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Fullerene (C_{20}) as a potential Nano carrier for the delivery of Procarbazine: A DFT study

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ABSTRACT: In this study, adsorption of procarbazine on the surface of fullerene (C_{20}) was studied computationally. For this purpose, the structures of fullerene (C_{20}), procarbazine and the derived products from the interaction of procarbazine with fullerene at three different configurations were optimized geometrically. Then, IR and frontier molecular orbital calculations were implemented on them in the temperature range of 278-314 K at 3˚ intervals. The obtained thermodynamic parameters including Gibbs free energy changes (ΔG_f), and formation enthalpy alterations (ΔH_f) have revealed that the adsorption of procarbazine is exothermic, spontaneous, one-sided and experimentally feasible at the both evaluated configurations. The influence of temperature on the thermodynamic factors of the desired process was also inspected and the results indicate that 298.15 K is the best temperature for the fullerene (C_{20}) substitution on procarbazine. Some HOMO-LUMO related parameters such as energy gap, electrophilicity, chemical hardness, maximum transferred charge index (ΔN_{max}) and chemical potential were also calculated and discussed in details.

Keywords: *Adsorption, Density functional theory, Drug delivery, Fullerene, Procarbazine*

INTRODUCTION

The Rapid advance in drug discovery methods has led to an exponential increase in new drugs. Due to the diverse physicochemical properties of various drugs, we need smarter drug delivery systems. The use of nano compounds is increasingly growing, so that it has penetrated all aspects of life. In the meantime, the use of nano compounds in medical processes has also become more and more used. One of the important aspects of nanotechnology that has been considered today is the use of nanoscience as a drug carrier in the treatment of cancer, in some cases the use of these compounds as therapeutic targets. Due to the rapid advances in the discovery of drugs and their different physical and chemical properties, it is necessary to have intelligent drug delivery systems [1]. Delivery systems have many limitations on the use of materials and production processes [2]. The materials of these systems should have a biocompatibility with the body so that they can be easily attached to the drug, can be removed from the body, and the production process is carefully controlled so that the product containing the drug does not reduce the biological activity of the drug (Attenuation of auditory N1 results from identity-specific action-effect pre-

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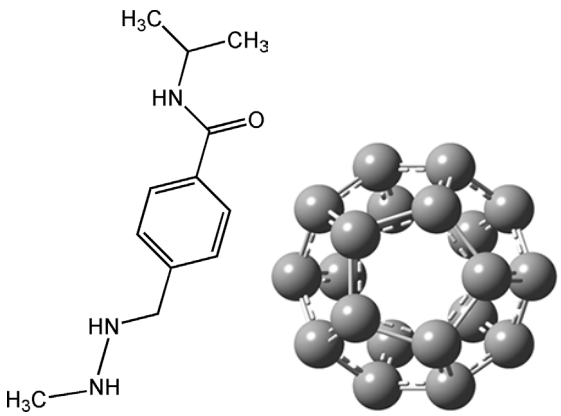

Fig. 1. Chemical structures of procarbazine and fullerene.

diction, Hughes, 2013) [3]. The chemical structure of procarbazine is shown in (Fig. 1). On the other hand, fullerene (C_{20}) is the smallest nanomaterial with a dodecahedral cage structure (Fig. 1). The structure of this fullerene is highly curved and it is composed of pentagonal ring. C_{20} has unique traits that make it an eminent sensing material like high conductance, great surface area/ volume ratio and excellent reactivity. Owing to the aforementioned special traits fullerene (C_{20}) has been applied in different traits including supercapacitors, electrochemical sensors, nanofiltration, adsorption, microextraction and drug delivery. In this respect, the performance of fullerene (C_{20}) as a nanocarrier for the delivery of procarbazine was investigated by DFT computations for the first time in this research [4-10].

COMPUTATIONAL DETAILS

At the outset, the structures of procarbazine, C_{20} and their derived products at 3 various configurations were designed by nanotube modeler 1.3.0.3 [11-13] and Gauss View softwares. Afterward, the designed structures were optimized geometrically. In the next step, IR and frontier molecular orbital calculations were implemented on them in the temperature range of 278-314 K at 3° intervals by Spartan software. The computations were done in the atmospheric pressure and gaseous phase. Density functional theory method and B3LYP/631G (d) basis set were chosen for the calculations because, in our former studies, this method and basis set had produced results that were in an admissible accordance with the experimental findings [12-14]. The evaluated reaction is as follows:

$$\text{Procarbazine} + C_{20} \rightarrow \text{procarbazine-}\ C_{20} \qquad (1)$$

RESULTS AND DISCUSSION

In order to find the most stable configuration [15], procarbazine interaction with C_{20} was scrutinized at 3 different conformers. As the provided data at Fig. 2 show clearly, in I-Isomer the drug is inserted near the nanostructure towards its amine functional group but in II-Isomer procarbazine is located near C_{20} towards its OH functional group. In III-conformer the adsorbate is placed near the adsorbent in a manner amine functional group and the benzene ring of the drug are in a parallel form towards fullerene. It should be noted that on the basis of the carried out IR computations, it was not seen any negative frequency at all of the studied structures [16,17].

Calculation and verifying the values of adsorption enthalpy changes (ΔH_{ad})

For acquiring enthalpy variations for the adsorption process of procarbazine, the succeeding equation was utilized. In this formula, Hth represents the obtained thermal enthalpy for the reactants and products of the evaluated process and ΔE^{o} is the symbol of total en-

I-Isomer II-Isomer III-Isomer

Fig. 2. Optimized Structure of procarbazine and fullerene complexes

ergy changes of the system which can be calculated by subtracting the total energy of the products from the sum of the total energy of reactants.

$$\Delta H_{ad} = \Delta E^{\circ} + (H_{th\ (Procarbazine-Fullerene)} - (H_{th\ (Procarbazine)} + H_{th\ (Fullerene)})) \quad (2)$$

The provided data in Table 1 clearly indicates that the reaction of procarbazine and C_{20} is exothermic at both configurations because the achieved ΔH_{ad} values are negative for both isomers. The influence of temperature on this variable was also checked out. As it can be seen from the Table 1, temperature does not have an obvious effect on enthalpy changes, because there is not a remarkable difference between the obtained ΔH_{ad} values at different temperatures. Hence, 298 K can be selected as the best temperature for the adsorption procedure of procarbazine. The next hidden point in the Table is that III-Isomer has lower enthalpy changes in comparison to other conformers at all temperatures. Thus, it can be deduced that the formation of III-Isomer is more exothermic and experimentally possible than the formation process of others [18].

Calculation and inquiring the values of Gibbs free energy alterations (ΔG_f)

In order to calculate the Gibbs free energy changes, equation 3 was applied. In this equation, Gth stands for the thermal Gibbs free energy that was computed by the software for the reactants and products of the desired procedure. And ΔE^{o} is heeded as a symbol for the total energy changes of the system.

$$\Delta G_{ad} = \Delta E^{\circ} + (G_{th\ (Procarbamazine-C20)} - (G_{th\ (Procarbazine)} + G_{th\ (C20)})) \quad (3)$$

The obtained ΔG_f values are reported in Table 2. As it is obvious from the Table the adsorption of procarbazine at all of the configurations are spontaneous due to the remarkable negative calculated Gibbs free energy changes. Moreover, the values of Gibbs free energy changes for III-Isomer are more negatives than other conformers. So, the synthesis process of II-Isomer is more spontaneous and experimentally feasible than the other products [19-21].

Frontier molecular orbital and Structural analysis

Some of the chemical and structural traits of procarbazine and its derivatives with C_{20} including the energy of HOMO and LUMO orbitals (E_H and E_L), the energy discrepancy between HOMO and LUMO molecular orbitals (HLG), the electrophilicity index (ω), maximum transferred charge index (ΔN_{max}), chemical potential (μ), chemical hardness (η), and dipole moment

Table 1. The values of enthalpy changes for the adsorption of procarbazine on the surface of C_{20} in the temperature range of 278.15-314.15 K.

Temperature (K)	I-Isomer (kJ/mol)	II-Isomer (kJ/mol)	III-Isomer (kJ/mol)
278.15	-1138.946	-1158.404	-1188.246
281.15	-1138.949	-1158.405	-1188.248
284.15	-1138.954	-1158.406	-1188.249
287.15	-1138.960	-1158.407	-1188.251
290.15	-1138.965	-1158.407	-1188.252
293.15	-1138.972	-1158.408	-1188.254
296.15	-1138.979	-1158.410	-1188.259
299.15	-1138.982	-1158.410	-1188.261
302.15	-1138.985	-1158.411	-1188.263
305.15	-1138.987	-1158.411	-1188.264
308.15	-1138.990	-1158.411	-1188.265
311.15	-1138.993	-1158.412	-1188.267
314.15	-1138.996	-1158.413	-1188.268

Table 2. The values of Gibbs free energy changes for the adsorption of procarbazine on the surface of C_{20} in the temperature range of 278.15-314.15 K.

Temperature (K)	I-Isomer (kJ/mol)	II-Isomer (kJ/mol)	III-Isomer (kJ/mol)
278.15	-1078.534	-1097.870	-1128.202
281.15	-1078.311	-1097.656	-1127.989
284.15	-1078.090	-1097.440	-1127.773
287.15	-1077.871	-1097.225	-1127.553
290.15	-1077.651	-1097.009	-1127.330
293.15	-1077.430	-1096.793	-1127.109
296.15	-1077.210	-1096.577	-1126.890
299.15	-1076.988	-1096.361	-1126.669
302.15	-1076.764	-1096.140	-1126.446
305.15	-1076.540	-1095.917	-1126.224
308.15	-1076.318	-1095.694	-1126.003
311.15	-1076.094	-1095.470	-1125.780
314.15	-1075.874	-1095.250	-1125.562

were calculated and reported in Table 3. In chemistry, HOMO is the highest occupied molecular orbital and LUMO is the lowest unoccupied molecular orbital and the energy difference between them is described as energy gap which is usually represented by HLG symbol. It should be mentioned that this variable was calculated by using equation 4. The provided data in Table 3 demonstrate that the energy gap has decreased after the adsorption of procarbazine on the fullerene. Energy gap has a direct relationship with conductivity so that the compounds with low HLG are more conductive than compounds with high HLG values because a high amount of HLG implies that the substance needs more energy for transferring the electron to the excited state. Hence, it can be deduced that the conductivity of pure procarbazine is lower than its derivatives with fullerene owing to the decrementing trend of HLG. Chemical hardness was the next inspected parameter which was calculated by equation 5. Chemical hardness shows the softness of a compound. In fact, the materials which have a low amount of chemical hardness will be more chemically smoother and vice versa. In addition, this parameter is related to the reactivity of the structure. Due to the fact the soft compounds can alter their electron density more conveniently in comparison to hard substances. Therefore, soft molecules can participate in chemical reactions more easily because the electron transmission which is necessary for the implementation of reactions can be done better in this type of compounds. As it can be seen, chemical hardness has decremented after the adsorption of procarbazine on the surface of fullerene. So, procarbazine-fullerene derivatives are more chemically softer and more reactive than pure procarbazine. The amount

Table 3. The values of Calculated E_H and E_L, HLG, chemical hardness (η), electrophilicity index (ω), the chemical potential (μ), the maximum amount of electronic charge index (ΔN_{max}) and dipole moment.

Compound	E_{LUMO} (eV)	E_{HOMO} (eV)	HLG (eV)	h (eV)	μ (eV)	ω (eV)	ΔN_{max} (eV)	Dipole Moment (Deby)
procarbazine	-7.420	6.100	13.520	6.760	-0.660	-34.619	0.098	3.340
I-Isomer	-4.550	3.660	8.210	4.105	-0.445	-18.934	0.108	13.080
II-Isomer	-4.760	3.390	8.150	4.075	-0.685	-12.121	0.168	11.790
III-Isomer	-4.590	3.570	8.160	4.080	-0.510	-16.320	0.125	10.730

of chemical potential which is essential for obtaining electrophilicity and maximum transferred charge capacity was also calculated by equation 6. Chemical potential experienced a tangible decline by binding of procarbazine to the surface of fullerene [22-24].

$$HLG = E_{LUMO} - E_{HOMO} \quad (4)$$

$$\eta = \frac{(E_{LUMO} - E_{HOMO})}{2} \quad (5)$$

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

$$\omega = \frac{\mu^2}{2\eta} \quad (7)$$

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad (8)$$

The electrophilicity index is an admissible criterion for checking out the tendency of a compound for absorbing the electron. This parameter was calculated by equation 7. When two molecules react with each other, one of them plays the role of a nucleophile whilst the other one acts as an electrophile. A material with high electrophilicity value will be more eager to absorb electron to it. The maximum transmitted charge capacity (ΔN_{max}) can be calculated by equation 8. A compound with a positive amount of ΔN_{max} will act as an electron acceptor and a material with a negative amount of ΔN_{max} will behave as an electron donor. As it can be witnessed, the amount of the both mentioned parameters have increased in procarbazine-fullerene derived products which substantiates that pure procarbazine has a lower propensity towards electron in comparison to its derivatives with fullerene. The next evaluated parameter is dipole moment which has an obvious relationship with the solubility of the studied compound in polar solvents like water. At it can be seen, the dipole moment of procarbazine increased substantially after its interaction with fullerene which indicates drug-fullerene complexes have higher bioavailability than pure drug without nanostructure [25-27].

CONCLUSION

In this research, procarbazine interaction with fullerene was investigated by DFT studies. The calculated Gibbs free energy changes and adsorption enthalpy variations confirmed the nanostructure has an exothermic and spontaneous interaction with procarbazine. The values of bandgap, chemical potential, chemical hardness and dipole moments showed procarbazine-fullerene derivatives are more reactive and biocompatible in comparison to the pure drug molecule without nanostructure. The theoretical results showed fullerene can be a potential nanocarrier for the delivery of procarbazine.

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