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Density Functional Theory Analyses of Non-Covalent Complex Formation of 6-Thioguanine and Coronene

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ABSTRACT. Quantum-chemical density functional theory (DFT) calculations were performed to examine the idea complex formation of 6-thioguanine (6TG) and coronene (COR) resulting 6TG@COR. The models were optimized to obtain the stabilized model of 6TG@COR complex system. 6TG was relaxed perpendicularly to the COR surface with possibility of existence of non-classical hydrogen bonds. The complex strength and formation were confirmed by the obtained values of energies for adsorption and frontier molecular orbitals (FMO). Additional visualized infrared (IR) spectra and density of states (DOS) diagrams also confirmed such 6TG@COR complex formation. Further analyses of atomic bond distances and Mulliken charges indicated the most significant changes of atomic features for those atoms of 6TG close to the interacting region with the COR surface. The achievements revealed the possibility of increasing efficiency and reducing deficiency by preventing 6TG from interacting with other substances in the combination mode with the COR surface. As a consequence, the results of this work proposed stable 6TG@COR complex system.

KEYWORDS. 6-Thioguanine; Coronene; Non-covalent; Complex; Adsorption; DFT.

INTRODUCTION. After the pioneering nanotechnology innovation, several attempts have been dedicated to extend such applications to the fields of biological systems especially targeted drug delivery processes.[1-5] In addition to the first introduced carbon nanotube (CNT), several other types of such nanostructures were developed such as graphene surfaces.[6-10] Graphene is a monolayer of carbon atoms with the benzene rings providing a proper surface for adsorption of other substances such as molecules and atoms.[11-15] In this case, relaxation processes of several biomolecules have been observed at the surface of graphene for developing this unique nanostructure for biomedical applications.[16-20] Indeed, nano-scaffolds have been seen as proper materials for applications in targeted drug delivery purposes especially for those drug with harmful side effects.[21-25] 6-Thioguanine (6TG) as a guanine derivative, is an anticancer drug for medications of several types of cancers.[26] In addition to useful impacts of 6TG medications for cancer patients, but the harmful effects are the unfavorable side effects of this nucleobase derivative drug.[27] Therefore, investigating useful scaffolds for targeted drug delivery purposes of 6TG is an important issue of efficient medication of cancer patients. In this regard, already proposed graphene scaffold for targeted drug delivery applications was examined in this work for 6TG.[28] To this aim, single-standing coronene (COR) structure was employed as a useful representative of graphene surface for adsorption of 6TG to make 6TG@COR

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complex system (Fig. 1).[29] Quantum-chemical computations were performed to obtain the geometry-optimized structures in addition to molecular and atomic scales descriptors (Table 1 and Figs. 1-4). As a consequence, molecular models and the corresponding physicochemical properties were provided to investigate the main problem of this work for proposing a novel scaffold for TG delivery process. Indeed, computer-based works are important regarding their remarkable role to study materials in the lowest molecular and atomic scales even subatomic units.[30-32]

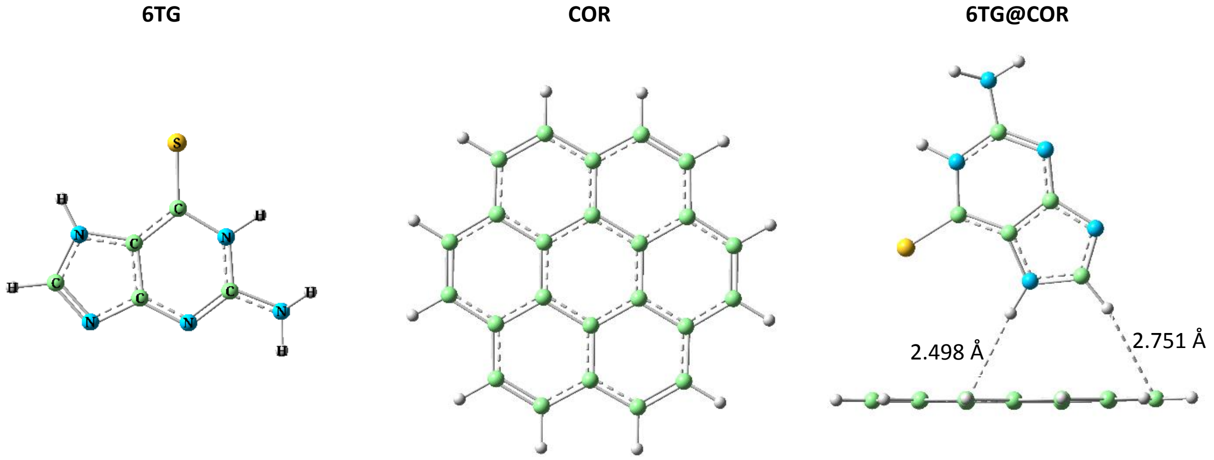

6TG **COR** **6TG@COR**

Fig. 1: Models representations of 6TG, COR and 6TG@COR.

METHODOLOGY. Density functional theory (DFT) calculations were performed for the molecular models of this work (Fig. 1) at the B3LYP/6-31G* theoretical level as implemented in the Gaussian program.[33] First, each model of 6TG ($C_5H_5N_5S$) and COR ($C_{24}H_{12}$) were obtained from the ChemSpider structural bank with IDs of 2005804 and 8671 respectively.[34] Next, both models were individually optimized to obtain the minimized-energy structures. Subsequently, re-optimization was performed to obtain the best relaxation of 6TG at the surface of COR providing 6TG@COR complex structure (Fig. 1). All optimized models were confirmed by performing vibrational frequencies calculations avoiding the existence of any imaginary frequency. These calculations provided the molecular model systems for further discussion regarding their evaluated molecular and atomic features descriptors. As included in Table 1, total energy (E), adsorption energy (AE), ionization potential (IP), electron affinity (EA), energy gap (EG), and Fermi energy (FE) were obtained as quantitative values of molecular descriptors. Additionally, visualized infrared (IR) spectra and density of states (DOS) diagrams were included in Figs. 2 and 3. For further investigating the features of 6TG before and after adsorption process of 6TG@COR complex formation, bond distances and Mulliken charges of atoms were exhibited in Fig. 4. Hence, the molecular and atomic scales properties were all evaluated for discussing the optimized model systems for proposing 6TG@COR complex formation. It is important to note that the current work was done by the advantage of computations for molecular systems to show their atomic and molecular scales descriptors for materials characterizations.[35-41]

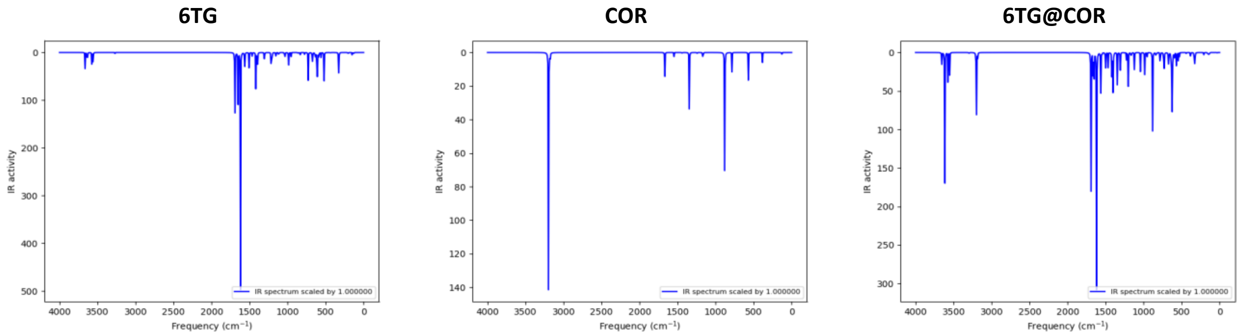
RESULTS & DISCUSSION. In this work, an idea of complex formation of 6TG@COR consisting of 6TG and COR (Fig. 1) was investigated based on quantum-chemical DFT calculated results. Each model system of individual 6TG and COR was optimized first and the complex system of 6TG@COR was re-optimized next to explore the best conformational relaxation of 6TG at the COR surface. As mentioned earlier, this COR model was investigated as the representative of graphene surface for scaffold applications in biomedical systems especially for drug delivery purposes. The results indicated that the optimized models of all three models could be obtained by performing such calculations, in which the quantitative results were listed in Table 1. Indeed, such descriptors of chemical structures could very well describe the chemistry of structures even physics of structures upon electronic systems and their corresponding properties, which are both important for further investigating the chemical systems.

Table 1: Molecular descriptors for the models.*

Descriptor	6TG	COR	6TG@COR
E /eV	-23552.382	-25086.685	-48639.109
AE /eV	n/a	n/a	-0.042
IP /eV	5.662	5.452	5.298
EA /eV	1.516	1.411	1.581
EG /eV	4.146	3.041	3.717
FE /eV	-3.589	-3.432	-3.439

*See Fig. 1 for the optimized models. AE = $E_{Complex}$ – Sum of $E_{Components}$, IP = -HOMO (Energy of the highest occupied molecular orbital), EA = -LUMO (Energy of the lowest unoccupied molecular orbital). EG = LUMO – HOMO, FE = ½ (HOMO + LUMO).

Values of E were used to evaluate AE for the adsorption strength of 6TG@COR complex, on which the value was reasonable for such molecular system. It was shown in Fig. 1 that the best conformation relaxation of 6TG was almost perpendicular to the COR surface with two interacting bonds of 2.498 and 2.751 Å for N-H…C and C-H…C interactions. By availability of non-classical hydrogen bonds in the biological systems,[42] it could be supposed here that the obtained two non-covalent interacting modes of 6TG with COR might be such types of non-classical hydrogen bonds. The interacting bond distances were reasonable for confirming such idea in addition to the value of AE. More analyses of the molecular systems were focused on the energy levels of IP and EA as the most important features of frontier molecular orbitals (FMO) for the structural systems. Indeed, such molecular orbitals features could very well define the electronic behavior of molecules including electronic donating or accepting transferring. Therefore, recording the results of IP and EA were important for our model systems to see the effects of such 6TG@COR complex formation on the original electronic features of FMO for the molecular systems. Different levels of obtained IP and EA for individual 6TG and COR models could reveal possible electronic migrations from these two molecular systems in cases of electron donating and accepting. Therefore, occurrence of intermolecular interactions between them could be supposed to make 6TG@COR stabilized complex system. The results of AE, IP and EA values almost approved these idea of non-covalent complex formations of 6TG@COR as visualized in Fig. 1 of molecular show. Each of EG and FE also approved the changes of FMO features in the complex systems in comparison with the individual models through significantly highlighted trend regarding the electric distributions of the molecules. Electron transferring capability defines dominant features of molecules.



6TG **COR** **6TG@COR**

Fig. 2: IR spectra of optimized 6TG, COR and 6TG@COR model systems.

The visualized IR spectra (Fig. 2) for the individual and complex models also approved the formation of 6TG@COR complex regarding the significant changes of spectrum of individual models in comparison with the complex system. Such results showed that the peaks of vibrational frequencies were changed in the complex model as a combination of peaks of individual models. Movements of peaks to higher or lower fields could be described regarding the vibrational energy changes in different systems to show somehow the strength of such chemical bonds or interactions. Furthermore, the visualized DOS diagrams (Fig. 3) of optimized models exhibited the changes of FMO distribution regarding the complex formation of 6TG@COR model in comparison with other individual ones.

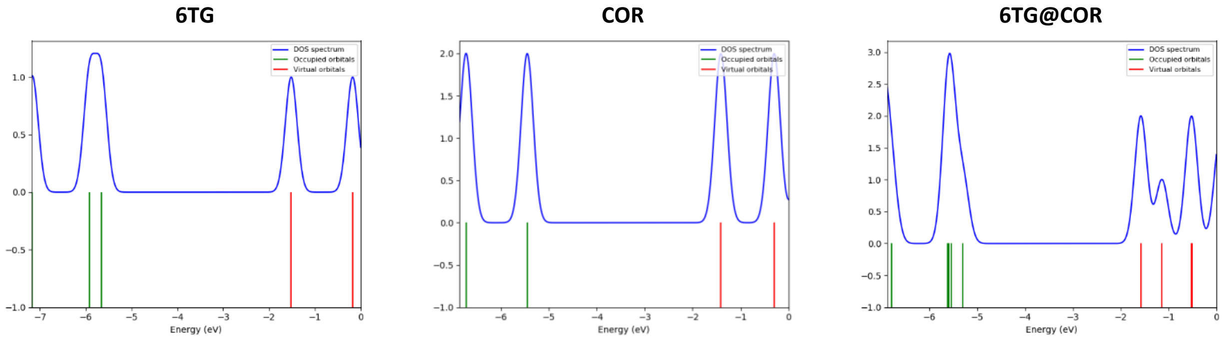


Fig. 3: DOS diagrams of optimized 6TG, COR and 6TG@COR model systems.

Further analyses of the models were focused on atomic feature descriptors of 6TG before and after complexation with COR, in which the results were visualized in Fig. 4. As could be seen by the bond distances, the atomic positions of 6TG detected the effects of such complexation with deviations of new distances from earlier ones. It could be noted that the most changes of bond distances were observed for those bonds close to interacting region, in which those of other bonds were almost negligible. Furthermore, the values of Mulliken charges also indicated he changes of atomic charges more significant than the bond distances, in which more atoms were detected such perturbations to electronic features of atomic sites. Indeed, it is very much important for tracking the changes of systems before/after modifications.

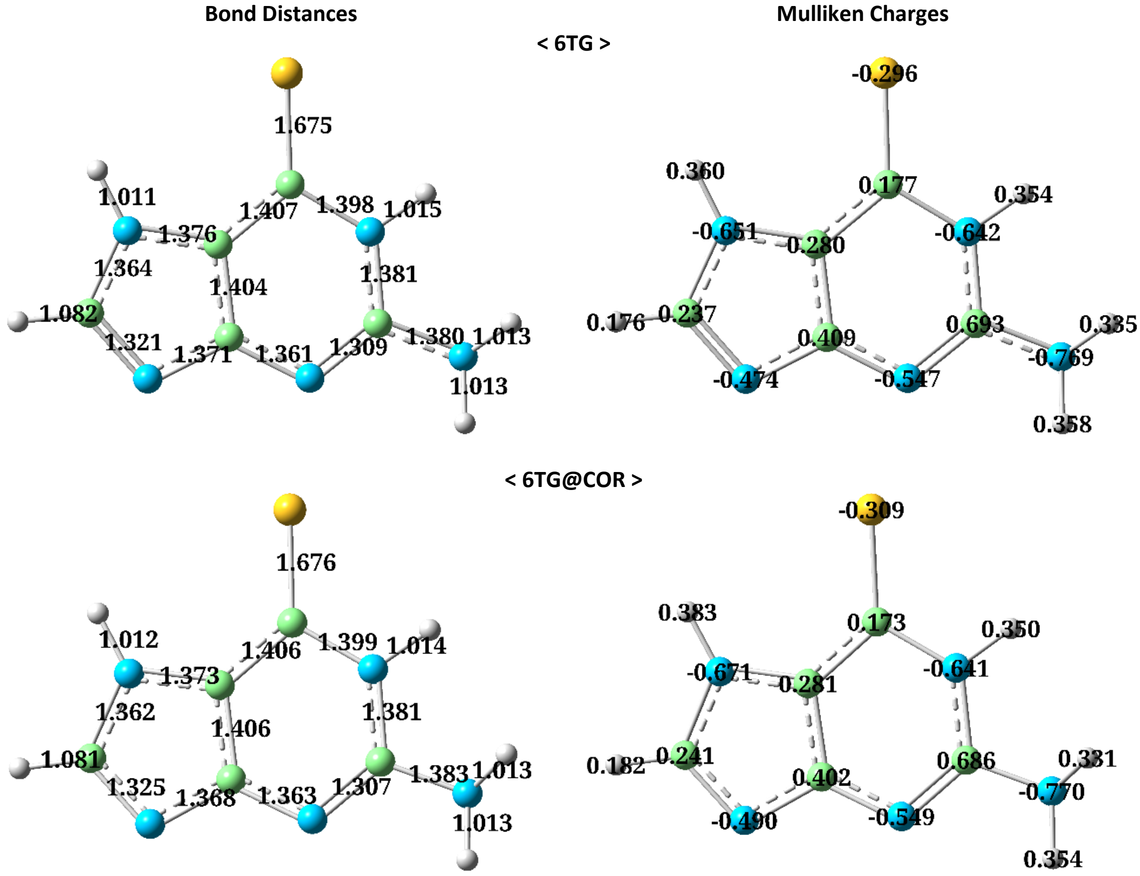


Fig. 4: Bond distances and Mulliken charges of 6TG before and after complex formation.

As a consequence, such atomic features descriptors of 6TG before and after complex formation approved the idea of complex formation of 6TG@COR for further analysis on drug delivery purposes. Indeed, such combination of drug with the surface could prevent it from contributing to interactions with other targets leading to much oriented delivery up to the correct target in drug delivery processes. It could be an important achievement in both cases of increasing efficiency of medications and reducing deficiency of unfavorable side effects for the patients. Indeed, several other investigation are required to provide such facility for targeted drug delivery of 6TG using a COR scaffold. Indeed, it is very much important for chemical modifications of medicinal related compounds to serve specific features of chemical systems regarding chemistry and physics of matters.

CONCLUSION. Within this work, an idea of complex formation of 6TG@COR system was investigated by quantum-chemical DFT calculations. The model of 6TG@COR complex was obtained regarding performed optimization processes for the individual models first and the complex model next. The results indicated the best conformational relaxation of 6TG perpendicular to the COR surface proposing the idea of existence of some types of non-classical hydrogen bonds. Further analyses indicated reasonable vale of AE for the complex strength in addition to already proper values of energy levels of IP and EA for such electron migration occurrence. The visualized IR and DOS spectra also approved the existence of 6TG@COR complex model. Atomic analyses of the features for 6TG before and after complexation process indicated deviations of bond distances and Mulliken charges because of complexation process. Although most significant changes were seen for those atoms of TG close to interacting region with the COR surface, but such changes might prevent TG from interacting with other substances during the delivery process increasing the efficiency/reducing the deficiency. As a consequence, such 6TG@COR model could be proposed for further investigation in order to designate application of COR scaffold for adsorbing TG for specific applications.

DISCLOSURE STATEMENT. The author(s) did not report any potential conflict of interest.

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