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Research Paper

Computational Investigation on Anti-Cancer Drugs/ Carbon Nanotube as a Drug Delivery System

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Abstract

Chemotherapy effects on cancer cells and normal cells that grow and divide quickly. The use of methods to reduce the side effects of chemotherapy is always considered. Nanotechnology open the novel new ways for this purpose. Drug delivery with Nano compounds is very useful for decreasing side effects of drugs. In addition, the use of computer methods increases the speed of reaching the best results and reduces the costs of research processes. In this study, the interactions between single wall carbon nanotube and the molecules of anti-cancer drugs was investigated. Energy, dipole momentum and the NMR chemical shift of Busulfan, Fluorouracil and Mercaptopurine in binding with CNT are calculated in density functional theory methods (DFT) and Hartree-Fock (HF) with 3-21G and STO-3G basis sets. We also tested solubility after the optimization. At the B3LYP level of theory we find a very good performance of the computational calculations that allows to distinguish structures and active sites of systems by NMR calculation step.

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1. INTRODUCTION

Drug delivery systems (*DDS*) can improve the efficacy of treatment for pharmaceutical compounds [1]. A significant limitation for any drug therapy is the inherent toxicity of drug molecules. Many compounds may cause substantial toxicity such as chemotherapy drugs. These harmful effects can significantly limit the clinical application of many new compounds. Controlled delivery by DDS mitigates many of these side effects [2]. Nanotechnology has interfaced very closely with drug delivery. Nano carriers can be easily utilized for developing novel carriers and be One of the popular drug delivery compound. This drug delivery system is highly attractive for scientists because of their special properties. The shape and size of nanoparticles (*NPs*) make them the critical component with ability to navigate drug molecules in the body. The need for improved delivery systems motivated the development and application of Nano technologies to have more effective DDS. Nanomaterials have improved the quality of life not only in the treatment of diseases but also in many fields [3-19]. This study has been carried out by using QM method to compare the efficiency of carbon nanotube in delivery some drug molecules which are used in chemotherapy. Busulfan is a chemotherapy drug that is used for treatment of leukemia. Mercaptopurine is used to treat acute lymphocytic leukemia and Fluorouracil is one of the most commonly used drugs for treating cancer. They are most often used drugs in combination with other cancer drugs to treat many types of cancer including: anal cancer, head and neck cancers and breast cancer.

2. COMPUTATIONAL METHOD

In this study, the interactions between single wall carbon nanotube and the molecules of anti-cancer drugs was investigated. For this purpose, Construction and geometry optimization of initial structures of single wall carbon nanotube and anticancer drugs have been done by using Nano tube modeler, Chem. Office, Hyper Chem.7 package [20], Gauss view and Gaussian 03 computational package [21,22]. The combination of CNT and the molecules of anticancer drugs: busulfan (*BUS*.), Fluorouracil(*FLU*.), Mercaptopurine (*MRC*.) have been optimized by UFF, AM1, DFT and Hartree-Fock (*HF*) methods [23]. dipole moment and total energy calculations of these systems have been done by HF and DFT levels of theory by 3-21G and STO-3G and B3LYP basis sets [24] and

NMR spectroscopy of the systems (*BUS.: CNT, FLU.: CNT, MRC.: CNT*) were calculated by the gauge-including atomic orbital approximations (*GIAO*).

3. RESULTS AND DISCUSSION:

In the process of investigating the combination of anticancer drugs and CNT to achieve more information about these important systems, total energy and dipole moment of these systems were calculated which were reported in Table 1. The results represent that BUS.: CNT has the most negative energy value than FLU.: CNT and MRC.: CNT and then has the most structural stability amongst the two other systems. So, the order of stability obtained is thus: BUS.: CNT > FLU.: CNT >MRC.: CNT. According to the amount of dipole momentum, the solubility of busulfan: CNT is more than the other systems.

Table 1. Theoretically values of total E (kcal) and dipole moment (Debye) calculated by interaction of anti-cancer drugs, busulfan, Fluorouracil, Mercaptopurine with outer surface of SWCNT.

Drug: CNT	BUS.: CNT	FLU.: CNT	MRC. :CNT
E/kcal. mol	-590.3489	-361.5721	-275.6368
Dipole moment/debye	8.7041	5.3912	3.5469

In the investigation of drugs, it is very important to determine the active sites of the compounds that is important in the interaction of drugs with the other molecules and NMR is a useful method for this purpose. In NMR spectroscopy the isotropic chemical shielding (σ_{iso}), chemical shielding ($\Delta\ \sigma$), asymmetry parameter (η)and δ for atoms of the systems were calculated from structural data by the following equations [25-27]:

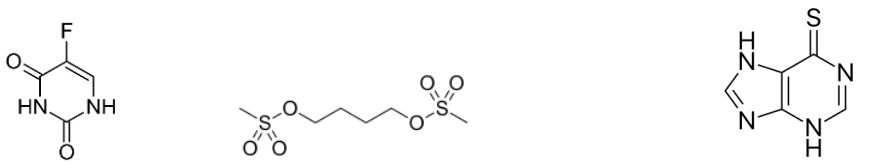
$$\text{If } |\sigma_{11} - \sigma_{iso}| \geq |\sigma_{33} - \sigma_{iso}| \quad (1)$$

$$\Delta\sigma = (\sigma_{11} - (\sigma_{22} + \sigma_{33}))/2\ ,\ \ \delta = \sigma_{11} - \sigma_{iso}\ \ ,\ \ \eta = (\sigma_{22} - \sigma_{33})/\delta \quad (2)$$

$$\text{and if } |\sigma_{11} - \sigma_{iso}| \leq |\sigma_{33} - \sigma_{iso}| \quad (3)$$

$$\Delta\sigma = (\sigma_{33} - (\sigma_{22} + \sigma_{11}))/2 \quad , \quad \delta = \sigma_{33} - \sigma_{iso} \quad , \quad \eta = (\sigma_{22} - \sigma_{11}) / \delta \qquad (4)$$

After optimization the structures by B3LYP, the structural information of CNT binding to drugs molecules show that the most stable compound obtained by connecting the fluorouracil molecule to the carbon nanotube by the nitrogen atom in the heterocycle ring of fluorouracil (N14). The connection of Mercaptopurine to the carbon nanotube was done by the nitrogen atom in the heterocycle ring of Mercaptopurine (N7) and about busulfan connection was done by S molecule to SW-carbon nanotube(S40). In MRC.: CNT system, the maximum density of electrons was localized on nitrogen atom. This density was localized on nitrogen atom of Pyrazine cycle in FLU.: CNT system and about BUS.: CNT, the oxygen atoms around the S atom have the most density of electrons. These results show that the density of electrons of the systems are attracted by the atoms with high electronegativity. So, the atoms with the most electron density are active sites of these systems and have the most tendency for reaction.



a b c

Fig1. The Molecular Structures of a) fluorouracil, b) busulfan, c) Mercaptopurine

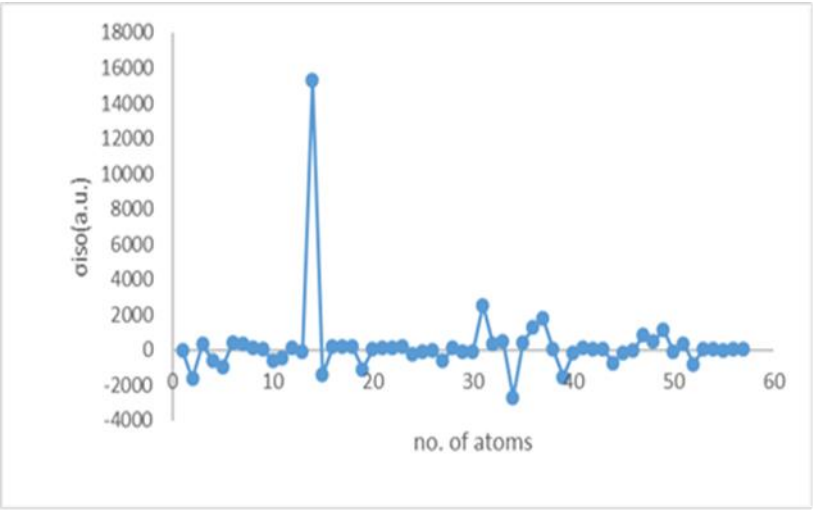


Fig 2. σ_{iso} parameter for FLU.: CNT system.

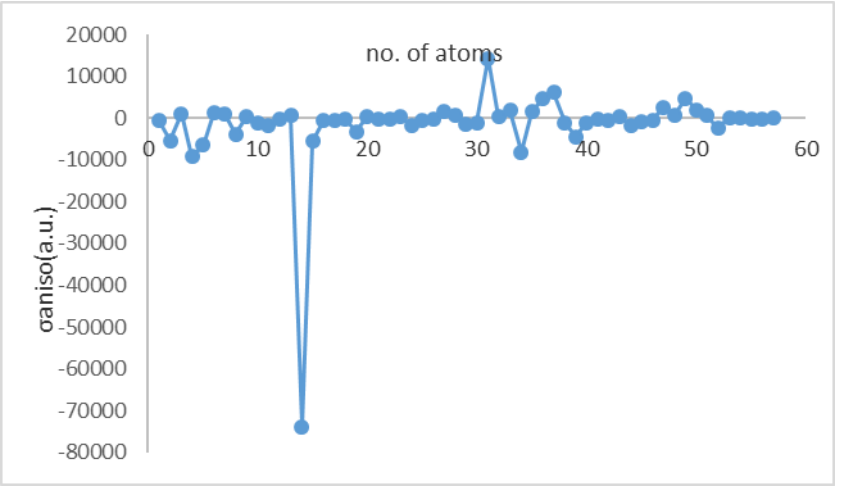


Fig3. σ_{aniso} parameter for FLU.: CNT system.

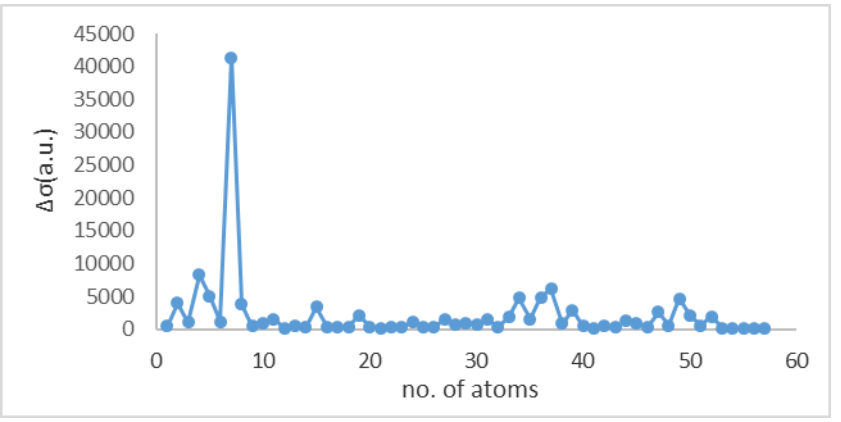


Fig4. Δσ parameter for MRC.: CNT system.

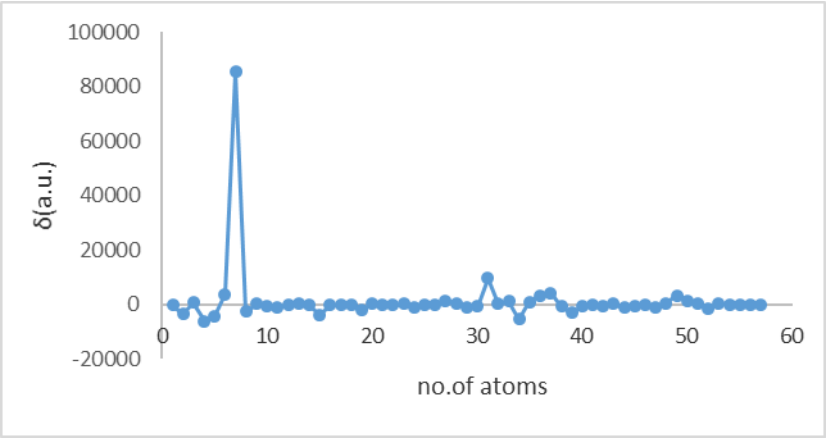


Fig 5. δ parameter for MRC.: CNT system.

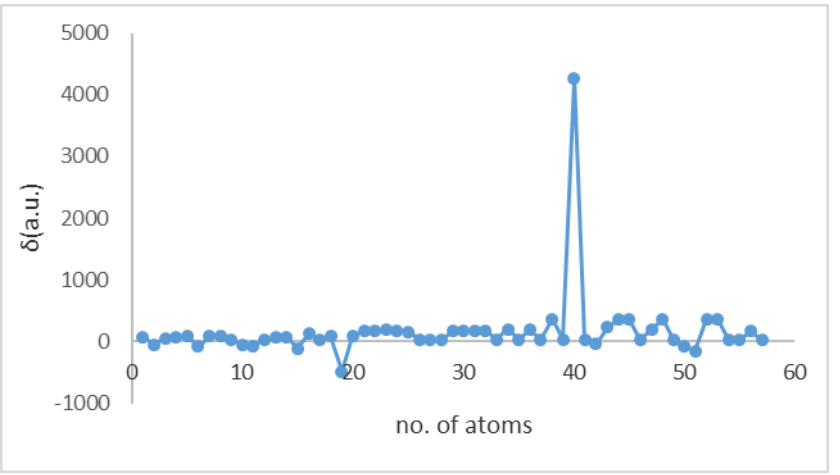


Fig6. δ parameter for BUS.: CNT system.

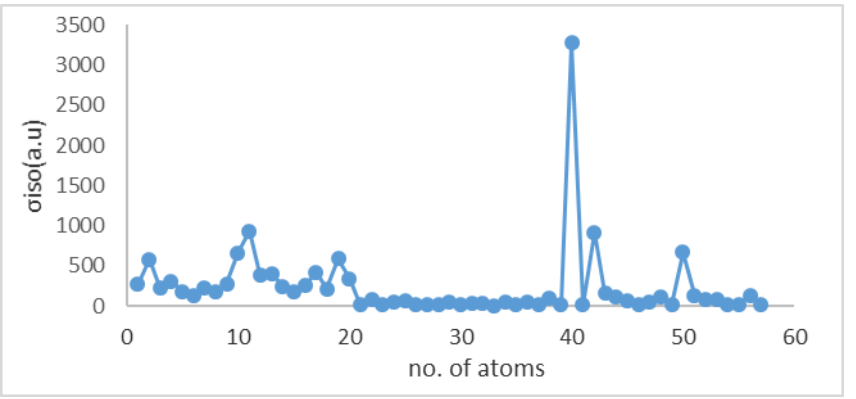


Fig7. σiso parameter for BUS.: CNT system

4. CONCLUSION

The results show that the combination of busulfan to CNT is more stable than Mercaptopurine and fluorouracil. Also the solubility of busulfan in the aqueous solution is more than the other systems. We can determine the active site of these systems which can help to predict the future reactions of these drug molecules in the body.

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