

Effect of the Methyl Group on the Stability and Twisting of Flavonoids

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Abstract: Four flavonoids were theoretically studied through B3LYP/6-311 ++G** method in order to evaluate the effect of flavonoid structural features on its stability and its ring planarity, applying the dihedral calculation. In this study were evaluated structures with a methyl group at positions 3 and 7 and the presence or not of the glucosyl group. The dihedral angle between AB to C rings, Huckel charges and intramolecular hydrogen bonds were assigned.

Key words: flavonoids, DFT, stability

1. Introduction

Flavonoids is a class of phytochemicals/phytonutrients originated from polyphenols of low molecular weight found in several plants¹. They present good effects on human health such as active role on sickness healing. These compounds are classified as the most important natural colorants and flavors besides presenting a wide range of biological activities, highlighting the anti-inflammatory² and antioxidant³ properties. They are found in hydro and liposoluble forms, and as aglycones (without sugar units) or glycosides flavonoids^{4,5,6}.

Some great sources of flavonoids are the seeds and fruits of plants from the Leguminosae and Compositae families⁷. More than 5000 flavonoids have been identified in the nature and classified according to their chemical structure. This class of compounds is subdivided in 9 subgroups: flavones, flavonols, flavanones, flavanes, isoflavones, anthocyanins, flavanonols (flavan-3-ol or catechins), chalcones and dihydrochalcones. The computational chemistry is a powerful tool that can help better understanding some of the doubts questioned in this work. With the advance of the computational chemistry, is even more needed and easy to explain some experimental observations based on the quantum chemistry⁸ from many studies found on literature^{9,10,11-14}. This kind of study provides valuable information at low costs, that allows to understand the effect of the different structural features of the compounds. Some theoretical studies about a great variety of flavonoids were published¹², where some of them focus on the energetic properties of these compounds and the effect of the hydroxyl groups on the structure. In this perspective, this work presents the results from a study of four glycoside flavones. Figure 1 shows the representation of the general structure for flavonoids, including the ones discussed in this research. This molecular structure is characterized by charge delocalization on the studied molecules from ring A to B through C due to the double bond C2-C3. Then, the main question of this work is to understand how the presence of the methyl group affects the charge delocalization and how it is related to the geometrical and molecular parameters and the

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molecular energy, as well as the twisting profiles around the C2-C1' bond and its effect on rotation properties of catechol (ring B). The intramolecular hydrogen bonds will also be studied. Density Functional Theory (DFT) was applied in this work since it provides confident results between the precision and computational requirements, considering the compounds studied and its properties.

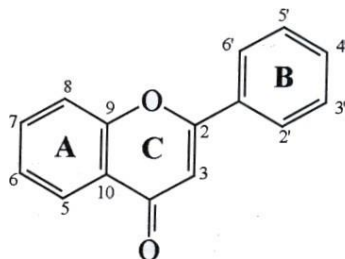


Figure 1. Molecula skeleton of flavone showing atoms numeration and named rings

The flavones have the same basic structure derived from the original molecule presented in Figure 1 and the optimized structures for the compounds I-IV studied in this work are presented in Figure 2. In these compounds, the methyl, glucosyl and hydroxyl groups are alternating in the positions 3 and 7.

2. Materials and Methods

COMPUTATIONAL METHODS

DFT calculations were performed with the Gaussian 05¹⁵ pack according to the Density Functional Theory, using the exchange of corrected functional gradient of Becke¹⁶ and Lee- Tang-Parr functional correlations¹⁷. For these parameters, the B3LYP method was used¹⁸. The set of bases 6-311 ++G ** was used for the calculations presented in this work. The atomic charges, bonds length and dihedral angles were calculated for the optimized structures in gas phase and in vacuum.

3. Results and Discussion

Structural features

The optimizations of the four structures presented in Figure 2 were performed and the intramolecular hydrogen bonds in the structures and the main molecular parameters are showed in Table 1.

As discussed in Santiago Aparicio work²⁰, the dihedral angle between ring B and the plane formed by rings A and C is about 20° for flavones without the hydroxyl group and 0° for the ones with hydroxyl group at position 3. In our results is observed that both structures with the methyl group presented a dihedral angle, between the plane of the rings A-C and B (C3-C2-C1'-C2') of -71,36° (Structure I) e 0,49° (Structure II), and the structures with the hydroxyl, -23,18° (Structure III) and -0,05° (Structure IV). The values obtained indicate that the glucosyl group present on structures at position 3, confirms the significant change in the dihedral angle. This observation can also be explained by the intramolecular hydrogen bonds present in these molecules. On structure I, the hydrogen bond between the hydroxyl hydrogen 7 at the glucosyl group with the oxygen at position 2' from ring B, can justify the non-coplanarity between these rings, once this bond is 1.85341 Å, which is considered as strong bond²¹. On structure II the rings are almost coplanar and that is

explained by the hydrogen bond between the oxygen bonded to methyl at position 3 and the hydrogen at position 2' from B ring, where the distance is 2.29746 Å.

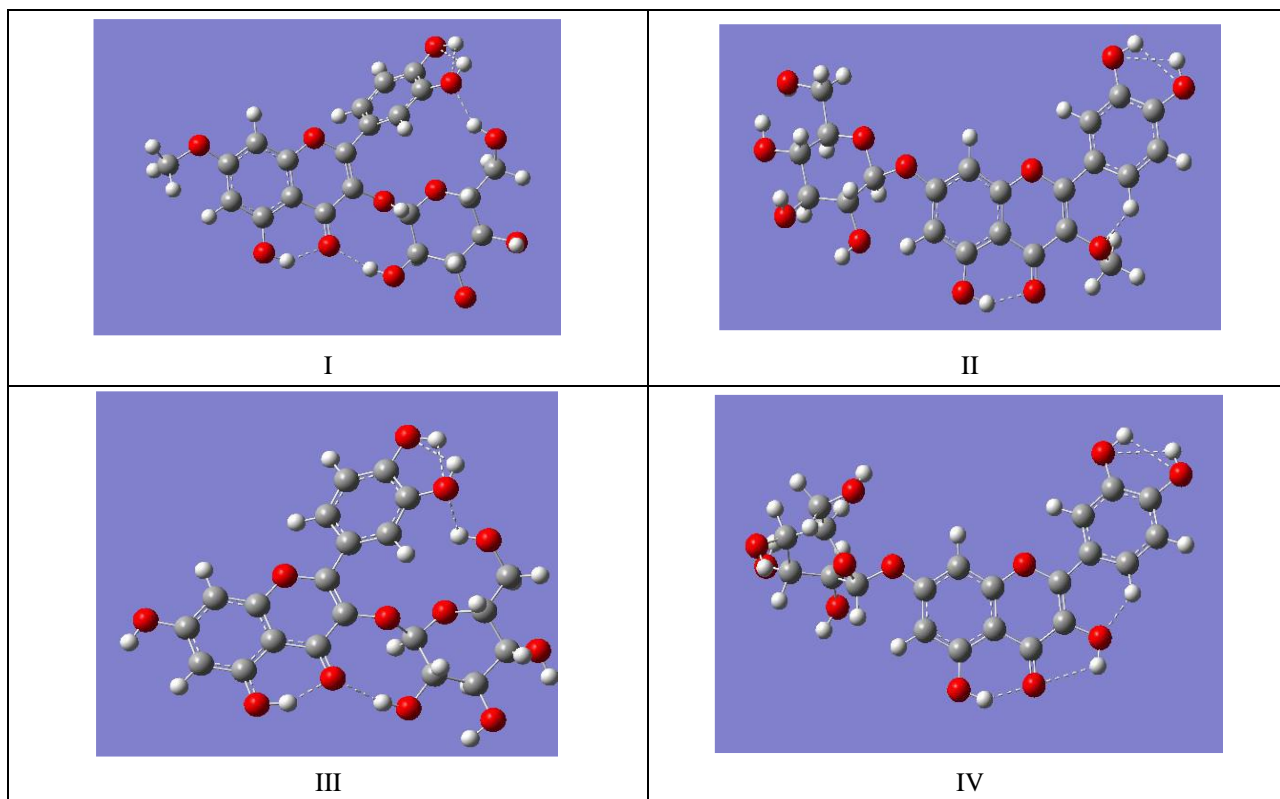


Figure 2 - Optimized structures of the studied flavonoids I-IV from the calculation in gas phase on B3LYP//6-311 ++G** theoretical level, with indication of the hydrogen bonds. Atom Colour code: Oxygen (red), carbon (grey) and hydrogen (white).

For structures III and IV, that have the hydroxyl changing by glucosyl, follows the same tendency of III that has the sugar unit at position 3, the B ring has a small rotation due to the hydrogen bond between the hydroxyl hydrogen 7 at glucosyl unit with the oxygen at position 2' at B (1.91915 Å), and for structure IV, the rings can be considered coplanar, where the intramolecular bond between the hydrogen at position 2' and the oxygen at position 3 is considered strong (1.79635 Å). Table 2 shows the intramolecular hydrogen bonds on these structures.

In terms of stability, is observed that when the glucosyl in the molecule is at position 3, it is more stable than its correspondent at position 7. Since the atom of C, O and H has a contribution of -38.2792077 a.u., -74.46309364 a.u and -0.56119365 a.u, respectively, for the stabilization energy of a molecule (not considering the contributions from hydrogen bonds, radicals and ions), it is possible to compare the stabilization of the four structures (IIV).

Table 1. Main geometrical and energetic parameters from the studied flavones I-IV in gas phase calculated in the B3LYP / 6-311 ++ G ** theoretical level.

Structure	r C4=O	r 3-OH	r 5-OH	r 3'-OH	r 4'-OH	τ 3-2-1'-2'	E	μ
I	1.235	--	0.975	0.961	0.959	-71.36	-1754.21225084	6.77
II	1.230	--	0.965	0.961	0.941	-00.49	-1754.20708701	6.25
III	1.263	--	0.994	0.966	0.969	-23.18	-1714.92226364	4.31
IV	1.234	0.951	0.985	0.963	0.968	-00.05	-1714.90002062	4.21

Atom numeration as Figure 1. Interatomic distances, r in Å; dihedral angles, τ , in degrees; energy E in a.u.; dipole moment, μ , in D.

Table 2 – Intramolecular hydrogen bonds in Å.

Structures	C2'H-O3	O3'H-O4'	O4'H-O3'	O5H-O4	O3H-O4	O5glucH-O4	O2glucH-O3'
I	3.30500	2.50884	2.50348	1.81243	-----	1.79802	1.85341
II	1.80116	2.49596	2.49636	1.81245	-----	-----	-----
III	3.17287	2.15164	2.18359	1.691006	-----	1.91232	1.91915
IV	1.79594	2.49790	2.49531	1.82113	2.35792	-----	-----

Table 3 - Huckel charge calculated by the B3LYP method with base 6-311 ++ G ** for I-IV

Structures	C4=O	C3-O	C5-O	C7-O	C4'-O	C5'-O
I	0.602	0.556	0.554	0.516	0.547	0.523
II	0.571	0.544	0.558	0.527	0.549	0.532
III	0.609	0.550	0.557	0.542	0.568	0.526
IV	0.594	0.544	0.559	0.531	0.550	0.568

Therefore, removing one CH₂ group from the structures I and II, it is obtained an energy of -1714.90063333 a.u and -1714.8854695 a.u, respectively. The comparison of the four calculated energies for I-IV, we can conclude that having a hydroxyl group (structure III) instead of a methyl group results in a more stable molecule, which agrees with the lower dipole moment for this structure. The Table 3 shows the Huckel charges, and it can be observed that the most electronegative atom is the carbonyl oxygen and that on the structure III the charge is bigger. The crescent order for these oxygens from the structures would be III>I>IV>II. This crescent order for the Huckell charge on the carbonyl oxygen is equivalent to the crescent order of the stability of the studied structures, confirming that the structures with the glucosyl at position 3 is more stable than when it is at position 7, regardless if they have hydroxyl or an methyl group at position 7.

4. Conclusion

It can be concluded from this work that the methyl group decreases the stability on the studied structures, either if they are at 3 or 7 position, but the structures with the glucosyl at position 3 are more stable than when the glucosyl is at position

7, no matter if it has a hydroxyl or a methyl group. It can also be concluded that the methyl group does not influence on the ring B twisting, once it is connected with an oxygen that has an intramolecular bond with the hydrogen at position 1' at ring B. On the other hand, when the flavone has the glucosyl unit at position 3, the tendency is that the planarity of ring B in relation to the ring A-C does not occurs. The Huckel charge has a linear relationship with the stability of the studied structures.

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