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TD-DFT Study on the Toxicity Prediction of Thiopental Sodium

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Abstract

In this study, Thiopental sodium investigated natural toxicity and reactivity at the TD-DFT/CAM-B3LYP level, theoretically. Using the Parr formula, the interaction between 4- thiopental sodium molecule and nucleic acid (NA) bases (adenine, thymine, cytosine,uracil and guanine) were investigated. Charge transfer that are important in the formation of chemically bonded adducts causing cancer are quantitatively calculated. Our results show that thiopental sodium has low toxicity with calculations of reactivity descriptors.

Key Words: Thiopental sodium, time-dependent density functional theory, (TD-DFT), toxicity.

1. Introduction

Thiopental sodium with IUPAC name (monosodium 5-ethyl-5-[(1RS)-1-methylbutyl]-4,6-dioxo-1,4,5,6-tetrahydropyrimidine-2-thiolate) is a short-acting effective anesthetic drug. In its structure, nucleic acids, coenzymes, vitamins and antibiotics are important in terms of containing the ring of pyrimidine [1]. Pyrimidine compounds are also important for use in hypnotic drugs for the nervous system. In addition, the use of compounds containing donor atoms such as nitrogen and sulfur in the form of thiouracil makes thiopental sodium more important as anti-cancer and antiviral activities [2].

There are experimental studies of thiopental sodium compound related to many biological systems [1,3-5]. These studies consisted of thiopental sodium compound experimentally, structurally, thermally and in specific doses of thiopental sodium, the blood pressure and heart rate changes in mice, melatonin level in children and toxicity of liver organ. Experimental toxic studies are both costly and very labor intensive.

Toxic substances act as electron acceptors during the charge transfer phase. This fact has been verified in previous studies [6-8]. DFT-based reactivity parameters [9], which play an important role in most research. Global hardness (η), electrophilicity, chemical potential (μ) and electronegativity (χ) are a few examples of these reactivity descriptors. Toxicity is thought to result from possible transfer of charge between a toxin and a biosystem [10-12]. Here, a model biosystem was constructed from selective nucleic acid bases, since a toxin is expected to interact with NA bases .

Biological experiments are often limited in terms of sample, time and cost. In this context, recent studies have shown that the DFT-based reactivity descriptors are advantageous and can be compared with the experimental observations [9]. The reactivity descriptors calculated using the DFT method play an important and reliable role in many studies [13-20].

In this study, the DFT-based reactivity and toxicity of the thiopental sodium were determined. For this purpose, HOMO-LUMO energy levels of the optimized molecule were calculated. We calculated the amount of charge transfer between a model biosystem and a thiopental sodium molecule. We chose nucleic acid (NA) bases (adenine, thymine, cytosine, uracil and guanine) as a model biomolecule in this study.

2. Methods and Materıals Samples

2.1. Theoretical Calculation

All quantum chemistry density functional theory (DFT) calculations are carried out using GAUSSIAN 09 package [21]. The geometry of thiopental sodium is optimized by using a new hybrid exchange–correlation functional named a Coulomb-attenuated hybrid exchange-correlation functional (CAM-B3LYP), which includes both the hybrid qualities of B3LYP and the long-range corrention presented by Tawada et al. [22]. Previous studies [23-25] on similar molecular systems with CAM-B3LYP in comparison because it provides reliable results, we used the same basic set in this study.

It is important to explain the reactivity of a chemical species, the most occupied molecular orbital named HOMO, and the least empty molecular orbital named LUMO. This was first recognized by Fukui

[26]. There is an direct correlation between E_{HOMO} and toxicity. E_{HOMO} is often associated with the electron donor ability of the molecule. A molecule's high HOMO energy ensures that the appropriate receptor molecules have the potential to provide low energy electrons to the empty molecular orbital. Similarly E_{LUMO} is an indication of the ability of the molecule to accept electrons. The less valuable the E_{LUMO}, the more probable it is that the molecule would accept electrons. As a results, concerning the value of the energy of the gap $\Delta E = E_{LUMO}-E_{HOMO}$, larger values of the energy difference will provide low reactivity to a chemical reaction. The global hardness (η) has been indicated to be a very powerful tool global index of reactivity in atoms, molecules and clusters [27,28]. The theoretical definition of chemical hardness has been provided by the density functional theory as the second derivative of electronic energy with respect to the number of electrons N, for a constant external potential $V(r)$:

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r)} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{V(r)} \quad (1)$$

where E is the total energy, N is the number of electrons of the chemical species and μ is the chemical potential, which is identified as the negative of the electronegativity χ as defined by Iczkowski and Margrave [29]. By applying finite difference approximation to Eq. (1) we get the operational definition for η as:

$$\eta = (IP - EA)/2 \quad (2)$$

Eq. (2) can be rewritten as follows using Koopmans' [43/27] theorem as:

$$\eta = \frac{\varepsilon_{LUMO} - \varepsilon_{HOMO}}{2} \quad (3)$$

Parr et al [30] introduced the global electrophilicity index (μ) in relation to chemical potential and hardness as:

$$\omega = \frac{\mu^2}{2\eta} \quad (4)$$

The global interactions between the compounds of NA bases have been determined using the parameter ΔN transferred from a system A to system B, and is represented by [31]:

$$\Delta N = \frac{\mu_B - \mu_A}{2(\eta_A + \eta_B)} \quad (5)$$

For the possible toxicity of the thiopental sodium, the various reactivity and descriptors such as chemical hardness (η) calculated using Eq. (3), chemical potential (μ) defined as: μ=-(ε_LUMO+ε_HOMO)/2, electrophilicity index (ω) using Eq. (4) are obtained. We have obtained the amount of charge transfer [25] between headline molecule and model biomolecules by using Eq. (5).

3. Results and Discussion

3.1. Reactivity Descriptors and Frontier Molecular Orbitals

The optimized geometry of thiopental sodium is shown in Figure 1 with the atom numbering. Frontier molecular orbitals (HOMO and LUMO) were calculated at the at the TD-DFT/CAM-B3LYP level of theory.

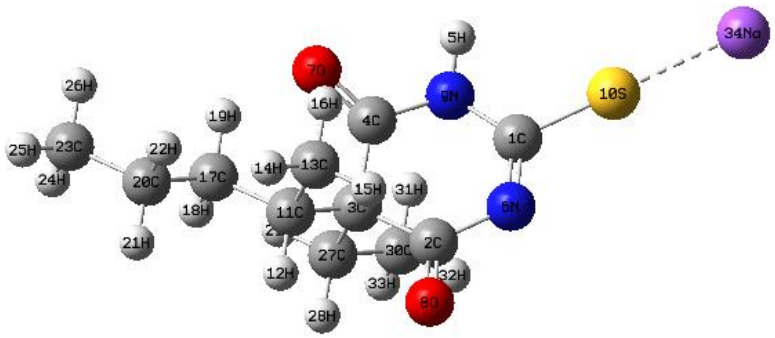

Fig. 1. The optimized geometric structure of thiopental sodium.

The 3D diagram for the two most important molecular orbitals named HOMO, LUMO in the most stable state of the head molecule is shown in Fig.2. It shows that the HOMO and LUMO orbitals are localized on the pyrimidine ring. Also, red color indicates the presence of electrons or negative charges, and the green color indicates the absence of electrons or positive charges. For thiopental sodium, HOMO orbital energy was calculated as 7.90 eV, 0.57 eV for LUMO level. The HOMO-LUMO energy gap was estimated at 7.33 eV at the TD-DFT/CAM-B3LYP level. This high HOMO-LUMO energy gap means good stability, low reactivity and low toxicity for thiopental sodium.

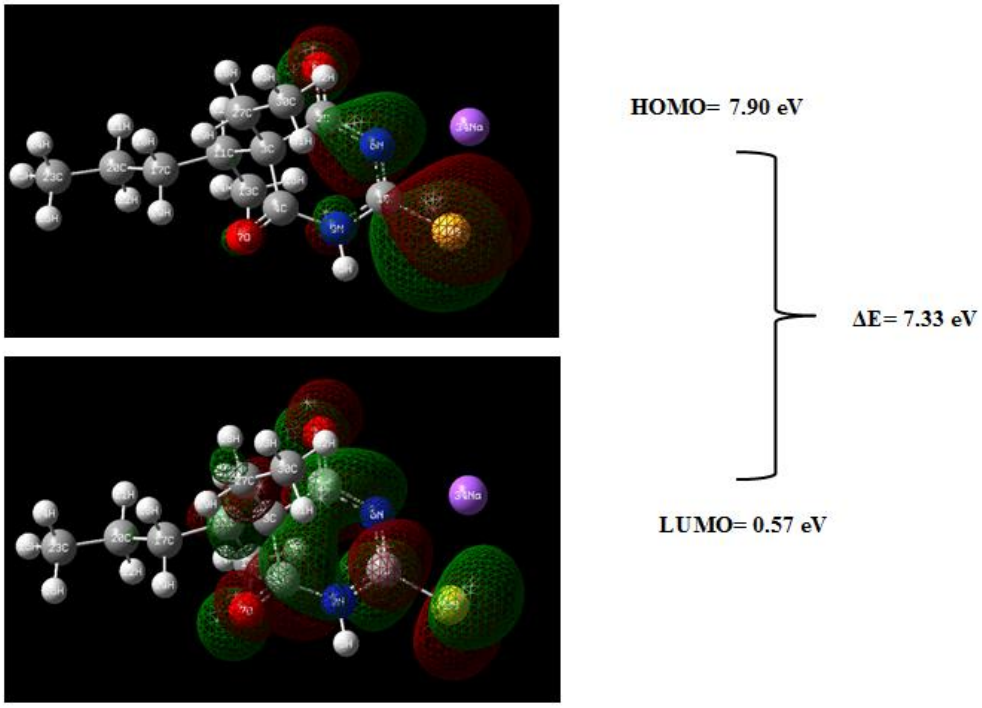

Fig.2. Frontier molecular orbitals of thiopental sodium.

The global chemical reactivity descriptors such as chemical hardness, electronegativity and electrophilicity index of Thiopental sodium optimized at CAM-B3LYP/6-311++G(d,p) are calculated and are listed (Table 1).

Table 1. The calculated energies values of thiopental sodium molecules using by the TD-DFT/ CAM-B3LYP method using 6-311G++(d,p) basis set.

	Water
E_{total} (Hartree)	-1249.7145
E_{HOMO} (eV)	-7.90
E_{LUMO} (eV)	-0.57
E_{HOMO-1} (eV)	-8.03
E_{LUMO+1} (eV)	0.11
$E_{HOMO-1-LUMO+1\ gap}$ (eV)	7.92
$E_{HOMO-LUMO\ gap}$ (eV)	7.46
Chemical hardness (h)	3.66
Electronegativity (χ)	4.24
Chemical potential (μ)	-4.24
Electrophilicity index (ω)	2.46

Table 2 reports the total electronic energy (E) and global reactivity descriptors (χ, η and μ) for nucleic acid bases *viz*., Adenine, Guanine, Cytosine, Thymine, Uracil . There is always electron flows from less electronegative system to more electronegative system [32]. Charge transfer calculation for detecting electron transfer between thiopental sodium and bases are reported showing clearly the electron donating nature of thiopental sodium. To quantitatively estimate the electron transfer in the interaction of nucleic acid bases with thiopental sodium, we have calculated the amount of charge transfer between thiopental sodium and model biomolecules by applying Eq. 5. Table 2 shows that the ΔN values of other receptors except for Uracil are positive. Therefore, thiopental sodium acts as an electron acceptor in the reaction with other receptors except uracil. Again, it was calculated to be smaller than the chemical potential thiopental sodium of nucleic acid bases other than uracil. Therefore, when thiopental sodium interacts with the model biomolecule except for a uracil, electrons flow to thiopental sodium.

Table 2. Calculated electronic energy, chemical hardness and chemical potential and between a NA bases a thiopental sodium molecule NA bases and the amount of charge transfer of the NA bases .

Bases	Electronic energy (eV)	Chemical Hardness (eV)	Chemical Potential (eV)	ΔN
Adenine	-12720.504	2.68	-3.79	1.422
Thymine	-12362.028	2.70	-4.17	0.230
Guanine	-14768.821	2.67	-3.51	2.316
Cytosine	-10750.465	2.52	-3.92	0.997
Uracil	-11291.830	2.80	-4.37	-0.435

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