RESEARCH ARTICLE

A DENSITY FUNCTIONAL THEORY INVESTIGATION OF THE SURFACE INTERACTION OF PROPOFOL DRUG WITH SILICON DECORATED C_{60} FULLERENE

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ABSTRACT

The fullerenes and their derivatives have been widely used for the purpose of drug delivery and sensor applications lately. Within the fullerene family, C_{60} appears as the most important one due to its versatile physical and chemical properties. Propofol is an important anesthetic drug with reduced cardiovascular risk. In the framework of this study, adsorption properties, the nature of interaction, some important electronic properties including chemical hardness and electrophilicity index of propofol and silicon decorated C_{60} system were examined. The interaction was also monitored by examining the vibrational spectroscopic changes at the hydroxyl edge of propofol molecule. It was observed that propofol is strongly adsorbed from the hydroxyl site to silicon doped fullerene cage and the complex system became more reactive following the adsorption.

Keywords: Propofol, Fullerene, C_{60}, DFT, QTAIM

1. INTRODUCTION

Propofol also known as 2,6-diisopropylphenol is an anesthetic drug having reduced cardiovascular and respiratory risks which makes it important among the sedative drugs [1-3]. Although the risk of contaminated propofol is well known, sepsis and endotoxemia are still possible which sometimes lead to mortality [4, 5]. In order to lessen the possible risk of contamination several agents such as lidocaine have been used [6].

Due to their versatile physical and chemical properties, fullerenes and their doped forms with various impurity atoms such as aluminum and silicon have been lately an important part of the drug delivery and sensor application systems to reduce the possible side effects of the drugs under taken [7-9]. Among the fullerene family, C_{60} is the most abundant and have been paid extensive attention for biomedical applications [10]. It has been also shown that by adding impurity atoms the electronic properties of the fullerenes can be manipulated [11, 12].

It is very well known that the experimental evaluations for testing the possible drug candidates are time consuming and requires a lot of efforts. At this point theoretical based assessments of drugs appear as an important tool to conduct more object oriented studies. Density functional theory (DFT) has been widely used to enhance physical, chemical, electronic, spectroscopic, and structural properties of many different fullerene types lately [13-15]. In this work, the nature of interaction between the propofol and silicon modified fullerene C_{60} was investigated by the examination and interpretation of shifts in the OH vibrational band and by the calculation of the adsorption energies (E_{Ads}) between the impurity inserted fullerene cage and the propofol. Moreover, some important physical and chemical properties including, chemical hardness (η), band gap energy (E_g) between the highest occupied and lowest unoccupied molecular orbitals (HOMO–LUMO) and electrophilicity indexes (ω) were investigated. The nature of interaction was further examined by analyzing the electrostatic potential (ESP) map analyses. All the obtained findings were also discussed in brief.

2. COMPUTATIONAL DETAILS

Propofol and SiC$_{59}$ were first optimized in gas phase. Then vibrational frequency calculations were carried out to make sure that no imaginary frequencies obtained at the end of the calculations. No geometric limitations were employed during optimizations. The resultant structure for the gas phase calculation is given in Figure 1. The adsorption energy calculations were carried out with M06-2X functional which is known to produce acceptable results in the literature. However, it overestimates HOMO-LUMO results [16]. Therefore, for the calculation of electronic parameters B3LYP functional was preferred along with 6-31G(d) basis set [17]. Relative stability evaluations of the examined structures were carried out based on the adsorption energies and calculated as following [18]:

$$E_{Ads} = E_{complex} - [E_{SiC59} + E_{propofol}] \tag{1}$$

In the given equation, $E_{complex}$, E_{SiC59} and $E_{propofol}$ are the optimized energies of the given structures. The values of ω and η were calculated by using following equations [19, 20]:

$$\omega = \mu^2/2\eta \tag{2}$$
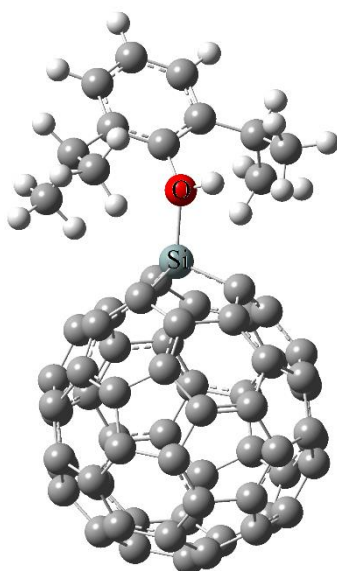$$\eta = [-E_{HOMO} - (-E_{LUMO})]/2 \tag{3}$$

Figure 1. Optimized structure of SiC$_{59}$ and propofol system in the gas phase with M06-2X/6-31G(d).

The quantum theory of atoms in molecules (QTAIM) method was used to examine the electron density and bonding characteristics of the investigated systems [21]. The molecular structures were built with GaussView visualization program [22]. All the optimizations and vibrational frequency computations were carried out with Gaussian program [23].

3. RESULTS AND DISCUSSIONS

Based on the ESP map analyses, the active site of propofol molecule was chosen as hydroxyl group (Figure 2). The active site of SiC$_{59}$ was selected as Si atom regarding the previously published studies [18]. The adsorption energy of SiC$_{59}$…Propofol complex was calculated as -22.75 kcal/mol. Following the application of basis set superposition error (BSSE) correction this value was found as -18.15 kcal/mol. The calculated adsorption energy is in the range of a possible chemisorption energy range [24]. Some important bond lengths are given in Figure 3 together with the fragmental pictogram of the

interacted sites of the examined system. The average Si—C bond length for the SiC_{59} fullerene was calculated as 1.830 Å. Following the interaction with the propofol, related value was found as 1.797 Å. Si—O bond length was found 1.889 Å which can be considered in the range of possible partially covalent interaction [18]. The O—H bond length of free isolated propofol was calculated as 0.965 Å. The same value was shifted to 0.979 Å after the interaction with SiC_{59} which also be monitored as vibrational changes in the hydroxyl group of propofol.
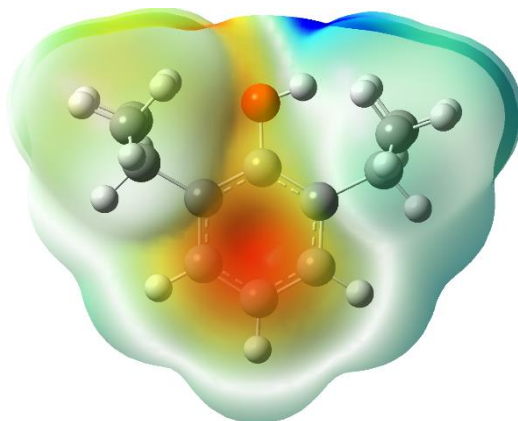

Figure 2. ESP of propofol (Blue: more positive than +0.03 (a.u.) and red: more negative than -0.03 (a.u.)).

The OH stretching vibration for the free isolated single propofol was calculated as 3885 cm^{-1}. Following the interaction with SiC_{59}, the related value was shifted to 3660 cm^{-1} which indicates the change in the electron density of OH group. This situation can be further seen in the NBO charge analyses of hydroxyl group. Before the interaction, NBO charge of silicon atom in the SiC_{59} cage was calculated as +1.286 and the NBO charge of oxygen atom in the propofol molecule was found as -0.704. After the interaction between propofol and SiC_{59} the related values were calculated as +1.930 and -0.774, respectively.
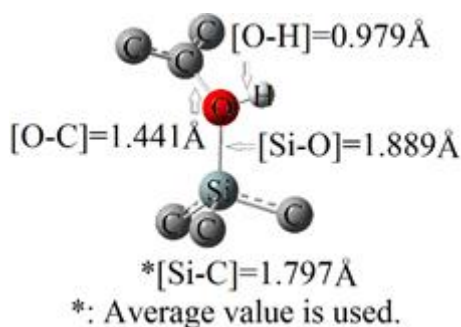

Figure 3. Pictogram of interaction edge between propofol and SiC_{59} calculated by M06-2X/6-31G(d).

The values of η and ω can be considered as indicators of chemical stability and reactivity [25]. When compared to SiC_{59}, η value of the propofol and SiC_{59} complex system slightly decreased from 1.085 to 1.074 eV. Furthermore, the value of ω also decreased from 10.330 to 6.575 eV. The HOMO-LUMO gap energy also reduced from 2.169 to 2.148 eV which shows a 0.1% change in the E_g energy addressing a slight increase in the reactivity of the complex system [25].

The QTAIM discussion can be used to further analyze the nature of interaction. At this point, the investigation of electron density ρ, Laplacian of electron density $\nabla^2\rho$ and electronic energy density H are informative. In general, it was previously shown that if $\nabla^2\rho < 0$ and H<0 the interaction is covalent. If $\nabla^2\rho > 0$ and H<0, the interaction is partially covalent and if $\nabla^2\rho > 0$ and H>0 the interaction shows

non-covalent characteristics [26]. In present study, $\nabla^2\rho$ and H were calculated as 0.316 and -0.016 a.u, respectively which indicates partially covalent interaction

4. CONCLUSIONS

In scope of this work, adsorption of propofol drug molecule by silicon doped C_{60} fullerene cage and electronic properties of the propofol and SiC_{59} complex system were examined based on DFT method. It was observed that the adsorption energy was negative which indicates that the interaction is exothermic and can occur spontaneously. Further, based on the QTAIM results, it was observed that interaction is partially covalent in nature. It was also seen that the reactivity of the complex system increases slightly compared to SiC_{59} fullerene cage following the interaction. The percent E_g energy change was found quite small with a value of around 0.1% which reflects that the sensitivity of SiC_{59} to the presence of propofol molecule is very low.

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