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Interaction between doped C_{60} fullerenes and piperazine-2,3,5,6-tetraone: DFT simulation

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Abstract: Piperazine and tetraone-related compounds are widely used in the drug industry. Heteroatom-doped fullerenes are studied as new types of sensor devices, and medical applications are studied as drug delivery vehicles. In this work, Si- or Al-doped C_{60} fullerenes and their interactions with piperazine-2,3,5,6-tetraone (ppto) molecule and some important structural or electronic properties were examined using the density functional theory (DFT). Results indicate that doped C_{60} fullerenes might be used to diagnose the presence of ppto as delivery vehicle and sensor because of their high adsorption energies and change of band gap energies.

Keywords: DFT; drug delivery; fullerene; sensor; surface interaction.

Introduction

Heterocyclic compounds are widely available in nature, and they have been known as an essential part of life (Hasaninejad et al., 2011). Nitrogen-including heterocyclic molecules are the largest portion of chemical entities, and they are the important constituent of many natural products and biologically active pharmaceuticals (Noga et al., 1986). Synthesis and investigation of tetraone-related compounds have received attention especially because of their antitumor activity (Sanner et al., 1992; Jin et al., 1998). It is accepted that piperazine derivatives are of interest in pharmacy and drug industry (Alver and Parlak, 2010; Bağlayan et al., 2012).

Since the first appearance in 1985, fullerenes have received considerable attention because of their potentials as suitable candidates for drug delivery systems (Kroto et al., 1985; Bakry et al., 2007; Singh and Lillard, 2009). They were also employed in the search of sensors and organic photovoltaic devices owing to their versatile electronic properties (Hassani and Tavakol, 2014; Bashiri et al., 2017). We recently reported on favipiravir adsorption onto undoped and Si-doped C_{60} fullerenes (Parlak et al., 2017). Eight interaction edges of favipiravir as a potential drug for Ebola virus were considered for adsorption, and binding energies ranging from about –17 to –44 kcal/mol were obtained.

In view of the above literature information and in continuation with our interests in the investigation of interaction between drug and fullerene, the primary objective of this research was to provide theoretical background for fullerene C_{60}-related complexes for possible future applications in sensor and drug delivery science. Within this objective, we were interested in understanding the chemical and electronic properties such as binding energy (E_b), solvent energy (E_s), chemical hardness (η), band gap energy (E_g) between the highest occupied/lowest unoccupied molecular orbitals (HOMO-LUMO) and electrophilicity index (ω). To understand the solvent effect on the investigated properties, gas phase and water media computations were performed. To have a better understanding of the nature of the interaction between the doped fullerene and ppto, electrostatic potential (ESP) and natural bond orbital (NBO) analyses were also carried out. The structural changes and nature of interactions were interpreted in terms of the shifts in nuclear magnetic resonance (NMR) frequency of Al and Si nuclei.

Computational studies

All the structures studied were built and optimized in the gas phase and in water as the solvent together with the frequency calculations. The optimization process was repeated until imaginary frequency was not observed, and thus the resultant structure belongs to a minimum on the potential energy surface. Computations were carried out using the B3LYP functional and the 6-31G(d) basis set. Basis set superposition error (BSSE) calculations were also conducted at the same level of theory. Stability of the complexes studied in this work was analyzed by considering their E_b values (Parlak et al., 2017):

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$$E_b = E_{complex} - [(E_{MC59} \text{ where } M = \text{Si or Al}) + E_{ppto} \quad (1)$$

In Equation 1, $E_{complex}$, E_{MC59}, and E_{ppto} are the optimized energies of the examined structures. ω and η were calculated as described earlier (Bashiri et al., 2017; Parlak et al., 2017). To analyze charge distributions and fundamentals of interactions, NBO analyses were carried out (Reed et al., 1985, 1988). The polarizable continuum model was employed to examine the solvation effect (Tomasi et al., 2005). Calculations of Wiberg bond index (WBI) and Fuzzy bond order (FBO) were performed with the Multiwfn program (Lu and Chen, 2012). Gaussian, GaussView, and GaussSum programs were used for the calculations and to make a pictogram of the examined structures (Dennington et al., 2008; O'Boyle et al., 2008; Frisch et al., 2009).

Results and discussion

Calculated ESP map on the molecular surface of a single molecule in gas phase is given in Figure 1. ESP results imply that oxygen atoms seem as the most probable active sites for the title molecule. Optimized molecular structures of the complexes in the gas phase are given in Figure 2. In earlier studies, Si and Al atoms were chosen as active sites (Hazrati and Hadipour, 2016). E_b and E_s of the structures are given in Table 1. It is observed that introduction of water as solvent leads to a decrease in the magnitude of E_b energies, and this means that the complexes interact more strongly in the gas phase compared to water as the solvent. Solubilities of Si-based complexes are comparable to those of Al-based complexes with the values of –11.22 and –11.09 kcal/mol, respectively, as shown in Table 1. It is also found that AlC_{59}…C=O complex results with a higher E_b energy in magnitude compared to SiC_{59}…C=O complex with a value of −48.08 kcal/mol in the gas phase. After BSSE corrections, this value is found as −42.41 kcal/mol. As observed from Table 1, these MC_{59}…ppto structures with single and double C=O approach to the same minima.

In Equation 1, it is easy to see that the higher in magnitude or more negative E_b energy of Al-doped complexes when compared to Si-doped complexes is because of the lower optimized energy of the AlC_{59} structure. It is better to note that, as Si atom is valence isoelectronic with C atom compared to AlC_{59}, SiC_{59} yields higher E_b energy in magnitude (Bashiri et al., 2017). Furthermore, in Figure 3, some important structural parameters are given. It is observed from Figure 3 that Al-doped system produces larger bond angles, longer [6-6] and [6-5] bonds and the distance from the centroid of the triangle occupied by carbon atoms to

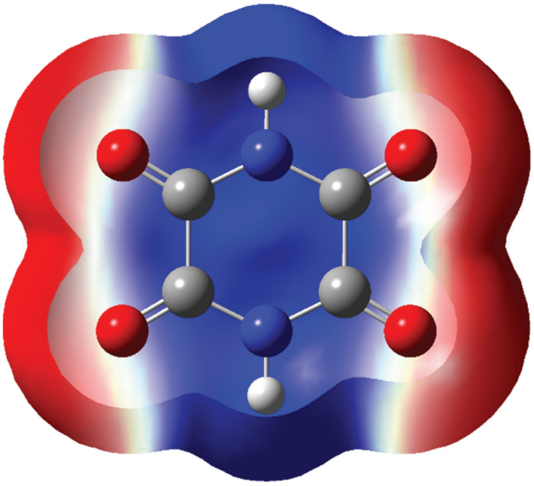

Figure 1: ESP map of ppto.

Table 1: Energetic parameters (kcal/mol) of the structures.

Structure	B3LYP/6-31G(d)		
	E_b (gas)	E_b (water)	E_s
SiC_{59}…ppto			
C=O	−20.59	−19.42	−11.22
BSSE corrected	−14.73	−13.99	–
Both C=O	−20.59	−19.13	−10.93
BSSE corrected	−14.73	−13.30	–
AlC_{59}…ppto			
C=O	−48.08	−43.88	−11.09
BSSE corrected	−42.41	−38.22	–
Both C=O	−48.08	−43.88	−11.09
BSSE corrected	−41.41	−38.22	–

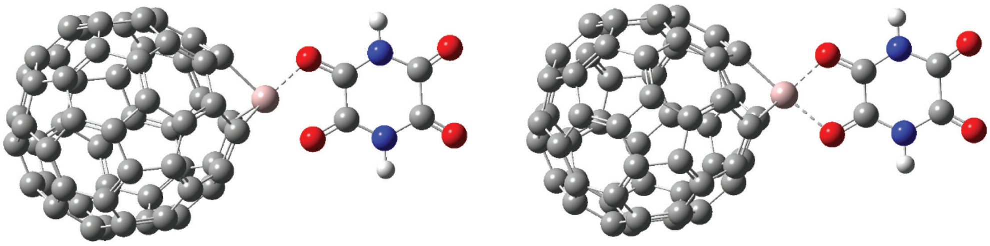

Figure 2: Optimized structure of the investigated complexes.

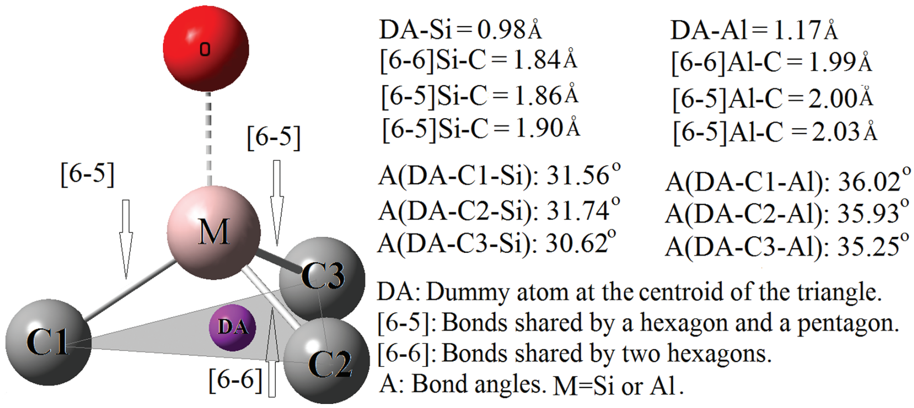

Figure 3: Pictogram of the interaction edge.

the dopant atom is longer with Al-doped system when compared to Si-doped system, which makes Al more exposed to nucleophilic attack to produce more stable complexes.

In order to make a more numerical assessment about the interacting edges between doped fullerene cages and the title molecule, the partial accumulated charges on the surfaces of the examined structures were also obtained by calculating the NBO charges as given in Table 2. NBO calculations give the relations where the possible acceptor-donor couples occur (Hassani and Tavakol, 2014; Parlak et al., 2017). In Table 2, it is seen that negative NBO charges of oxygen atom of ppto molecule and positive NBO charge of dopant atoms imply the existence of acceptor-donor couples between Si or Al and the O atoms in the examined structures. WBI and FBO data can be used to understand how strong the covalent bonding occurs between two atoms (Parlak et al., 2017). The calculated WBI and FBO values given in Table 2 show that the strength of the covalent bond characters between dopant and oxygen atoms decreases from gas phase to water as the solvent leading a decrease in the stability as well, which is in compliance with the changes in E_b energies.

Table 2: Population analyses of the structures.

Structure	Atom	Valence numbers	NBO charge	FBO	WBI
Gas					
Ppto	O	2.078	−0.502	–	–
SiC_{59}	Si	3.604	1.286	–	–
SiC_{59}…C=O	Si	4.087	2.038	1.093	0.838
	O	1.982	−0.765		
AlC_{59}	Al	3.321	1.642	–	–
AlC_{59}…C=O	Al	3.508	1.754	0.861	0.704
	O	1.947	−0.739		
Water					
Ppto	O	2.048	−0.538	–	–
SiC_{59}	Si	3.608	1.303	–	–
SiC_{59}…C=O	Si	4.026	2.004	1.084	0.805
	O	2.055	−0.728		
AlC_{59}	Al	3.210	1.735	–	–
AlC_{59}…C=O	Al	3.510	1.756	0.858	0.700
	O	1.938	−0.743		

It is observed that while electrophilic character of SiC_{59}…C=O complex is slightly increased from gas phase to water, the reverse of this is observed with the complex of AlC_{59}…C=O (Table 3). In this search, the implicit solvent model was chosen for the assessment of solvent effect. According to this model, water is taken as a continuous medium rather than taken as explicit solvent molecules (Tomasi et al., 2005). Henceforth, water as the solvent inevitably leads to different amounts of alterations with the polarizability of the examined systems resulting in different strength in the nucleophilic and electrophilic regions of the investigated structures.

Chemical hardness of both complexes is reduced from the gas phase to water. It is also observed that E_g of SiC_{59}…C=O complex is smaller than the complex of AlC_{59}…C=O, which implies that SiC_{59}…C=O complex has

Table 3: Electronic parameters (eV) of the structures.

Structure	E_{HOMO}	E_{LUMO}	E_g	η	ω
Gas					
SiC_{59}	−5.818	−3.649	2.169	1.085	10.330
SiC_{59}…C=O	−5.156	−4.306	0.850	0.425	26.332
AlC_{59}	−5.377	−3.119	2.258	1.129	7.992
AlC_{59}…C=O	−5.395	−4.168	1.227	0.614	18.633
Water					
SiC_{59}	−5.687	−3.517	2.170	1.085	9.760
SiC_{59}…C=O	−4.917	−4.173	0.744	0.372	27.765
AlC_{59}	−5.254	−3.017	2.237	1.119	7.645
AlC_{59}…C=O	−5.198	−4.011	1.187	0.594	17.861

higher reactivity than $AlC_{59}\ldots C{=}O$ complex (Hassani and Tavakol, 2014; Bashiri et al., 2017; Moradi et al., 2017; Parlak et al., 2017). E_g values of the Si- and Al-complexes are largely reduced by about 61% and 46% (66% and 47% in water), respectively, which exponentially increase the conductivity (Table 3).

It is well known that NMR frequencies are sensitive to the electron density around a nucleus. Owing to the interaction, electron densities around dopant atoms are likely to differ. To investigate this correlation, the relative NMR frequency shifts of Si and Al dopants were also calculated with B3LYP/6-31G(d) method by choosing the water as solvent. Chemical shifts of Si- and Al-nuclei change from 103 and 189 ppm from doped fullerenes SiC_{59} and AlC_{59} to the resultant complexes. These shifts address changes in electron density around the dopant atom following the possible interaction with oxygen atom of ppto.

Conclusions

Some important structural, chemical, and electronic properties of piperazine-2,3,5,6-tetraone molecule and Si- or Al-doped C_{60} fullerene cages were examined with DFT method by employing B3LYP/6-31G(d) level in the gas phase and water. Based on E_b energy, it can be deduced that all complexes interacting with one or two carbonyl groups have almost the same minima and the strongest interaction occurs between $AlC_{59}\ldots C{=}O$ complex. Water causes a decrease in the strength of E_b energies. NBO, WBI, and FBO address the interaction that occurs between the dopant atoms and the oxygen atom of ppto molecule. The E_b energy values of the examined complexes also indicate the occurrence of possible chemisorption. It is found that gap energies show dependence on the optimization medium, and they decreased from the gas phase to water. After the ppto adsorption, the gap energy of the complexes decreases, increasing the electrical conductivity exponentially, and thus they might be used as sensor and delivery vehicles.

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