Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 81 (10) 1161–1169 (2016)
JSCS–4916
UDC 546.76+66.093.1:547.61'918:621.78.063
Original scientific paper

Solvatochromism of naringenin in aqueous alcoholic mixtures

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(Received 27 March, revised 21 April, accepted 25 April 2016)

Abstract: The spectral change of naringenin in binary mixtures of water with methanol, ethanol or 1-propanol was studied by UV–Vis spectrophotometry at 25 °C. The effect of the solvent was investigated by analysis of the electron transition energy at the maximum absorption wavelength as a function of the Kamlet and Taft parameters of the mixtures by means of linear solvation energy relationships. The nonlinear response of the solvatochromism was explained based on solute–solvent and solvent–solvent interactions. The possible preferential solvation of naringenin by each of the solvents was studied through a modified preferential solvation model that considers the hydrogen bonding interactions between the prior solvents due to solvent–solvent interactions. The preferential solvation parameters and local mole fraction distribution around the solute were calculated. The results indicated that naringenin prefers to be more solvated by the complex solvating species and organic solvents than water.

Keywords: solvatochromism; naringenin; preferential solvation; binary mixtures.

INTRODUCTION

Solvation and solution chemistry are very important topics in all areas of chemistry, especially in physical chemistry because of the influence of solvent on the kinetics and thermodynamics of reactions.[1] A solvent effect may be understood in terms of nonspecific and specific solute–solvent interactions in pure solvents. However, the situation is complicated in mixed solvents due to the variety of solute–solvent interactions and possibility of solvent–solvent interactions. Preferential solvation occurs when the solute interacts differently with each of the solvating species. In addition, solvent–solvent interactions may affect the type and extent of the solute–solvent interactions.[1–8]

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doi: 10.2298/JSC160327060F

The concept of solvatochromism can be simply used to study the solvent effect in pure and mixed solvents. The spectral properties of the solute may be changed depending on the nature of the solvent interaction with the ground and excited states of the solute. A hypsochromic shift appears when the solvent interacts more with the ground state than with the excited state. On the other hand, more stabilization of the excited state leads to a bathochromic shift of the spectrum.[1] Accordingly, solvatochromism is a result of the difference in the energy of solvation between the ground and excited states, and thus can be conveniently analyzed to gain valuable information regarding solute–solvent interactions.[1–10] The main aspects regarding solvatochromism from the last seven years was recently reviewed in the literature.[11]

Flavonoids are a class of benzopyrone compounds richly available in fruits, wines, teas, seeds and vegetables. Flavonoids are well known due to their functionality, including anti-inflammatory, antimicrobial, antioxidant, anti-HIV activities, anticancer and topoisomerase inhabitation.[12,13] Naringenin, Fig. 1, belongs to a group of flavonoids named flavanones.

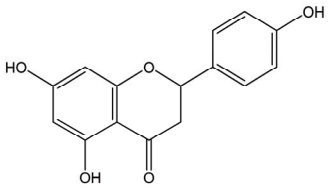

Fig. 1. The structure of naringenin.

This flavanone has the ability to inhibit *in vitro* the growth of cancer cells in humans and, as such, acts as an estrogenic, antioxidant, anticarcinogenic, and anti-oxidative agent. Naringenin has a protective effect on heart disease and Alzheimer's disease. It not only reduces the production of the infectious hepatitis C virus in cell cultures, but also lowers the levels of cholesterol and triglycerides and the circulating LDL to HDL ratio.[13,14] From a dietary point of view, naringenin exists in the skin of tomatoes, citrus fruits and especially in grapefruit juice.[15] Despite its abundance in the human diet, the bioavailability of naringenin is limited by its hydrophobic structure and hence, poor water solubility.

The solubility of the solute is fundamentally related to the extent and types of solute–solvent interactions. Detailed knowledge about these interactions is essential for the development of extraction, purification and separation processes, and hence, in the selection of the proper method for enhancement of solubility in the pharmaceutical industry. In line with this, the study of solvatochromism gives an opportunity to gain insight to solute–solvent interactions in the solvation shell of the solute. Therefore, in this work, the solvatochromism of naringenin was studied in aqueous solutions of methanol, ethanol and 1-propanol. It is noteworthy that the use of co-solvents, such as ethanol, is an effective technique in

the design of pharmaceutical formulations for solubility enhancement of poorly soluble drugs.[16] In addition, methanol, ethanol and, to lesser extent, 1-propanol are widely used in the literature as co-solvents for the extraction of phenolic compounds, such as naringenin.[17]

EXPERIMENTAL

Methanol, ethanol and 1-propanol were purchased as the purest grade from Merck. Naringenin was supplied by Sigma. Double-distilled water with a conductivity of 1.3±0.1 μS was used. A Shimadzu 2100 UV–Vis spectrophotometer was used with a Pentium 4 computer to collect the spectral data of the naringenin solutions in 10 mm quartz cells thermostatted at 25±0.1 °C.

Accurately weighed amounts of pure solvents were mixed to prepare 20 mL of binary mixtures over the full mole fraction range from pure water to pure alcoholic solvent. A concentrated solution of naringenin was obtained in pure ethanol. Volumes of the stock solution (30 μL) were pipetted into 10 mL volumetric flasks and were dried under reduced pressure to remove all the ethanol. Then 3.0 mL of previously prepared binary mixture was added and sonicated in the water bath for 20 min. For all binary mixtures, a clear naringenin solution was obtained with a final concentration of the 5.25 μM. The spectral data of naringenin were collected over the range 200 to 400 nm with an accuracy of ±0.05 nm. All measurements were repeated at least three times. The wavelength of the maximum absorption was found from the first derivative of the absorption data.

RESULTS AND DISCUSSION

Solvent effect

The energy of electron transition from the ground to the excited state of naringenin, E_T, was calculated at the maximum absorption wavelength, λ_{max}, as:

$$E_T = \frac{h c N_A}{\lambda_{max}}$$

where h, c and N_A are Planck's constant, the speed of light in vacuum and Avogadro's number, respectively. The calculated values of E_T are reported in Table I for the full range of mole fractions.

The value of ET corresponds to the nature of the ground and the excited state and the extent of their interaction with the solvent. For a quantitative explanation of solvent effect, Kamlet and Taft parameters, KAT, were used to scale the properties of solvent at the molecular level.[18–20] The KAT parameters involve π^*, β and α, defining the dipolarity–polarizability and the ability of a solvent to act as a hydrogen bond acceptor and hydrogen bond donor respectively.[18–22] The quantity π^* comprises the electrostatic nonspecific effect of the solvent, whereas β and α refer to specific effects of the solvent in solute–solvent interactions. According to linear solvation energy relationships (LSER) concept, the value of E_T could be explained by a linear function of the contributions of the nonspecific and specific solute–solvent interactions.[18–25] Therefore, a general multiparametric equation was derived to correlate E_T with the KAT parameters:

$$E_T = A_0 + a\alpha + b\beta + p\pi^* \quad (1)$$

TABLE I. The E_T values (kJ mol^{-1}) of naringenin in different initial mole fractions of binary aqueous alcoholic solvents at 25 °C

x_2^0	Solvent		
	Water–methanol	Water–ethanol	Water–1-propanol
0.00	415.80	415.80	415.80
0.10	413.72	414.08	413.86
0.20	412.65	412.44	412.15
0.30	411.94	411.16	410.88
0.40	411.44	410.24	409.96
0.50	411.09	409.61	409.33
0.60	410.81	409.19	408.84
0.70	410.67	408.84	408.49
0.80	410.52	408.63	408.21
0.90	410.38	408.49	408.00
1.00	410.31	408.35	407.87

In Eq. (1), the regression coefficients, *a, b,* and *p*, represent the contribution of hydrogen bond donor acidity, hydrogen bond acceptor basicity and dipolarity––polarizability of the solvent, respectively, to E_T. The intercept, A_0, quantify E_T in the gas phase. It should be noted that the presence of each of regression coefficients in the final model is related to the significance of their corresponding solvent property in solute–solvent interactions.[2–8,21–25]

The obtained E_T values for each binary mixture were correlated within the framework of Eq. (1) with the KAT solvent parameters by application of multiple linear regressions analysis.[26] All the required KAT solvent parameters were extracted from the literature for each binary mixture as a function of the mole fraction.[27] In the regression analysis, all single, dual and multiparameteric models were considered with their statistical tests. The best-correlated model was statistically the one with the lowest standard deviation values, the correlation coefficient, r^2, closer to unity and the highest *F*-test value. Thus, it was found that the solvent effect on the solvatochromism of naringenin can be adequately explained in aqueous methanol, ethanol and 1-propanol binary mixtures by Eqs. (2)–(4), respectively:

$$E_T = 388.01(1.96) + 19.93(2.18)\alpha + 3.64(0.68)\pi^* \quad (2)$$
$$r^2 = 0.97,\ F\text{-test} = 123.24$$
$$E_T = 387.36(2.04) + 19.91(2.72)\alpha + 4.47(1.01)\pi^* \quad (3)$$
$$r^2 = 0.98,\ F\text{-test} = 184.85$$
$$E_T = 399.61(0.82) + 13.99(1.04)\pi^* \quad (4)$$
$$r^2 = 0.95,\ F\text{-test} = 179.58$$

in which, the standard deviations are given in parentheses.

The results indicate that the type and extent of the solvent effect is different in each aqueous binary mixture. In the aqueous solutions of methanol and ethanol, significant contributions were found for α and π^*. According to the regression coefficients, the sensitivity of E_T to α is approximately 5.5 and 4.5 time greater than π^* in water–methanol and water–ethanol mixtures, respectively. In other words, the specific interactions explain mainly the variation in E_T of naringenin with increasing mole fraction of methanol and ethanol in the aqueous solutions. The positive sign of both α and π^* indicate that the value of E_T decreases when hydrogen bond donor acidity and polarity of the solvent decreases on increasing the concentration of methanol or ethanol in the solution. Similarly, the value of E_T decreases on increasing the mole fraction of 1-propanol in the aqueous binary mixtures. However, in aqueous 1-propanol solutions, electrostatic nonspecific interactions have the most pronounced effect on the solvatochromism of naringenin.

To the best of knowledge, the literature indicates that, among flavonoids, only the solvatochromism of flavone and its 7-hydroxy derivative have been investigated in some pure and binary solvents.[28,29] Sancho *et al.* reported that the absorption maxima of flavone and 7-hydroxyflavone are well correlated with α and π^*, and β in pure nonaqueous solvents, respectively.[28] However, according to Serdiuk *et al*., there was no significant correlation between the position of the maximum in the spectra of 7-hydroxyflavone and the solvent parameters in pure alcoholic solvents.[29] In addition, in aprotic solvents, the solvatochromism of 7-hydroxyflavone depends on π^* and β.[29] Such results, in accordance with the present findings, show the importance of specific interactions for the absorption spectra of flavonoids. Further quantitative comparisons cannot be made with the present data because no literature data are available for aqueous binary mixtures. However, it should be noted that solvatochromism is more complicated in mixed solvents due to the possibility of preferential solvation and the impact of solvent–solvent interactions on solute–solvent interactions.

Preferential solvation of naringenin

The variation curve of E_T *versus* the initial mole fraction of alcohol, x_2^0, is depicted in Fig. 2. All curves show a nonlinear pattern with respect to the ideal behavior, which is shown by dashed lines. Ideal behavior is a reference state in which the composition of solvents around the solute is the same as the bulk. Deviation from the ideal behavior is a visible sign of solvent–solvent interactions and preferential solvation. Preferential solvation occurs when the solvation shell is enriched by one of the solvating species in the mixed solvent. Fig. 2 shows a negative deviation towards the alcoholic solvent in all binary mixtures, which means that naringenin, may be preferentially surrounded by the alcoholic solvent having a lower E_T than water.

This conclusion is correct only in the case of ideal aqueous solutions, where interactions between the solvents are neglected. Accordingly, solvent–solvent interactions should be considered to gain reliable results. Hence, a modified preferential solvation model was used to analyze solvatochromism.[7,30–32] Based on this model, the competition of two solvents S1 and S2 to interact with the solute I is given by the following equations:

$$I(\mathrm{S2})_m + m\mathrm{Sl} \rightleftarrows I(\mathrm{Sl})_m + m\mathrm{S2} \quad (5)$$

$$I(\mathrm{S2})_m + m\mathrm{Sl2} \rightleftarrows I(\mathrm{Sl2})_m + m\mathrm{S2} \quad (6)$$

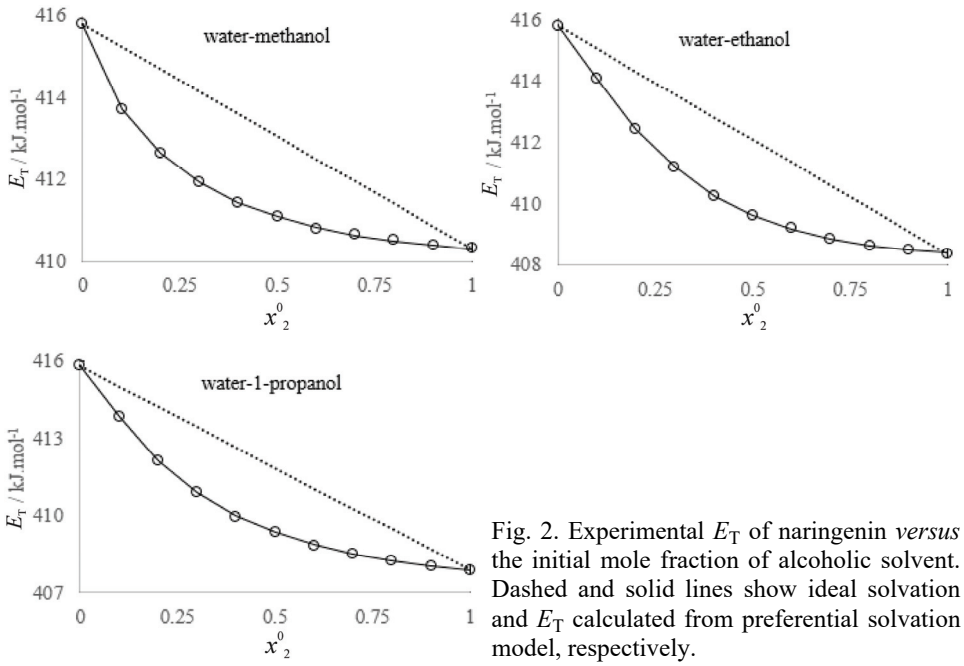

Fig. 2. Experimental E_T of naringenin *versus* the initial mole fraction of alcoholic solvent. Dashed and solid lines show ideal solvation and E_T calculated from preferential solvation model, respectively.

where I(S1), I(S2) and I(S12) are the concentrations of S1, S2 and S12 in the solvation shell of the solute, *i.e.*, local composition, respectively. S12 was used to show the solvating species formed by the solvent–solvent interactions between S1 and S2. In addition, m refers to the exchange number of solvent molecules, which affect solvatochromism. The bulk solvent–solvent interaction is considered in Eq. (7):

$$\mathrm{S1} + \mathrm{S2} \rightleftarrows \mathrm{S12} \quad (7)$$

The stoichiometric ratio used was 1:1 according to experimental and theoretical evidence in the literature.[33,34] The concentration of S1, S2 and S12 in the bulk are related to each other by the association constant, K_{assoc}, of Eq. (7), which can be calculated from the nonideal properties of binary mixture, such as

density values.[30–32] The value of K_{assoc} was calculated as 0.220, 0.032 and 0.012 M^{-1} in aqueous solution of methanol, ethanol and 1-propanol, respectively.[32] Knowing K_{assoc}, the real mole fraction of S1, S2 and S12 in the bulk were calculated *versus* the initial mole fraction of alcoholic solvents, x_2^0, from literature density data.[35,36]

By a simple manipulation, the local and bulk mole fraction of the solvating species can be related to each other by the equilibrium constant in Eqs. (5) and (6), called preferential solvation parameters:

$$f_{1/2} = \frac{x_1^L}{x_2^L}\left(\frac{x_2}{x_1}\right)^m \tag{8}$$

$$f_{12/2} = \frac{x_{12}^L}{x_2^L}\left(\frac{x_2}{x_{12}}\right)^m \tag{9}$$

$$f_{12/1} = \frac{f_{12/2}}{f_{1/2}} = \frac{x_{12}^L}{x_1^L}\left(\frac{x_1}{x_{12}}\right)^m \tag{10}$$

where, x_i^L and x_i are the local and bulk mole fractions of the solvating species *I*, respectively. The quantity $f_{i/j}$ is the above defined preferential solvation parameter. For example, $f_{1/2}$ gives the tendency of S1 to be more concentrated in the solvation shell of the solute relative to S2. In each region, the sum of the mole fractions of all species should be equal to unity:

$$x_1^0 + x_2^0 = x_1 + x_2 + x_{12} = x_1^L + x_2^L + x_{12}^L \tag{11}$$

The value E_T in a mixed solvent is the weighted local mole fraction average of E_T in each solvating species as:

$$E_T = E_1 x_1^L + E_2 x_2^L + E_{12} x_{12}^L \tag{12}$$

where E_i is the E_T of the solute in pure solvent *i*. Equation (12) can be rewritten as a function of the bulk mole fraction and preferential solvation by a combination of Eqs. (8)–(11):

$$E_T = \frac{E_2(x_2)^m + f_{1/2}E_1(x_1)^m + f_{12/2}E_{12}(x_{12})^m}{(x_2)^m + f_{1/2}(x_1)^m + f_{12/2}(x_{12})^m} \tag{13}$$

Nonlinear regression analysis was aimed at fitting the experimental values of E_T into Eq. (13). The results of the preferential solvation model are given in Table II.

In all binary mixtures, $f_{1/2}$ was lower than unity, indicating naringenin prefers to be more solvated by the alcoholic solvent than water. In addition, $f_{12/2} < 1$ and $f_{12/1} > 1$ indicate that the complex solvating species formed by solvent–sol-

vent interaction have lower and greater affinity to incorporate into the solvation shell of naringenin relative to the alcoholic solvent and water, respectively. It should be noted that $f_{12/2}$ was very close to unity in water–methanol mixtures; showing the local and bulk composition were similar in their respective concentration in S12 and S2. These results are in accordance with the molecular structure of naringenin and the nature of solvents. Naringenin is a hydrophobic solute having three hydroxyl groups in its structure; an alcohol is an organic solvent with more basicity than water; therefore, it is reasonable that naringenin prefers to be more solvated by pure alcoholic and hydrogen bonded S12 species than water.

TABLE II. The results of the preferential solvation model of the solvatochromism of naringenin in the binary aqueous solutions at 25 °C

Co-solvent	E_1	E_2	E_{12}	m	$f_{1/2}$	$f_{12/2}$	$f_{12/1}$
Methanol	415.80	410.30	410.95	0.92	0.21	1.02	4.90
Ethanol	415.80	408.35	413.11	1.04	0.17	0.21	1.29
1-Propanol	415.80	407.87	413.16	1.11	0.19	0.58	2.99

CONCLUSIONS

The solvatochromism of naringenin was investigated over the full mole fraction range of aqueous solutions of methanol, ethanol and 1-propanol at 25 °C. The linear solvation energy relationships concept indicated that the solvatochromism was controlled by the specific solvent effect in the water–methanol and water–ethanol systems, whereas the nonspecific electrostatic solvent effect had the biggest effect in the water–1-propanol system. Preferential solvation of naringenin was studied by a modified model. The model indicated that naringenin prefers to be more solvated by an alcoholic solvent rather than by water in all binary mixtures.

Acknowledgements. The authors gratefully acknowledge the financial support form the Research Council of Islamic Azad University Babol Branch.

ИЗВОД

СОЛВАТОХРОМИЗАМ НАРИНГЕНИНА У ВОДЕНИМ АЛКОХОЛНИМ СМЕШАМА

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Спектралне промене нарингенина су испитиване UV–Vis спектрофотометријом у бинарним смешама воде са метанолом, етанолом и 1-пропанолом на 25 °C. Ефекат растварача је праћен анализирањем електронске транзиционе енергије на таласној дужини апсорпционог максимума као функција Камлетових и Тафтових параметара смеше применом линеране везе енергије растварања. Нелинеарни одговор солватохромизма је објашњен на основу интеракција растворак–растварач и растварач–растварач. Могућа преференцијална растворљивост нарингенина у сваком од растварача је испитивана коришћењем модификованог модела преференцијалног растварања који узима у обзир

водоничне везе између растварача услед интеракција растварач–растварач. Израчунати су параметри преференцијалног растварања и локалне расподеле молских фракција око растворка. Добијени резултати указују да се наринген боље раствара комплексним врстама растварача и у органским растварачима у односу на воду.

(Примљено 27. марта, ревидирано 21. априла, прихваћено 25. априла 2016)

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