THEORETICAL ANALYSIS OF THE EFFECTS OF COUNTERIONS ON THE SUPRAMOLECULAR ARRANGEMENT OF SULFAMETHOXAZOLE

Álice Cristina Borges Morais[1]
Igor Dalarmelino Borges[2]
Luiz Eduardo Krüger Dias[3]
José Luís Rodrigues Martins[4]
Hamilton Barbosa Napolitano[5]

Introduction:

Sulfamethoxazole (SMZ) is a sulfonamide that acts by competitively inhibiting the formation of folate from p-aminobenzoic acid (PABA). In a drug development process, salt formation is a strategy to modulate its pharmacokinetic and physicochemical properties, such as: aqueous solubility, dissolution, purity, stability and toxicity. Among the Active Pharmaceutical Ingredients marketed in salt form, sulfamethoxazole belongs to the class of sulfonamides widely used in the treatment of urinary tract infections (PROHOTSKY; ZHAO, 2012). Sulfamethoxazole has low bioavailability, low permeability and low solubility, in addition to presenting low absorption by the intestinal mucosa and great variability is expected (ALSUBAIE et al., 2018). In this sense, a pharmaceutical strategy to overcome these challenges is to promote its formulation in the form of salt.

Objective:

This work aims to investigate the effect of counterions (sodium, bromine and chlorine atoms) on the supramolecular arrangement of sulfamethoxazole by the Density Functional Theory (DFT). The types of interactions that govern the crystalline systems of sulfamethoxazole salts were studied using the Quantum Theory of Atoms in Molecules (QTAIM) by Density Functional Theory at the CAM-B3LYP / 6-311G ++

[1] Graduada, Universidade Evangélica de Goiás - UniEVANGÉLICA: alicecristinaborges@outlook.com
[2] Graduado, Universidade Evangélica de Goiás: - UniEVANGÉLICA, alicecristinaborges@outlook.com
[3] Mestre, Universidade Evangélica de Goiás – UniEVANGÉLICA, luiz.dias@unievangelica.edu.br
[4] Doutor, Universidade Evangélica de Goiás – UniEVANGÉLICA, jose.martins@docente.unievangelica.edu.br
[5] Doutor, Universidade Evangélica de Goiás, – UniEVANGÉLICA, hbnapolitano@gmail.com

theory level (d, p), whose atoms were kept fixed in their cryptographic positions (YANAI; TEW; HANDY, 2004).

Metodology:

In this research, we used the Hirshfeld Surface Analysis to qualitatively and quantitatively understand the intercontacts that form the crystal lattice. Surface construction occurs by partitioning the electron density in the crystal into molecular fragments. Theoretical Calculus is used to calculate the electron density which is a descriptor of the different molecular and chemical properties of systems composed of atoms and molecules. The Functional Density Theory method is among the most important methods used in the quantitative description of the properties of the molecular system, including in the crystalline state. Kinetic stabilities, boundary molecular orbitals, HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) were also calculated. The design of the structures was generated with ORTEP-3 for Windows and the Mercury software. In the PLATON software, the possible interactions and hydrogen bonds were calculated and analyzed using the Crystal Explorer software. The SMZNa, SMZBr and SMZCl structures were obtained from the Cambridge Crystallographic Data Center (CCDC) under code 1129102, 891649 and 667353, respectively. (FARRUGIA, 2012; MACRAE et al., 2006; S.K. WOLFF, D.J. GRIMWOOD, J.J. MCKINNON, M.J. TURNER, D. JAYATILAKA, 2012; SPEK, 2003).

Results:

Sulfamethoxazole belongs to the class of sulfonamides and its polymorphs include different counterions such as sodium (Na+), bromine (Br-) and chlorine (Cl-). The sulfamethoxazole salts are SMZNa, SMZBr and SMZCl. These salts crystallized in a monoclinic solid state environment - SMZNa ($C_{10}H_{11}N_3O_3S$) Na^+ in space group 21/c, SMZCl ($C_{10}H_{11}N_3O_3S$)Cl- - in Cc and SMZBr ($C_{10}H_{11}N_3O_3S$) Br- in C2/c (DE MOURA OLIVEIRA; C. DE MELO; DORIGUETTO, 2019). The sulfur atom linked to the atoms O1, O2, C4 and N2 is present, an amine or amide group that differs in the counterion atom, since the one that contains the complex sodium atom at the angles Na - N2 -S1 = 95.44º, Na - O2 - S1 = 116.62º, Na - O1 - S1 = 97.41º, due to this the angle O1 –S - O2 = 112.7º has a lower value when compared to SMZBr (120.3ºi) and

SMZCl (120.9º) compounds. Furthermore, such a discrepancy in the angle N2 - S1 - C4 = 109.5º for SMZNa, N2 - S1 - C4 = 106.0 (1) for SMZCl and N2 - S1 - C4 = 104.4 (1) for SMZBr. Twist angles are needed to represent molecular conformations. The substitution effects by comparing SMZ salts differ only in the counter-ion, in the structures of SMZNa, SMZBr and SMZCl the main molecular backbone is identical for all, which may indicate, a priori, the same conjugation length. We report here a comprehensive study of structural and energetic properties of ionic structures observed in sulfamethoxazole (counterions Na +, Br– and Cl–). The supramolecular arrangement of SMZNa is stabilized by short contacts around the sodium alkali metal ion, while SMZBr is stabilized by N – H ⋯ Br and C – H ⋯ Br interactions. SMZCl has intermolecular interactions involving the counter-ion and the nitrogen atom. The overlap of the SMZNa, SMZBr and SMZCl molecular conformations shows the identical main molecular backbone with the same conjugation length. Boundary molecular orbitals by DFT showed that the structures of SMZ + and SMZ– ions are stable in drug salts, and it was possible to assign the sites in the molecule where both the SMZ molecule and its respective ions are susceptible to electrophilicity (or nucleophile) attacks with Fukui functions. MEP maps indicated the location of each of the Na+, Br- and Cl- counterions in supramolecular arrays, and the QTAIM parameters showed that the counterions are binding to ions in closed shell interactions for shared interactions - interactions from weak character, such as van der Waals and hydrogen bonds, to partially covalent interactions.

Conclusion:

Natural bonding orbitals showed that the hyperconjugations between the donor and acceptor orbitals support the stability of interactions between ions for the formation of salt crystals. The physicochemical properties and molecular modeling of SMZ salts (Na +, Cl^- and Br^-) are the basis for new pharmaceutical development stages of SMZ, such as formulations, solubility and stability.

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