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Interaction of biotin and oxybiotin with magnesium dication. A DFT treatment

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Abstract

The present computational study, considers the perturbational effect of magnesium cation on two biologically important molecules, biotin and oxybiotin within the restrictions of density functional theory at the level of B3LYP/6-31++G(d,p). The results reveal that both of the composite molecules have exothermic heat of formations and favorable Gibbs free energy of formation values at the standard state. They are electronically stable. Various quantum chemical data accompanying the considered perturbation have been collected and discussed including UV-VIS spectra. Both the HOMO and LUMO energies of oxybiotin+Mg^{+2} composite have been lowered down at unequal extents as compared to the biotin+Mg^{+2} composite in such a way that interfrontier molecular orbital energy gap value of it is much greater than the respective value of biotin+Mg^{+}.

1. Introduction

Through the years, a water-soluble vitamin, biotin, which serves as a coenzyme for some carboxylases in humans [1], has been the focus of interests in many publications experimentally as well as theoretically [1-8].

On the other hand, oxybiotin is an oxygenated analogue of biotin in which the sulfur atom is replaced by oxygen. Its structural relationship to biotin and its ability to replace biotin as an essential metabolite for various species of microorganisms and higher animals have been discussed in the literature by Axelrod et al., [9]. Oxybiotin is another active analogue of such an important bioactive molecule biotin. In the literature there exist many articles which have proved that oxybiotin has biotin like activity for many species, such as bacteria, yeast, rats and chicken [10-14].

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Hoffman achieved the first total synthesis of oxybiotin in its dl-form [15]. Later, Ohrui et al., reported the total synthesis of optically active (+)-oxybiotin [16]. Whereas, Reddy et al., described a versatile route for the stereo selective synthesis of oxybiotin [17]. Shelke et al. published a short enantio selective synthesis of (+)-oxybiotin [18].

In the present study, perturbations caused by an ubiquitous ion, magnesium dication, on biotin and oxybiotin have been considered within the constraints of density functional theory (DFT) and the basis set employed.

2. Method of Calculations

Presently, all of the initial structure optimizations of the considered structures leading to energy minima have been achieved by using MM2 approach which is followed by semi empirical PM3 (self consistent fields) molecular orbital method [19-21]. Then, the structure optimizations have been achieved using various basis sets within the framework of Hartree-Fock and finally by using density functional theory (DFT) at the level of B3LYP/6-31++G(d,p) [22,23]. It is noteworthy that the exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [24]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [25] and Lee, Yang, Parr (LYP) correlation correction functional [26]. In the present study, also normal mode analysis for each structure was done and yielded no imaginary frequencies for the $3N$–6 vibrational degrees of freedom, where N is the number of atoms in the system. This search has indicated that the structure of each molecule considered corresponds to at least a local minimum on the potential energy surface. Furthermore, all the bond lengths have been thoroughly searched in order to find out whether any bond cleavages occurred or not during the structure optimization process. All these computations were performed by using SPARTAN 06 [27].

3. Results and Discussion

Conversion of biotin to oxybiotin or vice versa theoretically is an intra molecular perturbation (centric perturbation) whereas Mg^{+2} composites of them can be considered as a certain kind of inter molecular perturbation without leading to any chemical bond formation [28-30].

Figure 1 shows the optimized structures of Mg^{+2} composites of biotin and oxybiotin together with direction of the calculated dipole moment vectors.

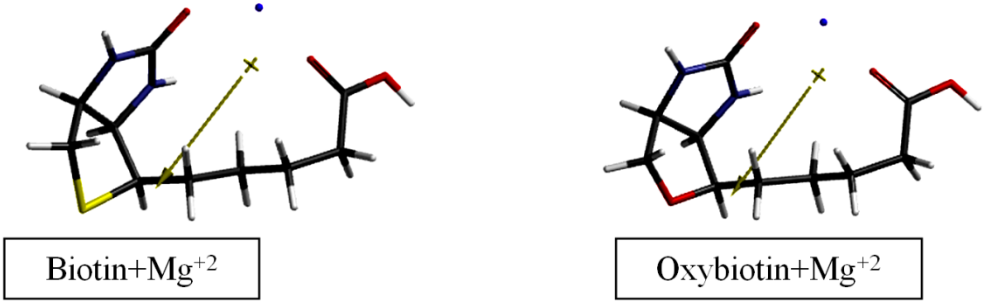

Figure 1. Optimized structures of Mg^{+2} composites of biotin and oxybiotin.

Table 1 lists some thermo chemical values of the composite systems considered. As seen in the table, both of the composites are characterized with exothermic heat of formation values and both have thermo chemically favorable Gibbs energy of formation values at the standard state.

Table 1. Some thermo chemical values of the composite systems considered.

System	H°	S° (J/mol°)	G°
Biotin+Mg^{+2}	-3474792.057	489.90	-3474938.142
Oxybiotin+Mg^{+2}	-2626793.888	480.15	-2626937.031

Energies in kJ/mol.

Table 2 shows some energies of Mg^{+2} composites of oxybiotin and biotin where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. As the data reveal, both of the structures are electronically stable.

Table 2. Some energies of the composite systems considered.

System	E	ZPE	E_C
Biotin+Mg^{+2}	-3475505.33	705.51	-3474799.82
Oxybiotin+Mg^{+2}	-2627522.52	714.33	-2626808.19

Energies in kJ/mol.

The difference between the respective data presented in Tables 1 and 2 are due to the centric perturbation, namely sulfur to oxygen replacement (or vice versa), which happens in the 5-membered ring as well as due to the consequent bond length and bond angle changes. Additionally the effect of the presence of the Mg^{+2} cation around organic structure are the responsible factors.

Figure 2 shows the calculated bond lengths of the parent molecules and the composite species considered.

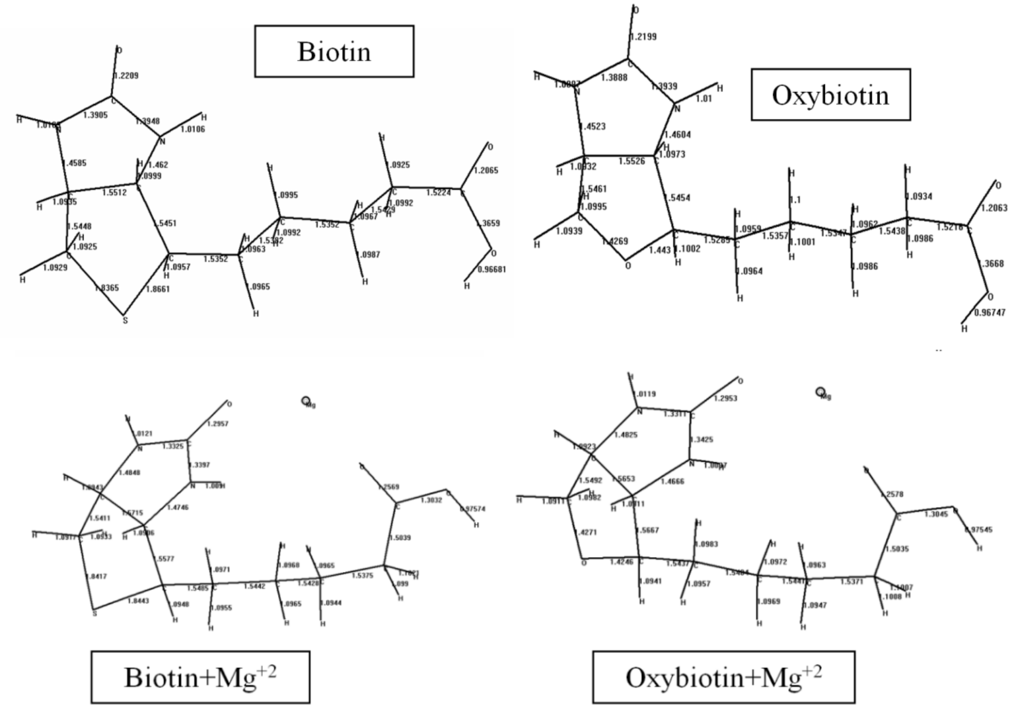

Figure 2. The calculated bond lengths of the species considered.

Table 3 shows the calculated distance of doubly bonded oxygen to Mg^{+2} in the composites. The respective distances considered are very comparable in each composite.

Table 3. The calculated distance of doubly bonded oxygen to Mg^{+2}.

System	$(HN)_2C=O$	HOC=O
Biotin+Mg^{+2}	1.854	1.870
Oxybiotin+Mg^{+2}	1.859	1.872

Distances in Å.

Table 4 lists some properties of the composites considered. In the table polar surface area (PSA) is defined as the amount of molecular surface area arising from polar atoms (N,O) together with their attached hydrogen atoms. The polarizability is defined according to the multivariable formula [27].

$$\text{Polarizability} = 0.08*V - 13.0353*h + 0.979920*h^2 + 41.3791$$

where V and h are the Van der Waals volume and hardness, respectively. Hardness is defined as,

$$\text{Hardness} = -(\varepsilon_{HOMO} - \varepsilon_{LUMO})/2$$

where ε_{HOMO} and ε_{LUMO} are the molecular orbital energies of the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbital energies, respectively.

As seen in the table, the dipole moment value of oxybiotin+Mg^{+2} composite is larger than the respective value of biotin+Mg^{+2}. The component wise analyses of the dipole moments are shown in Table 5.

Table 4. Some properties of the composites considered.

System	Dipole moment	Area (Å²)	Volume (Å³)	PSA (Å²)	Ovality	Polarizability
Biotin+Mg^{+2}	16.36	264.66	238.40	63.970	1.42	60.33
Oxybiotin+Mg^{+2}	16.87	255.64	228.76	71.917	1.41	59.26

Dipole moments in debye units. Polarizabilities in 10^{-30} m^3 units. Point group of both is C1.

Table 5. The dipole moment components of the systems considered.

	X	Y	Z
Biotin	-4.382906	-4.086664	4.263185
Biotin+Mg^{+2}	11.521395	0.581410	-11.598065
Oxybiotin	-4.608124	-4.105711	4.429157
Oxybiotin+Mg^{+2}	12.300831	3.448856	-11.012694

In Debye units.

The greatest perturbation (in absolute value) occurs in X-component of the dipole moment as biotin changes into oxybiotin which apparently affects the direction of the dipole moment vector whereas in the presence of the cation the greatest perturbation takes place in the Y-component of the vector followed by the X-component.

Figure 3 shows the ESP charges on the atoms of the composites considered. It is to be noted that the ESP charges are obtained by the program based on a numerical method that generates charges that reproduce the electrostatic potential field from the entire wavefunction [27]. The charge on the cation is 1.696 and 1.693 esu in biotin+Mg^{+2} and oxybiotin+Mg^{+2} cases, respectively. Although the difference between them is not much, in each case the charge of the cation is less than the initial charge of it, (namely +2) which means that some electron population has been transferred from organic component to the cation in the composites. Probably, some interactions occur between the cation and the doubly bonded oxygen atoms of the organic components. This effect suffices to cause slight changes in the UV-VIS spectra (see below).

Note that magnesium cation may form some complexes [31]. The electronic configuration of Mg^{+2} is $1s^2 2s^2 2p^6$ and its the radius is 0.78 Å [31]. It is anticipated that at least a few compounds of it would show characteristics indicating the presence of the Mg^{+2} ion. Nevertheless, the ionic bond between the magnesium cation and other atoms possesses varying degrees of covalent character [31].

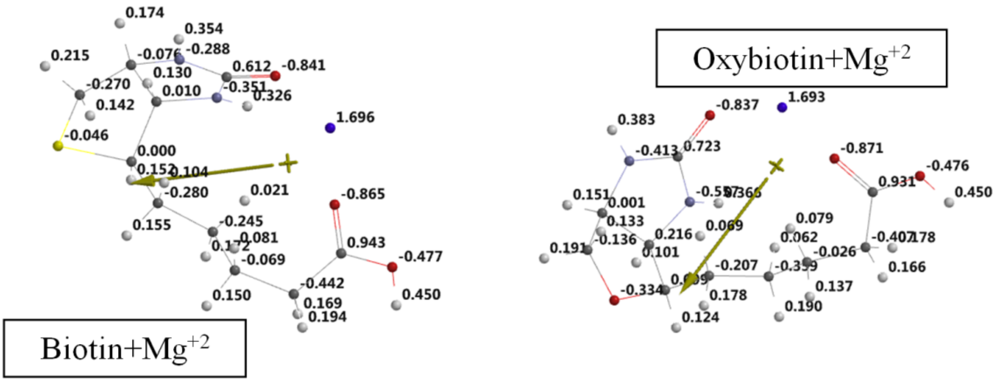

Figure 3. The ESP charges on the atoms of the composites considered.

Figure 4 displays the bond densities of the composites considered.

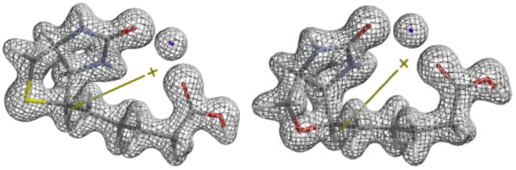

Figure 4. The bond densities of the composites considered.

Figure 5 shows some of the molecular orbital energy levels of the systems considered. As seen in the figure, oxybiotin molecular orbital energy levels are somewhat lowered as compared to the biotin case due to the greater electronegativity value of the oxygen atom relative to sulfur [32]. This is also true up to a certain extent for the oxybiotin+Mg^{+2} composite as compared to the composite of biotin. However the HOMO seems to be affected mostly and lowered considerably.

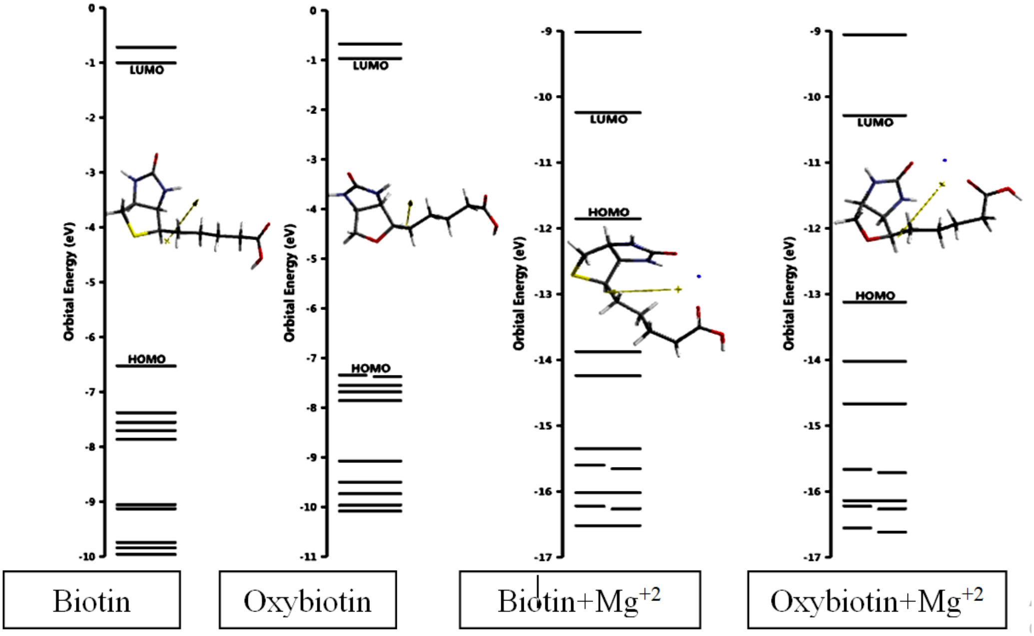

Figure 5. Some of the molecular orbital energy levels of the systems considered.

Table 6 lists the HOMO, LUMO energies and the interfrontier molecular orbital energy gap ($\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$) values of the composite systems considered. Both the HOMO and LUMO energies of oxybiotin+Mg^{+2} composite have been lowered down at unequal extents in such a way that $\Delta\varepsilon$ value of it much greater than the respective value of biotin+Mg^{+2} composite.

Table 6. The HOMO, LUMO energies and Δε values of the composite systems considered.

System	HOMO	LUMO	Δε
Biotin+Mg^{+2}	-1143.80	-988.02	155.78
Oxybiotin+Mg^{+2}	-1266.05	-992.49	273.56

Energies in kJ/mol.

Figure 6 shows the HOMO and LUMO patterns of the composites considered. As seen in the figure the HOMO is mainly confined to etheric sulfur or oxygen containing ring whereas the LUMO is provided in a great extent by the magnesium cation.

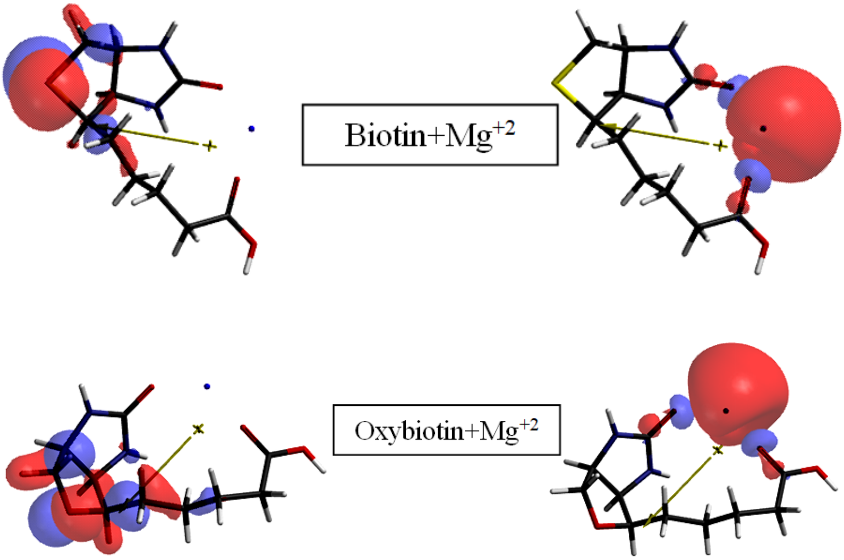

Figure 6. The HOMO and LUMO patterns of the composites considered.

Figure 7 displays the calculated (time dependent DFT) UV-VIS spectra of the parent molecules and their composites considered. The spectra of the parent molecules are confined to UV region of the spectra. The perturbational effect of the Mg^{+} cation is tremendous and in both composites a considerable part of the spectra also lies in the visible region. A comparison of the spectrums of the composites reveal that to a large extent they are quite comparable although their frontier molecular orbital energy gaps (Δε) values are not comparable at all (see Table 6). Note that the spectra are dictated not only by the transitions involving the HOMO-LUMO energy gap but some others are effective as well. The differences of intensities over the comparable regions suggest that the transition moments responsible for the peaks considered should be quite different.

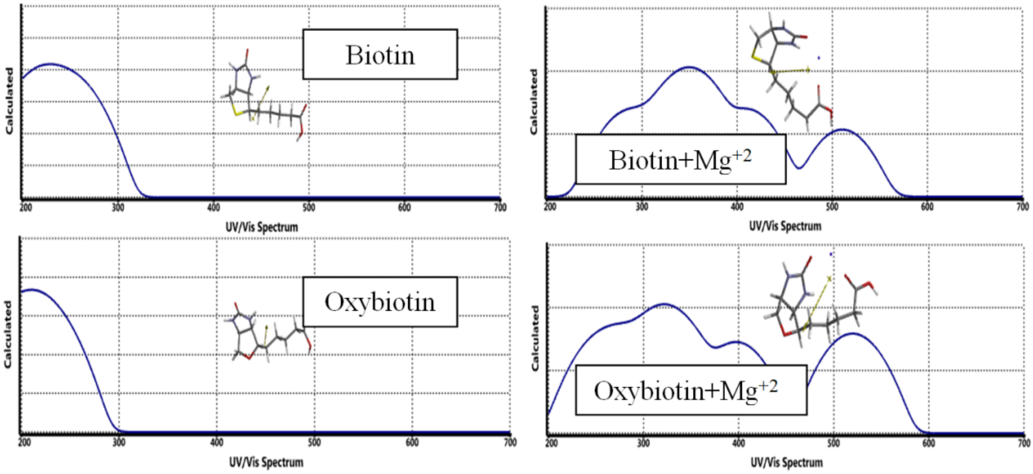

Figure 7. The calculated UV-VIS spectra of the systems considered.

4. Conclusion

In the present computational study, the perturbational effects caused by the presence of a magnesium cation on biotin and oxybiotin have been investigated within the restrictions of DFT at the level of B3LYP/6-31++G(d,p). The results indicate that in the vacuum conditions, both of the Mg^{+2} composite systems of biotin and oxybiotin are characterized with favorable Gibbs free energy of formation values and they are electronically stable. In each case the charge on the magnesium cation is less than +2 implying that some electron population has been transferred from organic component to the cation in the composites. It has been found that the HOMO and LUMO energies of oxybiotin+Mg^{+2} composite have been lowered down at unequal extents as compared to the biotin composite, thus the HOMO-LUMO energy separation is greater in the oxybiotin composite. Although their frontier molecular orbital energy gap values are not comparable, the calculated UV-VIS spectra of them to a large extent are quite comparable, because the spectra are dictated not only by the transitions between the frontier molecular orbitals but some others as well. It should be kept in mind that in aqueous medium the cation is most probably hydrated, thus its perturbative effect should be less compared to the vacuum case.

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