RESEARCH PAPER

Theoretical investigation of fullerene nano carrier anti-cancer drug delivery of Azacitidine

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ABSTRACT

Azacitidine, known under the brand Vidaza, has therapeutic applications for several health complications, including myelodysplastic syndrome, myeloid leukemia, and juvenile myelomonocytic leukemia. The fullerene, mainly C60, has many attractive properties such as physical and electrochemical properties, which can be useful for drug delivery. The current research has focused on the characteristics of Azacitidine concerning its reactivity and chemical structure, which may contribute to its anti-cancer effects. Accordingly, the process of Azacitidine adsorption on fullerene adsorbent was investigated in the gas phase utilizing DFT/B3LYP/6-311+G(d, p). The adsorption process on the adsorbent molecule was examined from a chemical perspective, along with the calculation of the adsorption energy. In addition, the chemical structure (dipolar moment (μ=2.56705)), thermodynamic features consisting of Gibbs free energy (-2354.94 kJ), enthalpy (-2354.80 kJ), entropy (+495.49 J/mol-kelvin), and thermodynamic capacity (226.74 J/mol-kelvin), together with effective electronic parameters such as (σ(0.15), μ(-3.49), ω(0.93), χ(3.49), and η(6.51) all data in eV) in illustrating the compound's chemical characteristics were estimated. Calculating the HOMO(-10.00 eV) and LUMO(3.02 eV) energy levels showed nine regions with chemical activity for Azacitidine, confirming that it is thermodynamically stable while also highlighting the role of this adsorption in Azacitidine delivery to biological mechanisms. Better nucleophilic behaviors can be obtained because the oxygen of the carbonyl group is more negatively charged due to the resonance happening for this molecule. The complex of Azacitidine with fullerene shows decrease in Chemical potential which illustrates more reactivity for the Complex.

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INTRODUCTION

Many studies have investigated the role of Azacitidine in treating myelodysplastic syndrome [1], considering that this drug was also approved by the American FDA in 2004 [2]. Azacitidine has been approved by the Food and Drug Administration for pediatric patients with newly diagnosed juvenile myelomonocytic leukemia (JMML) On May 20, 2022. Two randomized controlled trial studies compared the supportive treatment by the above-mentioned therapeutic agent. They found that the blood cell counts and bone marrow mor-

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phology were normalized totally or partially in 16% of myelodysplastic syndrome patients randomly receiving Azacitidine compared to the control group. Further, the study also revealed the independence of two-thirds of patients requiring blood transfusion due to the consumption of Azacitidine [3]. Some research has also focused on the effects of Azacitidine in myeloid [4] and myelomonocytic [5] types of leukemia.

Azacitidine, as a nucleoside cytidine chemical analog, has been considered for its antineoplastic activities through two mechanisms. The first mechanism operates at low-sode conditions and inhibits DNA methyltransferase leading to its hypomethylation [6]. The second mechanism works at high-dose conditions and is directly cytotoxin for bone marrow abnormal hematopoietic cells incorporating into DNA and RNA and leading to the death of these cells. The incorporation of azacitidine mainly takes place into RNA compared to DNA because it is a ribonucleoside. However, the incorporation of decitabine (5-aza-2'-deoxycytidine) is only possible for DNA because it is a deoxyribonucleoside. Given the aforementioned explanation, incorporating azacitidine into RNA disassembles polyribosomes while also resulting in imperfect ethylation and acceptor function of transfer RNA and inhibiting protein production. On the other hand, incorporating this drug into DNA is accompanied by a covalent binding with DNA methyltransferases, subsequently preventing DNA synthesis and bringing about cytotoxic effects. According to the available evidence, Azacitidine has been able to affect human immunodeficiency and T-lymphotropic [7] viruses in laboratory conditions.

The malignant (MC) and benign cells (BC) are two groups of Cancer cells. The MC is a kind of cell that multiplies and grows when spontaneous genetic mutations happen. The MC cells have maximal 1-2-1 mm^3 size. Necessary nutrients for tumors are provided by blood vessels and for this reason growth factors (GF) develop spontaneously in the blood vessel. This phenomenon is related to factors such as vascular endothelial growth factor (VEGF), primary fibroblast growth factor (BFGF), and a bunch of proteins. These factors cause the spontaneous capillary growth within the cancer cell since these blood vessels grow in a cancer cell as a tumor angiogenesis [8-10].

Fullerenes were discovered in 1985 and have since attracted considerable attention in various fields of science. Valuable information has been obtained from investigating the physical, chemical, and biological properties of fullerenes. Their three-dimensionality, hydrophobicity, size, and electronic configurations have made these compounds an attractive topic in medicinal chemistry. The therapeutic factor of these materials is the unique structure of their carbon cage and their wide scope for derivatization. Despite the low solubility of fullerenes in physiological environments, investigating the biological applications of these compounds has drawn much attention. The fullerene family, and mainly C60, has many appealing properties such as physical, electrochemical, and photo properties, which can be useful in various medical fields. An important usage of fullerene is producing singlet oxygen in high quantum yields when exposed to light. This action, along with the direct transfer of electrons from the excited state of fullerene and DNA bases, can be useful for the cleavage of DNA. On the other hand, fullerenes play a pivotal role in delivery systems as gene and anti-cancer drug carriers. [11-15].

Through computational chemistry, the prediction of the molecule structure, energy, and various known or unknown characteristics will be possible. The required computations are performed using digital computers with the ability of chemical system simulation. However, some computational procedures may not be appropriate for molecular investigations, which necessitates selecting more suitable theoretical methods in the first step. Single- and two-particle systems can be mentioned as accurately solvable systems in computational chemistry, where a center-mass coordinate system is used to transform the latter into the former. Multi-particle systems lead to complicated and lengthy mathematical calculations.

Studies have shown the use of Buckyball (C60) as an absorbent [16] in the case of different toxic and non-toxic chemicals [17], dies [18], and also wastewater [19-22]. The density functional theory (DFT) [23] has been used along with molecular dynamic calculations [18-31] to perform theoretical estimations for field investigations, among which nanocage [16, 32-35] can be mentioned.

The current study employed Buckyball (C60) to absorb Azacitidine in the gas phase considering the DFT with a 6-311+G(d, p) basis set.

MATERIALS & METHODS

Computational method

The chemical quantum calculations were per-

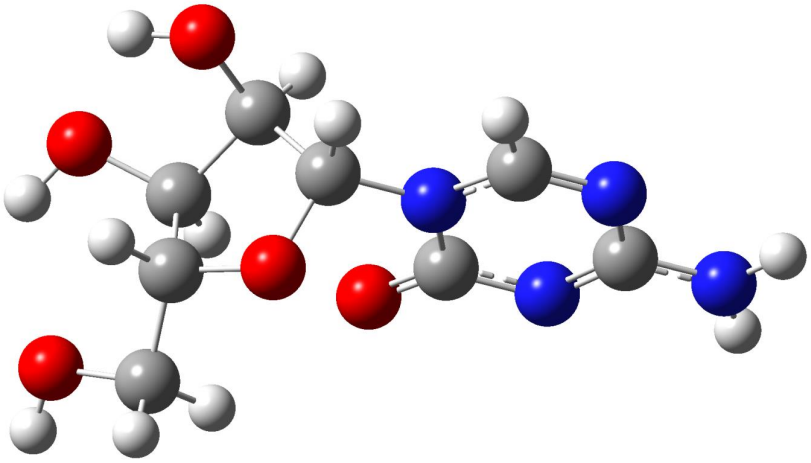

Fig. 1. Azacitidine optimized structure with B3LYP/6-311+G(d, p)

formed using the Gaussian 03 [36] package run on a supercomputer. The complete geometry optimizations, electric field gradient, thermodynamic properties, and electrical parameters were all investigated using the DFT with a three-parameter hybrid functional of Becke B3LYP and the 6-311+g(d, p) basis set. The current study utilized Buckyball C-C (C60 ih) as an absorbent, whose energy of adsorption was calculated in the formula below:

$$E_{ads}=E_{(B\text{-}Az)}-(E_{Azacitidine}+E_{Buckyball})$$

RESULTS AND DISCUSSION

According to the results obtained by the literature review, adopting nanocages with metallic atoms can effectively modify their electrical characteristics, chemical function, and reaction potential [37]. Therefore, the current study utilized B3LYP/6-311+G (d, p) for structural optimizations in the case of Azacitidine and Buckyball (C60, fullerene) while also adopting Azacitidine on Buckyball, the optimized structure of which can be observed in Fig. 1. There are nine active sites for Azacitidine, including five O and four N with unique chemical as well as electrochemical locations in Azacitidine, as indicated in Fig. 2. The electron density exerts different effects on the chemical reaction taking place in each position. Better nucleophilic behaviors can be obtained in the gas phase because the oxygen of the carbonyl group is more negatively charged which is due to resonance happening for this molecule. (Fig. 3)

HOMO and LUMO reflect the greatest occupied and the least unoccupied molecular orbitals, respectively. The HOMO and LUMO energy difference has been characterized as the HOMO-LUMO gap. These two concepts are occasionally introduced as frontier orbitals. Single molecular orbitals possess an estimated level of energy, used for molecular orbital (MO) sorting. Electrons are assumed to take up the lowest energy level of molecular orbitals initially. For instance, when molecules have sufficient electrons to occupy 15 molecular orbitals, the 15 ones which have the lowest levels of energy would be selected first. The molecular orbitals at the 15th and 16th levels of the list represent "highest occupied molecular orbital" (HOMO) and "lowest unoccupied molecular orbital" (LUMO), respectively. The energy difference between these two can be described as the band gap, which occasionally serves as criterion of molecule excitability. Accordingly, more minor energy levels would lead to easier excitation of the electrons, possibly facilitating the prediction of the luminescence characteristics of a substance. The HOMO energy reflects molecule capability of electron donation; therefore, the probability of electron donation by the molecule increases at higher values of E_{HOMO}. The LUMO energy reflects the molecule's capability to accept electrons, and consequently, the likelihood of electron acceptance by the molecule increases at lower values of E_{LUMO}. The gap in the molecule HOMO and LUMO energy levels is of great importance since it acts as a function of the molecule's reactivity. Ionization potential can be a substantial description of atom and molecule chemical reactivity; higher IP is associated with increased stability. More significant energy gaps are observed in hard molecules. Soft molecules demonstrate higher re-

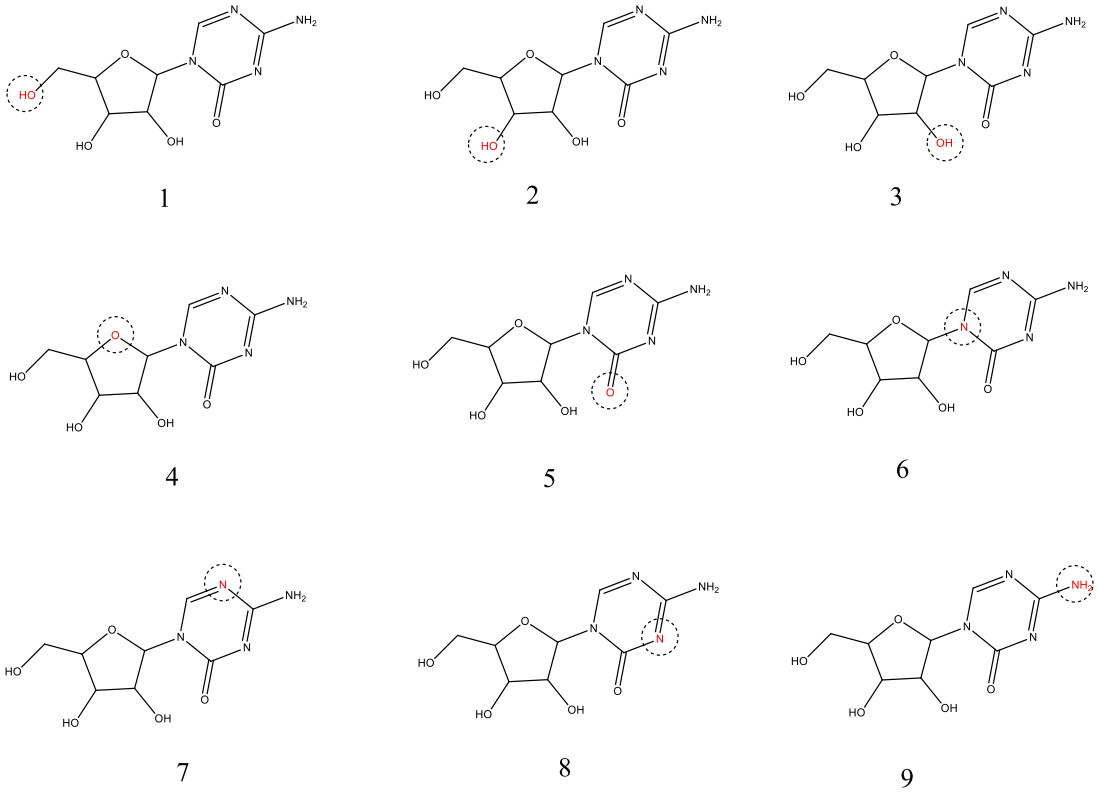

Fig. 2. Different active places in Azacitidine

activity compared to hard molecules because of offering electrons readily to those accepting them. It is possible to describe the molecule's capability to accept electrons using the electrophilicity index (Fig. 4). The HOMO energy is provided for weak electrons for their chemical reaction engagement. Considering the Azacitidine HOMO energy, excellent engagement is shown by it in chemical reactions, leading to the tendency to donate electrons donator because electronegative atoms (O, N) present Azacitidine chemical structure. Table 1 indicates data related to Azacitidine frontier (HOMO and LUMO) orbitals.

Dipole momentum introduces the compound's polarity into the reaction media. As shown in the first table, the Azacitidine dipole momentum is 2.56705 D for the gas phase. Polar impacts are associated with electronegative atoms in the chemical structure of (N and O atoms) related to Azacitidine. Furthermore, thermodynamic properties including Gibbs free energy (-2354.94 kJ), enthalpy (-2354.80 kJ), entropy (+495.49 J/mol-kelvin) as well as heat capacity (226.74 J/mol-kelvin)) of the compound were calculated. (Table 1)

Fig. 5 indicates all Azacitidine's active positions for the C60 adoption. Equal participation chances are provided by different C60 positions for chemical reactions because it has an Ih symmetric structure (Fig. 6), leading to no differences in reactions. Fig. 6 indicates the primary and optimized structures of Buckyball.

The capability of doing work and supplying heat is defined as energy. On the other hand, chemical energy potential is, by definition, any energy saved within the chemical bonds, playing an essential role in thermodynamic features and applicable to various fields of materials sciences, such as chemistry, physics, biology, and chemical engineering. It is possible to use chemical potential for the thermodynamic parameter computation related to different materials at specific pressures and temperatures. Additionally, the stability of substances, chemical compounds, and solutions can be determined using chemical potential and considering constant pressure and temperature. Azacitidine had a chemical potential (μ) of -3.49 eV, confirming that it is stable in the gas phase. The energy hidden in Azacitidine chemical bonds is reflected in the

Table 1. Azacitidine energy data and dipole momentum with B3LYP/6-311+G(d, p)

Parameters	Values
Energy	-2355.48 kJ
Gibbs free energy	-2354.94 kJ
Enthalpy	-2354.80 kJ
Entropy	495.49 J/mol-kelvin
Heat Capacity (Cv)	226.74 J/mol-kelvin
Dipole moment	2.56705 D
HOMO	-10.00 eV
LUMO	3.02 eV

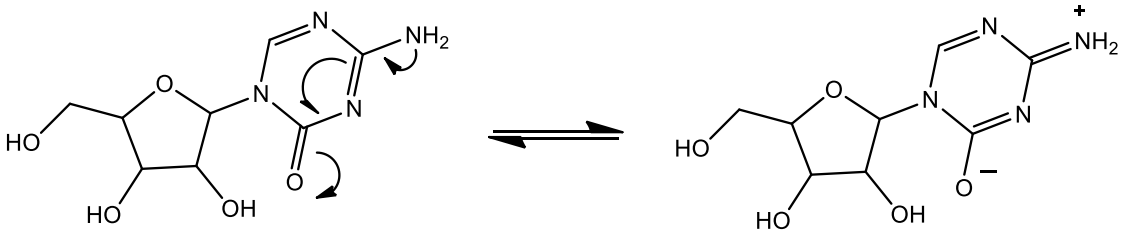

Fig. 3. Resonance in Azacitidine

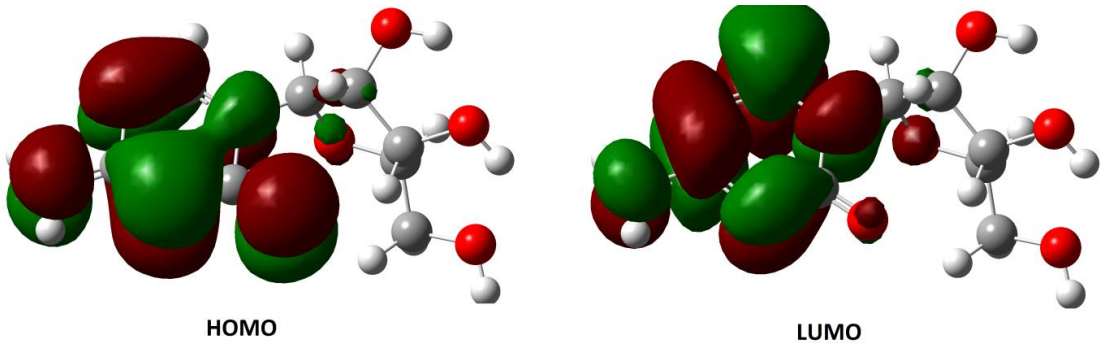

Fig. 4. The HOMO and LUMO for Azacitidine

Table 2. Azacitidine electronic parameters in the gas phase with B3LYP/6-311+G(d, p)

Parameter	IP (eV)	EA (eV)	μ (eV)	χ (eV)	η (eV)	σ (eV)	ω (eV)
value	10.00	-3.02	-3.49	3.49	6.51	0.15	0.93

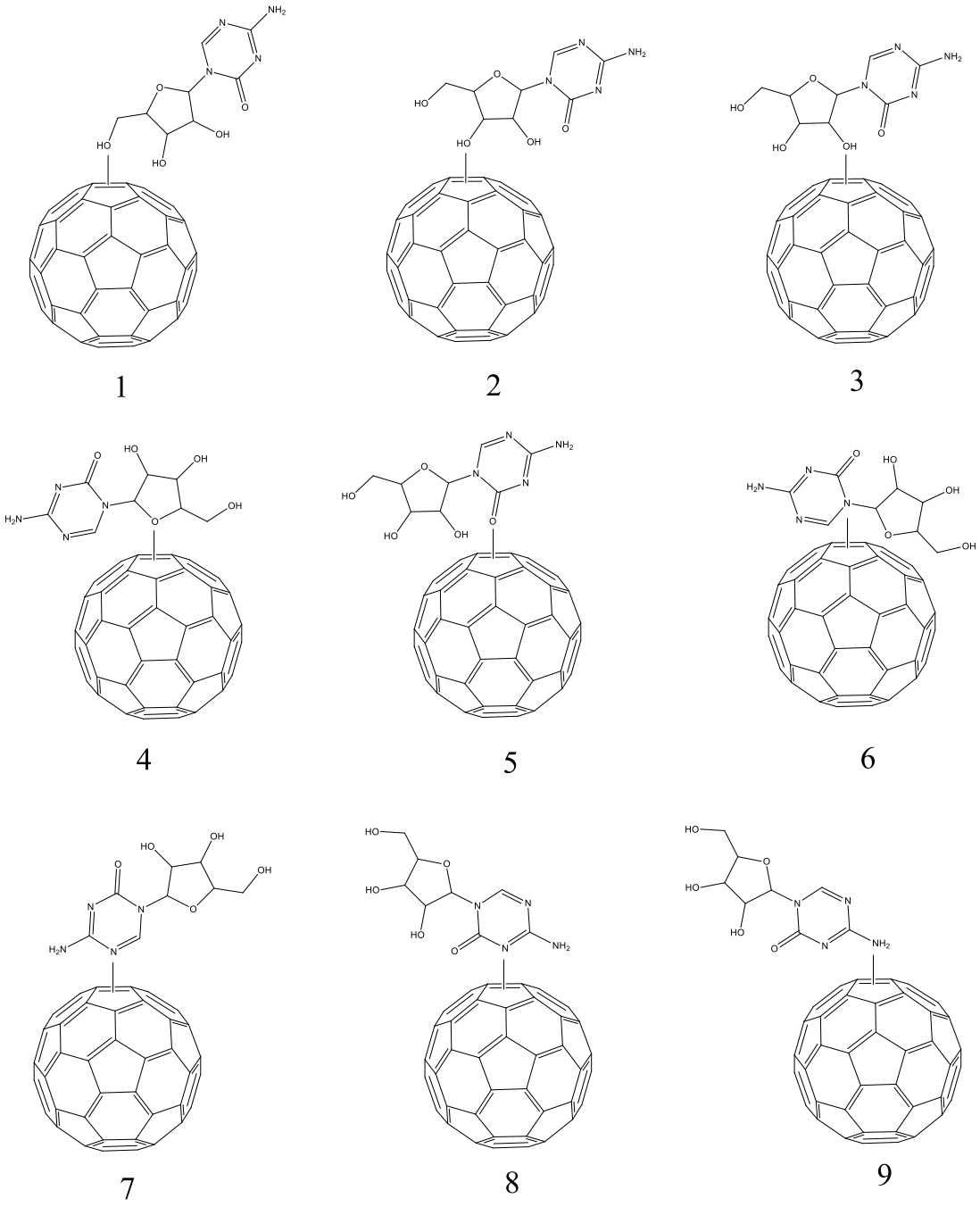

Fig. 5. Complexes of Azacitidine-C60 within various positions (9) of active sides

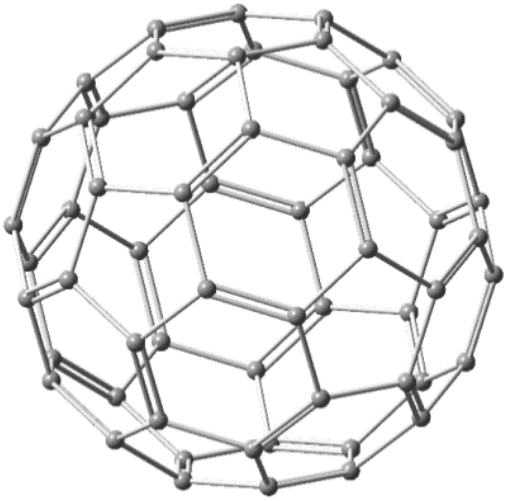

Fig. 6. C60(ih) optimized structure with B3LYP/6-311+G(d, p) E(-837.33 kJ)

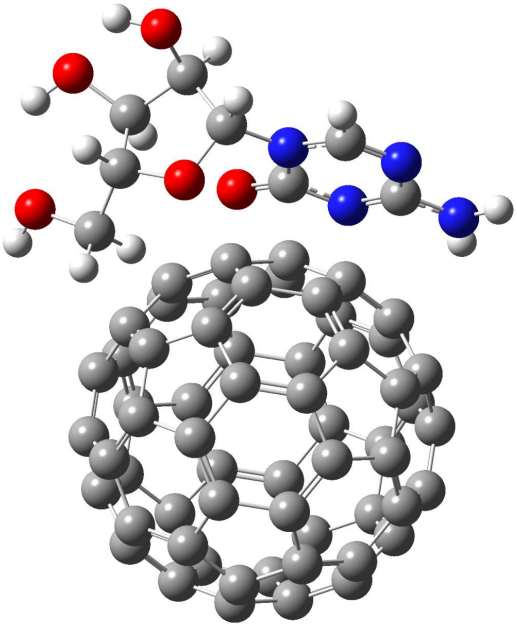

Fig. 7. The output of Azacitidine-C60 complex

negative energy.

Energy is produced when the energy is lost or gained by the atoms during chemical reactions. Energy is released and absorbed by exothermic and endothermic reactions, respectively. Negative energy is produced by the exothermic reactions, subsequently leading to a negative sign, while the second reaction leads to positive energy and a subsequent positive sign. The electro addition to neutral atoms, indicating the first electron affinity (EA), releases energy and brings about the negative charge. In contrast, adding electrons to negative ions with the second EA requires more energy, leading to the second electron's positive affinity due to overwhelming energy release from the process of electron attachment.

Table 2 shows Azacitidine reactivity parameters in the gas phase. Hence, Azacitidine had significant stability and reactivity within chemical reactions. The adoption of Azacitidine took place on C60. Table 3 shows the energy associated with the complexes shown in Fig. 5. Since the positions of different Azacitidine parts (various orientations for each active position) have other chemical spaces and dihedral angles, it can affect the composition energy and the adsorption product generation as a complex. The comparison between 9 different complexes of Azacitidine with C60 indicates that complex 5 is more stable than the others. This stability is due to the resonance in Azacitidine (Fig. 3), which makes the oxygen of the carbonyl group more negatively charged. This negative charge in Azacitidine helps to act as a better nucleophile and lets it react with C60 more easily. Fig. 7 shows the optimized structure related to complex 5.

Azacitidine behaves positively concerning EA energy. It means that Azacitidine is willing toward electron donation instead of electron acceptance. The molecule reactivity parameters, including electronegativity (χ), softness (σ), hardness (η), and electrophilicity index (ω), were extracted using the Koopman theory and the DFT technique. The ob-

Table 3. Energy in Azacitidine-C60 complexes

Az-C60 complexes	E(kJ/mol)	ΔE(KJ)
1	-8273.392	-5179.579
2	-8265.122	-5171.309
3	-8171.309	-5077.496
4	-8255.187	-5161.374
5	-8287.474	-5193.661
6	-8246.104	-5152.291
7	-8250.284	-5156.471
8	-8237.280	-5143.467
9	-8223.159	-5129.346

Table 4. Chemical parameters of Azacitidine, C60, and Az_C60

Molecular parameters	Azacitidine	C60	Az-C60
E HOMO	-0.36760	-0.3a0608	-0.29988
E LUMO	0.11109	-0.02320	-0.01847
ΔE HOMO-LUMO	0.47869	0.28288	0.28141
Ionization energy (IP)	0.3676	0.30608	0.29988
Electron affinity (EA)	-0.11109	0.0232	0.01847
Electronegativity (χ)	0.128255	0.16464	0.159175
Chemical potential (μ)	-0.128255	-0.16464	-0.159175
Chemical softness (s)	4.178069314	7.070135747	7.107067979
Chemical hardness (η)	0.239345	0.14144	0.140705
Global electrophilicitiyindex (ω)	0.001968534	0.00191696	0.001782499

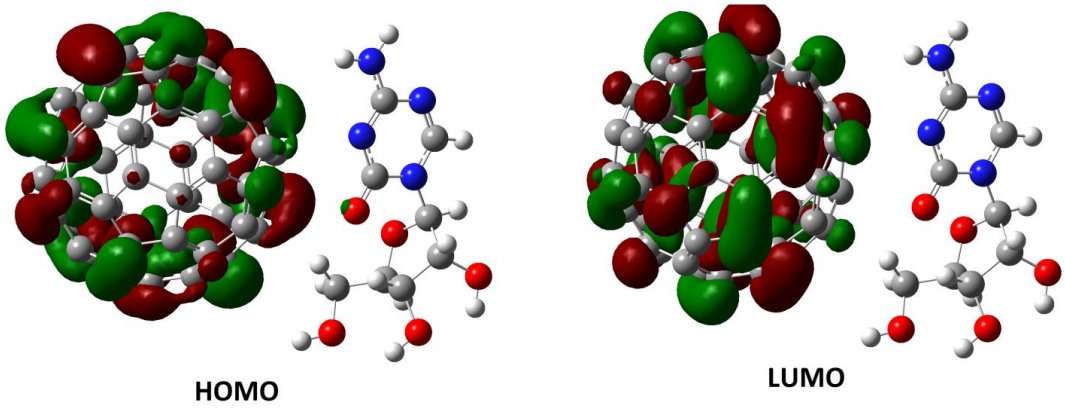

Fig. 8. The HOMO and LUMO for Azacitidine-C60 Complex

tained electronegativity (χ) values show the atom or molecule's power attraction as shown by HOMO and LUMO (Fig. 8). The symbols η and σ indicate the stability and reactivity status of chemical molecules and their potential for electron acceptance, respectively. Table 4 shows the molecule reactivity parameters for Azacitidine, C60, and Az-C60 (complex no. 5). The values of Chemical potential (μ) and ΔE for Azacitidine and Az_C60 (complex no. 5) illustrate that when Azacitidine makes a complex with C60, these two parameters become fewer in comparison to Azacitidine, indicating more reactivity for the complex.

CONCLUSION

The chemical reactivity and adoption of Azacitidine on Buckyball (C60) were investigated in the current study considering DFT B3LYP/6-311+G(d, p) in the gas phase. Azacitidine was active concerning the chemical structure and electronic parameters, enabling it to adobe on C60 and become stable. The chemical structure consists of the dipolar moment (μ=2.56705), for which thermodynamic characteristics (Gibbs free energy (G= 2354.94 kJ), Enthalpy (H= -2354.80 kJ), Entropy (+495.49 J/mol-kelvin), and thermodynamic capacity (226.74 J/mol-kelvin), along with electronic parameters, including (σ(0.15), μ(-3.49), ω(0.93), χ(3.49), and η(6.51) all data in eV) were calculated to justify the compound's chemical behaviors effectively. According to the estimations conducted for stability and reactivity by HOMO (-10.00 eV) and LUMO(3.02 eV), Azacitidine had nine sites with chemical activities, all being thermodynamically stable and the fifth structure being the most stable. As demonstrated by the collected data, HOMO

and LUMO values were -8.16 eV and -0.50 eV, respectively, for the Azacitidine complex on C60, as shown in structure 5, with the complex band gap reaching 7.66 eV. Accordingly, Azacitidine was adsorbed quite well on C60.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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