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Effect of the Environment on the Reactivity of 4′-Substituted Flavones and Isoflavones

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Abstract—The reactivity of flavones and isoflavones, substituted at the 4′ position by several types of electron-withdrawing or electron-donating groups, was studied by FMO theory in the gas-phase and in aqueous solution. The predictions of this theory were consistent with the experimental reactivity of analogue compounds, and also with the stability of the products of reaction of these compounds with different nucleophilic and electrophilic reagents. The preferences found in the gas-phase for the sites of reaction are retained in aqueous solution.

Introduction

There is increasing interest in scientific research directed towards the prevention of degenerative diseases, such as cancer and coronary disease. A large number of epidemiological studies have shown that a high consumption of fruits and vegetables, and some beverages such as black tea and wine, is associated with a reduced risk of cancer for many human organs.[1–5] Two known examples are the so-called 'French paradox': a correlation of a diet rich in fat with a low incidence of arteriosclerosis attributed to the ingestion of wine;[5] and the low incidence of estrogen-dependent cancer in populations that consume a typical oriental diet, rich in soybean and its derivatives.[6] A class of substances that contributes to the quimiopreventive properties of these products is the flavonoids.[7] The mechanism of action of flavonoids remains to be determined; however, they are reported as inhibitors of several enzymes,[8] as electrophilic reagents that attack potentially toxic intermediates,[9] and even as compounds with antioxidant properties.[9]

Because of the widespread presence of flavonoids in the plant kingdom, they are present in the diet of all plant-eating animals. The consumption of these compounds, constituted mainly by quercetin (60–75%), can vary from 2.6 mg/day in West Finland to 68.2 mg/day in Japan.[10] A large number of preparations that contain flavonoids as their main physiologically active constituents are used in clinical practice. One of the best known is the *Gingko biloba* extract, used in the treatment of peripheral vascular disease. Silymarin is used against hepatic disturbances caused by the excessive ingestion of alcohol,[11] and has been proposed in the therapies of breast[12] and prostate[13] cancer. Other flavonoids, such as diosmin (Daflon) and rutin (Venalot), are used in several countries to treat lymphoedema.[14,15]

In spite of the recent increased interest in the use of flavonoids in biomedical applications, little is known about the reactivity, and molecular and electronic structures of these compounds. Several crystal structures of flavone derivatives, such as 7-hydroxy-2′,3′,4′-trimethoxyflavone,[16] morin and myricetin,[17] hymenoxin,[18] 3-hydroxyflavone and 3-methoxyflavone,[19] have been reported. In all cases the benzo-γ-pyrone group (A- and C-rings) is planar, and the B-ring is at 30–40° in relation to the rest of the molecule, except for the 3-hydroxyflavone, which presents an angle of 5.5° in the crystal form. Some molecular orbital studies of flavonoids are also reported in the literature. The geometry of flavone was calculated by the AM1 and HF/STO-3G methods.[20] The geometry of 3-hydroxyflavone and 3-methoxyflavone were also optimized by the AM1 method.[19] The electronic structure of chromone [1-benzopyran-4(4H)-one] was calculated by semiempirical and ab initio molecular orbital methods.[21]

The rotation energies of the B-ring of flavone and isoflavone were determined by semiempirical and ab initio methods at the Hartree–Fock level and density functional theory in vacuum, and by MST/AM1 in water and chloroform.[22] It can be observed that the B-ring has free-rotation and there is little influence of solvents in the conformational preferences of these compounds. These data, together with the data for

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the bond length of C(2)–C(1′), indicate that there is no conjugation between the B- and C-rings.

Flavonoids are a class of very reactive secondary metabolites. It has been known for a long time that A- and B-rings in the flavone molecule (**1**) react more or less normally as aromatic rings. This is particularly true for the hydroxyflavones, which behave as phenols in substitution reactions. Many reactions of hydroxyflavones have been reported, such as nitration, sulphonation, bromination and also coupling with diazonium salts. In these examples the A-ring is preferentially attacked.[23] The C-ring is responsible for the majority of the typical reactions of flavonoids. Although the C-ring formally has a carbonyl group, flavones do not react normally with reagents such as hydroxylamine. On the other hand, Grignard reagents react normally with the carbonyl group of flavones, but the reaction products have been isolated only as anhydro-pyrylium salts.[23] Upon treatment with alkali the C-ring is opened giving a 1,3-diketone, which then usually undergoes further degradation. It is also known that benzo-γ-pyrones are strong bases.[24] Thus γ-pyrone derivatives, such as flavones and isoflavones, are protonated on O(11), as observed by formation of stable oxonium salts,[25] by vibrational spectroscopy of protonated flavone derivatives,[26] and by semiempirical calculation of flavones.[27]

Isoflavone (**2**) is generally stable to acidic reagents. Alkaline hydrolysis will usually transform an isoflavone into the corresponding deoxybenzoin and formic acid. Chemical reduction of isoflavones by lithium aluminium hydride gives isoflav-3-enes, but sodium borohydride reduces isoflavones to isoflavonols. The reaction of isoflavones with Grignard reagents, which is mechanistically equivalent to hydride reduction, proceeds by 1,4-addition and gives 2,4-disubstituted isoflavan-4-ols. Other reactions of isoflavones, such as oxidation and rearrangement, have been reviewed.[23]

Due to the lack of data about the reactivity of flavonoids, in this work we analyze the reactivity of flavone and isoflavone substituted at the 4′ on position by semi-empirical methods using the frontier molecular orbital (FMO) theory.[28,29] Linear free energy (LFER) correlations were obtained. The sites of acidic, basic, electrophilic and nucleophilic attack predicted by the FMO theory were compared with the predictions obtained by the experimental reactivity of analogous systems, comparing the stability of hypothetical products. Finally, we investigate the effect of water solvent on the stability of these different compounds using a self-consistent reaction-field (SCRF) method, and we analyze polarization effects on the molecular dipole moments.

Methods

Gas-phase calculations

The AM1 semi-empirical method,[30] as implemented in the MOPAC 6.0 program and MOPAC93R2,[31] was used to carry out the calculations. The geometry was fully optimized, without restrictions of symmetry by using Baker's algorithm.[32] The precision of SCF calculations was increased a hundred times by utilization of the keyword PRECISE, and the convergence of gradient criteria was 0.01. The atomic charges derived by electrostatic potentials were calculated through the MNDO method using the Besler, Merz and Kollman algorithm with all default options.[33] For the calculation of free energies in gas-phase (ΔG_{gp}) the free rotations were not considered.

Aqueous-phase calculations

The solvation free energies (ΔG_{sol}) were determined using a semi-empirical AM1 adapted version[34–38] of the SCRF developed by Miertus, Scrocco, and Tomasi[39,40] (MST/AM1). According to this method, the ΔG_{sol} is determined as the addition of electrostatic and steric contributions (Eq. (1)). The steric component was computed as the sum of the cavitation and van der Waals terms.

$$\Delta G_{sol} = \Delta G_{ele} + \Delta G_{cav} + \Delta G_{vdW} \quad (1)$$

Previous studies indicated that the root mean square deviation between the experimental value of ΔG_{sol} and the value estimated at the MST/AM1 level is 1.0 kcal/mol for water solvent.[37]

The free energy differences among the isomers in solution were calculated by the conformational free energy differences $\Delta(\Delta G_{conf})$ (Eq. (2)).

$$\Delta(\Delta G_{conf}) = \Delta(\Delta G_{sol}) + \Delta(\Delta G_{gp}) \quad (2)$$

Semi-empirical calculations were performed with an adapted version of MOPAC 7.0,[41] which permit MST calculations with water solvent.

Results and Discussion

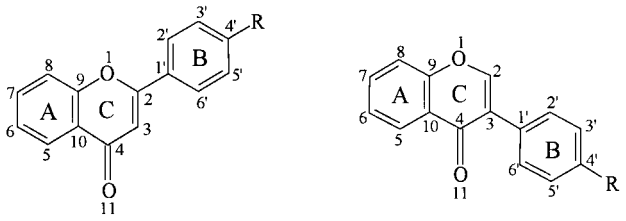
Gas-phase calculations

An analysis of bond lengths and bond orders indicate that flavone (**1**) and isoflavone (**2**) (Table 1), do not exhibit

Table 1. Free energies calculated in gas-phase (ΔG_{gp}) and in solution (ΔG_{sol}), and relative values [$\Delta(\Delta G_{gp})$], [$\Delta(\Delta G_{sol})$] and [$\Delta(\Delta G_{conf})$] (in kcal/mol) between flavone and isoflavone derivatives (roman and italic, respectively)

Substituent (R)	ΔG_{gp}	$\Delta(\Delta G_{gp})$	ΔG_{sol}	$\Delta(\Delta G_{sol})$	$\Delta(\Delta G_{conf})$
H	−25.0	0.9	−8.0	0.8	1.7
	−25.9		*−7.2*		
OH	−69.7	1.0	−10.8	0.8	1.8
	−70.7		*−10.0*		
NH_2	−29.5	0.3	−12.6	0.8	1.1
	−29.8		*−11.8*		
NO_2	−24.0	1.3	−9.9	0.4	1.7
	−22.6		*−9.6*		
OCH_3	−64.4	0.6	−9.1	0.4	1
	−65.0		*−8.7*		
$COCH_3$	−63.5	1.6	−10.5	0.1	1.7
	−65.1		*−10.4*		
CN	+4.9	1.7	−8.3	0.3	2
	+3.2		*−8.0*		
CF_3	−184.3	2.1	–[a]	–[a]	–[a]
	−186.4				
Cl	−33.8	1.3	–[a]	–[a]	–[a]
	−35.1				

[a] Some parameters are not available for these compounds.



Scheme 1. Structure of flavone (**1**) and isoflavone (**2**).

resonance between the B- and C-rings. The C-ring presents double bonds localized between C(2)–C(3) and C(4)–O(11), as already observed in our studies on chromone,[21] by Vrielynck et al., in a study on flavone,[20] and also by our calculations of the rotational barriers of the B-ring in **1** and **2**.[22] The substitution on position 4′ by any of the studied groups (OH, OCH_3, NH_2, NO_2, Cl, CF_3, CN and $COCH_3$) does not change the electronic structure of **1** and **2** (Scheme 1). Thus, the presence of electron-withdrawing or electron-donating groups in the B-ring does not affect the predominant resonance structure of flavone and isoflavone.

Isoflavone and its 4′-substituted derivatives are more stable than the corresponding flavones, (Table 1). There is a good correlation between the difference in Gibbs free-energy or corresponding isomers with the Hammett inductive, σ_1, and resonance, σ_R, parameters for *para* substituents:[42]

$$\Delta(\Delta G_{gp}) = 0.99 + 1.37\sigma_I + 1.52\sigma_R \quad (3)$$

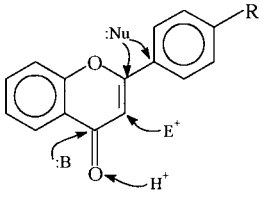
$$(n = 8;\ \ r = 0.856;\ \ s = 0,270;\ \ F = 14.88)$$

The only substituent that was excluded from this correlation was NO_2. This may be attributed to the fact that positive energy values are over-estimated for nitro compounds in the AM1 method.[43] Eq. (2) shows further evidence that the B-ring behaves as an aromatic system isolated from the A- and C-rings, confirming the former observations from the analysis of bond lengths and bond orders.

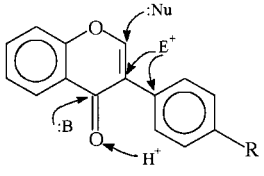
From the atomic charges calculated through the MNDO/ESP method, and from the HOMO and LUMO coefficients calculated by the AM1 method, it was possible to determine the sites of acidic, electrophilic, basic and nucleophilic attacks. The sites of reactions in these molecules were located by the use of FMO theory[28] and the results are presented in Fig. 1. The aromatic carbons of the A- and B-rings were excluded due to their low reactivity when compared with the atoms of the C-ring.

Analysis of the reactive sites in the substitute flavone does not show any correlation with the withdrawing or donating character of the substituents, for the acidic, basic and electrophilic attack. For the nucleophilic attack, on the contrary, these reactive sites are altered depending on the type of substituents. Electron-donating substituents, such as OH, OCH_3 and NH_2, preferentially cause reactions on C(2). Electron-withdrawing substituents, such as NO_2, CF_3, CN and $COCH_3$, cause reactions mainly on C(1′). In the isoflavone, nucleophilic attack is not influenced by the electronic character of the substituents, since C(2) is always the predominant reactive site. However, the site of electrophilic attack is altered by the different substituents. With electron-donating substituents, such as OH, OCH_3 and NH_2, the reactive site is on C(1′). With electron-withdrawing substituents, such as NO_2, CF_3, CN, $COCH_3$ and Cl, the predominant reactive site is on C(3). The high positive charges on C(4) make this site susceptible to basic attack. For all molecules studied the protonation occurs on the oxygen atom of the carbonyl group [O(11)]. These results are in agreement with literature data.[44]

In order to verify if the predictions of FMO theory were adequate for these systems, we studied the stability of the



(1)



(2)

Attack:	Site:	Substituent (R):
E^+	C(3)	H, OH, OCH_3, NH_2, NO_2, Cl, CF_3, CN, $COCH_3$
H^+	O(11)	H, OH, OCH_3, NH_2, NO_2, Cl, CF_3, CN, $COCH_3$
:Nu	C(2) C(1')	H, OH, OCH_3, NH_2, Cl NO_2, CF_3, CN, $COCH_3$
:B	C(4)	H, OH, OCH_3, NH_2, NO_2, Cl, CF_3, CN, $COCH_3$

Attack:	Site:	Substituent (R):
E^+	C(1')	H, OH, OCH_3, NH_2,
	C(3)	NO_2, Cl, CF_3, CN, $COCH_3$
H^+	O(11)	H, OH, OCH_3, NH_2, NO_2, Cl, CF_3, CN, $COCH_3$
:Nu	C(2)	H, OH, OCH_3, NH_2, NO_2, Cl, CF_3, CN, $COCH_3$
:B	C(4)	H, OH, OCH_3, NH_2, NO_2, Cl, CF_3, CN, $COCH_3$

Figure 1. Sites of acidic (H^+), basic (OH^-), electrophilic (E^+), and nucleophilic (Nu:) attack of substituted flavones and isoflavones, obtained by FMO theory.

Table 2. Heat of formation (ΔH_f) and differences of enthalpy variation [$\Delta(\Delta H_f)$] calculated in gas-phase (in kcal/mol) for different reactions with flavones. MST/AM1 free energies of solvation in water (ΔG_{sol}) and relative values [$\Delta(\Delta G_{sol})$] are also displayed

Reagent	Attack site	Flavone				4′Hydroxyflavone				4′-Nitroflavone			
		ΔH_f	$\Delta(\Delta H_f)$	ΔG_{sol}	$\Delta(\Delta G_{sol})$	ΔH_f	$\Delta(\Delta H_f)$	ΔG_{sol}	$\Delta(\Delta G_{sol})$	ΔH_f	$\Delta(\Delta H_f)$	ΔG_{sol}	$\Delta(\Delta G_{sol})$
H^-	C(2)	−31.8	0.0	−87.2	0.0	−77.3	0.0	−77.8	10.4	−37.6	2.8	−68.4	30.4
	C(4)	−7.7	24.1	−78.4	8.8	−52.3	25.0	−88.2	0.0	−12.4	28.0	−77.3	21.5
	C(1′)	–[a]	–	–[a]	–	–[a]	–	–[a]	–	−40.4	0.0	−68.0	30.8
	N[C(4′)]	–[a]	–	–[a]	–	–[a]	–	–[b]	–	−8.0	32.4	−98.8	0.0
I^-	C(2)	−15.7	0.0	–[b]	–	−60.5	0.0	–[b]	–	–[c]	–	–[b]	–
	C(4)	−7.7	8.0	–[b]	–	–[c]	–	–[b]	–	−20.1	1.4	–[b]	–
	C(1′)	–[a]	–	–[a]	–	–[a]	–	–[a]	–	−21.5	0.0	–[b]	–
	N[C(4′)]	–[a]	–	–[a]	–	–[a]	–	–[a]	–	–[c]	–	–[b]	–
OH^-	C(2)	−63.5	18.4	−88.4	0.0	−129.4	0.0	−78.3	16.8	−88.8	0.0	−69.0	26.0
	C(4)	−81.1	0.0	−81.9	6.5	−102.8	26.6	−95.1	0.0	−67.6	21.2	−78.6	16.4
	C(1′)	–[a]	–	–[a]	–	–[a]	–	–[a]	–	−75.6	13.2	−72.4	22.6
	N[C(4′)	–[a]	–	–[a]	–	–[a]	–	–[a]	–	−34.6	54.2	−95.0	0.0
H^+	C(2)	221.3	66.6	−50.9	0.0	177.0	68.4	−58.1	35.7	234.9	66.3	−67.4	0.0
	C(3)	169.9	15.2	−48.5	2.4	121.9	13.0	−53.3	40.5	187.1	18.5	−60.4	7.0
	O(11)	154.7	0.0	−42.2	8.7	108.6	0.0	−51.2	42.6	168.6	0.0	−62.6	4.8
	O[C(4′)]	–[c]	–	–[c]	–	160.6	52.0	−93.8	0.0	–[a]	–	–[a]	–
I^+	C(2)	–[c]	–	–[b]	–	–[b]	–	–[b]	–	–[c]	–	–[b]	–
	C(3)	194.6	1.6	–[b]	–	146.5	0.0	–[b]	–	211.8	5.1	–[b]	–
	O(11)	193.0	0.0	–[b]	–	147.0	0.5	–[b]	–	206.7	0.0	–[b]	–
	O[C(4′)]	–[a]	–	–[b]	–	195.4	48.9	–[b]	–	–[a]	–	–[b]	–
Br^+	C(2)	242.7	58.2	–[b]	–	148.1	11.9	–[b]	–	–[c]	–	–[b]	–
	C(3)	184.5	0.0	–[b]	–	136.2	0.0	–[b]	–	202.0	0.0	–[b]	–
	O(11)	197.0	12.5	–[b]	–	150.9	14.7	–[b]	–	210.9	8.9	–[b]	–
	O[c(4′)]	–[a]	–	–[b]	–	200.3	64.1	–[b]	–	–[a]	–	–[b]	–

[a] This attack site was not analysed for these molecules since it was not important.
[b] Some parameters are not available for these compounds.
[c] It was not possible to obtain acceptable results for these molecules.

Table 3. Heats of formation (ΔH_f) and differences of enthalpy variation [$\Delta(\Delta H_f)$] calculated in gas-phase (in kcal/mol) for different reactions with isoflavones. MST/AM1 free energies of solvation in water (ΔG_{sol}) and relative values [$\Delta(\Delta G_{sol})$] are also displayed

Reagent	Attack site	Isoflavone				4′Hydroxyisoflavone				4′-Nitroisoflavone			
		ΔH_f	$\Delta(\Delta H_f)$	ΔG_{sol}	$\Delta(\Delta G_{sol})$	ΔH_f	$\Delta(\Delta H_f)$	ΔG_{sol}	$\Delta(\Delta G_{sol})$	ΔH_f	$\Delta(\Delta H_f)$	ΔG_{sol}	$\Delta(\Delta G_{sol})$
H^-	C(2)	−47.5	0.0	−67.9	11.3	−92.2	0.0	−68.9	10.4	−62.0	0.0	−58.4	46.5
	C(4)	−10.9	36.6	−79.2	0.0	−56.3	35.9	−79.3	0.0	−16.7	45.3	−70.9	34.0
	N[C(4′)]	–[a]	–	–[a]	–	–[a]	–	–[a]	–	−4.4	57.6	−104.9	0.0
I^-	C(2)	−30.4	0.0	–[b]	–	−75.0	0.0	–[b]	–	−42.7	0.0	–[b]	–
	C(4)	−7.8	22.6	–[b]	–	−53.1	21.9	–[b]	–	−13.0	29.7	–[b]	–
	N[C(4′)]	–[a]	–	–[a]	–	–[a]	–	–[a]	–	–[c]	–	–[b]	–
OH^-	C(2)	−104.0	0.0	−69.3	12.6	−148.8	0.0	−70.9	15.4	−117.1	0.0	−60.5	38.5
	C(4)	−65.4	38.6	−81.9	0.0	−106.4	−42.4	−86.3	0.0	−70.6	46.5	−76.5	22.2
	N[C(4′)]	–[a]	–	–[a]	–	–[a]	–	–[a]	–	−32.1	85.0	−98.7	0.0
H^+	C(2)	188.7	28.4	−47.6	4.5	136.9	21.1	−53.2	30.2	209.4	37.8	−56.8	9.1
	C(3)	185.0	24.7	−52.1	0.0	140.5	24.7	−58.3	25.1	187.1	15.5	−60.5	5.4
	C(1′)	191.4	31.1	−51.3	0.8	136.2	20.4	−54.7	28.7	–[a]	–	–[a]	–
	O(11)	160.3	0.0	−45.8	6.3	115.8	0.0	−55.9	27.5	171.6	0.0	−65.9	0.0
	O[C(4′)]	–[c]	–	–[c]	–	151.8	36.0	−83.4	0.0	–[a]	–	–[a]	–
I^+	C(2)	215.4	16.1	–[b]	–	163.7	5.6	–[b]	–	235.7	24.5	–[b]	–
	C(3)	211.5	12.1	–[b]	–	167.5	12.8	–[b]	–	225.0	13.8	–[b]	–
	C(1′)	214.2	14.9	–[b]	–	161.2	6.5	–[b]	–	–[a]	–	–[b]	–
	O(11)	199.3	0.0	–[b]	–	154.7	0.0	–[b]	–	211.2	0.0	–[b]	–
Br^+	C(2)	204.0	0.8	–[b]	–	160.3	9.1	–[b]	–	224.8	9.8	–[b]	–
	C(3)	201.8	1.4	–[b]	–	157.5	6.3	–[b]	–	215.4	0.4	–[b]	–
	C(1′)	205.7	2.5	–[b]	–	151.2	0.0	–[b]	–	–[a]	–	–[b]	–
	O(11)	203.2	0.0	–[b]	–	158.6	7.4	–[b]	–	215.0	0.0	–[b]	–

[a] This attack site was not analysed for these molecules since it was not important.
[b] Some parameters are not available for these compounds.
[c] It was not possible to obtain acceptable results for these molecules.

reaction products of **1** and **2**, and their derivatives 4′-substituted by OH and NO_2, with hard and soft nucleophiles and electrophiles, such as H^-, I^-, OH^-, H^+, I^+ and Br^+. The reaction sites predicted by FMO theory were confirmed by experimental reactivity data of analogue systems. Results are displayed in Tables 2 and 3.

In general, analysis of the product stability indicates that the results from FMO theory are in good agreement with the reactivity observed experimentally (see Tables 2 and 3, and Fig. 1). However, some exceptions are noted for reaction with the hydroxyl group. By FMO theory the hydroxylation would occur on C(4), as observed for carbonyl compounds in general, but analysis of the products indicates that, except for **1**, the site of attack of the studied compounds is on C(2). For soft electrophiles, I^+ or Br^+, some discrepancies can be noted between both analyses. In these cases it can be verified that the more stable products are formed by addition on the oxygen atom of the carbonyl group [O(11)], indicating a possible preference of these electrophiles for a site with high charge density. For the reaction of hydroxylated derivatives of **1** and **2** with I^+, the more stable products are those predicted by FMO theory for attack of a soft electrophile. This result is in opposition to those observed for other compounds studied, where the attack occurs on O(11). In this case the hydroxyl group would increase the soft electrophilic character of I^+, probably by changes in the electronic density and orbitals of these compounds.

These observations demonstrate that FMO theory produces results consistent with experimental reactivity data and with the stability of the products formed. In spite of several criticisms of this theory, it has afforded satisfactory results in the interpretation of several systems,[45–48] provided that the limits of applicability are respected.[29] These results predict the reactivity of flavones and isoflavones towards several electrophiles and nucleophiles, and further experimental work is required to validate these predictions.

Solvent-phase calculation

In order to ascertain if the solvent modifies the reactive sites predicted in the gas-phase, atomic charges as well as HOMO and LUMO coefficients were computed in aqueous solution. The results indicated that the preferences found in the gas-phase for the sites of reaction are retained in aqueous solution. Thus, atomic charges were enhanced by aqueous solvent, however, their relative order was the same as that in the gas-phase. In addition, significant variations were not observed in the HOMO and LUMO coefficients computed in aqueous solution with respect to those predicted in the gas-phase. The fact that the reactivity does not change can be attributed to limited interactions of these compounds with the water.

Free energies of solvation (ΔG_{sol}) in aqueous solution for flavones and isoflavones substituted on the 4′-position are displayed in Table 1. Results indicate that isoflavones are better solvated than flavones, the solute–solvent interaction being on average 0.5 kcal/mol more favorable for the former than the latter. Thus, the stability showed in the gas-phase by isoflavones with respect to flavones is reinforced in aqueous solution. It may be noted that the stability variation in solution does not correlate with the polarity variation of the substituent groups, as can be observed by the higher solvation energy of NO_2 as compared with NH_2.

Conformational free energy differences $\Delta(\Delta G_{conf})$ indicate that in solution isoflavones are more stable than flavones by 1.6 kcal/mol on average. The variation of $\Delta(\Delta G_{conf})$ with Hammet parameters indicate a weaker correlation with respect to that displayed previously for $\Delta(\Delta G_{gp})$ (Eq. (4)).

$$\Delta(\Delta G_{gp}) = 1.62 + 0.42\sigma_I + 0.90\sigma_R \quad (4)$$

$$(n = 6;\ \ r = 0.491;\ \ s = 0,151;\ \ F = 1.446)$$

The poor correlation observed for $\Delta(\Delta G_{sol})$ can be attributed to the fact of the variation of these values (see Table 1) is lower than the accuracy provided by the MST/AM1 method which introduces noise effects. Previous studies indicated that the root mean square deviations between experimental values of ΔG_{sol} in aqueous solution and those estimated by MST/AM1 are 1 kcal/mol, which is larger than $\Delta(\Delta G_{sol})$ values.

The results displayed in Tables 2 and 3 indicate that the solvent plays a crucial role in the stability of the different products. The $\Delta(\Delta G_{sol})$ contribution predicted for the different compounds depends mainly on the influence of electrophiles and nucleophiles in the solute–solvent interactions. Thus, for a family of molecules, differences in the 'in solution' term are related with the bulk solvent, whereas the gas-phase contributions depend on characteristics which are intrinsic to the compound. These results agree with the general observation in organic chemistry according to which the reactive preferences of a given compound change with the polarity of the environment.

Table 4 shows the dipole moments for the different flavones and isoflavones computed in both gas-phase (μ_{gp}) and aqueous (μ_{aq}) environments. The relation μ_{aq}/μ_{gp} provides a measure of the solvent polarization effect on molecular dipole moments. It is worth noting an increase ranging from 40 to 90% in aqueous solution with respect to the gas-phase. Thus, an enhancement of the separation of charge is obtained in aqueous solution, and its magnitude was not the same for all the molecules. A detailed inspection of the results indicates that the polarization of the dipole moments is independent of the family of compounds, i.e. flavones and isoflavones, but depends primarily on the substituent. The increase in the charge separation of the

Table 4. Dipole moments (Debye) for flavone and isoflavone derivatives in the gas-phase (μ_{gp}) and in aqueous (μ_{aq}) environments

Substituent (R)	Flavone			Isoflavone		
	μ_{gp}	μ_{aq}	μ_{aq}/μ_{gp}	μ_{gp}	μ_{aq}	μ_{aq}/μ_{gp}
H	3.563	6.399	1.796	2.641	4.353	1.648
OH	4.332	7.233	1.670	3.037	4.533	1.493
NH_2	4.648	7.808	1.680	3.083	4.109	1.333
NO_2	4.668	6.508	1.394	8.192	11.532	1.408
OCH_3	3.213	5.055	1.573	4.109	7.834	1.907
$COCH_3$	4.683	7.699	1.644	7.331	11.147	1.521
CN	3.136	5.090	1.623	5.907	8.652	1.465

different compounds is related to the increase of their reactive characteristics with respect to the gas-phase as can be noted from the decrease of the energy difference between the HOMO and LUMO orbitals (data not shown).

Conclusions

The effects of substitution of the hydrogen atom at the 4′ position of flavones and isoflavones by several types of electron-withdrawing or electron-donating groups were analyzed. It may be noted that 4′-substituted isoflavones are more stable than the corresponding flavones. A good correlation between the difference in Gibbs free-energy of corresponding isomers with Hammett parameters was obtained, which indicates that the B-ring is an isolated π system and does not interact with the chromone group.

The reactivity (acidic, basic, electrophilic and nucleophilic) of these compounds was determined by FMO theory. It may be noted that the predictions of this theory are in agreement with the limited experimental data for the reactivity of these compounds in the literature. The FMO theory was tested by comparison of the stability of the reaction products predicted by this theory with the experimental reactivity of analogous systems. The good correlation observed indicates that this theory is adequate to predict the reactivity of substituted flavones and isoflavones.

The stability and the reactivity of these compounds were also studied in aqueous solutions. It may be observed that the reactivity does not change in solution in contrast with the relative stability. These results indicate that the solvent plays a crucial role in the stability of these compounds. It may also be noted that there is a polarization of solute in the solvent, and that this polarization depends mainly on the substituent.

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