# CHIH-DFT determination of the molecular structure, infrared and ultraviolet spectra of the flavonoid quercetin

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## Abstract

The flavonoids are phenolic substances of low molecular weight, about which are known around 8000 individual compounds. They are abundant in vegetal tissues, apple being one of the most important (particularly its skin). These compounds are characterized to have a high antioxidant activity, which confers to them pharmacological properties useful for the treatment of several diseases. In this work, we make use of a new model chemistry within Density Functional Theory, which is called CHIH-DFT, to calculate the molecular structure of quercetin, as well to predict its infrared and ultraviolet spectra. The calculated values are compared with the experimental data available for this molecule as a mean of validation of our proposed chemistry model. The predicted results are in excellent agreement with the experimental ones.

## Introduction

Flavonoids are phenolic substances characterized for a low molecular weight and they are abundant in plant tissues, apple being one of the most important (particularly its skin) [1,2]. In the human body they show a lot of biological properties as antioxidants, antiallergenic, antibacterial, antifungal, antiviral and anticarcinogenic agents. These characteristics confers to them pharmacological properties useful for the treatment of diseases that go from allergies, bacterial and viral infectious



processes, to those of greater risk like the coronary diseases, cancer and HIV [3 – 5]. The mechanism by which flavonoids carry out their properties, mainly their antioxidant power, is either by inhibiting the formation or activity of reactive oxygen species, or by direct interaction with DNA, enzymes and membrane receptors. The flavonoid guercetin is characterized by showing the major number of properties, antioxidant being the most and one of the most abundant in fruit and plant tissues [1,4,6]. In apple skin, quercetin represent the third part of total flavonoids (100 mg/100 g apple skin) [3]. In reference to quercetin bioavailability, it is known that onion quercetin glycosides are absorbed up to 52% by the human plasma [3]. Quercetin molecule interacts with DNA through the hydrophobic segment on its structure (it is an intramolecular hydrogen bond). Glycosylated flavonoids, among which is quercetin (rutin), are denominated P vitamins due to their effect in the regulation of the capillarity permeability, showing hypertensive effects. Also they diminish the risk in diseases like the diabetes [7]. Taking into account the importance that flavonoids have due to their multiple properties, especially endogenous antioxidant power in the human organism, as well as the facility by which they can be acquired through the diet by consumption of fruits and vegetables, the study of flavonoids, specially quercetin, is considered a subject of great interest. The constant investigation that has prevailed during several decades on this subject has led to descriptive advances since it has not settled down the relation between structure and properties of these compounds. This is the reason by which their therapeutic application has been limited. The recent creation of methods of computational chemistry that allow to go farther in the knowledge of structures and



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properties, together with experimental studies, represents one of the best tools existing at the present time, in order to do important advances in this field. The objective of this work is to perform a detailed calculation of the molecular structure of quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one), as well as to predict its infrared (IR) and ultraviolet (UV– vis) spectra, by using a new model chemistry within Density Functional Theory (DFT) [8] specially tailored to study heterocyclic systems and to validate the calculated results by comparison with the experimental data available for this molecule.

All computational studies were performed with the GAUSSIAN 03W [9] series of programs with density functional methods as implemented in the computational package. The equilibrium geometries of the molecules were determined by means of the gradient technique. The force constants and vibrational frequencies were determined by the FREQ calculations on the stationary points obtained after the optimization to check if there were true minima. The basis sets used in this work were 3-21G<sup>\*</sup> and 6-31G(d,p) (for their explanation see Ref. [10]). Additionally, the CBSB2\*\*, CBSB7, CBSB4 and CBSB1 basis sets were used. The CBSB7 has the form 6-311G(2d,d,p) and has been developed by Petersson and co-workers as a part of the Complete Basis Set CBS-QB3 energy compound method [11]. It was designed for obtaining the best results for optimization of geometries and they found that this basis set was necessary for obtaining acceptable results on the full G2 test set [12]. The CBSB2<sup>\*\*</sup> basis set is essentially the same as 6-31G(d,p), but with the exponents for the d functions taken from the 6-311G basis set, and is also called 6- $31G^{++}$  [10,13,14]. The CBSB4 basis set is identical to 6-31+G(d,p) on H– Si and to 6-



31+G(df,p) on P, S and CI. The CBSB1 basis set is identical to 6-31+g(d,p) on H and He, to 6-311 G(2df) on Li– Ne, and to 6-311 g(3d2f) on Na– Ar. The CBSB2\*\*, CBSB4 and CBSB1 basis sets are also part of the CBS-QB3 method [11]. Density functionals used in this study are a modification of those incorporated in the GAUSSIAN 03W computational package [9]. To this end, we have defined a new model chemistry that we have found empirically that works well with heterocyclic molecules. The implementation is a slight different version of the PBE0 hybrid density functional [15]. In the PBE0 (or PBE1PBE one-parameter) functional, there is only one coefficient which is theoretically adjusted to 0.25, reflecting the mix of Hartree-Fock or exact exchange and the DFT exchange which is represented by the PBE density functional [16]. The correlation part is also represented by the PBE correlation functional [16] with coefficient equal to one. Our proposed density functional model, which we have called PBEg, is the same as PBE0, but with the mixing coefficient g which adopts different values depending on the number of heteroatoms in the studied molecule, or, in turn, of its molecular structure. The value of g can be calculated through the following empirical formula.  $q = 0.02 + 0.14 \times FHA \times FV + 0.03 \times AHA$ ; where FHA is the first heteroa-tom chosen as the one less electronegative, FV is valence factor which represents the oxidation state of the FHA (i.e. one for the first oxidation state, two for the second, and so on), and AHA are the number of additional heteroatoms besides the FHA. For example, for the 1,2,5-thiadiazole molecule, the g coefficient will be g=0.02+0.14+10.03x2 =0.22; thus implying that 22% of HF exchange will be mixed with 78% of PBE exchange. Similarly, for 1,2,5-thiadiazole 1,1-dioxide, the g coefficient will be



g=0.02+0.14+3 0.03x2=0.50; reflecting 50% of HF exchange and 50% of PBE exchange. For those cases in which the molecule has several heterocyclic rings, we will calculate the coefficient g by averaging the coefficient for each heterocycle. Thus, in our case for the molecule of quercetin, the value of the mixing coefficient g for the entire molecule will be g 0.16; implying the mix of 16% of HF exchange and 84% of PBE exchange.

In order to define our model chemistry, we have to couple the proposed density functional with one or more basis sets. In this way, the new model chemistry that we have called CHIH-DFT can be represented by the expression CHIH PBE*g*/basis sets. There are three different CHIH-DFT model chemistries. CHIH(small) that uses the 3-21G\* basis set for geometry optimizations and frequency calculations, and the CBSB2\*\* basis set for the calculation of the electronic properties; CHIH(medium) that uses the CBSB2\*\* basis set for geometry optimizations and frequency calculations and the CBSB2\*\* basis set for geometry optimizations and frequency calculations and the CBSB2\*\* basis set for geometry optimizations and frequency calculations and the CBSB4 basis set for the electronic properties; and CHIH(large) which uses the CBSB7 basis set for geometry optimizations and frequency calculations and the CBSB1 basis set for the electronic properties. In this way, by considering a compromise between accuracy and CPU time, the CHIH(large) will be used for small heterocyclic molecules, the CHIH(medium) for medium-sized molecules and the CHIH(small) for large heterocyclic molecules.

The calculation of the ultraviolet spectrum (UV– vis) of quercetin has been performed by solving the time dependent Kohn – Sham equations according to the method implemented in GAUSSIAN 03W [17 – 20]. The equations have been solved for 10 excited states. The IR and ultraviolet (UV–vis) spectra were calculated and



visualized using the SWizard program [21].

## **Results and discussion**

Table 1

The results for the equilibrium conformation of the neutral molecule of quercetin calculated with the CHIH (large), CHIH(medium) and CHIH(small) together with the PBE0 results with two different basis sets are reported in Table 1, and the representation of the molecular structure of this molecule showing the atomic labelling and numbering is presented in Fig. 1. The results are compared with the experimental X-ray crystallography determination of the molecular structure of quercetin [22–24]. The agreement is

Interatomic bond distances (Å) for the quercetin									
molecule Bond distance	PBE0/3-21G*	PBE0/CBSB2**	CHIH(s) <sup>a</sup>	CHIH(m) <sup>a</sup>	CHIH(I) <sup>a</sup>	Exp. <sup>t</sup>			
C(1)-C(6)	1.388	1.392	1.392	1.392	1.388	1.360			
C(5) - C(6)	1.399	1.406	1.403	1.406	1.403	1.400			
C(1) - C(2)	1.418	1.424	1.423	1.424	1.421	1.419			
C(1)-O(25)	1.347	1.335	1.351	1.335	1.334	1.364			
C(2)-C(3)	1.401	1.407	1.405	1.407	1.405	1.391			
C(2)-C(12)	1.416	1.429	1.417	1.429	1.428	1.421			
C(3)-O(9)	1.376	1.356	1.382	1.356	1.354	1.369			
C(3)-C(4)	1.382	1.391	1.385	1.391	1.388	1.389			
C(5)-O(23)	1.369	1.354	1.374	1.354	1.353	1.358			
C(4) - C(5)	1.397	1.399	1.402	1.399	1.395	1.386			
C(11)-C(12)	1.440	1.449	1.442	1.449	1.447	1.440			
C(12)-O(13)	1.285	1.262	1.293	1.262	1.259	1.268			
C(10)-C(11)	1.361	1.374	1.367	1.374	1.370	1.360			
O(9)-C(10)	1.390	1.371	1.396	1.371	1.370	1.368			
C(10)-C(14)	1.452	1.462	1.454	1.462	1.460	1.474			
C(11)-O(27)	1.370	1.350	1.374	1.350	1.349	1.355			
C(14)-C(15)	1.406	1.411	1.411	1.411	1.408	1.397			
C(14)-C(16)	1.403	1.408	1.408	1.408	1.405	1.393			
C(15)-C(17)	1.380	1.387	1.384	1.387	1.384	1.390			
C(17)-C(21)	1.392	1.394	1.410	1.409	1.405	1.386			
C(17)-O(29)	1.405	1.409	1.377	1.356	1.356	1.384			
C(19)-C(21)	1.373	1.356	1.388	1.392	1.388	1.373			
C(19)-H(22)	1.384	1.392	1.089	1.092	1.090	1.386			
C(21)-O(31)	1.386	1.367	1.391	1.367	1.367	1.385			
O(27)-H(28)	1.010	0.983	1.018	0.983	0.981	0.906			
O(25)-H(26)	1.035	0.995	1.046	0.995	0.993	0.948			
O(23)-H(24)	0.989	0.965	0.994	0.965	0.964	0.914			
O(29)-H(30)	0.995	0.968	1.000	0.968	0.967	0.990			
O(31)-H(32)	0.986	0.964	0.991	0.964	0.963	0.975			

<sup>a</sup> For an explanation of symbols, see

<sup>b</sup> text. Crystallographic results-Refs.

generally very good: the standard error of the differences between the



experimental and the calculated bond lengths and bond angles being very low. Although not shown in the tables, an analysis of the torsional angles reveals that the three rings are planar. The standard deviation for e comparison of the calculated versus the experimental results are 0.0048 for the CHIH(large) model, 0.0056 for the CHIH(medium) model, 0.0052 for the CHIH(small) model, 0.0056 for PBE0/CBSB2\*\* and 0.0315 for PBE0/3-21G\*, in all cases for the interatomic bond distances.



Fig. 1. Molecular structure of the quercetin molecule calculated with the CHIH(medium) model chemistry.

For the interatomic bond angles, the standard deviations are 0.071 for the CHIH(large) model, 0.062 for CHIH(medium), 0.156 for CHIH(small), 0.050 for PBE0/CBSB2\*\* and 0.153 for PBE0/3-21G\*. Three intermolecular hydrogen bonds are observed: two with the carbonyl group and the other between the hydroxyls groups in ring B. The distances are: 1.716 Å O(13) - H(26), 1.948 Å O(13) - H(28), and 2.113 Å O(31) - H(30). In order to choose our model, we have adopted the criteria of not using more than 750 basis functions in the calculation of the electronic properties. For a molecule like quercetin, this implies to use the CHI(medium) model chemistry. It should be noticed that although we have considered the CHIH(large) model in order to be able to do a comparison between models, the CHIH(medium)



which is faster, could also be used to study the molecular structures of

Thus, we have used the CHI(medium) model chemistry for the calculation of the electronic properties (Table 2).

The molecular dipole moment is perhaps the simplest experimental measure of charge density in a molecule. The accuracy of the overall distribution of electrons in a molecule is hard to quantify, since it involves all the multipoles. From the present calculations, the total energy and the total dipole moment of the ground state with the CHIH(medium) model chemistry are 21103.048 a.u. and

2.8522 Debye for quercetin, which implies that this molecule is a relatively polarized system and thus, probably soluble in polar solvents like water and methanol.

The shape of the total electron density for the quercetin molecule is presented in Fig. 2. The calculated molecular volume is 187.216 cm<sup>3</sup> mol<sup>-1</sup> This property is important



Table 2         Interatomic bond angles (degrees) for the quercetin molecule									
Bond angle	PBE0/3-21G*	PBE0/CBSB2**	CHIH(s) <sup>a</sup>	CHIH(m) <sup>a</sup>	CHIH(l) <sup>a</sup>	Exp. <sup>b</sup>			
C(1)-C(6)-C(5)	120.4	120.0	120.4	119.7	119.7	119.1			
C(2)-C(1)-C(6)	118.6	119.4	118.5	119.4	119.4	121.5			
C(6)-C(1)-O(25)	121.6	120.5	121.8	120.5	120.4	119.8			
C(2)-C(1)-O(25)	119.9	120.1	119.8	120.1	120.2	118.8			
C(1)-C(2)-C(12)	120.0	121.4	119.9	121.4	121.5	122.5			
C(3)-C(2)-C(12)	120.1	119.3	120.1	119.3	119.4	120.4			
C(2) - C(3) - O(9)	119.5	120.5	119.6	120.5	120.4	120.1			
C(2)-C(3)-C(4)	121.5	121.9	121.5	121.9	122.0	123.0			
C(3)-C(4)-C(5)	118.1	117.7	118.1	117.7	117.7	117.2			
C(4) - C(3) - O(9)	119.0	117.6	118.9	117.5	117.6	117.0			
C(6)-C(5)-O(23)	122.2	121.4	122.3	121.4	121.3	120.1			
C(4) - C(5) - C(6)	121.5	122.1	121.5	122.1	122.1	122.1			
C(4) - C(5) - O(23)	116.3	116.5	116.2	116.5	116.6	117.8			
C(2)-C(12)-C(11)	117.7	117.0	117.9	117.0	116.9	116.8			
C(2)-C(12)-O(13)	124.5	124.7	124.5	124.7	124.6	122.8			
C(11)-C(12)-O(13)	117.8	118.4	117.6	118.4	118.4	120.5			
O(9) - C(10) - C(11)	119.2	119.4	119.1	119.4	119.4	120.7			
C(11)-C(10)-C(14)	127.7	128.2	127.7	128.2	128.3	128.1			
O(9) - C(10) - C(14)	113.2	112.4	113.2	112.4	112.4	111.2			
C(10)-C(11)-C(12)	121.3	121.1	121.3	121.1	121.2	120.8			
C(12)-C(11)-O(27)	113.9	114.3	113.7	114.3	114.3	117.5			
C(10)-C(11)-O(27)	124.8	124.6	125.0	124.6	124.5	121.7			
C(3)-O(9)-C(10)	122.3	122.6	122.1	122.6	122.7	121.3			
C(10)-C(14)-C(16)	121.4	121.7	121.2	121.6	121.7	121.5			
C(15)-C(14)-C(16)	119.7	119.0	119.7	119.0	118.9	119.0			
C(14)-C(15)-C(17)	120.4	120.9	120.4	120.9	120.9	120.3			
C(14)-C(16)-C(19)	119.6	120.1	119.7	120.1	120.0	120.6			
C(15)-C(17)-C(21)	119.5	119.6	119.5	119.5	119.5	120.0			
C(21)-C(17)-O(29)	119.0	120.3	121.6	120.1	120.1	118.2			
C(16)-C(19)-C(21)	120.2	120.5	118.9	120.3	120.3	119.9			
C(17)-C(21)-C(19)	120.6	120.0	120.2	120.5	120.6	120.2			
C(19)-C(21)-O(31)	126.3	125.0	126.4	125.0	125.0	119.3			
C(11)-O(27)-H(28)	103.5	102.5	102.8	102.5	102.9	110.3			
C(1)-O(25)-H(26)	107.4	106.2	106.8	106.2	106.6	101.9			
C(5)-O(23)-H(24)	110.6	108.6	110.0	108.6	108.9	113.2			
C(17)-O(29)-H(30)	106.8	106.9	106.2	106.9	107.3	112.6			
C(21)-O(31)-H(32)	111.8	109.5	111.3	109.5	109.8	101.8			

<sup>a</sup> For an explanation of symbols, see text.
 <sup>b</sup> Crystallographic results—Refs. [22–24].





Fig. 2. Total electronic density of the quercetin molecule calculated with the CHIH(medium) model chemistry.

due to its relationship to applications like determining if a molecule will fit in the active site of an enzyme, or establishing the cavity size for solvation calculations [25]. The IR spectrum for the quercetin molecule calculated with the CHIH(medium) model chemistry is displayed in Fig. 3. The experimental IR spectrum, in the region between 600 and 1800 cm<sup>21</sup> has been reported in the literature [22].

The principal peaks, without any scaling, are as follows (the experimental results are shown in parenthesis):

- 273 cm<sup>-1</sup>: O(31)–H(32) out-of-plane bending
- 406 cm<sup>-1</sup>: O(23)–H(24) out-of-plane bending
- 643 (637) cm<sup>-1</sup>:C(11)–O(27)–H(28) out-of-plane bending
- 800 cm<sup>-1</sup>: C(4)–H(7) and C(6)–H(8) out-of-plane bending
- 1173 (1168) cm<sup>-1</sup>:C(5)–O(23)–H(24) in-plane bending





Fig. 3. Infrared spectrum (IR) of the quercetin molecule calculated with the CHIH(medium) model chemistry.

- 1238 (1238) cm<sup>-1</sup>: O(9) C(10) C(14) asymmetric stretching
- 1374 (1383) cm<sup>-1</sup>: C(14)–C(10) stretching and C(11)–
- O(27)-H(28) in-plane bending
- 1439 (1410) cm<sup>-1</sup>: C(3) C(2) O(9) asymmetric stretching
- 1552 (1562) cm<sup>-1</sup>: rings A and B deformation
- 1657 (1664) cm<sup>-1</sup>: C(12)–O(13) stretching
- 3252 cm21: C(16)-H(20) stretching
- 3530 cm21: C(27)-H(28) stretching
- 3843 cm21: C(31)–H(32) stretching

The ultraviolet spectra (UV– vis) of the quercetin molecule calculated with the CHIH(medium) model 21 chemistry is displayed in Fig. 4. The experimental UV– vis spectrum has been reported in the literature [22]. The shapes of both spectra,



calculated and experimental, are the same. The theoretical positions are in good agreement with the experimentally bands, even if these bands may be affected by solvent effects. The wavelength belonging to the HOMO– LUMO+1 transition will take place at 266 nm, while the HOMO– LUMO transition and thus the maximum wavelength will take place at 385 nm. As the HOMO– LUMO transition takes place in the ultraviolet region, close but out of the visible zone, it can be predicted that this molecule will be colorless.



Fig. 4. Ultraviolet spectrum (UV-vis) of the quercetin molecule calculated with the CHIH(medium) model chemistry.

# Conclusions

In this work, a new model chemistry within DFT (the CHIH chemistry model) has been presented and the methodology has been applied to the study of a molecule belonging to the antioxidant flavonoids family. The molecular structure for quercetin (2-(3,4-dihydroxyphe- nyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one) has



been determined by using the CHIH(medium) model chemistry. A comparison has been made with the results from the experimental X-ray crystallography for this molecule. The agreement is generally very good. It is worth to note that the results obtained with the (faster) CHIH(medium) model chemistry are very similar to those of the CHIH(large), thus implying that equally accurate results could be obtained in a reasonable time in the study of heterocycles.

The shape of the total electronic density of this molecule as well as some electronic parameters like the total energy and the dipole moment was displayed. The calculated molecular volume for the molecule has been also reported. The IR and ultraviolet (UV– vis) spectra for quercetin have been predicted according to the CHIH(medium) model chemistry, and an assignment of the principal peaks have been achieved. The results were compared to take note of similarities and differences. The shape of the UV– vis spectra and the maximum absorption wavelength belonging to this molecule have been presented.

The CHIH model chemistry appears to be a useful tool for the study of the molecular structure and electronic properties of heterocycles, and further applications to several molecular systems are being pursued in our laboratory.

### Acknowledgements

This work has been supported by Consejo Nacional de Ciencia y Tecnolog´ıa (CONACYT, Mexico) under Grant. No. 34697-U/2000. D.G.M. is a researcher of CONACYT and CIMAV. A.M.M.W. gratefully acknowledges a fellow- ship from CONACYT.

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