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Theoretical analysis of the reactivity of chloroquine and hydroxychloroquine

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Chloroquine (CQ) and Hydroxychloroquine (HCQ) have a low safety margin and its toxic effects are closely related to the ingested dose. Both drugs were tested for reactivity under different conditions but still need to be understood. A thermodynamic and kinetic study with control the electronic properties also show the reaction of the molecule. In this study, theoretical calculations have been performed using Density Functional Theory (DFT) and Hartree-Fock (HF) to find the band gap energy and determine a suitable basis set. A computation based on B3LYP level was accomplished to obtain the geometrical structures for both CQ and HCQ molecules. Based on the B3LYP/6-31G(d,p) basis set, DFT measurements of frontier molecular orbitals and molecular electrostatic potentials have been implemented for both CQ and HCQ. The atomic charge distribution of nitrogen and oxygen is calculated for CQ and HCQ using DFT and HF on a basis set 6-31G**. *Ab initio* DFT with HF at 6-31G** basis set is performed for thermodynamic analysis for both CQ and HCQ structures.

Keywords: Chloroquine, Density Functional Theory (DFT), ESP, MOMO-LUMO, Hydroxychloroquine, Hartree-Fock (HF)

Chloroquine (CQ) is an amine-acidic form of quinine[1,2] and was synthesized by Bayer in Germany in 1934. Hydroxy-chloroquine (HCQ) belongs to the molecular family of chloroquine and the 4-aminoquinoline drugs. The basic structure of both CQ and HCQ is shown in Fig. 1. HCQ is produced from chloroquine by the adding a hydroxyl group to the end of the chain. HCQ has identical chloroquine-like pharmaco-kinetics, with fast gastrointestinal absorption and renal removal. Nevertheless, both drugs slightly different in clinical conditions and toxic levels[3]. CQ is still used as malaria treatment and prevention. HCQ is less toxic and more dissolve compared with chloroquine metabolite which results in fewer adverse effects and is safer[4-6]. Recently, disorders such as systemic lupus erythematosus and rheumatoid arthritis have been treated using CQ/HCQ. CQ and HCQ have been used for the treatment of HIV with different results[7]. It is explored with encouraging results that the CQ / HCQ are able to inhibit certain corona viruses, such as SARS-CoV-1[8,9]. Both CQ and HCQ are inexpensive and readily available in all around the world for medicines, moreover, their safety profiles are well known for decades of experience administering. The mixture of CQ and HCQ has been great advantages for the treatment of COVID-19, the result takes many months to found novel treatment[10]. CQ and HCQ have been used in clinical practice with an established safety profile for many years[3]. HCQ has been reported to cause gastrointestinal upset[11]. Additionally, CQ and HCQ have long been used for treatment retinal toxicity, which is related to the dose of the drug[12-14]. It was reported that CQ can be used for treatment isolated cardiomyopathy[15] and heart rhythm disturbance[16]. People who have problem with their liver and the kidney should be careful with CQ and

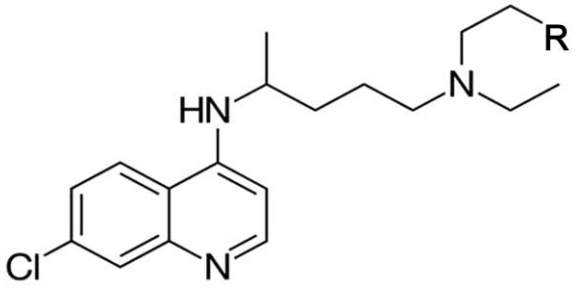

Fig. 1 — Basic structure of Chloroquine (R = H) / Hydroxychoroquine (R = OH)

HCQ as drug treatment.[17,18], additionally, using CQ/HCQ as treatment for confirmed cases of COVID-19 may increase the risk of toxicity[17].

The Gaussian package is a very good way for measuring electronics structure. Over the last few years, one of the theoretical modeling widely used is density functional theory (DFT), which showed better performance for molecular simulation and exchange-correlation. Many molecular properties are now calculated using DFT[19]. In reviewing the previous literature survey for DFT, it is found that the model is more accurate for theoretical analysis[20-24]. This research aims to explore the energetic and structural properties of the CQ and HCQ to find the structure reactivity.

Materials and Methods

The geometrical structure of CQ and HCQ was optimized by both DFT and Hartree-Fock (HF) theory, with different basis sets, using Gaussian software 09. First, six different basis set for each method (DFT & HF) was conformed to obtained the energy band gaps. The second-lowest energy level was used to optimize for further studies. The vibrational frequency for both drugs was calculated to confirm the optimized structure. Finally, Frontier molecular orbital, which is described as Highest Occupied Molecular Orbital (HOMO) – Lowest Unoccupied Molecular Orbital (LUMO) energy, molecular electrostatic potential (ESP), thermodynamic properties and atomic charge density were calculated by both DFT and HF.

Results and Discussion

Energy band gaps

Firstly, the optimized structures of the molecules were calculated using Gaussian 09. The energy band gaps were associated with different basis sets which were listed in Table 1. The energy band gaps for the HF approach have higher values compared to the DFT, as illustrated in Table 1. All basis sets for both methods are very close to each other. 6-31G** basis set has been chosen for further studying because it has lower energy levels and contains more parameters[25].

Geometrical structures

Fig. 2 shows the most stable structure for both drugs which was optimized by DFT with a basis set 6-31G**,which determined the dipole moment and orientation of the molecules. The geometry of both molecules clearly forms a different globular structure which effectively exposes all reactive sites to other reactive molecules. The structure conformation of CQ and HCQ helps a better understanding about the reactivity of a molecule. However, it is capable of interacting with conformational limited sites of larger molecules such as enzymes.

Frontier molecular orbitals

Frontier molecular orbital theory describes the interactions between HOMO-LUMO. The simplest one includes the gap between HOMO and LUMO of a neutral system. It is important for the determination of molecular characteristics[26]. Lack of HOMO – LUMO has far-reaching implications for organic reactivity[27]. A large HOMO – LUMO gap alludes to high stability in complexes for the molecules in the sense of their lower transfer of charge. Another characteristic attribute connected to the distance between HOMO- LUMO is polarizability, soft molecules with small energy gaps are becoming more polarizable than hard molecules. Fig. 3 shows the energy levels distributions of the HOMO-1, HOMO, LUMO, and LUMO+1 orbitals computed by B3LYP/6-31G(d,p) for both CQ and HQC. As can be seen that a higher energy band gap appeared between HOMO-1 and LUMO+1 which is equal to -0.20724 eV for HQC compared with CQ which is equal to -0.16112 eV. Also, the energy level between HOMO and LUMO for HCQ is greater than CQ. Those results approve that the HCQ is more stable and less reactive than CQ.

Table 1 — Energy band gaps for both HF and DFT at different basis sets

Basis sets	Chloroquine		Hydroxychloroquine	
	HF method	DFT method	HF method	DFT method
	Energy band gaps (eV)	Energy band gaps (eV)	Energy band gaps (eV)	Energy band gaps (eV)
3-21G	10.468	4.329	10.443	4.440
6-31G	10.367	4.247	10.354	4.427
6-31G*	9.638	4.174	9.611	4.352
6-31G**	8.982	4.171	8.952	4.351
6-311G	10.291	4.223	10.280	4.356
6-311G*	9.553	4.182	9.570	4.397

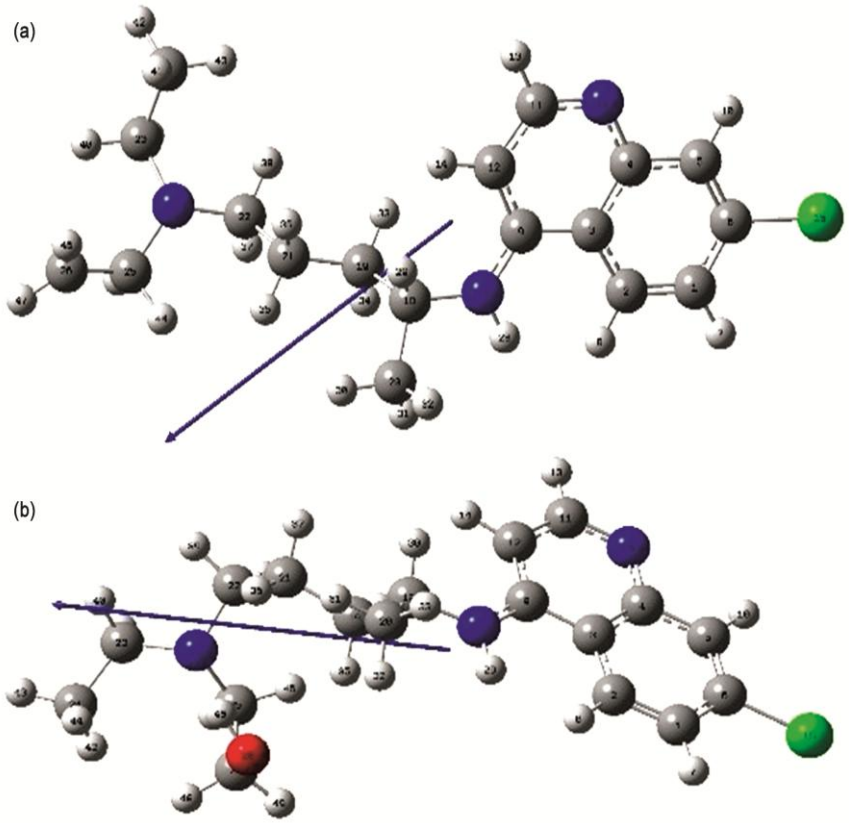

Fig. 2 — Optimized structures of (a) Chloroquine and (b) Hydroxychloroquine (The optimization was performed by DFT at B3LYP/6-31G(d,p) level and vector orientations are shown for each structure)

Ionization potential expressed as $I = -E_{HOMO}$ is the minimum amount of energy required to extract an electron from an atom or molecules in the gaseous states. For a molecule, ionization energy can be calculated using HOMO and LUMO energy values. Electron affinity, $A = -E_{LUMO}$, is the amount of energy released when an electron captured by a molecule in the gaseous state. The electronic chemical potential $\mu = (E_{HOMO} + E_{LUMO})/2$ shows the tendency of the molecule for electron acceptor or donor. Chemical hardness, $n = I\text{-}A/2$, is the measurement of the prevention of the weight transfers in a molecule. The molecule with higher values of chemical hardness has little or no Passing weight[28,29]. Chemical softness is inversely related to chemical hardness, $S = 1/2n$. The parameter values of the electronic structure determined using the B3LYP method 6-31G** are listed in Table 2. Table 2 shows that the HCQ has more hardness than CQ, i.e., the CQ has more softness and polarizable which acts as a strong electronic acceptor due to the large μ compared with HCQ.

Molecular electrostatic potential

Molecular electrostatic potential (ESP) forms around molecules in a space at point r (in atomic units) and mathematically can be expressed as follows:

$$V_{(r)} = \sum_{A} \frac{Z_A}{\lceil R_A - r \rceil} - \int \frac{\rho_{(r)} d\acute{r}}{\lceil \acute{r} - r \rceil}$$

where Z_A is a nucleus charge located at R_A, and p(r) is electronic density. The first and second terms represent the nuclei and electrons' effect, respectively. The two terms are opposite and consequently they have opposite signs. The potential (V) is a function of distance (r) and the total charge distribution (electrons + nuclei) of the molecule indicates the net electrostatic effect at r. Partial charges, dipolar moment, electronegativity, and the position of the molecule's chemical reactivity are all associated with the electrostatic potential. It offers a visual way of understanding the relative polarity of a molecule. Regions with low electron density is represented by blue colour which shows that the nuclear charge is

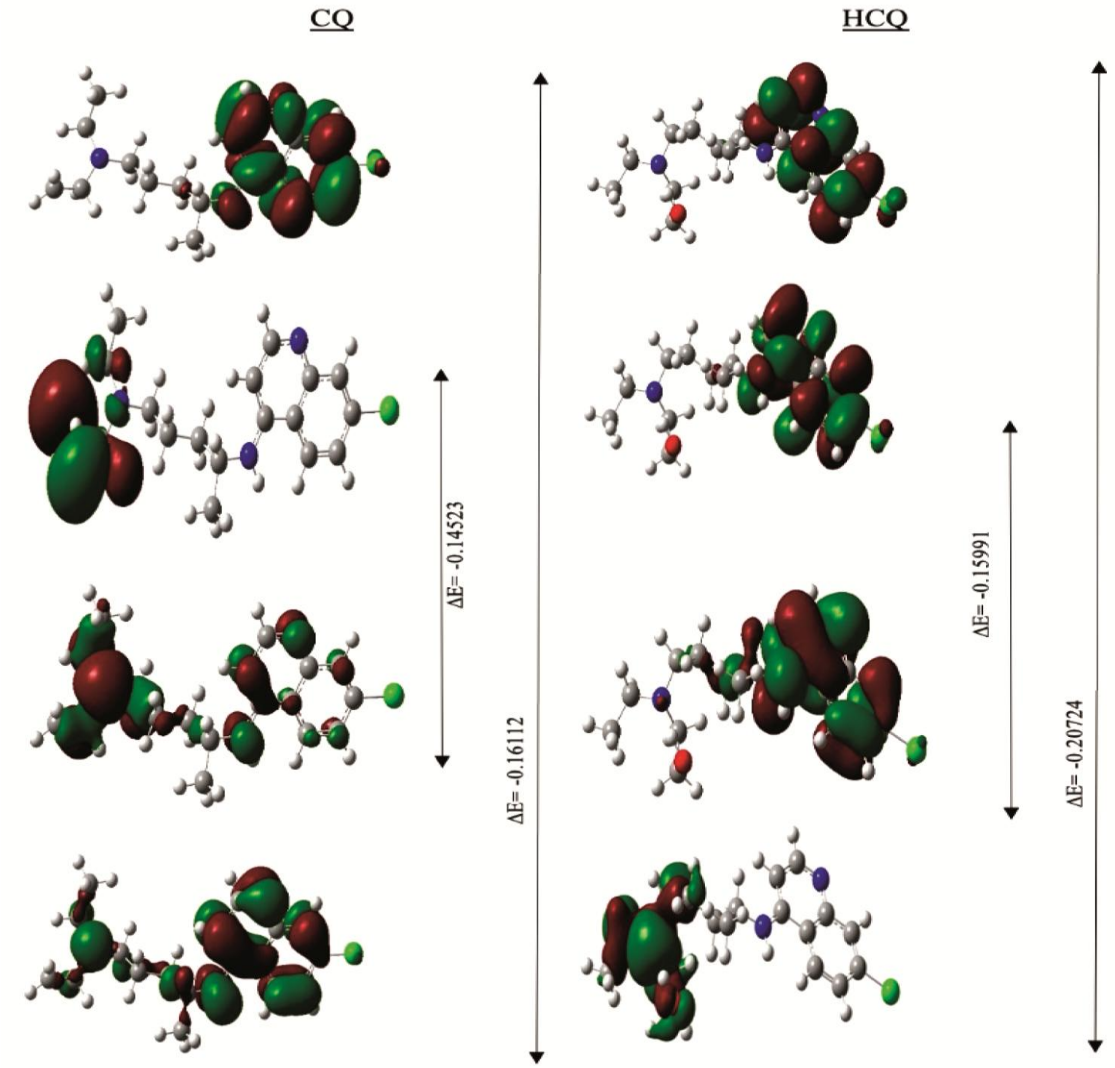

Fig. 3 — Molecular orbital energy levels for the HOMO, HOMO -1, LUMO, and LUMO + 1 of the QC & HQC computed at B3LYP/ 6-31G(d,p) level

Table 2 — Electronic parameters for both CQ and HCQ

In a Basis Set B3LYP/ 6-31**G	Equations	Result of Chloroquine	Result of Hydroxychloroquine
E_{HOMO} (eV)	-	-0.21546	-0.21615
E_{LUMO}(eV)	-	-0.07023	-0.05624
E_{HOMO-1} (eV)	-	-0.21951	-0.23552
E_{LUMO+1} (eV)	-	-0.05839	-0.02828
$\Delta E = E_{HOMO} - E_{LUMO}$(eV)	HOMO - LUMO	-0.14523	-0.15991
I (eV)	$I = -E_{HOMO}$	0.21546	0.21615
A (eV)	$A = -E_{LUMO}$	0.07023	0.05624
μ(eV)	$\mu = E_{HOMO+} E_{LUMO}/2$	0.142845	0.136195
η(eV)	$\eta = I-A/2$	0.072615	0.079955
S (eV)	$S = 1/2n$	1.075534	1.059591

incompletely veiled and has a positive electrostatic potential which is proton repulsion. In contrast, where the density of electrons in a molecule is dense is red-colored on the surface of the ESP, the negative refers to the Electrostatic potential, which is proton attractive. The graphically molecular electrostatic potential surface (ESP or MEP) is an assessment of the energy interaction between a positive charged (proton) and solvent accessible surface points with a set of values as defined by Connolly[30-32]. Fig. 4 shows the electrostatic potential for CQ and HCQ. These surfaces depict the shape, the size of the charge density, and the site of chemical reactivity of the molecules. Separate colors indicate the different surface values of the electrostatic potential. Fields with the most positive electrostatic potential are shown in blue, fields with the most

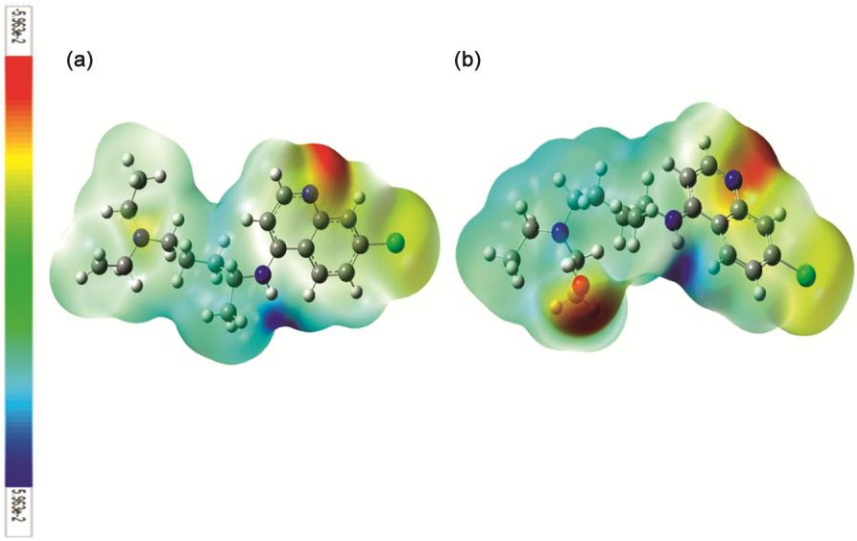

Fig. 4 — Molecular electrostatic potential map calculated at B3LYP/6-31G(d,p) level. (a) CQ and (b) HCQ

negative electrostatic potential are shown in red, and fields with zero potential in revealed with green. The potential increased through red < yellow < green <blue pattern. The electrostatic potential maps for the HCQ structure show more negative fields (in two different positions) compared with CQ (one position), moreover, the more-green fields have appeared on the HCQ structure, which means more zero potential. The blue position (positive electrostatic potential) for both the structures is the same.

Mulliken charge

Atomic charges were determined using Mulliken theory[20] and described in Table 3 — Electronic parameters for both CQ and HCQ.

Table Calculations at a lower theoretical level based on DFT/6-31 G** allocated more negative charges on selected atoms in all structures HCQ, especially oxygen and nitrogen atoms. According to HF calculations made based on 6-31 G**, it is obvious that lower theoretical rates would result in slightly lower charges on nitrogen atoms for the HCQ structure, while a difference in atomic charges of nitrogen atoms can be seen in the CQ structures. Collectively, 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. For CQ, both methods show that the nitrogen atoms have lower negative charge distribution, i.e., nitrogen atoms have a relatively lower interaction with other species. Only nitrogen of pyridine has a negative charge. The results for Mulliken charge distribution reveals that the HCQ is nucleophilic while QC is electrophilic compounds. Furthermore, the charge densities are highly depends on the chosen theory level used for the calculations and atoms in equations.

Table 3 — Mulliken atomic charges distribution for nitrogen and oxygen atom

Atom	Chloroquine		Hydroxychloroquine	
	HF method Energy band gaps (eV)	DFT method Energy band gaps (eV)	HF method Energy band gaps (eV)	DFT method Energy band gaps (eV)
N16 (pyridine)	-0.152432	-0.098893	-0.157928	-0.115692
N17 (HNC_2)	0.556272	0.598730	-0.079802	-0.043772
N27 (NC_3)	0.357395	0.327747	0.008610	-0.023111
O28 (COH)	-	-	-0.513690	-0.401387

Thermodynamic analysis

The thermodynamic calculation for both CQ and HCQ at *Ab initio* using two different basis sets (HF/6-31G** and B3LYP/6-31G** is listed in Table 4. The calculations provide total energy and different energy levels for both structures. The energy of the molecule is a combination of total energy, nuclear repulsion energy, electronic energy, and zero-point energy. The potential energy and kinetic energy are represented by the interaction of molecule and the forming of the molecules. In our calculation results, CQ has less total energy, nuclear repulsion, and electronic energy, therefore HCQ has more total energy value than CQ. Quantum mechanically, the lowest possible energy is

Table 4 — Chloroquine and Hydroxychloroquine energies computed

Energy (kcal/mol)	Basis set	Drugs	
		Chloroquine	Hydroxychloroquine
Ab_initio			
Total energy	HF/6-31G**	283.822	294.764
	B3LYP/6-31G**	263.262	280.322
Nuclear repulsion energy	HF/6-31G**	1125166.7201	1246464.2776
	B3LYP/6-31G**	1125166.5946	1246464.4031
Electronic energy	HF/6-31G**	- 827169.4375	- 874495.0494
	B3LYP/6-31G**	- 831285.4638	- 878878.2068
ZPE	HF/6-31G**	270.1214	282.2875
	B3LYP/6-31G**	253.5868	265.6699

Table 5 — Calculate enthalpy and entropy of Chloroquine and Hydroxychloroquine

Parameters	(Kcal/mol) Base	Structure	
		Chloroquine	Hydroxychloroquine
Enthalpy	HF/6-31G**	284.3871	298.3062
	B3LYP/6-31G**	263.8052	280.7982
Gibbs Free Energy	HF/6-31G**	235.5672	252.1335
	B3LYP/6-31G**	226.2173	230.798

available for zero-point energy. HCQ shows a higher level for zero-point energy in all the basis sets compared with CQ. Table 5 displays the calculation results obtained for enthalpy and Gibbs free energy of CQ and HCQ drugs. In our study, the enthalpy and Gibbs free energy of HCQ are higher according to both parameters and basis sets.

Conclusions

DFT and HF calculation of CQ and HCQ were performed to obtain energy band gaps using lower energy basis set 6-31G**. The geometrical structures of the molecules were determined using DFT at 6-31G** level. Both CQ and HCQ are present in biological environment and they show the different reactivity. The stability of the structure was an important contribution to the overall reactivity. By obtaining a map of electron density with a molecular electrostatic potential surface, information about the shape, size, and location of high electronegativity was obtained. The band gap and the reactivity of the molecules were estimated using the B3LYP/ 6-31G(d,p) process throughout LUMO+1, LUMO, HOMO & HOMO-1. Atomic charge distribution was calculated to view of the higher electron density areas as a potential interaction site, such as nitrogen and oxygen. CQ is shown the higher reactivity with a good polarizable than HCQ. Thermodynamic results showed the properties of both drugs.

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