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A systematic study on solubility and solvation of bioactive compound chrysin in some water + cosolvent mixtures

Sedigheh Feizi [a], Morteza Jabbari [a,*], Ali Farajtabar [b]

[a] School of Chemistry, Damghan University, 36716-41167 Damghan, Iran
[b] Department of Chemistry, Jouybar Branch, Islamic Azad University, Jouybar, Iran

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ABSTRACT

The equilibrium solubility of flavonoid chrysin was evaluated using UV–Vis spectrophotometric method in various mixed solvents comprising 0–100% (v/v) dimethylformamide (DMF) and tetrahydrofuran (THF) in water and constant temperature (25.0 ± 0.1) °C. From solubility data, the Gibbs free energy changes involved with the dissolution process of chrysin were also determined. The obtained results showed that the solubility of chrysin increases by increasing the DMF and THF proportion in solution. Furthermore, the preferential solvation parameters of the solute chrysin by co-solvents DMF and THF, $\delta x_{cosolv,S}$, were derived using the inverse Kirkwood-Buff integrals (IKBI) approach. From the $\delta x_{cosolv,S}$ data, it was found that water is the preferred solvent in the solvation shell of chrysin in water-rich mixtures but the co-solvents DMF and THF are preferred in intermediate compositions to pure co-solvent. The variation of this parameter in the binary mixtures studied is discussed based on types of intermolecular solute-solvent interactions and structural characteristics of flavonoid chrysin.

1. Introduction

The solubility of water-insoluble compounds in aqueous co-solvent solution plays an important role in the chemical, environmental, pharmaceutical, and biotechnological industries. Moreover, in order to determine proper solvents and to design an optimized production process, it is necessary to know the solubility of the compounds in different solvents [1,2]. A major drawback in formulation development for natural bioactive compounds is their poor aqueous solubility and bioavailability [3]. In addition to the solubility, the solvation process of solute molecules in solvent mixtures is very important in pharmaceutical and biochemistry sciences to obtain complete information about physicochemical and biochemical characteristics for bioactive systems. Nevertheless, preferential solvation phenomenon that describes as preferable composition of a solvent around the solute molecule in solvation layer, for many pharmaceutical compounds has not been studied until now. An accurate knowledge about this phenomenon would lead to a better comprehending of the molecular interactions occurring during the solution processes.

So far, many theoretical and empirical approaches have been applied for the elucidation of the problem of the preferential solvation [4]. In this way, the use of inverse Kirkwood-Buff integral (IKBI) method of Ben-Naim is an efficient technique for analyzing the preferential solvation of non-electrolyte compounds in solvent mixtures. This approach describes the local solvent proportions around the solute with respect to the bulk composition of the co-solvent mixtures [5–8].

Flavonoids as natural polyphenolic phytochemicals are ubiquitous in fruit and vegetable derived foods and have long been associated with a variety of beneficial bioactivities important in cancer prevention and health promotion. The high potency and low systemic toxicity of these natural compounds make them viable alternatives to conventional therapeutic drugs, so that recent years have witnessed an explosive growth of research on various bioactive flavonoids having important therapeutic activities [9–11]. Chrysin with the IUPAC name 5,7-dihydroxy-2-phenyl-4H-chromen-4-one, is one of important naturally occurring flavonoids which possesses a wide range of biological activities and pharmacological effects, such as anti-inflammatory, antihypertension, antioxidant, anti-allergic and antihemolytic properties [10–13]. However, the flavonoid chrysin is limited to use in the pharmaceutical field because of its poor aqueous solubility and hence low absorption [14]. This flavonoid is found at high levels in honey and propolis and in much plant extracts [12]. A sketch of molecular structure of chrysin is shown in Scheme 1.

The study described in this paper focuses on measurement of the equilibrium solubility of antioxidant agent chrysin in pure solvents including water, DMF and THF, and different binary mixtures of water + DMF or THF (10–90% by v/v) using UV–Vis spectrophotometric method to expand the database on experimental solubility for this flavonoid. Furthermore, the solubility results obtained were used to evaluate the preferential solvation of chrysin in the mixed solvent systems based on the IKBI method. It may be concluded that the data presented

* Corresponding author.
E-mail address: m_jabari@du.ac.ir (M. Jabbari).

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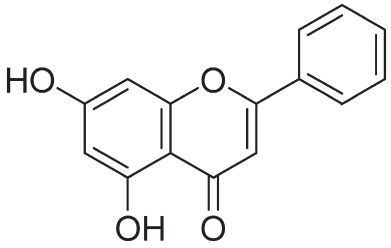

Scheme 1. Chemical structure of flavonoid chrysin.

in this study enhance existing information related to the physicochemical behavior of chrysin in various pure organic solvents and in their aqueous mixtures.

2. Experimental section

2.1. Materials and apparatus

Flavonoid chrysin ($C_{15}H_{10}O_4$), was supplied from Aldrich as analytical reagent grade material and was used without any purification process. The solvent DMF and THF used in the experiment was obtained from Merck and was used as received. During the study, all the solutions were freshly prepared daily using ultrapure water (with a specific conductivity $<1.2\ \mu S\ cm^{-1}$). All chemicals and solvents used were of the highest quality available. The absorbance readings of the chrysin solutions were carried out by a Perkin-Elmer (Lambda 25) UV–Vis spectrophotometer in conjunction with a LabTech LCB-R08 thermo-circulator, using quartz cells of 10 mm optical path.

2.2. Procedure for solubility measurement

The experimental setup used for the solubility measurements of flavonoid chrysin was to first add an excess amount of chrysin to a 10 mL dual-wall glass flask containing a known volume (3–5 mL) of each composition of co-solvents DMF or THF (0–100% v/v) in water. The flask was maintained at constant temperature 25.0 °C through circulating water by a thermostat with a precision of ±0.1 °C that was provided from a constant-temperature water bath. The experimental pressure was also maintained at atmospheric pressure of 0.1 MPa. To reach equilibrium, the solution was constantly stirred using a magnetic stirring bar running at 400 rpm for at least 4 h. Thereafter, the solution was allowed to settle approximately 2 h prior to analysis. The sample then were centrifuged at 5000 rpm for 10 min and the upper portion was taken, filtered, and transferred to volumetric tubes at the same temperature as the solution temperature to avoid any precipitation. After evaporating the solvent under reduced pressure, a known volume of the neat co-solvent was pipetted into the tubes. Finally, the absorbance of diluted samples was measured using a UV–Vis spectrophotometer over the wavelength range of 200 to 400 nm and with 0.1 nm intervals. With the aim of ensuring the reproducibility and saturation of the solutions, all dilutions and solubility measurements were performed at least in duplicate, and the mean values were reported.

In order to estimation of the amount of chrysin in the solution, a calibration curve was obtained using standard solutions in the appropriate concentration range of chrysin in neat co-solvent DMF or THF to determine the molar absorbance coefficient (ε) of chrysin. From the linear fitting of data at the wavelength of the maximum absorbance ($\lambda_{max} = 268.4$ nm and 269.4 nm in DMF and THF, respectively), the value determined for ε was 4.7720×10^4 and $3.5115 \times 10^4\ L\,mol^{-1}\,cm^{-1}$ in DMF and THF, respectively. The value of molar absorbance coefficient was utilized for quantitation of flavonoid chrysin in different solvent mixtures.

3. Results and discussion

3.1. Solubility data of chrysin

As mentioned earlier, the UV–Vis spectrophotometric technique was chosen for the quantitative analysis. From absorbance data obtained for saturated solutions of chrysin in different composition of DMF or THF and having the molar absorbance coefficient, the concentration of the solute chrysin (in mol dm^{-3}) was calculated and reported as the solubility (molar solubility, S_m). The solubility was also expressed in terms of mole fraction i.e. mole fraction solubility using molar solubility data as follows:

$$x_S = \frac{S_m}{S_m + \left(\frac{1000d}{x_{H_2O}M_{H_2O} + x_{cosolv}M_{cosolv}}\right)} \quad (1)$$

where x_{H2O} and x_{cosolv} are the mole fraction of water and the co-solvents used, M_{H2O} and M_{cosolv}, are the molecular weight of water and the co-solvents, equal with 73.09, 72.11 and 18.02 g mol^{-1}, for DMF, THF and water, respectively. The parameter d represents the density of the solvent mixtures (in g cm^{-3}), which its values in different binary mixtures of water + DMF or water + THF have been gathered from the literature [15,16]. The experimental values of mole fraction solubility as well as molar solubility of chrysin in pure solvents water, DMF and THF, and aqueous mixtures of them at temperature 25 °C and atmospheric pressure of 0.1 MPa are reported in Table 1. Each solubility value reported is an average of at least two independent experiments. The solubility data indicate that the solubility of chrysin in the mixtures of DMF or THF and water increases with the increasing mole fraction of the co-solvents, such that equilibrium chrysin solubility in mole fraction increased from 6.67×10^{-6} in pure water to 1.27×10^{-2} and 1.81×10^{-2} in neat DMF and THF, respectively. As a comparison, from results gathered in Table 1 it is clear that the solubility values of chrysin in water + THF mixtures are at least 1.30 to 3.10 times higher compared with those values obtained in water + DMF co-solvent mixtures. Therefore, the solubility of chrysin in the solvents investigated follows the order: THF > DMF > water. This behavior should be due to the more similarity of chrysin polarity with these solvents. The presence of the aromatic rings in the chrysin structure makes this flavonoid a less polar compound. The solubility of flavonoid chrysin in pure water was measured previously and value of 1.86×10^{-5} reported for mole fraction solubility of it at 25.0 °C [17]. This disagreement can be related to several reasons including the difference in the experimental method, or difference in equilibration times and saturation dynamics, as has been described in the literature [18]. Unfortunately, no work on the solubility of this flavonoid in aqueous mixtures of DMF and THF has been reported until now in the literature for comparison.

3.2. Gibbs free energies of dissolution of chrysin

For an electrically neutral molecule, the standard molar Gibbs free energy for the dissolution process, ΔG^o_s, at a constant temperature, can be calculated according to the following thermodynamic relationship [19]:

$$\Delta G^o_s = -RT \ln x_s \quad (2)$$

where R is the universal gas constant (8.3145 J K^{-1} mol^{-1}), T is absolute temperature and x_S is the mole fraction solubility of solute dissolved in solvent.

The Gibbs free energy changes that takes place during the dissolution process (ΔG^o_s) of chrysin in water + DMF and water + THF mixed solvents was calculated using experimental solubility data (x_S) and are listed in Table 2. The ΔG^o_s value appears to be reasonable regarding the interaction between the solute and solvents. The positive