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Computational Assessments of an Iron-Doped Graphene Surface for the Drug Delivery of Thiotepa Anticancer: Evaluating Structural and Electronic Features

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Abstract: Density functional theory (DFT) based computational assessments were performed to examine the benefits of employing an iron-doped graphene (IDG) surface for the drug delivery of thiotepa (TEP) anticancer. The parental IDG and TEP models were optimized, and their stabilized structures were combined with each other to make IDG-TEP complexes during the re-optimization calculations. Two configurations, A and B, were found for the complex models by the relaxation of each of sulfur or nitrogen atom of TEP towards the IDG surface. Although the Fe…S interaction of A configuration was the strongest interaction in the two configurations, the results indicated a higher strength for the B configuration with three Fe…N interactions. Additionally, the evaluated features of molecular orbitals analyses indicated significant variation among the models from the single to complex states, in which the results were found to be learned about the occurrence of electronic transferring processes. To summarize the results of this work, formations of IDG-TEP complexes in both A and B configurations could be proposed for further investigations in the fields of drug delivery processes, in which the IDG could work in the roles of careers and identifiers for the adsorbed TEP substance.

Keywords: DFT; anticancer; thiotepa; adsorption; graphene.

1. Introduction

Besides the advantages of living in the current modern societies, occurrences of serious known and unknown diseases are the real disadvantages for the human health systems [1-3]. In addition to appearing temporarily pandemic diseases with awful impacts on all sides of life systems, some other types of diseases have been known for several years but without a certain treatment [4-6]. In recent years, COVID-19 has been a shocking pandemic with many infected patients and mortality numbers worldwide [7-9]. Other diseases of inappropriate lifestyles are other important health systems problems to solve [10-12]. On the other hand, cancer, with various harmful impacts on physiological systems, is one of the most serious unsolved medical treatment issues [13-15]. Considerable types of invasive and non-invasive protocols have been developed to deal with cancer patients, but a certain therapeutic solution has not yet been identified [16-18]. Accordingly, considerable efforts have been made to improve the anticancer drugs for treating cancer patinas non-invasive [19-21]. Thiotepa (TEP) is an organophosphorus

compound with the formula of $(C_2H_4N)_3PS$ (Figure 1), which has been known as an anticancer drug with the efficiency of treating various types of cancer for years [22-24]. TEP could work individually or in combination with other chemotherapy drugs for treating cancer with or without total body irradiation [25-27]. Earlier works reported the success of TEP medication for patients with neoplastic diseases, adenocarcinoma, and breast, thyroid, and bladder cancers [28-30]. However, arising serious adverse effects such as liver and lung toxicities and bone marrow suppression limited the therapeutic range of TEP [31-33]. In this regard, improving the efficacy of TEP has been found important in recent works efforts [34-36].

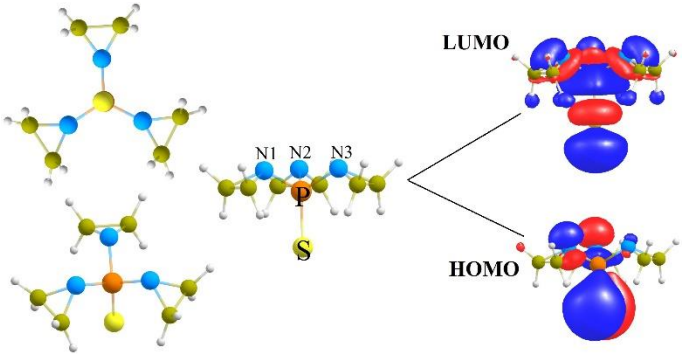

Figure 1. The optimized structure (different views) and frontier molecular orbitals patterns of TEP.

One way of approaching such improvements is designing novel drug delivery platforms, in which the innovation of nanostructures has led to the generation of such nano-based platforms [37-39]. Indeed, the high surface area of a nanostructure could make it suitable for adsorbing external substances with a feature role of the carrier for setting up drug delivery platforms [40-42]. To this aim, learning details of such communications between molecules of nanostructure and drug components could help to reveal insights on how to design a new platform [43-45]. Although numerous research works have been done on developing biomedical-related applications of nanostructures to this time, further investigations are still required to approach more specific details and applications [46-50]. Hence, this work was done to assess iron-doped graphene (IDG) (Figure 2) for the drug delivery of TEP anticancer.

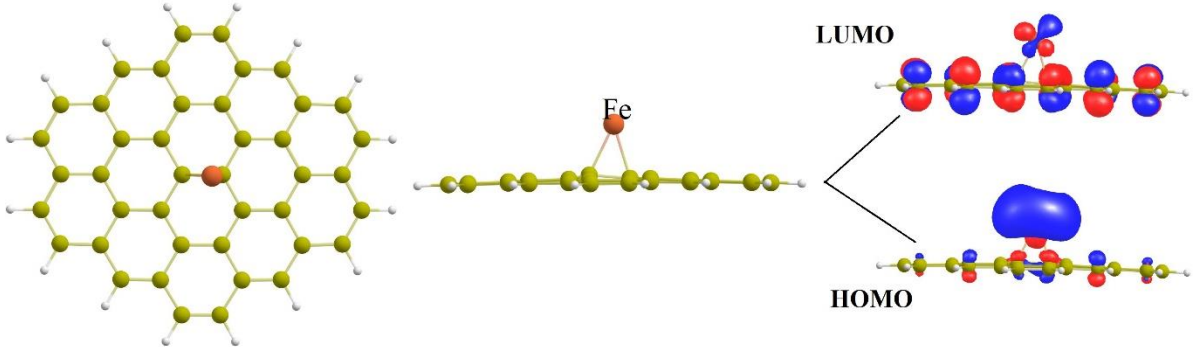

Figure 2. The optimized structure (different views) and frontier molecular orbitals patterns of IDG.

The main goal of this work was explored by performing computations on molecular and atomic scales of the investigated models [51-53]. Graphene itself is a honeycomb monolayer of carbon atoms with a very high surface area. The iron-doped region could bring a specific site of interactions for this unique surface [54-56]. Accordingly, the models were assessed based on the evaluated features to learn details of IDG-TEP combinations (Figure 3) for approaching a better level of designing a nano-based drug delivery platform for this anticancer.

2. Materials and Methods

This work was done to make an assessment of the benefits of employing a representative model of iron-doped graphene (IDG) for the drug delivery of thiotepa (TEP) anticancer through evaluating structural and electronic features (Figures 1 and 2). To this aim, density functional theory (DFT) calculations were performed for geometry optimizations to provide stabilized singular structures for participating in a complex formation of IDG-TEP (Figure 3). Two A and B configurations were obtained from examining interactions between IDG and TEP substances. In this regard, the related structural and electronic features were evaluated (Tables 1 and 2) to examine the details of investigated models for a solution for this work's problem. The calculations were performed at the level of B3LYP-D3/6-31G* of DFT using the Gaussian software [57].

Additionally, details of interactions were found by means of quantum theory of atoms in molecules (QTAIM) analyses [58-60]. This work was done as a type of computational chemistry-based work to investigate the materials at the smallest molecular and atomic scales [61-65]. Accordingly, detailed information on singular models of IDG and PET and bimolecular models of IDG-PET were investigated to approach a point of assessing the benefits of IDG for employment in the drug delivery platform of PET anticancer.

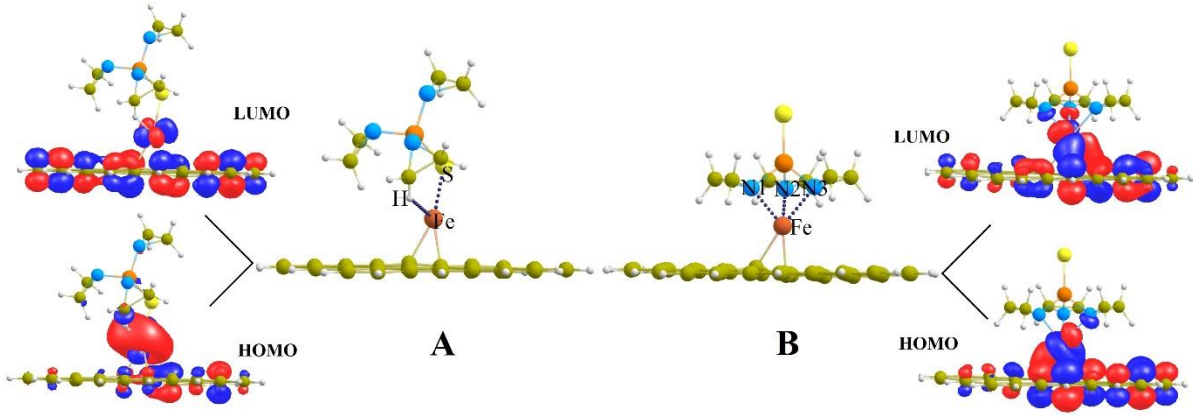

Figure 3. The optimized structures of IDG-TEP complexes in two **A** and **B** configurations and their frontier molecular orbitals patterns.

Table 1. QTAIM analyses.*

IDG-TEP	Interaction	Distance Å	Rho au	Del^2-Rho au	H au	E_A kcal/mol
A	Fe…S	2.183	0.0933	0.2294	-0.0343	-41.651
	Fe…H	2.476	0.0162	0.0406	-0.0081	
B	Fe…N1	2.036	0.0752	0.3992	-0.0197	-60.493
	Fe…N2	2.036	0.0752	0.3991	-0.0197	
	Fe…N3	2.146	0.0616	0.2761	-0.0108	

*A and B configurations of IDG-TEP are shown in Figure 3. QTAIM values of bonding total electron density, bonding Laplacian of electron density, and bonding energy density were shown by Rho, Del^2-Rho, and H. The value of molecular adsorption energy was shown by E_A.

3. Results and Discussion

As shown in Figures 1 and 2, singular structures of thiotepa (TEP) anticancer and iron-doped graphene (IDG) surface were the parental models of this work to assess the benefits of employing IDG for the drug delivery platform of TEP. The models were optimized, and their stabilized structures were obtained. Next, they were combined with being involved in new optimization calculations of IDG-TEP complexes. As a result of examining different conformations of TEP at the IDG surface, A and B configurations were obtained (Figure 3) by

the relaxation of each side of TEP towards the IDG surface. It is worth mentioning that developing pharmaceutical applications is indeed a non-stop process focusing on various sides of drug development and medical applications [66-70]. As described in Table 1, two types of interactions, including Fe…S and Fe…H, and one type of interaction, including Fe-N, were found for obtaining each of the A and B configurations of IDG-TEP complexes. In this regard, the models were analyzed to learn details of such interactions, in which the configuration B with Fe…N type of interaction among three involving interactions was found at the higher level of adsorption strength. Values of E_A were found to be -41.651 kcal/mol and -60.493 kcal/mol for A and B configurations meaning a higher adsorption strength for the B configuration than the A configuration. Fe…S interaction of A configuration was placed at the highest strength for one interaction, but the models were generally found to be distinguished by their total strengths of interactions and relaxed configurations with a higher favorability of adsorption for B than A. But it should be noted that both models were strong enough to be formed, and their energy results indicated that the models were in acceptable modes of interactions for forming physically interacting systems. In this regard, the models were found suitable in their stability and relaxed configurations. Based on the results of Table 1, the substances of the B configuration were at a closer distance to each other than the substances of the A configuration. In this regard, the models were detected in different levels of adsorption strengths. Each of the values of Rho, Del^2-Rho, and H for the bonding conditions were meaningful values for showing the strength of interaction or adsorption in the formation of IDG-TEP models. Additionally, the values of molecular adsorption energy affirmed such adsorption strength in the models. As a consequence, an initial hypothesis of the formation of the IDG-TEP complex was approached regarding the major problem of this work.

By the evaluated features of QTAIM analyses of interacting systems, the formation of the IDG-TEP complex was affirmed in two A and B configurations. Subsequently, the features of molecular orbitals analyses were evaluated (Table 2) to learn details of the electronic properties of the investigated systems. Energy levels of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are dominant for determining a molecular system's electron transferring situations. In this regard, energy distances of HOMO and LUMO levels are defined by the values of energy gap (EG), in which the value of EG is very useful for determining a mode of reactivity of a molecule or its participation in internal/external electron transfer processes. Besides such quantitative values, patterns of HOMO and LUMO are also very important for showing the frontier molecular orbitals distributions around the molecular systems. Subsequently, diagrams of the density of states (DOS) could show variations of molecular orbitals before HOMO and after LUMO levels. The evaluated patterns of HOMO and LUMO of the investigated models were exhibited in Figures 1-3, and the illustrated diagrams of DOS were exhibited in Figure 4.

As listed in Table 2, values of HOMO and LUMO were significantly different for TEP and IDG substances, which could make them suitable for participating in interactions with each other. The evaluated values of EG were 7.487 eV and 1.991 eV for TEP and IDG, which were changed in the IDG-TEP complexes to 1.855 eV and 1.468 eV for A and B configurations. Here, with the obtained values of EG, it could be mentioned that the final HOMO and LUMO features of complex models were more similar to those of a single IDG than those of a single TEP. Accordingly, the patterns showed significant distributions of HOMO and LUMO at the surface of IDG substance in both A and B complexes. This is an important achievement for combinations of a drug and a nanostructure for approaching drug delivery purposes. The

complex models were found achievable, and their molecular orbitals features indicated a dominant role of IDG for adsorbing the TEP substance. The physically interacting nature of such adsorption made the model possible for formation, and the molecular orbitals features indicated the benefits of employing the IDG surface for restricting the electronic features of adsorbed TEP substance. In a targeted drug delivery platform, it is very important to carry a drug up to reaching a known target, and the drug should not interact with other substances to avoid the appearance of any side effects. In this regard, it could be assumed that the employed IDG could work as a suitable surface for conducting a successful role of drug carriers in a protective mode.

Table 2. Frontier molecular orbitals analyses.*

Model	HOMO eV	LUMO eV	E_G eV
TEP	-6.129	1.358	7.487
IDG	-4.078	-2.096	1.991
IDG-TEP: A	-3.751	-1.896	1.855
IDG-TEP: B	-3.043	-1.575	1.468

*The models were shown in Figures 1-3. HOMO, LUMO, and E_G stand for energy of the highest occupied molecular orbital, energy of the lowest unoccupied molecular orbital, and energy gap of HOMO and LUMO levels.

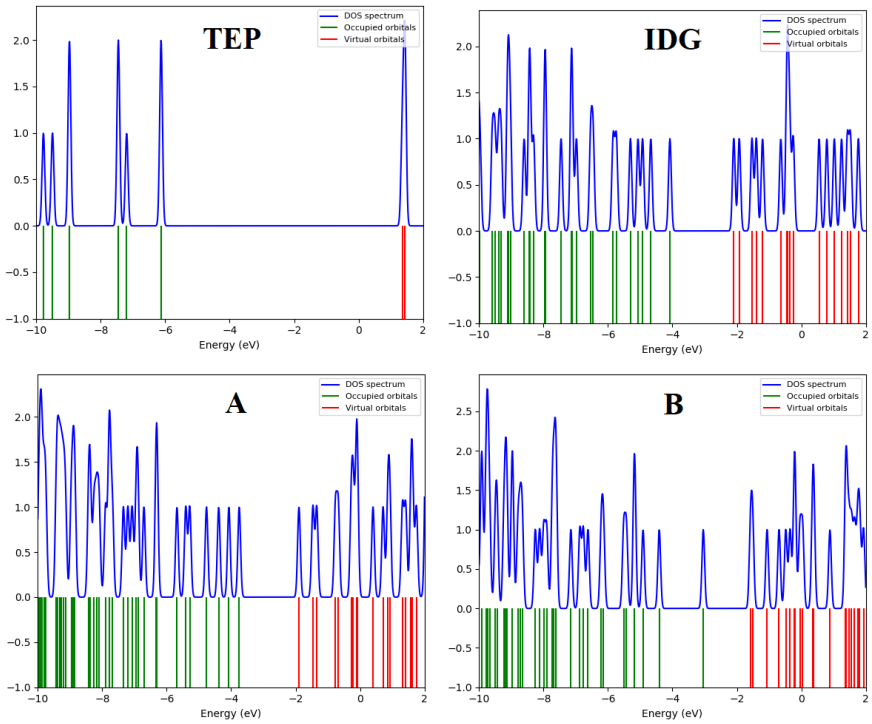

Figure 4. Diagrams of DOS for the optimized structures of TEP, IDG, and **A** and **B** of IDG-TEP complexes.

By measuring variations of DOS diagrams (Figure 4), a sensor function could also be expected for the IDG surface for recognizing the type of adsorbed configuration besides detecting an occurrence of the adsorption process. To this point, the role of IDG could be known in two different ways: the adsorption of TEP substance and the identification of configuration type. Returning again to the illustrated DOS diagrams, it could be obvious that the impacts of IDG-TEP complex formations were different in A and B configurations, revealing the importance of performing such computational chemistry investigations for learning details of chemical systems and processes. Detailed examinations of values of HOMO and LUMO of TEP, IDG, and IDG-TEP models could reveal indications of electronic transferring processes. The movements of HOMO and LUMO to upper and lower levels could show a new electronic feature of the model regarding its role in electron accepting or donating.

In other words, electronic ionization and affinity could be very well defined using such HOMO and LUMO levels and their variations.

Additionally, the illustrated DOS diagrams showed that not only the exact HOMO and LUMO levels but other levels before HOMO and after LUMO could also detect such significant impacts. Indeed, interactions in the combined models are important evidence of electronic transferring processes, in which measurements of HOMO and LUMO levels could show such meaningful impacts of electronic systems. By these achievements, the models were detectable in modes of adsorption configurations, and again, they were detectable by measuring the electronic systems of molecular orbitals features in different states.

4. Conclusions

To summarize the achievements of this work, some remarks could be mentioned. First, IDG worked as an appropriate surface for adsorbing the TEP substance. Second, TEP relaxed in two configurations, A and B, at the surface of IDG regarding the relaxation of each side of S of N atoms towards the iron-doped region of IDG. Third, the iron-doped region played a dominant role in the surface to manage the adsorption of TEP substance. Fourth, the models were stabilized by the evaluated values of molecular energy adsorption and QTAIM features. Fifth, the Fe…S interaction was very stronger than each of Fe…H and Fe…N interactions. Sixth, the results of frontier molecular orbitals revealed significant changes in such electronic systems for the models in the interacting state. And finally, formations of IDG-TEP complexes indicated different relaxation configurations for the TEP substance at the IDG surface with meaningful strengths and the possibility of recognition, which made them a considerable platform for approaching drug delivery purposes.

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Conflicts of Interest

The authors declare no conflict of interest.

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