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Fullerene effect on chemical properties of antihypertensive clonidine in water phase

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ABSTRACT

Purpose: Today considerable advances have been achieved in application of nano-particles. Fullerene is one of the artificial forms of carbon element. Long life cycle of medicines in the human body is a success factor in delivery of medicine to the specific place. Lots of nano-particles are being developed in this field and from a medical point of view, achieving such goals is vital. The aim of this study was to investigate the effect of fullerene chemical properties of antihypertensive clonidine drug in water by density functional theory (DFT) methods.

Materials and Methods: This study was carried out using computerized calculations of Gaussian program in Becke 3-parameters Lee-Yang-Parr (B3lyp/6-31g level in water on clonidine drug and its fullerene connected form. Impact of fullerene on an anti-blood pressure medicine known as clonidine was analyzed as changes in some properties including energetic levels, stability, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) levels, chemical hardness, and electrophilicity properties.

Results: Clonidine lowers blood pressure by decreasing the levels of certain chemicals in blood. This allows blood vessels to relax and the heart to beat more slowly and easily. Results indicated that combining medicine and C_{60} considerably decreases the energy level and increases the bipolar momentum. Therefore, solubility and reacting ability of the medicine increases in solution phase of the water.

Conclusion: Totally, combining fullerene structure to an anti-blood pressure medicine, like clonidine, as a nano-carrier enhances the reaction ability of the medicine and it gains more solubility properties in the human body.

Keywords: anti-blood pressure; clonidine; fullerene; water; computational methods.

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INTRODUCTION

In the recent years, many studies have been done on the structure of fullerene and its derivative forms to drugs as medicalnano-carrier compounds. The theoretical studies of the electronic structure related to the calculations of natural bond orbitals are used to predict physical-chemical properties of donor-acceptor systems. Clonidine was probably investigated and prescribed as an antihypertensive drug in the 1950s for the first time. Later on it has found new uses, including treatment of some types of neuropathic pain, opioid detoxification, sleep hyperhidrosis, plus being used as a veterinary anesthetic drug.

Clonidine is used to treat anxiety and panic disorder. It is also Food and Drug Administration (FDA) approved to treat attention-deficit hyperactivity disorder (ADHD) in an extended release form. It is becoming a more accepted treatment for insomnia, as well as for relief of menopausal symptoms. Clonidine is increasingly used in conjunction with stimulants to treat ADHD, for which it is administered in late afternoon or evening for sleep. This is because it sometimes helps to moderate ADHD-associated impulsive and oppositional behavior, and may reduce tics, a problem in which a part of the body moves repeatedly and suddenly.[1] Clonidine can be used in the treatment of Tourette syndrome (specifically for tics).[2]

Clonidine has been studied along with methylphenidate for treatment of ADHD.[3,4] In 2010, the FDA approved the use of clonidine either as an adjunct to traditional stimulant therapy or as a immunotherapy in the treatment of ADHD. Clonidine may be used to ease withdrawal symptoms associated with the long-term use of narcotics, alcohol and smoking. It can alleviate opioid withdrawal symptoms by reducing the sympathetic nervous system response such as tachycardia and hypertension, as well as reducing sweating, hot and cold flushes, and general restlessness.[5]Its sedation effect is also useful although its side effects can include insomnia, thus exacerbating an already common feature of opioid withdrawal.[6] Clonidine can be used for migraine headaches and hot flashes associated with menopause.[7,8]

Clonidine also has several off-label uses, and has been prescribed to treat psychiatric disorders including stress, sleep disorders, and hyperarousal caused by post-traumatic stress disorder, borderline personality disorder, and other anxiety disorders.[9-10] Clonidine is also a mild sedative, and can be used as premedication before surgery or procedures.[11] Its epidural use for pain during heart attack, postoperative and intractable pain has also been studied extensively.[12]

Clonidine treats high blood pressure by stimulating α_2-receptors in the brain, which decreases cardiac output and peripheral vascular resistance, lowering blood pressure. It has specificity towards the presynaptic α_2-receptors in the vasomotor center in the brainstem. This binding decreases presynaptic calcium levels, thus inhibiting the release of norepinephrine. The net effect is a decrease in sympathetic tone. It has also been proposed that the antihypertensive effect of clonidine is due to agonism on the I1-receptor (imidazole) which mediates the sympatho-inhibitory actions of imidazolines to lower blood pressure.[13]

Fullerene is one of the artificial forms of carbon element which is made by heating graphite. Due to its similarity to ball, it is called buck ball. Low solubility of the fullerene in fluids limits it application as a medicinal effective material. But hydrophobic size, three-dimensionality and electron properties cause its use as medicine. For example, their spherical form causes ability and position of fullerene molecules in enzymes or cells hydrophobic solutions. This action causes interesting medicinal properties which increase rate of such characters by adding nano properties of this structure.[14-16]The aim of this study was to investigate the effect of fullerene chemical properties of antihypertensive clonidine drug in water by density functional theory (DFT) methods.

MATERIALS AND METHODS

The structures of clonidine and Fullerene clonidine (FCL) were designed primarily using Gauss View version 3.1 and nanotube modeler version 1.3.0.3 (Figure 1). The optimization and natural bond orbital calculations were done with water solvents with polarized continuum model (PCM) and then in gas. Afterwards, the obtained results were compared with each other. The optimization and natural bond orbital calculations of all systems were done by DFT method using Becke, 3-parameter, Lee-Yang-Parr (B3LYP) method and the standard 6-31G basis set, by Gaussian W98 suit programs. All computations were done under one atmosphere pressure and 298 Kelvin temperature. In this study properties such as energetic levels, stability, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) levels, chemical hardness and electrophilicity properties were investigated.[17]

The electrophilicity concept was expressed for the first time in 1999 by Parrand colleagues.[18] The electrophilicity and the maximum amount of electronic charge indices are related to electronic charge. The maximum amount of electronic charge index, ΔN_{max}, describes the charge capacity of the molecule that the electrophone system may accept by equation 1. A positive value of ΔN_{max} index for a system acts as an electron acceptor, whereas a negative value of ΔN_{max} index acts as an electron donor. The electrophilicity index, ω, in atomic units is a measure of electrophilic power of a molecule it is given in equation 2. When two molecules react with each

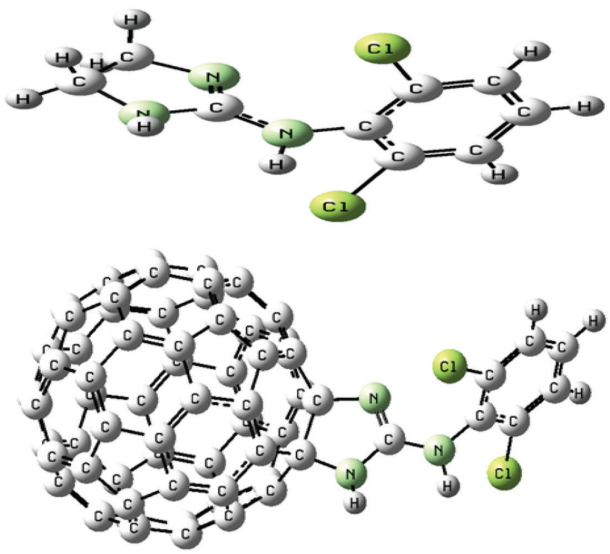

Figure 1. Clonidine and FCL obtained by B3LYP/6-31G level of theory.
Keys: FCL, Fullerene Clonidine; B3LYP, Becke 3-parameters Lee-Yang-Parr.

other, one molecule behaves as a nucleophile, whereas the other acts as an electrophone. A higher electrophilicity index shows higher electrophilic power of a molecule. So the quantity of ω describes the propensity of the system to acquire additional electronic charge from the environment, described in equation 1. In equations 3 and 4, μ and η are the chemical potential and the chemical hardness, respectively. Both quantities may be approximated based on the energies of frontier molecular orbital's (EHOMO and ELUMO).The low values of μ and η, characterize a good electrophone species.[19-23]

$$\Delta N_{max}=\frac{-\mu}{\eta} \quad (1)$$

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

$$\mu=\frac{1}{2(E_{HOMO}+E_{LUMO})} \quad (3)$$

$$\eta=\frac{(E_{HOMO}+E_{LUMO})}{2} \quad (4)$$

RESULTS

Clonidine is as a drug for high blood pressure. The electron density in clonidine and FCL obtained by B3LYP/6-31G level of theory are shown in Figure 3. When clonidine is linked to fullerene, the fullerene can attract electrons to itself via the aromatic rings. This is in agreement with the calculated natural bond orbital charges of the clonidine and FCL molecules, because negative charge on all similar atoms of only clonidine are greater than the FCL molecule. Moreover, FCL has

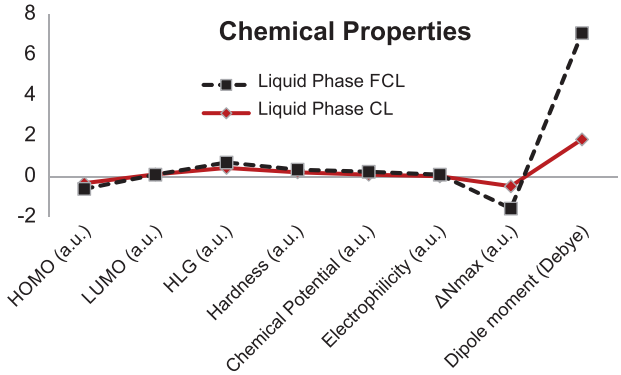

Figure 2. Diagram of calculated EHOMO and ELUMO, chemical hardness, ΔN_{max}, h, chemical potential, μ, electrophilicity index, ω, and the maximum amount of electronic charge index in atomic units and dipole moment (Debye) for clonidine and FCL obtained by B3LYP/6-31G level.
Key: FCL, Fullerene Clonidine; B3LYP, Becke 3-parameters Lee-Yang-Parr; EHOMO, Energy of Highest Occupied Molecular Orbital; ELUMO, Energy of Lowest Unoccupied Molecular Orbital.

generally the valence electron population in atomic units which is lower than clonidine for carbons, nitrogen, oxygen and hydrogen atoms in similar position for FCL and clonidine**.** The quantum molecular descriptors for clonidine and FCL molecule are summarized in Table 1.

Energy gaps (ELUMO and EHOMO) decrease for FCL. This lowering of energy gaps may be able to increase the reactivity of the FCL, because chemical hardness of FCL is less than clonidine, and charge transfer is done better in FCL than clonidine. The amount of charge transfer in molecules, calculated using the ΔN_{MAX} method, is given in Table 1. A positive value of ΔN_{MAX} indicates that the molecule acts as an electron acceptor, while a negative value of ΔN_{MAX} indicates that the molecule act as an electron donor. In the FCl the ΔN_{MAX} values are negativein respect to clonidine, indicating that FCL molecule acts as an electron donor stronger than clonidine. Also the results

Table1. Quantum molecular description calculated for clonidine and FCL obtained by B3LYP/6-31G level in liquid phase.

Indices	Liquid Phase	
	Clonidine	FCL
HOMO (a.u.)	-0.32026	-0.27894
LUMO (a.u.)	0.11571	-0.01283
HLG (EHOMO-ELUMO) (a.u.)	0.43597	0.26611
Hardness $(\eta=\frac{(E_{HOMO}+E_{LUMO})}{2})$ (a.u.)	0.217985	0.133055
Chemical Potential $(\mu=\frac{1}{2(E_{HOMO}+E_{LUMO})})$ (a.u.)	0.102275	0.145885
Electrophilicity $(\omega=\frac{-\mu^2}{2\eta})$ (a.u.)	0.023993	0.079976
$\Delta Nmax=\frac{-\mu}{\eta}$ (a.u.)	-0.46918	-1.09643
Dipole moment (Debye)	1.8434	5.238

Keys: HOMO, Highest Occupied Molecular Orbital; LUMO, Lowest Unoccupied Molecular Orbital; HLG, HOMO-LUMO Gap; FCL, Fullerene Clonidine, a.u., atomic unite, B3LYP, Becke 3-parameters Lee-Yang-Parr.

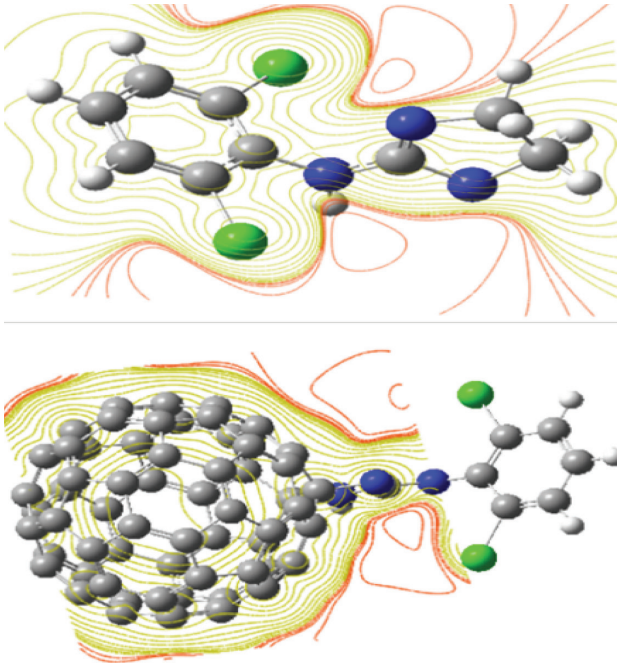

Figure 3. Flow of electron density in clonidine and FCL obtained by B3LYP/6-31G level.
Key: FCL, Fullerene Clonidine; B3LYP, Becke 3-parameters Lee-Yang-Parr.

of the calculations showed that, when structure of clonidine is linked to nano-fullerene, the dipole moment in FCL increased. Also, the chemical potential of FCL decreased, while the electrophilicity value in FCL increased (Table 1).

DISCUSSION

Dipole Moment

The results have revealed that when the structure of clonidine is linked to nano-fullerene, the dipole momentin FCLis increased. This is an effective factor which has a direct relationship with solubility. The higher amount of this factor causes more solubility inside the polar solvent (Table 1). Also reactivity and conductivity is increased.

HOMO and LUMO Indices

The HOMO and LUMO energies for the moleculeare different parallel applied functions. The FCL has a band gap less than clonidine. A small HOMO-LUMO gap in atomic units automatically means small excitation energies to the excited states. Therefore FCL is more conductive than clonidine (Table 1). Also, EHOMO is the first vertical ionization energy and ELUMO the electron affinity of the molecules.

Chemical Potential

When structure of clonidine is linked to fullerene, the chemical potential of FCL was decreased, in the liquid phase (Table 1). The chemical potential (μ) gradually increases with increase of the applied external electric field strength.

Chemical Hardness

FCL has chemical hardness less than clonidine. A concise definition of chemical hardness states that a hard molecule has a large HOMO-LUMO gap and a soft molecule has a small HOMO-LUMO gap, so FCL is softer than clonidine. Soft molecules with a small gap will have their electron density and are changed more easily than a hard molecule. So FCL is more reactive than clonidine, Also the chemical potential of FCL was decreased, in the liquid phase (Table 1).

Electrophilicity Index

The electrophilicity value in FCL was increased in this study. The electrophilicity index is a measure of electrophilic power of a molecule. When two molecules react with each other, one molecule behaves as a nucleophile system, whereas the other acts as an electrophone system. A higher electrophilicity index shows higher electrophilicity of a molecule. So FCL has higher electrophilicity than clonidine. Therefore, FCL is a stronger Lewis acid (Table 1). The electrophilicity index is a measure of electrophilic power of a molecule. When two molecules react with each other, one molecule behaves as a nucleophile, whereas the other one acts as an electrophile. A higher electrophilicity index shows higher electrophilicity of a molecule.

Maximum Amount of Electronic Charge Index

The most accepted electron charge can be calculated by ΔN_{max} parameter. The obtained results for this parameter were obtained like the previous parameters which showed an increase for FCL. A positive value of ΔN_{max} indicates that charge flows to system, or our system acts as an electron acceptor, whereas a negative value of ΔN_{max} indicates that charge flows from system or our system acts as an electron donor. So FCL is an electron acceptor or a Lewis acid (Table 1).

Natural Charges and Valence Electrons

The result of valence electron populationin atomic units, for carbons, nitrogen, oxygen and hydrogen atoms in similar position for FCL and clonidine show that in FCL the valence electron population is generally lower than clonidine. So C_{60} has power of electron affinity (Figure 3).

CONCLUSION

The structural and electronic structures of clonidine and FCL were investigated theoretically by performing DFT calculations at the B3LYP/6-31G level, in the liquid phase. The results showed that FCL had a band gap less than clonidine. Also, chemical hardness in FCA was lower than clonidine. So according to electrophilicity and ΔN_{max} parameter, FCL is a softer acid than clonidine. In terms of chemical reactivity, it can be concluded that soft molecules will be more reactive than hard molecules for uni-molecular reaction such as isomerization and dissociation. This can be useful for future pharmaceutical researches, since this action can cause interesting medicinal properties.

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