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A theoretical study on the characteristics of the intermolecular interactions in the active site of human androsterone sulphotransferase: DFT calculations of NQR and NMR parameters and QTAIM analysis

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ABSTRACT

A theoretical study at the level of density functional theory (DFT) was performed to characterize noncovalent intermolecular interactions, especially hydrogen bond interactions, in the active site of enzyme human androsterone sulphotransferase (SULT2A1/ADT). Geometry optimization, interaction energy, ^{2}H, ^{14}N, and ^{17}O electric field gradient (EFG) tensors, ^{1}H, ^{13}C, ^{17}O, and ^{15}N chemical shielding (CS) tensors, Natural Bonding Orbital (NBO) analysis, and quantum theory of atoms in molecules (QTAIM) analysis of this active site were investigated. It was found that androsterone (ADT) is able to form hydrogen bonds with residues Ser80, Ile82, and His99 of the active site. The interaction energy calculations and NBO analysis revealed that the ADT molecule forms the strongest hydrogen bond with Ser80. Results revealed that ADT interacts with the other residues through electrostatic and Van der Waals interactions. Results showed that these hydrogen bonds influence on the calculated ^{2}H, ^{14}N, and ^{17}O quadrupole coupling constants (QCCs), as well as ^{1}H, ^{13}C, ^{17}O, and ^{15}N CS tensors. The magnitude of the QCC and CS changes at each nucleus depends directly on its amount of contribution to the hydrogen bond interaction.

1. Introduction

The sulfonation process was first characterized in the late 1870s by Eugen Baumann. It has since been shown that Sulfonate conjugation is an important pathway in the biotransformation of numerous xenobiotics and endobiotics such as drugs, chemical carcinogens, hormones, bile acids, neurotransmitters, peptides, and lipids [1]. Biological sulfonation reaction is catalyzed by members of the sulphotransferase (SULT) supergene family [2]. These enzymes catalyze the transfer of a sulfuryl group from 3′-phosphoadenosine 5′-phosphosulfate (PAPS), the universal sulfuryl group donor molecule, to a hydroxyl or amino-group on an acceptor substrate [2]. Human hydroxysteroid sulphotransferase (SULT2A1), which was originally named as dehydroepiandrosterone (DHEA) sulphotransferase, is able to sulfonate various steroid and their derivatives, including (DHEA), androsterone (ADT), testosterone (TES), estradiol (EST), and many other endogenous steroids [3–5].

ADT sulfonation is one of the main catabolism processes of androgens in human liver before urinary excretion [6], which is catalyzed by enzyme human SULT2A1 containing the ADT substrate (SULT2A1/ADT, Protein Data Bank (PDB) ID: 1OV4) in human liver [7]. Free ADT structure is shown in Fig. 1 [8]. Androsterone sulfate (ADTS) is the most abundant circulating 5α-reduced androgen metabolite in serum [9].

Moreover, the binary complex crystal structures of enzyme human SULT2A1 have been reported in the presence of DHEA (SULT2A1/DHEA, PDB ID: 1J99) [10], as well as in the presence of 3′-phosphoadenosine 5′-phosphate (PAP) and in the absence of the substrate (SULT2A3, PDB ID: 1EFH) [11]. The structural comparison of the SULT2A1/ADT with the SULT2A1/DHEA shows that their sequence identity and similarity are 99.7% and 100%, respectively. The partially structural differences between them are only in some residues and the flexible loops [7]. These enzymes possess an α/β-fold with a central four-stranded parallel β-sheet surrounded by α-helices on both sides [7,10]. Previous studies have demonstrated

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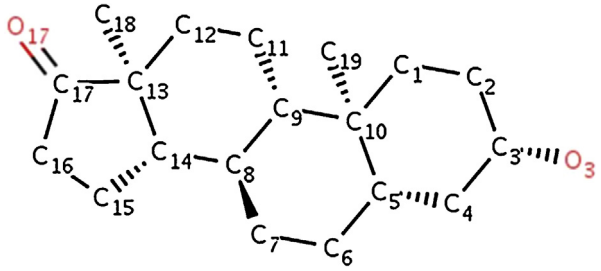

Fig 1. Structure of androsterone (ADT).

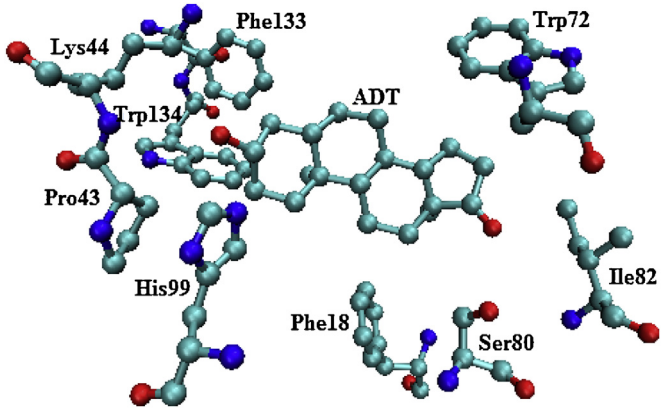

Fig. 2. The structural model of the active site amino acids of the SULAT2A1/ADT (model I).

that there are two distinct orientations for locating substrate within the active site of the SULT2A1/DHEA, the catalytic and the alternative [10]. However, there has been only one substrate orientation identified within the active site of the SULT2A1/ADT [7]. Superimposing these two enzymes indicates that the location of the ADT substrate is close to the location of the DHEA substrate in the proposed alternative orientation [7].

It is obvious that noncovalent intermolecular interactions, especially hydrogen bonds (HBs), play a unique role in the ADT binding in the active site of the SULT2A1/ADT. The crystal structure of this enzyme shows that the ADT contributes to the two HB interactions with neighboring amino acids [7]. Firstly, the O-3 atom of ADT is able to form an HB with Nε-2 atom of His99. Secondly, the O-17 atom of ADT forms an HB with the hydroxyl oxygen of Ser80.

Conventionally, noncovalent forces are divided into two types. The first type of forces has the electrostatic nature (such as HB) [12] and the second type which arises as a result of the simultaneous electron correlation of separated subsystems (such as dispersion interactions) [13]. Although dispersion interaction is very weaker than the HB interaction, it plays a fundamental role in the substrate binding within the active site of the interested enzyme. In order to describe accurately the nature of the intermolecular interactions, the use of the appropriate computational methods is essential to study this active site. Theoretical studies have shown that the M06 series of functionals are very appropriate to study accurately in biological systems [14]. The main objectives of this study are to characterize the nature of noncovalent intermolecular interactions between ADT and neighboring amino acids in the active site of the SULT2A1/ADT by using density functional theory (DFT). For this purpose, we applied the quantum theory of atoms in molecules (QTAIM) analysis for this active site.

On the other hand, the HB interaction is a complex phenomenon and different theories exist about its precise physical nature [15]. In many investigations, the HB interactions are described in terms of electrostatic and charge transfer (delocalization) forces and it is believed to be the best characterized type of noncovalent interactions [16–19]. Due to electrostatic nature of the HB interactions, it is necessary to use proper techniques for more accurate investigation of the HB properties. Nuclear quadrupole resonance (NQR) and nuclear magnetic resonance (NMR) spectroscopies are the most versatile and powerful techniques to study the properties of various types of the HB interactions [19,20]. Electric field gradient (EFG) and chemical shielding (CS) tensors are highly sensitive to the electron distribution around those quadrupole nuclei, e.g., ^{2}H, ^{17}O, and ^{14}N, and magnetic nuclei, e.g., ^{1}H, ^{13}C, ^{17}O, and ^{15}N, respectively, which contribute to the HB interactions in the hydrogen-bonded systems [21–23]. Furthermore, it is well known that traditional quantum chemistry codes are able to compute CS and EFG tensors [19,20]. Many theoretical studies have demonstrated that quantum chemical calculations of NMR and NQR parameters are useful tools in assigning experimental NMR and NQR spectra [24,25]. In addition, Wu et al., have shown that quantum chemical CS and EFG tensors calculated with DFT technique are in good agreement with the experimental values [26,27]. In general, DFT level is among the most popular and versatile method for NMR and NQR calculations in quantum chemistry and the solid state physics [20,28]. Since EFG and CS tensors are very sensitive to the local intermolecular HB interactions, this study has evaluated EFG and CS tensors at the sites of the mentioned quadrupole and magnetic nuclei, respectively, by using DFT calculations in the SULT2A1/ADT active site. Moreover, based on Natural Bonding Orbital (NBO) theory, the HB formation is the result of hyperconjugative charge transfer from lone pair of an electron donor (A) into antibonding σ^{*}_{B-H} orbital of an electron acceptor (B) [29,30]. In this paper, because of charge transfer nature of the HB interaction, NBO analysis was performed in order to find a rational relation between NQR parameters, as well as NMR parameters, and charge transfer phenomenon.

2. Model building

Amino acid residues forming the active site of the SULT2A1/ADT at 4 Å distance away from substrate consist of Phe18, Pro43, Lys44, Trp72, Ser80, Ile82, His99, Phe133, and Trp134, as well as the ADT molecule [7]. ADT interacts with these residues through the different types of intermolecular interactions. In order to investigate the nature of these interactions, the mentioned residues along with the ADT molecule were separated from the other parts of the SULT2A1/ADT. Therefore, a structural model was constituted that is referred as the first model (model I).

In order to investigate the effects of the HB interactions on EFG and CS tensors of those nuclei involved in HB interactions, the SULT2A3 was selected as an original structure because its sequence identity and similarity with SULT2A1/ADT is 92.7% and 93.0%, respectively. Therefore, residues Phe18, Pro43, Lys44, Trp72, Ser80, Ile82, His**99**, Phe133, and Trp134 were separated from the other parts of the SULT2A3 and are called as the second model (model II). In both models, a $-CH_3$ group and an $-OCH_3$ group were added to the N- and C-terminal ends of each free residue, respectively. Models I and II can be observed in Figs. 2 and 3, respectively.

3. Computational aspects

All calculations were performed by using GAMESS electronic structure package [31]. The crystalline structures of the SULT2A1/ADT and the SULT2A3 are available from PDB website [7,10]. Since all atomic coordinates, except hydrogen atoms, were directly taken from a X-ray diffraction structure, a partial geometry optimization was done in order to locate accurately the positions of the hydrogen atoms of each model, with the frozen positions of the other atoms, using the M06-2X and M06-L functionals.