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Research Paper

DFT/NBO analysis of interaction between a CNT and anti-cancer drugs

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ABSTRACT: Having conducted fundamental projects, scientists have expressed their hope to develop the use of carbon nanotubes to release drugs. It is important to release drugs in cell without damaging healthy cells of tissues under study. Researchers have shown the fact that nanotubes can perform this function perfectly. To this objective, in the present study the interactions between four anti-cancer drugs with a carbon nanotube (CNT) (6,6), containing 60 carbon atoms, have been investigated. It is noteworthy that all of these drugs have functional groups, from which the reaction with the nanotube can take place. The Density Functional Theory (DFT) calculations have been performed by Beck, three-parameter, Lee-Yang-Parr (B3LYP) method and 6-31G(d) basis set for full optimization of drugs, nanotube and the formed complexes. The Natural Bond Orbital (NBO) analysis and frequency calculations have been also performed for all structures using B3LYP method and 6-31G(d) basis set in 298K. According to the results, among all drugs under study, only two complexes between Carmustine and nanotube can be thermodynamically formed in 298K. The stability constants are calculated thereby showing a considerably large amount. Therefore, the nanotube can be a useful container for this drug. Also, NBO analysis shows that there exist hyperconjugative effects arising from an overlap between occupied orbitals in drugs and unoccupied orbitals in nanotube.

Keywords: *Anti-cancer drug; Carbon nanotube; Drug delivery; Density functional theory; Natural bond orbital.*

INTRODUCTION

The outstanding mechanical and electronic properties of carbon nanotubes make them interesting candidates for drug delivery. Nowadays, in the modern world of medicine, the carbon nanotubes have proved their capability of passing through the cell shell. This has made scientists believe the point that such tubes can be used in releasing active drug molecules in the cells, especially the sensitive and essential molecules for particular diseases like cancer, AIDS and etc. To prepare these materials for such an important function, their physical and chemical properties have been investigated by many scientists [1]. Regarding to this interest, insoluble drug release from silica nanotubes [2] and the interaction of amphetamine and nanotubes [3] were investigated in drug delivery. Also the adsorption of leflunomide on zigzag carbon and boron nitride nanotubes has been studied [4]. Simultaneously, the adsorption of pristine and Al-doped boron nitride nanotubes with some platinium- based drugs [5] and application of a doped carbon nanotube composite in selective determination of an anticancer drug were investigated [6]. The ability of carbon nanotubes to release small molecule was among the first researches which have been done in drug delivery [7].

Applying different functional groups with their particular properties in various body cells is a concept that is issued in the field of biomedicine. However, identification of these functional groups and covalent or non-covalent bonds between nanotubes and these functional groups is a noticeable subject in chemistry [9]. The main aim in drug delivery is to release drugs in destroying cells (such as cancer cells) without damaging healthy cells of the tissue that is being treated [8]. To achieve this goal, this work has made endeavors to investigate the interactions between a nanotube and some anti-cancer drugs. The selected drugs are described in the following. The first one is Carmustine or BCNU (bis-chloroethylnitrosourea),

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simply defined as a mustard β-chloro-nitrosourea compound which is used in chemotherapy that is also applied in the treatment of several types of brain cancers, multiple myeloma and lymphoma [9]. Regarding the second category, it can be noted that Cyclophosphamide or cytophosphane, is nitrogen mustard obtained from the oxazaphosphorine group. Furthermore, it is used to treat some diseases like cancers and autoimmune disorders. The main use of cyclophosphamide is to treat lymphomas, brain cancers and leukemia [10]. The third one is Dacarbazine, an antineoplastic chemotherapy drug which treats malignant melanoma, pancreas carcinoma, sarcoma, and Hodgkin's lymphoma. Dacarbazine is used as an agent in metastatic melanoma treatment [10]. Doxorubicin, the fourth drug noted above, is used in cancer chemotherapy. Notably, it is derived from bacterial species. Doxorubicin is used for treatment of leukemia and Hodgkin's lymphoma, stomach, breast, lung, thyroid, ovaries cancers and so on [11,12].

Similarly, like many chemotherapy drugs, these drugs may have numerous serious side effects because they not only interfere with cancer cell growth but also with normal cell growth. Among the significant and serious side effects are birth defects, immune defect, headache, fatigue and diarrhea [10].

To prevent these side effects, in this work the interacting ability of an armchair nanotube (6,6) (length=6 Å), containing 60 Carbon atoms, with the mentioned drugs is investigated. So far, the probability of occurring covalent interaction between the mentioned drugs and carbon nanotubes (CNTs) has not been reported. This chemical interaction is studied in this work as a new approach to drug delivery.

EXPERIMENTAL

All calculations were performed using Density Functional Theory [13] with a hybrid functional B3LYP [14] and 6-31G(d) basis set in 298K. The work was carried out on a personal computer using ab initio quantum chemistry package (Gaussian 03) [15], Nanotube Modeler05 [16], GaussView05 [17] and Hyperchem7 [18] in order to study the possible reactions between $C_{60}H_{12}$ nanotube with the functional groups of the above-mentioned drugs.

It is considerable that some of these drugs have more than one functional group which can react with CNTs. For example Carmustine has two chloride groups as the sites where the reaction of nanotube with the drug can take place from. After full geometry optimizations, the frequency and Natural Bond Orbital (NBO) studies [19] were performed.

RESULTS AND DISCUSSION

Interaction with Carmustine

As it can be seen in Fig. 1, Carmustine has two sites to interact with the selected nanotube. Figs 2 and 3 show the formed complexes (complex 1 & 2) obtained from Carmustine (as an anti-cancer drug) and the mentioned nanotube. The obtained results, calculated from frequency study and NBO analysis, are indicated in Tables 1 and 2 respectively.

Frequency Analysis: It is clear that the enthalpy of a reaction (ΔH°) shows how much heat flows in or out of the reaction. The entropy (ΔS°) shows whether reactants are more disordered than products or not.

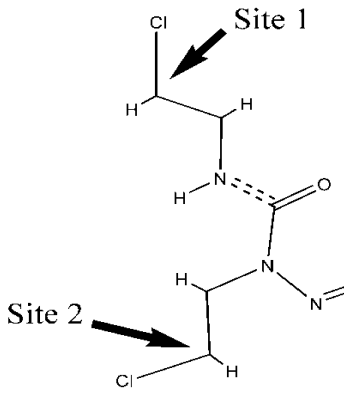

Fig. 1: Carmustine molecule and its two mentioned sites for reaction.

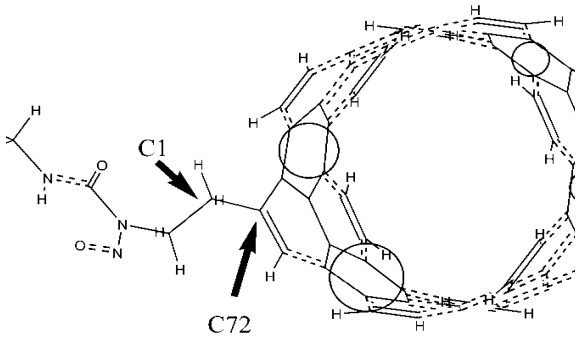

Fig. 2: The formed complex between first site of Carmustine and nanotube (6,6) (Complex 1).

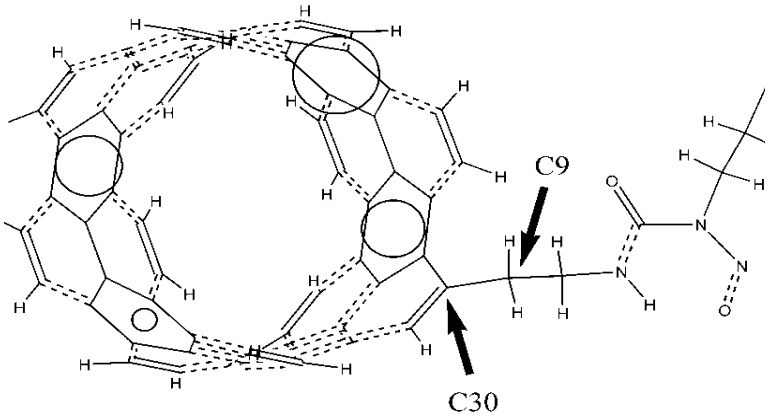

Fig. 3: The formed complex between second site of Carmustine and nanotube (6,6) (Complex 2).

Table 1: The frequency results for complexes formed between Carmustine and nanotube (6,6).

Agent	$\Delta S^0/kcalmol^{-1}K^{-1}$	$\Delta H^0/kcalmol^{-1}$	$\Delta E^0/kcalmol^{-1}$	$\Delta G^0/kcalmol^{-1}$	*Log K*
Complex 1	-0.0029	-15.0103	-15.0125	-14.1421	10.37
Complex 2	-0.0927	-143.4444	-142.8507	-115.8076	84.94

Table 2. The NBO results for complexes formed between Carmustine and nanotube (6,6).

Agent	Donor	Occupancy	Hybrid	Acceptor	E_2/kcalmol^{-1}	ΣE_2/kcal mol^{-1}
Complex 1	σ_{C1-C2}	1.97223	$SP^{2.91}$	σ^*_{C1-C72}	1.10	17.11
	σ_{C1-C2}			$\sigma^*_{C65-C72}$	1.65	
	σ_{C1-C2}			$\pi^*_{C71-C72}$	2.19	
	σ_{C1-H12}	1.98122	$SP^{3.14}$	σ^*_{C1-C72}	0.59	
	σ_{C1-H12}			$\sigma^*_{C71-C72}$	3.55	
	σ_{C1-H13}	1.97595	$SP^{3.36}$	$\sigma^*_{C65-C72}$	1.88	
	σ_{C1-H13}			$\sigma^*_{C71-C72}$	2.09	
	σ_{C1-C72}	1.97248	$SP^{2.65}$	$\sigma^*_{C65-C72}$	1.49	
	σ_{C1-C72}			$\sigma^*_{C71-C72}$	2.57	
Complex 2	σ_{C9-H19}	1.97149	$SP^{3.68}$	$\sigma^*_{C28-C30}$	1.46	15.31
	σ_{C9-H19}			$\pi^*_{C28-C30}$	3.40	
	σ_{C9-H20}	1.97247	$SP^{3.45}$	σ^*_{C9-C30}	0.67	
	σ_{C9-H20}			$\sigma^*_{C28-C30}$	6.23	
	σ_{C9-C30}	1.97696	$SP^{2.49}$	$\sigma^*_{C28-C30}$	0.91	
	σ_{C9-C30}			$\sigma^*_{C29-C30}$	2.64	

Finally, not only does the standard Gibbs free energy (ΔG°) tell us about whether the reaction takes place or not, but also it is employed to yield the stability constant of the reaction [20]. The results obtained from frequency study reveal that , and of both complexes formed from Carmustine and mentioned nanotube are negative. This means that the complex formations are performed thermodynamically. The calculated stability constants are shown in Table 1. The reactions are exothermic and less disordered. So the enthalpy is a suitable factor and the entropy is an ill-suited factor to form the complexes thermodynamically. According to the results, the stability constant for formation of complex 2 is much more than that of complex 1. Therefore, it can be proved that site 2 in Carmustine is more suitable for reacting with nanotubes. As a result, it can be noted that the interaction between nanotube and Carmustine takes place in this site.

NBO Analysis: In this work, a study of hyperconjugative interactions has also been completed. Hyperconjugation can be a stabilizing effect

which is made from an overlap between occupied and unoccupied orbitals, when they are properly oriented. This bonding-antibonding interaction which is noncovalent can be quantitatively presented as NBO approach. A second order perturbation interaction energy (E2) can describe this interaction [19]. The results reveal that hyperconjugation effect in complex 1 is more than the one in complex 2. This noncovalent bonding-antibonding interaction is produced by overlapping between the orbitals of selected drug and the σ^* or π^* orbitals of Carbon atom in the mentioned nanotube. The calculated occupancy and hybrids are shown in Table 2.

Interaction with Cyclophosphamide

Fig. 4 shows that Cyclophosphamide has one site to interact with the selected nanotube. Indeed, it has two chloride groups which are the same. Fig. 5 shows the formed complex (complex 3) obtained from Cyclophosphamide (as an anti-cancer drug) and nanotube. The obtained results, calculated from frequency study and NBO analysis, are shown in Tables 3 and 4, respectively.

Frequency Analysis: The results obtained from frequency study reveal that andof the complex formed between Cyclophosphamide and mentioned nanotube, are positive. Whereas is negative. This means that this complex formation is not performed thermodynamically. Thus, the stability constant cannot be calculated. The formation is endothermic and less disordered, so the enthalpy and the entropy are unsuitable factors to form this complex thermodynamically.

NBO Analysis: According to the results, there exist hyperconjugative effects in this complex. This noncovalent bonding-antibonding interaction is produced by overlapping between the orbitals of the selected drug and the * or orbitals of Carbon atom in the mentioned Nanotube. The calculated occupancy and hybrids are provided in Table 4.

Interaction with Dacarbazine

Fig. 6 indicates that Dacarbazine has two sites to interact with the selected nanotube. It has two amine groups in which the reactions with the nanotube take place. Fig.s 7 and 8 show the formed complexes (complex 4 & 5) obtained from Dacarbazine (as an anti-cancer drug) and this nanotube. The obtained results, calculated from frequency study and NBO analysis, are shown in Tables 5 and 6 respectively.

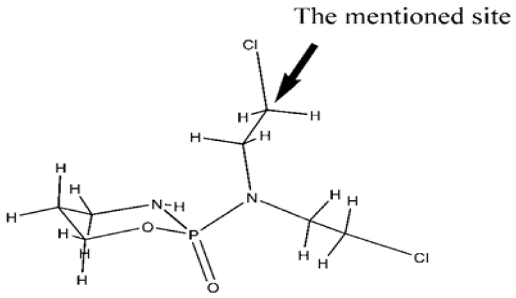

Fig. 4: Cyclophosphamid molecule and its mentioned site for reaction.

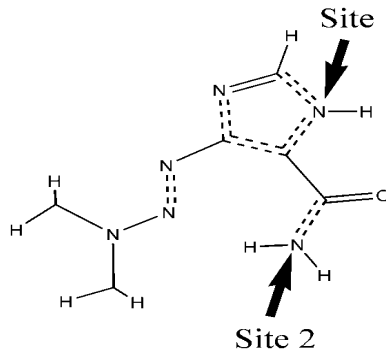

Fig. 6: Dacarbazine molecule and its two mentioned sites for reaction.

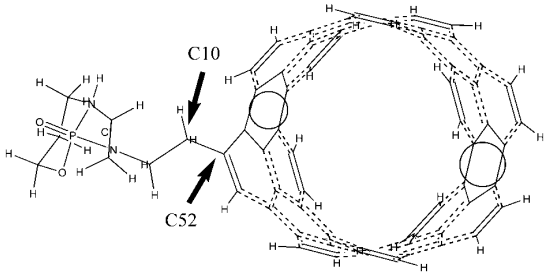

Fig. 5: The formed complex between Cyclophosphamide and nanotube (6,6) (Complex 3).

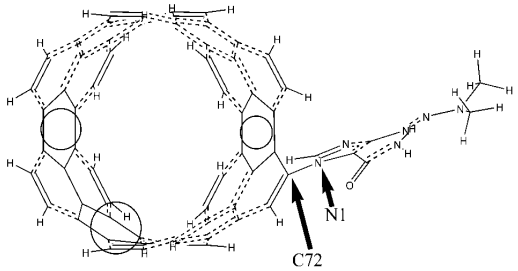

Fig. 7: The formed complex between first site of Dacarbazine and nanotube (6,6) (Complex 4).

Table 3: The frequency results for complex formed between Cyclophosphamide and nanotube (6,6).

Agent	ΔS^0/kcalmol^{-1}K^{-1}	ΔH^0/kcalmol^{-1}	ΔE^0/kcalmol^{-1}	ΔG^0/kcalmol^{-1}	Log K
Complex 3	-0.0090	2.0432	2.0439	4.7145	---

Table 4: The NBO results for complex formed between Cyclophosphamide and nanotube (6,6).

Agent	Donor	Occupancy	Hybrid	Acceptor	E_2/kcalmol^{-1}	ΣE_2/kcalmol^{-1}
Complex 3	$\sigma_{C10-H23}$	1.98147	$SP^{3.26}$	$\sigma^*_{C10-C52}$	0.52	17.24
	$\sigma_{C10-H23}$			$\sigma^*_{C43-C52}$	3.57	
	$\sigma_{C10-H24}$	1.97596	$SP^{3.37}$	$\pi^*_{C43-C52}$	2.11	
	$\sigma_{C10-H24}$			$\sigma^*_{C52-C60}$	1.85	
	$\sigma_{C10-C52}$	1.97370	$SP^{2.65}$	$\sigma^*_{C43-C52}$	2.63	
	$\sigma_{C10-C52}$			$\sigma^*_{C52-C60}$	1.51	
	σ_{C9-C10}	1.97544	$SP^{2.57}$	$\sigma^*_{C10-C52}$	1.2	
	σ_{C9-C10}			$\sigma^*_{C43-C52}$	2.3	
	σ_{C9-C10}			$\sigma^*_{C52-C60}$	1.55	

Table 5: The frequency results for complexes formed between Dacarbazine and nanotube (6,6).

Agent	ΔS^0/kcalmol^{-1}K^{-1}	ΔH^0/kcalmol^{-1}	ΔE^0/kcalmol^{-1}	ΔG^0/kcalmol^{-1}	Log K
Complex 4	-0.0137	17.8847	16.4043	21.9572	---
Complex 5	-0.0140	12.3845	10.9042	16.5543	---

Table 6: The NBO results for complexes formed between Dacarbazine and nanotube (6,6).

Agent	Donor	Occupancy	Hybrid	Acceptor	E_2/kcalmol^{-1}	ΣE_2/kcalm
Complex 4	$LP(1)N1$	1.53784	$SP^{99.99}D^{0.14}$	$\sigma^*_{C70-C72}$	4.74	14.39
				$\sigma^*_{C71-C72}$	3.66	
				$\pi^*_{C71-C72}$	5.99	
Complex 5	$LP(1)N1$	1.66426	$SP^{99.99}D^{0.02}$	$\sigma^*_{C53-C54}$	3.02	23.36
				$\pi^*_{C53-C55}$	17.61	
				$\sigma^*_{C53-C55}$	2.73	

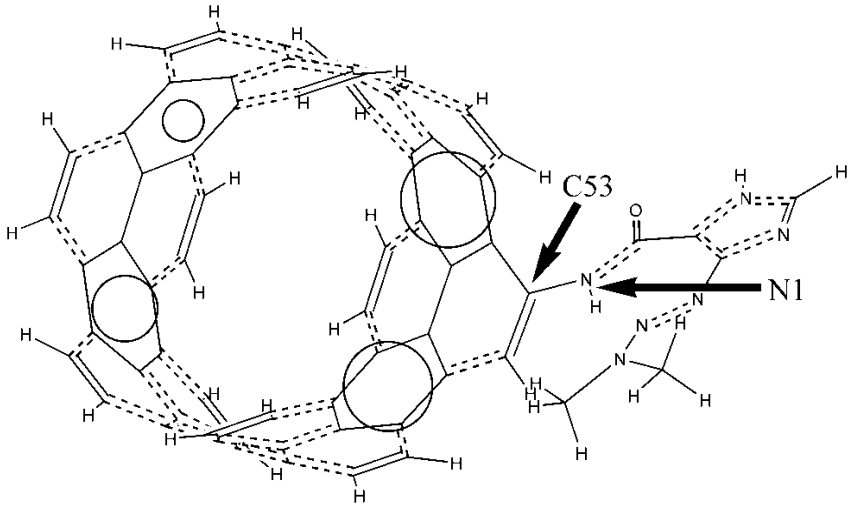

Fig. 8: The formed complex between second site of Dacarbazine and nanotube (6,6) (Complex 5).

Frequency Analysis: As it can be seen, andof the complexes formed from Dacarbazine and mentioned nanotube are positive, but is negative. This means that the complex formation is not performed thermodynamically. The stability constant therefore cannot be calculated; the formations are endothermic and less disordered. So the enthalpy and the entropy are ill-suited factors to form the complexes thermodynamically.

NBO Analysis: The results show that hyperconjugation effect in complex 4 is less than that of complex 5. This noncovalent bonding-antibonding interaction is produced by overlapping between the lone pair electron of Nitrogen in Dacarbazine and the σ or π orbitals of Carbon atom in nanotube. Table 6 shows the calculated occupancy and hybrids.

Interaction with Doxorubicin

As it can be seen in Fig. 9, Doxorubicin has several functional groups to interact with the selected nanotube. At first, one of its alcoholic groups was selected as the interaction site. The reason of selecting this functional group among the other functional groups is the fact that it has less steric hindrance in comparison with that of the other ones. Fig. 10 shows the formed complex (complex 6) obtained from Doxorubicin (as an anti-cancer drug) and the mentioned nanotube. The obtained results, calculated from NBO analysis, are shown in Table 7.

Frequency Analysis: Unfortunately, as a result of the enormous size, steric hindrance and the complexity of the molecule under study, the applied computer in this work did not manage to calculate the frequency data. Therefore, the other sites of this drug have not been investigated.

NBO Analysis: According to the results, a large hyperconjugative effect can be discovered in this complex between the lone pair of electron in Oxygen of Doxorubicin and the * or orbitals of Carbon atom in nanotube. The calculated occupancy and hybrids are shown in Table 7.

CONCLUSION

In this study, the complex formation probability between some anti-cancer drugs and an armchair nanotube was investigated. According to the results, among all drugs under study, only two complexes between Carmustine and the mentioned nanotube can be thermodynamically formed in 298 K. The stability constants are calculated thereby showing a considerably large amount. So the nanotube can be a useful container to release this drug in the special cells without showing side effects as a result of damaging healthy cells. In all complexes, the hyperconjugation effect can be observed.

ACKNOWLEDGEMENT

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Table 7: The frequency results for complex formed between Doxorubicin and nanotube (6,6).

Agent	Donor	Occupancy	Hybrid	Acceptor	E_2/kcalmol^{-1}	ΣE_2/kcalmol^{-1}
Complex 6	$LP(1)O66$	1.95425	$SP^{2.03}$	$\sigma^*_{C98-C100}$	6.23	43.7
				$\pi^*_{C98-C99}$	2.03	
	$LP(2)O66$	1.88938	$SP^{12.96}D^{0.1}$	$\sigma^*_{C98-C99}$	4.57	
				$\pi^*_{C98-C99}$	8.43	
				$\sigma^*_{C99-C100}$	2.10	
				$\pi^*_{C53-C55}$	17.61	
				$\sigma^*_{C53-C55}$	2.73	

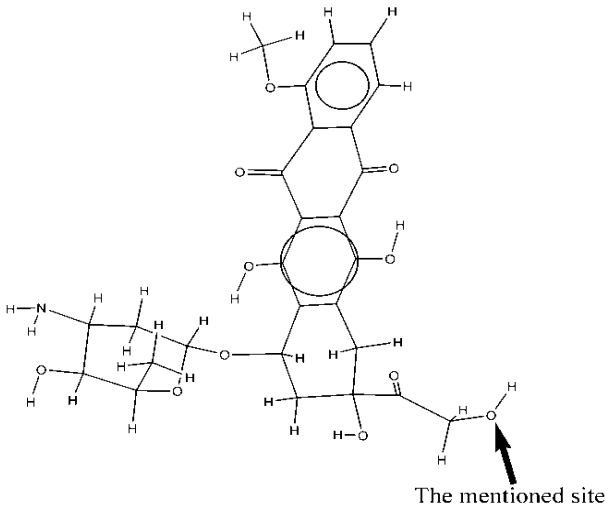

Fig. 9: Doxorubicin molecule and its mentioned site for reaction.

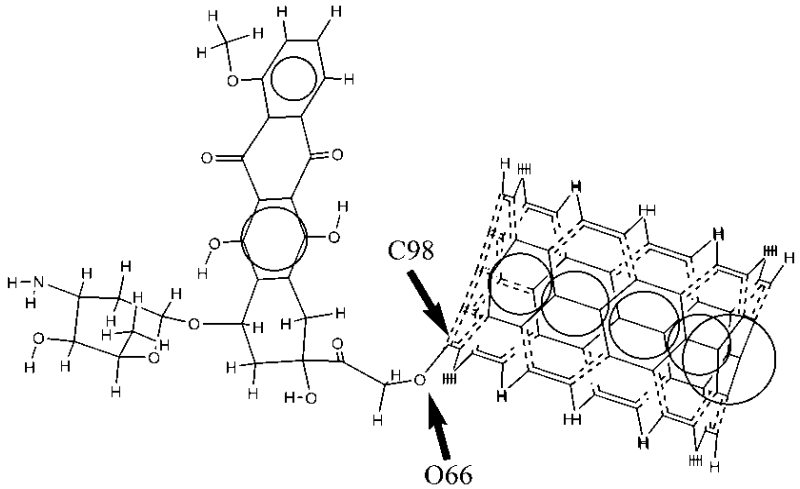

Fig. 10: The formed complex between Doxorubicin and nanotube (6,6) (Complex 6).

REFERENCES

[1] Prakash S., Malhotra M., Shao W., Tomaro-Duchesneau C., Abbasi S., (2011), Polymeric nanohybrids and functionalized carbon nanotubes as drug delivery carriers for cancer therapy. *Adv. Drug Deliv. Rev.* 63: 14–15, 1340-1351.

[2] Li J., Wang Y., Zheng X., Zhang Y., Sun C., Gao Y., Jiang T., Wang S., (2015), The synthesis and application involving regulation of the insoluble drug release from mesoporous silica nanotubes. *Appl. Surf. Sci.* 330: 374-382.

[3] Hafizi H., Najafi Chermahini A., Mohammadnezhad G., Teimouri A., (2015), A theoretical study on the interaction of amphetamine and single-walled carbon nanotubes. *Appl. Surf. Sci.* 329: 87-93.

[4] Raissi H., Mollania F., (2014), Immunosuppressive agent leflunomide: A SWNTs-immobilized dihydroortate dehydrogenase inhibitory effect and computational study of its adsorption properties on zigzag single-walled (6,0) carbon and boron nitride nanotubes as controlled drug delivery devices. *Eur. J. Pharm. Sci.* 56: 37-54.

[5] Shakerzadeh E., Noorizadeh S., (2014), A first principles study of pristine and Al-doped boron nitride nanotubes interacting with platinum-based anticancer drugs. *Phys. E.* 57: 47-55.

[6] Karadas N., Ozkan S. A., (2014), Electrochemical preparation of sodium dodecylsulfate doped over-oxidized polypyrrole/multi-walled carbon nanotube composite on glassy carbon electrode and its application on sensitive and selective determination of anticancer drug: Pemetrexed. *Talanta*. 119: 248-254.

[7] Wang B. S., Yoong S. L., Jagusiak A., Panczyk T., Ho H. K., Ang W. H., Pastorin G., (2013), Carbon nanotubes for delivery of small molecule drugs. *Adv. Drug Deliv. Rev.* 65: 1964-2015.

[8] Huang H., Yuan Q., Shah J. S., Misra R. D. K., (2011), A new family of folate-decorated and carbon nanotube-mediated drug delivery system: Synthesis and drug delivery response. *Adv. Drug Deliv. Rev.* 63: 1332-1339.

[9] Ewend M. G., Brem S., Gilbert M., Goodkin R., Penar P. L., Varia M., Cush S., Carey L. A., (2007), Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin. Cancer Res.* 13: 3637–3641.

[10] Takimoto C. H., Calvo E., (2005), Principles of oncologic pharmacotherapy. In Pazdur, R., Coia L. R., Hoskins W. J., Wagman L. D. Cancer Management: A Multidisciplinary Approach (9th ed.). 23–42. ISBN 978-1-891483-35-6.

[11] Friedman R., Caflisch A., (2009), Discovery of Plasmepsin Inhibitors by Fragment-Based Docking and Consensus Scoring. *Chem. Med. Chem.* 4: 1317–1326.

[12] Gamo F. J., Sanz L. M., Vidal J., Cozar C., Alvarez E., Lavandera J. L., Vanderwall D. E., Green D. V. S., Kumar V., Hasan S., Brown J. R., Peishoff C. E., Cardon L. R., Garcia-Bustos J. F., (2010), Thousands of chemical starting points for antimalarial lead identification. *Nature.* 465: 305–310.

[13] Perdew J. P., Ruzsinszky A., Tao J., Staroverov V. N., Scuseria G., Csonka G. I., (2005), Prescriptions for the design and selection of density functional approximations: More constraint satisfaction with fewer fits. *J. Chem. Phys.* 123: 062201-0622019.

[14] Becke A. D., (1993). A new mixing of Hartree-Fock and local density-functional theories. *J. Chem. Phys.* 98: 1372–1377.

[15] Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Gaussian 03 , Revision C.02 . Gaussian Inc. (2008).

[16] www.jcrystal.com/products/wincnt/.

[17] Frisch A., Nielsen A. B., Holder A. J., Gaussview user Manual , Gaussion Inc (2000).

[18] Http://www.hyper.com/.

[19] Glendening E. D., Reed A. E., Carpenter J. E., Weinhold F., NBO 3.0 Program Manual, http://www.ccl.net/cca/software/NT/mopac6/nbo.htm.

[20] Levine I. N., (1995), Physical chemistry. McGROW-HILL International editions.

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