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DFT application for chlorin derivatives photosensitizer drugs modeling

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ABSTRACT

Photodynamic therapy is an alternative form of cancer treatment that meets the desire for a less aggressive approach to the body. It is based on the interaction between a photosensitizer, activating light, and molecular oxygen. This interaction results in a cascade of reactions that leads to localized cell death. Many studies have been conducted to discover an ideal photosensitizer, which aggregates all the desirable characteristics of a potent cell killer and generates minimal side effects. Using Density Functional Theory (DFT) implemented in the program *Vienna* Ab-initio *Simulation Package*, new chlorin derivatives with different functional groups were simulated to evaluate the different absorption wavelengths to permit resonant absorption with the incident laser. Gaussian 09 program was used to determine vibrational wave numbers and Natural Bond Orbitals. The chosen drug with the best characteristics for the photosensitizer was a modified model of the original chlorin, which was called as Thiol chlorin. According to our calculations it is stable and is 19.6% more efficient at optical absorption in 708 nm in comparison to the conventional chlorin e6. Vibrational modes, optical and electronic properties were predicted. In conclusion, this study is an attempt to improve the development of new photosensitizer drugs through computational methods that save time and contribute to decrease the numbers of animals for model application.

1. Introduction

Modeling a real system is a highly complex task. Computer tools have been just developed recently [1–14] and for this reason, it is possible to note that there is discrepancies between the amounts of works dedicated to experimental research and those made by computer simulations. Photodynamic Therapy (PDT) investigations are mainly experimental and clinics procedures [15–17]. These analyses demand a long time in laboratory, and also require many supplies and reagents.

PDT is an alternative treatment against the cancer, which is a methodology less aggressive. Unlike chemotherapy and radiotherapy, it shows good results without cumulative toxicity, which guarantee the use of this treatment in immunocompromised patients. For this reason, the number of studies about the PDT has increased and is highlighted between new forms of cancer treatment [18,19]. This treatment is based on the interaction between a drug, which is a photosensitizing substance, an activating light, and molecular oxygen [20,21].

The aim of this study is to shed some light for optimization of photosensitizing drugs via computing modeling in order to guide experiments minimizing the number of photosensitizing to be tested in laboratory.

The changes in the photosensitizing molecule conformations helped to perform calculation of stability of the structures in order to find an optimized drug for activation functions. Other properties were also studied such as the vibrational modes and optical features of the illumined molecule. Modeling is a powerful tool for this study because it minimizes the use of chemical synthesis and cellular tests for each proposed drug. Thus, Density Functional Theory (DFT) may give reliable results providing a specific drug with less collateral effects and high efficiency when compared with old types of treatment.

1.1. Theoretical Methodology

The methodology is based on the DFT implemented in the *Vienna* Ab-initio *Simulation Package* (VASP) [22]. The electron–ion interactions between N, O, C, S and H atoms are described by Projector Augmented Wave (PAW) potentials [23,24] and the electron–electron exchange-

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correlation energy was simulated using the generalized gradient approximation (GGA) [25].

Single-particle orbitals were expressed in a plane-wave basis up to the energy of 400 eV. Atoms were assumed to be in their fully relaxed positions when the forces were smaller than 0.2 eV/Å.

The modeling assessment was performed by percentage error calculation, considering as base, the values expressed for the vibrational modes of chlorin e6 in a study by Gladkova et al. (2010) [26]. Thus, the error showing the divergence of results obtained by our simulations was compared with the experimental data given in the literature. As an alternative in this work was also carried out DFT calculations using Gaussian 09 program B3LYP functional with a single basis set 3-21G [27] for determine the vibrational spectra (FTIR) and the Natural Bond Analysis (NBO). All the illustrations were plotted using the Visual Molecular Dynamics (VMD) [28].

2. Modeling Chlorin

In order to make an ideal drug model the Photodithazine drug, which is cited as (chlorin e6), was used as the main structural prototype. The structure has a ring and branches of N- metil-D-glicosamina. The molecule absorbs between 650 and 680 nm [9].

Fig.1 (a) shows the chemical structure of the molecule found in literature [29]. Part (b) and (c) represent the Photodithazine model, in this work it was called by *Base Chlorin*.

The Base Chlorin geometry was built considering the Porphyrin ring as base [29,30]; moreover, carbon chain molecules were used to simulate some radical structures like the branches of the molecule. According to literature [31–33], these branches formed by hydrophobic radicals may improve the penetration of a drug in an animal membrane, which is mainly composed by phospholipids. This geometry conformation may be a possible explanation for the good penetration of this drug in tumor cells.

Fig. 2 shows two modified Base Chlorin models with the additional groups. In the right circle of the Fig. 2 shows a model called as Thiol Chlorin; this structure contains a thiol group (-SH) in its right chain. A second model (left circle), Hydrocarbon Chlorin, was suggested with an aliphatic carbon chain functionalized with a thiol group (-S $(CH_2)_6$) instead of a simple thiol group. This aliphatic chain is considered as an effective separator [34], thus, it may also be used to generate space between surface of carrier and the drug such as Chlorin. Nanoparticles are often used as drugs carrier [35–41], which are functionalized with different linker such as thiol group and lipoic acid [42,43]. In this context, the present work may help to answer questions about the possible interference of these linkers in the optical properties of the Photodithazine, which is functionalized with these additional groups.

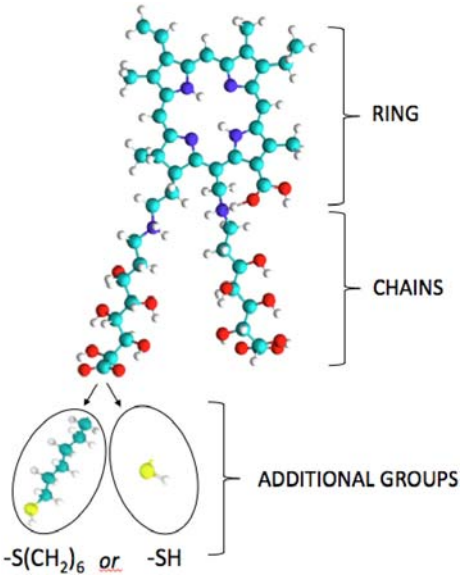

Fig. 2. - Representation of Base Chlorin modified with the additional groups. In the right circle Thiol Chlorin (—SH) and in left circle Hydrocarbon Chlorin (—S $(CH_2)_6$). The large spheres of red, dark blue, yellow and light blue correspond to O, N, S and C atoms, respectively, while the small white spheres represent H atoms. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

To evaluate possible changes in the chlorin geometry due to the biological environment other models were suggested in this work, as can be seen in the Fig. 3. It is known that different biological environment may have distinguished properties such as temperature, pH and also the presence of ions. It is suggested that some kind of drugs may change their conformation when they reach their target cells, for instance, cancer cells target. These geometry changes are important because they may be responsible for the drug accumulation inside the target cell. Thus, this work presents a possible transition of cis-like and trans-like conformation of the drug with presence of double bond in the ring's region close to the its branches (see Fig.1a).

3. Results and Discussions

3.1. Chlorin Structural Analysis

The first step of the model validation is shown in the Table 1, which contains results of the molecule energy evaluation. This study was

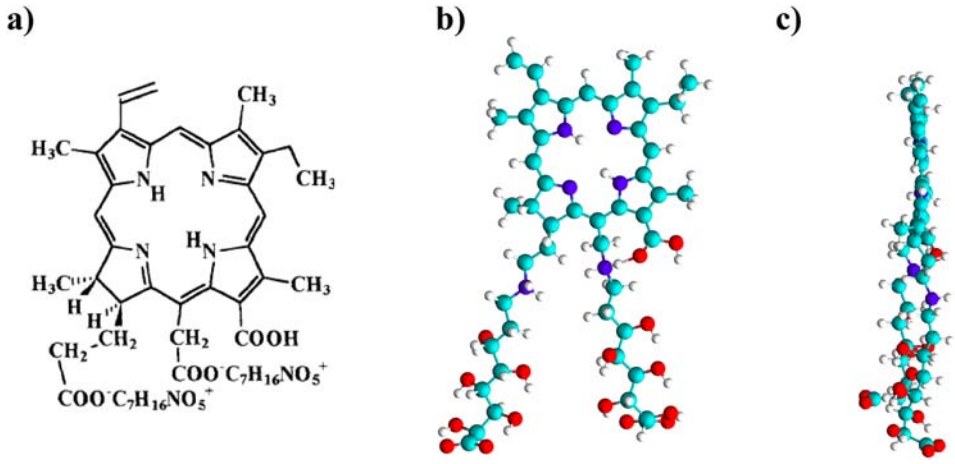

Fig. 1. (a) Chemical structure of Photodithazine drug [29], (b) drug model called by Base Chlorin (front view) and (c) Base Chlorin (side view). The large spheres of red, dark blue, and light blue correspond to O, N, and C atoms, respectively, while the small white spheres represent H atoms. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)