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Ab Initio Study of Flavonoids

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Abstract

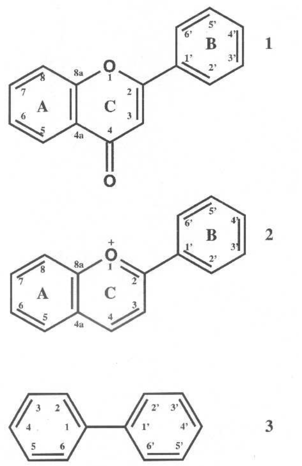
Flavone and the flavylium ion have been studued at Hartree-Fock, Møller-Plesset and B3LYP hybrid density functional level to determine the structures and barriers to internal rotation. Both molecules have a high perpendicular barrier about the single bond connecting the phenyl ring with the benzopyrone and benzopyrylium ring, respectively. In contrast to biphenyl both molecules have low coplanar barriers. B3LYP overestimates the perpendicular barrier heights compared to other methods. The dependence of the population and orbital energies on the torsion has been investigated and the structures of both flavonoids have been estimated by means of a reaction field model.

Introduction

Flavonoids are an active area of research as these plant compounds have antioxidative properties, they show probably protective effects against chronic diseases [**?**] and bind to a broad range of enzymes [2-4]. A series of flavonoids derived from flavone **1** has been investigated by X-ray crystallography [5-11], ESR [12], Raman and UV-vis spectroscopy [13]. Much less is known about anthocyanidins, a group of flavonoids derived from the flavylium cation **2**. Except for the plant pigment cyanidin (3,5,7,3',4'-pentahydroxyflavylium) [14], X-ray structure investigations have not been reported for anthocyanidins.

Recent computational studies relevant to life science have been carried out using semiempirical structure calculations and molecular superpositions of quercetin (3,5,7,3',4'-pentahydroxyflavone) and cyanidin with the indole derivative betanidin to explain the regioselectivity of betanidin glucosyltransferase towards flavonoids [15]. Flavonoid structure-activity relationships of HIV-1 integrase inhibitors [2] and adenosine receptor antagonists [16] have been analysed using the CoMFA method, docking simulations of novel inhibtors related to quercetine have been performed for aldose reductase [4] and the antioxidant activity of flavonoids has been explained by ab initio calculations with small basis sets [12].

A series of quantum chemical studies of flavonoids have been carried out at semiempirical level [6,7,10,13,15-20] and a few Hartree-Fock sudies have been published [12, 20]. Hitherto the semiempirical methods CNDO/2 [6], INDO [7], MNDO [19], AM1 [10,13,17-20] and PM3 [15-17,20] have been applied and it has been shown that torsional energy profiles determined with the AM1 and PM3 methods are quite different [17]. For the flavylium ion no studies of the torsional potential have been reported. In the present study ab initio and density functional calculations are presented to provide more accurate barriers and structural parameters of the parent compounds flavone and the flavylium cation. HOMO and LUMO energies are presented for different flavonoid conformations and a population analysis has been carried out to discuss barriers to internal rotation and structural changes in the context of electron density. Furthermore, the most stable conformations of monohydroxyflavonoids have been determined and the solvent influence on relative energies of different conformers has been estimated using a self consistent reaction field (SCRF) model.



Scheme 1

Method of Calculations

Ab initio calculations have been performed at HF/6-31G(d) [21, 22] level to optimize the structures of flavone and the flavylium ion in the coplanar, twisted and perpendicular conformation. The energy minima and internal rotation transition states have been verified by frequency calculations. Subsequent single point calculations have been carried out with the Møller-Plesset perturbation theory (MP2/6-31G(d)//HF/6-31G(d), MP2/6-311G(d,p)//HF/6-31G(d) and MP3/6-31G(d)//HF/6-31G(d)) in the frozen core approximation to determine the relative energies of different conformations. For comparison the structures have been optimized applying the B3LYP/6-31G(d) and B3LYP/6-311G(d,p) [23, 24] hybrid density functional methods. Solvent effects have been estimated using the self consistent isodensity model [25] with a dielectric of 78.5. Single center surface integration has been selected instead of the default multicenter method as the former method turned out to be more stable in the optimizations. All calculations were carried out with the programs GAMESS [26] and GAUSSIAN94 [27].

Initial structures for the calculation of monohydroxyflavonoids have been generated from the optimized flavone and flavylium cation structures. In general the optimizations at HF/6-31G(d) level have been started from both possible conformations of each hydroxy group in the plane of the aromatic rings.

Results and Discussion

STRUCTURES

The most relevant structure parameters determined with B3LYP/6-311G(d,p) method are given in Fig. 1. The bond distances from the DFT calculations are somewhat longer than the ones from HF calculations, which usually tend to be somewhat too short. For example, the average CH bondlength is 1.074 Å at HF/6-31G(d) and 1.084 Å at B3LYP/6-311G(d,p) level. Differences between

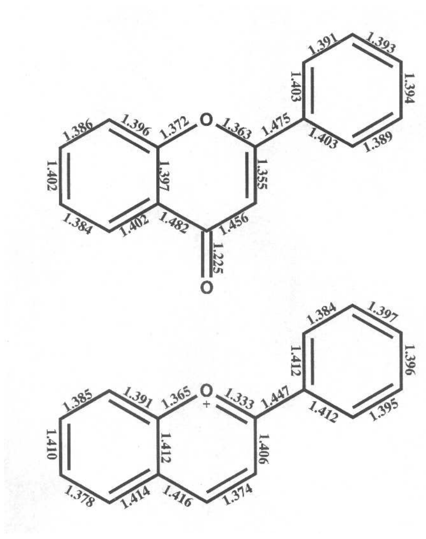


Figure 1: Molecular structures of flavone and the flavylium cation.

the angles calculated with the B3LYP and the HF method are smaller than one degree. As expected from the chemical formulas (Scheme 1), the structures of the flavylium ion and flavone differ mainly in the C-ring whilst the A and B- ring geometries are quite similar. The angles α(C8a-O1-C2)= 123.4 ° and α(C4-C4a-C5)= 124.7 ° are somewhat larger in the flavylium ion than the flavone angles of 120.1 ° and 121.6 °. Moreover, the distances r(O1-C2) and r(C3-C4) are shorter than in flavone, whereas r(C2-C3) is longer. The C5-C6 and C7-C8 bonds of both molecules are shorter than the other A -and B-ring bonds. The bond betwen C2 and C1' connecting the B- and C-rings has a length of 1.475 Å in flavone and 1.448 Å in the flavylium ion and the angle α(O1-C2-C3) is 121.9 ° in flavone and 118.7 ° in the ion.

INTERNAL ROTATION BARRIERS

Barriers to single bond internal rotation have been studied frequently by computational methods to determine relative energies for different conformations of various molecules [13, 17, 29-32]. At HF/6-31G(d) level the non-planar molecules flavone and flavylium have torsional angles τ(O1C2C1'C2') of 152 ° and 172 °, respectively (Table I). The barrier to internal rotation depends on the relative magnitude of the nuclear repulsion and electronic energies. For the coplanar conformation of flavone and the flavylium ion the nuclear repulsion energies are higher than for the perpendicular conformation (Table II), whereas the energies of twisted conformations are in between. However, the total energy shows a different behaviour. Both molecules have a low barrier towards the coplanar conformation (ΔE_0) and a high barrier towards the perpendicular conformation (ΔE_{90}). The increased perpendicular and the decreased coplanar torsional barriers of the flavylium ion compared to flavone are in line with the decrease of the twist angle. For example, MP3/6-31G(d)//HF/6-31G(d) predicts a perpendicular barrier of 2.99 kcal/mol for flavone, whereas 6.32 kcal/mol was

TABLE I. Total Energy E_{min} (H) for the most stable flavone and flavylium cation conformation with the torsional angle $\tau(O1C2C1'C2')$ ($^\circ$) and relative electronic ΔE and zero point energies ΔZPE (kcal/mol).

method	E_{min}	τ_{min}	ΔE_0	ΔZPE_0	ΔE_{90}	ΔZPE_{90}
flavone						
HF/6-31G(d)	-723.58758	152	0.45	-0.05	3.26	-0.23
HF/6-311G(d,p) //HF//6-31G(d)	-723.74156		0.35		3.09	
MP2/6-31G(d) //HF//6-31G(d)	-725.81510		0.91		2.94	
MP2/6-311G(d,p) //HF//6-31G(d)	-726.14248		0.90		2.30	
MP3/6-31G(d) //HF//6-31G(d)	-725.85532		0.74		2.99	
B3LYP/6-31G(d)	-728.07131	161	0.12	-0.05	4.27	-0.24
B3LYP/6-311G(d,p)	-728.24837	161	0.01		3.83	
SCIPCM/6-31G(d)	-723.59922	156	0.42		3.30	
flavylium						
HF/6-31G(d)	-649.09472	172	0.01	-0.03	7.41	-0.26
HF/6-311G(d,p) //HF/6-31G(d)	-649.22549	180	0.00		7.22	
MP2/6-31G(d) //HF/6-31G(d)	-651.13689		0.09		5.85	
MP2/6-311G(d,p) //HF/6-31G(d)	-651.42350		0.00		5.55	
MP3/6-31G(d) //HF/6-31G(d)	-651.18297		0.07		6.32	
B3LYP/6-31G(d)	-653.22067	179	0.01	-0.01	8.96	-0.36
B3LYP/6-311G(d,p)	-653.36856	179	0.01		8.43	
SCIPCM/6-31G(d)	-649.16895	168	0.09		6.75	

calculated for the flavylium ion. The coplanar barrier of flavone is 0.74 kcal/mol at this level, whilst the corresponding barrier of flavylium is only 0.07 kcal/mol. HF calculations lead to lower barriers than MP2 calculations. The barriers determined with MP3 single point calculations are between both lower level results and close to the MP2 data. This may indicate a fairly stable numerical result for the barrier heights. Nevertheless, for an accurate calculation of the extremely low barrier to coplanarity of the flavylium cation a consideration of the zero point energy and higher computational levels are necessary.

The zero point energies of different conformations lead only to minor corrections to the relative electronic energies listed in Table I. For example at HF/6-31G(d) level, the zero point energy difference between the most stable twisted conformation of flavone and the coplanar and perpendicular conformations are only -0.23 and -0.05 kcal/mol, respectively. The imaginary frequencies are 41 and 52 cm^{-1}. There is not much difference between the flavone and flavylium ion zero point energy differences, the latter are -0.26 and -0.03 kcal/mol and the corresponding frequencies are 11 and 71cm^{-1}. B3LYP calculations show a

Table II. Repulsion energies E_{rep} (H) and HOMO and LUMO energies (H) of flavonoids in different conformations.

molecule	method	coplanar	twisted	perpendicular
			E_{rep}	
flavone	HF/6-31G(d)	1071.23136	1071.21124	1069.25946
	B3LYP/6-311G(d,p)	1064.45673	1064.40437	1062.26222
flavylium	HF/6-31G(d)	967.08293	967.00627	964.81936
	B3LYP/6-311G(d,p)	960.81232	960.83118	958.58065
			E_{HOMO}	
flavone	HF/6-311G(d,p)			
	//HF/6-31G(d)	-0.3249	-0.3276	-0.3324
	B3LYP/6-311G(d,p)	-0.2428	-0.2432	-0.2467
flavylium	HF/6-311G(d,p)			
	//HF/6-31G(d)	-0.4567	-0.4568	-0.4622
	B3LYP/6-311G(d,p)	-0.3895	-0.3894	-0.3826
			E_{LUMO}	
flavone	HF/6-311G(d,p)			
	//HF/6-31G(d)	0.0607	0.0650	0.0821
	B3LYP/6-311G(d,p)	-0.0776	-0.0758	-0.0615
flavylium	HF/6-311G(d,p)			
	//HF/6-31G(d)	-0.1331	-0.1330	-0.1322
	B3LYP/6-311G(d,p)	-0.2610	-0.2610	-0.2678

close correspondence to these data and the relative energies of the twisted and coplanar flavylium conformations remain very similar, even after consideration of the zero point energy. The calculations confirm the AM1 torsional angles 150.8 of flavone [17] and the barrier height $\Delta E_0 = 0.4$ kcal/mol. Therefore the AM1 method seems to be suitable for the calculation of flavonoid structures, even though the perpendicular barrier $\Delta E_{90} = 1.5$ kcal/mol of flavone is only about half as high as the ones from the ab initio calculations. PM3 barriers and torsional angles do not measure up to the AM1 results. The barrier to the perpendicular conformation determined with the B3LYP method seems to be overestimated when compared to the HF, MP2 and MP3 results. Consequently, the structures derived from this hybrid DFT method are less twisted and the flavylium cation is even predicted to be almost planar. The overestimate of perpendicular torsional barrier heights agrees with the results presented by Karpfen [32], who concluded that some DFT variants overestimate the stability of planar π-systems.

The internal rotation potential of the flavonoids has interesting differences relative to the one of biphenyl **3** . This molecule has a low perpendicular barrier of 1.6 kcal/mol according to an electron diffraction study [33], which is in excellent agreement with the barrier of 1.58 kcal/mol derived from MP4(SDQ)/6-31G(d)//HF/6-31G* calculations [34]. The estimates of the coplanar biphenyl barrier are different, probably a consequence of the truncation of the Fourier expansion for the torsional potential analysis of the experimental data. The analysis of electon diffraction data led to $\Delta E_0 = 1.6$ kcal/mol, whereas 3.47

kcal/mol was determined with ab initio calculations. These theoretical and experimental coplanar barriers of biphenyl are much higher than the flavonoid barriers. There is a fundamental difference in the structure of both types of molecules. In the coplanar conformation the nonbonded distances between O1 and H6' are 2.327 Å in flavone and 2.375 Å in the flavylium ion. Such nonbonded C-H...O contacts with a distance between the hydrogen and the oxygen atom of about 2.5 Å have been identified in statistical surveys of crystal structures [35,36]. They may be considered as weak hydrogen bonds [37,38]. The nonbonded distances of 2.053 and 2.071 Å between the hydrogen atoms H3 at the C-ring and H2' at the B-ring are only slightly shorter than twice the nonbonded hydrogen radius of 1.1 Å, whereas the corresponding distance between both pairs of ortho-hydrogen atoms of biphenyl is 1.966 Å in the coplanar conformation. This leads to a substantial increase of the barrier and an extension of the C-C bondlength between both biphenyl benzene rings in the coplanar conformation [34], which is absent in flavonoids.

POPULATION ANALYSIS AND ORBITAL ENERGY

Heavy atom Mulliken electon densities of the flavonoids are shown in Figure 2. for the B3LYP/6-311G(d,p) level. Average hydrogen atom populations are 0.895 ± 0.004 and 0.862 ± 0.011 for flavone and flavylium, respectively. In both molecules C1' has the highest electron population of of the phenyl ring carbon atoms, which is just the opposite of biphenyl. C2 located in the B-ring is positively charged in contrast to C1' and the carbon atoms C4a and C8a connecting the A and C ring are oppositely charged. The electron density is affected in both molecules in the same way by the torsion. According to the population analysis the flavone C2-population increases from 5.762 in the twisted conformation to 5.868 in the perpendicular conformation and from 5.712 to 5.825 in flavylium. In contrast the C1' populations decrease from 6.145 to 6.068 in flavone and from 6.188 to 6.088 in flavylium. So the difference between the populations of C1' and the other B-ring carbon atoms is reduced in the perpendicular conformation. In addition to the C2 population, O1 is affected by the internal rotation. The population decreases from 8.335 to 8.305 in flavone and from 8.277 to 8.215 in flavylium. Other flavonoid atom populations are much less affected by conformational changes from the twisted to the perpendicular conformation. All populations in the coplanar conformation are not much different from the ones in the twisted conformation.

The total overlap populations between C2 and C1' increase from 0.750 in the twisted conformation to 0.804 in the perpendicular conformation of flavone. The corresponding changes from 0.816 to 0.822 in flavylium are much smaller. This is completely different to biphenyl, because the total overlap population in this molecule is lower in the perpendicular conformation than in the twisted one [34].

According to Koopmans' theorem the HOMO energy can be considered as an estimate of the first ionization potential. At Hartree-Fock level the flavone HOMO energy is affected by the internal rotation like in biphenyl [34], but the magnitude of the variation is smaller in the former molecule. Relative to the twisted flavone conformer, the HOMO energy increases 0.003 H in the coplanar conformation and it decreases 0.005 H in the perpendicular conformation. In flavylium the latter decrease amounts to 0.005 H, but for the planar

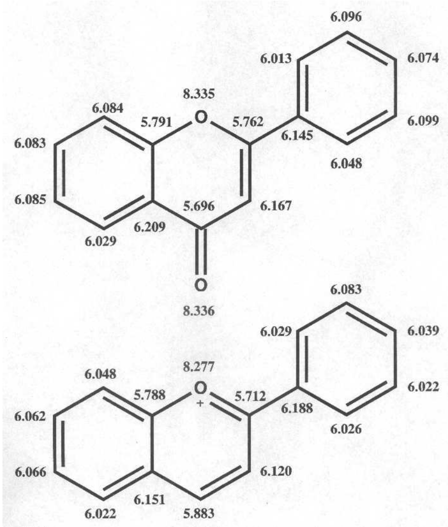


Figure 2: Mulliken populations of flavone and flavylium heavy atoms.

and twisted conformation nearly identical HOMO energies were computed. At B3LYP/6-311G(d,p) level HOMO energies are higher and LUMO energies are lower than at HF/6-311G(d,p)//HF/6-31G(d) level. In Fig. 3 the dependence of the HOMO on the molecular conformation is shown. In both coplanar flavonoids the HOMO is distributed over all three rings, whereas it is located only at the flavylium phenyl ring and at the flavone benzopyrone ring in the perpendicular conformation.

MONOHYDROXYFLAVONOIDS

The energies listed in Table III indicate that 5-hydroxyflavone and the 4- hydroxyflavylium cation are the most stable isomers. A hydroxy substituent at the benzopyrone ring has only small effects on the torsional angle τ of flavone (Table III). The most prominent effects result from substitutions at C3 and C8. Hydroxy groups at these atoms change the torsional angles of flavone in opposite directions from 152 $^{\circ}$ to 158 $^{\circ}$ and 147 $^{\circ}$, respectively. For the flavylium cation the torsional angle is modified by a C3 substitution from 172 $^{\circ}$ to 163 $^{\circ}$, whereas a C8 substitution leads to a coplanar structure (τ = 180 $^{\circ}$). A single substitution at the phenyl ring positions 2' or 3' leads to two different conformations α and β, either with C2' close to O1 (α, τ nearly 0 $^{\circ}$) or with C2' close to C3 (β, τ nearly 180 $^{\circ}$). The differences in the relative energy between both conformations are very small for a substitution at the 3'-position. For 3'-hydroxyflavone and the 3' -hydroxyflavylium cation as well, the α-conformations with torsional angles of 29 and 12 $^{\circ}$ are only 0.07 and 0.03 kcal/mol more stable than the β-conformations of with torsional angles of 152 and 167 $^{\circ}$. It can be concluded by virtue of these small energy differences, that the appearance of an α- or β-conformation of 3'-hydoxyflavonoids may depend more on the local environment , e. g. an enzyme or the crystal structure, than on the molecular

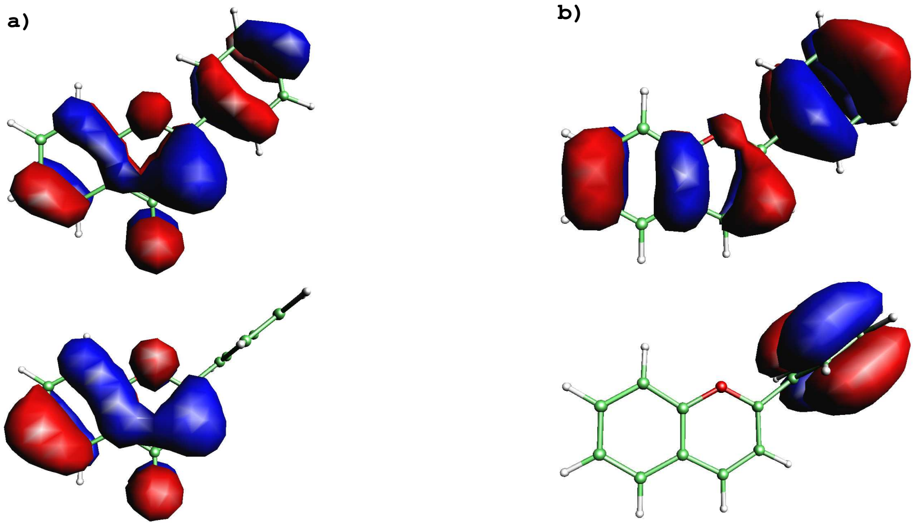


Figure 3: HOMO of flavone (a) and flavylium (b) in the coplanar and perpendicular conformation.

conformational energy difference. For substitutions at the 2'-position relative energy differences are larger and there is some difference for both molecules. For 2'-hydroxyflavone the α-conformation with $\tau = 37^\circ$ is 0.88 kcal /mol more stable than the β-conformation with $\tau = 138^\circ$. In the former conformation a hydrogen bond between O1 and H2' can be formed. In contrast to flavone, the β-conformation of the 2'-hydroxyflavylium ion with $\tau = 172^\circ$ is 2.25 kcal/mol more stable than the α-conformation with $\tau = {}^\circ 8$. In addition to the O1 atom the carbonyl oxygen atom of flavone can act as an acceptor atom. But all intramolecular hydrogen bonds of the monohydroxyflavonoids listed in Table IV have unfavourably low donor hydrogen acceptor angles a (D-H...A) formed by the donor D, the hydrogen and the acceptor atom A.

INFLUENCE OF A MEDIUM

Self consistent reaction field calculations have been used to investigate of the solvent influence on the conformation and relative energies. Since directed interactions such as hydrogen bonds are not included in the selected SCRF model, the results should be regarded as a rough estimate because quantitative accuracy cannot be expected. SCRF calculations at HF/6-31G(d) level indicate that the solvent with a dielectric of 78.5 has almost no influence on the torsional barrier of flavone, whereas the perpendicular barrier of the flavylium ion decreases from 7.40 to 6.74 kcal/mol. The torsional angle of flavylium is unchanged upon solvent influence and flavone gets somewhat more coplanar.

In most cases structural changes of monohydroxyflavones upon solvation are small (Table III). The most noteworthy effects can be observed for the 2' - hydroxyflavonoids. The torsional angle τ for the τ-conformer of flavone changes from 138 to 152. In the gas phase the α-conformation with a hydrogen bond O1...H2' is 0.88 kcal/mol more stable than the β- conformer, but in the solvent the β-conformer with H2' located at the side of O4 is slightly more stable. This

Table III. Total energy E(H) and relative energy Δ E_a (kcal/mol) for different torsional angles τ about the C2-C1' bond for monohydroxyflavonoids in the gas phase (left side) and in a continuum solvent (right side).

molecule	conformer	E^a	$\Delta E^a_{\alpha\beta}$	τ^a	$\Delta E^b_{\alpha\beta}$	τ^b
flavone		-723.58758		152		156
3-OH		-798.44029		158		153
5-OH		-798.45408		153		153
6-OH		-798.44103		152		155
7-OH		-798.44479		152		155
8-OH		-798.43997		147		152
2'-OH	α	-798.44237	0.00	37	0.00	43
	β	-798.44096	0.88	138	-0.14	152
3-'OH	α	-798.44195	0.00	29	0.00	24
	β	-798.44184	0.07	152	-0.16	152
4'-OH		-798.44366		155		161
flavylium		-649.09472		172		172
3-OH		-723.93704		163		157
4-OH		-723.96415		164		159
5-OH		-723.95435		173		173
6-OH		-723.94769		173		167
7-OH		-723.95460		168		163
8-OH		-723.94574		180		180
2'-OH	α	-723.94921	0.00	8	0.00	32
	β	-723.94921	-2.25	172	-2.03	165
3-'OH	α	-723.94813	0.00	12	0.00	15
	β	-723.94809	0.03	167	-0.26	161
4'-OH		-723.95605		180		179

[a] HF/6-31G(d)
[b] SCRF/6-31G(d), $\epsilon = 78.5$

Table IV. Intramolecular hydrogen bonds in monohydroxyflavonoids[a]

	flavone		*flavylium*	
D-H...A	r(H...A)	α(DHA)	r(H...A)	α(DHA)
O3-H...O4	2.080	115.7		
O5-H...O4	1.832	143.3		
O8-H...O1	2.204	110.6	2.347	105.0
O2'-H...O1	1.972	136.5	1.905	134.5

[a] D donor, A acceptor atom.

β-conformation is also the preferred conformation in the crystal structure of 2'-hydroxyflavone [11]. For the 2'-hydroxyflavylium cation the β-conformation is always more stable.

The torsional angle between the B- and C-ring planes of cyanidin bromide is about 170 in the X-ray structure [14], which is very close to the calculated flavylium cation torsional angles. Flavonoles appear to be more coplanar in the crystal than in the gas phase, most probably a consequence of packing effects. The torsional angles are 173° (3-hydroxyflavone [5]), 175° (5- hydroxyflavone [8]), 168° (6-hydroxyflavone [9]) and 170° (2'-hydroxyflavone [11]). For quercetin a dependence of the torsional angle of the physical state has been proposed. The crystal structures reveal a torsional angle of 175° [6, 7], but the Raman spectrum of quercetin in methanol solution has been interpreted in terms of a larger deviation from coplanarity [13]. This conformational change in different media is much more pronounced in biphenyl. The molecule is coplanar in the crystal structure [39], whereas the twist angle is $44.4 \pm 1.2^\circ$ according to gas phase electron diffraction study [34]. The latter angle is in close agreement with recent HF and MP2/6-31G(d) calculations. In contrast, the energy minimum is shifted somewhat to lower torsional angles by the B3LYP method [32].

A typical feature of the computed flavonol structures are intramolecular hydrogen bonds between the flavone O4 and the hydroxy groups at the nearby atoms in the gas phase and in the solvent. Hydroxy groups at C3 form a five-membered ring with a H...O4 distance of 2.080 Å and hydroxy groups at C5 form a six-membered ring with a H...O4 distance of 1.832 Å. These hydrogen bonds can be observed also in the experimental structures of 3- and 5- hydroxyflavone and quercetin [5,8,6]. In X-ray structures additional intermolecular hydrogen bonds are formed with water or neighbouring molecules to stabilize crystal packing patterns [5-7,11,14], especially for flavonoids with multiple hydroxy groups.

Conclusions

To sum up, ab initio calculations facilitate a study of flavonoid properties without bias of neighbouring molecules in crystal structures. Flavone is a non -planar molecule with a low barrier to planarity and a high perpendicular barrier, the coplanar and twisted flavylium conformations correspond to very similar energies. The B3LYP method overestimates the perpendicular barrier compared to HF and MP methods. The internal rotation has an influence on the geometry and the total Mulliken population of C-ring atoms. Solvent effects the structures of flavone and flavylium ions are small in general, but the relative energies of conformers may change.

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