Investigation of Structural Properties of Quercetin by Quantum Chemistry Methods

I.O. Protsenko, L.A. Bulavin

Taras Shevchenko National University of Kyiv, Faculty of Physics, Kyiv, Ukraine.

D.M. Hovorun

Institute of Molecular Biology and Genetics, NAS of Ukraine, Kyiv, Ukraine.

Institute of High Technologies of Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

Abstract. The aim of this work is an ab initio quantum mechanical investigation of spatial molecular structure of the quercetin molecule - a biologically active compound, which is widely used in medicine and pharmaceutics. The conformational analysis performed at the MP2/6-311++G(d,p) // DFT B3LYP/6-31G(d,p) theory level revealed as many as 12 conformations of quercetin molecule with relative Gibbs energies from 0 to 5.33 kcal/mole. The presence of strong intramolecular hydrogen bonds in the quercetin molecule was detected. Existence of these bonds can, in particular, explain quercetin's biological multifunctionality. The spatial structure of the most energetically favorable conformation has been found.

Introduction

Quercetin is a biologically active compound, which is contained in many plants, such as onion, garlic, carrot, whortleberries and others, also in red wine and green tea. It is widely used in medicine and pharmaceutics. In particular, it is used for prophylaxis and treatment of oncologic diseases, especially it restrains growth of leukemia. Earlier some of computational investigations of this molecule were reported in literature [1,2], but they were made at low theory level (AM1 [3]). That is why the further investigation of this molecule is important.

Nowadays quercetin is widely used in medicine in crystalline state. In Figure 1, the crystalline state of quercetin molecule is shown in two projections. It can be easily seen that in this state the molecule has twisted orientation of modified phenyl and hetero rings in molecule. The angle between modified phenyl and hetero rings is θ=47.8º. Note that hydroxyl groups do not lie in the same plane.

In spite of wide field of quercetin applications there is a question, in what way does it have so many functions? Nowadays this bioactive compound is used in a crystalline state (granules in pills) because its solubility in water is problematic.

The key to answer these questions may lie in conformational properties of this molecule. Indeed, taking 2 orientations for 5 hydroxyl groups along with 2 possible mutual orientations of hetero and modified phenyl rings one easily obtains an *a priori* estimate of possible conformation number of 64.

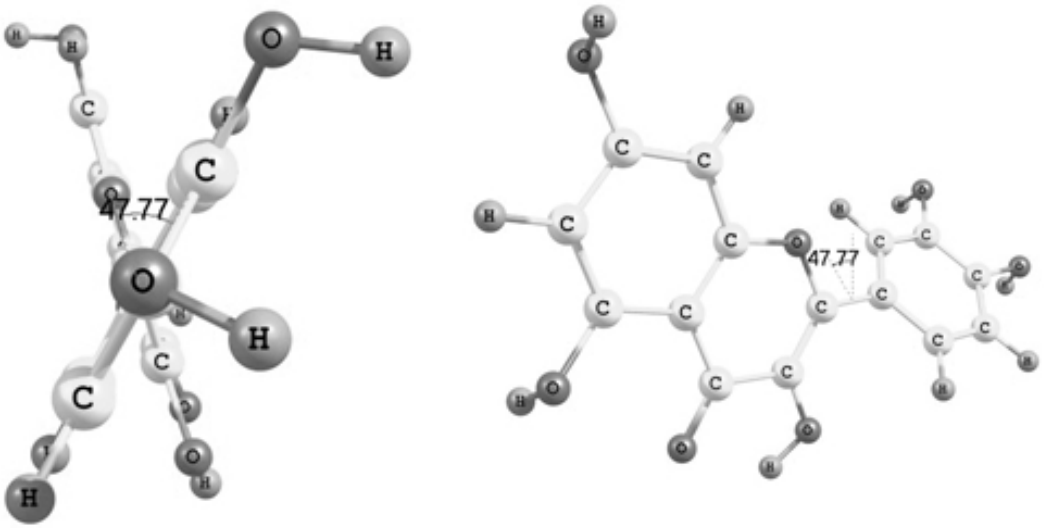

Figure 1. Quercetin molecule in crystalline state [4].

In the present work, we investigate conformational properties of the quercetin molecule in free state (in vacuum) by modern quantum chemistry methods. Such an investigation of quercetin would make it possible to estimate its structural factors of biological activity, in particular — the presence of strong intramolecular hydrogen bonds (H-bonds) in all conformers.

The mechanisms of conformers' interconversion were also of our interest.

Computational methods

The quercetin molecule conformations differ one another by mutual ring orientation (determined by torsion angle θ, defined as C_1–C_2–C_{10}–C_{11} – see Fig. 2) and hydroxyl groups rotations (described by torsions φ_1 = C_6–C_7–O_6–H_{10}, φ_2 = C_8–C_9–O_7–H_9, φ_3 = C_2–C_1–O_3–H_8 in hetero ring and φ_4 = C_{13}–C_{15}–O_5–H_6, φ_5 = C_{15}–C_{14}–O_4–H_7 in modified phenyl ring).

Round arrows in Figure 2 illustrate all possible ways of 'switching' from one conformation to another: by hydroxyl group rotation around single C–O bonds, and by modified phenyl and hetero ring rotation around single C_2–C_{10} bonds.

Initial geometries of the quercetin molecule were created by using standard interatomic distances and valence angles, and by setting each of torsion angles φ_1 – φ_5 and θ to 0° or 180°. These geometries were fully optimized without any structural restrictions using density functional theory (DFT) [5] calculation method implemented in Gaussian 03 [6] with the B3LYP [7] hybrid functional and the 6-31G(d,p) basis set.

We have found that after geometry optimization the values of φ_2 and φ_3 angles were the same and approximately equal 180° (as shown in Fig. 2) regardless of conformations of other parts of the molecule. Thus possible number of conformations was found to reduce from 64 to 16. That's why each conformation can be determined by only four angles (φ_1, φ_4, φ_5 and θ).

Moreover, it was established that only 12 of 16 remaining optimized structures are different. It should be kept in mind however that for each of these 12 conformers a mirror-symmetrical structure exists. But as far as mirror-symmetrical structures always have the same energy as well as other scalar physical properties, only one conformer from each pair was considered throughout this work.

For each of 12 possible conformations of quercetin molecule the oscillation spectra were calculated to ensure that their structures correspond to the potential energy minima and to calculate the thermal contributions to their Gibbs free energies (for the temperature T=298.15 K). In addition, their electron energies were calculated at the MP2/6-311++G(d,p) theory level.

To reveal intramolecular H-bonds in all conformers, the AIM method [8] implemented in the AIM 2000 software package was used. The H-bond energies were calculated by the method of Espinosa *et al.* [9].

To investigate the ways of quercetin molecule conformations interconversion suitable transition states were located by the quadratic synchronous transit (QST3) method [10].

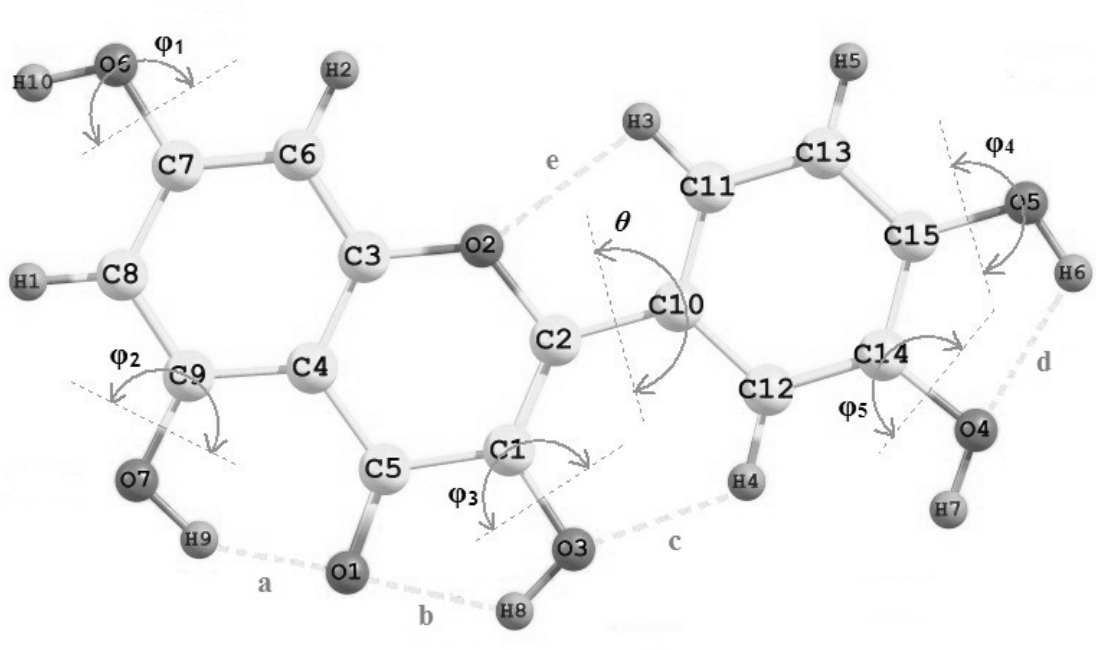

Figure 2. The quercetin molecule and its conformations layout view.

Results and Discussion

Table 1 outlines the values of torsion angles $\varphi_1 - \varphi_5$ and θ for all 12 stable conformations of quercetin molecule, their relative energies and dipole moments. The spatial structure of the energetically most favorable conformation **1** is depicted in Figure 2. This conformation is the most probable one for the molecule in free state (*e.g.* in gas phase). In contrast to all others conformations, it was found that conformer **1** has the lowest dipole moment.

The last column in the table describes properties of quercetin molecule in crystalline state and serves for comparison**.**

The transition states for each pair of quercetin's molecule conformers with the same values of $\varphi_1 - \varphi_5$ and different values of θ were also located. The transitions state was found using QST3 algorithm, while the initial transition state structure was obtained by rotating modified phenyl ring round single bond C_2–C_{10}. It was researched that all conformers that were studied have almost the same energy barrier heights. Figure 3 illustrates such a conformational interconversion process for conformers **1** and **2**.

Conformers **1** and **2** are shown in Fig. 3 as an equilibrium states. The conformation of the transition state (its relative electron energy is 4.1 kcal/mole) is shown between them.

Table 1. Energetic and structural data of all possible conformations of the quercetin molecule.

Conformer №		1*	2	3	4	5	6	7	8	9	10	11	12	**Quercetin's crystalline state**
Angle, deg.	φ_1	180	180	0	0	180	0	180	0	180	180	0	0	-90.3
	φ_2	180	180	180	180	180	180	180	180	180	180	180	180	98.4
	φ_3	180	180	180	180	180	180	180	180	180	180	180	180	-175.3
	φ_4	180	180	180	180	0	0	0	0	0	0	0	0	93.7
	φ_5	180	180	180	180	0	0	0	0	180	180	180	180	92.8
	θ	180	0	180	0	0	0	180	180	180	0	180	0	-42.2
Gibbs energy G, kcal/mole		0	0.37	0.30	0.85	0.54	0.68	0.90	1.32	4.68	4.94	5.10	5.33	22.18**
Dipole moment, Debye		0.3	4.1	2.8	5.6	2.6	5.2	4.7	6.9	2.7	1.4	4.5	3.6	1.8

* The spatial structure of energetically most favorable conformer **1** is shown in Fig. 2.

** The electron energy is given for crystalline state.

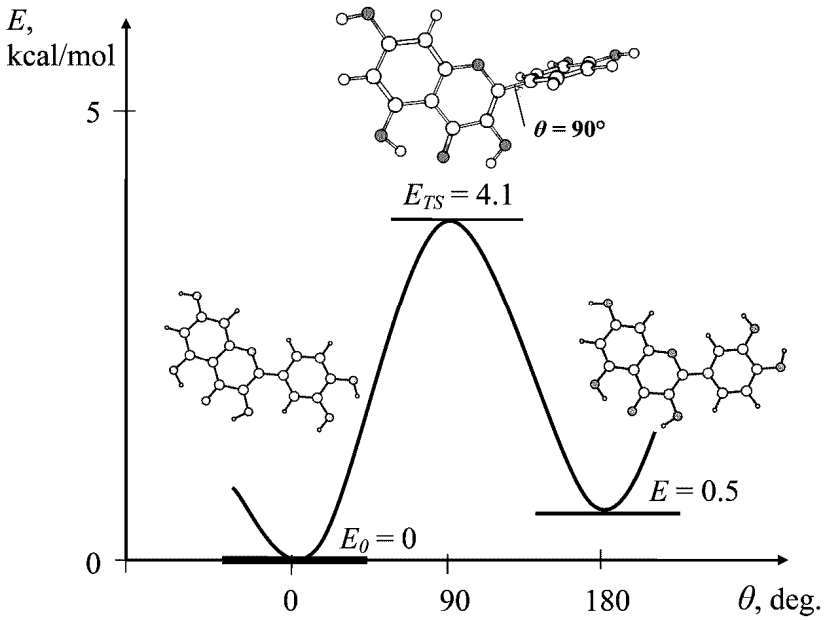

Figure 3. Transition state between different molecule conformations (conf. **1** to **2**).

Table 2. Physical and geometrical properties of O–H···O hydrogen bonds for first two conformations of the quercetin molecule.

H-bond in the conformer	Charge density ρ, a.u.	Laplacian of ρ, a.u.	H-bond's energy, kcal/mole	Distance O···O, Å	Angle O–H···O φ, °
Conformer #1					
a	0.04	0.12	10.47	2.6	149.0
b	0.03	0.09	7.61	2.6	120.7
c	0.02	0.07	4.66	2.9	101.7
d	0.02	0.08	5.17	2.7	114.3
Conformer #2					
a	0.04	0.12	10.57	2.6	149.0
b	0.03	0.09	7.48	2.6	120.3
c	0.02	0.06	4.37	2.9	101.6
d	0.02	0.08	5.15	2.7	114.3
e	0.02	0.07	3.92	2.7	98.0

As it shows in Fig. 3, modified phenyl and hetero rings are orthogonal to each other in the transition state (we call that an 'orthogonal transformation').

All possible intramolecular H-bonds for each of 12 conformers were also investigated. They are depicted by dotted lines (a, b, c, d, e) in Fig. 2. Properties of H-bonds of the same type (e.g., **a:** O_7-H_9···O_1) were detected to be similar to each other. Conformer **1** and **2** can be served as an example (Table 2). Table 2 contains H-bonds properties for first two conformers: the geometrical properties, charge density and its Laplacian in the bond critical points [8], and H-bonds energy.

We see that the H-bonds **a** and **b** are those of the highest energy. This fact can explain the 'behaviour' of hydroxyl groups O_7H_9 and O_3H_8, which always adopt the same orientation ('looking' to O_1) after molecule's geometry optimization irrespective of their initial orientation**s**.

Conclusion

The *ab initio* investigation has shown that the quercetin molecule can adopt any of 12 mirror symmetrical conformations, which, in contrast to crystalline conformation, do not have the «twisted orientation» of planar hetero and modified phenyl rings.

The most energetically favorable conformation was found, and all H-bonds in each conformation were investigated. Most of the conformers have the same number of H-bonds. The H-bonds of the same type differ in the energy just for 0.1-0.3 kcal/mole from conformation to conformation.

In different conformations, dipole moments differ drastically being an example of how significant can quercetin properties depend on the conformation. Probably, by this way the quercetin molecule**'s** multifunctionality can be explained.

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References

[1] Williamson G., Manach C., Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies, *Am. J. Clin. Nutr.*, 81, 243–255, 2005.
[2] Bogdan T.V., Trygubenko S.A., Hovorun D.M. and others, Conformational analyze of quercetin molecule, *Science notes NaUKMA*, 19, 465–460, 2001.
[3] Middleton E., Jr., Kandaswami C., Theoharides T.C., The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer, *Pharmacol. Rev*., 52(4), 673–751, 2000.
[4] Geometry was taken from Protein data bank: PDB Chemical Component QUE. http://ligand-expo.rcsb.org/reports/Q/QUE.
[5] Kohn W., Sham L.J., Self-consistent equations including exchange and correlation effects, *Phys. Rev*., 140(4), A1133–A1138, 1965.
[6] Frisch, M.J. Trucks, G.W., Schlegel H.B. et al., Gaussian 03, Revision C.02, Gaussian, Inc., Wallingford CT, 2004.
[7] Becke A.D., Density-functional thermochemistry. III. The role of exact exchange, *Chem. Phys.*, 98(7), 5648–5652, 1993.
[8] Bader, R.F.W., Atoms in molecules: a quantum theory, *Oxford University Press: Oxford, U.K.*, 1990.
[9] Espinosa E., Molins E., Lecomte C., Hydrogen bond strengths revealed by topological analyses of experimentally observed electron densities, *Chem. Phys.*, 285, 170–173, 1998.
[10] Foresman J.B., Frisch A., Exploring chemistry with electronic structure methods, 2 ed., *Gaussian Inc.*, 1996.