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# Preferential solvation of quercetin in aqueous aprotic solvent mixtures

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*Abstract*: Solvatochromism of quercetin was studied in binary mixtures of water with dimethyl sulfoxide, *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide at 25 °C by UV–Vis measurements. For all mixtures, a non-linear trend was observed in spectral shifts plotted against the bulk mole fractions. Deviation from ideal behaviour indicates that the solvation shell of quercetin differs in composition from the bulk because of preferential solvation. The solvent exchange model was applied in the analysis of solvatochromic data in order to quantify the extent of preferential solvation in the case of solute–solvent and solvent–solvent intermolecular interactions. The results show that the solvation shell of quercetin is enriched in aprotic solvent and the complex that was formed by the interaction between water and an aprotic solvent, over the whole composition range. The distribution of the solvent species in the solvation cage was obtained from the calculation of the local mole fractions as a function the bulk composition. It shows that the solvent–solvent interactions have great influence on the solvation behaviour of quercetin in aqueous aprotic solvent mixtures.

*Keywords*: solvatochromism; quercetin; preferential solvation; binary mixtures.

## INTRODUCTION

Chemistry of a solute in solution is closely related to the structure of the solute's microenvironment. Intermolecular interactions occurring on the molecular level between a solute and a solvent govern the microenvironment structure, which in turn define medium-dependent physicochemical properties of a solute. Knowledge on the microstructure of a solvent in the solvation shell of a solute is of critical importance for physical chemists to understand and predict the solvent effect on thermodynamics and kinetics of process. In this regard, solvatochromic studies present a convenient approach for achieving a detailed insight into the characterization of the microenvironment around a solute. Solvatochromism refers to the phenomena in which the spectral behaviour of a

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solute is affected by the change of a solvent.[1] Difference in stabilization of the ground and the excited state of a solute upon an interaction with a solvent is mainly responsible for this phenomena. Therefore, the solvatochromic signals convey direct information about the nature of solute-solvent interactions, which can be used to characterize properties and structure of a solvent in the presence of a solute.[1–17]

In a pure solvent, the solvent composition is the same for both bulk and solvation shell regions. However, the arrangement of solvent molecules can be varied around the solute, due to solute-solvent interactions, depending on the nature of a solute and solvent. In this respect, several methods have been proposed on the basis of solvatochromism that permits the quantification of the solvent characteristics at the molecular level of interactions.[1] The case of mixed solvents is of particular interest, because of the possibility of the occurrence of preferential solvation. This event arises when each solvent component of a mixture interacts in different extent with the solute, which gives rise to compositional difference of a solvent between bulk and a solvation shell area. In addition to the preferential solvation, the microstructure of a solvation shell is affected by the mutual interactions of solvent components that lead to the formation of a new solvating species in the presence of the solute. Since the characteristics of a solvation shell are defined by its composition and local interactions, the analysis of the dependence of solvatochromism on the composition of solvent mixtures provides means for the quantitative description of the preferential solvation and the estimation of the local composition around the solute.[7–9]

In this work, the solvatochromism of quercetin, Fig. 1, was analyzed in aqueous binary mixtures of dimethyl sulfoxide, *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide, in order to study the preferential solvation and to estimate the local composition of solvent components in the solvation shell. Quercetin is a flavonol, a subgroup of polyphenolic natural compound named flavonoids. Quercetin is well known because of its widespread beneficials for human health.[18] The knowledge of solvation properties of quercetin is of crucial importance for the improvement of its extraction and purification techniques, design of drug formulation, and understanding of the solution chemistry of quercetin.

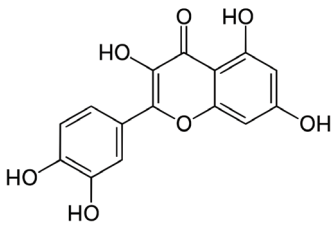


Fig. 1. Chemical structure of quercetin.

## EXPERIMENTAL

The aprotic solvents dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMAC) were supplied in the purest grade from Merck. Quercetin (IUPAC name: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one) was purchased from Sigma. Water was double-distilled (conductivity of 1.3±0.1 μS/cm). UV–Vis spectrophotometer (PG Instrument, model T80) was used to record the absorption spectra of solutions of quercetin in a 10 mm quartz cells that was thermostatted at 25±0.1 °C.

The binary mixtures were prepared by mixing the accurate weighted amounts of pure solvents over the full composition ranges. A stock solution of quercetin was prepared in ethanol, then 30 μL of ethanolic solution was transferred into 10 mL volumetric flasks, and dried under vacuum. Afterwards, 3.0 mL of each binary mixture was pipetted into each flask and it was sonicated until a clear and homogenous solution was formed. The final concentration of quercetin was 5.02 μM. The spectral data acquisition was done over the wavelength range of 300 to 500 nm with an accuracy of ±0.05 nm at the lowest scan rate. The wavelength for maximum absorption, $\lambda_{max}$, was determined by Gaussian peak fitting on Origin Lab 8.5. All reported data are the average from at least three replications.

## RESULTS AND DISCUSSION

### *Solvatochromism of quercetin*

The $\lambda_{max}$ of quercetin as a function of mole fraction of DMSO, DMF and DMAC in aqueous binary mixtures is presented in Table I. This wavelength is assigned to the electronic transition from the ground state to first excited state, and belongs mainly to HOMO→LUMO transition.[19] The frontier molecular orbitals are delocalized over the whole conjugated system of quercetin (Fig. 1), and have $\pi$ and $\pi^*$ character.

For solvatochromic analysis, it is highly recommended to convert $\lambda_{max}$ to the intermolecular energy transition using $E_T = 119626.8/\lambda_{max}$ in kJ mol$^{-1}$. The value of $E_T$ reflects the polarity of solvation shell, and conveys direct information on local structure of solvent around the solute.[1–17] The calculated values of $E_T$ are plotted in Fig. 2 *versus* the full mole fraction of aprotic solvents in binary mixtures. As Fig. 2 shows, in overall, a bathochromic shift occurs when the mole fraction of an aprotic solvent increases in mixtures. The dipole moment of quercetin increases in its excited state, with respect to the ground state.[20] In this view, it is expected that the decrease in polarity of a solvent when an aprotic solvent mole fraction increases in a binary mixture leads to a hypsochromic shift. However, the hydrogen bond basicity of a solvent has a considerable negative effect on the electronic transition energy of quercetin.[20] It means that, as observed in Fig. 2, bathochromic shifts occurs and $E_T$ decreases as the hydrogen bond basicity of mixture increases by raising the mole fraction of DMSO, DMF and DMAC.[21]

All mixtures exhibit strong deviation from linear solvatochromism. The dashed lines in Fig. 2 refer to the linear solvatochromism in which the characteristics of solvents do not differ in a bulk mixture and a solvation shell of a solute. The deviation of the linear solvatochromism in binary mixtures is a visible

sign of the effect of solvent–solvent interactions and preferential solvation. The negative deviation of solvatochromism towards aprotic solvents may point to the fact that that quercetin is preferentially solvated by aprotic solvents, over the full composition ranges in these mixtures. This inference is acceptable only when the mixture behaves ideal. According to this critical issue, the solvatochromic data should be analyzed by the explicit consideration of the effect of a solvent–solvent interactions, in order to gain reliable results.

TABLE I. The $\lambda_{max}$ values (nm) of quercetin at various initial mole fraction of aprotic solvent in binary aqueous solutions at 25 °C

| $x_2^0$ | Solvent | | |
|---|---|---|---|
| | Water–DMSO | Water–DMF | Water–DMAC |
| 0.00 | 366.8 | 366.8 | 366.8 |
| 0.01 | 368.0 | 368.9 | 370.2 |
| 0.02 | 368.6 | 370.5 | 372.3 |
| 0.03 | 369.2 | 371.6 | 373.5 |
| 0.05 | 370.0 | 373.4 | 374.4 |
| 0.07 | 370.8 | 373.6 | 375.0 |
| 0.10 | 371.7 | 374.5 | 375.6 |
| 0.12 | 372.1 | 374.8 | 375.9 |
| 0.15 | 373.0 | 375.0 | 376.3 |
| 0.20 | 374.0 | 375.4 | 376.6 |
| 0.25 | 374.5 | 375.8 | 376.8 |
| 0.30 | 375.0 | 376.0 | 376.9 |
| 0.35 | 375.5 | 376.3 | 377.0 |
| 0.40 | 376.0 | 376.7 | 377.1 |
| 0.45 | 376.4 | 376.9 | 377.2 |
| 0.50 | 377.0 | 377.1 | 377.3 |
| 0.55 | 377.4 | 377.3 | 377.4 |
| 0.60 | 377.6 | 377.4 | 377.5 |
| 0.65 | 377.9 | 377.5 | 377.7 |
| 0.70 | 378.2 | 377.6 | 377.8 |
| 0.75 | 378.5 | 377.8 | 377.9 |
| 0.80 | 378.8 | 378.0 | 378.0 |
| 0.85 | 379.2 | 378.1 | 378.2 |
| 0.90 | 379.4 | 378.1 | 378.3 |
| 0.95 | 379.6 | 378.1 | 378.5 |
| 1.00 | 379.6 | 378.0 | 378.6 |

*Preferential solvation of quercetin*

The solvent exchange model is among the most successfully used models to investigate the preferential solvation in mixed solvents.[7–11,22–25] This model considers the effect of a solvent-solvent interaction to preferential solvation, allowing the quantification of the extent of preferential solvation by each solvent components, as well as of the local composition of solvents in the solvation shell of

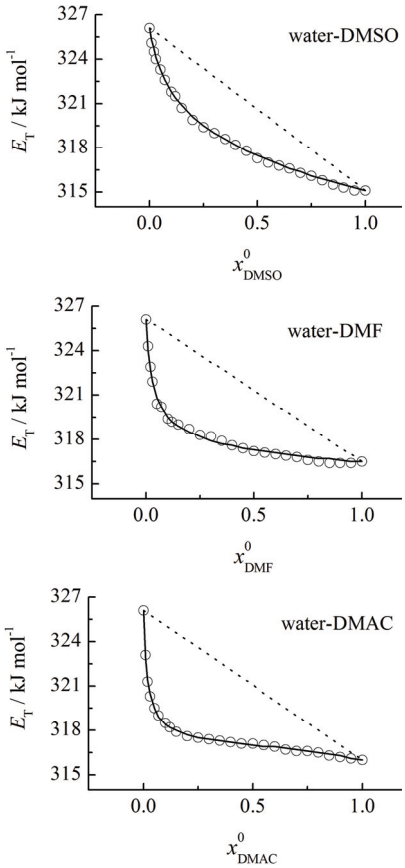


Fig 2. The value $E_T$ of quercetin *versus* the initial mole fraction of aprotic solvent. Dashed and solid lines refer to the linear solvatochromism and $E_T$ calculated by preferential solvation model, respectively.

the solute. This model is based on two-step solvent exchange equilibria as Eqs. (1) and (2):[10,22–25]

$$\mathrm{I(S2)}_m + m\mathrm{S1} \leftrightarrows \mathrm{I(S1)}_m + m\mathrm{S2} \quad (1)$$

$$\mathrm{I(S2)}_m + m/2(\mathrm{S1}) \leftrightarrows \mathrm{I(S1)}_m + m/2(\mathrm{S2}) \quad (2)$$

I is quercetin; S1 is water; S2 is DMSO, DMF or DMAC; I(Si) shows that quercetin is surrounded fully by solvent I; S12 shows the solvent complex formed by the interaction of S1 and S2. The term $m$ is an index of the number of the exchanged molecules of solvent that affects solvatochromism. The local composition of solvent $i$, $x_i^L$, is related to the bulk composition of solvent $i$, $x_i^0$, by the following expressions:

$$f_{1/2} = \frac{x_1^L}{x_2^L}\left(\frac{x_2^0}{x_1^0}\right)^m \quad (3)$$

$$f_{12/2} = \frac{x_{12}^{L}}{x_{2}^{L}} \sqrt{\left(\frac{x_{2}^{0}}{x_{1}^{0}}\right)^{m}} \tag{4}$$

In fact, $f_{i/j}$ are equilibrium constants for the two exchange equilibria, defined in the Eqs. (1) and (2), on the mole fraction scale. The value of $f_{i/j}$ quantifies the extent of the preferential solvation of a solute by a solvent $i$, with respect to the solvent $j$; $f_{i/j} = 1$ means no preferential solvation; $f_{i/j} > 1$ describes the preferential solvation of a solute by the solvent $i$ relative to the solvent $j$. In addition, the $E_T$ is a function of the local mole fractions:

$$E_T = E_T(S1)x_1^L + E_T(S2)x_2^L + E_T(S12)x_{12}^L \tag{5}$$

herein $E_T(Si)$ is the averaged value of $E_T$ in solvent $i$. Considering the sum of mole fractions in both phases equals unity, introduction of Eqs. (3) and (4) into Eq. (5) gives:

$$E_T = \frac{E_T(S2)(x_2^0)^m + f_{1/2}E_T(S1)(x_1^0)^m + f_{12/2}E_T(S12)\sqrt{(x_1^0x_2^0)^m}}{(x_2^0)^m + f_{1/2}(x_1^0)^m + f_{12/2}\sqrt{(x_1^0x_2^0)^m}} \tag{6}$$

where the unknown parameters are $E_T(S12)$, $f_{1/2}$, $f_{12/2}$ and $m$ that can be calculated by fitting the experimental data into the Eq. (6).

Once $f_{1/2}$, $f_{12/2}$ and $m$ are estimated, the local mole fraction of solvents can be calculated by following equations:

$$x_1^L = \frac{f_{1/2}(x_1^0)^m}{f_{1/2}(x_1^0)^m + (x_2^0)^m + f_{12/2}\sqrt{(x_1^0x_2^0)^m}} \tag{7}$$

$$x_2^L = \frac{(x_2^0)^m}{f_{1/2}(x_1^0)^m + (x_2^0)^m + f_{12/2}\sqrt{(x_1^0x_2^0)^m}} \tag{8}$$

$$x_{12}^L = \frac{f_{12/2}\sqrt{(x_1^0x_2^0)^m}}{f_{1/2}(x_1^0)^m + (x_2^0)^m + f_{12/2}\sqrt{(x_1^0x_2^0)^m}} \tag{9}$$

In this work, the experimental $E_T$ data were fitted into the Eq. (6) using non-linear regression analysis from Origin Lab 8.5. Table II summarizes the results obtained by the exchange solvent model.

As the solid lines in Fig. 2 and the regression coefficients ($r^2$ very close to unity) show, the solvent exchange model describes well the solvatochromism of quercetin in aqueous solutions of DMSO, DMF and DMAC. The local mole fractions of the solvent components were calculated as a function of the bulk mole fraction, and are plotted in Fig. 3.

TABLE II. Preferential solvation parameters of quercetin in binary aqueous mixtures at 25 °C

| Co-solvent | $E_1$ / kJ mol$^{-1}$ | $E_2$ / kJ mol$^{-1}$ | $E_{12}$ / kJ mol$^{-1}$ | $m$ | $f_{2/1}$ | $f_{12/1}$ | $r^2$ |
|---|---|---|---|---|---|---|---|
| DMSO | 326.1 | 315.1 | 320.8 | 2 | 28.8 | 17.3 | 0.99 |
| DMF | 326.1 | 316.5 | 318.7 | 2 | 82.6 | 39.0 | 0.99 |
| DMAC | 326.1 | 316.0 | 317.3 | 2 | 24.6 | 56.2 | 0.99 |

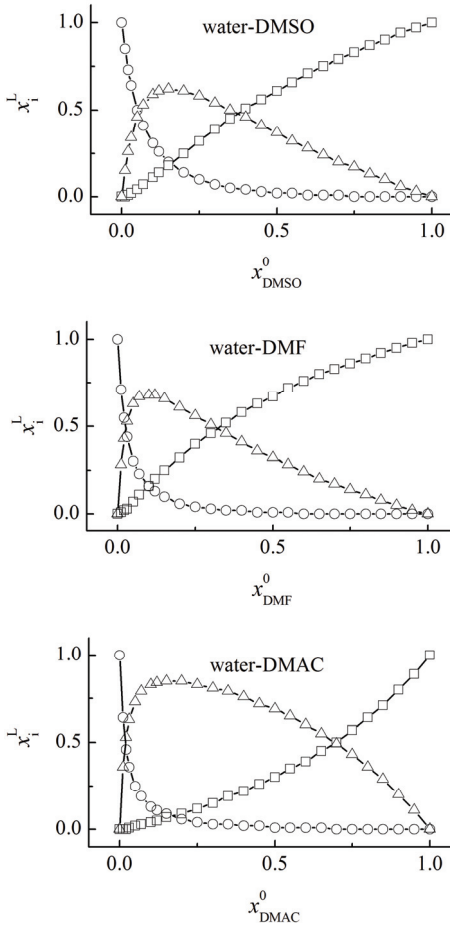


Fig 3. Local mole fractions around quercetin: $x_1^L$ (○), $x_2^L$ (□), $x_{12}^L$ (△) as a function of the bulk mole fraction of DMSO, DMF and DMAC in the binary mixtures at 25 °C.

The preferential solvation analysis indicates that, in all binary mixtures, three solvent components involving water, aprotic solvent and a complex formed by the hydrogen bonding between water and aprotic solvents contribute to the solvation shell structure. It means that the solvent–solvent interactions have significant effect on solvatochromism in these mixtures. In all binary mixtures $f_{2/1}$ is higher than unity, meaning quercetin is preferentially solvated by aprotic solvents, with respect to water. In addition, $f_{12/1} > 1$ reveals that a complex solvent formed by the solvent-solvent interactions has the higher concentration, and it

goes into the solvation shell of quercetin. The value of $f_{2/1}$ is higher than $f_{12/2}$ in aqueous mixtures of DMSO and DMF, indicating that the order of preferential solvation in these mixtures is S2 > S12 > S1. On the contrary, $f_{12/1} > f_{2/1}$ in aqueous mixtures of DMAC shows the order of preferential solvation is as S12 > S2 > S1. Fig. 3 reveals that upon the addition of DMSO, DMF and DMAC to pure water, the solvation shell of quercetin becomes enriched by an aprotic solvent and a complex solvent (S12). This result is in agreement with the molecular structure of quercetin (Fig. 1), because quercetin has several hydroxyl groups on its structure, which makes it a potent hydrogen bond donor solute. Local mole fraction of a complex solvent reaches a maximum around $x_2^0$ of 0.15 in aqueous mixtures of DMSO, 0.10–0.12 in aqueous mixtures of DMF and 0.15–0.20 in aqueous mixtures DMAC. As clear in Fig. 3, the solvation shell of quercetin is fully saturated with an aprotic solvent, and a complex solvent over the whole composition range.

## CONCLUSION

The solvatochromism of quercetin was analyzed over the full mole fraction range of aqueous binary mixtures of DMSO, DMF and DMAC at 25 °C. The solvent exchange model was successfully used to describe the observed non-linear solvatochromism. The results indicate that both the preferential solvation and the solvent-solvent interactions are responsible in this matter. The spectral data analysis reveals that quercetin is preferentially solvated by aprotic solvents and complex solvents, in comparison to water in all binary mixtures. The local mole fractions of solvents components were calculated as a function of bulk composition. Results show that the solvation shell of quercetin is mainly enriched by aprotic solvents and complex solvents, over the whole composition range.

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## ИЗВОД

## ПРЕФЕРЕНЦИЈАЛНА СОЛВАТАЦИЈА КВЕРЦЕТИНА У ВОДЕНИМ СМЕШАМА АПРОТИЧНИХ РАСТВАРАЧА

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Солватохромизам кверцетина је испитиван у бинарним смешама воде и диметил-сулфоксида, *N*,*N*-диметилформамида и *N*,*N*-диметилацетиламида на 25 °C, UV–Vis спектроскопијом. За све смеше детектован је нелинеарни тренд спектралних помераја у зависности од запреминских молских фракција. Одступање од идеалног понашања указује да се састав солватационе сфере кверцетина разликује од запреминског састава смеше због преференцијалне солватације. Модел измене растварача је коришћен у анализи солватохромних података да би се квантификовао степен преференцијалне солватације у смислу интермолекулских интеракција растворена супстанца–растварач и растварач–растварач. Резултати показују да је солватациона сфера кверцетина обогаћена апротичним раствара-

чима и комплексом који се формира услед интеракција између воде и апротичног растварача, у читавом опсегу концентрација. Расподела врста растварача у солватационој љусци је добијена из прорачуна локалног молског удела у функцији запреминског састава. Показано је да интеракције растварач–растварач имају велики утицај на солватацију кверцетина у воденим смешама апротичних растварача.

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