Intramolecular interactions in a target specific anti-tumor nanodrug: a theoretical study

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Abstract
Through this authoritative report, an application of fragment molecular orbital (FMO) method on a functionalized carbon nanotube (CNT) has been proposed. A targeted anti-tumor nanodrug, based on CNT that converges towards cancerous cells, has been innovated in this regard. The anticancer drug cisplatin and the target selector arginine-aspartate-glycine acid (RGD) have been attached via poly ethylene glycol (PEG) on CNT. This nanodrug has been divided into 12 fragments including CNT as one of them. General atomic molecular electronic structure system (GAMESS), an ab initio package, has been used for calculations. The contributions of various fragments have been discussed in terms of inter-fragment interactions. Results indicate that the CNT shares the important role in stabilizing the different parts of its derivatives. In addition, this report proves CNT as a fragment for FMO method.

1. Introduction

Carbon nanotubes (CNTs), due to their unique structural and outstanding physical properties, are now playing the key role to the advancement in almost all the fields of science [1–7]. The various applications of CNTs are still in progress. The studies, based on surface [3, 8, 9], dimensionality [8, 10–12], toxicity [13–16], sensing and medicinal [11, 17–19], etc properties of CNT, have been found in literature. The action in which the CNT inserts into the interior of cell [20] and kills the DNA [21], originates the present article. DNA quashing becomes enhanced if CNT is modulated with the anti-tumor drugs [22]. Cisplatin is one of the anti-tumor drugs. Cisplatin binds with DNA through cross-linked and hence stops the replication, causes cell death (optosis) [22, 23]. Nonetheless, this anti-tumor drug destroys both the healthy and the cancerous DNA. Therefore, in addition to cancer drug cisplatin, CNTs should be targeted to reduce the side effects and to prevent the death of healthy cells. Some sensors such as arginine-aspartate-glycine acid (RGD) and its various derivatives detect a specific protein, integrin αvβ3 receptor [24]. Cancerous cells produce this protein in higher density [25]. RGD binds with this specific protein by strong attraction and hence works as a sensor to search the cancer site [24, 25]. Thus CNT has more possibility to reach at the cancer locality if it is modulated with such detectors. The attachment of drugs and RGD are preferred through poly ethylene glycol (PEG). PEG has the ability to break itself due to the presence of UV light or change in pH and hence facilitates the control drug delivery [21, 26]. The surface modulation of CNTs, therefore, falls under the important categories to shape a nano-sensor.

In vitro synthesis of proposed molecule possibly accommodates the sub-steps, namely, (1) the synthesis of PEGylated cisplatin [27], (2) the synthesis of PEGylated RGD [28] and (3) the functionalization of carboxylic group on CNT surface [29]. The final step to prepare the proposed drug involves the attachments of PEGylated cisplatin and PEGylated RGD, obtained from the first two steps, by replacing the hydrogen atom from carboxylic groups that are covalently bonded with the carbon atoms on CNT surface through step (3).

Accuracy does matter. Due to the capability to predict in higher accuracy, computational method particularly ab initio is used world wide. Ab initio method, even so, takes more time for the larger systems and is difficult to converge. A very recent development of an other approach, known as fragment molecular orbital (FMO) method, initially developed by Kitaura et al., is now worthwhile for ab initio study for larger molecules.
having higher numbers of atoms [30, 31]. FMO method applies by dealing the molecule in smaller pieces or fragments. The fragment may be the various parts of a large molecule or the non-bonded molecules or atoms. FMO also ensures the different \textit{ab initio} methods for different fragments. FMO method, along with converging the larger molecular systems, has advantages in parallel computing. Depending on the number of processors, all or some of the fragments can be broadcast at the same time on a multiprocessor machine to save computational cost [30–32]. The applications of FMO method on various larger or smaller systems have been found in some other studies [32–36]. However, CNT as one of the fragments using FMO method has yet not been found in literature. Our aim in present study is to introduce the CNT as a fragment for FMO method and consequently to check its role in stabilization of orientation of attached molecular system through intramolecular interactions. Subsequently, this study will work as a new bridge for first principle method and its applicability on nanostructures and hence opens the path for search of such bridges as mentioned by Adessi \textit{et al} 2009 [37].

2. Method of Calculations

Long time ago, self consistent field theory (SCF) was proposed by an eminent physicist and mathematician Dauglas Hartree and a Soviet physicist Vladimir Aleksandrovich Fock. Hartree–Fock (HF) SCF, in a simplified form, is found somewhere else [38]. A block diagram of Hartree–Fock self consistent field theory has been shown in figure 1. A similar diagram has also been designated in our recent paper [39]. In figure 1, first of all the basis set \((\chi_m)\) has been chosen and has started with an initial guess of field matrix elements \(c_{ij}\). Basis sets MINI [40] and model core potential (MCP) [41] have been conceived to apply. To save the computational time for the heavy atoms having higher number of electrons, MCP is applied. MCP implements all valence electrons to participate whereas core electrons to treat as one-electron relativistic pseudo-potential during the calculations [41]. CAMB3LYP handles long range correlation of interactions in density functional theory (DFT) module set [42]. Generally, larger molecules are supervised by CAMB3LYP DFT code.

Field matrix decides what proportion of basis functions \(\chi_m\) has to combine to constitute the molecular orbitals \(\varphi_i\) as,
\[ \varphi_i = \sum_{n=1}^{m} c_i \chi_n \]  

(1)

Normalization of molecular orbital generates density matrices, overlap integrals S and Fock matrices F. Overlap integrals can be given as,

\[ S = \langle \chi_d \mid \chi_m \rangle \]  

(2)

Fock matrix together with overlap integral and field matrix lead the Hartree–Fock–Roothans equation as,

\[ (F - ES)C = 0. \]  

(3)

where, C is the field matrix having the same meaning as \( c_i \). Equation (3) gives the energy value. However, this energy may or may not be minimum during the first cycle. A convergence criteria is then employed in which if energy is not minimum, the process goes to update the field matrix by choosing the different values for one or more of \( c_i \). The iteration goes on till convergence. Once convergence is achieved then the two iterations give the same energy value. The action is then completed for monomer energy [38]. After completing the monomer energy calculation, the process starts for dimer (two bodies) energy. The expression used to calculate the total intramolecular interaction has been given by following equation [30]:

\[ E_{total} = \sum_{\Gamma} E_{\Gamma} + \sum_{\Gamma > \Lambda} \Delta E_{\Gamma \Lambda} + \sum_{\Gamma > \Lambda > \Omega} \Delta E_{\Gamma \Lambda \Omega} - \Delta E_{\Gamma} - \Delta E_{\Lambda} + \Delta E_{\Omega} - \Delta E_{\Gamma \Lambda} - \Delta E_{\Gamma \Omega} - \Delta E_{\Lambda \Omega} + \ldots, \]  

(4)

where, \( E_{total} \) is the total energy, which is the sum of one body (FMO1), two body (FMO2), three body (FMO3) up to n-body (FMOn) interactions. \( \Delta E_{\Gamma \Lambda} \) can further be expressed as,

\[ \Delta E_{\Gamma \Lambda} = E_{\Gamma \Lambda} - E_{\Gamma} - E_{\Lambda}. \]  

(5)

Similarly, \( \Delta E_{\Lambda \Omega} \) and \( \Delta E_{\Gamma \Omega} \) can also be expressed [25]. The potential, exercised for interaction among FMO, has been assigned as follows:

\[ U_{\chi \chi_m}^{\xi} = \sum_{\Omega \neq \xi} \sum_{\omega \neq \Lambda} \sum_{\omega \neq \Omega} \langle \chi_l \mid -q_a \frac{g_a(\mid r - r_a \mid)}{\mid r - r_a \mid} \chi_m \rangle \]  

(6)

where, \( \xi \) is equal to \( \Gamma \) for monomer, \( \Gamma, \Lambda \) for dimer and \( \Gamma, \Lambda, \Omega \) for trimer. \( \chi_l \) and \( \chi_m \) are atomic orbitals or basis functions while \( \Omega \) varies for N fragments. The inter-fragment distance is \( \mid r - r_a \mid = r \) (say). Where, \( r_a \) and \( r \) are position vectors for atom ‘a’ having charge \( q_a \) and for an arbitrary fragment respectively. The function \( g_a(\mid r - r_a \mid) \) is a Gaussian–type function, comes into picture due to charge penetration correction in classical electrostatic charge on hydrogen like atoms and can be given by the relation [38],

\[ g_a(\mid r - r_a \mid) = 1 - \alpha e^{-\beta(\mid r - r_a \mid)^2} \]  

(7)

where, the values \( \alpha = 1 \) and \( \beta = 1 \) are found to fit best to parameterize the above equation for better results [43, 44]. An ab initio package, general atomic molecular electronic structure system (GAMESS) [45, 46], not limited to only the mathematics discussed above, has been used for calculations [31].

### 3. Results and discussion

A typical fragment division for the molecule proposed, has been shown in figure 2. The RGD and cisplatin have been attached via PEG on CNT. FMO1 and FMO2 are the methods for one and two body problems to calculate monomer and dimer energy respectively. FMO1 results in all the graphs depicted in figure 3. Figure 3(a) shows the monomer energy \( (E_{\Gamma}) \) for each fragment through a separate column. This figure reveals that the CNT has higher monomer energy value in comparison to others whereas cisplatin containing fragment has that of second higher. Monomer energies of rest are small except fragment 8. The monomer energy depends on the number of atoms, proportionally. This rule is, yet, fair only for the molecules or fragments of the same atom. If the atoms are different, then the electronic distributions at the center of the concerned atom of a fragment are also taken into account [38]. Platinum atom, having atomic number 78, has higher dense orbital on the single center, hence has higher energy due to one electron interactions with nucleus in fragment 4 (a cisplatin containing fragment). While in the case of CNT, monomer energy is higher due to the higher number of atoms.

Self interactions give monomer energy. The molecular properties, namely, dipole, total energy and virial ratio over the FMO-iteration number have been also arranged in figure 3. In a particular FMO-iteration, a number of SCF iterations are involved. 21 FMO-iterations have been reported. Dipole moment of the proposed molecule, given in figure 3(b), fluctuates up to few iterations before to be stabilized at the value of 12 debye. Total energy \( (E_{total}) \), plotted in figure 3(c), approaches to optimized state, asymptotically. In addition, the ultimate test for a molecule to exist, the virial ratio that is the fraction of magnitude of potential energy \( \mid V \mid \) to kinetic energy \( T \) of the system as \( \mid V \mid / T \), apted in figure 3(d), should be a distinct universal value [47, 48]. This distinct universal value is equal to 2 [47, 48]. Although, in present contemplate, \( \mid V \mid / T \) is 2.005. The deviation of 0.005 is quite small.
and arose because of the basis set truncation error. The constant virial ratio \((2.005)\) indicates the equilibrium state achieved by the fine tuning of \(|V|\) and \(T\) respectively [47, 48]. Meanwhile, since the latter three quantities show optimized state with FMO-iterations, ensures that the FMO method is applicable to CNT derivatives. That is what was searched by Adessi et al. 2009 [37]. In addition, since the FMO source code has been executed for the whole molecule of 12 fragments successfully, the bonds that connect the CNT and corresponding attachments, therefore, undoubtedly admitted to exist [9].
Outcomes of FMO2 method have been demonstrated through figure 4. The inter-fragment distance \( r \), plotted in figure 4 (a), explores that the fragment 8 and 6 have highest separation while fragment 7 and 5 have second highest. In addition, \( r \), due to the nearest neighbor, is always negligible to accommodate covalent bondings. A careful observation evinces the occurrence of covalent bonding of fragments 2, 6, 10 and 12 with CNT. These bindings are crucial. The dimer energies \( E^{\Gamma \Lambda} \), depicted in figure 4 (b), reveal that the every interaction with CNT is higher than that of others. This is because of CNT with \( m = n \) is regarded as metal type of conductors. Such CNTs have more surface charge density \([6, 7]\). Since, the selected CNT \((4, 4)\) is \( m = n \) type, hence its dominance in inter-fragment interactions. That is why CNT dictates the stability of orientation of different fragments. Such role of CNT is also supported by other workers \([8, 9, 36]\). Fragment 4 is cisplatin containing fragment and is revealing second higher dimer interaction energy after CNT. Since cisplatin kills DNA \([22, 23]\), hence CNT is also being predicted to do so. This is in accordance with earlier studies \([21, 26]\). Meaning by the proposed molecule has enhanced ability to rapture the DNA. In winding up, due to the presence of RGD that shows strong inter-fragment attractions, the proposed molecule is expected to shift towards cancerous DNA and hence achieves a targeted drug delivery. This conclusion endorses the current outcomes \([25]\).

Further, the binding energy \( E^{\Gamma \Lambda} - E^{\Gamma} - E^{\Lambda} \), shown in figure 4 (c), must be supplied to detach a fragment against the vicinity of interactions imposed by all other fragments including the strength of inter-fragment bonds, comes out to more or less equal. Except fragment 9, binding energy is approximately equal to -15 Kcal/mole for all other fragments. While in case of fragment 9, that nearly appears to -30 Kcal/mole. Since the fragment 8 has been bonded with fragment 9 twice, the binding energy, therefore, for fragment 9 turns just doubled. Bonding of fragment 8 with 9 as twice is also evident from figure 2. Consequently, it can be stated that the molecular orbital for a complete molecule, in FMO method, persists its meaning even after breaking into various fragments i.e. into various molecular orbitals. Again, applying the reason that the CNT has selected here armchair type (4, 4), its charge polarization is respectably higher \([3–7]\). This, indeed, explains why the polarization energy \( E_{pol}^{\Lambda} \) as in figure 4 (d), is effective due to CNT in addition to nearest neighbors interactions. So, even in polarization interactions, CNT shows its crucial role. In addition, the distance between fragment 6 and fragment 7 is not zero instead equal to 6.60 Å, specifying that they are not neighbors. Actually, they have...
placed to either side of CNT, as also evident from figure 2. Since \( r \) is large, the polarization interactions energy \( E_{polb} \) explored in figure 4(d), for fragment 7 from fragments 6 to 1, are almost zero.

Furthermore, the polarization energies respectively for fragment 8 due to fragment 7 and for fragment 9 due to fragment 8, are considerably higher, which can also be noticed from figure 4(d). This suggests that the RGD that parted in fragments 7, 8, 9 and 11 respectively, has more ability to polarize. RGD, therefore, drives the important contribution to pull the whole molecule towards the interacting targets. This further supports the recent findings [25].

Moreover, we have successfully introduced the CNT for FMO method. The confirmations for establishment of bonds of attachments on CNT through molecular orbital theory offers as the precursors to predict the such a system to exist. The proposed system has three fold advantages in anti-tumor drug designing. The first one is that the higher strength of two bodies attractions for CNT and cisplatin with other fragments is resembling their DNA killing capacity. The second one is the presence of RGD that makes the system suitable for target (integrin \( \alpha_3\beta_3 \) receptor) selections. The third advantage is due to control drug delivery via breaking the PEG through suitable radiation or pH. Nevertheless, once FMO passes a molecular system to optimize, various other calculations like spectra, molecular dynamics, monte-carlo, etc. using \textit{ab initio}, DFT, TD-DFT, etc. can be done for each fragment separately through FMO1 and for a pair of fragments through FMO2 method [45, 46]. Therefore, the current task is immensely helpful for drug designing, electronics, nanobiotechnology and other interfaces where CNTs or probably any nanotubes are involved.

4. Conclusion

The study, based on FMO method, opens the new path to link the first principle techniques and its applicability on CNT. The analysis of virial ratio confirms that the study of modulation of carbon nanotube, through FMO method, is possible. Heavy metal with a basis set (MCP) too participates in FMO run along-with CNT. The inter-fragment interactions reveal that the CNT, in present case, causes solely to stabilize the orientation of distinct fragments. High polarization energy of RGD predicts that it may be pulled along with the whole molecular towards the interacting targets. This further supports the recent findings [25].

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Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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