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Investigating the performance of nano structure C_{60} as nano-carriers of anticancer cytarabine, a DFT study

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ABSTRACT

In this research study, stability, chemical properties, and thermodynamic parameters nano-derivatives of the cytarabine with the fullerene C_{60} nanostructure were calculated in the range of 298.15-310.15 K at the B3LYP/6-31G* level of theory. Possible isomers of the cytarabine (four different configurations) with C_{60} molecule were considered, and the effect of temperature on the thermodynamic parameters was studied. The adsorption energy, Gibbs free energy changes (ΔG_{ad}), enthalpy (ΔH_{ad}) variations, thermodynamic equilibrium constant, specific heat capacity, chemical hardness, energy gap, and electrophilicity were evaluated, as well. The results indicated that the adsorption of the cytarabine with fullerene C_{60} is spontaneous. In addition, the calculated specific heat capacity values revealed that, the C_{60} can be utilized as a sensing material in the construction of thermal biosensors for cytarabine determination.

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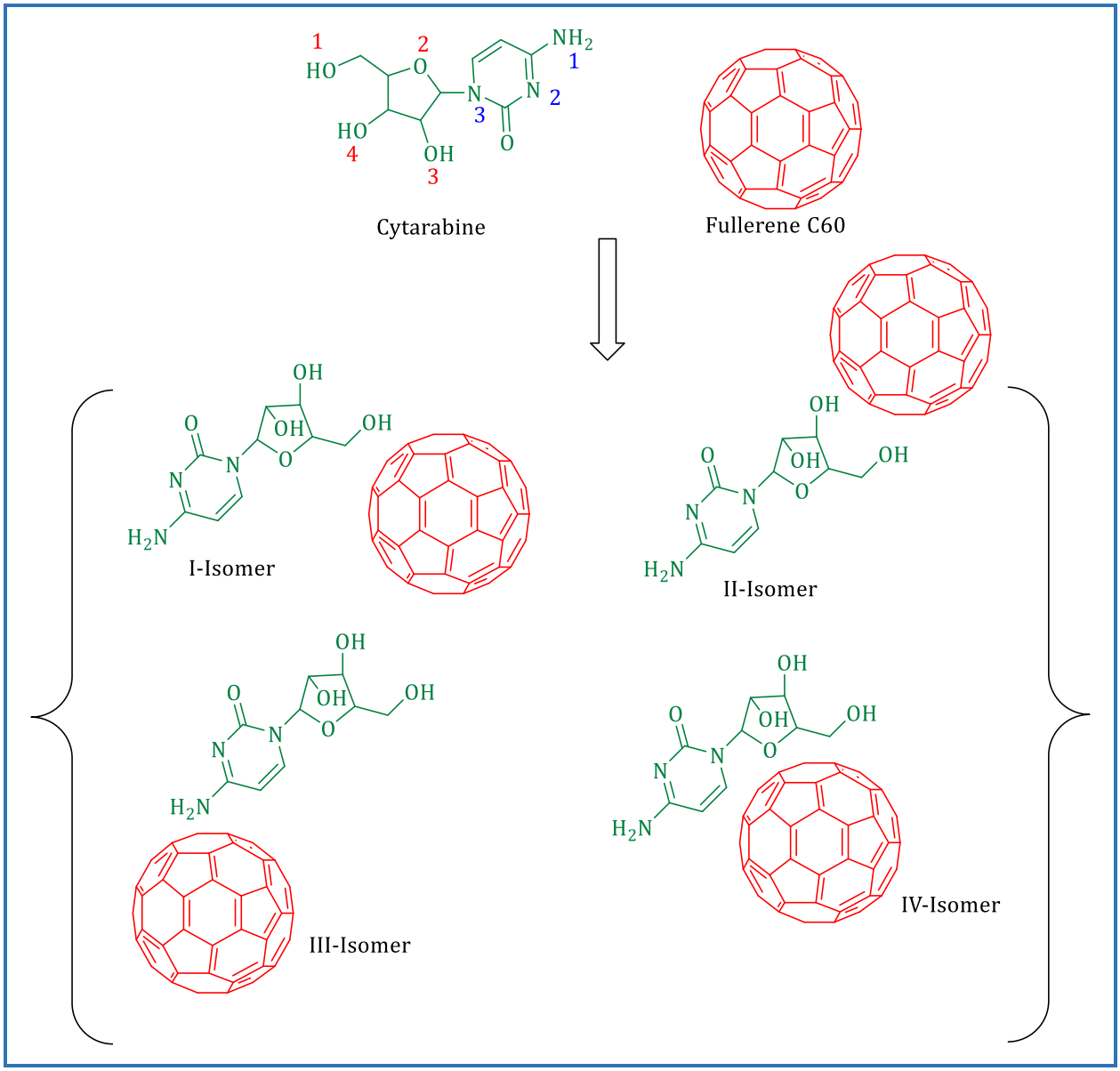
Graphical Abstract



Introduction

Cancer is one of the toughest diseases, and medications play an important role in treating them, meaning that their chemical and biological properties should be preserved until they reach the target. It has many chemotherapy drugs, as well. At the same time, development of a carrier system is effective in treating cancer. Nanotechnology is a revolutionary and effective way to transfer the medicine to tissues and cells [1]. Various carriers can be used to control time, place of delivery of drugs, drug release rates, and reduce drug toxicity. The application of nanotechnology in medical

sciences, known as a nanoparticle, has accelerated the diagnosis, imaging, and treatment of many diseases [2–9]. Some of the problems associated with chemotherapy are solved by the nanoparticle formula of these drugs. The main advantage of these compounds is that they have exposed to permeation and preservation (EPR) phenomena in comparison with natural tissues, and another advantage is that the dose can be reduced [10]. For example, by changing the size of the surface or structure using carbon nanostructures such as fullerene, this drug can circulate in the plasma and move to the minimum target cells. It is expected that the combination of nanostructures and drugs may increase in future clinical treatments instead of traditional drugs [11–18]. Fullerene C_{60} is shown in the structural form of Figure 1**a**. The C_{60} Fullerene structure is also called the Bucky ball because of its similarity to the soccer ball. Carbon nanotubes belong to fullerenes, a structured family entirely composed of carbon [19, 20]. Each fullerene carbon contains the SP^2 hybrid and the sigma transplant with three other atoms. Figure 1**b** illustrates cytarabine structure. Natural DNA replication is inhibited by mitosis inhibition [21]. Of course, there are several side effects including, nausea and digestive problems such as headache, dizziness, skin rash, hair loss, itching, difficulty swallowing, abdominal pain, anal wounds, and infants. Systematic measurements of cytarabine solubility in water, methanol, ethanol, and ethanediol at atmospheric pressure using gravimetric at temperature (153.15-333.15) K were investigated. Melting temperature and molecular fusion denomination, ΔH_{ad} of cytarabine were measured. The results showed that the solubility of cytarabine in all solvents investigated was endothermic, in four solvents, there was a tendency to increase the amount of water, and it appears from ethanol, methanol, and ethanol, respectively. This behavior can be attributed to the interaction between the pole and the viscosity of the respective solvents. The solubility of the cystatin in these solvents increases with enhancing the temperature [22]. Based on this paper, calculations were carried out in the gas phase and water. The level of Fe_3O_4 @ SiO_2 was modified with an anticancer drug, cystatin. X-ray diffraction (XRD), Fourier infrared spectroscopy (FT-IR), transmission electron microscopy (TEM) were employed to evaluate the structural properties of the samples. The results showed that the crystalline phase of iron oxide was magnetite and the average size of Fe_3O_4 @ SiO_2-cytarabine was about 23 nm. In addition, the determination of Fe_3O_4 @ SiO_2-cytarabine level by FT-IR revealed that the successful coating of Fe_3O_4 with SiO_2 and the binding of cytarabine to the Fe_3O_4 @ SiO_2-cytarabine level was *via* hydroxyl group. The results showed that the effect of magnetic Fe_3O_4 @ SiO_2-cytarabine nanoparticles on cells was about twice as high as cytarabine [23]. The purpose of this research is to investigate the effect of absorption of cytarabine and C_{60} fullerene nanoparticles in different conditions. Therefore, the absorption energy and thermodynamic parameters in the gas and gas solvent phase were investigated. These interactions were investigated in the temperature range from 158 K to 151 K. Formerly, this test was done for

other drugs or with some other nanostructures; however, the calculating cytarabine with fullerene C_{60} in gas phases and water dissolving at various temperatures was completely new.

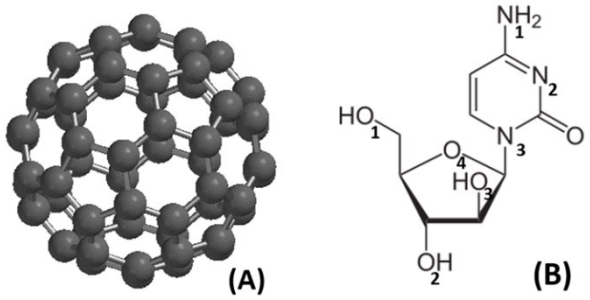


Figure 1. a) Chemical structure of fullerene C_{60}, b) molecular structure of cytarabine

Experimental

Computational details

First, the fullerene structure was obtained drawn using the nanotube modeler software. The structure of the cytarabine and other structures were placed drawn in four different positions by Gauss view software. Then, the thermodynamic parameters were calculated using the density functional theory at B3LYP/6-31G (d) for each position mode. This the 6-31G (d) basis series set was selected because in the previous reports in the case of similar structures the results were consistent with the experimental data previously reported [24–27]. All the calculations were done at the 298.15 until 310.15 K using spartan software. The adsorption process is as follows:

$$\text{Cytarabine} + C_{60} \rightarrow \text{Cytarabine - } C_{60} \quad (1)$$

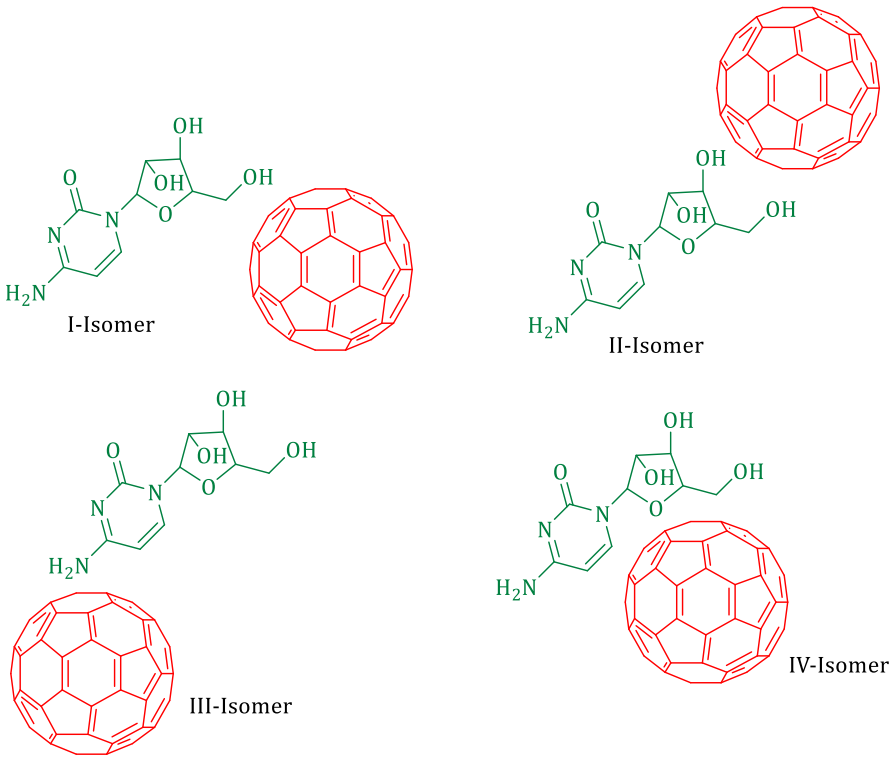
Results and Discussion

Evaluating structural features

As shown in Scheme 1, cytarabine approaches fullerene from four positions. Each of the derivatives of these materials with a nano-fullerene is named with an abbreviation to make it easy to understand; in the following, this naming is explained: from two positions (with oxygen) called isomers **I** and **II**, and two other positions (with nitrogen), which are called isomers **III** and **IV**.

Determining and evaluation of enthalpy changes values of formation of C_{60} reaction with cytarabine

The adsorption of the compounds and the amount of released energy can be determined by approaching the two structures. Equation (2) was used to calculate the values of the enthalpy formation for the C_{60} substitution process.



Scheme 1. Optimized structures of cytarabine derivatives with C_{60}

This means to subtract the total energy of the whole product of a reaction from the sum of the total energy of the raw material. H_{th} is used as the thermal enthalpy symbol for each of the components of the reaction.

$$\Delta H_{ad} = H_{th}\,(\text{Drug-}\,C_{60}) - (H_{th}\,(\text{Drug}) + H_{th\,(C60)}) \qquad (2)$$

Cytarabine is exothermic and since the values of ΔH_{ad} for all derivatives are negative then the energy is transferred from the system to the environment. This has no significant effect on the performance of the reaction because, despite this increase, the amount of enthalpy changes is negative. In addition, to investigate the effect of temperature on carbon nanotubes substitution process, all thermodynamic parameters are calculated at a temperature range of 298.15 until 310.15 Kelvin at intervals of 1° to 1°. The values are clearly presented in Table 1. Increasing the temperature gradually increases the amount of enthalpy changes, and as the temperature increases, the process of forming the desired compounds becomes more exothermic. The optimum temperature for the synthesis of all the derivatives in both water phase and the gas phases is 298 K. Given the calculated enthalpy in the gas phase, the enthalpy of the **IV**-Isomer is more negative, therefore, the probability of the adsorption of this side is higher; but in the water solvent phase, the adsorption rate of the **II**-Isomer is higher.

Table 1. The values of enthalpy changes of C_{60} and cytarabine in the a) gas phase and b) water solvent, at a temperature of 298.15 until 310.15 Kelvin

Temperature (K)		ΔH_{ad} (KJ/MOL)			
		I	**II**	**V**	**VII**
298.15	a	-7316.46	-6979.66	-6907.96	-6308.63
	b	-7610.93	-7826.04	-7595.78	-7596.96
299.15	a	-7316.45	-6979.66	-6907.95	-6308.63
	b	-7610.93	-7826.04	-7595.78	-7596.96
300.15	a	-7316.45	-6979.66	-6907.95	-6308.63
	b	-7610.93	-7826.03	-7595.77	-7596.95
301.15	a	-7316.44	-6979.65	-6907.94	-6308.62
	b	-7610.92	-7826.03	-7595.76	-7596.94
302.15	a	-7316.44	-6979.65	-6907.93	-6308.62
	b	-7610.92	-7826.03	-7595.76	-7596.94
303.15	a	-7316.43	-6979.65	-6907.93	-6308.62
	b	-7610.92	-7826.03	-7595.75	-7596.93
304.15	a	-7316.42	-6979.64	-6907.92	-6308.62
	b	-7610.91	-7826.02	-7595.74	-7596.93
305.15	a	-7316.42	-6979.64	-6907.91	-6308.61
	b	-7610.91	-7826.02	-7595.74	-7596.92
306.15	a	-7316.41	-6979.64	-6907.91	-6308.61
	b	-7610.91	-7826.02	-7595.73	-7596.91
307.15	a	-7316.4	-6979.63	-6907.9	-6308.61
	b	-7610.91	-7826.01	-7595.72	-7596.91
308.15	a	-7316.4	-6979.63	-6907.89	-6308.6
	b	-7610.9	-7826.01	-7595.72	-7596.9
309.15	a	-7316.39	-6979.63	-6907.89	-6308.6
	b	-7610.9	-7826.01	-7595.71	-7596.9
310.15	a	-7316.38	-6979.62	-6907.88	-6308.6
	b	-7610.9	-7826	-7595.7	-7596.89

[a] value of gas phase

[b] value of solvent phase

Calculation and evaluation of Gibbs free energy changes and cytarabine with fullerene derivatives

Equation (3) was used to calculate the Gibbs free energy (ΔG_{ad}) variations. G_{th} is the thermal Gibbs energy calculated by spartan software for each component of the reaction. It is obtained from the subtraction of the total energy of the total reaction products and the sum of the total energy of the reactants. Results are presented in Table 2, indicating that fullerene substitution on cytarabine is spontaneous. Because its ΔG_{ad} is much less than the **II**-Isomer Gibbs free energy variations. Although, the G_{th} quantity has experienced a sharp decrease after the process, the value of this parameter was significantly negative in all cases. The values of Gibbs free energy changed gradually by increasing the temperature. In the water solvent phase, the highest synthesis efficiency was related to the isomer **II** at room temperature.

$$\Delta G_{ad} = G_{th\ (Drug\text{-}C60)} - (G_{th\ (Drug)} + G_{th\ (C60)}) \quad (3)$$

Evaluation of energy of cytarabine and their derivatives with C_{60} in gas and water solvent phases

The adsorption reaction under investigation has three isomeric states, the second isomer having the most stable state and the lowest energy (Scheme 1). The reaction in the solvent phase does perform better than the gas phase, as shown in Figure 2.

$$\Delta E_{ad\ (\mathbf{I}\text{-Isomer})} > \Delta E_{ad\ (\mathbf{II}\text{-Isomer}} > \Delta E_{ad\ (\mathbf{III}\text{-Isomer}))} > \Delta E_{ad\ (\mathbf{IV}\text{-Isomer})}$$

Table 2. Gibbs free energy variations for substitution reaction formation of C_{60} and cytarabine in the a) gas phase and b) in water solvent phase, at a temperature 298.15 until 310.15 Kelvin

		ΔG_{ad} (KJ/mol)			
Temperature (K)		**I**-Isomer	**II**-Isomer	**III**-Isomer	**IV**-Isomer
298.15	a	-7533.57	-7195.58	-7125.66	-6524.72
	b	-7548	-7762.95	-7534.47	-7535.06
299.15	a	-7534.84	-7196.85	-7126.93	-6525.98
	b	-7547.76	-7762.71	-7534.24	-7534.83
300.15	a	-7536.12	-7198.11	-7128.2	-6527.25
	b	-7547.52	-7762.47	-7534	-7534.6
301.15	a	-7537.39	-7199.39	-7129.48	-6528.52
	b	-7547.28	-7762.23	-7533.77	-7534.36
302.15	a	-7538.67	-7200.66	-7130.76	-6529.79
	b	-7547.04	-7761.99	-7533.53	-7534.12
303.15	a	-7539.96	-7201.94	-7132.05	-6531.07
	b	-7546.81	-7761.76	-7533.31	-7533.9
304.15	a	-7541.25	-7203.23	-7133.34	-6532.36

305.15	b	-7546.57	-7761.52	-7533.08	-7533.66
	a	-7542.54	-7204.51	-7134.63	-6533.65
	b	-7546.34	-7761.29	-7532.85	-7533.44
306.15	a	-7543.84	-7205.81	-7135.93	-6534.94
	b	-7546.11	-7761.05	-7532.62	-7533.2
307.15	a	-7545.13	-7207.1	-7137.23	-6536.24
	b	-7545.88	-7760.82	-7532.39	-7532.97
308.15	a	-7546.43	-7208.41	-7138.53	-6537.54
	b	-7545.64	-7760.59	-7532.15	-7532.73
309.15	a	-7547.73	-7209.71	-7139.84	-6538.85
	b	-7545.41	-7760.35	-7531.92	-7532.5
310.15	a	-7549.04	-7211.02	-7141.14	-6540.16
	b	-7545.18	-7760.12	-7531.68	-7532.26

[a] value of gas phase

[b] value of solvent phase

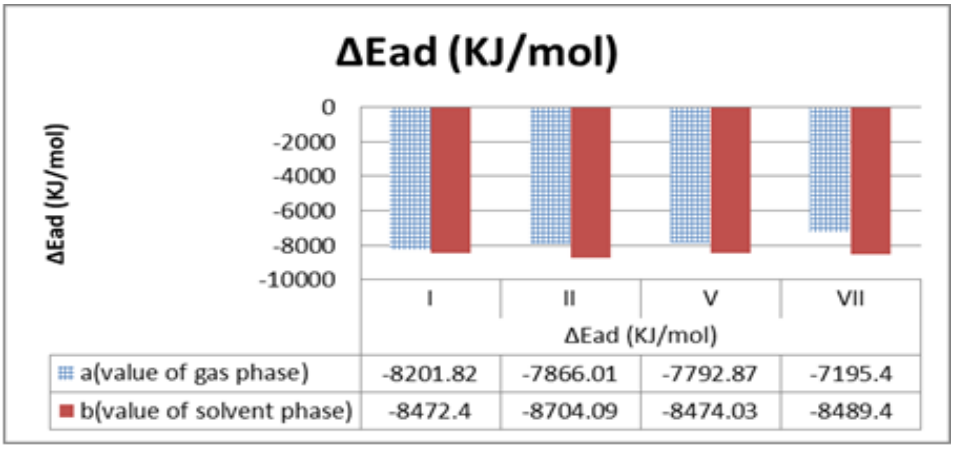


Figure 2. Energy of cytarabine and its derivatives with fullerene (C_{60}) in a) gas phase, in the b) water solvent

Structural properties

As seen in Table 3, the density of cytarabine increased after adsorption with pure fullerenes. In addition its structural properties such as level and zero-point energy enhanced after approaching fullerene. The distance and the rate of orbital p participation were investigated, as well. The adsorption intervals in the C-O_1 and C-O_2 positions are looser than that of the N-C_1 position. In other words, the adsorption was looser and easier. The highest increase in the bond intervals was between oxygen number 2 of cytarabine and carbon of fullerene. According to the IR studies, there are no negative

frequencies for any of the structures and the lowest frequency reported in Table 3, which are all positive, approves it.

Molecular orbital calculations

The highest occupational molecule orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) play a significant role in chemical stability of the molecule HOMO represents the ability to give an electron, and LUMO indicates the ability to accept an electron. The energy gap between HOMO and LUMO specifies the reactivity, polarize ability, and the chemical hardness or softness of the molecule that is usually represented by the HLG and equation (4), where E_H and E_L are the energy of HOMO or LUMO orbitals, respectively. Energy gap has a direct relationship with the electrical conductivity of the molecule. Compounds with small energy gap can easily transfer electrons from the barrier to the conduction strip. Thus, the materials that have less energy gap indicate more electrical conductivity than molecules with a higher energy gap. Table 4 indicates that the energy gap was significantly increased after cytarabine bounding. In fact, after substitution, conductivity rates have significantly declined. The next parameter is the chemical hardness (η), which can be calculated using equation (5). Chemical hardness was used to determine the reactivity of a new compound as molecules structurally softer could easily change their electron density. In addition, electronic transmissions that are necessary for chemical reactions are better and easier in soft compounds.

Table 3. Adsorption energy, lowest observed frequencies, bound distances, mass, volume and density for cytarabine and its derivatives with fullerene

	Chemical properties				
	Cytarabine	I-Isomer	II-Isomer	III-Isomer	IV-Isomer
Energy (KJ/mol)	-2289522	-8186644	-8186638	-8188557	-8188558
Area (Å^2)	233.24	656.29	657.35	652.26	652.31
Mass (amu)	239.19	963.88	963.88	963.88	963.88
Volume (Å^3)	208.13	808.54	809.12	810.37	809.55
Density (amu/Å^3)	1.15	1.19	1.19	1.19	1.19
Lowest frequency (cm^{-1})		0.53	1.11	1.29	1.80
Bond distances	---	6.52	4.62	3.82	3.43

The data provided in Table 4 indicate that after the reaction with the fullerene the reactivity of cytarabine was decreased, as the chemical hardness of derivatives was higher than that of the pure

Table 4. HOMO and LOMO orbital values, energy chip, chemical hardness, chemical potential, electrophilicity, maximum loaded transferred to system and dipole moment for cytarabine and its derivatives with fullerene C_{60}

	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{gap} (eV)	η (eV)	Dipole moment (debye)
Cytarabine	-5.9	5.2	11.2	5.6	5.0
I	-5.8	2.8	8.6	4.3	4.6
II	-5.7	2.8	8.6	4.3	5.2
III	-5.4	3.2	8.6	4.3	6.2
IV	-5.5	1.3	8.6	4.3	5.8

drug. The electrophilicity (ω) and the maximum load transmitted to the system (ΔN_{max}) both indicated good quantities for determining the inclination of a compound to adsorb electron.These parameters were calculated using equations (7) and (8). When two molecules react, one of them acts as an electrophile and the other one plays the role of a nucleophile. The compound with higher electrophilicity and charge capacity tends to act as an electron receptor. The molecule with lower electrophilicity and charge capacity tends to accept the electron. As shown in the Table 4, electrophilicity of the cytarabine was significantly reduced after the binding to the fullerene, so it has a lower tendency to adsorb the electron. The dipole moment of the structures was studied, as well. This parameter is a good measurement to examine the solubility of the molecules in polar solvents. The molecules with higher dipole moments have better solubility in water solvents and compounds with less bipolar moments have lower solubility in dipole solvents. According to the results, after binding with fullerene, the dipole moment except for **I**-Isomer have increased. Therefore, fullerene derivatives with cytarabine are more soluble in water solvent than pure drug without substitution.

$$HLG = E_L - E_H \quad (4)$$

$$\eta = (E_L - E_H)/2 \quad (5)$$

$$\mu = (E_L - E_H)/2 \quad (6)$$

$$\omega = \mu^2/2\eta \quad (7)$$

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

Conclusions

In this study, the effect of the cytarabine anti-cancer drug with the fullerene C_{60} carbon nanostructure at the B3LYP/6-31G (d) level of theory examined. The thermodynamic parameters results indicated that this reaction is exothermic, spontaneous, one-way, and non-equilibrium. The

highest reaction efficiency was observed at room temperature. The length of the N-C, C-O adsorption bonds, and density values indicated that the speed and pressure of reaction because of the carbon nano-structure substitution. In the gas phase, the energy of the first state (the interaction from the oxygen one) and then the second state (the interaction from the second side of the oxygen) was negative. The reason for this can be explained in the space between the oxygen levels of one of the loops. In the water phase, due to the reaction of one oxygen with a solvent, surface absorption was carried out through the second oxygen and its energy was more negative. The analysis of the molecular orbitals indicated that the carbon nano-structure derivatives of cytarabine had lower conductivity and reactivity. As the theoretical studies indicated that the reaction is possible empirically, the empirical study of the synthesis of these derivatives is recommended**.**

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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