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Molecular Structure and Proton Affinities of the 4*H*-1-Benzopyran-4-one Molecule and Its Hydroxylated Derivatives

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Flavonoids are a class of low molecular weight phenolic compounds widely distributed in the plant kingdom.[1] They have displayed potential pharmacological applications as antibacterial, antioxidant, anticancer, and antiallergy agents.[2−6] Furthermore, there has been a considerable recent interest in flavonoids since substantial evidence has been accumulated that they exhibit anti-HIV activity.[7,8] These compounds consists of a benzene ring fused with a γ-pyrone ring, which are usually denoted A- and C-rings, respectively. The most important chemical property of these compounds is the enhanced reactivity of the C-ring, which was discovered more than 30 years ago.[9−12] More specifically, the strong acid/base properties of the C-ring were considered particularly relevant since protonation of substrates occurs during numerous biochemical processes and, in some cases, is the key step of the entire process. On the other hand, the molecular geometries and the electronic structures of **1**−**3** were investigated at both semiempirical[13,14] and ab initio levels using a minimal basis set.[15] Furthermore, the solvation of **1** was recently investigated using combined SCRF/Discrete methods.[16] Nevertheless, there are some questions related to chemical properties of flavonoids that remain unknown. Thus, the site of protonation of flavonoids is obscure, although experimental studies in γ-pyrone derivatives[10−12] suggest that the protonation occurs not in the heterocyclic oxygen but on the carbonyl oxygen. On the other hand, the possible existence of π-conjugation in the C-ring has not been ascertained. These points are of crucial interest to understand both the chemical and biological properties of flavonoids. This work describes the results of a quantum mechanical study about the acid/base properties of flavonoids in the gas phase and aqueous solution. For this purpose, three of the most important flavonoids were selected: 4*H*-1-benzopyran-4-one (**1**), 2-hydroxy-4*H*-1-benzopyran-4-one (**2**), and 3-hydroxy-4*H*-1-benzopyran-4-one (**3**). Furthermore, the existence of π-conjugation in the C-ring has been also investigated.

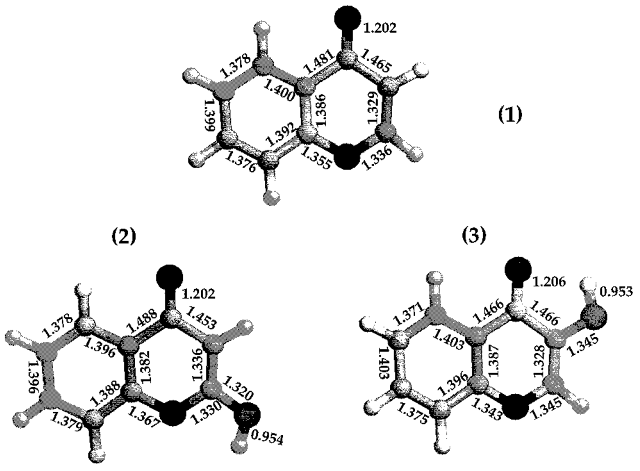
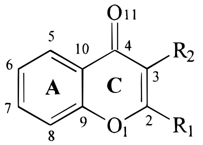


Figure 1. Optimized geometries for 4*H*-1-benzopyran-4-one (**1**), 2-hydroxy-4*H*-1-benzopyran-4-one (**2**), and 3-hydroxy-4*H*-1-benzopyran-4-one (**3**).



1: R_1=H; R_2=H

2: R_1=OH;R_2=H

3: R_1=H; R_2=OH

The optimized geometries for compounds **1**−**3** were obtained by performing ab initio calculations at the HF/6-31+G(d) level using the Gaussian-94 program.[17] Figure 1 shows the optimized geometries and the calculated bond distances for the three compounds. In all cases completely planar structures were found. As was expected, the A-ring displays a bond length alternation pattern typical of a benzenoid structure in the three compounds. However, the bond lengths clearly indicate that the π-conjugation is not extended across the C-ring. More specifically, the bond length alternation pattern is absent for the sequence C3−C2−O1−C9. Figure 2 displays the HF/6-31+G(d) geometries of **1**−**3** protonated at O1 and O11 atoms. In **1-O1(+)**, **2-O1-(+)**, and **3-O1(+)**, the hydrogen atom attached to O1 atom lies out of the plane that contains the other atoms, whereas in **1-O11(+)**, **2-O11(+)**, and **3-O11(+)** all the atoms are within the same plane. The optimized bond lengths reveal that the protonated forms of **1**−**3** do not present π-conjugation in the C ring, the benzenoid-type alternation pattern of the A ring being even lost in some cases. Molecular geometries optimized at the same level of theory for the anionic forms **2(−)** and **3(−)** are also displayed in Figure 2. The bond lengths in the A ring are very similar to those obtained for the neutral compounds retaining a benzenoid type alternation pattern.

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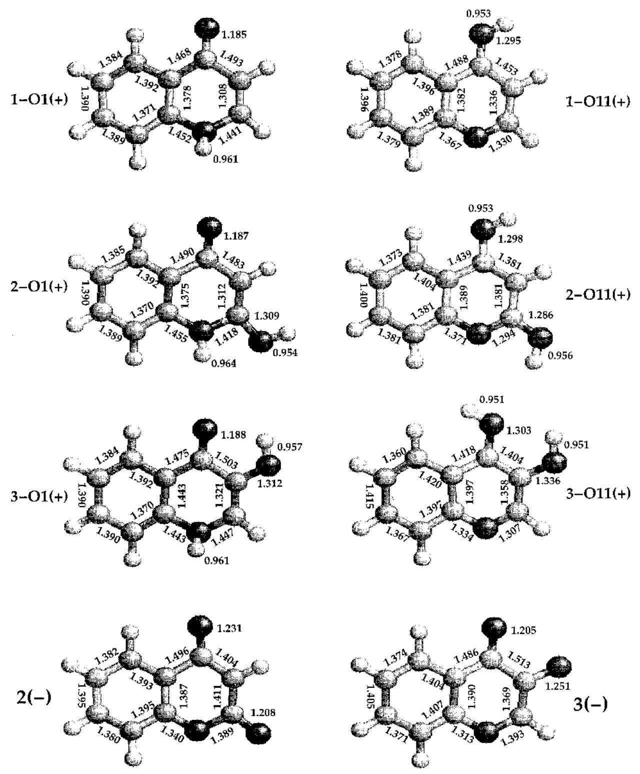

Figure 2. Bond lengths of the optimized geometries for protonated and deprotonated forms of 4*H*-1-benzopyran-4-one (**1**), 2-hydroxy-4*H*-1-benzopyran-4-one (**2**), and 3-hydroxy-4*H*-1-benzopyran-4-one (**3**).

Table 1. HF/6-31+G(d) and MP2/6-31+G(d) Energies[a] of 4*H*-1-Benzopyran-4-one (1), 2-Hydroxy-4*H*-1-benzopyran-4-one (2), and 3-Hydroxy-4*H*-1-benzopyran-4-one (3) in Their Neutral, Protonated, and Deprotonated Forms (Proton Affinities[b] Are Also Displayed)

compd	HF/6-31+G(d)	MP2/6-31+G(d)	PA_{HF}	PA_{MP2}
1	−494.045 123	−495.532 061		
1-O1(+)	−494.312 103	−495.790 385	167.5	162.1
1-O11(+)	−494.402 771	−495.877 820	224.4	217.0
2	−568.913 980	−570.579 459		
2-O1(+)	−569.177 145	−570.836 494	165.1	161.2
2-O11(+)	−569.281 102	−570.932 835	230.4	221.7
2 (−)	−568.393 239	−570.076 404	326.8	315.7
3	−568.901 340	−570.572 025		
3-O1(+)	−569.172 410	−570.832 091	170.1	163.2
3-O11(+)	−569.244 859	−570.907 804	215.6	210.7
3 (−)	−568.324 847	−570.016 934	361.7	348.3

[a] In atomic units. [b] In kcal/mol.

The HF and MP2 energies computed in the gas phase with the 6-31+G(d) basis set for the neutral, protonated, and deprotonated forms of **1**−**3** are listed in Table 1. The proton affinities, which were estimated as the difference between the energies of the neutral and charged forms, are also listed in Table 1. The HF method overestimates the proton affinities by ~4−9 and 11−13 kcal/mol for the acid and base species, respectively, when compared with MP2 results. Nevertheless, the two methods provide qualitatively similar information. Thus, inspection of the protonated forms reveals that protonation at the O11 atom led to more stable compounds than protonation at the O1 atom, the energy difference between them being about 50−60 kcal/mol. Therefore, we can conclude that the species protonated at the O1 atom are the strongest acids. On the other hand, it can be seen from Table 1 that **2** is the strongest base, whereas **3** is the weakest one. The proton affinities of **2(−)** and **3(−)** indicate that the latter is the strongest base by a difference of about 32 kcal/mol.

Table 2. Free Energies of Hydration[a] (ΔG_{hyd}) and Electrostatic (ΔG_{ele}) and Nonelectrostatic (ΔG_{nonele}) Contributions to ΔG_{hyd} for 4*H*-1-Benzopyran-4-one (1), 2-Hydroxy-4*H*-1-benzopyran-4-one (2), and 3-Hydroxy-4*H*-1-benzopyran-4-one (3) in Their Neutral, Protonated, and Deprotonated Forms (Protonation Affinities[a,b] Are Also Displayed)

compd	ΔG_{hyd}	ΔG_{ele}	ΔG_{nonele}	$\Delta\Delta G_{hyd}$	PA
1	−5.0	−6.8	1.8		
1-O1(+)	−69.0	−70.4	1.4	−64.0	226.1
1-O11(+)	−51.3	−52.8	1.5	−46.3	263.3
2	−8.6	−11.0	2.4		
2-O1(+)	−71.7	−73.6	1.9	−63.1	224.3
2-O11(+)	−56.1	−58.0	1.9	−47.5	269.2
2 (−)	−68.4	−71.0	2.6	−59.8	255.9
3	−4.6	−7.0	2.4		
3-O1(+)	−66.4	−68.3	1.9	−61.8	225.0
3-O11(+)	−55.1	−57.2	−2.1	−50.5	261.2
3 (−)	−73.7	−76.3	2.6	−69.1	279.2

[a] In kcal/mol. [b] PA computed from the addition of the energies calculated at the MP2/6-31+G(d) level in the gas phase and the ΔG_{hyd}.

A polar solvent like water may exercise a large influence on the reactive properties of heterocycles. Therefore, we decided to explore the role of water in the protonation energies using a self-consistent reaction-field (SCRF) algorithm. The free energies of hydration were determined using the AM1 semiempirical optimized version[18] of the SCRF developed by Miertus, Scrocco, and Tomasi.[19,20] Accordingly, the cavities were built using standard van der Waals radii and a scale factor of 1.2.[18] The free energies of hydration (ΔG_{hyd}) are listed in Table 2, where both the electrostatic and nonelectrostatic contributions to ΔG_{hyd} are also shown. The ΔG_{hyd} for the three neutral compounds reveal that **2** is better hydrated than both **1** and **3**, the ΔG_{hyd} being very similar for the two latter compounds. This result can be rationalized in terms of the dipole moments (3.82, 5.67, and 3.41 D for **1**, **2**, and **3**, respectively) since, as expected from previous studies, the larger the dipole moment, the greater the electrostatic interactions with the bulk water.[21,22]

The proton affinities in aqueous solution were estimated from the addition of the energies calculated at the MP2/6-31+G(d) level in the gas phase (Table 1) and the free energies of hydration. Results are included in Table 2. The difference between the proton affinities for the forms protonated at the O1 and O11 positions decreases in aqueous solution by about 12−18 kcal/mol. However, the forms protonated at the O1 atom are the strongest acids in aqueous solution like in the gas phase. On the other hand, the strength of **1** and **3** as bases is very similar in aqueous solution, whereas **2** results the strongest base. The protonation energies of **2(−)** and **3(−)** show similar trends revealing an enhancement of their base character.

In summary, the results show that protonation on the carbonyl oxygen is more favored than on the heterocyclic oxygen in both the gas phase and aqueous solution. These results are in agreement with the experimental data reported for γ-pyrones.[10−12] The protonation energies reveal that **2-O11(+)** is the most stable compound, indicating that **2** is a stronger base than **1** and **3**. Conversely, the results obtained for **2(−)** and **3(−)** reveal that **3** is more acidic than **2**.

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