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Adsorption and Thermodynamic Behaviour of Fluorographene with Melphalan Drug as Nanocarrier for Drug Delivery System

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Abstract-Fluorinated graphene (FG) has special physicochemical properties and a unique structure that make it very promising for use in biological fields. However, its strong hydrophobicity and chemical inertness severely restrict its further applications, and little research has been done on how to use FG as a drug nanocarrier. Within this research, the interaction studies of fluorinated graphene or fluorographene (FG) and melphalan (MEL) drug is studied through Density Functional Theory (DFT). The electronic properties and thermodynamic properties are analysed and tabulated using Gaussian 09 package with B3LYP functional and 6-311G basis set. Relying on the results, the FG-MEL complex adsorbs through physisorption process, reaction is exothermic and stable. Accordingly, the FG-MEL complex can act as a carrier in anticancer activity.

Keywords: Melphalan, Fluorographene, adsorption, anticancer

1. Introduction

A complicated set of disorders marked by the uncontrollable division and expansion of aberrant cells, cancer is a powerful opponent in the field of health. These cells have the ability to infiltrate and damage neighbouring tissues, preventing organs from operating normally. Cancer can take many different forms, each with its own characteristics and difficulties. There are many different risk factors for cancer, such as a person's genetic makeup, exposure to toxins, poor lifestyle choices, and specific illnesses. For a great number of cancer patients, improved outcomes have been achieved by early detection and advances in treatment techniques like immunotherapy, chemotherapy, and surgery. A multidisciplinary strategy is used to combat cancer, integrating research, medical knowledge, and community awareness-building [1]. Even though cancer is still a very difficult disease to treat, new discoveries in medicine and continuing research give hope for improved cancer prevention, detection, and treatment methods in the future.

Graphene and its derivatives are intriguing prospects for a variety of biomedical applications, such as drug delivery and cancer treatment, because of their special qualities, which include high surface area, superior electrical conductivity, and the capacity to functionalize their surfaces [2]. A novel graphene derivative called fluorinated graphene or fluorographene (FG) has all of the strong qualities of its parent material, including good photothermal characteristics, high specific surface area, excellent thermal stability, and biocompatibility. In the scientific literature, fluorographene's specialized application as an anticancer medication was not well-established or extensively studied. Fluorographene and other graphene derivatives are the subject of continuous research in the field of nanomaterials; it's possible that additional advancements have emerged since then.

Because of its exceptional physical and chemical characteristics, fluorographene has garnered significant interest from the scientific community since its discovery. Fluorographene is not chemically inert, as evidenced by a number of experiments, and it reacts chemically in a variety of ways in the environment [3].

One chemotherapeutic medication that is part of the alkylating agent class is melphalan (MEL). It is frequently used to treat a number of cancers, most notably ovarian and multiple myeloma, which is a malignancy of the bone marrow's plasma cells. Melphalan inhibits the ability of cancer cells to divide by tampering with their DNA, which ultimately results in the death of the cells. Depending on the particular treatment plan, it is given either orally or intravenously [4].

In this work, the electronic properties of Fluorographene (FG) adsorbed with melphalan (MEL) drug is studied using Density Functional Theory.

2. Computational Details

The Gaussian 09 [5] quantum chemistry software program was used to perform geometry optimizations, adsorption analysis, frontier molecular orbital (FMO), and electronic and thermodynamic investigations. Melphalan's adsorption on Fluorographene was computed and examined using the DFT Generalized Gradient Approximation with Becke 3-parameter Lee-Yang-Parr(B3LYP) [6] functional with the 6-311G as standard basis set. No imaginary frequencies were observed, and all of the frequencies that were collected were positive numbers that indicated the structural configuration's global minima. The adsorption process's thermodynamic characteristics are made up of Gibbs free energies (G), entropies (S), and enthalpies (H) of the system is calculated in the gas phase at 298.14 K and 1 atm. The adsorption energy of melphalan drug upon fluorographene is calculated as

$$E_{ads} = E_{FG\text{-}MEL}-(E_{FG}+E_{MEL}) \quad (1)$$

Where E_{FG} is the total energy of fluorographene, E_{MEL} is the total energy of melphalan drug and $E_{FG\text{-}MEL}$ is the total energy of fluorographene adsorbed with melphalan drug system.

To examine the effects of interacting species, electronic characteristics such as HOMO, LUMO, and HOMO-LUMO energy gaps (E_g) were computed.

Additionally, the following relations were used to determine the ΔG_{ad}, ΔH_{ad}, and ΔS_{ad} in order to investigate the thermodynamic feasibility.

$$\Delta G_{ads} = G_{FG\text{-}MEL}-(G_{FG}+G_{MEL}) \quad (2)$$
$$\Delta H_{ads} = H_{FG\text{-}MEL}-(H_{FG}+H_{MEL}) \quad (3)$$
$$\Delta S_{ads} = S_{FG\text{-}MEL}-(S_{FG}+S_{MEL}) \quad (4)$$

In this case, the variations in enthalpy, entropy, and Gibbs free energy are represented as ΔH_{ads}, ΔS_{ads}, and ΔG_{ads}, respectively. The energies that are present when the drug adsorbed over the fluorographene are H_{FG}, S_{FG} and G_{FG}.

3. Results and Discussions

3.1 Optimized geometry

Fig. 1 (a) shows the optimized geometry of FG in the vacuum phase. In this sheet there are 58 atoms in which 14 hexagonal rings of carbon surrounded with 16 fluorine atoms. After the optimization, the C-C bond was calculated to be 1.415-1.42 A°. The C-F bond was calculated to be 1.37 A°.

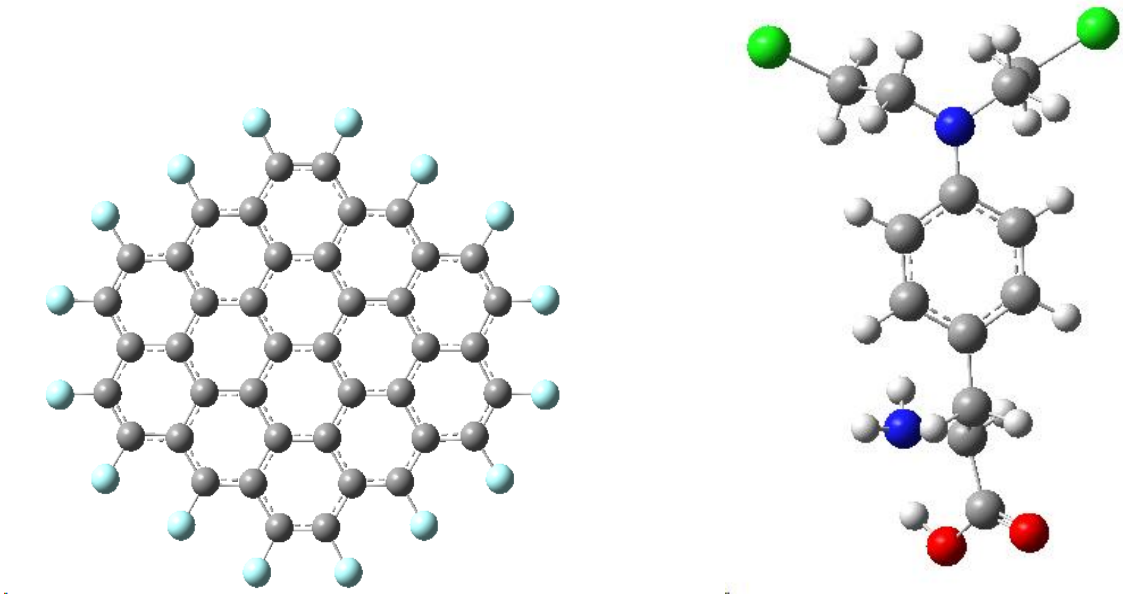

Fig 1 (a) Optimized geometry of FG (b) Optimized geometry of MEL

After the optimization, fluorographene holds the planar structure without disturbing the bond length. The computed energy band gap (E_g) between the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbitals (HOMO) is based on the B3LYP functional. Energy gap is computed using the formula

$$E_g = E(LUMO)-E(HOMO) \quad (5)$$

The energy gap of FG and MEL were 2.41eV and 5.09 eV respectively.

Table 1. The calculated electronic and thermodynamic properties of FG, MEL and FG-MEL complex using B3LYP/6-311G method.

Property	**FG**	**MEL**	**FG-MEL**
Dipole moment (Debye)	0	4.88	5.24
E_{HOMO} (eV)	-6.64	-6.13	-6.14
E_{LUMO} (eV)	-4.22	-1.03	-4.08
E_g (eV)	2.41	5.09	2.04
E_{ads} (eV)	-	-	-0.36
μ (eV)	-5.43	-3.58	-5.10
Ƞ (eV)	1.21	2.55	1.02
S (eV)	0.41	0.19	0.49
ω (eV)	12.22	2.52	12.75
ΔH_{ads} (kcal/mol)	-	-	-7.27
ΔS_{ads} (kcal/mol)	-	-	-26.86
ΔG_{ads} (kcal/mol)	-	-	19.59

3.2 Electronic properties

The findings of an investigation into the impact of several factors on the electrical characteristics of the FG-MEL delivery system are shown in Table 1. After the adsorption, the HOMO, LUMO energy levels of the drug on the surface of the nanomaterial is decreased from -1.04eV to -4.08 eV. Whereas the HOMO and LUMO energy levels of the fluorographene after adsorption with the drug increased from -6.64 eV to -6.13 eV thereby resulting the energy gap decreased from 2.41 eV to 2.04 eV from fluorographene to the system. As the gap difference is small, so the charge transfer is also small. The energy gap difference calculated is giving as 15% shows a sensing nature to the system.

The assessment of intramolecular or intermolecular interactions depends on the charge distribution within a molecule. A molecule's asymmetric charge distribution throughout its entirety gives birth to a dipole moment. One of the few experimental measures that may be directly linked to a molecule's charge distribution is the dipole moment. There are several methods available for experimentally determining the dipole moment. However, due to their equipment sensitivity and susceptibility to error causes, the majority of approaches have restricted and unreliable usage [7]. Therefore, it is crucial to compute dipole moment values using theoretical techniques. Fluorographene is insoluble in water. Theoretically we are getting the value 0 which confirms the insoluble nature of fluorographene. The dipole moment of melphalan is 4.88 Debye and after adsorption the complete system's dipole moment was 5.24 Debye resulting the change in soluble nature. The adsorbed system is more soluble in water clearly indicating the favourable usage in anticancer activity.

3.3 Thermodynamic analysis

To investigate the adsorption process's viability, the thermodynamic parameters including entropy (ΔS_{ads}), Gibb's free energy (ΔG_{ads}) and enthalpy (ΔH_{ads}) changes [8] were computed in Table 1 in order to fully comprehend the melphalan's adsorption behaviour on the fluorographene. Because the change in enthalpy has negative values, the adsorption of melphalan on the adsorbent is classified as an exothermic reaction. The free energy changes show a positive value which depicts the non-spontaneous reaction. The entropy value showing negative value represents the stability of the system.

3.4 Quantum molecular descriptors

In order to interpret the data about the chemical stability and reactivity of the adsorbate and its adsorbents, quantum molecular descriptor (QMD) investigations are required. The following formulas can be used to compute global reactivity descriptors, such as global hardness (h), global softness (S), and global electrophilicity index (u), in accordance with Koopman's theorem [9,10].

$$\mu = -\left(\frac{E_{LUMO}+E_{HOMO}}{2}\right) \quad (6)$$

$$\eta = \frac{E_{LUMO}-E_{HOMO}}{2} \quad (7)$$

$$S = \frac{1}{2\eta} \quad (8)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (9)$$

The complex substance is evidently chemically stable because the chemical potential (μ) values of FG are negative both before and after the MEL drug is adsorbed. Furthermore, it may be inferred from the μ fluctuations that the MEL will be the source of the spontaneous electron movement pathway leading to FG. Global electrophilicity (ω) is another electronic feature of the named compounds that has changed due to the MEL adsorption on FG. This parameter quantifies a compound's propensity to accept electrons. Nevertheless, it was discovered that the MEL and the FG-MEL complex had ω values of 2.52 eV and 12.75 eV, respectively. Thus, it might be deduced that FG-MEL complex is more electrophilic than drug. More intriguingly, the electrophilicity index data show that FG may function as an electrophile material and take up electrons from the MEL during the adsorption process, in good agreement with the chemical potential analysis. The global softness (S) is showing the values 0.41 eV, 0.19 eV and 0.49 eV for FG, MEL and FG-MEL systems which indicate the increasing order

of softness value for the complex system than compared to the bare one. And it shows a reactive nature for the complex system enhancing the interaction. The FG, MEL and FG-MEL complexes have global hardness values (η) of 1.206 eV, 2.549 eV, and 1.022 eV, in that order. It is clear from the table that there have been very minor changes in μ, η, S and ω. This suggests that the complexes' structural stability and molecular toxicity have not changed significantly during the drug delivery procedure. While delivering medications in a biochemical environment, appropriate delivery agents maintain their structural stability and do not produce any molecular toxicity.

Conclusion

Through DFT calculations, the potential of fluorographene as drug delivery vehicles for anticancer medications was examined in this work. The stability of the complexes is indicated by the fact that, upon geometric analysis, the interatomic bond lengths remain relatively unchanged following the anticancer drug surface adsorption by fluorographene. The examined complex adsorption energies with negative values in the gas phase shows that the interaction between the anticancer drug and fluorographene is advantageous and occurs non-spontaneously. From the dipole moment value, it shows the solubility nature. And the quantum chemical descriptors less toxicity implicating the recommendation for the drug delivery.

References

[1] Organization, W.H., WHO recommendations on self-care interventions: human papillomavirus (HPV) self-sampling as part of cervical cancer screening, 2020.

[2] Chong Cheng, Shuang Li, Arne Thomas, Nicholas A. Kotov, and Rainer Haag, "Functional Graphene Nanomaterials Based Architectures: Biointeractions, Fabrications, and Emerging Biological Applications", *Chemical Reviews*, Vol 117, no 3, pp 1826-1914, 2017.

[3] Demetrios D. Chronopoulos, Aristides Bakandritsos, Martin Pykal, Radek Zbořil, Michal Otyepka, Chemistry, properties, and applications of fluorographene", *Applied Materials Today*, Vol 9, pp 60-70, 2017.

[4] Firoozeh Abolhasani Zadeh, Saade Abdalkareem Jasim, Mohammad Javed Ansari, Dmitry Olegovich Bokov, Ghulam Yasin, Lakshmi Thangavelu, Maryam Derakhshandeh, "Boron carbide nanotube as targeted drug delivery system for melphalan anticancer drug", *Journal of Molecular Liquids*, Vol 354, 118796, 2022.

[5] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox., Gaussian 09, Revision E.01, Gaussian 2013. Wallingford CT.

[6] A. D. Becke, "Density-Functional Exchange-Energy Approximation with Correct Asymptotic Behavior", *Phys. Rev. A*, Vol 38, pp 3098-3100, 1988.

[7] Anjaly Das, Aparna Das, Bimal Krishna Banik, "Influence of dipole moments on the medicinal activities of diverse organic compounds", *Journal of the Indian Chemical Society*, Vol 98, no 2, 100005, ISSN 0019-4522,2021.

[8] A.S. Ghasemi, Mohammad Ramezani Taghartapeh, Alireza Soltani, Peter J. Mahon, "Adsorption behavior of metformin drug on boron nitride fullerenes: Thermodynamics and DFT studies", *Journal of Molecular Liquids*, 2019, Vol 275, pp 955-967.

[9] R. G. Pearson, "Chemical hardness and density functional theory", *Journal of Chemical Sciences*, Vol 117, no 5, pp 369-377, 2005.

[10] N.M. O'Boyle, A.L. Tenderholt, K.M. Langner, cclib, "A library for package-independent computational chemistry algorithms", *J. Comput. Chem*., Vol 29, pp. 839-845, 2008.