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Adsorption of cytarabine on the surface of fullerene C_{20}: a comprehensive DFT study

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Abstract

In this study, the adsorption of Cytarabine on the surface of C_{20} was evaluated by density functional theory. At first, the structures of fullerene, drug, and their complexes were optimized, geometrically. Then, IR and frontier molecular orbital computations were performed on them in the vacuum and aqueous phase. The calculated adsorption energies, Gibbs free energy changes (ΔG_{ad}) and adsorption enthalpy changes (ΔH_{ad}) revealed that the adsorption process of Cytarabine is experimentally feasible, spontaneous, exothermic and non-equilibrium. The effect of temperature on the adsorption process was also checked out and the results indicated that the optimum temperature for the interaction of fullerene with the drug is 298 ˚K. The frontier molecular orbital parameters such as band gap, chemical hardness, electrophilicity, chemical potential, and charge capacity were also studied and the results proved that C_{20} is an ideal electroactive sensing material for fabricating novel sensors for determination of Cytarabine. The values of dipole moment have also revealed that the bioavailability and biocompatibility of the drug have also improved after adsorbing on the surface of fullerene.

Keywords: Cytarabine; adsorption; density functional theory; fullerene (C20).

Introduction

After heart disease, cancer is the second reason of death in Iran and developing countries in the world. Proper use of the drug in the treatment of cancer should be considered. The chemical and biological properties of drug should be protected until it reaches the target site. Chemotherapy drugs have serious side effects. Therefore, the development of highly effective drug delivery systems is necessary. It is expected that the use of nano-structures and drugs instead of traditional drugs is going to be increased in the future in the clinical treatments. One of the nanostructures is fullerene via its similarity to the soccer ball is called as Bucky ball as well [2]. The simplest C_{20} fullerene is shown in structural form Figure 1.A. The main discovery of fullerenes in 1985 occurred. Their spherical shape makes fullerene molecules to be placed in hydrophilic solvent solutions of enzymes or cells,

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and leading to interesting medicinal properties. Cytarabine (Cytosar) is of common drugs used to treat leukemia chemotherapy [3]. Figure 1.B represents its structure. In the cell cycle in S phase, as a competitive inhibitor of the DNA polymerase enzyme, it rapidly is converted to Cytosine triphosphate and, since cells needs the DNA replication to be divided, DNA natural replication is disrupted through inhibiting the mitosis [4]. Of course there are many side effects including: nausea and digestive problems such as headache, dizziness, skin rash, hair loss, itching, difficulty in swallowing, abdominal pain, anal wounds, infancy, etc. A systematic measure of pure solubility of Cytarabine in four solvents of water, methanol, ethanol and ethanediol was performed in 2017 with a granulator using gravimetric method at pressure of 1 atm and temperature of 298.15 ± 310.15 K. The results indicated that the solubility of Cytarabine is an endothermic process in all solvents. Cytarabine can be dissolved in polar solvents as well as Water> Ethanediol> Methanol> Ethanol. The solubility of Cytarabine in these solvents increases with increasing the temperature [5]. This aims of current study is investigating the interaction of drug with the Nano sized structure using adsorption process of Cytarabine with C_{20} fullerene in different situations. Thus, the adsorption energy and thermodynamic parameters in gas and water solvent phases were investigated. The chemical bond of these interactions was evaluated in the temperature ranging from 298.15 to 310.15 K; the optimum temperature was determined to be 298.15 by comparing the results of and the best interaction position of the drug with the nanostructure was considered. Earlier, this was empirically done for cancer drugs With some nanostructures, but theoretical study of Cytarabine with C_{20} fullerene in the gas and water solvent phases at various temperatures is completely new. Other measures taken are correction of Cytarabine Surface with colic acid which was conducted in 2016 in China [6-16].

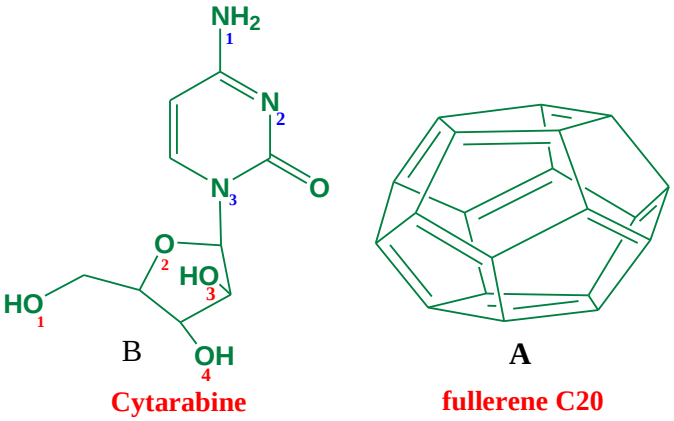

Figure 1. Chemical structure of Fullerene C_{20} (A) and Cytarabine (B)

Computational methods

First, the fullerene structure was obtained using the Nanotube Modeler software. The structure of the Cytarabine and other structures were placed in seven different positions by Gauss View software. Then, using the Gaussian and Spartan software, the thermodynamic parameters were calculated using the density functional theory at B3LYP / 6-31G (d) for each position. The 6-31G (d) basis set was selected because in the previous reports in the case of similar structures the results were consistent with

experimental data [17-23]. All calculations were done at the 298.15 until 310.15 K using Spartan software. The adsorption process is as follows:

Cytarabine + C_{20}→ Cytarabine-C_{20} (1)

As shown in Figures 2, Cytarabine can approach Fullerene from seven different positions.

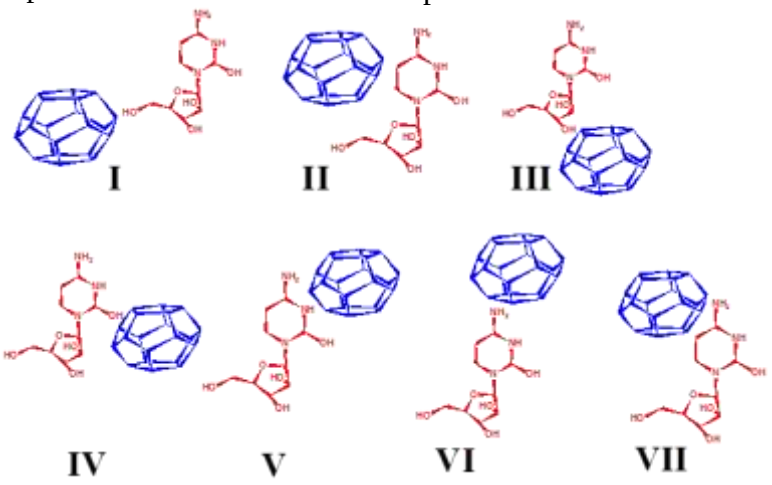

Figure 2 . Optimized Structures of Cytarabine derivatives with C_{20}

Results and discussions

Evaluation of the Energy of Cytarabine and their derivatives with C_{20} in gas and aqueous solvent phases

Comparing the Energies of each structure of cited seven different positions in gas phase it was determined that structure V (shown in Figure 2) has the lowest energy barrier. It seems that the reaction in the water solvent phase is more probable than gas phase. Of course, in the aqueous solvent phase, the sixth state is more neutral and more stable, than gas phase (Table 1):

$\Delta E_{ad\ V\text{-}Isomer} > \Delta E_{I\text{-}Isomer} > \Delta E_{II\text{-}Isomer} > \Delta E_{III\text{-}Isomer} > \Delta E_{IV\text{-}Isomer} > \Delta E_{VII\text{-}Isomer} > \Delta E_{VI\text{-}Isomer}$

Table 1. Adsorption Energy of Cytarabine and its derivatives with fullerene (C_{20}) in gas phase (a) in the aqueous solvent (b)

	ΔE(KJ/mol)						
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**
a	-7709.817304	-7703.924372	-7700.23108	-7688.882356	-8134.479624	-7686.530695	-7688.514261
b	-7896.155239	-7088.185987	-7087.53313	-7030.60412	-8474.22808	-7176.870763	-7141.261261

Determining and evaluation of the enthalpy changes values of adsorption of C_{20} 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 adsorption enthalpy drug C_{20} complex.

$\Delta H_{ad} = H_{Th\ (Drug\text{-}\ C20)} - (H_{Th\ (Drug)} + H_{Th\ (C20))}$ (2)

As the results in Table 1 show, adsorption of fullerene C_{20} with Cytarabine is done exothermically, and energy is transferred from the system to the environment, as the values of ΔH_{ad} are obtained for all the derivatives are negative. 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 K until 310.15 K with 1 degree intervals. The values are clearly presented in Table 2. With gradually increasing the temperature 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. In given calculated enthalpies show that the enthalpy of the V Isomer is more negative, therefore, the probability of the adsorption from V Isomer position is higher.

Table 2. The values of enthalpy changes of C_{20} and Cytarabine in the gas phase (a) and water solvent (b) at temperature range from 298.15 until 310.15 K

Temperature (K)		ΔH_{ad} (KJ/MOL)						
		I	II	III	IV	V	VI	VII
298.15	a	-6822.213651	-7082.715651	-7077.2387	-7068.724651	-7504.503651	-7066.8537	-7068.769651
	b	-7016.856332	-6209.234332	-6206.7973	-6152.702332	-6289.152332	-7596.8083	-6263.773332
299.15	a	-6822.210376	-6816.676376	-6811.1974	-6802.683376	-7238.467376	-6800.8104	-6802.727376
	b	-7016.855058	-6209.231058	-6206.7931	-6152.699058	-6289.153058	-7596.8021	-6263.768058
300.15	a	-6452.186339	-6816.674101	-6811.194101	-6802.680101	-7238.469101	-6800.805101	-6802.723101
	b	-7016.852783	-6209.227783	-6206.788782	-6152.694783	-6289.152783	-7596.795783	-6263.762783
301.15	a	-6452.044064	-6816.671826	-6811.189826	-6802.676826	-7238.470826	-6800.799826	-6802.718826
	b	-7016.850508	-6209.225508	-6206.784507	-6152.691508	-6289.154507	-7596.789507	-6263.758507
302.15	a	-6451.901789	-6816.667551	-6811.184551	-6802.672551	-7238.470551	-6800.792551	-6802.713551
	b	-7016.849232	-6209.223232	-6206.780232	-6152.687232	-6289.155232	-7596.784232	-6263.754232
303.15	a	-6451.757514	-6816.664276	-6811.179276	-6802.667276	-7238.470276	-6800.786276	-6802.707276
	b	-7016.845958	-6209.218958	-6206.774958	-6152.682958	-6289.154958	-7596.776958	-6263.747958
304.15	a	-6451.614239	-6816.662001	-6811.176001	-6802.664001	-7238.472001	-6800.780001	-6802.703001
	b	-7016.844682	-6209.216683	-6206.771682	-6152.679682	-6289.156682	-7596.771682	-6263.743682
305.15	a	-6451.468964	-6816.658726	-6811.171726	-6802.659726	-7238.471726	-6800.773726	-6802.697726
	b	-7016.841408	-6209.212407	-6206.766408	-6152.674407	-6289.156407	-7596.764407	-6263.737407
306.15	a	-6451.323689	-6816.655451	-6811.167451	-6802.656451	-7238.473451	-6800.768451	-6802.693451
	b	-7016.840132	-6209.211132	-6206.763132	-6152.672132	-6289.158132	-7596.759133	-6263.734132
307.15	a	-6451.177414	-6816.653176	-6811.163176	-6802.652176	-7238.474176	-6800.762176	-6802.688176
	b	-7016.836858	-6209.206858	-6206.757858	-6152.666858	-6289.157858	-7596.751858	-6263.727858
308.15	a	-6451.030139	-6816.648901	-6811.157901	-6802.646901	-7238.474901	-6800.754901	-6802.681901
	b	-7016.834583	-6209.203583	-6206.753582	-6152.662582	-6289.159583	-7596.745583	-6263.722583
309.15	a	-6450.882864	-6816.645626	-6811.152626	-6802.642626	-7238.478626	-6800.748626	-6802.676626
	b	-7016.832307	-6209.200308	-6206.748308	-6152.658308	-6289.163308	-7596.739308	-6263.717308
310.15	a	-6450.734589	-6816.641351	-6811.147351	-6802.638351	-7238.481351	-6800.741351	-6802.670351
	b	-7016.829033	-6209.197032	-6206.743032	-6152.654033	-6289.166033	-7596.733033	-6263.711033

Calculation and Evaluation of the Gibbs free energy Changes and Cytarabine with Fullerene Derivatives

Equation (3) is used to calculate the Gibbs free energy (ΔG_{ad}) variations. G_{th} is the thermal Gibbs free energy calculated by Spartan software for each component of the reaction [24]. Results are presented in Table (3), indicating that absorption of fullerene on Cytarabine is spontaneous. In general, show that the value of this parameter is significantly negative in all cases, then it is expected that the absorption reaction of all compounds is likely.

$$\Delta G_{ad}=G_{th\ (Drug\text{-}C20\ )} - (G_{th\ (Drug)} + G_{th(C20)}) \quad (3)$$

Table 3. Gibbs free energy variations for substitution reaction formation of C_{20} and Cytarabine

Temperature (K)		ΔG_{ad} (KJ/MOL)						
		I	**II**	**III**	**IV**	**V**	**VI**	**VII**
298.15	**a**	-6764.941	-6759.107	-6752.810	-6745.649	-7178.154	-6744.905	-6746.575
	b	-6959.586	-6151.663	-6148.406	-6095.664	-6228.839	-7540.897	-6207.616
299.15	**a**	-6764.720	-6758.886	-6752.590	-6745.437	-7177.932	-6744.697	-6746.366
	b	-6959.364	-6151.440	-6148.185	-6095.451	-6228.616	-7540.687	-6207.406
300.15	**a**	-6764.499	-6758.663	-6752.369	-6745.224	-7177.709	-6744.480	-6746.156
	b	-6959.143	-6151.218	-6147.964	-6095.238	-6228.393	-7540.471	-6207.196
301.15	**a**	-6764.276	-6758.440	-6752.147	-6745.010	-7177.484	-6744.262	-6745.941
	b	-6958.920	-6150.995	-6147.742	-6095.024	-6228.169	-7540.253	-6206.981
302.15	**a**	-6764.056	-6758.219	-6751.927	-6744.798	-7177.262	-6744.047	-6745.724
	b	-6958.701	-6150.774	-6147.523	-6094.813	-6227.947	-7540.038	-6206.765
303.15	**a**	-6763.841	-6758.003	-6751.713	-6744.592	-7177.046	-6743.837	-6745.513
	b	-6958.486	-6150.559	-6147.309	-6094.607	-6227.731	-7539.828	-6206.554
304.15	**a**	-6763.628	-6757.788	-6751.498	-6744.386	-7176.830	-6743.628	-6745.303
	b	-6958.273	-6150.344	-6147.094	-6094.402	-6227.515	-7539.619	-6206.344
305.15	**a**	-6763.414	-6757.574	-6751.277	-6744.180	-7176.615	-6743.419	-6745.094
	b	-6958.058	-6150.128	-6146.872	-6094.194	-6227.299	-7539.409	-6206.134
306.15	**a**	-6763.199	-6757.358	-6751.055	-6743.966	-7176.398	-6743.209	-6744.883
	b	-6957.843	-6149.913	-6146.650	-6093.981	-6227.082	-7539.199	-6205.923
307.15	**a**	-6762.986	-6757.144	-6750.835	-6743.753	-7176.183	-6743.000	-6744.672
	b	-6957.629	-6149.698	-6146.430	-6093.768	-6226.867	-7538.990	-6205.712
308.15	**a**	-6762.771	-6756.928	-6750.613	-6743.539	-7175.968	-6742.784	-6744.453
	b	-6957.415	-6149.482	-6146.208	-6093.554	-6226.652	-7538.774	-6205.493
309.15	**a**	-6762.557	-6756.713	-6750.392	-6743.325	-7175.755	-6742.567	-6744.236
	b	-6957.202	-6149.269	-6145.988	-6093.341	-6226.440	-7538.558	-6205.277
310.15	**a**	-6762.343	-6756.498	-6750.171	-6743.105	-7175.543	-6742.350	-6744.018
	b	-6956.986	-6149.052	-6145.765	-6093.119	-6226.226	-7538.339	-6205.057

In the gas phase (a) and in aqueous solvent phase (b) at a temperature 298.15 until 310.15K.

Examining the structural properties

In Cytarabine complexes with C_{20} area, mass, volume increased after adsorption of Cytarabine with pure fullerenes compared to Cytarabine. Also, according to the information in Table 4, its structural properties, such as the zero point energy, increased after fullerene closure. The distances were investigated too. The adsorption intervals in the N_3-C_1 and C_1-O_1 positions are looser than N_3-C_1 position. In other words, the absorption is more comfortable. According to the IR studies, there are no negative frequencies for any of the structures and therefore the results approve the structures are in stationary states.

Table 4. Lowest observed frequencies, bond distances, Zero-point energy, mass, volume and density for Cytarabine and its derivatives with fullerene

	Chemical properties							
	Cytarabine	I-Isomer	II-Isomer	III-Isomer	IV-Isomer	V Isomer	VI Isomer	VII Isomer
Area (Å2)	233.24	429.25	427.07	418.76	420.49	395.93	424.47	425.01
mass (amu)	239.187	483.439	483.439	483.439	483.439	483.439	483.439	483.439
volume (Å3)	208.13	435.67	435.47	434.63	434.82	424.62	437.95	435.40
density (amu/Å3)	1.15	1.10	1.11	1.11	1.11	1.13	1.10	1.11
Lowest frequency (cm^{-1})	---	1.4143	3.3108	3.0792	6.9872	13.3877	5.3843	6.6643
Bond Distances (Å)	---	3.5546	3.1553	2.8376	3.1304	2.7316	2.9392	6.4911
		C_1-O_1	**C_1-O_2**	**C_1-O_3**	**C_1-O_4**	**C_1-N_1**	**C_1-N_2**	**C_1-N_3**

Evaluation of the results of molecular orbital calculations

The Highest Occupational Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) play a significant role in the chemical stability of the molecule [25]. The energy gap between HOMO and LUMO specifies the reactivity, polarize ability, and the chemical hardness or softness of the molecule is usually calculated by the HLG (equation 4). In this equation, E_{HOMO} and E_{LOMO} are respectively the energy of HOMO and LUMO orbitals respectively. Energy gap has a direct relationship with the electrical conductivity of the molecule. The Compounds with small energy gap can easily transfer electrons from the barrier to the conduction bands. Thus, the materials that have less energy gap indicate more electrical conductivity than molecules with a higher energy gap. The results provided in Table (5) indicate that the energy gap is significantly increased after Cytarabine bounding. In fact, after adsorption, the conductivity of complexes have significantly increased. The next parameter is the chemical hardness (η), which can be calculated by equation (5) [27]. Chemical hardness is a good measure to determine the reactivity of a new compound because molecules structurally softer can easily change their electron density. In addition, electronic transmissions that are necessary for chemical reactions are better and easier in soft compounds. The data provided in Table 5 indicate that after adsorption of Cytarabine with the fullerene the chemical hardness of complexes is lower than of Cytarabine. 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 adsorption of electrons. These parameters are calculated using equations (7) and (8), respectively. When two molecules react, one of them acts as an electrophile and another one plays the role of a nucleophile. The compound with higher electrophilicity and charge capacity tends to act as an electron receptor. On the other hand, a molecule with lower electrophilicity and charge capacity tends to accept the electron. As shown in the Table 5, the electrophilicity of the Cytarabine is significantly reduced after the binding to the fullerene, so it has a lower tendency to adsorption of electrons. The dipole moment of structures was studied too. This parameter is a good measure to examine the solubility of molecules in polar solvents. Molecules with higher dipole moments have better solubility in water solvents and compounds with less bipolar moments have lower solubility in dipole solvents [30]. According to the results, after binding with fullerene the dipole moment except for I-Isomer, for other Isomers have increased. Therefore, fullerene derivatives with Cytarabine are more soluble in water solvent than pure drug without substitution [28-30].

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

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

$$\mu = (E_{LUMO} + E_{HOMO})/2 \quad (6)$$

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

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

Table 5: HOMO and LUMO, band gap (HLG), chemical hardness (η),electrophilicity index (ω), the maximum amount of electronic charge index (ΔN_{max}) and dipole moment for Cytarabine and its derivatives with fullerene C_{20}

Conclusion

In this study, the effect of the Cytarabine as anti-cancer drug with the fullerene C_{20} carbon nanostructure at the B3LYP/6-31G (d) level of DFT theory was examined. The thermodynamic

parameters results indicated that this reaction is exothermic, spontaneous, one-way, and non-equilibrium. The highest reaction efficiency is observed at room temperature. The values of the length of the N-C, C-O bonds indicated that the adsorption in V Isomer and VI Isomer are chemical. The analysis of molecular orbitals showed that C_{20} derivatives of Cytarabine had higher conductivity and reactivity. Considering that, theoretical studies indicated that this reaction is possible. Therefore, the experimental study of the adsorption of these derivatives is recommended.

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