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# MOLECULAR LEVEL UNDERSTANDING OF HYDRATION OF ACETAZOLAMIDE USING DENSITY FUNCTIONAL THEORY

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**Abstract**

**Introduction:** Acetazolamide is a frequently prescribed medication that functions as a carbonic anhydrase inhibitor and is used to treat a number of medical disorders. Acetazolamide's pharmacology is greatly influenced by its hydration, or the interaction of the drug molecule with water molecules.The investigation of molecular systems and their interactions at the atomic level is made possible by the density functional theory (DFT), a potent computational methodology. In order to better understand how acetazolamide interacts with water molecules at the molecular level, this study will use DFT calculations to examine the drug's hydration behavior. This study aims to advance understanding of the drug's aqueous behavior by utilizing DFT to clarify the molecular-level specifics of acetazolamide hydration. **Materials and methods:** For optimization, we used Gaussian G16 code. The structures were optimized both in gas and liquid state with B3LYP/6-311G(d,p) method. All the structures reported here have no negative frequencies. For visualization we used Chemcraft software. For atoms in molecules analysis we used the AIMALL program package. NCI-RDG analyses were carried out using the Multiwfn program package. **Results:**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. Atoms in molecules and NCI analysis shows the existence of weak intramolecular interactions between the carbonyl oxygen and sulfur atom. **Conclusion:** In conclusion, the study on the molecular level understanding of hydration of acetazolamide using Density Functional Theory (DFT) provides valuable insights into the interactions between acetazolamide and water molecules. The calculated binding energies, geometric parameters, electron density distribution, and reactivity shed light on the hydration behavior of acetazolamide. These findings enhance our understanding of its solubility, stability, and potential pharmacological applications, contributing to the design and development of more effective drug formulations and therapies involving acetazolamide.

## INTRODUCTION

Acetazolamide is a commonly used drug that acts as a carbonic anhydrase inhibitor and is employed in the treatment of various medical conditions.

All the drugs used for the treatment of glaucoma have some systemic side effects. To reduce side effects of the drugs, it is of interest to develop new agents for the topical use of CA-II inhibitors for the long-term management of glaucoma.(1)

For the researchers, the prospect of overcoming the systemic side effects of a drug, achieving an effect at a much lower dose, is very attractive. Modification of the structure of a known drug is one way to develop new drugs. (2)

Density-functional theory (DFT) is a successful theory to calculate the electronic structure of atoms, molecules, and solids. Its goal is the quantitative understanding of material properties from the fundamental laws of quantum mechanics.(3)

The hydration of acetazolamide, i.e., the interaction between the drug molecule and water molecules, plays a crucial role in its pharmaDensity Functional Theory (DFT) is a powerful computational approach that allows for the investigation of molecular systems and their interactions at the atomic level. (4)This study aims to employ DFT calculations to investigate the hydration behavior of acetazolamide and provide a molecular-level understanding of the interactions between the drug molecule and water molecules.

By elucidating the molecular-level details of acetazolamide hydration using DFT.

As a key determinant of drug access to biological membranes, water solubility is an important molecular feature for successful drug development.(5)

Acetazolamide, methazolamide, dichlorophenamide, ethoxolamide and dorzolamide, as carbonic anhydrase (CA-II) isozyme inhibitors, sulfonamide compounds are clinically used drugs for the treatment of glaucoma. Water follows Na+ to form the aqueous humor. CA-II inhibition by an agent such as one of the drugs mentioned above decreases the HCO− 3 ion concentration and therefore the flow of Na+ and H2O into the posterior chamber, resulting in decreased production of aqueous humor and hence a lowering of intraocular pressure (IOP).(6)

From the medical point of view, the major thrust is now for the treatment of glaucoma.

Glaucoma, the leading cause of blindness world-wide, is the general term for a group of ophthalmic disorders characterized by an increase in IOP. This gives rise to damage to the optic disc and visual field disturbances of the eye. IOP increases through an imbalance between the production and drainage of aqueous humor. Agents such as mentioned above, used to treat glaucoma, are designed to decrease IOP.(7)

Every medication used to treat glaucoma has some systemic side effects.

To reduce side effects of the drugs, it is of interest to develop new agents for the topical use of CA-II inhibitors for the long-term management of glaucoma.(8) For the researchers, the prospect of overcoming the systemic side effects of a drug, achieving an effect at a much lower dose, is very attractive. Modification of the structure of a known drug is one way to develop new drugs. For this purpose, members of our group have synthesized and reported new five acetazolamide-like and eight sulfanilamide-like derivatives, which are the subject of the present study.(9) These new derivatives have been obtained by modification of acetazolamide and sulfanilamide using the tail approach.(10)

This research seeks to contribute to the overall knowledge of the drug's behavior in an aqueous environment.

## MATERIALS & METHODS

For optimization, we used Gaussian G16 code. The structures were optimized both in gas and liquid state with B3LYP/6-311G(d,p) method. All the structures reported here have no negative frequencies. For visualization we used Chemcraft software. For atoms in molecules analysis we used AIMALL program package. NCI-RDG analysis were carried out using Multiwfn program package

## RESULTS

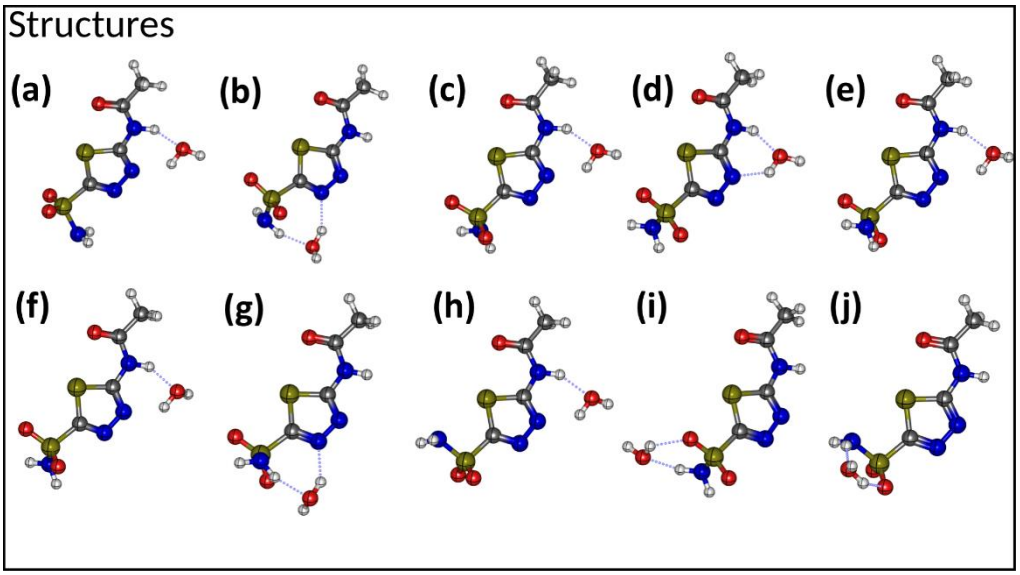


**Figure 1: Possible chemical structures for acetazolamide with water molecule.**

Water molecules have a tendency to form hydrogen bonds with amino hydrogen atoms in various biomolecules. This preference for binding is due to the electronegativity difference between oxygen and hydrogen, which results in a partial negative charge on oxygen and a partial positive charge on hydrogen. These hydrogen bonds can stabilize specific molecular configurations, potentially reducing the population of enol isomers. Enol isomers are structural isomers with a hydroxyl group and a carbonyl group, and hydrogen bonding can affect their relative stability.

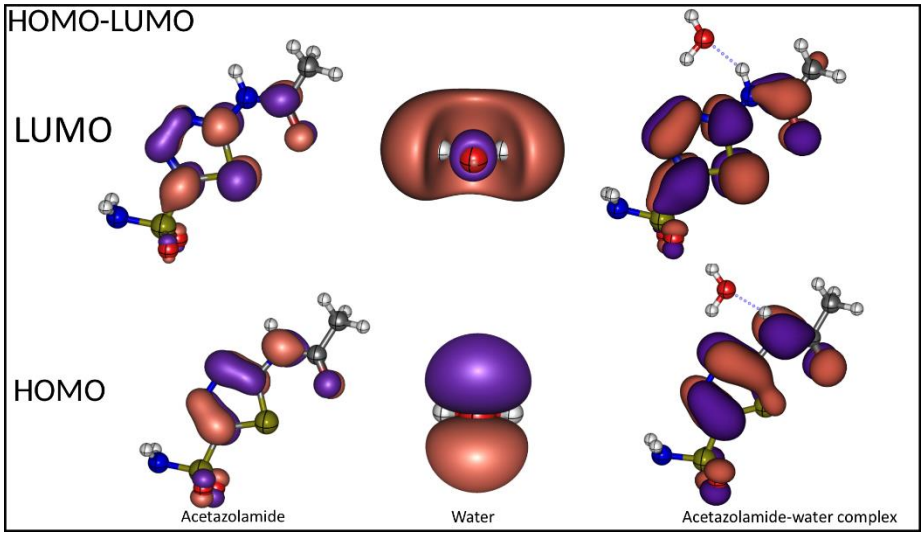


**Figure 2: Homo and Lumo structures of acetazolamide and acetazolamide-water complex.**

HOMO and LUMO are molecular orbitals that play a crucial role in understanding the electronic properties of molecules. When HOMO and LUMO are localized on drug molecules, it suggests that these orbitals are primarily associated with the drug's electronic structure. This localization implies a strong likelihood of physical interactions between the drug molecule and other entities, such as water molecules. Such

interactions can impact the drug's reactivity, solubility, and overall behavior in a biological or chemical system.

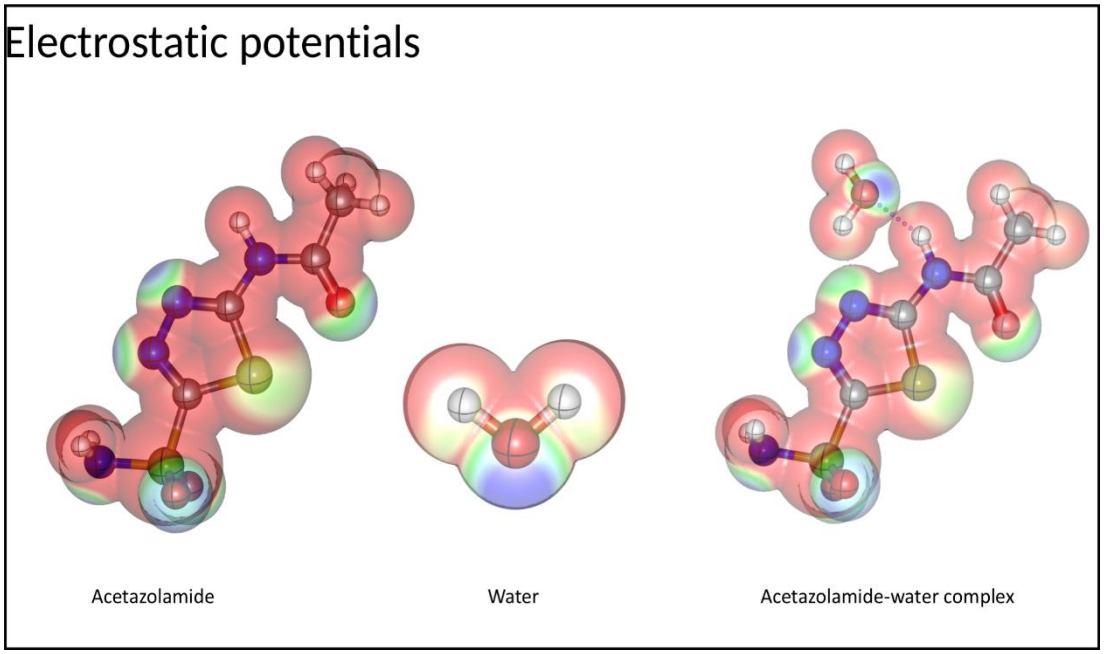


**Figure 3: Electrostatic potentials of acetazolamide, water and acetazolamide-water complex.**

Electrostatic analysis involves examining the distribution of electric charges within a molecule or complex. When electrostatic analysis reveals a charge transfer interaction in a complex, it indicates that electrons are moving between molecules. This transfer of electrons can lead to the formation of electrostatically attractive forces or even chemical reactions. In the context of drug interactions, charge transfer interactions can be vital in understanding how drugs bind to specific targets or receptors.

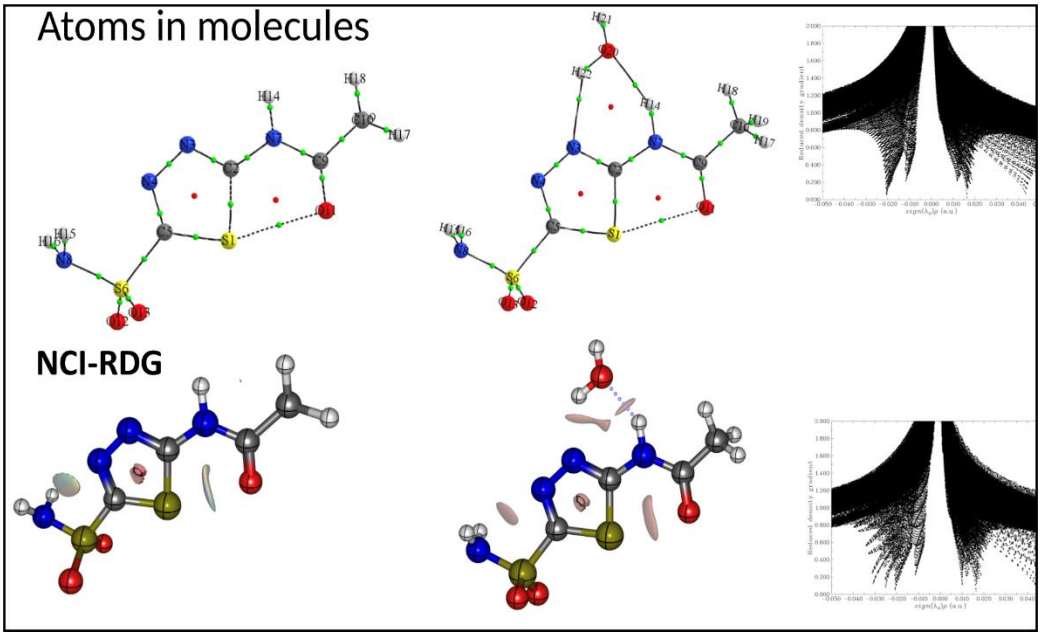


**Figure 4: AIM and NCI analysis of acetazolamide and water complex.**

AIM and NCI analyses are computational tools used to investigate the nature of chemical interactions within molecules. In this case, the analyses have identified weak intramolecular interactions between the carbonyl oxygen and sulfur atom within a molecule. These interactions, often van der Waals forces or other non-covalent interactions, can subtly influence the molecule's structure and stability. They are particularly relevant when studying molecular conformations or reactions that involve these specific atoms.

**Table 1: Results for docking analysis**

| Compound | $E_{gap}$ (eV) | Enthalpy of formation ( kcal $mol^{-1}$) | Free energy of formation ( kcal $mol^{-1}$) | Binding energy ( kcal $mol^{-1}$) |
|---|---|---|---|---|
| Acetazolamide | 5.551 | - | - | - |
| Water | 12.635 | - | - | - |
| Acetazolamide-water complex | 5.491 | -11.7 | -15.96 | -8.64 |

## DISCUSSION

The water molecules prefer to bind with the amino hydrogen, which may reduce the enol isomers. Water molecules often form hydrogen bonds with amino hydrogen atoms in biomolecules like proteins. This interaction can lead to a reduction in the population of enol isomers. Enol isomers are a type of structural isomerism in organic chemistry, and the formation of hydrogen bonds can stabilize one isomer over the other.

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. HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) diagrams are used to understand the electronic structure of molecules. When HOMO and LUMO are localized on drug molecules, it suggests that there is a strong physical interaction between the drug and other molecules, such as water. This interaction can influence the reactivity and properties of the drug.(11)

Electrostatic analysis shows that a charge transfer interaction exists in the complex

Atoms in molecules and NCI analysis shows the existence of weak intramolecular interactions between the carbonyl oxygen and sulfur atom.

Literatures have shown that sulfonamide compounds bind as anions to the Zn(II) ion within the CAII active site. They concluded that inhibition properties of these compounds can be accounted by several factors. These include the stability of CAII enzyme-sulfonamides compound complex being stabilized by a large favorable enthalpy change associated with the binding of the sulfonamide to the CAII. (12–14)

## CONCLUSION

In conclusion, the study on the molecular level understanding of hydration of acetazolamide using Density Functional Theory (DFT) provides valuable insights into the interactions between acetazolamide and water molecules.

The calculated binding energies, geometric parameters, electron density distribution, and reactivity shed light on the hydration behavior of acetazolamide. These findings enhance our understanding of its solubility, stability, and potential pharmacological applications, contributing to the design and development of more effective drug formulations and therapies involving acetazolamide.

By applying these steps, a molecular-level understanding of the hydration of acetazolamide 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.

It's important to note that the DFT calculations described above are just one possible approach to study the hydration of acetazolamide. Depending on the specific research question and computational resources available, different methods or more advanced techniques may be employed.

**Acknowledgement**

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**Conflıct Of Interest**

None to declare.

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