Solubility of Flavonoids in Organic Solvents

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The solubility of quercetin, isoquercitrin, rutin, chrysin, naringenin, and hesperetin was quantified in acetonitrile, acetone, and *tert*-amyl alcohol. The solubility was strongly affected by both the nature of the solvent and the flavonoid structure. The highest solubility was obtained in acetonitrile for hesperetin (85 mmol·L^{-1}) and naringenin (77 mmol·L^{-1}) and in acetone (80 mmol·L^{-1}) for quercetin. The lowest solubility value was obtained with rutin in acetonirile (0.50 mmol·L^{-1}). The thermodynamic properties of flavonoids were also measured (melting point, enthalpy of fusion, and solid heat capacity) and predicted (liquid heat capacity, solid phase activity, and activity coefficient). Glycosylated flavonoids are characterized by a low melting point and a high enthalpy of fusion compared to the aglycon ones. Contrary to the data reported for other compounds, there is no clear correlation between the solubility of flavonoids and their thermodynamic properties. However, the conformational study showed that the flavonoids having a torsion angle OC2C1′C6′ of 40° are characterized by a high solubility.

Introduction

Flavonoids are frequently present in nature and easily extracted from many different plants. Their protective effect against lipid peroxidation of membranes, involved in several physiological and pathological disorders, such as inflammation, atherosclerosis, ischemia, toxicity of oxygen, and chemical substances, has been largely studied.[1−7] Many of these compounds are already used in pharmaceutical, cosmetic, and food preparations.[4,8−13] However, their solubility is very low in water,[8,10,14−16] being about (0.12, 0.5, < 0.01, and 0.4) g·L^{-1} at 20 °C for rutin, naringin, quercetin, and neohesperidine dihydrochalcone, respectively.[17−19] The solubility also depends on the pH.[16] At pH 1.5, the solubilities of hesperetin and naringenin are ($0.06 \cdot 10^{-3}$ and $0.025 \cdot 10^{-3}$) g·L^{-1}, respectively, whereas at pH 8, they increase 4-fold. The nature of the solvent also has a strong effect on the solubility. Benavente-Garcia et al.[19] measured the solubility of the neohesperidine dihydrochalcone in various water + ethanol mixtures and at different temperatures. They showed that the solubility of this compound at 20 °C in ethanol and in a mixture of ethanol + water (1:1, v/v) is, respectively, (12 and 123) g·L^{-1}. Moreover, these authors reported that for temperatures higher than 70 °C solubility increases significantly. With the objective to establish a rational approach and to explain the solubility of some compounds, several studies have been devoted to developing a correlation between the thermodynamic and structural properties and the solubility of these compounds. In some, it was shown that the solubility of compounds can be correlated to their thermodynamic properties.[20] Moreover, the structural studies revealed that solubility is affected by the ability of compounds to form hydrogen bonds with the surrounding solvent.[21]

For flavonoids, despite the great interest in these compounds over recent years, only few data dealing with their solubility are available. The main aim of this work is to measure solubility, melting point, and enthalpy of fusion and to predict the heat capacity and activity coefficient for six flavonoids (quercetin, isoquercitrin, rutin, chrysin, naringenin, and hesperetin). Moreover, the structural properties (angle of torsion, double bond (C2−C3)) of these compounds were also studied. All these data were analyzed to understand the observed differences in flavonoid solubility.

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Experimental Section

Materials. Quercetin [849061-97-8] (≥ 98 % purity), rutin [207671-50-9] (≥ 95 % purity), naringenin [67604-48-2] (≥ 95 % purity), and hesperetin [69097-99-0] (≥ 98 % purity) were purchased from Sigma. Chrysin [480-40-0] (≥ 95 % purity) and isoquercitrin [482-35-9] (≥95 % purity) were purchased from Acros and Extrasynthese, respectively. Vinyl acetate [108-05-4] (≥99 % purity) was purchased from Aldrich. Acetonitrile [75-05-8] (≥ 99.9 % purity), *tert*-amyl alcohol [75-85-4] (≥ 99 % purity), and acetone [67-64-1] (≥ 99.9 % purity) were purchased from Merck.

Solubility Measurement. The experimental setup used for the solubility measurements of different flavonoids was an automated synthesis workstation (Chemspeed ASW 1000) equipped with 27 mL microreactors (Figure 1). Before each experiment, solvent (15 mL) was dried with 4 Å molecular sieves during 24 h, and the temperature was set at the desired level ((50, 60, and 70) °C) and then transferred to the flavonoid (excess). The solution was stirred at a constant temperature, at 500 rpm using a Chemspeed vibration system, until equilibrium was reached. Samples of the solution were automatically withdrawn, at several intervals, and placed in vials at the same temperature as the solution temperature to avoid any precipitation. The samples were then filtered (0.22 μm) and analyzed by HPLC. The obtained data were fitted by a two polynomial degree using Kaleidagraph software.[22] When the difference in the flavonoid solubility value between measurements was less than 2 %, equilibrium was completed. The standard deviation was calculated after three repetitions. Measurement of water content in

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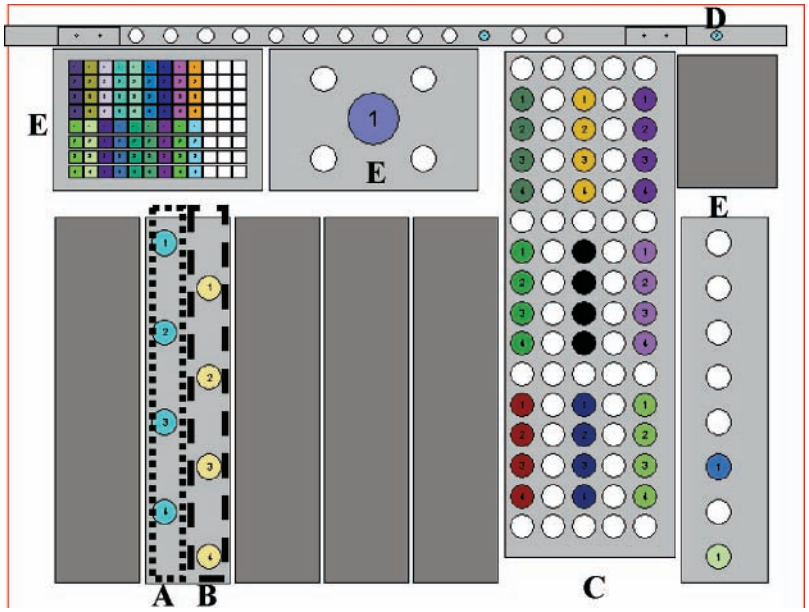

Figure 1. Chemspeed workstation for the experimental study of the solubility measurements. A, reactors for solvent drying; B, reactors for the kinetic solubilization; C, autosampler; D, filtration on 0.22 μm and injection on HPLC; E, area for solvent and sample preparation not used in this study.

all mixtures, except those of acetone, was performed using the Karl Fischer titration method. In all these measurements, the water content was about 0.15 % (w/w).

Analytical Methods. (a) HPLC Analysis. The solubility of flavonoids was monitored by HPLC. Analyses were carried out in a system (Lachrom, Merck) equipped with a column (Apollo C18, 250 × 4.6 mm, Alltech), a column oven (L-7350, Merck), an auto-injector (L-7200, Merck), and a UV detector (Merck) at (254 and 280) nm. The different compounds were separated using a methanol (A) + water (B) elution system. A three-step gradient was applied with the following volume ratios: 0 min (40:60), 5 min (100:0), 10 min (100:0), and 15 min (40:60). The elution flow rate was 1 mL·min^{-1}. Elution was performed at 55 °C.

(b) Water Content Analysis. The water content was determined by a coulometric Karl Fisher apparatus (KF737II coulometer). Three replicates were realized by sample. Hydranal-coulomat AG-H (Sigma) was used as a reagent.

(c) DSC Measurements. Melting points, enthalpies of fusion, and heat capacities were determined by differential calorimetric scanning using a Perkin-Elmer Pyris 1. Samples of (2 to 8) mg were placed in hermetically sealed aluminum pans (Perkin-Elmer); an empty pan was used as a reference in all cases. Measurements were performed over a temperature range including the flavonoid melting temperature (298.15 to 673.15) K. A temperature increment of 283.15 K·min^{-1} was used throughout the study. Nitrogen was used as the purge gas. The calculation of the area under the transition peak allowed the phase transition energy, $\Delta_{fus}H$, to be evaluated.

The solid heat capacity (C_p^s) of the sample was determined by the ratio of the differential power to the sample mass and the rate of temperature increase.

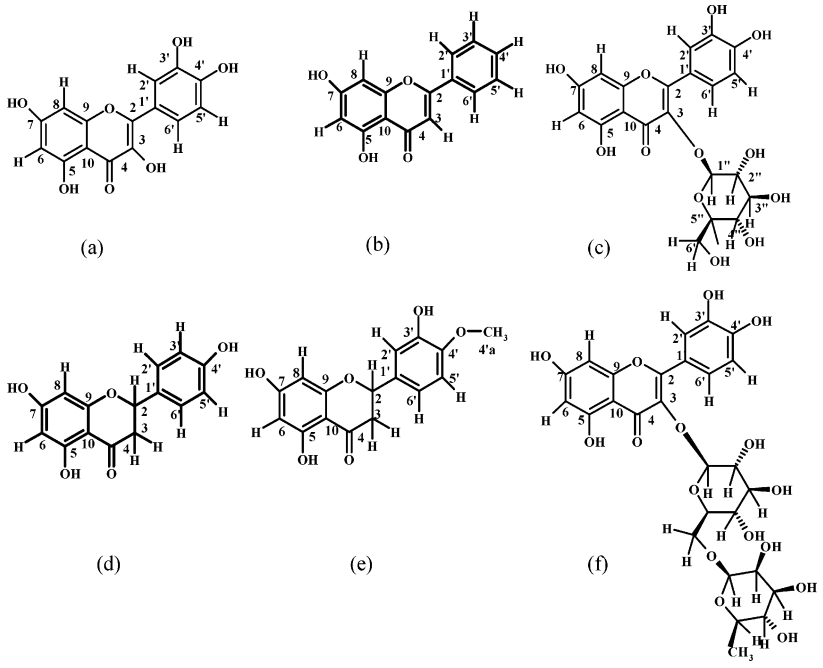

Figure 2. Chemical structure of (a) quercetin, (b) chrysin, (c) isoquercitrin, (d) naringenin, (e) hesperetin, and (f) rutin.

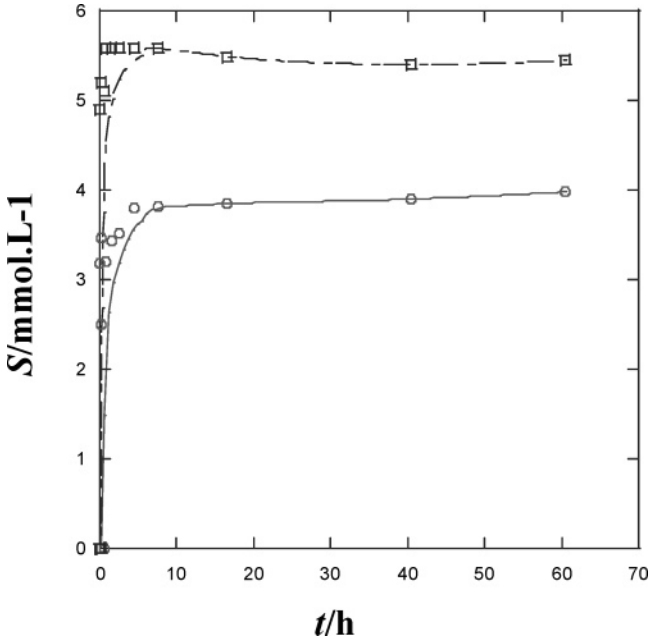

Figure 3. Kinetic dissolution profiles of □, quercetin and ○, isoquercitrin in acetonitrile at 50 °C. *S*: solubility at the time (*t*).

Table 1. Solubility, *S*, and Coefficient of Partition, Log *P*, of Rutin, Isoquercitrin, Quercetin, Chrysin, Naringenin, and Hesperetin in Acetonitrile at 50 °C at 48 h

flavonoid	S/mmol·L^{-1}	log P^a
rutin	0.50 ± 0.01	−1.97
isoquercitrin	3.90 ± 0.06	−1.18
quercetin	5.40 ± 0.79	0.28
chrysin	6.00 ± 0.13	1.75
naringenin	77.00 ± 0.03	1.99
hesperetin	85.00 ± 0.07	1.73

[a] Calculated by HyperChem software.[28]

Table 2. Solubility, *S*, of Quercetin, Isoquercitrin, Naringenin, and Hesperetin in Acetonitrile at (50, 60, and 70) °C

	S/mmol·L^{-1}		
flavonoid	T/°C = 50	T/°C = 60	T/°C = 70
quercetin	5.60 ± 0.79	6.80 ± 0.09	7.05 ± 0.05
isoquercitrin	3.90 ± 0.06	3.70 ± 0.07	4.12 ± 0.07
naringenin	77.00 ±0.03	80.00 ± 0.07	88.00 ± 0.03
hesperetin	85.00 ± 0.07	90.00 ± 0.04	93.00 ± 0.02

Thermodynamic Properties Estimation. (a) Equilibrium Relationship. The activity of the dissolved solute in the saturated solution equals that of pure solid

$$a_i^{\mathrm{s}} = a_i^{\mathrm{sat}} = \gamma_i^{\mathrm{sat}} x_i^{\mathrm{sat}} \qquad (1)$$

Equation 1 shows that the mole fraction solubility (x_i^{sat}) of a compound can be predicted if the activity (a_i^{s}) of the pure solid and the activity coefficient (γ) of the solute in the saturated solution can be predicted. Obviously, the standard state of the definition of the solution activity coefficient must be the same as that of the activity of the solid phase.

Table 4. Experimental Values of Melting Points, T_f, Enthalpies of Fusion, $\Delta_{fus}H$, and Solid Heat Capacities, C_p^s, of Flavonoids at 50 °C

flavonoid	T_f/K	$\Delta_{fus}H$/kJ·mol^{-1}	C_p^s/J·mol^{-1}·K^{-1}
quercetin	595.15 ± 0.70	41.5 ± 0.60	585.9 ± 166
isoquercitrin	471.15 ± 1.50	49.8 ± 0.90	941.9 ± 27
naringenin	523.15 ± 0.60	39.8 ± 0.30	259.7 ± 32
hesperetin	499.22 ± 1.00	35.9 ± 0.08	906 ± 531
rutin	450.15 ± 1.50	82.3 ± 0.07	915 ± 158
chrysin	558.15 ± 1.10	39.2 ± 0.10	200.6 ± 114

After several approximations, the solid phase activity $a^s(T)$ at temperature T can be estimated by eq 2

$$a^{\mathrm{s}}(T) = \exp\left[\frac{\Delta_{\mathrm{fus}}H}{R}\left(\frac{1}{T_{\mathrm{f}}} - \frac{1}{T}\right) - \frac{\Delta C_p}{R}\left(\ln\frac{T_{\mathrm{f}}}{T} - T_{\mathrm{f}}/T + 1\right)\right] \qquad (2)$$

where $\Delta_{fus}H$ is the enthalpy of fusion at the melting point, T_f. The heat capacity difference between the melt and the solid phase ($C_p^l - C_p^s$) = ΔC_p is assumed to be independent of temperature.[23] This assumption is not always justified. However, the reference state is a supercooled melt, the properties of which cannot, in general, be determined by experiment but only from extrapolation of data above the melting point.[23] Hence, the assumption is usually accepted. In chemical engineering literature, there are two alternative assumptions commonly employed: the first one is that ΔC_p at T_f is equal to zero, and the second is that it is equal to fusion entropy at the melting point. For the determination of ΔC_p, predictions of liquid heat capacity (C_p^l) and solid heat capacity (C_p^s) with group contribution (GC) methods have been proposed.[24,25] In fact, Pappa et al.[26] showed that three schemas can predict the ΔC_p. For aromatic compounds $\Delta C_p = C_p^l - C_p^s$.

(b) Group Contribution Method for C_p^l. Ruzicka and Domalski[27] developed a group contribution method to predict the liquid heat capacities of organic compounds from the melting to the boiling point. According to these authors, the method has an average absolute percent deviation (AAD) of 1.9 % from the melting point to the normal boiling point for 4000 experimental values that correspond to hydrocarbons (C_2−C_{48}).

Log P Calculation. The coefficient of the partition octanol + water was calculated using the QSAR Module implemented in the HyperChem 7 molecular visualization and simulation program.[28]

Molecular Modeling. To explain the differences in solubility, a molecular modeling study was carried out on flavonoids by using the Austin Model 1 (AM1) method implemented in HyperChem 7 molecular visualization and simulation program.[28]

Results and Discussion

The solubility and the thermodynamic properties of quercetin, chrysin, isoquercitrin, naringenin, hesperetin, and rutin (Figure 2) were determined. The effects of the nature of the solvent (acetonitrile, acetone, and *tert*-amyl alcohol), the temperature, and the cosolvent on the solubility of these compounds were also quantified. Moreover, the structural conformation of the six flavonoids was investigated, in a vacuum, using the AM1 calculation.

Table 3. Solubility, *S*, of Quercetin, Isoquercitrin, and Rutin in *tert*-amyl Alcohol, Acetone, and Acetonitrile at 50 °C

	S/mmol·L^{-1}			
	solvent			
flavonoid	*tert*-amyl alcohol	acetone	acetonitrile	acetonitrile + vinyl acetate
quercetin	67.01 ± 0.57	80.08 ± 1.00	5.40 ± 0.79	6.29 ± 0.19
isoquercitrin	66.11 ±2.00	30.04 ± 0.45	3.90 ± 0.06	4.10 ± 0.10
rutin	60.03 ± 0.40	13.50 ± 0.34	0.50 ± 0.01	−

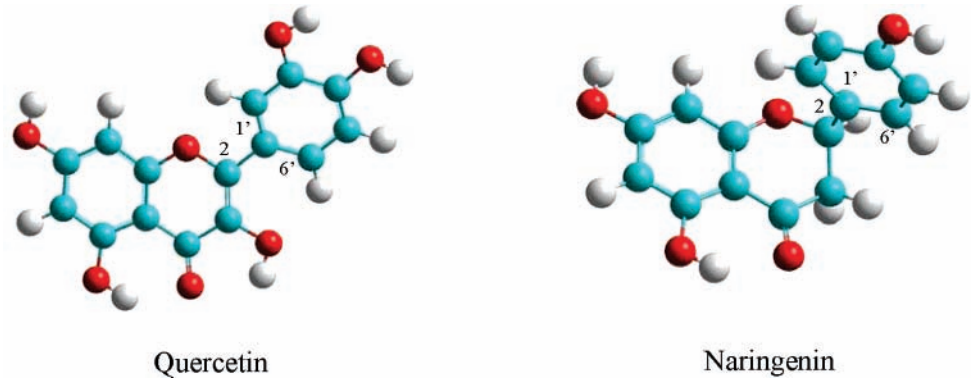

Figure 4. Quercetin and naringenin structures optimized by the AM1 method.

Kinetic Study of Flavonoid Solubility in Acetonitrile. The evolution of the soluble concentration of quercetin and isoquercitrin vs time, at 50 °C, is reported in Figure 3. This shows that a plateau was reached after 10 h. At this plateau, the concentrations are about (5.40 and 3.90) mmol·L^{-1} for quercetin and isoquercitrin, respectively. Similar operating conditions were used for studying the solubility of chrysin, naringenin, hesperetin, and rutin. The solubility values obtained at the equilibrium are reported in Table 1. The highest solubility, 85 mmol·L^{-1}, was reached with hesperetin, whereas the lowest one, 0.50 mmol·L^{-1}, was obtained with rutin. As rutin is a diglycosylated flavonoid, it seemed that the presence of two sugar parts is the origin of this compound's low solubility in acetonitrile. No correlation was observed between the hydrophobicity (log *P*) and the solubility.

As has previously been mentioned, solubility can be affected by temperature. To evaluate the effect of this factor, three set points were investigated (50, 60, and 70) °C. The results obtained are summarized in Table 2. It appears that the solubility of isoquercitin, hesperetin, naringenin, and quercetin, in acetonitrile, increased by (5, 9, 13, and 20) %, respectively, when the temperature increases from (50 to 70) °C. Similar observations were made by Benaventa-Garcia et al.[19] when they studied the solubility of neohesperidin dihydrochalcone in water and ethanol.

Effect of the Nature of the Solvent on Flavonoid Solubility. To determine the effect of the nature of the solvent, the solubilities of rutin, isoquercitrin (glycosylated forms), and quercetin (aglycon form) were measured and compared at 50 °C in *tert*-amyl alcohol, acetone, and acetonitrile. The results obtained at 48 h are summarized in Table 3. This indicates that for the aglycon form (quercetin) solubility was high in acetone (80 mmol·L^{-1}) and in *tert*-amyl alcohol (67 mmol·L^{-1}) and lower in acetonitrile (5.40 mmol·L^{-1}). For glycosylated forms (isoquercitrin and rutin), high solubility was observed in *tert*-amyl alcohol ((66 and 60) mmol·L^{-1}, respectively). The presence of a sugar group (rutin and isoquercitrin) decreases the solubility in polar solvents (acetone and acetonitrile).

The solubilities of rutin and quercetin at 20 °C and hesperetin and naringenin at 37 °C in water are very low. They are about (0.20, 0.03, 7.94·10^{-4}, and 3.67·10^{-3}) mmol·L^{-1}, respectively.[16,17−19]

The use of vinyl acetate ((862 and 1324) mmol·L^{-1}) with isoquercitrin and quercetin, respectively, as cosolvent, or as an acyl donor in enzymatic acetylation, showed an increase in the solubility of isoquercitrin and quercetin by (5 and 14) %, respectively. The observed variation, due to the addition of the cosolvent, remained low compared to that obtained by Tsavas et al.[29] for glucose solubility in a mixture of *tert*-amyl alcohol + octanoic acid.

Thermodynamic Properties of Flavonoids. For all the flavonoids studied, experimental data of T_f, $\Delta_{fus}H$, and C_p^s were determined from the DSC scan (thermogram). However, due to the decomposition of flavonoids close to the melting point, it was difficult to determine the C_p^l values. Thus, C_p^l was predicted by using the method developed by Ruzicka and Domalski.[27]

The experimental and predicted data for the different properties of quercetin, isoquercitrin, rutin, naringenin, chrysin, and hesperetin are summarized in Tables 4 and 5. The analysis of these data revealed that the glycosylated flavonoids are characterized by a low melting point and a high enthalpy of fusion compared to those of aglycon. Moreover, contrary to Gracin and Rasmuson,[20] in our case, no relationship was observed between solubility and T_f and $\Delta_{fus}H$. These authors also reported that the higher the stability, the lower the solid-phase activity and the lower the solubility. The estimated data of a^s and γ (Table 5) do not confirm this assessment. However, as a^s and γ are estimated from experimental values of C_p^s with a high standard deviation value for some compounds, the conclusion drawn from these data will be carefully interpreted. The absence of a clear correlation between the solubility and the thermodynamic properties could be attributed to the fact that the flavonoid, in contrast to the phenolic acids studied by Gracin and Rasmuson,[20] is formed by three rings and several OH groups which can react strongly with surrounding media.

Structural Properties of Flavonoids. As mentioned above, some papers have shown that differences in solubility can be explained by the structural properties of these compounds. To verify this hypothesis in the case of flavonoids, we studied their conformational structure in a vacuum.

The conformations obtained in a vacuum with the AM1 method showed that the structures of rutin, isoquercitrin,

Table 5. Estimation of Liquid Heat Capacities, C_p^l, Solid-Phase Activities, a^s, and Activity Coefficients, γ, of Flavonoids at 50 °C

flavonoid	C_p^l / J·mol^{-1}·K^{-1}	ΔC_p / J·mol^{-1}·K^{-1}	a^s	γ / acetonitrile	γ / tert-amyl alcohol	γ / acetone
quercetin	591.63	5.75	0.0010	3.40	0.14	0.17
isoquercitrin	1024.19	82.28	0.0065	31.60	0.89	2.90
naringenin	600.04	340.32	0.9499	232.40		
hesperetin	574.20	–	–	–		
rutin	1389.99	475.00	0.0058	221.80	0.90	5.90
chrysin	428.74	228.08	0.3054	959.20		

quercetin, and chrysin are characterized by a torsion angle θ (OC2C1′C6′) of about −25°, whereas for naringenin and hesperetin, this was about 40° (Figure 4). A similar torsion angle θ was observed by Russo et al.[30] and Rodriguez et al.[31] for quercetin when they used this method (AM1).

The magnitude of this torsion angle θ seemed to be related to the presence or the absence of the double bond between C2 and C3. In fact, our data showed that the absence of a double bond led to a torsion angle θ of flavonoids of about 40° and to a high solubility in acetonitrile (naringenin and hesperetin). Using the Amber force field, van Acker et al.[32] showed that the structure of naringenin and hesperetin was not planar.

Conclusion

In this paper, the solubility of quercetin, isoquercitrin, rutin, chrysin, naringenin, and hesperetin was quantified in acetonitrile, acetone, and *tert*-amyl alcohol. On the basis of our results, solubility can be seen to be strongly affected by the nature of both the solvent and the flavonoid structure. The highest solubility was reached within hesperetin (85 mmol·L^{-1}), whereas the lowest one was obtained with rutin (0.5 mmol·L^{-1}). It would consequently appear that the presence of a sugar group is at the origin of the low solubility of this compound in acetonitrile. For all studied flavonoids, melting point, enthalpy of fusion, and solid heat capacity were measured, and liquid heat capacity, solid phase activity, and activity coefficient were predicted. The presence of sugar in the glycosylated flavonoids led to a low melting point and a high enthalpy of fusion. Contrary to the data reported for other compounds, there is no clear correlation between the solubility of flavonoids and their thermodynamic properties. This behavior seems to be due to the conformational structure. Flavonoids with a torsion angle OC2C1′C6′ of 40° are characterized by a high solubility. The determination of solvation energy will be the next step of our investigation in an attempt to explain the differences in solubility observed among the six compounds studied.

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