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Orginal Research Article

Analysis of structural, and electronic properties of clopidogrel drug adsorption on armchair (5, 5) Single-walled carbon nanotube

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ABSTRACT

Single-walled carbon nanotubes (SWCNTs) have been widely utilized in many types of applications, cinfirming their excellent role as carriers of drugs with a highly site-selective delivery capability. As nanotubes can release drugs into the tissue cells without damaging the healthy cells, it is necessary to determine the structural properties of drugs–SWCNTs complexes which may lead to the development of optimal SWCNTs as new effective drug transporters. In this work, a theoretical study of structural properties and reactivity of clopidogrel drug with C (5, 5) carbon nanotubes is presented. Computational and chemical simulations were carried out for clopidogrel, SWCNT and clopidogrel-SWCNT by B3LYP/6-31+G with the Gaussian 09 program and then energies of all optimized configurations were evaluated by the M06-2X density functional method. The highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), natural bond orbital (NBO), global reactivity descriptors and density of states (DOS) of clopidogrel and SWCNT were calculated. The results show that there is a relationship between the energy gap and the DOS. The nature of interaction and bonding between the clopidogrel and SWCNT is physisorption as the adsorption energy and charge transfer is small, and adsorption distance is large. Generally, the results of our simulation studies demonstrated that, the carbon nanotubes have a high potential to be considered as carriers of clopidogrel in drug delivery systems. Band gaps of clopidogrel-SWCNT complex, which were computed by B3LYP method, are 1.777 and 1.860 eV in gas and the solution phases, respectively. Also, the dipole moment of clopidogrel-SWCNT complex in solution phase is 5.286 Debye, which is higher than the gas phase (3.234 Debye). These results show the effect of the solvent on the complex.

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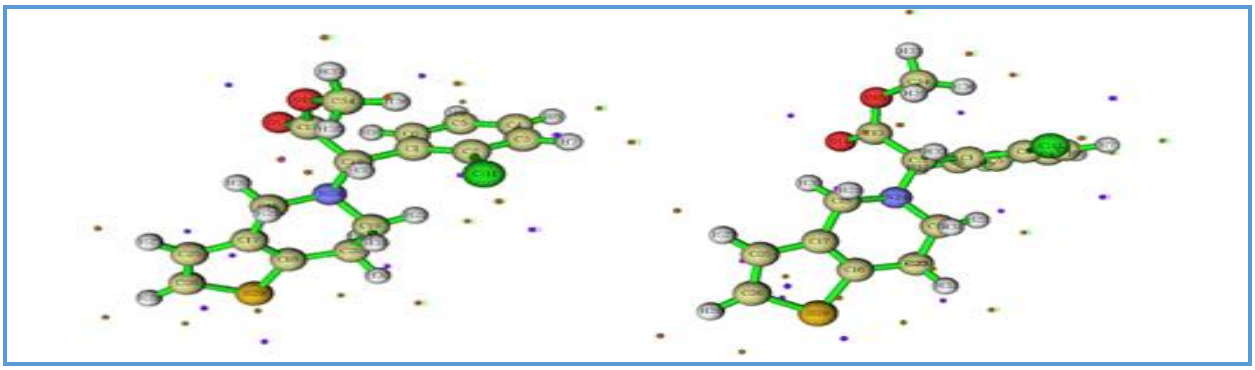
Graphical Abstract



Introduction

It is recognized that carbon nanotubes are be categorized as carbon allotropes [1]. Carbon nanotubes were discovered in 1991 by Iijima *et al*. [2]. Researchers soon realized the unbelievable carbon nanotube properties such as large surface area and novel electronic and physical characteristics [3–7]. Carbon nanotubes have potential applications in electrochemical and biological sensors [8–10]. Biological sensors have the capability of identifying different kinds of biomolecules and ions [11, 12]. One of the most important applications of carbon nanotubes is their application in medical technologies and subsequently, theoretical and experimental investigations of carbon nanotubes in drug delivery systems as drug carriers with a high target selectivity and sensitivity have attracted a great deal of interest [13–15]. These systems are capable of releasing drugs into the target organ with no side effects to peripheral organs and the attachment of carbon nanotubes to biomolecules can either be covalent or non-covalent [16, 17]. Atherosclerosis is a chronical and inflammatory disease, which is generated by the accumulation of platelets and fatty acids in arteries [18, 19]. Atherosclerosis is one of the main causes for heart attacks and death amongst adults. Clopidogrel with chemical formula, $C_{16}H_{16}ClNO_2S$, is a pharmaceutical precursor of tinopyridin, which is utilized as an inhibitor of platelets and undesirable coagulations [20]. Clopidogrel is one of the most useful drugs, reducing the symptoms of atherosclerosis. To recognize the importance of nanotubes and their application in drug delivery systems, many theoretical studies have been carried out to investigate the interactions between the carbon nanotubes and drug species. Xu *et al*. [21] carried out a theoretical study of carbon and boron nitride nanotubes as carriers containing anti-AIDS drugs in 2018. They demonstrated that the adsorption of anti-AIDS drugs on carbon nanotubes has a physical nature with a potential application in drug delivery systems. Hesabi and co-workers [22] evaluated the adsorption of an anticancer drug on carboxylate functionalized carbon nanotubes and showed that the adsorption of drug has a negative enthalpy effect and is an exothermic process, especially in aqueous solutions. Li *et al*. [23] carried out a theoretical investigation on the adsorption of cisplatin anticancer drug on aluminum doped carbon nanotubes. Their results indicated that nano carriers possess high cisplatin adsorption compatibility [23]. Daneshmehr investigated carbon nanotubes as carriers of quercetin anticancer drug [24]. Hafizi *et al.* evaluated the interaction of amphetamine with different

carbon nanotubes. They found that physisorption was the most dominant phenomenon in their theoretical investigations and the interaction was a thermodynamically desirable process [25]. Saikia et.al utilized density functional theory (DFT) to study the interaction of 2-methyl heptyl nicotinate with carbon nanotubes and they claimed that these structures may be considered as a suitable carrier for 2-methyl heptyl nicotinate [26]. Hamedani and co-workers studied the interaction of folic acid with the surface of carbon nanotubes which have zigzag structures. Their results were in agreement with theoretical calculations and indicated that the bonding energies between carbon nanotubes and folic acid are negative and decrease with increasing the number of functionalization [27]. We studied the structural and electronic properties of the clopidogrel and SWCNTs complexes and investigated the interactions between the clopidogrel and chair structured SWCNTs in both gas and the solution. The results of this research may help to gain a deeper understanding of the interaction between clopidogrel drug and carbon nanotube. Also, in order to perform further pharmacological studies, it seems that it is necessary to investigate the adsorption properties of drugs and nanotubes. The experimental methods are very laborious, expensive and require complex equipment; therefore computational methods could provide valuable details about the interaction of the clopidogrel and the SWCNT.

Experimental

Computational Methods

The computational simulations of clopidogrel, carbon nanotubes and drug-SWCNT complexes were performed by Becke's three-parameter Lee-Yang-Parr hybrid functional (B3LYP) [28] with 6-31+G basis set using Gaussian 09 program [29] in gas and solution phases. The energies of all configurations were optimized by M062X [30]. The conformers were considered to be minima based on the absence of imaginary frequencies. DFT methods are conventional approaches which are taken to calculate the electronic structure of atoms and molecules and they are based on Hohenberg-Kohhn theories [31]. The aim of DFT calculations is designing functionalities of electronic densities and energies [32–34]. The fundamental concepts, which were used in this study, are M062X/6311++G (d, p) and B3LYP/6311++G(d, p) [35]. These concepts are useful for determining energy levels and structural optimizations of compounds. M062X and B3LYP methods were used to calculate energy levels and determine optimized structures of compounds, but the latter method is one of the most accurate ways to calculate energy levels [36–39]. M062X method is an ideal choice for the determination of the hydrogen bonding with elements of the main groups in periodic table [40]. The pristine and most reactive carbon nanotubes, which contain 80 carbon atoms and 20 saturated hydrogen atoms, were used in this study [41]. The C-C bond length of these nanotubes is 1.42 Å, which is in agreement with the bond length of sp^2 hybridization mode. The diameter and the length of carbon nanotubes were determined to be 6.78 and 9.84 Å respectively. Theoretical study of the solvent effect on the structural properties has been studied [42–44]. In this work, all calculations for solvent effects were addressed through a self-consistent reaction field (SCRF) employing the integral equation formalism polarized continuum model (IEFPCM) [45]. It has found that this method is very useful and can describe accurately the charge distribution of solute outside of the PCM cavity [46, 47]. Calculations

were performed to determine the optimal reactive sites for the attachment of clopidogrel to SWCNTs. Determination of the reactive sites on carbon nanotubes required determination of Fukui indices, electrostatic potential, and barrier orbitals. The quantum descriptors, which give information about the chemical reactivity of molecules, are: Energy of highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), band gap (ΔE), ionization potential (I), electron affinity (A), global hardness (η), chemical potential (χ), global softness (σ), dipole momentum (μ) and electronegativity (ω) [48–50]. The Equations 1 were used to calculate quantum descriptors:

$$\eta = \frac{I - A}{2} = \frac{(E_{LUMO} - E_{HOMO})}{2}$$

$$A = -E_{LUMO}\ \Delta E = E_{LUMO} - E_{HOMO}\ I = -E_{HOMO}$$

$$\omega = \frac{\chi^2}{2\eta} = \frac{(E_{HOMO} + E_{LUMO})^2}{4(E_{LUMO} - E_{HOMO})}$$

$$\sigma = \frac{1}{\eta} = \frac{2}{(E_{LUMO} - E_{HOMO})}$$

$$\chi = \frac{I + A}{2} = \frac{-(E_{HOMO} + E_{LUMO})}{2}$$

The effect of the quantum chemical parameters on the chemical reactivity of molecules has been observed in many articles. For example, The Si-doping on the structure and properties of graphyne by the quantum mechanics method studied by Ghiasi *et al.* [51], this can also be seen in the references [52–54].

Density of states (DOS) is used to compare the results of band gap with DOS results. The magnetic, electric and optical properties of any structure depend strongly on its density of states. DOS was performed with the help of Multiwfn program software [55].

Variations in the electron densities of clopidogrel were investigated by using natural bonding orbitals (NBO) analysis after and before the adsorption of clopidogrel molecules on the surface of SWCNTs. The NBO method is useful for calculating bonding orbitals which have the maximum electron densities [56, 57]. The NBO was calculated by Gaussian 09 program [29].

The attachment capability of a molecule to carbon nanotubes depends on the electric charge of the chelate atoms. The Mulliken's charges play a significant role in the application of quantum chemical calculations to molecular systems [58]. Mulliken's charges are determined from the analysis of Mulliken densities and by using the approximations of partial atomic charges obtained from computational procedures. Consequently, investigation of charge transfer between the clopidogrel and SWCNTs in the gas phase was carried out using the Mulliken atomic charges.

The adsorption energy of the clopidogrel molecules on SWCNTs was calculated using the Equation 2.

$$E_{ads} = E_{(SWCNT+D)} - (E_{SWCNT} + E_D) \qquad (2)$$

Where, E_{ads} is the interaction energy between clopidogrel and SWCNTs (C80H20). $E_{(SWCNT+D)}$, E_{SWCNT}, and E_D are the energy of whole species (SWCNTs and clopidogrel), total optimized energy of SWCNTs, and total energy of clopidogrel molecules, respectively.

Results and Discussion

Initially, the optimized structures of the clopidogrel and SWCNTs were determined by the B3LYP method in both gas and solution phases. There were no significant changes in the length and the angle of the bonds in both phases. The C-C bond length of SWCNTs was calculated to be 1.37 and 1.44 Å in gas and solution phases, respectively. These are close to the real value (1.42 Å) and this indicated the strength and stability of this bond. Figures 1 and 2 illustrate the HOMO and LUMO of clopidogrel

and SWCNTs which have been calculated by B3LYP and M062X methods.

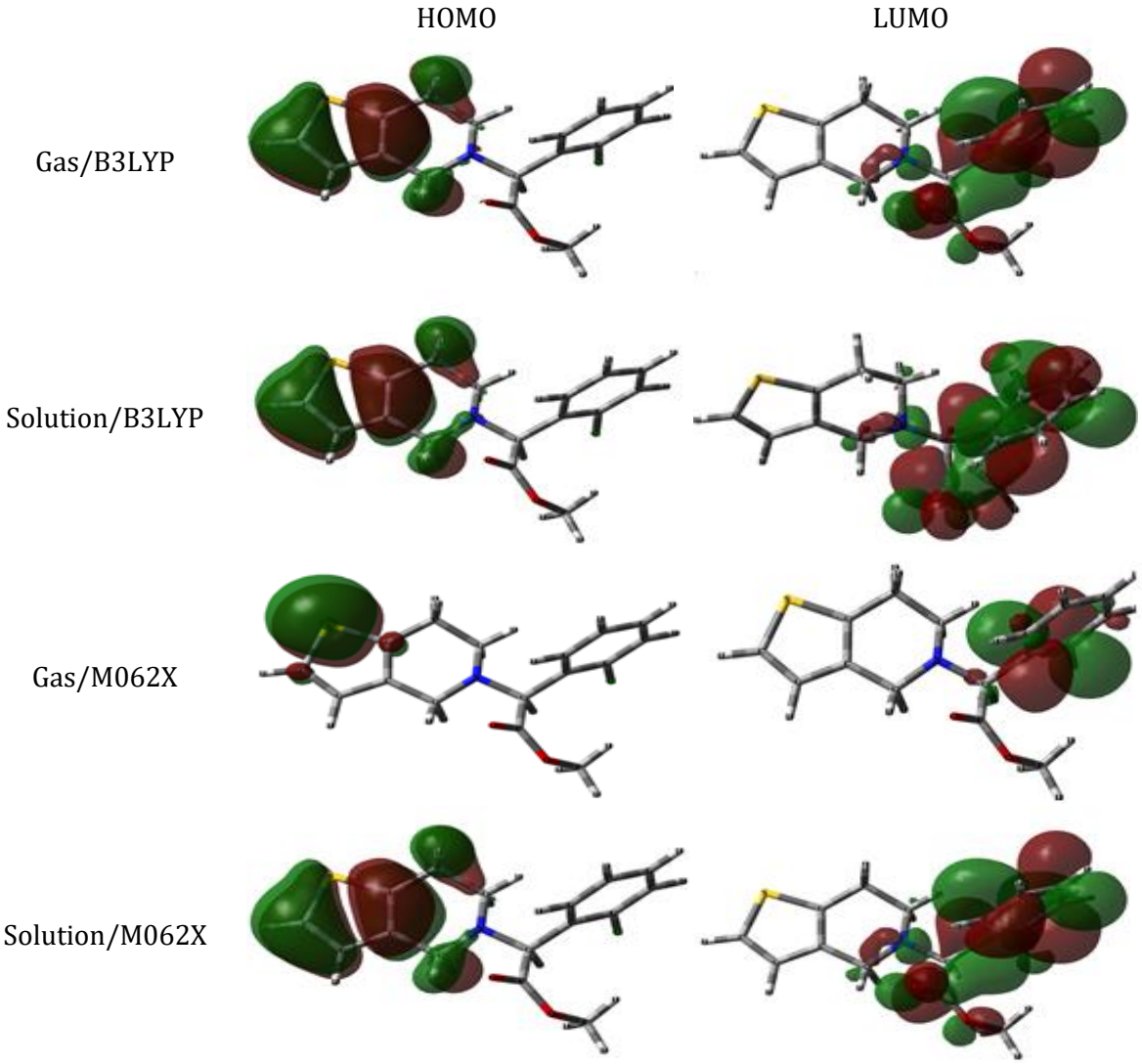
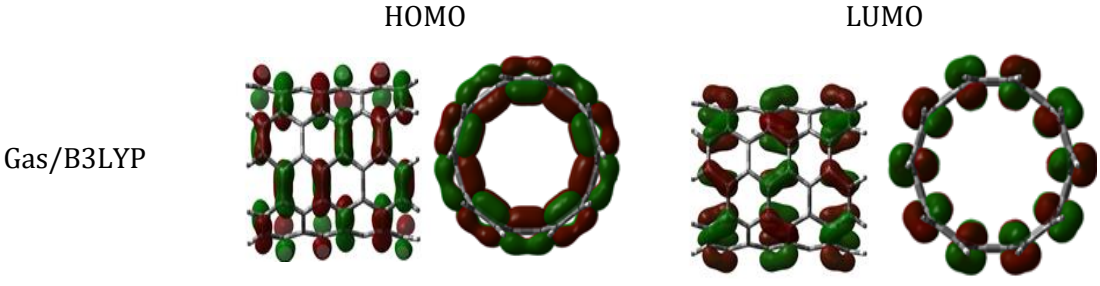


Figure 1. Orbital depiction of HOMO and LUMO in clopidogrel drug in gas and solution phases with B3LYP and M062X methods.



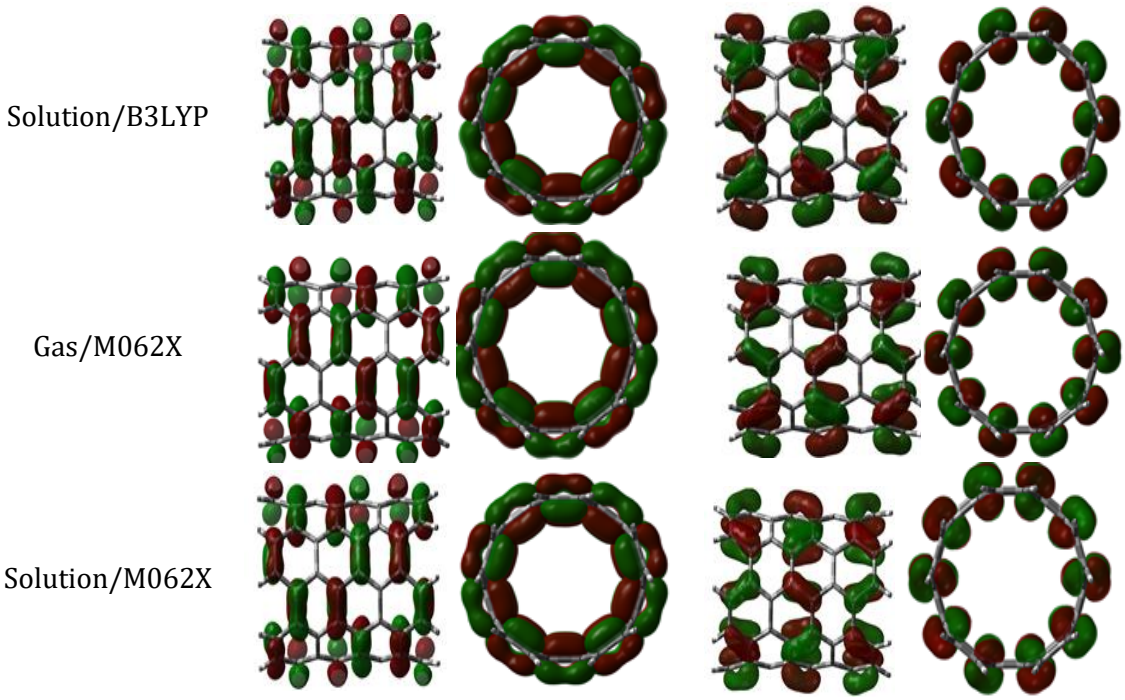


Figure 2. Orbital depiction of HOMO and LUMO in SWCNTs in gas and solution phases with B3LYP and M062X methods.

Figures 1 and 2 also show that in most cases, HOMO of clopidogrel is located on the sulfur atom of clopidogrel. However, the HOMO of clopidogrel in its the gas phase, which was calculated by M062X method, is not located on the sulfur atom. In other cases, the HOMO was distributed over sulfur and nitrogen containing rings. LUMOs of clopidogrel are distributed over nitrogen, oxygen, and chlorine containing rings. HOMO and LUMO of carbon nanotubes have a similar behavior to those of clopidogrel (Figure 2). HOMO and LUMO are distributed over the axis of nanotubes. The results of band gap calculations and quantum descriptors for clopidogrel, SWCNTs and Drug-SWCNT complexes are presented in Table 1. The band gaps of clopidogrel and SWCNTs were mostly observed in solution phase and this phenomenon can be attributed to the high reactivity of clopidogrel and SWCNTs in the gas phase. Ionization potential is a basic description of the chemical reactivity of atoms and molecules. The high ionization potential pertains to towering stability. Ionization potential calculations indicated (Table 1) that the clopidogrel and carbon nanotubes possess the high ionization potential and are stable in solution phase. The high stability of clopidogrel and carbon nanotubes in solution phase was confirmed by B3LYP method. The high stability behavior of clopidogrel and carbon nanotubes in solution phase is attributed to the low reactivity of these compounds. Chemical potentials of clopidogrel and carbon nanotubes are higher in solution phase than in the gas phase and therefore the reactivity of clopidogrel and carbon nanotubes is higher in solution phase than in the gas phase. The polarity of a molecule describes its dipole moment. Table 1 represents the dipole momentum of clopidogrel is high in solution phase, suggesting its adsorption on the surface of SWCNTs is easily achievable. Other chemical quantum descriptors are also presented in Table 1.

Table 1. Quantum molecular descriptors of clopidogrel and (5, 5) CNT in the gas and solution phases by B3LYP and M062X methods and drug-(5, 5) CNT complexes in gas phase by B3LYP and M062X methods

Property	Drug				(5,5)CNT				Drug+(5,5)CNT			
	gas		Solution		gas		Solution		gas		Solution	
	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X
E_{HOMO}(eV)	-6.228	-7.615	-6.375	-7.746	-4.665	-5.507	-4.806	-5.711	-4.667	-5.386	-4.809	-5.675
E_{LUMO}(eV)	-1.361	0.622	-1.332	-0.417	-2.905	-2.440	-3.021	-2.614	-2.890	-2.447	-2.949	-3.047
ΔE(eV)	4.867	8.238	5.042	7.329	1.760	3.066	1.785	3.096	1.777	2.939	1.860	2.628
I(eV)	6.228	7.615	6.375	7.746	4.665	5.507	4.806	5.711	4.667	5.386	4.809	5.675
A(eV)	1.361	-0.622	1.332	0.417	2.905	2.440	3.021	2.614	2.890	2.447	2.949	3.047
η(eV)	2.433	4.119	2.521	3.664	0.880	1.533	0.892	1.548	0.888	1.469	0.930	1.314
χ(eV)	3.794	3.496	3.853	4.081	3.785	3.974	3.914	4.162	3.779	3.917	3.879	4.361
σ(eV)-1	0.410	0.242	0.396	0.273	1.136	0.652	1.120	0.645	1.125	0.680	1.075	0.761
ω(eV)	2.958	1.483	2.945	2.273	8.139	5.149	8.579	5.595	8.034	5.219	8.089	7.235
μ(Debye)	3.735	3.778	5.787	5.809	0.0001	0.0001	0.0000	0.0000	3.234	3.272	5.286	5.303

The (5, 5) carbon nanotubes have a high tendency to accept electrons from clopidogrel and this tendency is attributed to high electronegativity and low levels of LUMO energy of (5, 5) carbon nanotubes. Therefore, SWCNTs are electrophile and this statement is in agreement with Ref. [59]. The electrophilic behavior of (5, 5) carbon nanotubes has been confirmed by electrophilic charge transfer (ECT) method. The ECT was calculated using the Equation 3 [60].

$$ECT = (\Delta N_{\max})_A - (\Delta N_{\max})_B = 2\left[\omega_A X_A - \omega_B X_B\right] \quad (3)$$

Where A and B are nucleophile and electrophile species, respectively. If ECT>0, then A can be regarded as an electron acceptor and B as electron donator. If ECT>0, the charge transfer pathway will be from B to A. The charge transfer pathway will be reversed when ECT<0. In order to calculate ECT, SWCNTs and clopidogrel were taken as A and B respectively. Table 1 shows the ECT is positive in both gas and solution phases. Therefore, SWCNTs are electrophiles and clopidogrel is a nucleophile.

The orientation of SWCNTs-clopidogrel complex was determined by Fukui function, electrostatic potential and barrier orbital functions. The Fukui function specifies the locations of electrophile and nucleophile species. Equations 4 and 5 are Fukui functions for nucleophilic and electrophilic attacks [61]:

$$f^{+}(k) \cong P_{N+1}(k) - P_N(k) \quad (4)$$

$$f^{-}(k) \cong P_N(k) - P_{N-1}(k) \quad (5)$$

$P_N(k)$, $P_{N+1}(k)$ and $P_{N-1}(k)$ are the accumulation of electrons on k neutral atom, anion and cation respectively. Considering that carbon nanotubes are electrophilic, the $f^-(k)$ computations of clopidogrel should be taken into the accounts. Equation 6 was used to determine reactive sites of SWCNTs [61]:

$$f^2(k) = \left[f^{+}(k) - f^{-}(k) \right] \quad (6)$$

When $f^2(k)>0$, the reactive sites are suitable for nucleophilic attack. When $f^2(k)<0$, the reactive sites are suitable for electrophilic attack. Equation 6 can also be written in terms of softness parameter [61]:

$$s^{+}(k) \cong S f^{+}(k) \quad (7)$$

$$s^{-}(k) \cong S f^{-}(k) \quad (8)$$

Table 2 shows $f^+(k)$, $f^-(k)$, $f^2(k)$, $Sf^+(k)$, and $Sf^-(k)$ of clopidogrel in gas phase.

Multiwfn program software was utilized to determine reactive sites by the electrostatic potential method. Figure 3 is a plot of electronic potential for clopidogrel. Figure 3 shows the

blue color points are the points which have more negative charges and the red color points are the points with less electronegativity. Table 3 present the energies of the electrostatic potential at maximum and minimum points which were calculated by B3LYP method. The barrier orbitals are depicted in Figure 1. HOMO represents charge densities and LUMO is depicted as a region of charge deficiency.

The orientation of interaction between SWCNT and clopidogrel can be determined by Fukui function, electrostatic potential and barrier orbital functions. There is no proof which one of computational methods is most reliable and therefore most of the structural orientations of SWCNTs and clopidogrel were determined and optimized by using the results of all three methods. Thus, the best optimized structure of SWANT-clopidogrel complex is presented in Figure 4. Distances of oxygen, nitrogen, and sulfur atoms of clopidogrel to SWCNTs are related to structural orientations of SWCNTs and clopidogrel.

Thus, the best optimized structure of SWANT-clopidogrel complex is presented in Figure 4. Distances of oxygen, nitrogen, and sulfur atoms of clopidogrel to SWCNTs are related to structural orientations of SWCNTs and clopidogrel.

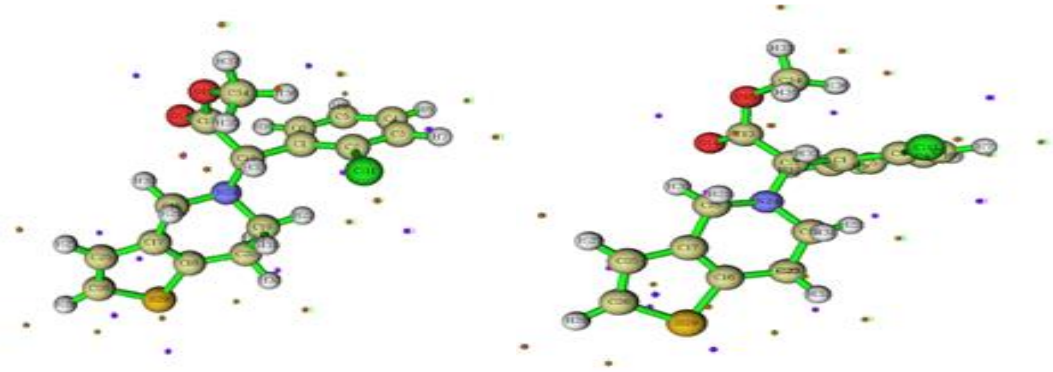


Figure 3. An electron potential map for clopidogrel from two directions

Table 2. The results of $f^{+}(k)$, $f^{-}(k)$, $f^{2}(k)$, $Sf^{+}(k)$ and $Sf^{-}(k)$ for clopidogrel drug in gas phase with B3LYP method

Atom	P_N	P_{N-1}	P_{N+1}	$f^{+}(k)$	$f^{-}(k)$	$f^{2}(k)$	$s^{+}(k)$	$s^{-}(k)$
C1	0.057	0.079	0.346	0.289	-0.021	0.311	0.328	-0.024
C2	-0.193	-1.716	0.060	0.253	1.523	-1.269	0.288	1.731
C3	0.468	1.611	0.558	0.090	-1.143	1.233	0.103	-1.299
C4	-0.342	3.212	-0.500	-0.158	-3.554	3.396	-0.179	-4.039
C5	-0.542	0.995	-0.698	-0.156	-1.538	1.382	-0.177	-1.747
C6	0.099	-1.154	0.037	-0.061	1.254	-1.315	-0.069	1.425
H7	0.220	-1.358	0.307	0.087	1.578	-1.491	0.099	1.793
H8	0.175	-2.829	0.251	0.076	3.005	-2.929	0.086	3.414
H9	0.190	-0.503	0.267	0.077	0.693	-0.616	0.087	0.788
H10	0.232	0.266	0.288	0.056	-0.033	0.089	0.063	-0.038
Cl11	0.192	0.613	0.082	-0.109	-0.421	0.312	-0.124	-0.479
C12	-0.290	-0.000	-0.356	-0.065	-0.290	0.224	-0.074	-0.330
C13	-0.501	-0.576	-0.613	-0.112	0.075	-0.187	-0.127	0.085
O14	-0.173	-0.240	-0.179	-0.006	0.066	-0.073	-0.007	0.076

O15	-0.031	-0.127	-0.069	-0.037	0.096	-0.134	-0.042	0.109
C16	0.671	0.382	0.752	0.080	0.288	-0.207	0.091	0.328
C17	0.179	0.176	0.507	0.328	0.002	0.325	0.373	0.003
C18	-0.630	-0.508	-1.070	-0.439	-0.122	-0.317	-0.499	-0.138
C19	-0.449	-0.705	-0.615	-0.165	0.256	-0.421	-0.188	0.290
C20	-0.703	-0.299	-1.080	-0.376	-0.404	0.027	-0.428	-0.459
H21	0.134	0.141	0.276	0.141	-0.006	0.147	0.160	-0.007
H22	0.154	0.319	0.234	0.079	-0.164	0.244	0.090	-0.187
H23	0.180	0.135	0.237	0.057	0.044	0.013	0.065	0.050
N24	0.645	0.845	0.937	0.291	-0.200	0. 492	0.331	-0.227
C25	-0.400	-0.369	-0.396	0.003	-0.031	0.034	0.004	-0.035
C26	-0.024	-0.111	-0.015	0.009	0.087	-0.077	0.010	0.099
H27	0.142	0.174	0.210	0.068	-0.032	0.100	0.077	-0.036
H28	0.252	0.277	0.336	0.083	-0.025	0.108	0.095	-0.028
S29	-0.556	-0.598	-0.545	0.010	0.042	-0.031	0.012	0.047
H30	0.219	0.237	0.321	0.101	-0.017	0.119	0.115	-0.020
H31	0.120	0.087	0.280	0.160	0.033	0.127	0.182	0.037
H32	0.181	0.131	0.249	0.068	0.049	0.018	0.077	0.056
H33	0.164	0.326	0.413	0.248	-0.161	0.410	0.282	-0.184
C34	-0.357	-0.366	-0.378	-0.021	0.008	-0.029	-0.024	0.009
H35	0.170	0.119	0.159	-0.010	0.050	-0.061	-0.012	0.057
H36	0.148	0.191	0.155	0.007	-0.043	0.050	0.008	-0.048
H37	0.196	0.140	0.245	0.048	0.055	-0.007	0.054	0.063

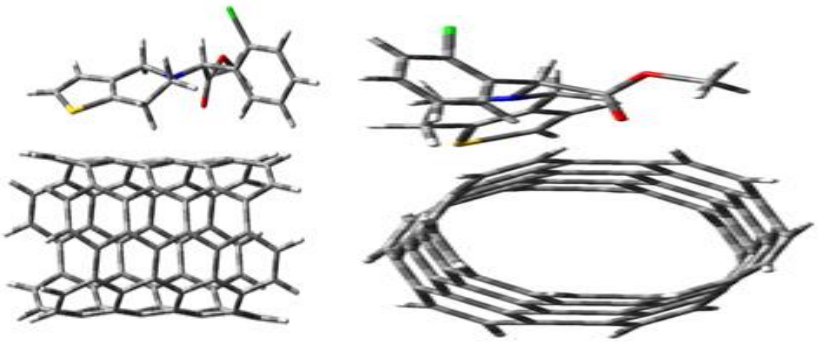


Figure 4. The optimized structure after adsorption of clopidogrel on the (5,5) CNT in gas phase by B3LYP method

Table 3. Electrostatic potential energy for the maximum and minimum points of clopidogrel in gas phase by B3LYP method

No.(Red)	Energy	No.(Blue)	Energy
1	0.784	1	-0.812
2	0.626	2	-1.732
3	-0.606	3	-0.630
4	0.583	4	-1.635
5	-0.499	5	C
6	0.371	6	-0.554
7	0.985	7	-0.258

8	0.496	8	0.189
9	0.831	9	-0.148
10	0.864	10	-0.219
11	0.998	11	-0.135
12	0.871		
13	0.563		
14	0.713		
15	0.526		
16	0.965		
17	0.569		
18	0.958		

Table 1 shows the band gap calculations and molecular quantum descriptors of clopidogrel-SWCNT complexes. The band gap of the clopidogrel-SWCNT complex was different from the band gap of clopidogrel or SWCNTs. Band gaps of clopidogrel-SWCNTcomplex, which were computed by B3LYP and M062X methods, are 1.777 and 2.939 eV, respectively. Similarly, the quantum descriptors of clopidogrel-SWCNT complexes are different from quantum descriptors of clopidogrel or SWCNTs (Table 1). Figure 5 depicts the plots of density of states (DOS) of clopidogrel, carbon nanotubes, and clopidogrel-SWCNT complexes. DOS of clopidogrel in solution phase, which was calculated using the B3LYP method, is similar to its DOS in the gas phase. Conversely, DOS of clopidogrel, carbon nanotubes and clopidogrel-SWCNT complexes, which were calculated by M062X method, are different from the DOSs which were calculated by B3LYP method. The highest DOS was obtained in the gas phase using an energy of 0.001 Hartree. A comparison of DOS with band gap calculations shows that the DOS results are in good agreement with band gap results and this is consistent with band gap and DOS results which were calculated by the B3LYP method in both solution and gas phases (0.007 Hartree). Additionally, a similar behavior was observed about utilization of the M062X method for computation of band gap and DOS (0.034 Hartree). The range of band gap was in good agreement with the range of molecular orbitals (HOMO and LUMO). DOS plots have regions with zero values and these zero regions are in the range of HOMO and LUMO. Figures 5**d** and 5**c** demonstrate that both the M062X and B3LYP calculations provided same DOS values for SWCNTs in solution and gas phases. Figure 5**e** shows that DOSs of clopidogrel-SWCNT complexes are in an acceptable agreement with band gap. Table 4 shows the natural bonding orbitals (NBO) after and before the adsorption of clopidogrel on the surface of SWCNTs in the gas phase. Table 4 also shows the electron densities of orbitals have changed. For example, under normal circumstances, the electron densities of 3s and 3p orbitals in sulfur atom are 1.61 and 3.96, respectively. These values have now increased to 1.66 and 3.97 whereas the electron densities of 4s and 4p orbitals have decreased by more than 0.01. No change was observed about 3d orbital. Importantly, the electron densities of 2s and 2p orbitals in oxygen atom adjacent to SWCNTs exhibited a variation of 0.02 after and before adsorption. The electron density of 3d orbital has decreased by 0.01 after adsorption of clopidogrel and may reach zero. Table 4 shows variations of electron densities of orbitals for other atoms. Mulliken's atomic charges of clopidogrel, SWCNTs and clopidogrel-SWCNTs complexes were calculated and the results are given in Table 5.

Atomic charges of clopidogrel were computed by both M062X and B3LYP methods in gas and solution phases. The results of the two methods are not similar, suggesting the occurrence of charge transfer in the adsorption process. This behavior was also observed in the case of SWCNTs. For example, the charges on O14, which is the closest atom to carbon nanotubes, were determined to be -0.125 and -0.206 in gas and solution phases respectively. These values indicate that there is a charge transfer as much as -0.081. Additionally, there are charge transfers for H23, N24, S29, and C34 atoms in both phases. The observed charge transfer for H23, N24, S29, and C34 atoms were -0.068, -0.098, +0.002, and -0.007 respectively. If Mulliken's charges are considered in the gas phase, then the key atoms can be identified after and before their adsorption on the surface of carbon nanotubes. Charge transfers for O14, H-23, N24, S29, and C34 were calculated to be +0.045, -0.242, +0.068, +0.493, and +0.135 respectively by B3LYP method. M062X method gave different results for the O14, H23, N24, S-29, and C34 atoms which are +0.343, -0.033, -0.143, +1.18 and -0.004.

Table 4. The natural electron configuration of some atoms of the clopidogrel drug before and after adsorption on the (5,5) CNT in gas phase

Atom	B3LYP		M062X	
	Before adsorption	After adsorption	Before adsorption	After adsorption
O14	2s(1.69)2p(4.87)3d(0.01)	2s(1.71)2p(4.89)	2s(1.69)2p(4.88)3d(0.01)	2s(1.71)2p(4.89)
H23	1s(0.79)	1s(0.77)2s(0.01)	1s(0.78)	1s(0.77)2s(0.01)
N24	2s(1.28)2p(4.21)3p(0.01)	2s(1.25)2p(4.26)3p(0.01)	2s(1.28)2p(4.23)3p(0.01)	2s(1.25)2p(4.26)3p(0.01)
S29	3s(1.61)3p(3.96)4s(0.01)3d(0.02)4p(0.02)	3s(1.66)3p(3.97)3d(0.02)4p(0.01)	3s(1.59)3p(3.97)4s(0.01)3d(0.02)4p(0.02)	3s(1.66)3p(3.97)3d(0.02)4p(0.01)
C34	2s(1.08)2p(3.11)3p(0.01)3d(0.01)	2s(1.09)2p(3.09)3p(0.01)3d(0.01)	2s(1.08)2p(3.12)3p(0.01)3d(0.01)	2s(1.09)2p(3.09)3p(0.01)3d(0.01)

Table 5. Mulliken atomic charge of some atoms of the clopidogrel drug before and after adsorption on the (5,5) CNT

Atom	Before adsorption						After adsorption			
	B3LYP			M062X			B3LYP		M062X	
	gas	Solution	Charge transfer	gas	Solution	Charge transfer	gas	Charge transfer	gas	Charge transfer
O14	-0.125	-0.206	-0.081	-0.164	-0.255	-0.091	-0.080	+0.045	0.179	+0.343
H24	0.192	0.124	-0.068	0.206	0.213	+0.007	-0.050	-0.242	0.173	-0.033
N24	0.470	0.372	-0.098	0.618	0.501	-0.117	0.538	+0.068	0.475	-0.143
S29	-0.621	-0.619	+0.002	-0.561	-0.567	-0.006	-0.128	+0.493	0.619	+1.18
C34	-0.326	-0.333	-0.007	-0.355	-0.381	-0.026	-0.191	+0.135	-0.359	-0.004

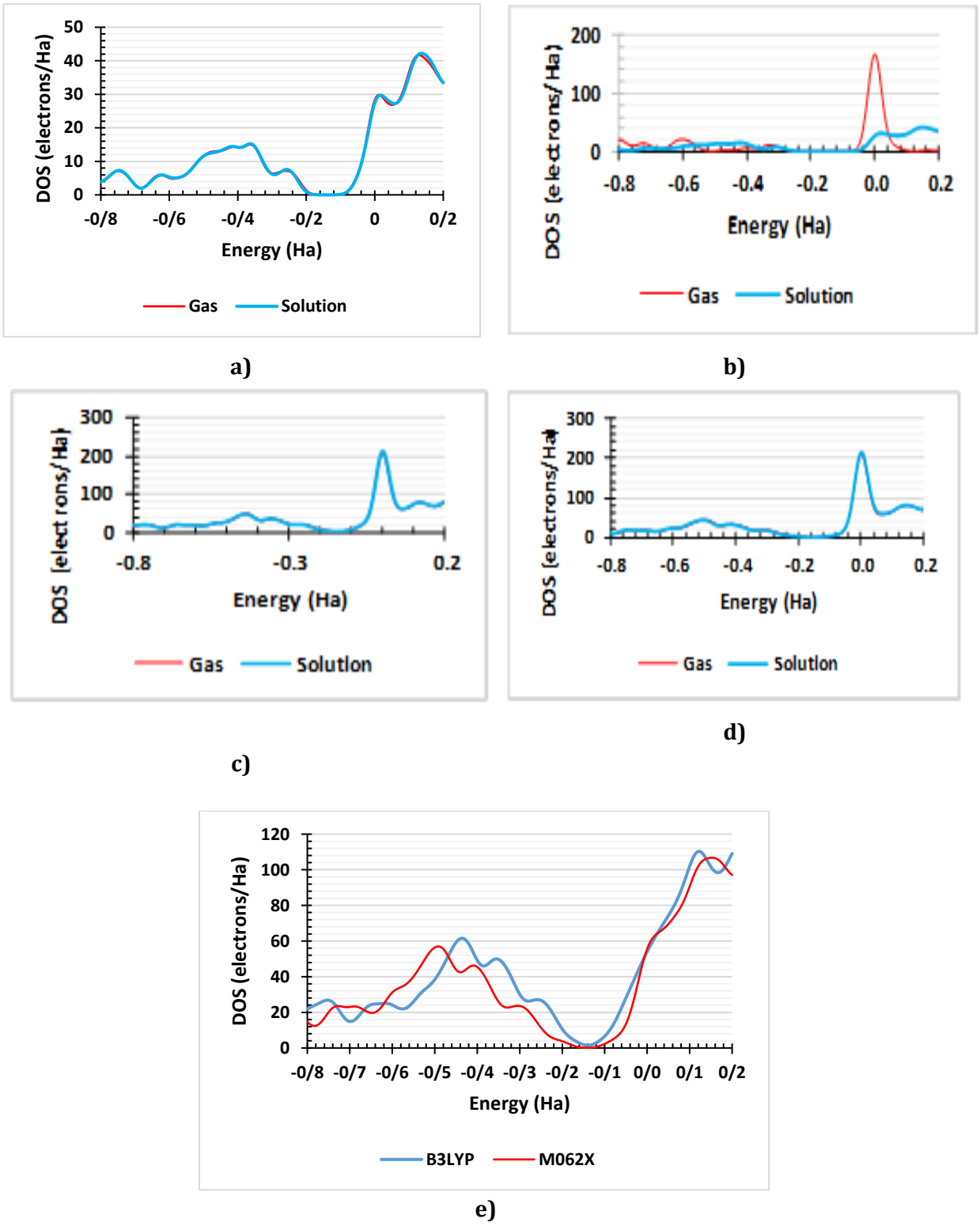


Figure 5. Density of states (DOS) for clopidogrel drug in gas and solution phases by a) B3LYP and b) M062X methods, and (5,5) CNT in gas and solution phases by c) B3LYP and d) M062X methods, and e) clopidogrel drug-(5,5) CNT complexes in gas phase by B3LYP and M062X methods

Bond lengths and angles of several important atoms of clopidogrel were determined prior and after their adsorption on the SWCNTs (Table 6). It can be seen that bond lengths and angles have changed after adsorption process. C29-S16 bond length was 1.742 Å before adsorption and it increased to 1.814 Å after adsorption. On the other hand, the bond angle of O14-C13-O15 was 118.453 before adsorption and then it increased to 122.985 after adsorption. A similar trend was also observed for the other atoms. Table 6 demonstrates the bond lengths and angles before and after adsorption of clopidogrel on SWCNT and also distances between the atoms of clopidogrel and the SWCNT. The shortest distance was found to be between the O14 of clopidogrel and C90 of carbon nanotubes (2.368 Å).

Table 6. Structural property of some atoms of the clopidogrel drug and (5,5) CNT before and after adsorption

Property	Before adsorption	After adsorption
Band Length(Å)		
O14–C13	1.201	1.231
H23–C20	1.096	1.092
N24–C18	1.471	1.473
S29–C16	1.742	1.814
S29–C26	1.738	1.809
C34–H36	1.090	1.090
Band Angle(0)		
O14–C13–C12	123.105	127.551
O14–C13–O15	118.453	122.985
C12–N24–C18	111.594	111.174
S29–C26–H28	119.909	119.227
C26–S29–C16	91.418	89.496
H30–C17–C18	109.343	109.034
Distance(Å)		
O14–C90	-	2.368
H23–C71	-	3.607
N24–C71	-	4.119
S29–C51	-	2.950
C34–C110	-	4.701

Equation 2 was used to calculate the interaction energy between clopidogrel and SWCNT and the results are tabulated in Table 7. If E_{ads}<0 then the adsorption will be exothermic [62]. The adsorption of clopidogrel on the surface of carbon nanotubes leads to E_{ads}=-1.734 eV energy and therefore the process is exothermic. According to the amounts of adsorption energies, large adsorption distance (2.291-4.756) and small charge transfer indicate that clopidogrel drug is weakly bounded to SWCNT and clopidogrel-SWCNT through van der Waals-type interactions. Therefore, these interactions can be identified as physisorption.

Table 7. Calculated adsorption energies of clopidogrel drug on the (5,5) CNT in gas phase by B3LYP and M062X methods (eV)

Property	B3LYP	M062X
E_D	-45800.644	-45790.181
E_{SWCNT}	-83286.344	-83256.464
$E_{(SWCNT+D)}$	-129088.722	-129048.487
E_{ads}	-1.734	-1.841

Conclusions

IN this research study, the structural and electronic properties of the clopidogrel, SWNT, and clopidogrel-SWNT complexes were investigated using the DFT calculations. The orientation of interaction between the SWCNT and the clopidogrel was determined using the Fukui function, electrostatic potential and barrier orbital functions. The clopidogrel molecule was weakly bounded to SWCNT through van der Waals type interaction, and this interaction had the physical nature of the adsorption process. The negative adsorption energy indicated that the nature of the interaction is exothermic. The simulation and computational studies were carried out and we gained a deeper understanding of the interaction between the clopidogrel and the SWCNT. The results of this work provided invaluable information regarding clopidogrel, SWNT and clopidogrel-SWNT. This interaction causes that the HOMO level shift from -4.667eV in gas phase to -4.809eV in solution phase, while the LUMO level changes by about 0.059. As a result, the HOMO-LUMO gap is increased from 1.777 to 1.860 eV. The difference between energies gap in two phases is 0.025eV, and this small difference is also seen in the DOS spectra for SWNT. For clopidogrel, the energy levels of the HOMOs are -6.2228 and -6.375 eV and the energy levels of LUMOs are −1.361 and -1.332 eV in gas and solution phases, respectively. This may be due to the greater solvent polarization effect on the nitrogen, oxygen, sulfur and chlorine atoms.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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