10	2337.0
20	2341.3
30	2345.6
40	2349.9

The validity of the obtained pK_a values was checked with the famous chemometrics algorithm DATAN (Table II). As can be seen from Fig. 6, acidic constants (pK_{a1}, pK_{a2}) in different percentages of ethanol in water increased with increasing percentage of ethanol in the solvent. This phenomenon can be explained with the fact that the solvation powers of water and ethanol are different. Water has a high solvation power (dielectric constant ε = 78.36, donor number = = 33) but the solvation power of ethanol (dielectric constant ε = 24.55 donor number = 15) is less than that of water.[14] According to the Coulomb law,[15] the attraction force (F) between two oppositely-charged ions, namely q^- and q^+, at a distance r is given by:

$$F = 8.988\times10^{9}\frac{q^{-}q^{+}}{\varepsilon r^{2}} \qquad (15)$$

where ε is the dielectric constant of the solvent. As can be seen from Eq. (15), the attraction force is inversely proportional to the dielectric constant. The dielectric constants of water and ethanol are 78.36 and 24.55, respectively. Thus, the larger value of the dielectric constant leads to the smaller attraction between two ions. One practical consequence is that the dissociation of acid into ions (H^+ and A^-) is greater in water than in ethanol.

When the percent of ethanol is increased in the solution, the dielectric constant of the solvent decreases and, consequently, the extent of dissociation of an acid decreases.[34] Moreover, water has a high donor number, making it a strong

Lewis base. Ethanol is less basic than water and hence, acids are weaker in this solvent. Thus, it is expected that the addition of ethanol with a lower donor number and dielectric constant to water decreases the extent of interaction of the acid anions and protons with the solvent, which decreases the acidity constant of the acid.[14] At pH < 9.0, caffeic acid is stable and above pH 9.0, its oxidation produces the semiquinone radical and therefore, the accuracy of the pK_{a3} value will be poor.[35] Since there are two hydroxyl groups in the benzene ring of caffeic acid, it is important to determine which hydroxyl group is the more likely subject of deprotonation in binary mixtures of ethanol–water. In the process, only $\Delta G_{soln}(HA^{2-})$ varies while $\Delta G_{soln}(H_2A^-)$ and $\Delta G_{soln}(H^+)$ are the same for these two deprotonation processes. Therefore, the study of $\Delta G_{soln}(HA^{2-})$ can accurately predict the most acidic hydroxyl group.

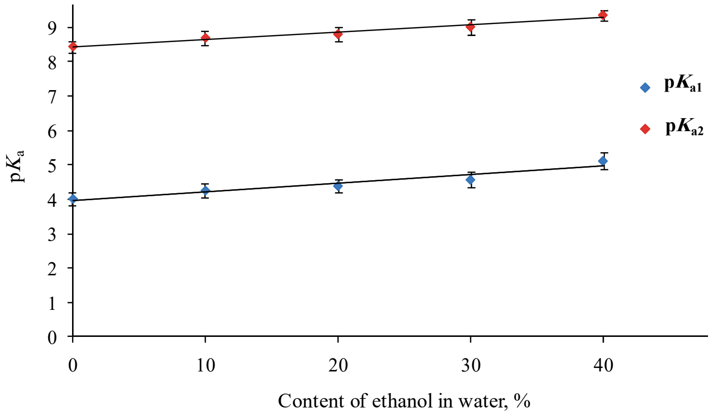

Fig. 6. The acidic constants (pK_{a1}, pK_{a2}) in different percentages of ethanol in water.

According to Table I, Gibbs energy change shows that the *para*-hydroxy anion is more stable compared with *meta*-hydroxy anion form and thus, the *para*-hydroxy group is more acidic than the *meta*-hydroxy group. Furthermore, the acidity constants of caffeic acid obtained in this work were compared with other works[36–38] and the results are listed in Table IV. According to Table IV, the acidity constants of caffeic acid obtained in this work are in good agreement with those previously reported.

TABLE IV. Comparison of the pK_a values of caffeic acid obtained in this work with those previously determined

Method	Solvent	pK_{a1}	pK_{a2}	Ref.
UV–Vis spectroscopy	Water	4.44	7.60	37
Potentiometry–chemometrics	Water	4.38	8.58	38
Potentiometry	Water	4.45	8.66	39
UV–Vis spectroscopy	Water	4.02	8.43	This work
ab initio	Water	4.69	–	This work

CONCLUSIONS

Due to the important role of polyphenols in human health, in the present paper, the behavior of the acidity constants of caffeic acid in binary ethanol/water mixtures was studied by a multi-wavelength spectrophotometric method and an *ab* initio quantum mechanical method. The results obtained by NAS indicate that the proposed method is an effective method for the calculation of the acid dissociation constants of caffeic acid solution with high spectral overlap. The obtained results for investigation of pK_{a1} and pK_{a2} of caffeic acid in mixtures of water and ethanol revealed that pK_{a1} values (4.02, 4.26, 4.39, 4.57 and 5.11) and pK_{a2} (8.43, 8.68, 8.79, 9.00 and 9.34) increase with increasing the ethanol percent (0, 10, 20, 30, 40 vol. %) in water and the obtained results are in good agreement with the results of the Gaussian method. In strong alkaline solution, oxidation of the acid is inevitable and therefore, the accuracy of the pK_{a3} value is poor. Briefly some novelties of this work are: *i*) calculating Gibbs energy change of HA^{2-} to confirm that pK_{a2} and pK_{a3} are related to the *para* and *meta* positions of caffeic acid, respectively; *ii*) good agreement between the *ab initio* quantum mechanical method and NAS on the results of UV–Vis spectroscopy.

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ИЗВОД

ОДРЕЂИВАЊЕ pK_{a} КОФЕИНСКЕ КИСЕЛИНЕ У МЕШОВИТОМ РАСТВАРАЧУ КОРИШЋЕЊЕМ МЕТОДА СИГНАЛА ЧИСТОГ АНАЛИТА И *ab initio* ТЕОРИЈЕ

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Због биолошких ефеката компоненти фенолних киселина, храна богата полифенолима је значајан део хумане и животињске исхране. У овој студији одређена је константа киселости кофеинске киселине (3,4-дихидроксициметне киселине) у бинарним смесама етанол–вода, спектрофотомеријски, користећи алгоритам сигнала додатог чистог аналита (NAS) и *ab initio* квантномеханички метод. NAS је ефикасан хемометријски алгоритам за анализу кисело–базних равнотежа система спектрофотометријским методом. На различитим pH вредностима, расподела киселинских врста се добија из матрице апсорпционих података и ова процедура даје могућност да се алтернативно добију pK_{a} кофеинске киселине. Резултати су показали да су pK_{a1} и pK_{a2} повећане са повећањем молског односа етанола у води као растварачу. *Ab initio* израчунате промене Гибсове енергије показују да је *para*-хидрокси група киселија од *meta*-хидрокси групе. Црвени помаци различитих молекулских врста кофеинске киселине добијени *ab initio* квантномеханичким методом су у доброј сагласности са резултатима UV–Vis спектроскопије.

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