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A theoretical probe on the non-covalent interactions of sulfadoxine drug with pi-acceptors

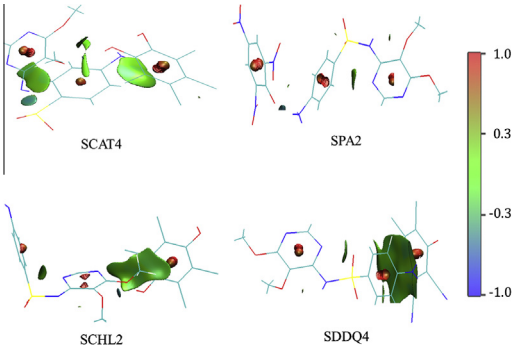
L. Sandhiya, K. Senthilkumar *

Department of Physics, Bharathiar University, Coimbatore 641 046, India

HIGHLIGHTS

- The interaction between sulfadoxine and pi-acceptors is studied.
- The nature of the non-covalent interaction has been addressed from NCI plot.
- IR and NMR spectra are used to characterize the complexes formed.

GRAPHICAL ABSTRACT



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ABSTRACT

A detailed analysis of the interaction between an antimalarial drug sulfadoxine and four pi-acceptors, tetrachloro-catechol, picric acid, chloranil, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is presented in this study. The interaction of the amine, amide, methoxy, C—H groups and π electron density of the drug molecule with the acceptors are studied using DFT method at M06-2X level of theory with 6-31G(d,p) basis set. The interaction energy of the complexes is calculated using M06-2X, M06-HF, B3LYP-D and MP2 methods with 6-31G(d,p) basis set. The role of weak interactions on the formation and stability of the complexes is discussed in detail. The two aromatic platforms of sulfadoxine play a major role in determining the stability of the complexes. The electron density difference maps have been plotted for the most stable drug interacting complexes to understand the changes in electron density delocalization upon the complex formation. The nature of the non-covalent interaction has been addressed from NCI plot. The infrared spectra calculated at M06-2X/6-31G(d,p) level of theory is used to characterize the most stable complexes. The SDOX-pi acceptor complexation leads to characteristic changes in the NMR spectra. The ^{13}C, ^{1}H, ^{17}O and ^{15}N NMR chemical shifts have been calculated using GIAO method at M06-2X/6-311+G(d,p)//M06-2X/6-31G(d,p) level of theory. The results obtained from this study confirm the role of non-covalent interactions on the function of the sulfadoxine drug.

Introduction

Sulfonamides are bacteriostatic antimicrobials used in combination with other drugs to prevent various bacterial infections [1,2]. Sulfadoxine is an inexpensive drug and it is used as first-line therapy for malaria. It is an ultra-long lasting drug and have wide spectrum of antimicrobial activity when used in combination with pi-acceptors [3]. The sulfadoxine contains two important functional groups in the pharmaceutically relevant pH range of 4–9, i.e. one acidic amide moiety and one basic amine moiety. The amine nitrogen atom (—NH_2) is able to accept a proton, while

* Corresponding author. Tel./fax: +91 422 2422387.
E-mail address: ksenthil@buc.edu.in (K. Senthilkumar).

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the amide nitrogen atom (—NH) is able to donate a proton under specific pH conditions. This results in strong hydrogen bonding interaction between the sulfadoxine and pi-acceptors, which determines the binding and stability of the drug. Depending on the structure and functional group of the drug molecule, the interaction between the drug molecule and receptor can be hydrogen bonding, charge transfer or covalent interactions [4]. Favorably, the drug–receptor binding occurs by ionic association through hydrogen bonding, by charge transfer and also by the combination of these two forces [5]. Covalent interactions are less important in drug–receptor binding. The acceptor molecules are electron deficient systems with electron-withdrawing functional groups. The electrostatic interaction between a positively charged cation and a negatively charged electron cloud of π system is the strongest among the non-covalent interactions [6,7]. The interaction between drug molecules and pi-acceptors is the primary director of specificity, rate control and reversibility in many biochemical reactions.

The specific geometrical arrangement of sulfadoxine (SDOX) provides hydrogen bonds and some degree of water solubility. The structure of sulfadoxine is shown in Fig. 1. The SO_2NH group in the sulfadoxine acts as a good binding site for the acceptors [1]. The presence of S—N and S—O bonds enhance the formation of strong hydrogen bonding network [1]. The lone pairs in O and N-atoms is crucial in determining the acid–base properties of sulfadoxine at physiological pH. The presence of amine, amide and methoxy functional groups in sulfadoxine facilitate the hydrogen-bonding and charge transfer interactions with acceptor molecules like tetrachloro-catechol (CAT), chloranil (CHL), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and picric acid (PA). These acceptors are known to yield hydrogen-bonded and charge-transfer complexes with variety of electron donors [8,9]. The structure of these acceptors is shown in Fig. 1. The common binding sites for these acceptors are the NH_2 and CH groups. In these motifs, the N—H----X^-, (N—H)$^+$----X^-, O—H----X^-, (O—H)$^+$----X^- and C—H----X^- (X is an electronegative atom) interactions are responsible for the binding of the acceptors with the drug molecule. A previous study on the interaction between anti-Alzheimer drug galanthamine with benzene molecules reveal that among the various hydrogen bond donor groups of the molecule, CH group plays a vital role [10]. Previous theoretical studies show that the electrostatic contribution to hydrogen bonding decreases in the order of O—H > N—H > C—H [11,12]. As a consequence of the electrostatic interaction between donor and acceptor molecules, the energy of the highest occupied molecular orbital (HOMO) centralized on the donor decreases and the energy of the lowest unoccupied molecular orbital (LUMO) centralized on the acceptor increases, resulting in strong interaction between donor and acceptor molecules [13].

The phenolic OH group present in CAT acts as a good hydrogen bond donor and it often undergoes deprotonation [14]. The chloride anion present in the CAT and CHL showed a distinct tendency when it comes closer to SDOX. The chlorine atom present in the CHL effectively involves in halogen bonding with the nucleophiles such as S, N and O of SDOX and also hydrogen bonding with the electrophiles. The halogen bonding is also an important interaction in the context of drug design [15–18]. The halogen bonding interaction is attributed as the presence of a small positive electrostatic potential end cap along the C-Y (Y is the halogen atom) bond vectors and the anisotropic distribution of electron density around halogen atom [19]. The majority of the structural and energetic aspects of halogen bonding are similar to that of the hydrogen bonding. Hence, the quantification of the interaction between SDOX and acceptors with Cl-atom is important to understand the drug–acceptor binding.

The charge transfer and the formation of hydrogen and halogen bonds in a drug–acceptor complex is an exchange process [5]. Refat [20] studied the charge-transfer reactions of SDOX with pi-acceptors such as, CHL, DDQ and PA and characterized the donor–acceptor complexes by FTIR, NMR, TG-DTG and electronic absorption. As discussed before, in addition to the charge transfer reactions, the other non-covalent interactions between the donor and the acceptor is very important to determine the drug–receptor binding. In the study by Refat, the formation of donor–acceptor complexes through non-covalent interactions was not reported. These complexes are more stable than the charge-transfer complexes. Studying the interaction between drug molecule and pi-acceptor is one of the main tasks in testing and evaluating the drug molecule. Formation of relevant hydrogen bonds is responsible for inhibitor binding in the receptor. The substitution of electron withdrawing or electron donating groups or molecules having such functional groups on the drug molecule leads to opposite effects on the activity of the drug. A detailed study on different types of hydrogen bond formation between sulfadoxine and selected pi-acceptors will greatly facilitate to understand such effects. Hence, in order to understand the interaction between the SDOX drug and pi-acceptors, a systematic theoretical study on the non-covalent interactions existing between SDOX and pi-acceptors is essential. The aim of the present work is to study the interaction of the SDOX drug with pi-acceptors such as CAT, CHL, PA and DDQ using electronic structure calculations. The thermodynamics of complexation and stability of the complexes are investigated in terms of enthalpy, entropy and free energy changes. The strength of the non-covalent interactions is studied through interaction energies. This work also provides a consistent description of the vibrational and NMR spectra of the stable complexes in order to gain a better understanding of the interaction between SDOX drug and pi-acceptors.

Computational methodology

The geometry of the monomers and complexes formed from the interaction of SDOX with pi-acceptors are optimized using DFT-M06-2X method [21] with 6-31G(d,p) basis set. The M06-2X functional has been proved to be the best suited functional for the study of non-covalent interactions [22,23] and provide accurate results for thermodynamics and kinetics. The harmonic vibrational frequencies were calculated for all the stationary points to identify their nature. The interaction energy of the complexes formed through non-covalent interactions is calculated at M06-2X, M06-HF [24], B3LYP-D [25,26] and MP2 methods [27–29] with 6-31G(d,p) basis set. The interaction energy is calculated by taking the difference between the total energy of the product complex and the sum of the total energy of the monomers. The basis set superposition error (BSSE) is a common artifact in the calculation of interaction energy which leads to inaccurate interaction energies. BSSE arises due to a small overlap of monomer orbitals in the combined complex compared to the isolated components. BSSE is eliminated using counterpoise method of Boys and Bernardi [19]. The change in electron density due to the SDOX-pi acceptor complex formation is obtained by subtracting the sum of the electron densities of the monomers from the total electron density of the complexes formed. The difference in densities was plotted with an isodensity value of 0.2 e/au^3. The nuclear magnetic resonance (NMR) spectroscopic shieldings of the isolated molecules and most stable complexes have been calculated using the gauge-independent atomic orbital (GIAO) method at M06-2X/6-311+G(d,p)//M06-2X/6-31G(d,p) level of theory [30]. The chemical shift is obtained by subtracting the calculated magnetic shielding for the nuclei of interest from the shielding of nuclei in reference compound (tetramethylsilane (TMS) for ^{13}C and ^{1}H, H_2O for ^{17}O, and NH_3 for ^{15}N). All these calculations were performed with Gaussian 09 program package [31].