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MOLECULAR LEVEL UNDERSTANDING OF HYDRATION OF CLOXIQUINE USING DENSITY FUNCTIONAL THEORY

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Abstract

Understanding the hydration of cloxiquine at the molecular level is essential for elucidating its interactions with water molecules and its behavior in aqueous environments. In this study, dispersion-corrected density functional theory (DFT) combined with wave functional analysis was employed to investigate the nature of interactions between cloxiquine and water molecules. The nucleoside-water complexes were examined, focusing on the binding sites of water molecules with cloxiquine. Optimization of structures was conducted using the Gaussian G16 code, employing the B3LYP/6-311G (D, P) method in both gas and liquid states. Results revealed that water molecules predominantly bind to the 3′–OH hydrogen and nucleobase of cloxiquine, in addition to interactions with the 5′–OH hydrogen atom. Electrostatic potential analysis highlighted the positive region near the 5′–OH hydrogen of the ribose unit in cloxiquine, while Quantum Theory of Atoms in Molecules (QTAIM) analysis demonstrated medium-strength hydrogen bonds between water and cloxiquine. Moreover, QTAIM and Energy Decomposition Analysis (EDA) indicated that intermolecular bonds are noncovalent and electrostatic dominant, with 2D Reduced Density Gradient (RDG) plots showing additional spikes due to interactions with 2′C hydrogen. In conclusion, the study provides insights into the hydration of cloxiquine, elucidating the noncovalent interactions and electrostatic potentials governing its behavior in aqueous environments. Understanding these molecular-level interactions is crucial for furthering our knowledge of cloxiquine's pharmacological properties and may inform the development of more effective drug formulations.

Keywords: DFT, Electrostatic Potentials, Non-Covalent Interactions, Cloxiquine.

INTRODUCTION

Density Functional Theory (DFT) stands as a cornerstone in computational quantum mechanics, offering a powerful tool for unraveling the electronic structure and properties of atoms, molecules, and solids(Khan et al., 2024; Varshan & Prathap, 2022).

Its versatile application spans across various scientific domains, including chemistry, physics, and materials science, revolutionizing our understanding of molecular behavior and facilitating advancements in diverse fields(Chaouiki, Chafiq, & Ko, 2024).

At its core, DFT revolves around the calculation of electronic energy by accounting for the intricate interactions between electrons and atomic nuclei within a system(Besley, 2021; Raj, Martin, Kumar, & Prathap, 2024). By solving the Schrödinger equation for the electron density distribution, DFT enables predictions of a myriad of properties crucial for comprehending molecular behavior.

These properties encompass molecular geometries, energies, vibrational frequencies, and electronic properties, laying the groundwork for profound insights into molecular dynamics and reactivity(Bassey et al., 2023; Prathap & Lakshmanan, 2022).

When applied to the study of hydration at the molecular level, DFT emerges as a formidable tool for simulating the intricate interplay between water molecules and

solutes like molecules or ions. In the context of hydration, DFT offers a wealth of information, shedding light on several key aspects:

Binding Energies: DFT allows for the determination of the strength of interactions between water molecules and the solute(Eichinger, Tavan, Hutter, & Parrinello, 1999; Kumaresan et al., 2022). By quantifying binding energies, researchers can discern the number of water molecules bound to the solute and elucidate the energetic cost associated with hydration.

Geometry Changes: Through DFT calculations, researchers can explore how the solute's geometry undergoes alterations upon hydration(Raj et al., 2024). This encompasses changes in bond lengths, angles, and conformations, providing valuable insights into the structural dynamics of the hydrated complex(Prathap & Jayaraman, 2022; Šponer, Cang, & Cheatham III, 2012).

Solvation Effects: DFT captures the influence of the solvent (typically water) on the electronic properties of the solute. This solvation effect can induce modifications in the solute's reactivity or spectroscopic properties, influencing its behavior in aqueous environments(BABU & MOHANRAJ, 2020; Orozco & Luque, 2000).

Hydrogen Bonding: DFT elucidates the formation and strength of hydrogen bonds between water molecules and the solute, which play a pivotal role in solvation phenomena. Understanding hydrogen bonding patterns is crucial for comprehending the stability and solubility of hydrated complexes.

Energetics and Thermodynamics: DFT provides valuable insights into the thermodynamics of hydration, including enthalpy, entropy, and free energy changes. These thermodynamic parameters offer crucial information regarding the energetics of hydration processes.

Reaction Pathways: Through DFT simulations, researchers can predict potential reaction pathways occurring during hydration, such as proton transfers or other chemical transformations(Mohanraj, Varshini, & Somasundaram, 2021; Zhou & Han, 2018). This predictive capability aids in understanding the underlying mechanisms driving hydration phenomena.

It's important to note that DFT calculations necessitate expertise and specialized software for setup and interpretation(Kashif, Zareef, Aftab, Khan, & Barakat, 2020; Puzzarini, Bloino, Tasinato, & Barone, 2019; Yuvaraj, Sangeetha, & Kavitha, 2020). Additionally, the accuracy and reliability of results hinge on the chosen computational methods and parameters.

Nonetheless, the insights gleaned from DFT simulations deepen our understanding of chemical processes at the molecular level, paving the way for advancements in drug design, materials science, and numerous other scientific endeavors. In the specific context of cloxiquine hydration, DFT offers a unique opportunity to explore the intricate interactions between water molecules and the solute at the atomic level. By leveraging DFT calculations, researchers can uncover vital information regarding bond lengths, angles, and energies involved in the hydration process, thereby enhancing our understanding of cloxiquine's behavior in aqueous environments and its potential pharmacological implications(Aditya, Girija, Paramasivam, & Priyadharsini, 2021; Latosińska & Latosińska, 2011).

MATERIALS AND METHODS

Computational Software and Methodology:

The computational investigation utilized Gaussian 16 (Revision C.01); a suite of programs renowned for its efficacy in density functional theory (DFT) calculations. The optimization of structures was conducted without symmetry constraints using the M06-2X/6–311 + G(d,p) method, augmented with Grimme's D3 dispersion correction. This choice of methodology was motivated by prior studies attesting to the accuracy of the M06-2X functional, particularly in capturing noncovalent interactions and thermochemical properties. To ensure the identified structures corresponded to true minima, vibrational analysis was performed using the M06-2X-D3/6–311 + G(d,p) method, confirming the absence of imaginary frequencies indicative of saddle points.

Energetics and Thermochemistry:

The binding energy of the water molecule to cloxiquine was evaluated using the equation: ΔEBSSE=E (B.H2O) −(E(B)+E (H2O)) +EBSSE

Here, E (B.H2O) represents the energy of the cloxiquine-water complex, E(B) is the energy of the isolated cloxiquine, E (H2O) denotes the energy of the isolated water molecule, and EBSSE accounts for the basis set superposition error.

Analysis of Intermolecular Interactions:

To elucidate the main intermolecular interactions stabilizing the cloxiquine-water complex, a multifaceted approach was adopted. This included:

Quantitative Molecular Electrostatic Potential Analysis (MESP):

MESP analysis was conducted to assess the electrostatic interactions between the molecules.

Natural Bond Orbital (NBO) Analysis:

NBO analysis provided insights into the nature of bonding interactions within the complex.

Quantum Theory of Atoms in Molecules (QTAIM) Analysis: QTAIM analysis was employed to characterize critical points in the electron density distribution, offering insights into bonding patterns.

Energy Decomposition Analysis (EDA):

EDA facilitated the dissection of the total interaction energy into individual components, shedding light on the contributions of various interactions.

Noncovalent Interaction Analysis - Reduced Density Gradient (NCI-RDG) Analysis:

NCI-RDG analysis was utilized to visualize regions of noncovalent interactions within the complex.

Visualization and Software Packages:

Visualization of molecular structures and analysis results was accomplished using Chemcraft software. Additionally, AIMALL and Multiwfn program packages were employed for QTAIM and NCI-RDG analyses, respectively.

Structural Considerations:

The starting point for investigating the cloxiquine-water complex was the optimized geometry of cloxiquine, considering its anti-configuration due to its relevance in DNA double helix formation. The placement of the water molecule around cloxiquine adhered to strong and weak hydrogen bonding distances, ensuring comprehensive exploration of potential binding sites and hydrogen bonding forces between the molecules.

Optimized Geometries of Nucleosides and Deoxynucleosides:

The optimized geometries of nucleosides and deoxynucleosides, essential for understanding hydration dynamics, were provided for reference.

RESULTS

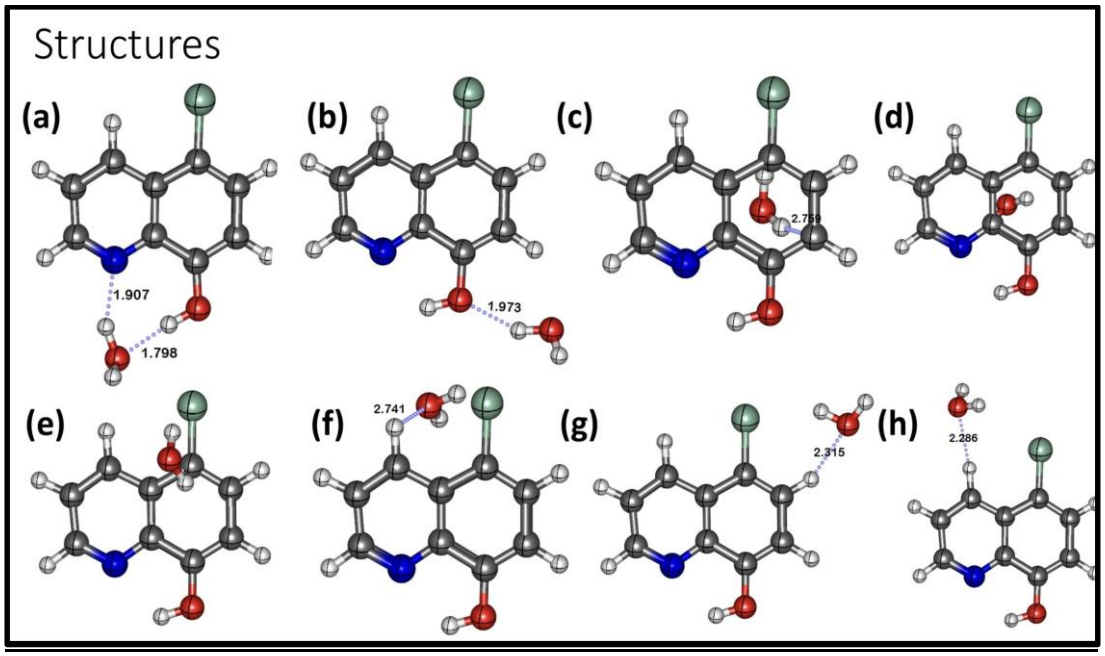

Figure 1

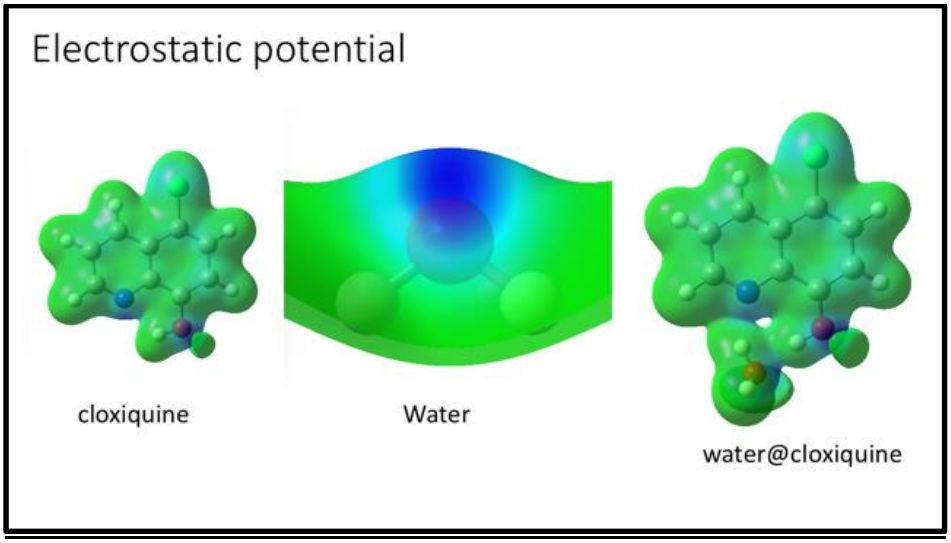

Figure 2: Nature of intermolecular interaction

The electron-rich regions, depicted in red, and electron-deficient regions, shown in blue, in the cloxiquine-water complexes were computed at the M06-2X-D3/6–311 + G (d, p) level of theory, revealing directional interactions between molecules based on selective positive and negative potentials. Additionally, the localization of Vs, max and Vs,min values, along with their quantitative measurements, highlighted notable changes in potential distribution upon hydration, indicative of altered electrostatic interactions within the complexes.

Homo lumo distribution

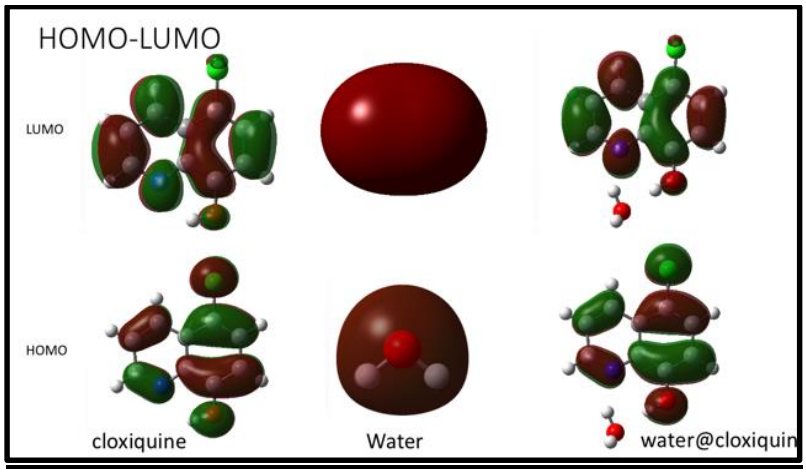

Figure 3

HOMO stands for highest occupied molecular orbital. LUMO stands for lowest unoccupied molecular orbital. The energy difference between the HOMO and LUMO is termed the HOMO-LUMO gap. HOMO and LUMO are sometimes referred to as frontier orbitals. Each molecular orbital has a calculated energy level. Chemists sort the molecular orbitals (MOs) by energy levels. Chemists assume that the electrons will occupy the lowest energy level MOs first. For example, if a molecule has enough electrons to fill 15 MOs, the 15 MOs with the lowest energy levels will be occupied. The 15th MO on the list would be called the "highest occupied molecular orbital" (HOMO) and the 16th MO on the list would be the "lowest unoccupied molecular orbital" (LUMO). The difference in the HOMO's energy level and the LUMO's energy level is called the band gap. The band gap can sometimes serve as a measure of the excitability of the molecule: the smaller the energy, the more easily a molecule's electrons will be excited. For example, this can help predict whether a substance will have luminescence. The water molecules prefer to bind with the amino hydrogen, which may reduce the enol isomers The HOMO-LUMO diagrams show that HOMO and LUMO are localized on the drug molecules, implying the existence of physical interaction between water and drug. Electrostatic analysis shows that a charge transfer interaction exists in the complex.

By applying these steps, a molecular-level understanding of the hydration of cloxiquine can be obtained using density functional theory. This information can be valuable for predicting the drug's behavior in aqueous environments, including its solubility, stability, and interactions with biological systems(Lipinski, Lombardo, Dominy, & Feeney, 1997; Smiline Girija, 2020).

It's important to note that the DFT calculations described above are just one possible approach to study the hydration of cloxiquine. Depending on the specific research

question and computational resources available, different methods or more advanced techniques may be employed.

Comparison of enthalpy and entropy formation of cloxiquine and water

Table 1

Table E_{gap}, Enthalpy and Entropy of formation

Compound	E_{gap} (eV)	Enthalpy of formation (kcal mol^{-1})	Free energy of formation (kcal mol^{-1})	Binding energy (kcal mol^{-1})
cloxiquine	6.217	-	-	-
Water	12.635	-	-	-
cloxiquine@Water complex	6.060	-6.68	2.50	-8.68

To identify the relative stability of cloxiquine and water complexes, we computed the binding energies of the stable complexes. The BSSE corrected binding energies for nucleoside and deoxynucleoside-water complexes, are provided in Table 1. Among the binding energies of nucleoside-water, the A-H2O complex has the highest interaction energy. The binding energy for cloxiquine - water varies only a little and lines in the range of 6.217 to -8.68. The binding energy of the complexes computed by BP86, B3LYP-D3, M06-2X, M06L and M06-2X-D3 are summarized and compared in Table 2. The widely used hybrid B3LYP functional with D3 dispersion correction and the pure BP86 functional provides higher binding energy for nucleoside-water complexes compared to the M06-2X-D3 functional. Similarly, the meta GGA functional M06L, predicts the stability of nucleoside-water complexes closer to the M062X-D3 functional values(Sathiyamoorthy, Suvitha, Sahara, & Kawazoe, 2021). While in the case of deoxynucleosides, most of the functionals provides lower stability for the complexes. A comparison between functionals M06-2X-D3 and M06-2X with and without dispersion correction, clearly show that dispersion terms improve the stability of the complexes. Thus B3LYP-D3 functional, was found to perform significantly with lower performance, while the dispersion interactions contribute significantly to the stability of the water complexes.

DISCUSSION

Comparing the interactions observed in cloxiquine-water complexes with those in free nucleobases and DNA/RNA molecules offers valuable insights into the hydration dynamics of biomolecular systems(Wood, 2016). In free nucleobases, such as adenine, guanine, cytosine, and thymine, water molecules typically interact with the carbonyl oxygen and amine hydrogen atoms, except for adenine, where bonding occurs through the N3 nitrogen and amine hydrogen.

This pattern of interaction suggests a preference for hydrogen bonding between water and functional groups containing oxygen and nitrogen atoms in nucleobases. In

nucleosides and deoxynucleosides, where nucleobases are linked to a ribose sugar moiety, water molecules tend to bind to one of the hydroxyl groups in the ribose ring. This interaction pattern reflects the availability of hydroxyl groups in the sugar backbone for hydrogen bonding with water molecules.

The charge delocalization in nucleobase-water complexes mainly occurs in the vicinity of the water molecule, as revealed by AIM analysis. Strong hydrogen bonding with a non-covalent nature and electrostatic dominance characterizes these interactions, indicating the importance of electrostatic forces in stabilizing nucleobase-water complexes. In contrast, cloxiquine-water complexes exhibit several medium to strong hydrogen bonds with a non-covalent nature. EDA analysis highlights the dominance of electrostatic interactions in all complexes, suggesting that electrostatic forces play a significant role in stabilizing these complexes.

Additionally, NCI-RDG analysis confirms the presence of hydrogen bonding interactions in cloxiquine-water complexes. Interestingly, weak van der Waals interactions are observed in cloxiquine-water complexes, contributing to their stability. This observation implies that, in addition to hydrogen bonding, van der Waals interactions play a crucial role in stabilizing cloxiquine-water complexes, potentially making them more stable than nucleobase-water complexes.

Overall, comparing the nature of interactions in cloxiquine-water complexes with those in free nucleobases and DNA/RNA molecules provides valuable insights into the hydration behavior of biomolecular systems. These insights deepen our understanding of the molecular mechanisms underlying hydration processes and can inform the design of novel therapeutic agents or materials targeting biomolecular interactions with water(Naczynski, Tan, Riman, & Moghe, 2014).

CONCLUSION

In conclusion, this study provides valuable insights into the nature of cloxiquine-water interactions, shedding light on the preferred binding sites and the factors contributing to complex stability. Through computational techniques such as MESP, AIM, NCI-RDG, and EDA analysis, the most favorable interaction sites and the role of electrostatic forces in stabilizing cloxiquine-water complexes were elucidated. By employing density functional theory (DFT), a molecular-level understanding of cloxiquine hydration was achieved, offering predictions regarding the drug's behavior in aqueous environments. This information is crucial for assessing aspects such as solubility, stability, and interactions with biological systems, thereby aiding in the development of more effective pharmaceutical formulations. It is important to acknowledge that while DFT calculations serve as a valuable tool in studying cloxiquine hydration, other computational methods or advanced techniques may also be employed depending on the specific research objectives and available resources.

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Conflict Of Interest

None to declare

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