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Investigation of fullerene (C_{60}) effects on chemical properties of Metoprolol: A DFT study

R. Ahmadi**; S. Pourkarim

Young Researchers and Elite Clube, Yadegar-e-Imam Khomeini (RAH) Shahre-rey Branch, Islamic Azad University, Tehran, Iran

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ABSTRACT: In this research at the first Metoprolol drug and its fullerene derivative were optimized. Natural bond orbital (NBO), nuclear Indepndent chemical shift (NICS) and finally IR calculations, for these compounds were carried out at the B3LYP/6-31G* quantum chemistry level. Different parameters such as energy levels, the amount of chemical shift in different atoms, the amount of HOMO/LUMO, chemical potential (μ), chemical hardness (η), Thermodynamic properties were determined. Metoprolol is the generic form of the brand-name drug Lopressor, prescribed to treat high blood pressure. In this study we used fullerenes, as nano drug carriers, and Fulleren drevatives of Metoprolol drug were studied. The data in Tables and graphs and shapes were compared and discussed.

Keywords: *Chemical potential; Density functional theory (DFT); Fullerenes; Metoprolol; Nano drug carriers.*

INTRODUCTION

Nanostructures can be categorized into following forms according to their structures: diamonds with sp^3 hybridization, Graphite with sp^2 hybridization, Hexagonal diamonds with sp^3 hybridization, fullerenes with SP^2 hybridization, Nanoparticles, Graphene, single-layer and multi-layer nanotubes, Crystal Nanostructures (Xing, *et al.*, 2014). All these forms of nanostructures produce unique Pharmaceutical and electronic properties. Graphenes have a two-dimensional structure of a single layer of carbon like chicken wire (Rastegar, *et al.*, 2013).

Metoprolol is a beta-blocker that affects the heart and circulation (blood flow through arteries and veins). Metoprolol is used to treat angina (chest pain) and hypertension (high blood pressure) (Veloutsou, *et al.*, 2014). It is also used to treat or prevent heart attack. Metoprolol may also be used for other purposes not listed in this medication guide. Metoprolol is used alone or in combination with other medications to treat high blood pressure. It is also used to prevent angina (chest pain) and to improve survival after a heart attack (Fleet, *et al.*, 2014). Extended-release (long-acting) metoprolol is also used in combination with other medications to treat heart failure. Metoprolol is in a class of medications called beta blockers. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure (Wong, *et al.*, 2014). To-

(*) Corresponding Author - e-mail: roya.ahmadi.chem@hotmail.com

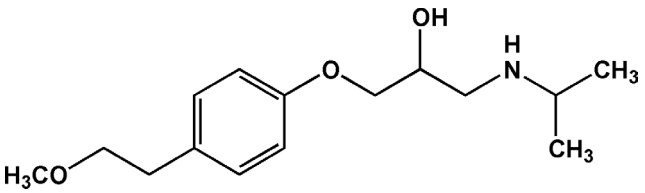

Fig. 1: (RS)-1-(Isopropyl amino)-3-[4-(2-methoxyethyl) phenoxy]propan-2-ol.

day considerable advances have been accomplished in applications of nano- particles specifically in medical sciences. Fullerene is one of the other artificial forms of carbon element. Long life cycle of medicines in the human body is a successful factor in delivery of medicine to the specific place. Lots of nano-particles are being developed in this field. In this study, the metoprolol linked on fullerene (C_{60}), and then the drug and its fullerene derivatives were optimized (Ung, *et al.*, 2013). Then NBO (Regiec, *et al.*, 2014) and NICS calculations (Elhage, *et al.*, 2013) for compounds were performed in B3LYP/6-31G*. Studies of NICS (σ iso) were performed for all conditions and changes in chemical shift (δ) of the desired compound were considered. The chemical potential (μ) and chemical hardness (η) of the compound were studied. This drug is classified as a drug therapy as an adjuvant in the treatment of hypertension and congestive heart failure (CHF). The aim of present study was to evaluate the effect of fullerene on chemical properties of Metoprolol (Beheshtian, *et al.*, 2012).

COMPUTATIONAL DETAILES

All structure relating to structure of Metoprolol and nano Fullerene- Metoprolol were designed primarily with use of Gauss view 5.0.8. In order to do final optimization, Gaussian 98 program of package DFT method were used. However, for this purpose, 6-31G* basis set was used. Computations were done in gas phase (Beheshtian, *et al.*, 2013). In this study, Metoprolol drug and its 3 fullerene derivatives investigated (Fig. 2).

RESULT AND DISCUSSION

Table (1) values of energies of the frontier molecular orbitals (E_{HOMO} and E_{LUMO}, eV), Electronic chemical potential, μ (eV), Chemical hardness, η (eV), calculated at the B3LYP/6-31G* level of theory.

The results showed that the calculated energy gap is typically much higher of the Metoprolol than Metoprolol attached to Fullerene in each three connection on the other hand the amount of that in each four Metoprolol binds to Fullerene to connection forms is different and mostly the same compared with the ac-

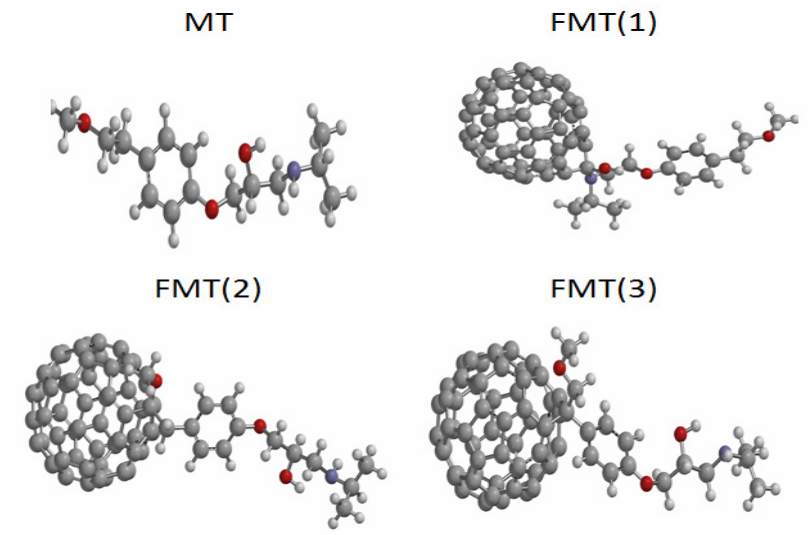

Fig. 2: View of Metoprolol alone and Metoprolol derivatives have been obtained from carbon connection of Metoprolol C_{28} to Fullerene and shown briefly FMT (1), C_{14} to Fullerene and shown briefly FMT (2) and C_{11} to Fullerene and shown briefly FMT (3)

Table 1: Values of energies of the frontier molecular orbitals (EHOMO and ELUMO, eV), Electronic chemical potential, μ (eV), Chemical hardness, η (eV).

Indices	Temperature = 298.15 K, Pressure = 1 atm				
	C60	MT	FMT(1)	FMT(2)	FMT(3)
E_{HOMO} (eV)	-9.83	-6.46	-9.29	-9.34	-9.15
E_{LUMO} (eV)	-2.57	7.4	-2.84	-2.45	-2.31
Dipole Moment (debye)	0.00	3.18	3.6	5.74	7.68
HLG=E_{LUMO}-E_{HOMO} (eV)	7.26	13.86	6.45	6.89	6.84
ΔN_{MAX}=-m/h	0.0111	-0.0768	0.0129	0.0123	0.0128
ω=-m^2/2 h (Ev)	0.0030	0.9804	0.0027	0.0031	0.0033
μ =1/2(E_{LUMO}-E_{HOMO}) (eV)	-0.0403	0.5319	-0.0412	-0.0424	-0.044
η =(E_{LUMO}-E_{HOMO})/2 (eV)	3.63	6.93	3.225	3.445	3.42

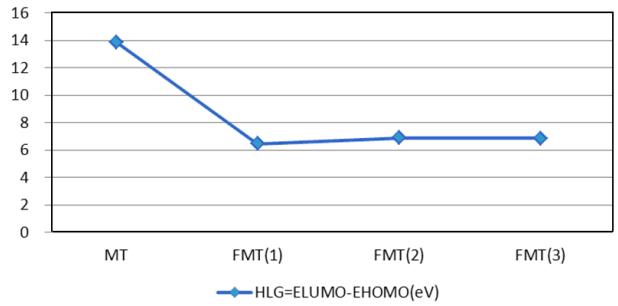

Fig. 3: Results of the survey molecular orbital energy levels of the drug and three Fullerene derivative in B3LYP/6-31G*

curacy of thousands (Fig. 3).

MT > FMT (2) > FMT (3) > FMT (1)

Since most of the weight of human blood is composed of water and it is a polar solvent, so the amount and the process of the change in dipole moment in Nano-drugs and Metoprolol in free mode are also important. Minimum value of dipole moment in order is first related to MT. In total the dipole moment FMT (3) alone is higher than the other combinations. So we expect that when FMT (3) arrived our body, it is more soluble than other four combinations in water that is a polar solvent dissolved and has more solubility (Fig. 4).

Chemical hardness indicate amount of the electron transfer from HOMO to LUMO, as much as chemical hardness is more, electron transfer from HOMO to LUMO is harder and consequently system reactivity decrease. In comparison with chemical hardness among Metoprolol and three combination of Nano-drug, we resulted like energy gap that chemical hardness of MT is more than three other combination (Fig. 5).

Negative chemical potential is a symbol of system stability. The calculated results showed that the chemical potential Nano-drugs 1,2,3 and that is the same and the lowest and then is a chemical potential, the calculated highest value of the chemical potential allocate to Nano-drug 2 the more chemical potential the more reaction molecular or in the other words that type is more reactive (Fig. 6).

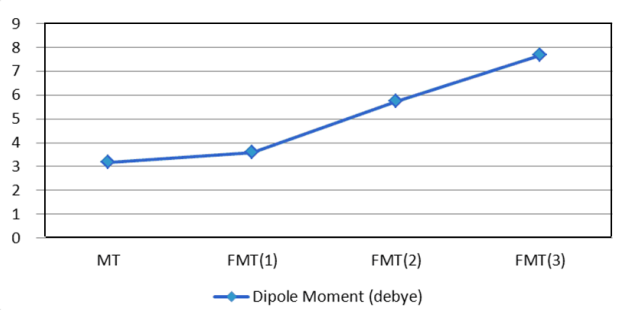

Fig. 4: The amount of dipole moment in FM, FMT (1), FMT (2), and FMT (3) is calculated in B3LYP/6-31G* level

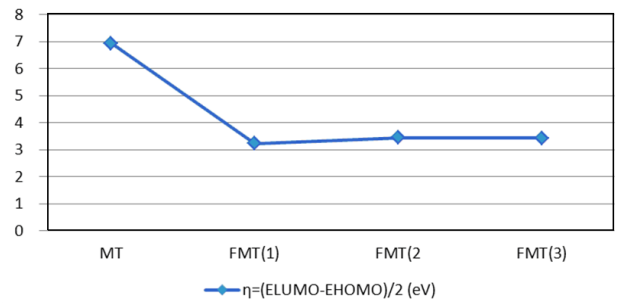

Fig. 5: Result obtained from chemical hardness in MT, FMT (1), FMT (2), and FMT (3) is calculated in B3LYP/6-31G* level

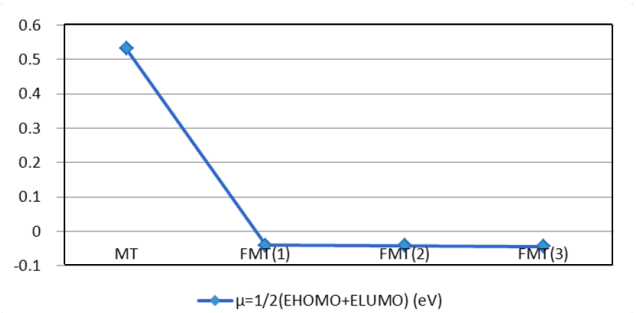

Fig. 6: The result of the chemical potential of Metoprolol and its Fullerene derivatives

Current ring creates a magnetic field perpendicular to the ring and the effect of H ring outside circle caused more chemical shift for H, consequently reduce the amount of covering factor. Survey results of the calculations show that among derivatives Fullerene Metoprolol the most negative value of NICS is related to FMT (1) so the Hydrogen of ring 1 in FMT (1) has more chemical shift then this Hydrogen are better than others that participate in electrophilic substitution reaction (Table 2).

Survey of the Thermodynamics

In this work Metoprolol was linked to the fullerene, Metoprolol drug and its 3 fullerene derivatives investigated. Then compare Enthalpy (ΔH), Entropy (ΔS), Gibbs free energy (ΔG), (ΔE) Internal energy parameters between Metoprolol alone and Nano-fullerene-Metoprolol. The value obtained of Thermodynamics indicate that preparation of Nano - drug reaction is a reaction heat retention and is not spontaneously and we need to changing conditions and precise control (Table 3).

CONCLUSIONS

Computational Quantum Mechanics at the theory level of B3LYP/6-31G* on the structure of Metoprolol drug and its fullerene derivative and the results of this computation can be classified as follows:

- The investigation of all the parameters show that the attachment of Fluoxetine structure to Fullerene structure will influence the energy levels and dipole moment changes and these changes are able to be investigated in the electrical and chemical parameters of Fullerene Derivatives structure.
- The results showed that energy gap of MT is the highest and FMT (1) is the lowest. It should be noted that Derivatives of Metoprolol drug was done separately and only when the structure of Metoprolol was attached to conductivity of FMT (1) is the highest and MT is the lowest.
- Chemical potential of MT is more than FMT (2) and

Table 2: Amount of NICS (ppm).

NICS	0	0.5	1	1.5	2
Metoprolol	12.039	-8.5596	-11.885	-9.7672	-5.2085
FMT(1)	-9.6915	-11.922	-12.148	-8.6999	-5.3517
FMT(2)	-9.5456	-11.725	-11.965	-8.4618	-5.0464
FMT(3)	-9.2291	-11.387	-11.573	-8.1687	-4.9494

Table 3: Thermodynamics properties.

Temperature = 298.15 K, pressure = 1 atm			
	FMT(1)	FMT(2)	FMT(3)
ΔH° (kJ/mol)	166.2825	153.1895	151.034
ΔS° (J/mol.K)	-108.296	-111.559	-109.829
ΔG° (kJ/mol)	198.771	186.657	183.983

the following is FMT (3) and FMT (1).
- Chemical hardness of MT is the highest and the lowest value is related to FMT (1).
- Dipole moment of FMT (3) is highest.
- The investigation of all the parameters show that the attachment of Metoprolol structure to Fullerene structure will influence the Enthalpy (ΔH), Entropy (ΔS), Gibbs free energy (ΔG) changes are able to be investigated in the electrical and chemical parameters of Fullerene Derivatives structure.
-The calculation of the values in the Table 3 shows this trend, for Fullerene derivatives (ΔH>0), (ΔS<0) and (ΔG>0).
-Represents the energy, Enthalpy (ΔH), and the results show the reaction is endothermic, the results show this trend: FMT (1) > FMT (2) > FMT (3).
-Entropy (ΔS) represent irregularity and the results show a decrease in the amount of irregularities, the results show this trend: FMT (3) > FMT (2) > FMT (1).
-Gibbs free energy (ΔG) is the amount of energy available to a process and when it is positive (ΔG>0) is show non-spontaneous reaction, so the results show that, reactions are non-spontaneous, the results show this trend: FMT (1) > FMT (2) > FMT (3).

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AUTHOR (S) BIOSKETCHES

Roya Ahmadi, Associate Professor, Young Researchers and Elite Clube, Yadegar-e-Imam Khomeini (RAH) Shahre-rey Branch, Islamic Azad University, Tehran, Iran, *E-mail: roya.ahmadi.chem@hotmail.com*

Somayeh Pourkarim, M.Sc., Young Researchers and Elite Clube, Yadegar-e-Imam Khomeini (RAH) Shahre-rey Branch, Islamic Azad University, Tehran, Iran