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Study of Local Reactivity of Ricin Toxic A chain Based on Conceptual Density Functional Theory

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Abstract: The Ricin Toxic A chain RTA is a subunity of Ricin protein, which is a ribossome inactivator very toxic for humans. This protein is found in castor plant that is raw material for several valuable products. Hence, it is plenty interest in inactivation of RTA toxicity activity to insure industry biosafety[1]. The field computational molecular modeling provide useful tools to explore drug design, one of them that is growing for biological systems is the Reactivity Descriptors (RDs) developed by Hard and Soft Acid Base Theory, and Fukui's Frontier Molecular Orbital. The Conceptual Density Functional Theory rises in the process of establishing correspondence between the RDs and coefficients of the fundamental differential equation of DFT[2]. These descriptions cover global molecule's trends of charge transfer, polarization and electrostatic long range interactions[3]. Also, local reactivity trends derived from electron density changes as electron number vary[4]. Such descriptors are well established for small molecules, currently being applied for reaction rationalization[5], QSAR[6] and regioselectivity[4] studies. For large/biological system the application of RDs can be exemplified in the literature as: protonation state determination[7]; docking ligand score functions and evaluation of residue interactions[8]. Although, these studies relies on quantum mechanical methods with lack of electron correlation or without computing properly the protein and solvent environment effects on active sites. However, it is difficult to demand full ab initio treatment for such large systems as proteins. In the present work, we propose the use of Fragment Molecular Orbital (FMO)[9] method for efficient ab initio calculation to obtain local reactivity descriptors of RTA. FMO is a fragmentation scheme for quantum mechanical (QM) calculations that divides a large system in several monomers[9]. The FMO does not depend on empirical fitted parameters and are reported for providing accurate energies, orbital and densities for large system when compared with full ab initio calculations[10]. Then, we use the frontier molecular orbitals densities of RTA obtained with FMO to calculate the Fukui indices in order to describe local reactivity. The first calculations were performed using the 2-nbody FMO method[11] in GAMESS program, at HF/STO-3G level of theory without counting the solvent effect. The fragmentation was carried out using two protein residues by monomer. The Fukui indices for the electrophilic attack susceptibility from the electron density of a neutral charge state of RTA and a negatively charged. The results show that there is a spatial concentration of that descriptor, which is shown in Figure 1 by the rendered scalar field volume around the protein atoms. That region could indicate an active site for a electrophile ligand to react or dock. The FMO method allow us to calculate the descriptors using ab-initio or DFT treatment for a molecule containing more than 4000 atoms, accounting the electronic structure of the entire protein.

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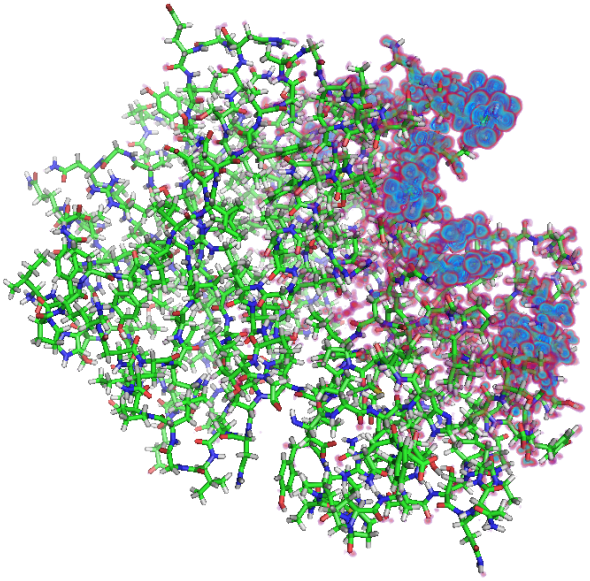

Figure 1: Volume rendering of Fukui's function of electrophilic susceptibility on RTA protein structure representation.

Keywords: RTA; Conceptual Density Functional Theory; Fragment Molecular Orbital
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