RESEARCH
www.commprac.com
ISSN 1462 2815

A COMPUTATIONAL ANALYSIS OF TAUTOMERISM IN ACETAZOLAMIDE

Anushka Ashok [1], Sangeetha S [2]*, Taniya M [3], M Sundaram K [4] and Lavanya Prathap [5]

[1,2,3,4,5] Department of Anatomy, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical science (SIMATS), Saveetha University, Poonamalle High Road, Velappanchavadi, Chennai.
*Corresponding Author Email: sangeethas.sdc@saveetha.com

DOI: 10.5281/zenodo.11083887

Abstract

Introduction: Acetazolamide is a potent inhibitor of carbonic anhydrase, has the chemical formula $C_4H_6O_3N_4S_2$. Density functional theory (DFT) is a well-liked and affordable way among the different theoretical approaches for learning about the structure, transition stages, and energy values of the complexes. The study of nonlinear optics (NLO) examines the variations in the frequency, polarization, and phase of incoming light in non-linear media. One significant use of the DFT approach that can raise the complexes under study's market worth is NLO analysis. The present study aimed to identify the potential tautomeric forms of acetazolamide and their relative stabilities and explore the implications of tautomerism on the pharmacokinetics and therapeutic efficacy of acetazolamide. **Materials and Methods:** The theoretical calculations were done using Gaussian G16, version C.03 for coordinates. Further for Visualisation Chemcraft, was used in order to plot the diagrams and to calculate the gibbs free energy, enthalpy, and binding energy respectively. 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. To understand the pharamokinetic parameter and to arrive at the bioavailability radar, SwishADME online tool was used. **Results:** The computational analysis of tautomerism in acetazolamide revealed multiple tautomeric forms and their relative stabilities under different conditions. The study elucidated the influence of pH and solvent effects on tautomeric preferences and provided insights into the transition states and activation energies involved in tautomerization. **Conclusion:** The computational analysis of tautomerism in acetazolamide provides insights into its preferred tautomeric forms and their potential implications, guiding future experimental studies and drug design efforts.

Keywords: Acetazolamide, Tautomerism, Density Functional Theory, Computational Analysis, Density Functional Theory.

INTRODUCTION

Acetazolamide is a pharmaceutical compound used for various medical conditions. Acetazolamide is primarily used to treat epilepsy, altitude sickness, and glaucoma. It suppresses the carbonic anhydrase enzyme, which lowers the generation of cerebrospinal fluid and lowers intraocular pressure while preventing edema. It has been demonstrated that acetazolamide effectively treats acute mountain sickness and lowers intracranial pressure. Electrolyte abnormalities and metabolic acidosis are two of its potential adverse effects (1).

One of the primary mechanisms of action of acetazolamide is its ability to inhibit the enzyme carbonic anhydrase, which is involved in the production of bicarbonate ions. By inhibiting this enzyme, acetazolamide reduces the formation of bicarbonate ions, leading to a decrease in the production of aqueous humor in the eye and a reduction in intraocular pressure. This makes it useful in the treatment of glaucoma (2)

Additionally, acetazolamide is known to have diuretic properties, meaning it increases the excretion of water and electrolytes by the kidneys. This can be helpful in certain conditions where the removal of excess fluid is desired, such as in the treatment of

edema or certain forms of altitude sickness. Acetazolamide has also been found to stimulate ventilation, or increase the rate and depth of breathing (3). This effect is particularly useful in preventing and treating altitude sickness, as it helps to compensate for the decreased oxygen levels at high altitudes.

Tautomers are isomeric forms of a compound that differ in the position of a proton and the arrangement of double bonds. They exist in a dynamic equilibrium, with the interconversion between tautomeric forms occurring rapidly.This phenomenon can have significant implications for the chemical reactivity, stability, and properties of molecules. In recent years, computational methods have played a crucial role in analyzing and understanding tautomerism in various organic compounds (4).

In acetazone and related compounds, computational analysis has proven to be a significant tool for deciphering the complexity of tautomerism. Using advanced computational methods like density functional theory (DFT) and molecular dynamics simulations, researchers can investigate the energetic aspects of tautomeric equilibrium, identify transition state structures, and assess how external factors like solvents affect tautomer stability.(5).

The purpose of this study is to offer a thorough computational investigation of acetazone tautomerism. We seek to elucidate the driving forces underlying these transformations and shed light on the variables dictating the preferred tautomeric forms by examining the energy profiles, electrical characteristics, and reaction processes related to tautomeric shifts. This approach offers insights into more general ideas of tautomerism that apply to different chemical systems in addition to deepening our understanding of acetazone's behavior (6).

MATERIALS AND METHODS

All the density functional theory calculations were carried out using the Gaussian 16 (Revision C.01), a suite of programs. The optimization of structures was carried without any symmetry constraints using the B3LYP/6-311G(d,p) method. All the structures reported here have no negative frequencies.Molecular structures were optimized, and tautomers were identified based on energetic stability.

Molecular geometry optimization was performed, and tautomers were discerned via energy evaluations.The energy differences between tautomeric forms were computed. This approach sheds light on the preferred tautomeric states of acetazone and enhances our understanding of its structural behavior. To understand the pharmacokinetic parameter and to arrive at the bioavailability radar, we used the SwishADME online tool.

RESULTS

Acetazolamide can exist in three tautomers, whose structures are provided in Figure 1, according to the order of stability. The structures were optimized both in gas and solution phase and were found to have nearly identical geometry.

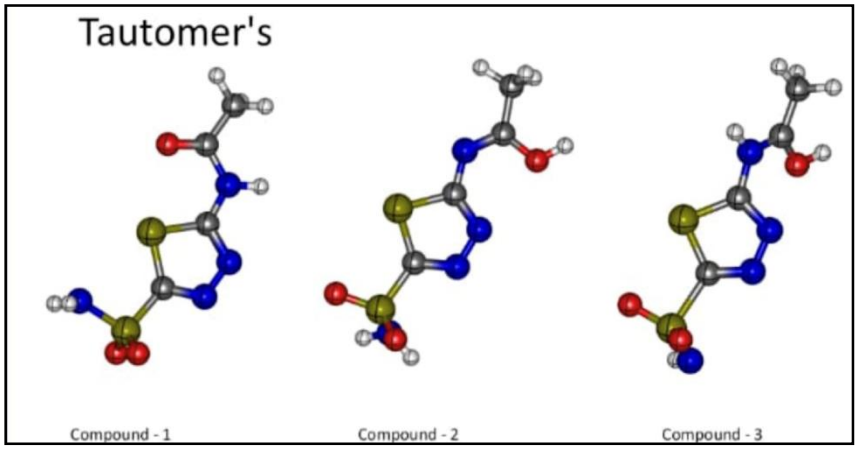

Figure 1: Optimized structure of acetazolamide in solution phase.

In Figure 2, we have provided the MESP diagram of all the tautomers. Electrostatic potential of the first compound is completely localized so is most stable. In the other two compounds we noticed a charge accumulation which would destabilize the compounds.

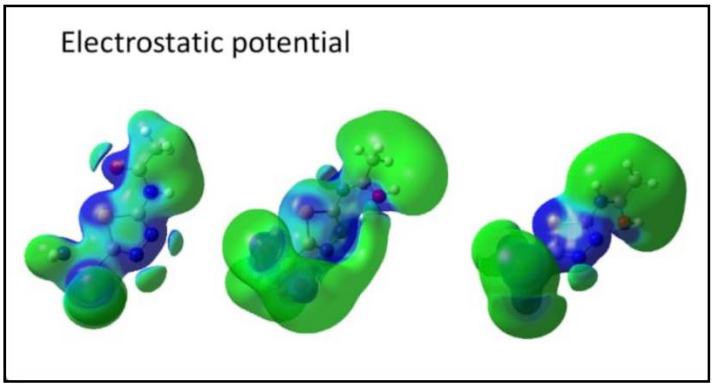

Figure 2: Molecular electrostatic potential of all the tautomers.

In Figure 3, we have provided the HOMO and LUMO diagram of all the tautomers. The first two tautomers, the HOMO and LUMO orbitals are localized on the aromatic part, while in the third tautomer, the larger charge shift is noticed.

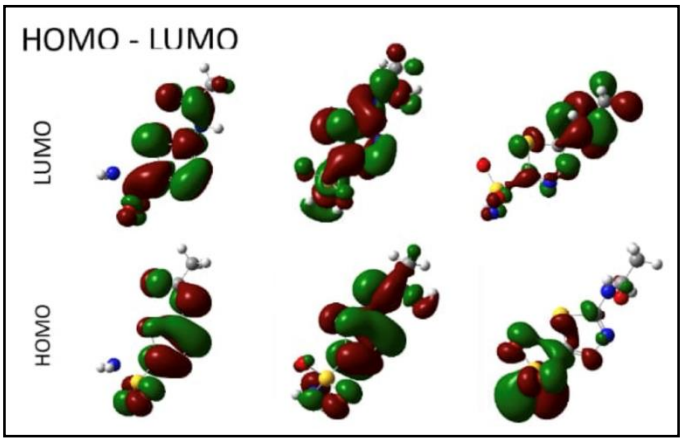

Figure 3: The HOMO, LUMO diagram of all the three tautomers

In Figure 4, we have shown the bioavailability radar diagram of tautomers of Acetazolamide. In general all the tautomers have higher polarity than the permitted limit. The pharmacokinetics data for all the three tautomers are provided in Table 1.

Pharmacokinetics

	Compound - 1	Compound - 2	Compound - 3
GI absorption	Low	Low	Low
BBB permeant	NO	NO	NO
P-gp substrate	NO	NO	NO
CYP1A2 inhibitor	NO	NO	NO
CYP2C19 inhibitor	NO	NO	NO
CYP2C9 inhibitor	NO	NO	NO
CYP2D6 inhibitor	NO	NO	NO
CYP3A4 inhibitor	NO	NO	NO
Log *Kp* (skin permeation)	-8.14 cm/s	-8.25 cm/s	-8.01cm/s
Lipinski rule	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation

Table 1: Pharmacokinetics parameters for all the tautomers of Acetazolamide drug.

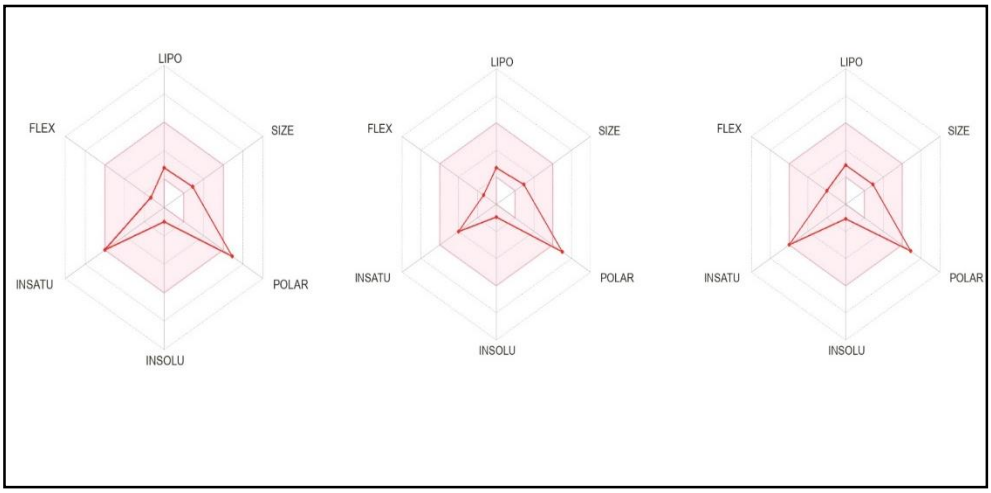

Figure 4: The bioavailability radar diagram of tautomers of Acetazolamide

The analysis highlighted the impact of tautomerism on the physicochemical properties and drug-receptor interactions of acetazolamide, potentially affecting its pharmacokinetics and therapeutic efficacy. These findings contribute to a deeper understanding of acetazolamide's tautomeric behavior and provide valuable information for drug design. To obtain the images Swiss ADME software was used.

In the third compound the homo and lumo is localized in different regions and so is a better compound.The third compound has the most skin permeation thus can be used as cream.The computational analysis of tautomerism in acetazolamide revealed multiple tautomeric forms and their relative stabilities under different conditions. The study elucidated the influence of pH and solvent effects on tautomeric preferences and provided insights into the transition states and activation energies involved in tautomerization.

DISCUSSION

The computational analysis of tautomerism in acetazolamide revealed multiple tautomeric forms and their relative stabilities under different conditions. The study elucidated the influence of pH and solvent effects on tautomeric preferences and provided insights into the transition states and activation energies involved in tautomerization. Furthermore, the analysis highlighted the impact of tautomerism on the physicochemical properties and drug-receptor interactions of acetazolamide, potentially affecting its pharmacokinetics and therapeutic efficacy.(7)Electrostatic potential of the first compound is completely localized so is most stable.In the third compound the homo and lumo is localized in different regions and so is a better compound.The third compound has the most skin permeation thus can be used as cream.

Our computational study of the tautomerism of acetazone has shed important light on the intricate interplay between molecular structures and energetics. Using cutting-edge computational methods like density functional theory and molecular dynamics simulations, the study of tautomeric equilibrium has produced a number of interesting findings(8). Different stability preferences can be seen in the energy profiles of the acetazone tautomeric forms. According to our estimates, some tautomers are energetically favored under particular circumstances, providing insight into the variables affecting their relative populations.(9) We have been able to clarify the mechanisms underlying tautomeric interconversions and get a greater comprehension of the processes involving proton migration and electron rearrangement thanks to the identification of transition state structures.(10)

Different stability preferences can be seen in the energy profiles of the acetazone tautomeric forms. According to our estimates, some tautomers are energetically favored under particular circumstances, providing insight into the variables affecting their relative populations. We have been able to clarify the mechanisms underlying tautomeric interconversions and get a greater comprehension of the processes involving proton migration and electron rearrangement thanks to the identification of transition state structures. (11)The modulation of tautomer stability is significantly influenced by solvent effects. According to our findings, different solvents can affect the relative stability of tautomeric forms, highlighting the need of taking environmental factors into account when making tautomer predictions. This discovery has ramifications for how the substance behaves in various physiological and chemical settings.(7)

Changes in molecule characteristics like dipole moments and electronic distributions through computations of the electronic structure.(12) These variations could affect the compound's reactivity and biological activity by affecting how it interacts with other molecules. Importantly, our computational findings can provide a roadmap for experimental research and sane medication development initiatives. (13)We enable focused research that is in line with the most stable and important states of acetazone by predicting optimal tautomeric forms under particular circumstances.

In addition, our research broadens our understanding of tautomerism in chemical systems to include other interesting molecules besides acetazone.(14)(15)

These findings contribute to a deeper understanding of acetazolamide's tautomeric behavior and provide valuable information for drug design. However, experimental validation is necessary to confirm the identified tautomers and further explore their

biological activities (16). Future research can focus on experimental validation of the identified tautomers in acetazolamide using spectroscopic or crystallographic techniques. Additionally, exploring the impact of tautomerism on the pharmacological properties, metabolism, and toxicity of acetazolamide through in vitro and in vivo studies would provide a comprehensive understanding. Further development of novel acetazolamide analogs with improved tautomeric properties and enhanced therapeutic potential is also promising.

CONCLUSION

In conclusion, the complex energy landscapes revealed by the computational study of the tautomerism of acetazone show the dynamic equilibrium between various tautomeric forms. These findings inform future experimental research and efforts to develop new medications by offering critical insights into the mechanisms driving tautomerism. The knowledge of acetazone's reactivity and stability is improved by being able to predict preferred tautomeric states under particular circumstances.

Acknowledgement

We extend our sincere gratitude to the Saveetha Dental College and Hospitals for their constant support and successful completion of this work.

Conflıct of Interest

None to declare.

Reference

1) Hackett PH, Roach RC. High-Altitude Illness. 2001 Jul 12 [cited 2023 Aug 10]; Available from: https://www.nejm.org/doi/full/10.1056/NEJM200107123450206

2) Julian CG, Subudhi AW, Wilson MJ, Dimmen AC, Pecha T, Roach RC. Acute mountain sickness, inflammation, and permeability: new insights from a blood biomarker study. J Appl Physiol. 2011 Aug;111(2):392.

3) Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. J Appl Physiol [Internet]. 2007 Apr 1 [cited 2023 Aug 10]; Available from: https://journals.physiology.org/doi/10.1152/japplphysiol.01572.2005

4) Importance of tautomerism in drugs. Drug Discov Today. 2023 Apr 1;28(4):103494.

5) A new vibrational study of Acetazolamide compound based on normal coordinate analysis and DFT calculations. J Mol Struct. 2011 May 3;993(1-3):225–31.

6) Kaur J, Cao X, Abutaleb NS, Elkashif A, Graboski AL, Krabill AD, et al. Optimization of Acetazolamide-Based Scaffold as Potent Inhibitors of Vancomycin-Resistant Enterococcus. J Med Chem [Internet]. 2020 Jul 28 [cited 2023 Aug 19]; Available from: https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.0c00734

7) Venkataramanan NS, Suvitha A, Kawazoe Y. Intermolecular interaction in nucleobases and dimethyl sulfoxide/water molecules: A DFT, NBO, AIM and NCI analysis. J Mol Graph Model. 2017 Nov;78:48–60.

8) Supuran CT, Scozzafava A, Conway J. Carbonic Anhydrase: Its Inhibitors and Activators. CRC Press; 2004. 376 p.

9) Spectroscopic behavior of metal–drug complexes. Infrared spectra of Cu(II) dimer complexes with acetazolamide (H2acm) and an analogue sulfonamide (B-H2ats). Vib Spectrosc. 1999 Jun 1;20(1):35–45.

10) Synthesis, crystal structure and electron density analysis of a sulfanyl 2-pyridone analogue: Tautomeric preference and conformation locking by S···O chalcogen bonding. J Mol Struct. 2020 Dec 15;1222:128798.

11) Intermolecular interactions in microhydrated ribonucleoside and deoxyribonucleoside: A computational study. Computational and Theoretical Chemistry. 2021 Oct 1;1204:113422.

12) Venkataramanan NS. Cooperativity of intermolecular hydrogen bonds in microsolvated DMSO and DMF clusters: a DFT, AIM, and NCI analysis. J Mol Model. 2016 Jul;22(7):151.

13) Venkataramanan NS, Ambigapathy S. Encapsulation of sulfur, oxygen, and nitrogen mustards by cucurbiturils: a DFT study. J Incl Phenom Macrocycl Chem. 2015 Oct 16;83(3):387–400.

14) Nature of bonding and cooperativity in linear DMSO clusters: A DFT, AIM and NCI analysis. J Mol Graph Model. 2018 May 1;81:50–9.

15) Prathap L, Jayaraman S, Roy A, Santhakumar P, Jeevitha M. Molecular docking analysis of stachydrine and sakuranetin with IL-6 and TNF-α in the context of inflammation. Bioinformation. 2021;17(2):363.

16) Venkataramanan NS, Suvitha A. Theoretical Investigation of the Binding of Nucleobases to Cucurbiturils by Dispersion Corrected DFT Approaches. J Phys Chem B. 2017 May 11;121(18):4733–44.