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Sensor application of doped C₆₀ fullerenes in detection of 1-(3-trifluoromethylphenyl)piperazine as an alternative to ecstasy

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Abstract: 1-(3-trifluoromethylphenyl)piperazine (TFMPP) is one of the commonly abused drugs in the illicit drug market. Its detection or identification is important to investigate. In this work, density function theory (DFT) approach was used to analyse silicon or aluminium doped C_{60} fullerenes and TFMPP interactions for possible sensor applications. Stabilities of the investigated systems were examined in terms of the adsorption energies of TFMPP onto Si and Al decorated fullerenes. It was found that AlC_{59} +TFMPP resulted in higher adsorption energies compared to SiC_{59} +TFMPP. We also considered the band gap energy and concluded that Si and Al decorated fullerenes are sensitive to the presence of TFMPP in both the gas phase and aqueous medium.

Keywords: 1-(3-trifluoromethylphenyl)piperazine; fullerenes; sensor; DFT; adsorption

1 Introduction

Piperazine derivatives are used in the drug industry and the number of drugs containing piperazine fragment have been increasing (Dukat et al., 1996; Glennon, 1987;

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Rapacz et al., 2015; Wang et al., 2016). As an example, arylpiperazines behave as nonselective agents to some serotonin receptors (Dukat et al., 1996). N-substituted piperazines are reported to show anti-cancer and antimicrobial properties (Jiang and Huang, 2012; Liang et al., 2004; Menezes et al., 2016). Some piperazine derived compounds have appeared in the illicit drug market and 1-(3-trifluoromethylphenyl)piperazine (TFMPP) is one of them (Andrés-Costa et al., 2017; Da Silva et al., 2018; Majrashi et al., 2018; Nikolova and Danchev, 2014; Staack et al., 2007). It is reported that TFMPP is able to lead psychoactive effects like those of 3,4-methylenedioxymethamphetamine commonly known as ecstasy (Haroz and Greenberg, 2006; Tsutsumi et al., 2005; Yarosh et al., 2007). Consequently, the detection of TFMPP is an important research subject.

Recently, the number of studies dealing with the detection of different types of drugs using fullerene cages have received attentions due to the versatile properties of fullerenes (Bashiri et al., 2017; Moradi et al., 2017). Fullerenes find applications in the production of organic photovoltaic devices, solar cells and in the medicinal chemistry as possible drug delivery vehicles (Cho et al., 2015; Guldi and Prato, 2000; Friedman et al., 1993; Renz et al., 2008). In this work, silicon and aluminium doped C₆₀ fullerenes and their interactions with TFMPP were examined using computational methods. It is well known that, within the computational applications, density functional theory (DFT) approach has been used for the study of drug related complexes (Hazrati et al., 2017; Parlak and Alver, 2017; Samanta and Das, 2017). The stabilities of the investigated complexes based on the binding or adsorption energies and their solubility properties were examined. Considering the changes in the HOMO-LUMO gap energies, the possibility of sensor applications of the Si and Al-doped C₆₀ fullerene cages for the detection of TFMPP was also investigated. The details of the calculations and results obtained are presented in this manuscript.

2 Results and discussion

The results of natural bond orbital (NBO) analyses of the structures we studied along with the NBO charge, valence numbers, Wiberg bond index (WBI) and Fuzzy bond order (FBO) are given in Table 1. Considering the results obtained from NBO charges and electrostatic potential surface (Figure 1), the interaction sites were chosen as nitrogen atom of TFMPP and the metal atom of the doped fullerene cages (Hazrati and Hadipour, 2016; Parlak and Alver, 2017).

Optimized structures of SiC₅₀+TFMPP AlC₅₉+TFMPP complexes are given in Figure 2. The calculated Si-N, and Al-N distances were found as

Table 1: Population analysis of N, Si and Al atoms for the examined structures.

		NDO VIII			
Structure	Atom	NBO charge	Valance number	WBI	FBO
			IIuiiibei		
Gas					
TFMPP	N	-0.719	3.203	-	-
SiC ₅₉	Si	1.313	3.592	-	-
AlC ₅₉	Al	1.713	3.311	-	-
SiC ₅₉ + TFMPP	N	-0.783	3.512	0.712 (0.866
	Si	1.890	4.026		0.000
AlC ₅₉ + TFMPP	N	-0.819	3.466	0.338	0.390
	Al	1.759	3.561	0.556	0.390
Water					
TFMPP	N	-0.732	3.194	-	-
SiC ₅₉	Si	1.348	3.602	-	-
AlC ₅₉	Al	1.809	3.199	-	-
SiC ₅₉ + TFMPP	N	-0.802	3.544	0.765	0.910
	Si	1.921	3.998	0.765	0.910
AlC ₅₉ + TFMPP	N	-0.838	3.504		
3,	Al	1.795	3.522	0.359	0.411

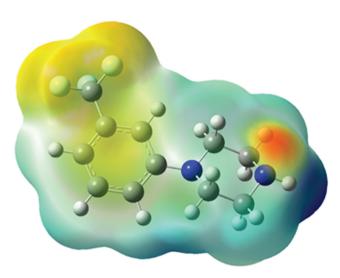


Figure 1: Electrostatic potential map of TFMPP.

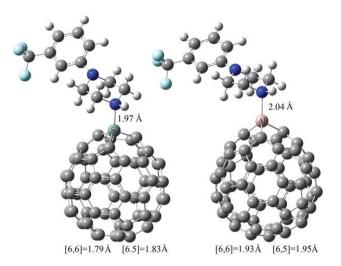


Figure 2: Optimized molecular geometry of the investigated structures.

1.97 Å and 2.04 Å correspondingly. C–C bonds in C_{60} fullerene shared by either two hexagonal or pentagonal rings are denoted as [6-6] and [6-5], respectively (Bashiri et al., 2017). For Si-doped complex, [6-6] and [6-5] bond lengths were calculated as 1.79 Å and 1.83 Å. As for Al-doped complex, the same bond lengths were found as 1.93 Å and 1.95 Å. When compared to C_{60} fullerene, it is found that structural changes based on bond lengths are larger with Al-doped complex system than Si-doped complex since unlike aluminium, the silicon is valence isoelectronic with carbon atom. It is also known that atomic size of a given element has an important effect on the bond length of two related nuclei (Moore and Stanitski, 2015). Therefore, it is also worth to note that atomic size of aluminium is larger than silicon causing alterations in the bond lengths of the structures being compared.

The corrected adsorption energies of SiC₅₉+TFMPP and AlC_{so}+TFMPP were calculated as -20.52 and -36.21 kcal/mol (Table 2), respectively, by means of basis set superposition error (BSSE). It is found that TFMPP is more strongly attached to the AlC_{59} cage. WBI and FBO parameters can be used to evaluate the character of bonding. Although, the calculated WBI and FBO values reflect that Si-doped cages show more covalent character compared the Al-doped compound, the binding energy of AlC₅₀+TFMPP is more negative when compared to Si-doped complex. This could be due to the fact that Al of AlC₅₉ is more projected out from the surface compared to the Si of SiC₅₉ as shown in Figure 2, which makes it more accessible for possible nucleophilic attack as previously reported (Moradi et al., 2017). It can be also concluded that SiC_{50} +TFMPP is slightly more soluble than AlC₅₉+TFMPP since its solvent energy is more negative (Table 2).

Table 2: Adsorption energy for the doped fullerenes and TFMPP interaction.

System	E _b (gas)	E _b (water)	E _s
B3LYP/ccpvdz			
SiC ₅₉ + TFMPP	-25.97	-35.39	-15.03
BSSE	5.45	5.47	
AlC ₅₉ + TFMPP	-41.43	-46.52	-13.99
BSSE	5.22	5.24	

In order to examine electronic sensitivity of Si-, Al-doped fullerene cages, equation 1 was taken into account (Ahmadi et al., 2012; Peyghan et al., 2013a):

$$\sigma \propto \exp(-E_{\sigma}/2kT)$$
 (1)

In this equation, σ is the electrical conductivity, k is the Boltzmann's constant, E_{σ} is the HOMO-LUMO gap energy and T is the temperature. It is clearly seen that change in E_{σ} has an exponential contribution to the conductivity. In Table 3, the E_{α} values of the systems studied are reported. It is observed that upon interaction with TFMPP, E_a values are reduced by 0.095 eV (4.42%) and 0.124 eV (5.53%) for Si and Al-doped systems. The reduction in the $E_{\mbox{\tiny g}}$, from AlC_{59} to AlC_{59} +TFMPP is larger than the reduction of E_g from SiC₅₉ to SiC₅₉+TFMPP. This implies that electronic sensitivity to TFMPP is larger for Al decorated fullerene than the Si decorated fullerene. It is known that lower E_a indicates higher reactivity or lower kinetic stability (Aihara, 1999). It is also observed that upon interaction with TFMPP and doped fullerene cages, the kinetic stabilities of the clusters are reduced from doped cages to the Si/Al+TFMPP clusters. In addition the gas phase calculations, the sensitivity assessments were carried out in water as well. It was found that the values $\Delta E_{_{g}}$ increase in water compared to gas phase calculations which means that detection of TFMPP based on the conductivity approach is more likely in water environment (Table 3). In order to clarify the limits of this work, it is better to remind that implicit solvent model was used in this study which means that the solvent is considered as a continuous medium (Tomasi et al., 2005). Henceforth, explicit water interactions which might affect the obtained parameters were not considered.

Density of state (DOS) plots of AlC₅₉ and AlC₅₉+TFMPP complexes in gas phase are given in Figure 3. When these are examined together with energy gap values, the interaction mechanism can be followed quantitatively. The charge transfer rates (ΔN) of the studied systems are also presented in Table 3 and all of them are negative which suggest that upon interaction charges at the interaction edges tend to move from TFMPP to M-doped fullerene cages.

Table 3: Energy gap and charge transfer rate of the studied systems.

System	ΔΝ	E _g	ΔE _g (%)
Gas			
SiC ₅₉	-	2.148	-
SiC ₅₉ + TFMPP	-0.243	2.053	4.42
AlC ₅₉	-	2.242	-
AlC ₅₉ + TFMPP	-0.173	2.118	5.53
Water			
SiC ₅₉	-	2.150	-
SiC ₅₉ + TFMPP	-0.219	1.929	10.28
AlC ₅₉	-	2.200	-
AlC ₅₉ + TFMPP	-0.155	2.021	8.14

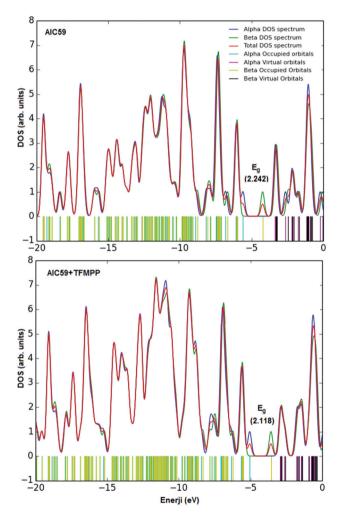


Figure 3: DOS plots of AlC₅₉ and AlC₅₉+TFMPP structures.

3 Computational methods

For this computational investigation, TFMPP and Si-, Al-doped fullerenes were optimized using the B3LYP hybrid functional and the cc-pVDZ basis set. This level of

calculation was chosen based on a search of the literature. It is reported that the B3LYP functional and the cc-pVDZ basis set have been used for nanotubes and fullerenes (Beheshtian et al., 2012; Beheshtian et al., 2013; Peyghan et al., 2013b). Frequency computations were carried out to make sure that imaginary frequencies were not obtained with optimized structures (Figure 2). The optimization process was repeated with small geometrical iterations until imaginary frequencies were not obtained at the end of optimization process. All computations were carried out in gas phase and in water as solvent. In order to examine solvent effect, the polarizable continuum model was considered (Tomasi et al., 2005). The binding or adsorption energies (E_L) energies were calculated using equation (2).

$$E_b = E_{Cluster} - [(E_{MC59} \text{ where } M = \text{Al or Si}) + E_{TFMPP}]$$
 (2)

The ΔN between the Si/Al decorated fullerenes and TFMPP was investigated as previously reported (Padmanabhan et al., 2007; Parr et al., 1999). In order to make a quantitative analysis and to determine the interaction edges on the scientific ground, the NBO analysis was carried out (Reed et al., 1985). Multiwfn program was used for the calculations of WBI and FBO so as to understand the nature of bonding (Lu and Chen, 2012). Gaussian and GaussView program were used for computations and visualization of the complexes (Dennington et al., 2008; Frisch et al., 2009).

4 Conclusions

As a summary, the following could be achieved from the research undertaken in this work;

- i. Based on the binding or adsorption energy considerations AlC_{so}+TFMPP is found more stable than SiC_{so}+TFMPP in both the gas phase and water.
- ii. E_g changes from gas phase to water suggesting that conductivity of the investigated complexes become more apparent in water.
- iii. Si and Al doped C_{60} fullerenes show electronic sensitivity to TFMPP drug molecule.
- iv. Upon adsorption of TFMPP with its —NH edge, the E of Si/Al-C₅₉ is decreased. This contributes to the electrical conductivity and can be converted into electrical signal showing that Si/AlC₅₉ is sensitive to the presence of TFMPP and might be considered as a potential sensor for the detection of TFMPP.

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