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ORIGINAL ARTICLE

Cycloaddition [2+2] interaction of some Corticosteroid drugs with C_{60} nano fullerene: A theoretical study

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Abstract

In this work, the quantum mechanics calculations were carried out to elucidate the adsorption behavior of some corticosteroid drugs (clobetasol, beclometasone, prednisolone, and methylprednisolone) on the surface of C60 nano-fullerene using density functional theory (DFT) at B3LYP/6-31G (d,p) level. After optimization of the structures, various parameters such as HOMO and LUMO energies, energy gap, adsorption energy, cohesive energy, chemical hardness, chemical potential, dipole moment, electrophilicity index and changes in the length of some bonds data were calculated. The results showed that the amounts of energy gap and chemical hardness are decreased with binding of corticosteroids to fullerene, while those of chemical potential and electrophilicity index are increased. It means that nanocarrier increases the drug reactivity. Also, binding and stabilization energies are increased. The C_{60}-Clobetasol, C60-Beclometasone, C_{60}-Prednisolone and C_{60}-Methylprednisolone presented the adsorption energy with the values of 54.3478, -6.5263, 45.1586, and 947.8854 KJ in gas phase, respectively. Moreover, the solubility of nanocarrier has increased in the water solvent compared to the gas phase. These results can be considered in pharmacy for these types of drugs and similar systems. The presence of oxygen atoms in the structure of drugs increases the ability of nano-fullerene as a drug carrier, because the ability of nitrogen atoms to protonation in acidic environment weakens their binding to fullerene in the target cell.

Keywords: *Adsorption Energy; Chemical Potential; Cohesive Energy; Density Functional Theory (DFT); Energy Gap.*

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INTRODUCTION

Corticosteroids are a group of steroidal hormones that are used as drugs in the treatment of many diseases, including neuromuscular disorders, inflammatory disorders, skin diseases, and the immune system, and even some cancers. The current study aimed to evaluate the effect of nano-fullerene C_{60} on the function of some of these drugs. These drugs include betamethasone, dexamethasone, hydrocortisone, triamcinolone, methylprednisolone, prednisone, clobetasol, beclometasone, fludrocortisone, fluocinolone, fluticasone, *etc* [1-4].

One of the methods for studying drugs is the use of Gaussian software and density functional theory (DFT). DFT is a computational method of quantum mechanics that is used in physics and chemistry to study the electronic ground state in multiple systems such as atoms, molecules, and dense phases. This theory expresses the characteristics of multi-electron systems by specific functions. For this reason, this theory is well-known as the functional density theory. Using a series of approximations in this theory has increased the accuracy of this method. The results of the DFT calculations are consistent with experimental results. This method can examine up to 500 atoms [5, 6].

Molecular interactions of the drugs are of importance in various processes of pharmacology, drug design, imaging, *etc*. Therefore, the

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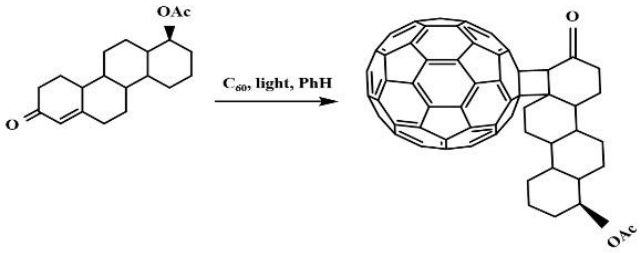


Fig. 1. The reaction of C_{60} and steroids.

interactions of drugs with the nanomaterials have been extensively studied [7-10]. Employing of the nanostructures as drug delivery carriers is one of the most mentioned items in this area [11-13]. Nanostructures can be considered as a very effective drug delivery system which can increase the drug efficiency due to the following reasons: biocompatibility; ability to slowly release of the drug in a controlled manner; protection of the drug's molecular structure; being smaller than the cell; increasing the drug's shelf life; reducing the dose required for the patient. Carbon nanostructures such as nanotubes, graphene, and fullerenes have received an extensive attention in pharmaceuticals science [14]. Due to the small size of these nanostructures, they can pass from the membranes easily and insert to the cell [15]. In recent years, attention to the computational chemistry has been increased in order to study the drug delivery systems. In fact, the development of drug delivery systems requires deeper studies containing more details [16-18]. In the recent years, fullerenes have become one of the nanostructures employed as a drug carrier. However, they have been less investigated by computational methods compared to the other nanomaterials [19, 20]. $C_{30}B_{15}N_{15}$ Hetero fullerene as a carrier of isoniazid drug and interaction of fullerene doped with 5-fluorouracil drug are some of the studies which have been reported by employing density functional theory (DFT) [21]. The drug must be protected from any chemical and enzymatic degradations before arriving to the target. Doping of the nanostructures with different functional groups is one of the common methods to increase its specific surface area. Therefore, some researchers have attempted to increase the charge capacity of drugs by doping of the nano materials. For example, Khodadadi *et al*. utilized nitrogen-doped graphene quantum dots to deliver methotroxate anticancer drug. Their results showed that the quantum dots of graphene doped with nitrogen improve the drug performance [22, 23]. Available data clearly shows that pristine C_{60} has no acute or sub-acute toxicity in a largevariety of living organisms, from bacteria and fungal to human leukocytes, and also in droso-phila, mice, rats and guinea pigs [24].

Fullerenes can easily participate in different cycloaddition reactions. These reactions often occur at room temperature. The fullerenes perform Diels-Alder reaction in the presence of the light by the method [2 + 2] more than the method [2 + 4]. Some different cycloaddition reactions [2 + 3] have also been reported that lead to a wide variety of products. The fullerene C_{60} reaction is performed with a steroid ketone easily. The reaction of C_{60} with steroids, (corticosteroids are from this family), is a type of cycloaddition [2 + 2] (Fig. 1) [25-27].

In this research, Gauss View software was used to design some corticosteroid drugs include clobetasol (**CLO.**), beclometasone (**BCL.**), prednisolone (**PRD.**), and methylprednisolone (**MPR.**), pristine C_{60}, and their complexes. The energies of the highest occupied and the lowest unoccupied molecular orbitals (HOMO & LUMO), energy gap (E_g) and quantum characteristics such as chemical potential (μ), chemical hardness (η), maximum charge transfer (ΔN_{max}), electrophilicity index (ω), *etc*. were calculated. [28-32].

COMPUTATIONAL METHODS

All structures were optimized by Gaussian 09 in theoretical level B3LYP/6-31G (d, p). For this purpose, Clobetasol, Beclometasone, Prednisolone and Methylprednisolone were attached to C_{60} fullerene (Figs. 2a, 2b, 2c, 2d). All complexes were also optimized at the same theoretical level in this work. The HOMO-LUMO values were also extracted from the Gaussian 09 output.

Adsorption energy ($E_{ads.}$) of CLO-, BCL-, PRD-,

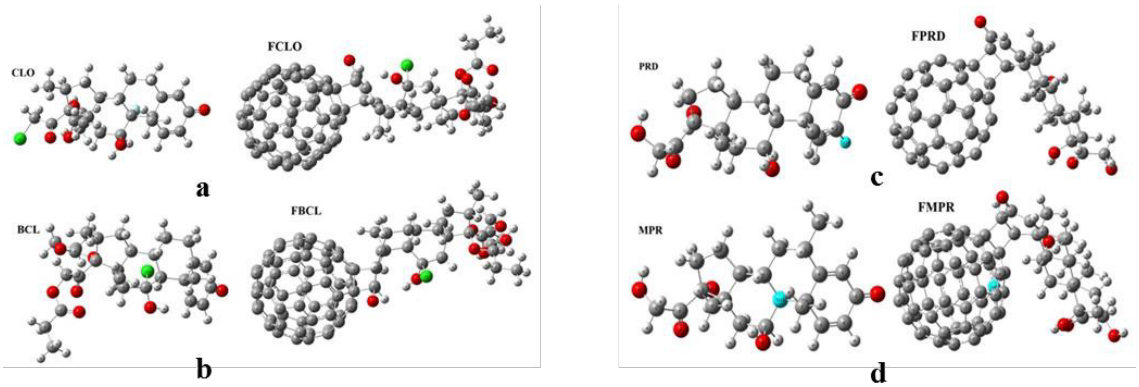


Fig. 2. Optimuzed structure of drugs and C_{60}-Drugs a) CLO, FCLO b) BCL, FBCL c) PRD, FPRD d) MPR, FMPR.

MPR- and C_{60} nano carriers was calculated using the following equation [33]:

$$E_{ads.} = \left[E_{C_{60}-R} \right] - \left[E_{C_{60}} + E_R \right] \quad (1)$$

Where E_R, $E_{C_{60}}$ and $E_{C_{60}-R}$ are energies of drugs, fullerene C_{60} and fullerene-drug complex, respectively.

Also, we calculated the cohesive energy (E_{coh}) of C_{60}-drug complexes. The stability of molecules can be defined with cohesive energy (or binding as well as formation energies) [34, 35]. E_{coh} could be calculated using the following formula.

$$E_{cho} = \left(E_{tot} - \sum_i n_i E_i \right) / j \quad (2)$$

Where E_{tot}, E_i, and n_i are the total energy of the drug-C_{60} complexes, the atomic energy and the number of atoms type *i* (*i* = C, H, O and Cl), respectively, and *j* is the total number of atoms present in the drug-C_{60} complexes. The cohesive energy values for **FCLO.**, **FBCL.**, **FPRD.**, and **FMPR.,** were calculated to be 344.12, -158.87, -164.57 and -163.19 kcal.mol^{-1}, respectively. It seems that the positive amount of cohesive energy in **FCLO.** is due to the presence of the electronegative F atom.

In order to evaluate the nanocarrier, drug and complex reactivity, quantum descriptors such as chemical potential (μ), global hardness (η) , electrophilicity index (ω), maximum charge transfer (ΔN_{max}), electronegativity (χ) and Fermi level (E_{FL}) were calculated. These indices were estimated through the following equations [36]:

$$E_g = E_{LUMO} - E_{HOMO} \quad (3)$$

$$\mu = -\frac{IP + EA}{2} \quad (4)$$

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

$$\omega = \frac{\mu^2}{2\eta} \quad (6)$$

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad (7)$$

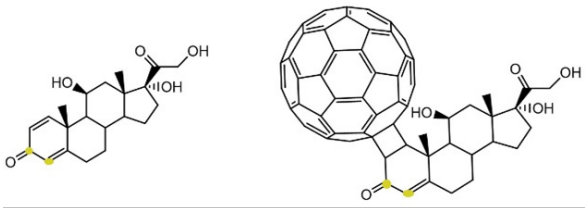
$$\chi = -\mu \quad (8)$$

$$E_{FL} = \frac{E_{LUMO} + E_{HOMO}}{2} \quad (9)$$

In these equations, E_{HOMO} and E_{LUMO} refer to the energies of HOMO and LUMO, respectively. IP and EA show the ionization and electron affinity energies. Also, the bond length, dipole moment and participation of s and p orbitals in drugs and drug-nanocarriers were calculated.

RESULTS AND DISCUSSION

In order to investigate the possibility of drug-fullerene reaction and the contribution of s and p orbitals in the carbon-carbon bond of drug molecules and drug-nanocarriers, it was selected a band on the drug and was measured its length before and after attach to fullerene (Fig. 3a, 3b). The results of bond length changes are presented in Table 1. As it is seen, attach drug to fullerene has reduced the intended bond length. This means that bond strength has increased. In other words, it has taken an acceptable interaction between drug



a **b**

Fig. 3. The band studied in a) drug (R) and b) drug- nanocarrier (C_{60}-R).

Table 1. The bond length (A^0) in drugs and drug-nanocarriers.

	CLO	FCLO	BCL	FBCL	PRD	FPRD	MPR	FMPR
Gas phase	1.46761	1.45949	1.46508	1.45631	1.46838	1.45925	1.46887	1.45973
Sol. phase	1.46213	1.45370	1.45964	1.45127	1.46183	1.45264	1.46234	1.45326

Table 2. The participation of s and p orbitals in drugs and drug-nanocarriers.

drugs	Bonds	The contribution of s and p orbitals
CLO	C_1-C_2	s(38.45%)+p(61.55%)C_1+s(37.96%)+p(62.04%)C_2
FCLO	C_1-C_2	s(24.30%)+p(75.70%)C_1+s(24.69%)+p(75.31%)C_2
BCL	C_1-C_2	s(37.79%)+p(62.21%)C_1+s(38.23%)+p(61.77%)C_2
FBCL	C_1-C_2	s(25.14%)+p(74.86%)C_1+s(24.33%)+p(75.67%)C_2
PRD	C_1-C_2	s(37.94%)+p(62.06%)C_1+s(37.86%)+p(62.14%)C_2
FPRD	C_1-C_2	s(24.12%)+p(75.88%)C_1+s(25.16%)+p(74.84%)C_2
MPR	C_1-C_2	s(38.10%)+p(61.86%)C_1+s(37.99%)+p(61.97%)C_2
FMPR	C_1-C_2	s(24.17%)+p(75.83%)C_1+s(25.14%)+p(74.86%)C_2

Table 3. Calculated total electronic energy (Hartree) and adsorption energy (KJ) of the derived products from the interaction between drugs molecules and fullerene in the temperature of 298K.

Drug	Total electronic energy (Hartree∗)		$E_{ads.}$ (KJ)
	R	$C_{60}-R$	$\left[E_{C_{60}-R}\right]-\left[E_{C_{60}}{}^{**}+E_R\right]$
Clobetasol	-1907.6416	-4193.2123	54.3478
Beclometasone	-2075.5266	-4361.1206	-6.8263
Prednisolone	-1192.8124	-3478.3868	45.1586
Methylprenisolone	-1232.4579	-3517.6890	947.8054

*Hartree=2625.49975 kJ/mol^{-1}
**$E_{C_{60}}$= -2285.5922 Hartree

and fullerene. The results (Table 2) show that the orbital share of s and p for C_1-C_2 bond in the single drug and the drug bound to C_{60} has significantly changed due to the conversion of double bond to a single bond. In other words, the hybridization of atoms C_1 and C_2 has changed from sp^2 to sp^3.

The dipole moment plays a key role in direct relation to solubility. The results (Table 4) exhibit that all the evaluated drugs and their fullerene derivatives have high dipole moment. The Clobetasol, Beclometasone, Prednisolone and Methylprednisolone drugs presented the dipole moment with the values of 5.9488, 7.2911, 7.6143, and 7.6618 Debye in gas phase and 8.3032, 11.4007, 11.1953 and 11.3471 Debye in solution phase (water), respectively. Eventually, the overall polarity and solubility in water for these drugs and nanocages-drugs will increase relative to gas phase. Since water forms a large percentage of the human body, increasing the dipole moment in the nano-carriers indicates an increase in the solubility of the nano-carrier foe the drug in the body [34].

Stability of the drug-nanocarrieres was evaluated by calculation of the adsorption energy (Table 3). Results show that when the drugs interact to C_{60}, adsorption energies will be positive (except

Table 4. Molecular orbitals energy and quantum descriptors (eV).

	phase	CLO	C_{60}-CLO	BCL	C_{60}-BCL	PRD	C_{60}-PRD	MPR	C_{60}-MPR
E_{HOMO}	gas	-6.3386	-5.8069	-6.3155	-5.8992	-6.3133	-5.8951	-6.2970	-7.2110
	sol.	-6.7520	-5.7628	-6.8581	-5.8260	-6.4273	-5.8129	-6.6652	-5.5118
E_{LUMO}	gas	-1.7007	-3.1892	-1.8547	-3.2616	-1.9677	-3.2610	-1.9576	-3.2580
	sol.	-1.9010	-3.1511	-2.0564	-3.1894	-1.7913	-3.1862	-1.7802	-3.1851
energy gap (E_g)	gas	4.6379	2.6177	4.4608	2.6376	4.3456	2.6341	4.3394	3.9530
	sol.	4.8510	2.6117	4.8017	2.6366	4.6360	2.6267	4.8850	2.3267
dipole moment (DM)	gas	5.9488	8.5066	7.2911	7.2206	7.6143	7.2815	7.6618	7.3611
	sol.	8.3032	11.3613	11.4007	11.0856	11.1953	11.0333	11.3471	11.1072
chemical potential (μ)	gas	-4.0196	-4.4980	-4.0851	-4.5804	-4.1405	-4.5780	-4.1273	-5.2345
	sol.	-4.3265	-4.4569	-4.4572	-4.5077	-4.1093	-4.4995	-4.2227	-4.3484
global hardness (η)	gas	2.3189	1.3088	2.2304	1.3188	2.1728	1.3170	2.1697	1.9765
	sol.	2.4255	1.3058	2.4008	1.3183	2.3318	1.3133	2.4425	1.1633
electrophilicity index (ω)	gas	3.4838	7.7292	3.7410	7.9542	3.9451	7.9568	3.9256	6.9314
	sol.	3.8587	7.6060	4.1375	7.7066	3.6209	7.7079	3.6501	8.1271
electronic charge index (ΔN_{max})	gas	1.7334	3.4367	1.8316	3.4732	1.9056	3.4761	1.9022	2.6484
	sol.	1.7838	3.4132	1.8565	3.4193	1.7623	3.4261	1.7288	3.7380
electronegativity (χ)	gas	4.0196	4.4980	4.0851	4.5804	4.1405	4.5780	4.1273	5.2345
	sol.	4.3265	4.4569	4.4572	4.5077	4.1093	4.4995	4.2227	4.3484
Fermi level (E_{FL})	gas	-4.0196	-4.4980	-4.0851	-4.5804	-4.1405	-4.5780	-4.1273	-5.2345
	sol.	-4.3265	-4.4569	-4.4572	-4.5077	-4.1093	-4.4995	-4.2227	-4.3484

C_{60}-BCL). Finally, negative adsorption energies of C_{60}-drug nano cages led to increasing in their stability. Since the amount of absorption energy is small, the adsorption type is physicaly. So there is no strong bond between fullerene and drug. On the other hand, the adsorption energy values of other drugs such as Clobetasol, Prednisolone and Methylprednisolone are extremely positive, thus, adsorption of these drugs is unstable on the nano fullerene. Therefore, adsorption of Beclometasone, Clobetasol, Prednisolone and Methylprednisolone on C_{60} can be considered as a drug delivery system [36].

LUMO is the lowest unoccupied molecular orbital and HOMO is the highest occupied molecular orbital. The values of these energy levels obtained from the NBO Gaussian output file information. Exploration of the HOMO-LUMO orbital images of the C_{60}-drugs showed that these orbitals are located on the fullerene ring (S1).

Energy gap (E_g) is a quantity that determines the reactivity of a molecule. When the E_g decreases, transferring of electron is easier between two levels of HOMO and LUMO, thus, reactivity increases. Significant decrease in E_g after attach drug to C_{60}, indicates that reactivity of drug increase after binding to C_{60}. According to Table 4, E_g of C_{60} is higher (2.87 eV) than C_{60}-drugs: C_{60}-CLO, C_{60}-BCL, C_{60}-PRD and C_{60}-MPR with values 2.61, 2.64, 2.63 and 2.33 eV in solution phase, respectively. On the other hands, E_g of **CLO.**, **BCL.**, **PRD.** and **MPR.** are equal to 4.85, 4.80, 4.64 and 4.88 eV. Fermi levels (E_{FL}) for drugs, fullerene, and nano cages are in agreement with the E_g value. Fermi level is the highest energy state occupied by electrons in a material at absolute zero temperature [34].

To better understand the electronic changes of the evaluated systems after drug absorption, density of states (DOS) have been calculated (Fig. 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h).

Chemical potential (μ) values show the affinity to the electron attraction. The negative values of chemical potential show that the charges transfer between two particles are spontaneously. The electron transfer occurs from a molecule with a higher chemical potential to a molecule with a lower one. In this work, the electronic chemical potentials (μ) for all drug-cage complexes are negative and in the range of -4.3484 to -5.2345 eV. According to Table 4, the chemical potential of the C_{60}-drugs are higher than drugs, indicating that the electron transfer in the corresponding complexes takes place from the fullerene to the drug.

Chemical hardness (η) indicates resistance to change in the electron density for a chemical system, and can explain the system stability. The chemical hardness of fullerene is reduced after absorption of drug (Table 4). Table 4 presents that chemical hardness for C_{60}-drugs including C_{60}-CLO, C_{60}-BCL, C_{60}-PRD, and C_{60}-MPR have the lowest values in gas and solution phase (≈1.31 to 1.98), while, the amount of chemical hardness for drugs are about 2.17-2.44 eV.

In organic chemistry, an electrophile is an electron absorbent, which is in positive or neutral

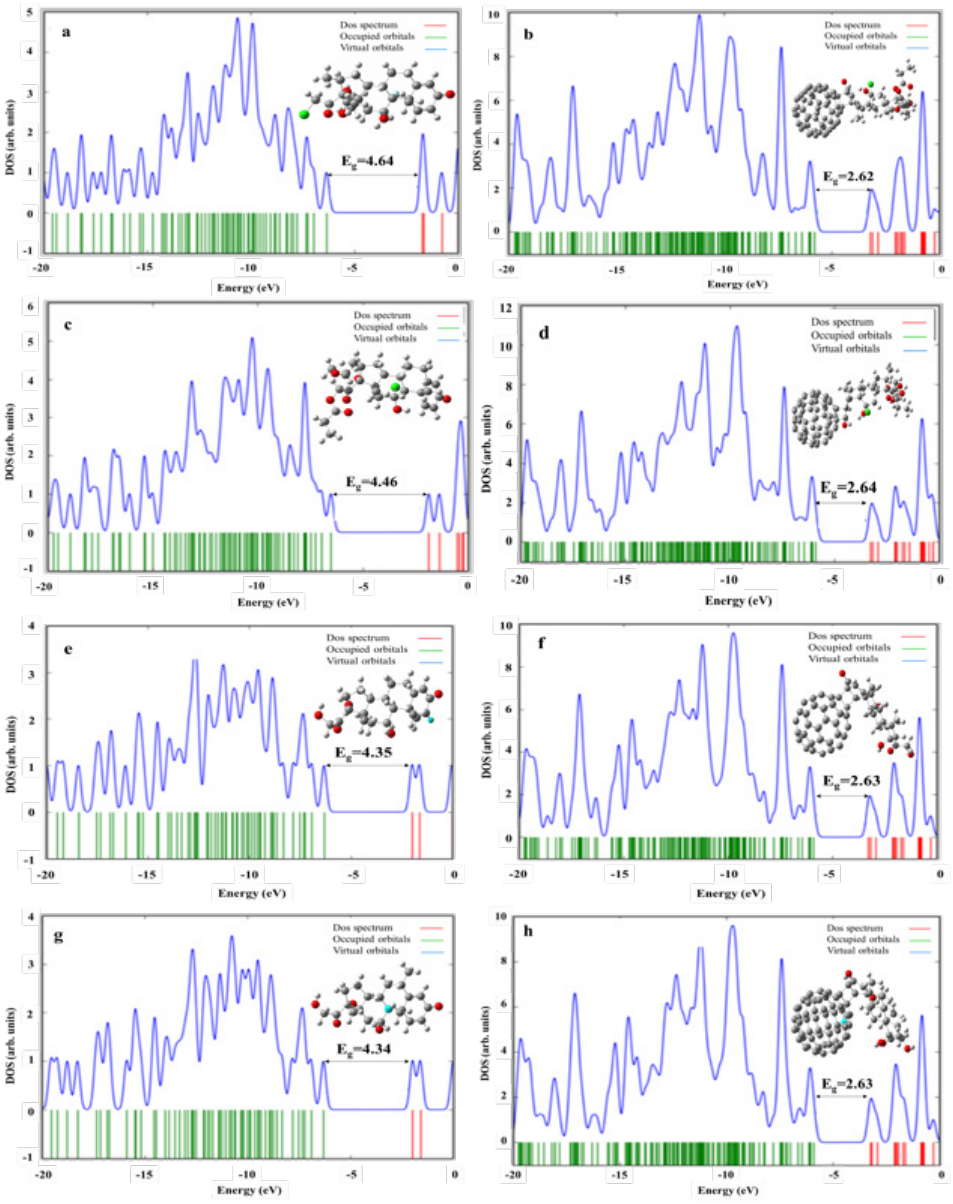


Fig. 4. Schematic of optimal structures and DOS plots of a) CLO b) FCLO c) BCL d) FBCL e) PRD f) FPRD g) MPR h)FMPR.

modes. They have certain empty orbitals for electron adsorption. When two molecules react each other, one molecule acts as a nucleophile, while the other plays the role of an electrophilic. Electrophilicity power (ω) is a parameter related to HOMO and LUMO that indicates the reactivity of the structure. In fact, the electrophilicity index is the energy stability when the system accepts electrons. In this work, the electrophilicity amount is almost doubled after the adsorption of the drug to fullerene.

The most electrical charge that an electrophilic system can accept is called ΔN_{max}. In other words, ΔN_{max} indicates the charge capacity of a molecule. According to the ΔN_{max} equation (eq. 7), the chemical hardness is decreased and the electrophilicity power is increased by increasing the chemical potential. When the system possesses more electron deficiencies, it becomes more positive, and thus, it is expected that the possibility of electron transfer to the system is increased. The results related to ΔN_{max} (Table 4)

show that the level of this parameter in nano cages is higher than the drugs [36].

Effect of the methyl group on the variability of reactivity in this class of drugs can be examined by comparing methylprednisolone and prednisolone. Methylprednisolone has the methyl group at the C_{11} position. The results show that in the gas phase, the electron donor groups reduce the energy gap as much as possible and increase the reactivity of the structure. In the case of water polar solvent, the electron donor groups cause increasing of the energy gap and the structural stability. In fact, the solvent molecules lead to reducing its reactivity and thus making the methyl structure more stable, through surrounding the structure. It was confirmed by the attributed data to the chemical potential, charge capacity, and electrophilic power.

The study of the effects of electron receptor groups on beclomethasone and clobetasol is slightly more complex. Clobetasol and beclomethasone drugs have halogen, ketone, and ester receptor groups in their structures. Both drugs have a halogen group (chlorine or fluoride) at C_8 position and an ester group at C_{16} position. The main difference between these two structures is relevant to the presence of keto-ester group in beclomethasone and haloccetone group (chlorine halogen) in clobetasol at C_{16} position.

Halogens are the electronegative groups that increase the reactivity. Obviously, in halogen-containing structures, clobetasol with two chlorine and fluorine halogens is more reactive than beclomethasone (one chlorine atom), regardless of the functional groups. The results provided in Table 1 confirm this matter. Comparison of clobetasol and beclomethasol drugs illustrates that the clobetasol energy gap is higher than that of the beclomethasone. In other words, regardless of the halogen type, the halocetone group has caused more stability of the structure than the cluster group. This means that beclomethasone is a medicine with higher reactivity compared with the clobetasol drug.

CONCLUSIONS

In this study, DFT calculations have been performed to evaluate the interactions between C_{60} fullerene and some corticosteroid drugs (clobetasol, beclometasone, prednisolone, and methylprednisolone) in order to investigate these compounds in drug design. Some important parameters have been calculated and reported in this work. The results of the evaluation of the bond length show that the bond length decreased after the attachment of the drug molecules to the fullerene C_{60}. In fact, after binding of the drugs to the fullerene C_{60} base, the bond length is decreased and the bond strength increased. The results of the NBO show that the contribution of s orbital from carbon-carbon bonds in drug carriers is significantly higher than the single drug, and the contribution of the p orbital has decreased. It indicates the bond strength after the reaction with fullerene C_{60}. The results show that in gas and solution phases, the energy level of HOMO orbitals has increased while the energy level of LUMO has decreased. In other words, the energy gap in the drug nano-carrier has reduced in both phases compared to the drug alone. Therefore, the electron transfers more easily from HOMO to LUMO in the drug and the reactivity increases. The chemical potentials are expected to change like electronegativity values. As chemical potentials increase, chemical hardness decreases and ultimately a suitable electrophilic addition is obtained. The results related to ΔN_{max} show that the level of this parameter in nano cages is higher than the drugs, thus, it is expected that the possibility of electron transfer to the system is increased. The results indicate an increase in the dipole moment of the studied drugs in the water solvent compared to the gas phase. Since water forms the main part of the body, this indicates that the solubility of the drug increases in the body by binding the drug to the nano-carrier, which is useful in the circulation of the drug in the body.

CONFLICT OF INTEREST

Authors have no conflict of interest.

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