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Fullerene (C_{24}) as a Nanocarrier for Procarbazine Anticancer Drug: A Density Functional Theory Investigation

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ABSTRACT

Procarbazine is an anticancer medicine with serious side effects in this respect the capability of fullerene C_{24} as a nanocarrier for this drug was scrutinized computationally. For this purpose, all of the studied structures were optimized geometrically, then IR and FMO calculations were performed on them in the temperature range of 278.15-308.15 K at 3° intervals. The obtained negative values of Gibbs free energy variations(ΔG_{ad}), adsorption enthalpy alterations (ΔH_{ad}), and great values of the thermodynamic equilibrium constant (K_{th}) prove that the interaction of the fullerene with procarbazine is exothermic, spontaneous, one-side, and experimentally feasible. The impact of temperature on the thermodynamic parameters of the reaction was also inspected and the results indicate that 278.15 K is the optimum temperature for the synthesis of all of the derived products from the interaction of procarbazine and the studied nanostructure. Some important structural parameters such as band gap, chemical hardness, chemical potential, electrophilicity, and maximum transferred charge capacity were also discussed in detail.

Keywords: Procarbazine; Fullerene; Density functional theory; Adsorption.

1. INTRODUCTION

The rapid advance in drug discovery methods has led to an exponential increase in new drugs [1-5]. Due to the diverse physicochemical properties of various drugs, we need smarter drug delivery systems [6-9]. 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 [10-15]. 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, and in some cases the use of these compounds as therapeutic targets. Due to the rapid advances in the discovery of drugs and their different

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physical and chemical properties, it is necessary to have intelligent drug delivery systems. Delivery systems have many limitations on the use of materials and production processes [15-19]. 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 [20].

C_{24} molecule is one of the smallest members of the fullerene family with a dodecahedral cage structure (Figure 1). This fullerene consists of hexagonal and pentagonal rings and has extreme curvature. Due to the fact that former reports have proved that fullerenes from C_{20} to C_{58} have narrow HOMO - LUMO gaps and prominent reactivity. It seems these small fullerenes can have a good impression on the features of anticancer drugs [21]. Hence, the effect of C_{24} cage impacts on the structural properties of procarbazine was evaluated by Ab initio calculations in this study, for the first time.

2. COMPUTATIONAL METHODS

In the beginning, the structures of the C_{24} cage, procarbazine, and the derived products of the reaction between procarbazine and nanostructures at three different configurations were designed primarily by nanotube modeler 1.3.0.3 and Gauss View Softwares. Then, the designed structures were optimized geometrically and in the next step, IR and FMO calculations were implemented on them in the temperature range of 278.15-308.15 K at 3˚ intervals by spartan software. All of the calculations were performed by density functional theory in the B3LYP/6-31G (d) basis set. The reactions were assumed in the gaseous phase and one atmosphere pressure. The studied reaction is as follows:

$$\text{Procarbazine} + C_{24} \rightarrow \text{Procarbazine-}C_{24} \qquad (1)$$

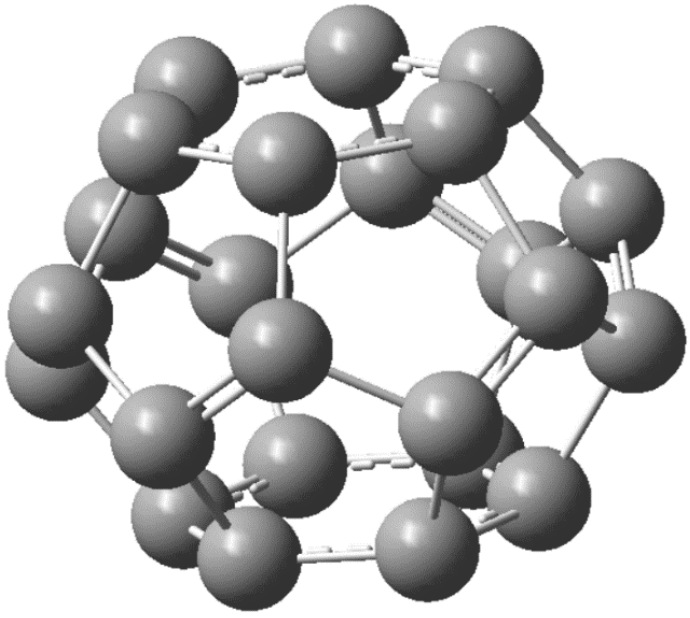

Fig. 1. Fullerene C_{24} cage structure.

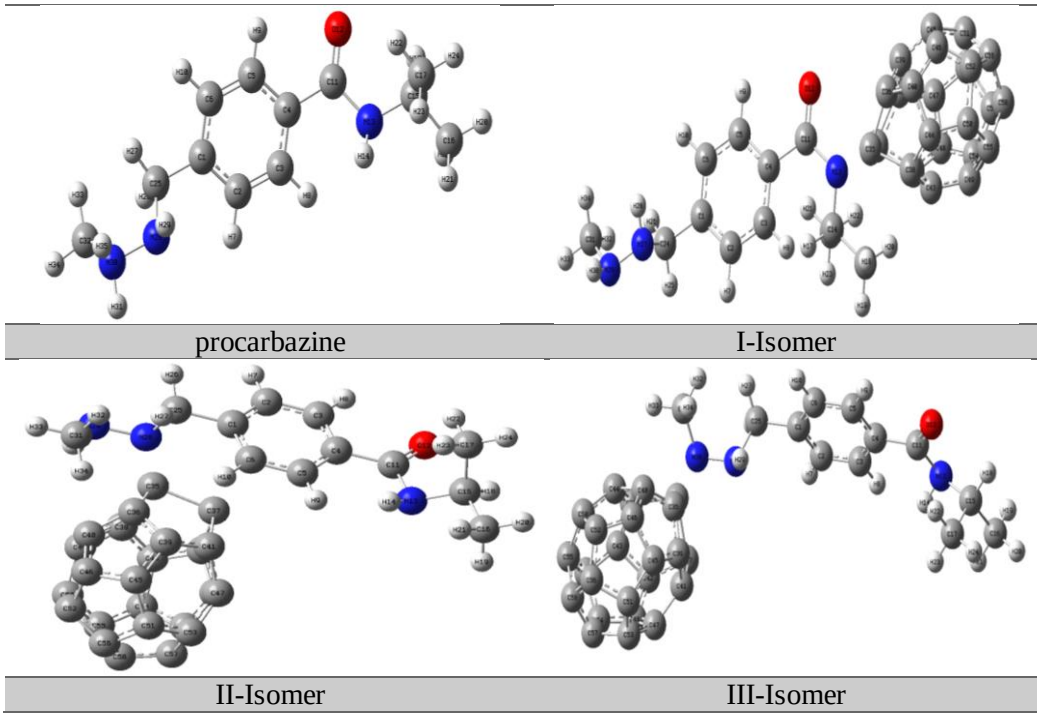

Fig. 2. The optimized structures of procarbazine and its derived products with C_{24} at 3 configurations.

3. RESULTS AND DISCUSSIONS

3.1. Evaluating the Structural Properties

As can be seen from Figure 2, the reaction of procarbazine with C_{24} was investigated from three sites. At I-Isomer, C_{24} was inserted near the carbonyl group of procarbazine. At II-Isomer, fullerene is located in parallel form towards the benzene ring of the medicine, and in III-Isomer, the nanostructure was placed near the amine group of procarbazine. The adsorption energy (ΔE_{ad}) values for each configuration that were calculated by equation 2, are reported in Table 1. As can be seen, the obtained values are negative for all of the studied conformers indicating the interaction of C_{24} with procarbazine is experimentally possible for all of the studied conformers.

$$\Delta E^{\circ} = (E_{(\text{procarbazine- C24})} - (E_{(\text{Procarbazine})} + E_{(\text{C24})})) \quad (2)$$

It should be noted that the IR calculations show that all of the structures do not have any negative frequency and the positive frequency values that are presented in the table have also confirmed this fact. Some bonds were also seen in the optimized structure indicating procarbazine interaction with C_{24} is a chemisorption.

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

In order to achieve adsorption enthalpy alterations values, the subsequent equation would be applied. In this formula, ΔE° is the symbol of variations in the total energy of the system which can be calculated by subtracting the total energy of the products from the total energy of the reactants. H_{th} also represents the thermal enthalpy values that were computed by the software for raw materials and products of the desired process.

$$\Delta H_{ad} = \Delta E^{\circ} + (H_{th\ (\text{Procarbazine- C24})} - (H_{th\ (\text{Procarbazine})} + H_{th\ (\text{C24})})) \quad (3)$$

As the provided data in Table 2, exhibit clearly the obtained ΔH_{ad} values for all of

the evaluated derivatives are negative. And this fact proves that the adsorption procedure is exothermic for all of the derived products from the reaction between procarbazine and fullerene. Indeed, the heat is transferred from the system to the environment in this process. As it can be witnessed from the table, the ΔH_{ad} values for I-Isomer are more negative than the formation enthalpy changes values of other conformers. Hence, it seems the reaction of procarbazine and C_{24} nanostructures from this situation is more exothermic and experimentally feasible. As it is obvious from the table, the temperature does not have a remarkable effect on the adsorption enthalpy changes values of all derivatives and it seems 298.15 K is the best temperature for the interaction procedure of all derived products.

3.3. Calculation and Verifying the Values of Gibbs Free Energy Changes (ΔG_{ad}) and Thermodynamic Constant (K_{th})

For calculating Gibbs free energy variations, the following equation was utilized. In this formula, G_{th} is the thermal Gibbs Free energy that was computed by the software for each material in the interaction procedure and ΔE° represents the total energy changes of the system.

$$\Delta G_f^{\circ} = \Delta E^{\circ} + (G_{th\ (Procarbazine-\ C24)} - (G_{th\ (Procarbazine)} + G_{th\ (C24)})) \quad (4)$$

As the calculated ΔG_f values in Table 3 demonstrate clearly, the synthesis process of all of the studied derivatives is spontaneous because this variable is negative for all of the derived products. The influence of temperature on this variable has also been checked out and the results indicate that the 278.15 K is the optimum temperature for the interaction process between fullerene and procarbazine of all of the evaluated derivatives. Because the values of Gibbs free energy alterations have increased by incrementing of temperature.

Table 1. Total energy, the lowest frequency, and bond lengths of tetryl and its derivatives with fullerene

Basis set 6-31g*-B_3LYP				
	Procarbazine	**I-Isomer**	**II-Isomer**	**III-Isomer**
ΔE_{ad}	-	-1897.818382	-1801.324217	-1833.843872
The lowest frequency (cm^{-1})	20.5806	13.9441	7.7166	7.3154
N13– C35 (Å)	-	1.48346	-	-
N28– C35 (Å)	-	-	1.49676	-
N30– C35 (Å)	-	-	-	1.49419

Table 2. The formation enthalpy changes values for the synthesis of the tetryl-fullerene derivatives in the temperature range of 298.15-398.15 K

Temperature(K)	**I-Isomer**	**II-Isomer**	**III -Isomer**
278.15	-1089.549	-995.517	-1026.798
281.15	-1089.559	-994.991	-1026.275
284.15	-1089.568	-994.462	-1025.750
287.15	-1089.576	-993.932	-1025.225
290.15	-1089.584	-993.401	-1024.697
293.15	-1089.594	-992.870	-1024.169
296.15	-1089.602	-992.339	-1023.639
299.15	-1089.608	-991.803	-1023.104
302.15	-1089.615	-991.267	-1022.569
305.15	-1089.620	-990.728	-1022.031
308.15	-1089.625	-990.188	-1021.493

The thermodynamic equilibrium constants of the desired reaction were also calculated by inserting the values of Gibbs free energy changes that were obtained in the last step at the following equation. In this formula, R and T denote the ideal gas constant and temperature respectively.

$$K = \exp(-\Delta G_f^\circ / RT) \quad (5)$$

As the reported data in Table 4 reveal clearly, the synthesis procedure for all of the derivatives is one-sided and non-equilibrium because the achieved thermodynamic constants are great values for all of the derived products of the reaction between procarbazine and fullerene nanostructure.

3.5. FMO Analysis

Some of the structural and energetic properties including the energy of HOMO and LUMO molecular orbital (E_H and E_L), the energy gap between HOMO and LUMO orbitals (HLG), electrophilicity (ω), maximum transferred charge (ΔN_{max}), chemical hardness (η), dipole moment, chemical potential (μ), and dipole moment were calculated and reported at Table 5. HOMO is the highest occupied molecular orbital and LUMO is the lowest unoccupied molecular orbital in chemistry, and the energy difference between them is known as the energy gap which is shown usually by HLG abbreviation. This parameter can be calculated by using equation 6. As it is obvious from Table 5, the amount of energy gap has decreased after procarbazine interaction with C_{24} in all of the evaluated derivatives. And owing to the fact that the compounds with lower

Table 3. The values of Gibbs free energy changes for the synthesis of tetryl-C_{20} derivatives in the temperature range of 298.15-398.15 K.

Temperature(K)	I-Isomer	II-Isomer	III -Isomer
278.15	-1024.903	-1039.679	-1071.509
281.15	-1024.675	-1039.453	-1071.289
284.15	-1024.445	-1039.226	-1071.067
287.15	-1024.216	-1039.001	-1070.841
290.15	-1023.986	-1038.774	-1070.611
293.15	-1023.757	-1038.549	-1070.382
296.15	-1023.527	-1038.325	-1070.153
299.15	-1023.295	-1038.099	-1069.921
302.15	-1023.060	-1037.868	-1069.688
305.15	-1022.819	-1037.634	-1069.455
308.15	-1022.578	-1037.400	-1069.223

Table 4. The values of the thermodynamic equilibrium constant for the synthesis of tetryl-C_{20} derivatives in the temperature range of 298.15-398.15 K.

Temperature(K)	I-Isomer	II-Isomer	III -Isomer
278.15	$3.675\times10^{+179}$	$1.425\times10^{+182}$	$5.379\times10^{+187}$
281.15	$8.416\times10^{+178}$	$3.203\times10^{+181}$	$1.160\times10^{+187}$
284.15	$1.945\times10^{+178}$	$7.268\times10^{+180}$	$2.528\times10^{+186}$
287.15	$4.541\times10^{+177}$	$1.666\times10^{+180}$	$5.554\times10^{+185}$
290.15	$1.070\times10^{+177}$	$3.856\times10^{+179}$	$1.230\times10^{+185}$
293.15	$2.54\times10^{+176}$	$9.013\times10^{+178}$	$2.754\times10^{+184}$
296.15	$6.118\times10^{+175}$	$2.128\times10^{+178}$	$6.229\times10^{+183}$
299.15	$1.481\times10^{+175}$	$5.069\times10^{+177}$	$1.420\times10^{+183}$
302.15	$3.619\times10^{+174}$	$1.216\times10^{+177}$	$3.269\times10^{+182}$
305.15	$8.896\times10^{+173}$	$2.943\times10^{+176}$	$7.595\times10^{+181}$
308.15	$2.207\times10^{+173}$	$7.187\times10^{+175}$	$1.782\times10^{+181}$

energy gap need lower energy for transferring the electron to the excited situation. It can be inferred that the conductivity of procarbazine has improved after its binding to the fullerene.

The next inspected variable was chemical hardness which was calculated by equation 7. Chemical hardness is an ideal standard for estimating the softness of a molecule. Indeed, if a structure has a high chemical hardness value it will be chemically harder. As it can be observed from the table, the chemical hardness of procarbazine-fullerene derivatives is lower than pure drug without nanostructure and given the fact that soft molecules can change their electron density more easily, this type of compounds could undergo chemical reactions more conveniently because the electron transmission, which is essential for the implementation of chemical reaction will be done comfortably in soft materials. Thus, it can be concluded that the reactivity of the fullerene derived products with procarbazine is higher than the reactivity of pure drug molecule. The chemical potential values that are necessary for obtaining electrophilicity and maximum transferred charge values were also calculated by means of equation 8. This parameter has also decremented after the connection of procarbazine to the surface of fullerene.

$$HLG=E_{LUMO} - E_{HOMO} \quad (6)$$

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

$$\mu = (E_{LUMO} + E_{HOMO})/2 \quad (8)$$

$$\omega = \mu^2/2\eta \quad (9)$$

$$\Delta N_{max}=- \mu/ \eta \quad (10)$$

The electrophilicity index which can be calculated by equation 9, is an excellent criterion for estimating the tendency of a substance towards electron. When two molecules take part in a reaction, one of them behaves as a nucleophile while the other one acts as an electrophile. And if a compound has a high electrophilicity value, it will have a high affinity for absorbing the electron. The maximum transferred charge index (ΔN_{max}) that was calculated by equation 10, demonstrates the charge capacity of a system. In fact, if a material has a positive value of ΔN_{max} it will act as an electron acceptor, but if a substance has a negative value of ΔN_{max} it will play the role of an electron donor. As it is clear from the table, both of the electrophilicity and maximum transferred charge values have increased after the adsorption of procarbazine on the surface of fullerene. This evidence proves that procarbazine has a lower tendency for absorbing the electron in comparison to its fullerene derivatives.

The dipole moment is a key factor that has a direct relationship with the solubility of a compound in polar solvents. Indeed, a structure with a high dipole moment has good solubility in polar solvents like water and a substance with a low dipole moment has poor solubility in polar solvents. The obtained results from the calculations have revealed that the solubility of procarbazine

Table 5. The values of Calculated E_H and E_L, HLG, chemical hardness (η), electrophilicity index (ω), chemical potential (μ), the maximum amount of electronic charge index (ΔN_{max}), and dipole moment

	EL(eV)	EH(eV)	HLG (eV)	η (eV)	μ (eV)	ω (eV)	.ΔNmax (eV)	Dipole Moment (Deby)
procarbazine	-7.420	6.100	13.520	6.760	-0.660	-34.619	0.098	3.340
I-Isomer	-5.250	3.070	8.320	4.160	-1.090	0.143	2.262	13.040
II-Isomer	-5.390	2.910	8.300	4.150	-1.240	0.185	0.299	12.910
III-Isomer	-5.270	3.060	8.330	4.165	-1.105	0.147	0.265	12.510

has improved after its interaction with C_{24}due to the increasing of dipole moment values in the fullerene derivatives.

CONCLUSIONS

In this research, procarbazine interaction with C_{24} was scrutinized in order to check the performance of C_{24} as a nanocarrier for the drug delivery of procarbazine. The theoretical results showed procarbazine interaction with C_{24} is exothermic, spontaneous, non-equilibrium and very strong. The results suggest procarbazine interaction with C_{24} is a chemisorption. The FMO parameters showed procarbazine- C_{24} complexes are more reactive and have a higher solubility than the pure drug without the nanostructure. Totally, it seems this nanostructure is an appropriate candidate for the drug delivery of procarbazine.

REFERENCES

[1] H. H. Cady, Acta. Cryst. 23 (1967) 601.
[2] P. C. Hariharan, W. S. Koski and J. J. Kaufman, Int. J. Quantum. Chem. 23 (1983) 1493.
[3] S. D. Harvey, R. J. Fellows, J. A. Campbell and D. A. Cataldo, J. Chromatogr. 605 (1992) 227.
[4] I. E. Lindstorm, J. Appl. Phys. 41 (1970) 337.
[5] A. Mustafa and A. A. Zahran, J. Chem. Eng. Data. 8 (1963) 135.
[6] S. R. Myers and J. A. Spinnato, Environ. Toxicol. Pharmacol. 24 (2007) 206.
[7] D. Majumdar, S. Roszakz, J. Leszczynski, Mol. Phys. 105 (2007) 2551.
[8] V. M. Bermudez, J. Phys. Chem. C, 111 (2009) 3719.
[9] V. M. Bermudez, J. Phys. Chem. C, 111 (2007) 9314.
[10] R. Ahmadi and M. R. Jalali Sarvestani, Int. J. Bio-Inorg. Hybrid. Nanomater. 6 (2017) 239.
[11] R. Ahmadi and M. Ebrahimikia, Phys. Chem. Res. 5 (2017) 617.
[12] [12] Y. Pan, W. Zhu and H. Xiao, Comput. Theor. Chem. 1114 (2017) 77.
[13] G. Han, R. J. Gou, F. Ren, S. Zhang, C. Wu and S. Zhu, Comput. Theor. Chem. 1109 (2017) 27.
[14] P. Ma, Y. Pan, J. C. Jiang and S. G. Zhu, Procedia. Eng. 211 (2018) 546.
[15] K. Wang, X. Fu, Q. Tang, H. Li, Y. Shu, J. Li and W. Pang, Comp. Mater. Sci. 146 (2018) 230.
[16] L. K. Sviatenko, L. Gorb, M. K. Shukla, J. M. Seiter, D. Leszczynska and J. Leszczynski, Chemosphere. 148 (2016) 294.
[17] D. G. Allis, J. A. Zeitler, P. F. Taday and T. M. Korter, Chem. Phys. Lett. 463 (2008) 84.
[18] P. Jain, J. Sahariya, H.S. Mund, M. Sharma and B.L. Ahuja, Comp. Mater. Sci. 72 (2013) 101.
[19] G. Fayet, L. Joubert, P. Rotureau and C. Adamo, Chem. Phys. Lett. 467 (2009) 407.
[20] C. T. Konek, B. P. Mason, J. P. Hooper, C. A. Stoltz and J. Wilkinson, Chem. Phys. Lett. 489 (2010) 48.
[21] M. Khaleghian and F. Azarakhshi, Int. J. Nano. Dimens. 7 (2016) 290.

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بررسی محاسباتی فولرن (C_{24}) به عنوان نانوحامل برای دارو ضد سرطان پروکاربازین با استفاده از نظریه تابعی چگالی

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چکیده

پروکاربازین یک داروی ضد سرطان است که عوارض جانبی زیادی دارد. از این رو، عملکرد نانو ساختار فولرن به عنوان یک نانوحامل برای این دارو به صورت محاسباتی مورد بررسی قرار گرفت. برای این منظور، تمامی ساختارها مورد بهینه سازی هندسی قرار گرفتند و سپس، محاسبات مادون قرمز و اوربیتال های جبهه بر روی آنها در گستره دمایی ۲۷۸/۱۵ الی ۳۰۸/۱۵ کلوین در فواصل دمای ۳ درجه مورد انجام، قرار گرفت. مقادیر منفی تغییرات انرژی آزاد گیبس، تغییرات آنتالپی جذب سطحی و مقادیر بزرگ ثابت تعادل ترمودینامیکی نشان داد که برهمکنش فولرن و پروکاربازین گرمازا، خودبخودی، یک طرفه و از لحاظ تجربی، امکان پذیر است. تاثیر دما بر روی تمام پارامترهای ترمودینامیکی برهمکنش نیز مورد بررسی قرار گرفت و نتایج حاکی از آن بود که دمای ۲۷۸/۱۵ کلوین بهترین دما برای تشکیل تمامی کمپلکس های حاصل از برهمکنش پروکاربازین و نانوساختار مطالعه شده است. برخی از پارامترهای ساختاری مهم از جمله گاف انرژی، سختی شیمیایی، پتانسیل شیمیایی، الکتروفیلیسیته و بیشترین بار انتقال یافته نیز به طور جامع مورد بررسی قرار گرفتند.

کلید واژه‌ها: پروکاربازین؛ فولرن؛ نظریه تابعی چگالی؛ جذب سطحی

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