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USE DENSITY FUNCTIONAL THEORY TO STUDY THE PHYSICAL PROPERTIES OF HYDROXYCHLOROQUINE

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Abstract

The purpose of this study was to obtain a suitable theoretical study for calculating electronic properties and the reaction of the molecule of Hydroxychloroquine. This study was made by Density Functional Theories (DFT) at the B3LYP level with 6-31G (d,p) basis set. To find the band gap energy, geometrical structures, electrostatic potential, HOMO, LUMO, tetrahedral angle and dihedral angle, reduced mass, and force constant. The result show atomic charge distribution of nitrogen, oxygen hydrogen, chlorine and carbon are calculated for Hydroxychloroquine. The tetrahedral angle and dihedral angle very close to the experimental value of electrostatic potential - regions rich in electrons, in the case of oxygen molecule are more electronegative is composed of nitrogen atoms, as the cooler tones (tending to blue) representing electron deficiency were especially marked in nitrogen, establishing this area as more electropositive. Reduced mass is (6 amu) atomic mass unit that the reduced mass is nearly between oxygen atoms and nitrogen. Mulliken charge Allocated more negative charges on selected atoms in all structures HCQ, especially oxygen and nitrogen atoms. Force constant of hydroxychloroquine reach (9.8mDyne/Å).

Keywords: Dihedral angle and DFT, HOMO, Hydroxychloroquine, LUMO, Tetrahedral angle.

1. Introduction

The relationship between chemistry and physics is one of the most discussed topics in the foundations and the philosophy of chemistry [1]. It is true that quantum chemistry is an "in-between" discipline resulting from the creative synthesis of the various traditions of chemistry, physics, and mathematics. It is also true that quantum chemists adopt a pragmatic perspective directed to solve particular problems with very different conceptual and experimental tools [2].

The use of molecular surfaces, either based on the molecular electron density or on simple geometric criteria, onto which local properties such as the molecular electrostatic potential (MEP) have been projected has a long tradition in the qualitative interpretation of chemical reactivity. The molecular electrostatic potential gives a powerful description of molecular properties, such as strong non-covalent interactions, that are predominantly electrostatic in nature [3].

In this work, the physical properties of Hydroxychloroquine are studied. Hydroxychloroquine HCQ is an arthritis medicine that also can be used to prevent malaria. Hydroxychloroquine with chemical formula (C18H26ClN3O), it is sold under the brand name Plaquenil, and it is also sold as a generic medicine [4]. And so does chloroquine CQ, that one was synthesized in 1934 by Hans Andersag at Bayer, as it became a major antimalarial drug after World War. It was considered a major advance in that it had strong antimalarial activity.

Hydroxychloroquine HCQ came along in the 1950s, and just has an extra OH group coming off of one of those N-ethyl's over at the end of the chain; it is quite similar. Omera et al. [5] studied the electronic properties of and hydroxychloroquine HCQ by use DFT and other theories like HartreeFock (H-F) But DFT is more accurate and can be used several basis sets. To find the band gap energy and determine a suitable basis set.

DFT was performed in order to predict the structural, chemical descriptors and optoelectronic properties of the drugs Hydroxychloroquine and Azithromycin It is observed from our studies that most of the descriptors presented show association with some processes, including absorption, blood-brain barrier transport, binding and even toxicity. Hence, the treatment of COVID-19 using Hydroxychloroquine and Azithromycin in some patients as single dose [6].

Hernandes et al. [7] used density functional theory (DFT) calculations of 1H NMR chemical shifts for several plausible molecular conformers and then find the best match with experimental NMR profile in solution for Chloroquine and hydroxychloroquine.

Hydroxychloroquine is used to prevent or treat malaria caused by mosquito bites. This medication is also used to treat certain auto-immune diseases (lupus, rheumatoid arthritis). It belongs to a class of medications known as disease-modifying antirheumatic. Numerous clinical tests in China have exposed chloroquine phosphate, an aminoquinoline used in malaria treatment, to be efficient against COVID-19. In addition, hydroxychloroquine was less toxic and more soluble than chloroquine [8].

Both chloroquine and hydroxychloroquine increase the pH and award antiviral effects. Besides, hydroxychloroquine is favoured over chloroquine due to its lower ocular toxicity. However, it has also been reported that the combination of HCQ

and azithromycin in 11 patients with severe COVID-19 has not achieved a positive clinical effect.

There is still a lack of randomized controlled trials of HCQ in the treatment of COVID-19 patients [9].The FDA had approved an Emergency Use Authorization (EUA) on March 28, 2020, to allow distribution of hydroxychloroquine to treat adults and adolescents and who are hospitalized with COVID-19, but who are unable to participate in a clinical study. However, FDA cancelled this on June 15, 2020, because clinical studies showed that hydroxychloroquine is unlikely to be effective for treatment of COVID-19 in these patients and some serious side effects, such as irregular heartbeat, Headache, dizziness, loss of appetite, nausea, diarrhea, stomach pain, vomiting and rash were reported [10].

2. Theory

The Gaussian program package is the gold standard quantum chemistry package available since the 70's. Models of a chemical system generally consist of the combination of a theoretical method such as DFT and B3LYP with a basis set. Each such unique pairing of method with basis set represents a different approximation to the Schrödinger equation. The full optimization of Hydroxychloroquine was carried out by Density Functional Theories (DFT) methods, using Gaussian 09 software auxiliary by Gaussian view 6.0, deMon (density of Montréal) is a software package for density functional theory (DFT) calculations. It uses the linear combination of Gaussian-type orbital approach for the self-consistent solution of the Kohn-Sham (KS) DFT equations.

The calculation of the four-center electron repulsion integrals is avoided by introducing an auxiliary function basis for the variational fitting of the Coulomb potential [11]. At the B3LYP level with 6-31G (d,p) basis set. Vibration frequencies were also calculated to the structure with optimized geometry and no imaginary frequency was obtained. Figure 1 shows the geometrically optimized of structure hydroxychloroquine. Currently this functional correlation exchange is the most used in DFT theory. The reactivity of the Hydroxychloroquine predicted by using the differences between the HOMO and LUMO orbitals via DFT approach. The mapped molecular electrostatic potentials (MEPs) are determined at the B3LYP/6-31G (d, p) optimized geometry.

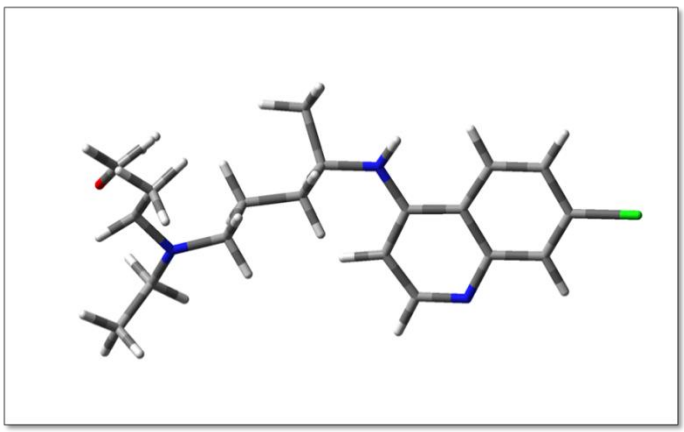

Fig. 1. shows the geometrically optimized of structure Hydroxychloroquine.

3. Results and Discussion

Electronic parameters are one of the main factors that govern the drug-receptor interaction, in this sense; the molecular electrostatic potential map (MEP) may be an alternative approach in order to understand the electrostatic contribution of these derivatives for the activity. The MEP is one of the descriptors used in most studies and intends to disclose the total molecular size [12]. Electrostatic potentials in the molecule are shown in Fig. 2, representing the positive potential of blueness and the region in the negative potential of the molecule, represented by the red colour Interactions between bio-molecules and drugs mainly include Hydrogen and halogen bonds dominated by electrostatic interactions. Molecular electrostatic potential (MEP) is the real spatial function most closely related to electrostatic effects, which is very suitable for dominance analysis electrostatic.

Analysis allows us to determine the most reactive electrophilic and nucleophilic regions of the molecule against the reactive biologic potentials. Indicate negative values of electrostatic potential - regions rich in electrons, in the case of oxygen molecule are more electronegative is composed of nitrogen atoms, as the cooler tones (tending to blue) representing electron deficiency were especially marked in nitrogen, establishing this area as more electropositive [13].

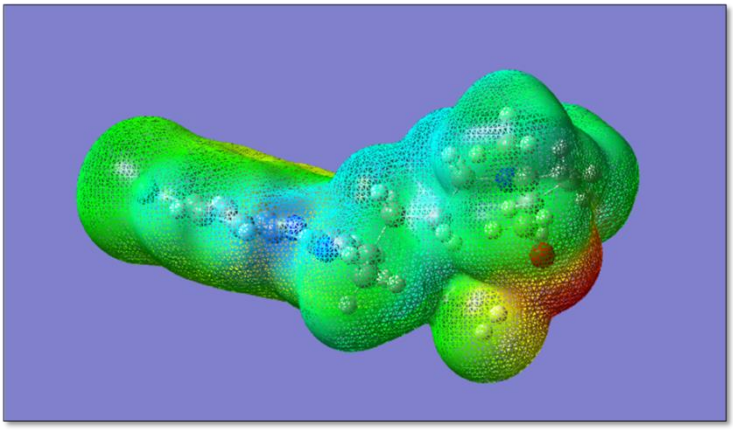

Fig. 2. Shows the electrostatic potential of Hydroxychloroquine.

Table 1 shows the population analysis Mulliken is based on the molecular orbital theory, are determined by the method Density Functional Theories (DFT). Allocated more negative charges on selected atoms in all structures HCQ, especially oxygen and nitrogen atoms. These values of atomic charge distribution on the oxygen of HCQ indicate that the structural component has possible sites for interaction with poor electronic molecules. While nitrogen atoms with more electrophilic species are more active and can role as radicals. Charge distribution illustrated quantitatively identifies chemical reactivity, structural regularities and intermolecular interactions [14].

In classical mechanics and quantum problems involving several particles, it is convenient to separate the motion of the centre of mass from the relative motion of the particles. This allows the separation of the motion of the group of particles as a whole (the centre of mass motion) from internal motions that can involve mutual

potential energies between the particles. Reduced mass is shown in Fig. 3. The reduced mass can be calculated from the follow equation:

$$\mu = \frac{M_1 * M_2}{M_1 + M_2} \quad (1)$$

Mass reduction reaches to (6 amu) atomic mass unit that the reduced mass is nearly between oxygen atoms and nitrogen. Electrons come out from oxygen faster than nitrogen and π bond between carbons [15].

Table 1. The analysis of population Mulliken.

Carbon (C)		Nitrogen (N)		Hydrogen (H)		Oxygen (O)		Chlorine (Cl)	
C1	**-0.013027**	**N7**	**0.000523**	**H2**	**0.001797**	**O47**	**0.575339**	**Cl 31**	**-0.000001**
C4	0.013391	N30	0.000149	H3	0.005250				
C9	-0.00012	N35	0.206937	H5	-0.000521				
C10	0.000084			H6	-0.000082				
C11	0.000217			H8	-0.000019				
C12	-0.000042			H15	-0.000008				
C13	-0.000045			H17	0.000003				
C14	-0.000081			H19	0.000003				
C16	0.000053			H21	-0.000002				
C18	0.000043			H22	-0.000002				
C20	-0.000034			H24	-0.000061				
C23	0.001922			H25	-0.000033				
C26	0.000044			H27	0.000023				
C32	0.000421			H27	0.000009				
C36	0.012457			H29	-0.000016				
C40	0.019562			H33	-0.000010				
C43	0.012167			H34	0.000299				
C49	-0.023414			H37	0.000639				
C52	0.119178			H38	-0.001297				
				H39	0.008353				
				H41	-0.004037				
				H42	-0.000114				
				H44	-0.000717				
				H45	-0.000568				
				H46	0.002132				
				H48	-0.001287				
				H50	0.013640				

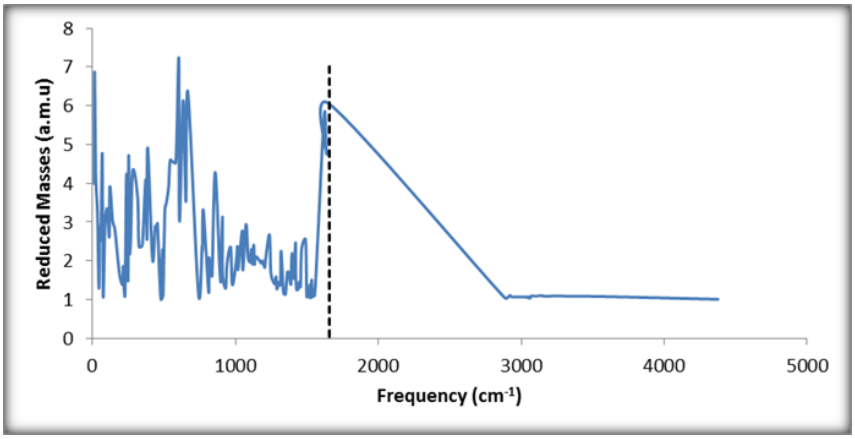

Fig. 3. shows the results of calculating the reduced mass of Hydroxychloroquine.

The value of force constant obtained by DFT is then used as an input for new calculations of hydroxychloroquine using a structural finite element method. It is shown that the DFT-computed bond force constants can be used as an input for less computationally demanding calculations of the elastic properties of hydroxychloroquine based on finite element or molecular mechanics structural approaches, with reasonable accuracy [16]. Figure 4 can be seen force constant of hydroxychloroquine reach (9.8 mDyne/Å).

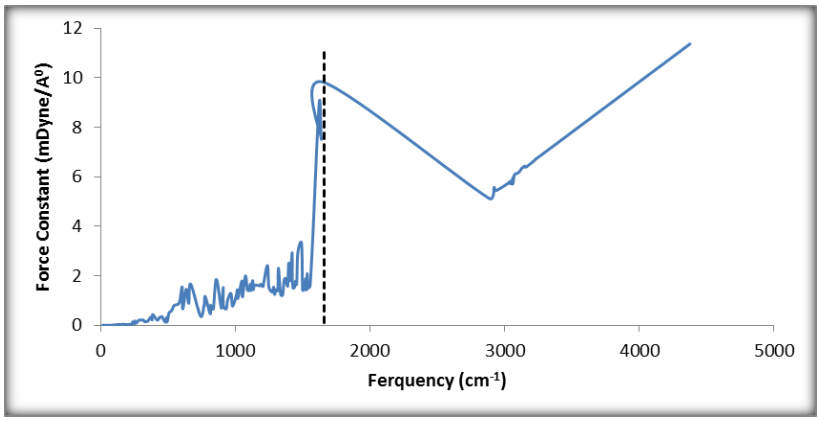

Fig. 4. display the results of calculating the force constant of Hydroxychloroquine.

The single most characteristic property of a chemical bond is its length, the shorter a particular bond, the greater its strength (Pauling 1940). Form Fig. 5, the shortest bond is between two hydrogen atoms and is equal to (0.74Å) and is very close to the experimental value. The highest peak of the bond is between carbon and hydrogen atoms (1.09Å) and is equal to the experimental value. The longest bond between two nitrogen and oxygen atoms (2.3Å), while the experimental value is (2.01Å). It has been very successful in the solution of many problems of organic chemistry [17].

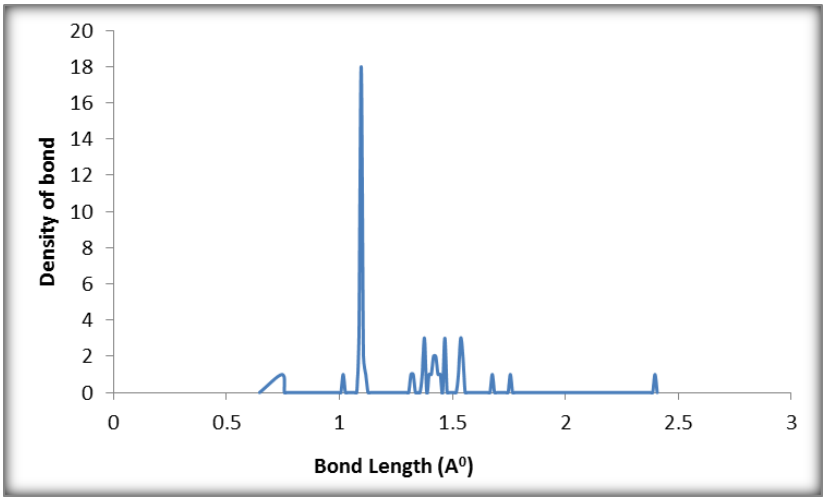

Fig. 5. shows the results of calculating the bond length of hydroxychloroquine.

Figure 6 shows the distribution of the values of hydroxychloroquine tetrahedral angles. The ideal bulk zincblende value of this angle at 109.47° is shown. The distribution shows a narrow range around this angle (109.47°± 2°), with the highest peak shifted one or two degrees from this value [18].

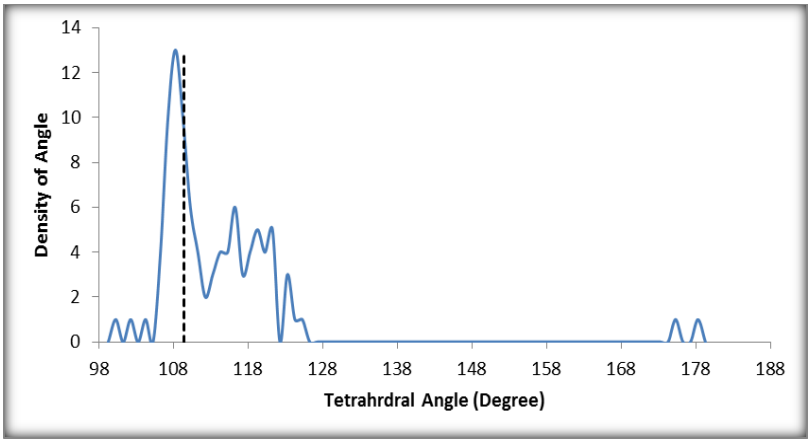

Fig. 6. Tetrahedral angles of hydroxychloroquine.

Energy gap since they are used to provide information on the transfer of charges. Lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) are very important parameters for quantum chemistry. These orbitals allow determining the manner the molecule interacts with other species. Figure 7 shows the density of energy states of geometrically optimized hydroxychloroquine. The values of the energy gap (2.648eV).The lowering of the HOMO-LUMO band gap is essentially a consequence of the large stabilization of the LUMO due to the strong electron-acceptor ability of the electron-acceptor group. The higher the energy of HOMO, the easier it is for HOMO to donate electrons whereas it is easier for LUMO to accept electrons when the energy of LUMO is low [19].

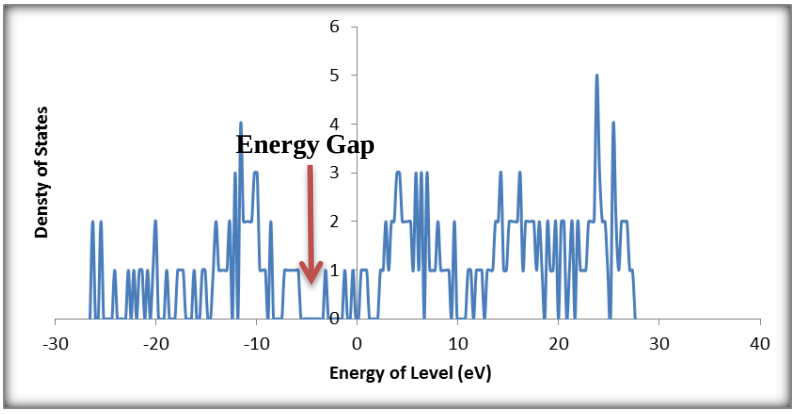

Fig. 7. Energy gap of hydroxychloroquine.

Dihedral angles between common neighbours around a given couple of bounded spheres. Shown that the most frequent configurations are the arrangements

with four and five common neighbours. For any real system where the dihedral angle ϕ is smaller than 180 [20]. Dihedral angle contribution in Fig. 8 for the dihedral angle. The ideal bulk zincblende values of these angles are ±60 and ±180 [21]. The dashed line represents the experimental value. The dihedral angle between (N-C-C-C) is (179), (C-C-C-H) is (179), (H-C-C-H) is (59) and (H-C-CH) is (59) very close to the experimental value.

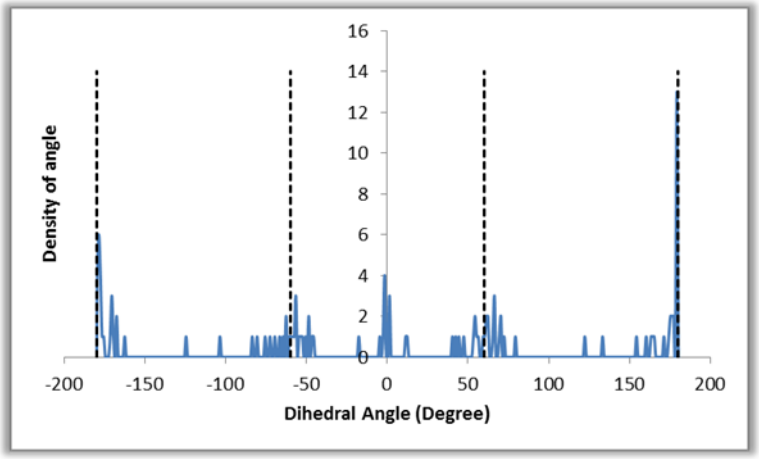

Fig. 8. shows the dihedral angle of Hydroxychloroquine.

4. Conclusion

The ground state molecular geometries of hydroxychloroquine theoretically studied by using and DFT method and B3LYP with 6-31G (d,p) basis set. The study shows that the Indicate negative values of electrostatic potential - regions rich in electrons, in the case of oxygen molecule are more electronegative is composed of nitrogen atoms, as the cooler tones (tending to blue) representing electron deficiency were especially marked in nitrogen, establishing this area as more electropositive.

Reduced mass is (6 amu) atomic mass unit that the reduced mass is nearly between oxygen atoms and nitrogen. Mulliken charge Allocated more negative charges on selected atoms in all structures HCQ, especially oxygen and nitrogen atoms. Force constant of hydroxychloroquine reach (9.8mDyne/Å).

Bond length of hydroxychloroquine the shortest bond is between two hydrogen atoms and is equal to (0.74 Å). The highest peak of the bond is between carbon and hydrogen atoms (1.09 Å). The longest bond between two nitrogen and oxygen atoms (2.3 Å).

The results have shown that distribution of the values of hydroxychloroquine tetrahedral angles. The distribution shows a narrow range around this angle (109.47º± 2º), with the highest peak shifted one or two degrees from this value. The values of the energy gap (2.648eV). The lowering of the HOMO-LUMO band gap is essentially a consequence of the large stabilization of the LUMO due to the strong electron-acceptor ability of the electron-acceptor group.

The dashed line represents the experimental value. The dihedral angle between (N-C-C-C) is (179), (C-C-C-H) is (179), (H-C-C-H) is (59) and (H-C-CH) is (59) very close to the experimental value.

Acknowledgment

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Nomenclatures

*AM*1	Austin Model 1
amu	Atomic mass units
M/Å	Meter / Angstrom
$M_{1,2}$	Mass

Greek Symbols

μ	Reduced mass.
Φ	Dihedral angle

Abbreviations

B3LYP	Becke's three parameter hybrid functional using the correlation functional of Lee, Yang, and Parr
CQ	Chloroquine
d,p	Polarization functions
DFT	Density Functional Theories
HCQ	Hydroxychloroquine
H-F	Hartree - Fock
K-S	Kohn-Sham
MEP	Molecular Electrostatic Potential
NDDO	Neglect of Differential Diatomic Overlap

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