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RESEARCH PAPER

Adsorption of melphalan anticancer drug on the surface of fullerene (C_{24}): a comprehensive DFT study

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ABSTRACT

Objective (s): The present study aimed to assess the adsorption of fullerene C_{24} with Melphalan anticancer agent in a solvent phase (water) at the B3LYP/6-31G (d) theoretical level.

Materials and Methods: Initially, the structures of Melphalan and fullerene complexes were optimized in four configurations. Afterwards, IR calculations and molecular orbital analysis were performed. In addition, some important parameters were assessed, including 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.

Results: According to the results, Gibbs free energy changes (ΔG_{ad}), enthalpy (ΔH_{ad}) variations, III-Isomer, and IV-Isomer were negatives at various temperatures, while for I-Isomer and II-Isomer were positives throughout the temperature range of 298.15-310.15 K.

Conclusion: Since according to the obtained results for adsorption of Melphalan on the C_{24} in , III-Isomer, and IV-Isomer were spontaneous at various temperatures, while I-Isomer and II-Isomer were not spontaneous throughout the temperature range of 298.15-310.15 K.

Conclusion: Since the adsorption of Melphalan with fullerene C_{24} is spontaneous. Moreover, the effects of temperature on thermodynamic parameters were investigated, and the calculated specific heat capacity values indicated that C_{24} could be utilized as a sensing material in the construction of thermal biosensors for Melphalan determination.

Keywords: *Anticancer Drug, Adsorption, Density Functional Theory, Drug Delivery, Fullerene (C24), Melphalan*

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INTRODUCTION

Use of various nanostructures as drug carriers has been on the rise. Conventional drugs (e.g., oral medicines and injection) are easily distributed throughout the body, affecting various systems and leading to the manifestation of the side-effects [1-5]. To achieve a particular effect, it is necessary to consume higher doses of a drug. Nanotechnology has made it possible to use targeted medications and control the time, place, and speed of drug release in the body. New targeted systems have fewer side effects, higher effectiveness, and better convenience. Since drugs are used for their therapeutic effects, proper protection is essential until the consumed drug reaches the target site in order to preserve the chemical and biological properties. Some drugs (e.g., anticancer drugs) are highly toxic and may cause adverse side-effects. If these agents are destroyed during release, their therapeutic effects diminish significantly. For instance, chemotropic drugs are partly toxic, and their increased dose may have irreversible effects and even lead to death [6-10].

In other words, if the drug is able to reach the target tissue directly, it does not affect the other parts of the body and could be remarkably more effective.

The nanoparticles used to transfer drugs have various structures, different sizes, shapes, and materials. In addition, every drug differs in terms of loading capacity, secretion, cellular targeting, and stability. Spherical fullerenes are known as 'Bucky Ball' and are similar to a soccer ball. Drugs are placed inside these structures, and antibodies or ligands could be placed on their surface [11-16].

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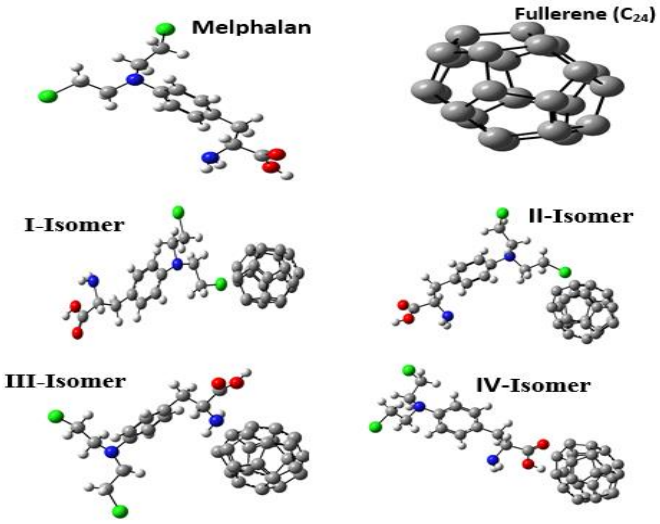

Fig 1. Structure of Melphalan, Fullerene (C24), and Melphalan Derivatives with C24 at Four Configurations

By locating specific ligands on the surface of fullerenes, they could attach to specific cell receptors, thereby targeting the drug delivery to a specific cell. In general, the goal of the surface optimization of fullerene nanoparticles is to increase the possibility of drug delivery to tumor cells and minimize drug side-effects. Use of chemicals in the treatment of cancer dates back to World War II, when nitrogen mustards and their derivatives were reported to have anti-tumor properties. Alkaline or pseudo-alkaline agents have been named as such since they are able to pair the alkaline group with a large number of electronegative groups in the cellular environment and create links between these groups. Alkylating drugs also attach a C_nH_{2n+1} alkyl group to the DNA [17-18]. Such example is Melphalan, which acts through the chemical change in the cellular DNA. The alkyl group often binds two DNA strands through guanine-nitrogen-7, thereby preventing DNA replication. Melphalan is an alkylating agent that eliminates the division of tumor cells and is used in the treatment of specific cancers, including multiple myeloma, ovarian cancer, and breast cancer. Melphalan is an anticancer drug that prevents the growth and spread of cancer cells in the body. This drug is also known as phenylalanine mustard and phenylalanine. Melphalan has been reported to exhibit beneficial therapeutic effects. However, its major disadvantage is nephrotoxicity, with nausea and vomiting as another side-effect. Use of fullerene as a drug delivery system has been proposed to overcome the mentioned complications. Fullerene has emerged as a promising candidate for drug delivery applications [19-21]. Some of the notable features of fullerene include solubilizing properties, high thermal stability, and good solubility in biological fluids [22]. According to a report by Isaacs et al., alkylating agents could be effectively solubilized using supramolecular solubilizing agents, which are highly versatile in the binding of several molecules of biomedical relevance. Therefore, drug delivery plays a pivotal role in promoting the safety of Melphalan. In order to estimate the capability of fullerene as a nano drug carrier for Melphalan, the effects of this nanostructure on the chemical properties of the drug should be investigated prior to administration [23]. The present study is the first to assess the effects of fullerene adsorption on the properties of Melphalan in a computational manner. The chemical structure of Melphalan is depicted in Fig 1.

Computational methods

Initially, the structures of Melphalan, fullerene C_{24}, and the derivatives of the cited nanostructure reaction with Melphalan were determined in four modes using the Gauss View 6.1 and Spartan software [24]. At the next stage, geometric optimization calculations, IR, and molecular orbitals were performed on the mentioned structures based on the density functional theory (DFT) and base series 6-31G (d) [24], with hybrid

B3LYP functions [24]. This basic series was selected as in previous reports, the results of which were consistent with the obtained experimental data. All the calculations were performed using the Spartan software within the temperature range of 298.15-310.15 K (from 1˚to 1˚). Moreover, some of the structural properties of Melphalan and its fullerene derivatives were investigated, including the highest occupied molecule orbital (HOMO)-the lowest unoccupied molecular orbital (LUMO) gap, chemical hardness (η), chemical potential (μ), electrophilicity (ω), and ΔN_{max}. In chemistry, HOMO and LUMO are molecular orbitals, and the energy difference between them is referred to as the HOMO-LUMO gap (HLG). HOMO is the highest occupied molecular orbital, and LUMO is the lowest unoccupied molecular orbital. HLG could be acquired using Equation 1. In Equation 2, *η* shows chemical hardness, which was calculated based on the mentioned formula. The electrophilicity Index (ω) [24] in atomic units is a measure of the electrophilic power of a molecule, which was determined using Equation 3. The maximum electronic charge index (ΔN_{max}) [24] describes the charge capacity of the molecule that is accepted by the electrophilicity system and could be calculated using Equation 4 [24, 25].

$HLG=E_{LUMO} - E_{HOMO}$	Equation	(1)
$\eta = (E_{LUMO} - E_{HOMO})/2$	Equation	(2)
$\omega = \mu^2/2\eta$	Equation	(3)
$\Delta N_{max}=- \mu/ \eta$	Equation	(4)

In the present study, the reactions were calculated using Equation 5, as follows:

Melphalan + C_{24}→ Melphalan -C_{24} *Equation (5)*

RESULTS AND DISCUSSION

Evaluation of the structural properties

As can be seen in Fig 1, Melphalan was located in four positions alongside the fullerene, and I-Isomer, II-Isomer, III-Isomer, and IV-Isomer have been presented as well. According to the information in Table 1, the density of Melphalan increased after pure adsorption with fullerene C_{24}. Other structural features also increased significantly after adsorption with fullerene, including the level and zero-point energy. In addition, the length of the bond and degree of orbital *p* participation were examined. In the I-Isomer and II-Isomer, they were longer and higher compared to the position of NH_2-C_{24}; in other words, the bond length was looser and more breakable comparatively. Since the position of NH_2-C_{24} in III-Isomer had a lower rate of orbital *p* participation compared to the other situations, it had a shorter bond and better adsorption comparatively (Table 1).

Calculation and analysis of the wnthalpy change values

The adsorption of the fullerene C_{24} reaction with Melphalan was used to derive the amount of enthalpy for the C_{24} adsorption process using Equation 6. The enthalpy values were obtained using the Spartan software. Additionally, the enthalpy of the adsorption was calculated at the B3LYP/6-31G level for Melphalan derivatives with fullerene, which was negative throughout the temperature range of 298.15-310.15 K. However, it was observed to be positive in I-Isomer and II-Isomer throughout the temperature range of 298.15-310.15 K (Table 2). The negative ΔH_{ad} indicated that III-Isomer and IV-Isomer were an exothermic reaction within the temperature range of 298.15-310.15 K. However, I-Isomer and II-Isomer were endothermic throughout the temperature range of 298.15-310.15 K. $\Delta H_{ad} = H_{th\ (Melphalan- C24)} – (H_{th\ (Melphalan)} + H_{th\ (C24)})$ Equation (6)

Effect of temperature on the fullerene substituent process

The thermodynamic parameters were calculated within the temperature range of 298.15-310.15 K (from 1˚to 1˚), and the obtained values were recorded. According to the information in Table 2, the temperature of the enthalpy changes gradually increased at higher temperatures. As a result, the formation process of the desired compounds became warmer at higher temperatures, and the optimal temperature for the synthesis of all the derivatives was estimated at 298.15 K.

Calculation and investigation of gibbs free energy changes and adsorption energy values of melphalan derivatives with fullerene C_{24}

Equation 7 was used to calculate the Gibbs free energy variation (ΔG_{ad}), where G_{th} showed the thermal energy released by the Gibbs based on the software calculations for each component of the reaction (Table 3). According to the obtained results, Melphalan, III-Isomer, and IV-Isomer were spontaneous at various temperatures, while

I-Isomer and II-Isomer were not spontaneous throughout the temperature range of 298.15-310.15 K.$\Delta G_{ad} = G_{th\ (Melphalan-\ C24)} - (G_{th\ (Melphalan)} + G_{th\ (C24)})$ Equation (7)

Adsorption energy is an appropriate parameter for the evaluation of the stability and mechanism of the adsorption process. In Equation 8, E_{ad} represented the adsorption energy of the optimized structures of fullerene, a drug molecule, and fullerene-drug derivative, respectively.

The obtained adsorption energy values are presented in Table 3. According to the information in this table, there was a strong interaction with fullerene since the adsorption energies were highly negative in the III-Isomer and IV-Isomer. It seems that the adsorption of the cited drug on the fullerene surface is exothermic.

On the other hand, the adsorption energy values of the other isomers were positive.

Therefore, it could be inferred that these isomers had no interaction with fullerene, and their adsorption process on the fullerene surface was endothermic and probably impossible experimentally.

Calculation and determining the specific heat capacity (C_V)

The specific heat capacity (C_V) values were obtained using the calculation by the Spartan software at the B3LYP/6-31G* level for the Melphalan derivatives with fullerene.

According to the information in Table 4, there

Table 1. Adsorption Energy, Minimum Frequency, Zero-point Energy, Density, Weight, and Bond Length of Melphalan and Its Derivatives with Fullerene C_{24}

	Melphalan	I-Isomer	II-Isomer	III-Isomer	IV-Isomer
Adsorption Energy (KJ/mol)	-	-2014.04	-2014.10	-3054.97	-2556.11
Area ($Å^2$)	305.99	488.49	488.53	503.08	506.37
Weight (amu)	307.21	559.02	559.02	559.02	559.02
Volume ($Å^3$)	281.61	521.24	520.95	536.24	536.97
Density (amu/$Å^3$)	1.09	1.07	1.07	1.11	1.11
Minimum Frequency (cm^{-1})	15.20	8.15	8.60	8.58	4.15
Bond Length (Å)	---	1.55	1.55	1.43	1.48
Orbital *p* Participation	---	2.92	2.94	2.19	2.83

Table 2. Values of Changes in Adsorption Enthalpy for Melphalan Adsorption in Temperature Range of 298.15-310.15 K

	ΔH_{ad} (KJ/mol)			
Temperature (K)	I-Isomer	II-Isomer	III-Isomer	IV-Isomer
298.15	2938.61	2399.88	-3093.08	-2411.60
299.15	2938.63	2399.91	-3093.10	-2411.63
300.15	2938.65	2399.94	-3093.13	-2411.65
301.15	2938.67	2399.96	-3093.15	-2411.68
302.15	2938.69	2399.99	-3093.18	-2411.71
303.15	2938.71	2400.02	-3093.21	-2411.74
304.15	2938.73	2400.05	-3093.23	-2411.77
305.15	2938.75	2400.07	-3093.26	-2411.80
306.15	2938.77	2400.10	-3093.29	-2411.82
307.15	2938.79	2400.13	-3093.31	-2411.85
308.15	2938.82	2400.16	-3093.34	-2411.88
309.15	2938.84	2400.19	-3093.36	-2411.91
310.15	2938.86	2400.22	-3093.08	-2411.94

was a tangible gap between the specific heat capacity values of Melphalan and the investigated isomers. Moreover, after the adsorption of Melphalan, a significant increase was observed in the C_V values of the evaluated isomers. The CV also had a direct correlation with thermal conductivity [25].

The thermal conductance of fullerene and Melphalan improved after the adsorption of Melphalan. A significant variation in the thermal conductivity of the sensing material plays a key role in the sensitivity of the designed analytical method in the development of thermal biosensors. Therefore, it could be concluded that Melphalan derivatives are a promising sensing material for the construction of thermal biosensors for the detection of Melphalan.

Considering that the previous findings in this regard have confirmed the interactions of Melphalan and its derivatives are exothermic, the heat production that is required for the appropriate function of these sensors was implemented spontaneously in the adsorption of Melphalan on fullerene.

The impact of the changes in the temperature on the specific heat capacity was also assessed in this study. According to the findings, the C_V value of each isomer increased by incrementing the temperature; therefore, it could be concluded that thermal conductivity ameliorated at higher temperatures, while drug sensitivity decreased with temperature. By increasing the specific heat capacity of Melphalan derivatives, drug sensitivity reduced depending on temperature, not decomposing by heat.

Analysis of the calculations of molecular orbitals

The most important frontier molecule orbital cells (e.g., HOMO and LUMO) play a pivotal role in the chemical stability of molecules [26]. HOMO shows the ability to give electrons, and LUMO shows the ability to accept electrons. The energy gap between HOMO and LUMO determines the reactivity, polarization, and hardness/softness of a molecule.

It is often represented by the HLG abbreviation and was calculated using Equation 1, where *EH* and *EL* show the energy of the HOMO and LUMO orbitals. The energy gap is directly correlated with the molecular electrical conductivity [27].

In fact, the compounds with small energy gaps could easily pass electrons from the barrier to the conductive strip, which means that the materials with fewer energy bands have higher electrical

Table 3. Values of Changes in Gibbs free energy Adsorption for Melphalan Adsorption in Temperature Range of 298.15-310.15 K

	ΔG_{ad} (KJ/mol)			
Temperature (K)	I-Isomer	II-Isomer	III-Isomer	IV-Isomer
298.15	2880.07	2338.91	-3049.03	-2381.60
299.15	2879.91	2338.91	-3048.81	-2381.63
300.15	2879.74	2338.91	-3048.58	-2381.65
301.15	2879.57	2338.91	-3048.36	-2381.68
302.15	2879.41	2338.91	-3048.14	-2381.71
303.15	2879.24	2338.91	-3047.91	-2381.74
304.15	2879.08	2338.91	-3047.69	-2381.77
305.15	2878.91	2338.91	-3047.46	-2381.80
306.15	2878.75	2338.91	-3047.23	-2381.82
307.15	2878.58	2338.91	-3047.00	-2381.85
308.15	2878.41	2338.91	-3046.77	-2381.88
309.15	2878.24	2338.91	-3046.55	-2381.91
310.15	2878.07	2338.91	-3046.32	-2381.94

$$Ead = E_{Melphalan\text{-}adsorbent} - (E_{Melphalan} + E_{adsorbent}) \quad \text{Equation (8)}$$

conductivity compared to the molecules with higher energy bands [28-30]. According to the information in Table 5, increased HLG gradually decreased conductivity. Furthermore, the energy gap values of all the inspected drugs reduced significantly after the adsorption process on the fullerene surface.

In fact, a drastic surge was observed in the conductivity and reactivity of the system after the adsorption of the drug on the fullerene surface. Chemical hardness (η) was another investigated parameter, the value of which could be obtained using Equation 2.

Chemical hardness is a good measure to estimate the reactivity of a new compound since the molecules that are structurally softer and have lower chemical hardness could easily change their electron density [31]. As a result, the essential electronic transmissions to chemical reactions are better and easier to use in soft compounds.

According to the data provided in the tables, Melphalan reaction reduced after the reaction with fullerene since all the derivatives obtained from fullerene had higher chemical hardness compared to the pure drug.

Chemical potential (μ) was also used to calculate the remaining parameters using Equation 3.

In addition, electrophilicity (ω) and the maximum load transmitted to the system (ΔN_{max}) were considered to be suitable quantities, showing the tendency of a compound to absorb electrons [32]; these parameters were calculated using Equations 4 and 5, respectively.

When two molecules react, one acts as an electrophile, and the other acts as a nucleophile, and the compound with higher electrophilicity and charge capacity tends to act as an electron receptor [33]. On the other hand, a molecule with low electrophilicity and capacity tends to accept the electron system. As is presented in the tables, the electrophilicity of Melphalan decreased significantly after fullerene binding. Therefore, it could be concluded that the tendency of Melphalan to absorb electrons decreased [34].

Polarity of the molecules

The dipole moment is a key factor that is directly correlated with solubility.

As such, compounds with higher dipole moments have better solubility [35]. In the present study, the solubility of the drug in the polar solvents improved after adsorption with fullerene due to the significant rise in the dipole moment value after adsorption to the fullerene surface. Moreover, the conductivity and reactivity of the drugs could enhance by increasing the dipole moment. However, in the case of III-Isomer, this led to decreased solubility, which implies that this

Table 4. Values of Changes in Specific Heat Capacity (CV) Adsorption for Melphalan Adsorption in Temperature Range of 298.15-310.15 K

	C_V (J/mol)				
Temperature (K)	Melphalan	I-Isomer	II-Isomer	III-Isomer	IV-Isomer
298.15	314.6873	430.3404	425.5995	436.1951	437.3482
299.15	315.3913	431.868	427.1392	437.7501	438.8901
300.15	316.0958	433.3957	428.6791	439.3052	440.4321
301.15	316.8008	434.9236	430.219	440.8605	441.9743
302.15	317.5063	436.4516	431.7591	442.4158	443.5167
303.15	318.2123	437.9796	433.2992	443.9712	445.0592
304.15	318.9188	439.5078	434.8394	445.5266	446.6018
305.15	319.6258	441.036	436.3796	447.0821	448.1444
306.15	320.3332	442.5642	437.9198	448.6375	449.6872
307.15	321.0411	444.0924	439.4600	450.1928	451.2299
308.15	321.7494	445.6206	441.0001	451.7481	452.7727
309.15	322.4581	447.1487	442.5402	453.3033	454.3154
310.15	323.1673	448.6768	444.0802	454.8583	455.8581

Table 5. Calculated EH and EL, Band Gap (HLG), Chemical Hardness, Electrophilicity Index (ω), Maximum Electronic Charge Index (ΔN_{max}), and Dipole Moment for Melphalan Adsorption Process

	E_H (eV)	E_L (eV)	HLG (eV)	η (eV)	μ (eV)	ω (eV)	ΔN_{max} (eV)	Dipole moment (debye)
Melphalan	-6.47	7.00	13.47	6.74	0.27	0.01	-0.04	5.98
I-Isomer	-4.55	2.67	7.22	3.61	-0.94	0.12	0.26	4.88
II-Isomer	-4.89	3.6	8.49	4.25	-0.65	0.05	0.15	3.53
III-Isomer	-5.05	3.45	8.50	4.25	-0.8	0.08	0.19	3.09
IV-Isomer	-5.18	3.32	8.50	4.25	-0.93	0.10	0.22	3.24

isomer had extremely poor water solubility [36].

CONCLUSION

According to the evaluation of the thermodynamic parameters. Melphalan drug reaction with fullerene C_{24} was exothermic, spontaneous, one-way, and non-equilibrium. In addition, the reaction had the highest efficacy at room temperature. Molecular orbit analysis also confirmed that fullerene derivatives had higher conductivity, electrophilicity, and reactivity compared to pure Melphalan. As proposed in theoretical studies, the reaction of fullerene with Melphalan is empirically possible. Therefore, the empirical investigation of the synthesis of these derivatives by the experts in this field is strongly recommended.

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