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Interaction of Biotin Tautomers with Magnesium Dication

Lemi Türker

Department of Chemistry, Middle East Technical University, Üniversiteler, Eskişehir Yolu No: 1, 06800 Çankaya/Ankara, Turkey; e-mail: lturker@gmail.com; lturker@metu.edu.tr

Abstract

In the present study, interactions of biotin tautomers and magnesium dication in their composites (in vacuum conditions) have been investigated within the constraints of density functional theory (DFT). Biotin may exhibit 1,3-proton tautomerism. All the composites presently considered have not only exothermic heat of formation values but also favorable Gibbs free energy of formation values. They are electronically stable. Various quantum chemical data have been collected and discussed including UV-VIS spectra. In all the cases, charge of the magnesium cation is less than the initial formal charge of +2 which means that some electron population has been transferred from biotin tautomers to the magnesium cation depending on the tautomeric structure or conformational form. The magnesium cation causes lowering of the frontier molecular orbitals in unequal extents and appears to be more effective on the LUMO energy level in some cases of the composites. Whereas in composite-B, it is more effective on the HOMO energy level. The calculated UV-VIS spectra occur in a large range of wavelengths such that some composites exhibit bathochromic shifts to above 600 nm.

1. Introduction

Biotin which is a water-soluble vitamin and serves as a coenzyme for some carboxylases in humans [1]. Biotin is also covalently attached to distinct lysine residues in histones, affecting chromatin structure and mediating gene regulation [2]. Various biotin derivatives, analogs, and antagonists are known [3]. Dethiobiotin, a sulfur-free analog of biotin, is the direct precursor of biotin during its biosynthesis in microorganisms. Biocytin is released on the enzymatic digestion of biotin-containing proteins. It is cleaved by biotinidase into biotin and lysine. The effect of biotin deficiency

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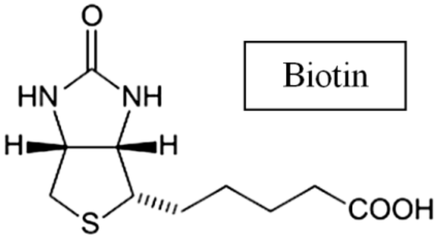
in animals, including humans, is quite severe. The best role of biotin is as the prosthetic group of several biotin-containing enzymes [3-5].



On the other hand, tautomerism plays some important and subtle role in some cases (especially proton tautomerism) [6]. Antonova and Antonov studied controlled shift in the position of tautomeric equilibrium which can be achieved in solution upon protonation or complex formation. Advantages and disadvantages of the described systems were discussed in order to provide further ideas for development [7].

Tautomerism of N-H protons in biotin has attracted some attention too. Such as Zhang *et al.,* employing the B3LYP/6-31G* methods found that activity differences of the two amide protons of biotin were different via perspective from proton transfer in the gas phase. Their results have revealed that for different conformation of biotin, the activities of the two amide groups are different. The 3-NH proton has been found to be more active than that of 1-NH for extended biotin, while less active for folded conformation, which indicated that the 1-NH proton of biotin is not always more active than the 3-NH proton [8]. Perrin and Dwyer reinvestigated proton exchange in biotin [9]. Some additional theoretical articles have appeared in the literature concerning biotin [10-17].

In the present study, interactions of biotin tautomers with magnesium dication in their composites (magnesium-dication having biotin tautomers) have been the focus of interest within the restrictions of density functional theory (DFT).

2. Method of Calculations

In the present study, all the initial structure optimizations of the structures leading to energy minima have been achieved by using MM2 method which is followed by semi empirical PM3 self consistent fields molecular orbital method [18-20]. Afterwards, the structure optimizations have been achieved within the framework of Hartree-Fock and finally by using density functional theory (DFT) at the level of B3LYP/6-31++G(d,p)

[21,22]. Note 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 [23]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [24] and Lee, Yang, Parr (LYP) correlation correction functional [25]. 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 geometry optimization process. All these computations were performed by using SPARTAN 06 [26].

3. Results and Discussion

Since tautomers having different structures possess dual reactivity, it is anticipated that biotin which may exhibit 1,3-proton type tautomerism should display variable biological properties (beside others) depending on its tautomer content (allelotropic mixture [19,20]). Note that substances which are isomeric under certain conditions are tautomeric under more drastic conditions [27,28].

Figure 1 shows the optimized structures of Mg^{+2} composites of biotin tautomers considered. Direction of the dipole moment vector for each composite has been shown as well. Note that some of the structures in Figure 1 stand for different conformers of the same tautomer, such as A and D or C and F. In the present treatment any zwitterionic possibility has been neglected.

In biotin molecule and in its Mg^{+2} composite N-H hydrogens of the carbamide moiety, are coplanar with the carbonyl group. This outcome has changed in some composites, e.g., in composite-B in which the nitrogen atom seems to possess an sp^3 type hybridization like in ammonia.

The electronic configuration of magnesium atom in the ground state is $1s^2 2s^2 2p^6 3s^2$. Its first and second ionization energies are 716 and 1450 kJ/mol., respectively [29]. In the +2 oxidation state the cation constitutes a closed shell system.

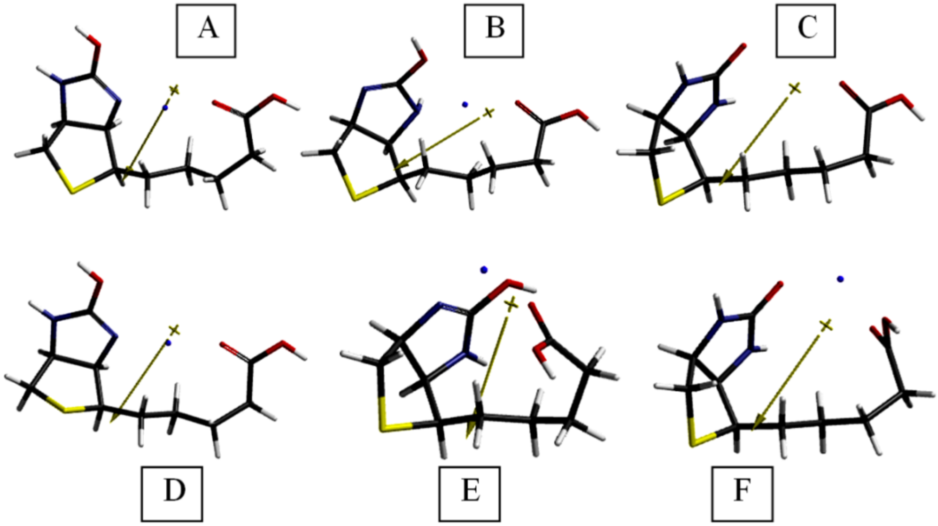


Figure 1. Optimized structures of Mg^{+2} composites of the tautomers considered.

The interaction between the magnesium cation and the tautomers causes some conformation changes of the flexible part of the organic component and in some cases the cation locates itself in the cavity of the tautomer.

Table 1 lists some thermo chemical values of the composites considered. All the composites have exothermic heat of formation values and favorable Gibbs' free energy of formations at the standard states. The algebraical orders of H° and G° values are the same as C<D<F<A<E<B. So composite-C (followed by D) is the most exothermic and the most favorable one among the others.

Table 1. Some thermo chemical values of the composites considered.

Composites	H°	S° (J/mol°)	G°
A	-3474759.816	486.42	-3474904.850
B	-3474661.569	480.79	-3474804.923
C	-3474792.057	489.90	-3474938.142
D	-3474778.09	488.42	-3474923.701
E	-3474684.778	489.17	-3474830.626
F	-3474775.228	488.31	-3474920.813

Energies in kJ/mol.

Table 2 contains some energies of the composites considered where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. The data in the table indicate that all the composites considered are electronically stable (in vacuum) and the stability order is that C>D>F>A>E>B. The electronic stability order of the isomers is the same as their order of G^o values with the change of sign.

Table 2. Some energies of the composites considered.

Composites	E	ZPE	E_C
A	-3475473.09	705.86	-3474767.23
B	-3475372.22	703.85	-3474668.37
C	-3475505.33	705.51	-3474799.82
D	-3475490.12	704.30	-3474785.82
E	-3475397.33	704.47	-3474692.86
F	-3475488.55	705.53	-3474783.02

Energies in kJ/mol.

Table 3 shows some properties of composites considered. The polarizability is expressed by a bivariable formula which is a function of Van der Waals volume and hardness [26]. Hardness is defined as,

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

Table 3. Some properties of composites considered.

Composites	Dipole moment	Polarizability	PSA (Å^2)	Area (Å^2)	Volume (Å^3)	Ovality
A	7.05	59.79	66.060	260.83	237.70	1.41
B	8.66	59.78	67.330	255.50	237.61	1.38
C	16.36	60.33	63.970	264.66	238.40	1.42
D	6.86	59.78	65.494	260.96	237.79	1.41
E	11.65	60.12	67.218	259.68	238.07	1.40
F	16.61	60.31	64.817	262.62	238.46	1.41

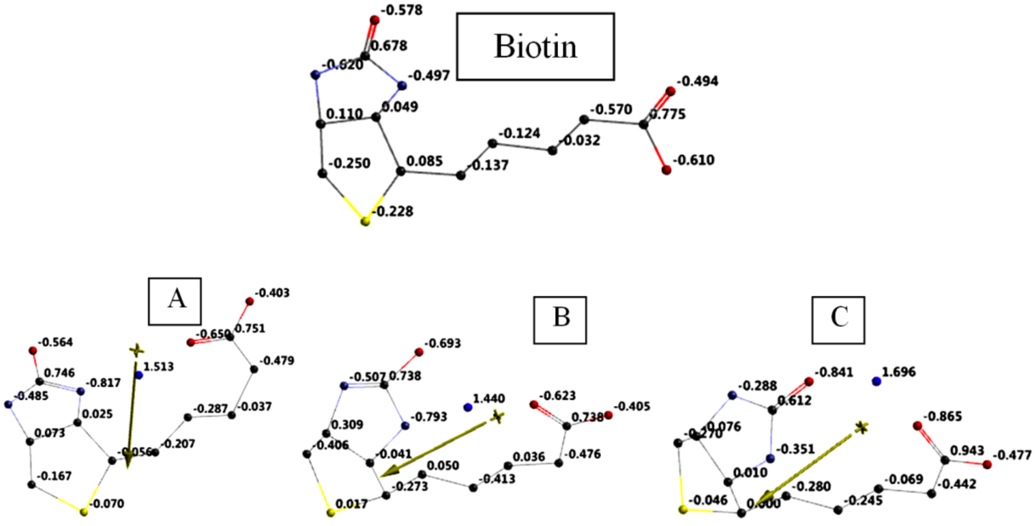
Dipole moments in debye units. Polarizabilities in 10^{-30} m^3 units.

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

Figure 2 displays the electrostatic potential (ESP) charges on the atoms of biotin and the composites considered. Note 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 [26].

As seen in Table 3, some of the composites possess quite high dipole moments depending on the structure and charge distribution. The interaction between the tautomers and the cation should be charge-charge and/ charge-dipole types or both.

Table 4 lists the ESP charges on the magnesium cation in the composites considered. As seen in the table in all the cases the charge on the cation is less than the initial formal charge of +2 which means that some electron population has been transferred from biotin molecule to magnesium cation depending on the tautomeric structure or conformational form. As seen in the table, in the case of composite-B, the cation has the lowest positive partial charge in the group which indicates more electron population has been transferred to the magnesium cation which might be indicative of complexation with some neighboring electron donor atom(s) around.



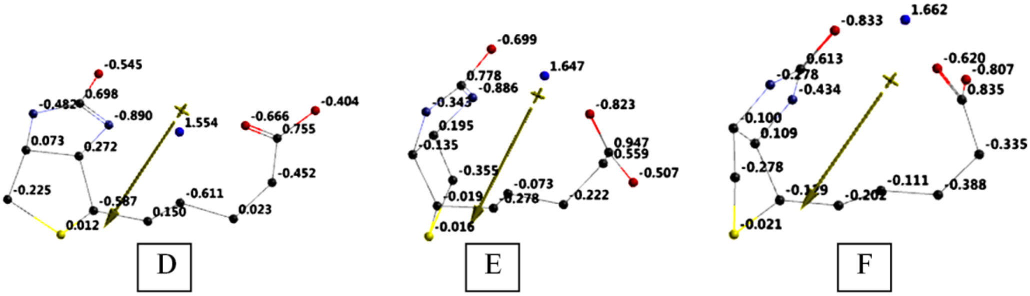


Figure 2. The ESP charges on the atoms of biotin and the composites considered (hydrogens not shown).

Table 4. The ESP charges on the magnesium cation in the composites considered.

A	B	C	D	E	F
1.513	1.440	1.696	1.554	1.647	1.662

In esu units.

Figure 3 shows the bond densities of the composites considered.

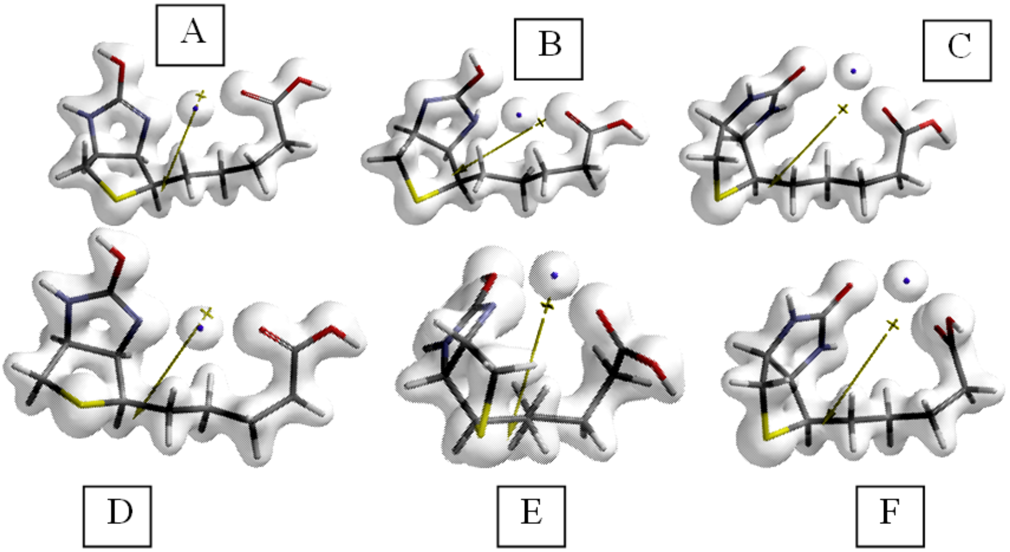


Figure 3. Bond densities of the composites considered.

Figure 4 displays some of the molecular orbital energy levels of the composites considered. As seen in the figure, the tautomerism and the accompanied some conformational changes not only affect the occupied inner-lying molecular orbital energy levels of the composites considered but also the distribution of the unoccupied molecular orbital energy levels. Composite-C is highly noticeable with its lowest-lying LUMO level among the group.

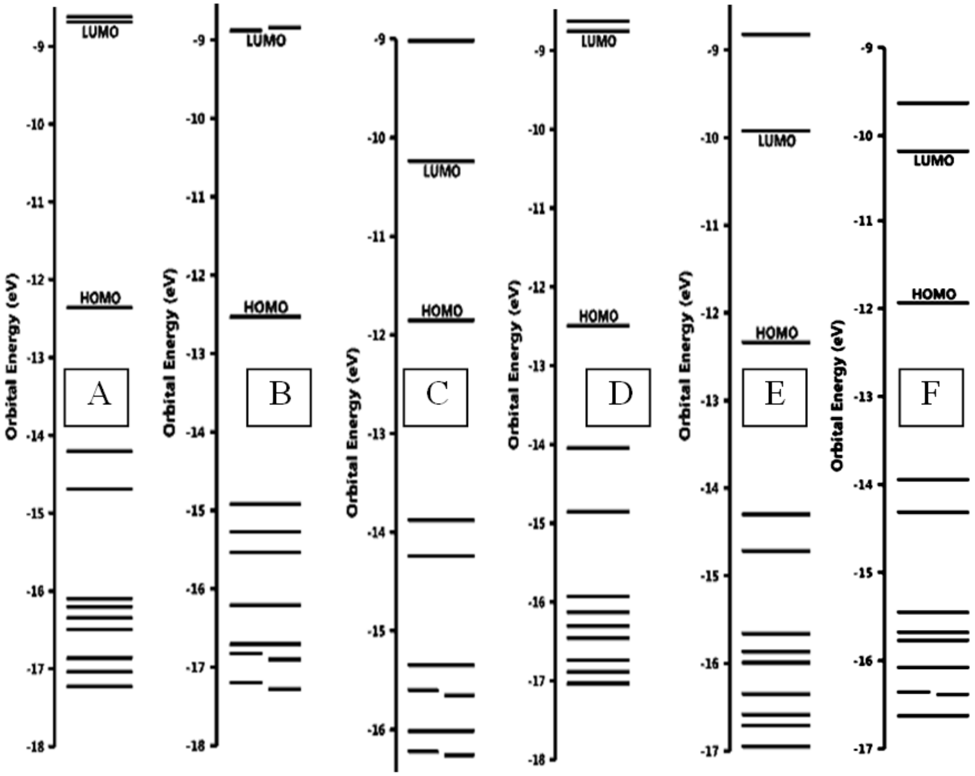


Figure 4. Some of the molecular orbital energy levels of the composites considered.

Table 5 lists the HOMO, LUMO energies and the intermolecular orbital energy gap ($\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$) values of the composites considered. The order of HOMO and LUMO energies are B<D<A<E<F<C and C<F<E<B<D<A, respectively. It seems Mg cation due to its electrostatic potential causes lowering of the frontier molecular orbitals in unequal extents and appears to be more effective on the LUMO level in the cases of composites-C, E and F. Whereas in composite-B, it is more effective on the HOMO energy level.

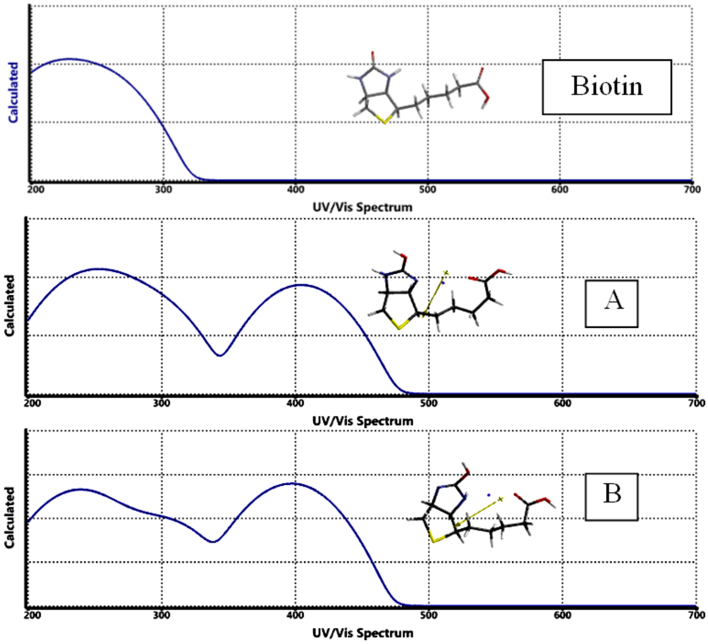
Table 5. The HOMO, LUMO energies and Δε values of the composites considered.

	A	B	C	D	E	F
LUMO	-838.08	-856.54	-988.02	-844.50	-957.26	-982.29
HOMO	-1192.03	-1209.03	-1143.80	-1205.24	-1190.35	-1151.59
Δε	353.95	352.49	155.78	360.74	233.09	169.3

Energies in kJ/mol.

Figure 5 shows the time dependent density functional (TDDFT) UV-VIS spectra of biotin and the composites (Biotin+Mg^{+2}) considered. The calculated UV-VIS spectrum of biotin is confined to ultraviolet region only whereas the respective spectra of the composites occur in a much larger range of wavelengths such that some composites exhibit some bathochromic shift to above 600 nm such as the case in spectrums E and F.

Figure 6 shows the LUMO maps of the composites considered. Note that a LUMO map displays the absolute value of the LUMO on the electron density surface. The blue color (if any exists) stands for the maximum value of the LUMO and the red colored region, associates with the minimum value. As expected the maximum value in each structure happens around the magnesium cation but its boundary is dictated by the structure.



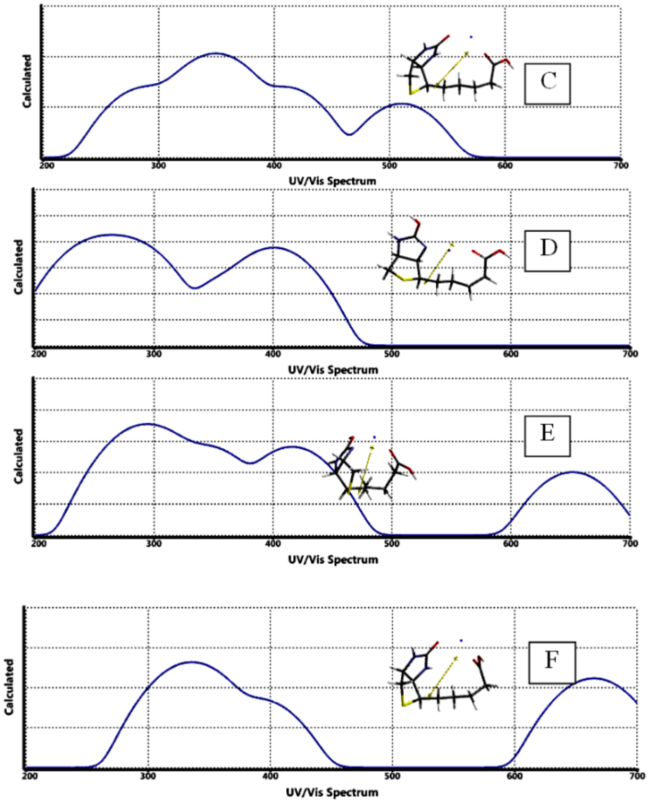


Figure 5. UV-VIS spectra of the composites considered.

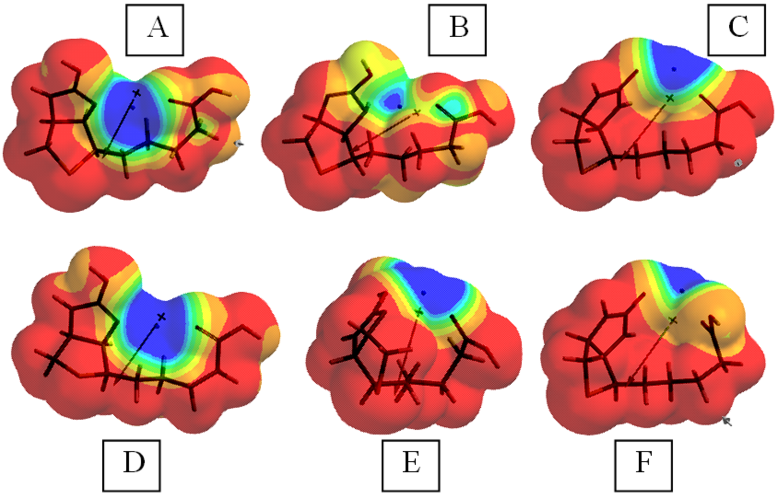


Figure 6. The LUMO maps of the composites considered.

As a remark, the perturbational effects exerted by the magnesium dication on the tautomers of biotin in the aqueous medium should not be as influential as they are in vacuum because of the shielding effect of water molecules around the magnesium cation and some counter anions present.

4. Conclusion

Within the restrictions of present DFT study at the level of B3LYP/6-31++G(d,p) the results indicate that in the vacuum conditions all the composites presently considered have exothermic heat of formation values and they are characterized with favorable Gibbs free energy of formation values. All the systems considered are electronically stable. In all the cases the charges of the magnesium cation is less than the initial formal charge of +2 which means that some electron population has been transferred from biotin molecule to magnesium cation depending on the tautomeric structure or conformational form. The results indicate that Mg cation causes lowering of the frontier molecular orbitals in unequal extents and appears to be more effective on the LUMO level. In general, the perturbations caused by the presence of magnesium cation affect many quantum chemical properties of the systems especially the molecular orbital energy levels, thus the calculated UV-VIS spectra differ from one composite to the other so that the spectra of the composites considered occur in a large range of wavelengths such that some composites exhibit bathochromic shift to above 600 nm.

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