Earthline Journal of Chemical Sciences
E-ISSN: 2581-9003; CODEN: EJCSB4
Volume 11, Number 1, 2024, Pages 147-161
https://doi.org/10.34198/ejcs.11124.147161

Perturbations on Oxybiotin Leading to Biotin. A DFT Treatment

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 computational study, conversion of oxybiotin to biotin by means of oxygen to sulfur replacement has been investigated within the restrictions of density functional theory at the level of B3LYP/6-31++G(d,p). Both of the molecules have not only exothermic heat of formations but also favorable Gibbs free energy of formation values at the standard state. They are electronically stable. Various quantum chemical data accompanying the perturbation considered have been collected and discussed including UV-VIS spectra. The oxygen to sulfur replacement highly affects not only the distribution of molecular orbital energy levels but also the energies of the molecular orbitals in such a way that going from oxybiotin to biotin the HOMO energy level raises up but the LUMO decreases. The both occur at unequal extents thus biotin exhibits some bathochromic effect compared to oxybiotin.

1. Introduction

Oxybiotin is another active analogue of such an important molecule biotin. It is proved that oxybiotin has biotin like activity for many species such as bacteria, yeast, rats and chicken [1-5].

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 was discussed in the literature [6]. Hoffman achieved the first total synthesis of oxybiotin in its dl-form [7]. Later, Ohrui et al., reported the total synthesis of optically active (+)-oxybiotin [8]. Reddy et al., described a versatile route for the stereo selective synthesis of

Received: November 23, 2023; Accepted: December 13, 2023; Published: December 18, 2023

Keywords and phrases: oxybiotin; biotin; vitamin; perturbation; density functional.

oxybiotin [9]. A short enantio selective synthesis of (+)-oxybiotin was published by Shelke et al. [10].

It became of particular interest to determine whether oxybiotin possesses intrinsic activity or whether its biological potency is due to its conversion into biotin. The evidence in the literature is conflicting on this point. Hofmann and Winnick [11], employing a differential assay procedure based upon the selective destruction of biotin activity by dilute potassium permanganate, have demonstrated that *Saccharomyces cerevisiae* and *Rhizobium trifolii* utilize oxybiotin as such and do not convert it into biotin. On the other hand, Rubin et al. [12] have presented data from balance studies on *S. cerevisiae*, which indicates that O-heterobiotin was converted into biotin or some other compound which possessed more activity for *S. cerevisiae* than did oxybiotin.

On the other hand, biotin is a water-soluble vitamin and serves as a coenzyme for some carboxylases in humans [13]. It has been the focus of interests in many publications experimentally as well as theoretically [13-20].

In the present study, perturbations on oxybiotin leading to biotin have been considered within the constraints of density functional theory (DFT).

2. Method of Calculations

Presently, all the initial structure optimizations of the 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 [21-23]. Then, 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) [24,25]. 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 [26]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [27] and Lee, Yang, Parr (LYP) correlation correction functional [28]. 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 [29].

3. Results and Discussion

Structurally, biotin differs from oxybiotin only by the presence of sulfur atom in biotin instead of oxygen atom in 5-membered ring of oxybiotin. In general, it is a centric perturbation. The main perturbation is the replacement of oxygen atom with sulfur in the skeleton of oxybiotin which causes some subsequent perturbations, e.g., variation of bond lengths, dipole moments etc. They are all implicitly related changes. Although, oxybiotin and biotin may have many tautomeric forms, presently the most probable ones are considered.

Oxygen and sulfur, which are two elements of the same group of the periodic table, occur in many biologically important molecules. Oxybiotin and biotin are just two of them. They are interesting because they are derived from the same analogous carbon structure by means of certain centric perturbations [30]. Note that theoretically the replacement of oxygen atom of 5-membered ring of oxybiotin by sulfur atom engender biotin structure.

In the ground state the electronic configurations of oxygen and sulfur are $1s^2 2s^2 2p^4$ and $1s^2 2s^2 2p^6 3s^2 3p^4$, respectively. Their atomic radii are 0.74 and 1.04 Å, respectively. Thus, oxygen to sulfur replacement firstly affects the size of the considered ring, thus perturbs certain bond angles and bond lengths primarily. As a result, the degree of certain lone-pair, lone-pair or σ-orbitals- lone-pair intermixing interactions may change which must have certain influence on the molecular orbital properties of the systems under consideration.

On the other hand, the Pauling electro negativities of oxygen and sulfur are 3.5 and 2.5, respectively [31].

Figure 1 shows the optimized structures of oxybiotin and biotin as well as direction of the dipole moment vectors.

Figure 2 shows the calculated bond lengths of the structures considered. As seen in the figure, bond lengths of biotin are generally longer than the respective ones in oxybiotin, however magnitudes of the changes are small. On the other hand, replacement of C-O bonds by C-S bonds is the only main factor dictating variations in apparent

differences between these molecules beside the electronegativity difference of oxygen and sulfur.

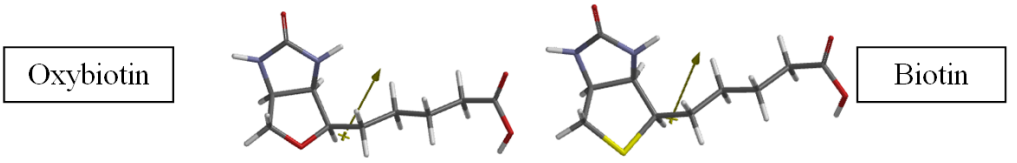

Figure 1. Optimized structures of oxybiotin and biotin.

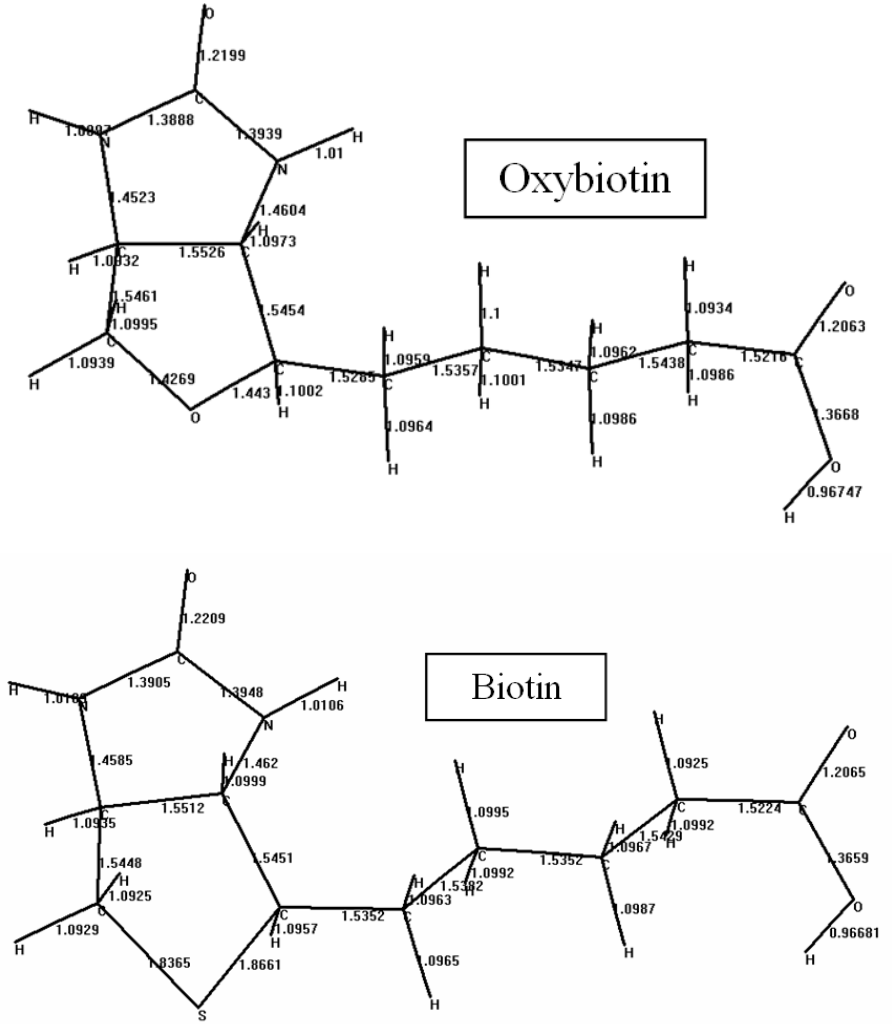

Figure 2. Calculated bond lengths (Å) of the structures considered.

Figure 3 shows numbering of atoms in oxybiotin and biotin and Table 1 lists some bond angles in their structures.

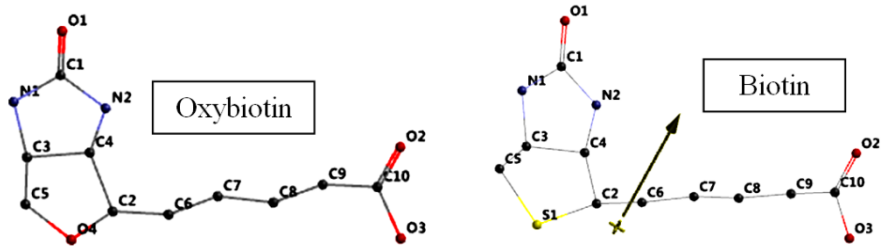

Figure 3. Numbering of atoms in oxybiotin and biotin (hydrogens not shown).

Due to the larger size of sulfur atom, one may expect a larger C-S-C angle than C-O-C. However, as seen in the table it is only 94.50°. In the present case, the calculated C-S bonds are 1.836 Å and 1.866 Å in contrast to C-O bonds in oxybiotin which are 1.42 Å and 1.44 Å. The 5-membered ring in biotin possesses somewhat deformed envelope conformation. Compounds containing divalent sulfur are analogous of the corresponding oxygen derivatives. Their bond angles are however substantially narrowed. In thioethers it is approximately varies between 97-99° [31]. Whereas in dimethyl ether and ethyl methyl ether the C-O-C angle is about 111°. Note that in CH_3SCH_3 the sulfur atom is tetrahedrally hybridized, that is two orbitals of the atom form σ-bonds and two are occupied by lone pairs [31].

Table 1. Some bond angles in oxybiotin and biotin.

Angle	Oxybiotin	Biotin
N1C1N2	106.57	106.54
C1N2C4	111.72	110.73
N2C4C3	100.65	100.04
C4C3N1	102.34	101.09
C3N1C1	111.10	110.31
C4C2X1	106.76	107.65
C2X1C5	111.35	94.50
X1C5C3	106.29	106.96
C5C3C4	102.33	107.93
C3C4C2	104.12	110.34

X1: O (Oxybiotin), S (Biotin). Angles in degrees.

Figure 4 shows the electrostatic potential (ESP) charges on atoms of oxybiotin and biotin. 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 [29].

The data in Figure 4 reveal that in biotin structure the charges on atoms of the lactam ring are smaller in absolute value than the respective charges of oxybiotin. As for the other ring atoms, the sulfur has much smaller (in absolute value) charge than the oxygen atom as expected from their electro negativities. The charges on the adjacent carbon atoms in each ring are not symmetrical. The carbon bearing the substituent has positive charge in both of the molecules although in the biotin case it is much smaller. The other carbon atom, adjacent to the oxygen or sulfur is negatively charged but in biotin case it is more negative than the case of oxybiotin. This effect occurs in both of the structures, namely one of the C-X bonds is longer than the other C-X bond in the ring, irrespective of whether X is oxygen or sulfur. At first sight it seems mainly due to the effect of side chain attached to the ring.

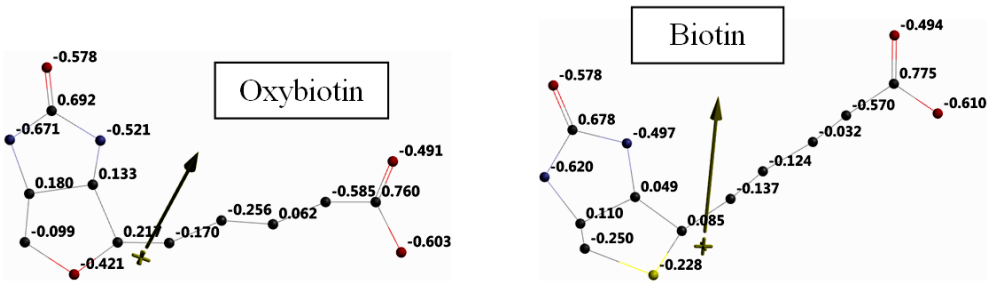

Figure 4. The ESP charges on atoms of oxybiotin and biotin (hydrogens not shown).

Table 2 lists the dipole moment components of the molecules considered. As seen in Table 2, the greatest perturbation (in absolute value) occurs in X-component of the dipole moment which apparently affects the direction of the dipole moment vector (see Figure 4).

Table 2. The dipole moment components of the molecules considered.

Molecule	X	Y	Z
Oxybiotin	-4.608124	-4.105711	4.429157
Biotin	-4.382906	-4.086664	4.263185
Δ	0.225218	0.019047	-0.16597

In Debye units. Δ (relative to oxybiotin).

Some properties of the molecules considered are shown in Table 3. Where hardness is defined as [29],

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

where ε_{HOMO} and ε_{LUMO} are the molecular orbital energies of the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbital energies (Frontier molecular orbital energies), respectively. Whereas, the polarizability is defined according to the multivariable formula [29].

$$\text{Polarizability} = 0.08*V - 13.0353*h + 0.979920*h2 + 41.3791$$

where V and h are the Van der Waals volume and hardness, respectively.

Table 3. Some properties of the molecules considered.

Molecule	Dipole moment	E_{aq}	Solvation Energy	Hardness	Log P	Polarizability
Oxybiotin	7.60	-2103576.93	-82.06	307.525	-0.84	57.90
Biotin	7.35	-2951554.30	-82.46	266.41	-0.12	58.88

Point group of all is C_1. Energies in kJ/mol. Dipole moments in debye units. Polarizabilities in 10^{-30} m^3 units.

Log P values of oxybiotin and biotin are quite different from each other. Note that hydrophilic compounds (having low octanol/water partition coefficients) are found primarily in aqueous regions.

The chemical function descriptors (CFD) oxybiotin and biotin are shown in Figure 5.

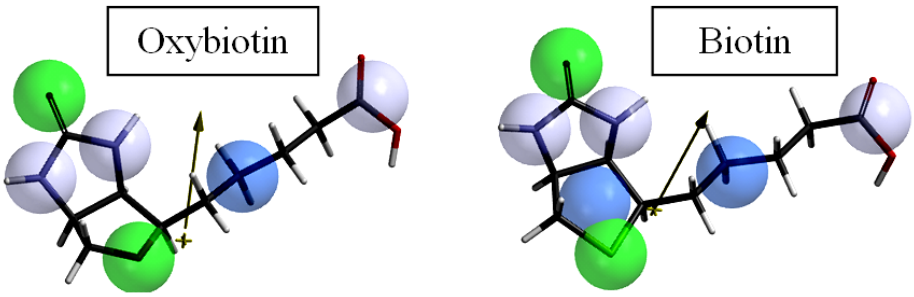

Figure 5. The chemical function descriptors (CFD) of oxybiotin and biotin (Green: HBA; Purplish: HBA, HBD and +ionizable; Bluish: Hydrophobe).

In the figure different colors stand for different descriptors. Note that CFDs are attributes given to a molecule in order to characterize or anticipate its chemical behavior. Note that HBA and HBD mean hydrogen bond acceptors and donors, respectively. As seen in the figure, oxygen to sulfur perturbation in the structure of oxybiotin imports the property of hydrophobic character in the 5-membered ring of biotin (see Figure 5).

Table 4 shows some thermo chemical values of the molecules considered. As seen in the table, both of the molecules are characterized with exothermic heat of formation values and both have thermo chemically favorable Gibbs energy of formation values at the standard state.

Table 4. Some thermo chemical values of oxybiotin and biotin.

Molecule	H^o	S^o (J/mol^o)	G^o
Oxybiotin	-2102773.302	464.82	-2102911.89
Biotin	-2950764.248	472.67	-2950905.16

Energies in kJ/mol.

Table 5 shows some energies 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 5. Some energies of oxybiotin and biotin.

Molecule	E	ZPE	E_C
Oxybiotin	-2103494.86	705.21	-2102789.65
Biotin	-2951471.83	698.14	-2950773.69

Energies in kJ/mol.

Figure 6 shows some of the molecular orbital energy levels of the species considered. As seen in the figure, oxygen to sulfur replacement highly affects the distribution of molecular orbital energy levels. The centric perturbation also affects the energies of the molecular orbitals.

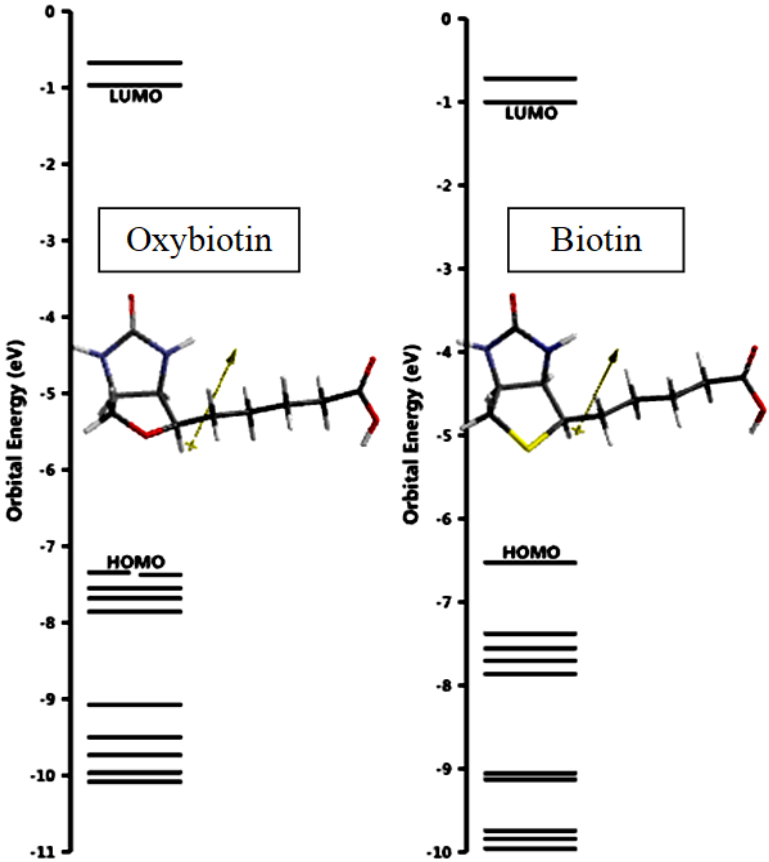

Figure 6. Some of the molecular orbital energy levels of the species considered.

Table 6 tabulates the HOMO, LUMO energies and the interfrontier molecular orbital energy gap ($\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$) values of oxybiotin and biotin. The data reveal that the perturbation is mainly effective on the HOMO energies and the energy of biotin has been raised up relative to oxybiotin whereas the LUMO energy has been lowered down somewhat.

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

Molecule	ε_{HOMO}	ε_{LUMO}	Δε
Oxybiotin	-708.38	-93.33	615.05
Biotin	-629.70	-96.88	532.82

Energies in kJ/mol.

The oxygen atom being more electronegative than sulfur attracts electrons more strongly and should lower the molecular orbital energy levels but both the oxygen and sulfur atoms have lone-pair of electrons which might interfere with σ-orbitals to raise the molecular orbital energy levels. These effects should take place at unequal extents, in such a way that going from oxybiotin to biotin the HOMO energy level raises up but the LUMO decreases at unequal extents. Consequently, the order of interfrontier molecular orbital energy gap values (Δε) is biotin < oxybiotin. Thus, in the calculated spectra of the molecules, biotin exhibits some bathochromic effect compared to oxybiotin (see Figure 7). Figure 7 is the UV-VIS (time-dependent DFT) spectra of the molecules considered.

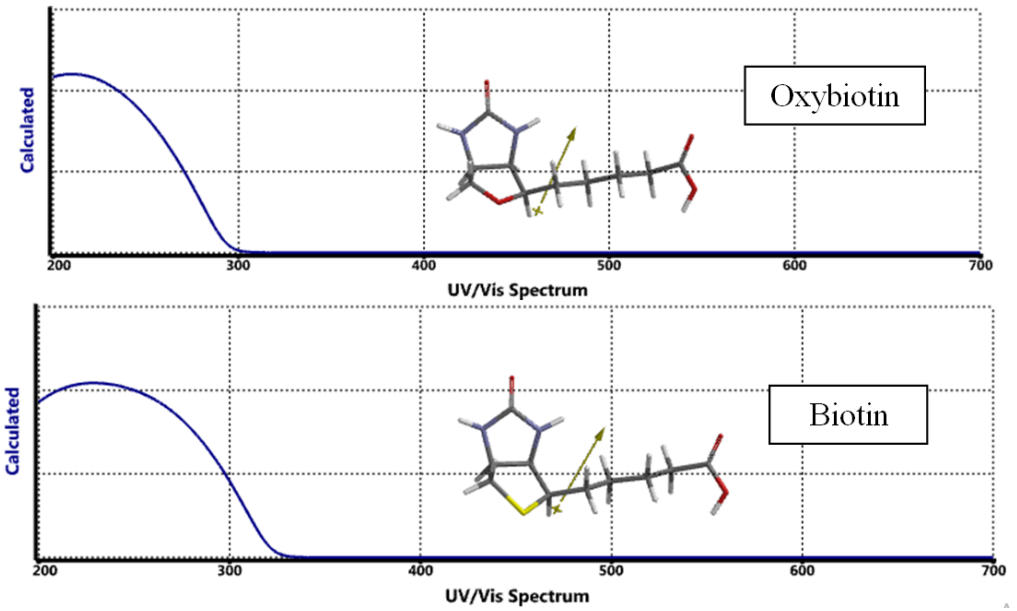

Figure 7. UV-VIS spectra of the species considered.

Figure 8 shows the HOMO and LUMO patterns of oxybiotin and biotin. In each case, the HOMO spreads over the ring atoms but in the case of biotin mainly the atomic orbitals of ring, containing the sulfur atom contribute in to the HOMO. In both of the structures the substituent atoms contribute almost nothing into the HOMO. Note that the electronic configurations of sulfur and oxygen atoms are different. Their valence shells originate from different period of the periodic table. Whereas in both cases the LUMO spreads over the side chain atoms only. No contribution comes from both of the ring atoms.

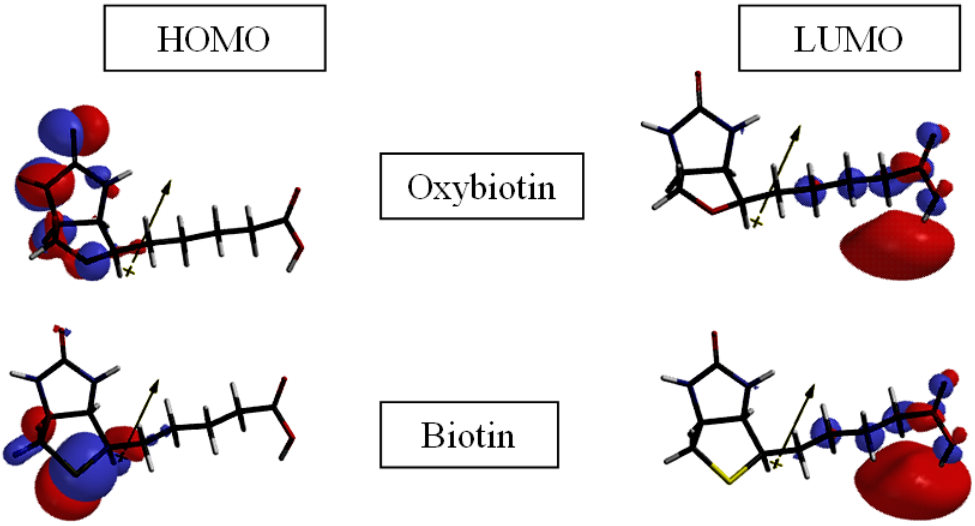

Figure 8. The HOMO and LUMO patterns of oxybiotin and biotin.

Figure 9 shows the local ionization maps of the molecules considered where conventionally red/reddish regions (if any exists) on the density surface indicate areas from which electron removal is relatively easy, meaning that they are subject to electrophilic attack. The sulfur atom seems to be more favorable site in biotin than the oxygen atom in oxybiotin.

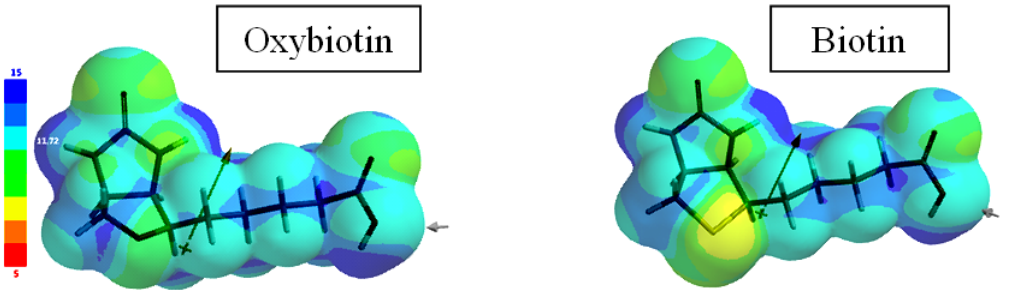

Figure 9. The local ionization maps of the molecules considered.

Figure 10 shows the LUMO maps of the species 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.

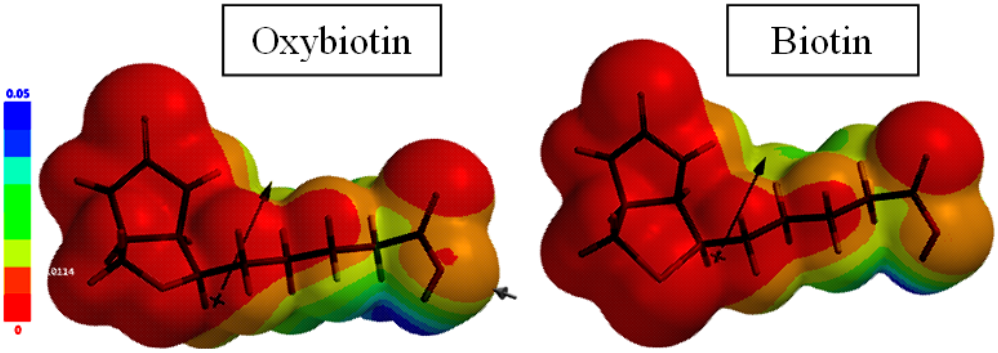

Figure 10. The LUMO maps of the species considered.

The data presented by the figures suggest that in general these quite similar structures should not suffer much from oxygen to sulfur perturbation in terms of electrophilic and nucleophilic character.

4. Conclusion

In the present computational study, within the restrictions of DFT study at the level of B3LYP/6-31++G(d,p), the perturbational effects arising from oxygen to sulfur replacement on oxybiotin to yield biotin structure have been investigated. It puts some light on how such a replacement in structure of oxybiotin affects some properties of it.

The results indicate that in the vacuum conditions, both oxybiotin and biotin are characterized with favorable Gibbs free energy of formation values and they are electronically stable. In the structures oxygen and sulfur atoms carry negative partial charges. Substituent also exerts some perturbational effect so that in each structure α-carbons to oxygen or sulfur atom possess positive and negative partial charges. One of the ring carbons at the point of attachment becomes partially negative but the other α-carbon acquires negative charge. In general bond lengths of biotin are longer than the respective ones of oxybiotin. The greatest perturbation (in absolute value) occurs in X-component of the dipole moment which apparently affects the direction of the dipole moment vector. The oxygen to sulfur replacement highly affects the distribution of molecular orbital energy levels as well as the energies of the molecular orbitals. Going from oxybiotin to biotin the HOMO energy level raises up but the LUMO decreases at unequal extents so that biotin exhibits some bathochromic effect compared to oxybiotin. Over all, oxygen to sulfur perturbation in the structure of oxybiotin imports some

hydrophobic character to the sulfur having ring of biotin. However, the perturbations should not cause oxybiotin to be significantly different from biotin. In fact oxybiotin has biotin like activity for many species.

References

[1] Pilgrim, F.J., Axelrod, A.E., Winnick, T., & Hofmann, K. (1945). The microbiological activity of an oxygen analog of biotin. *Science*, *102*, 35-36. https://doi.org/10.1126/science.102.2637.35

[2] Duschinsky, R., Dolan, L.A., Flower, D., Rubin, S.H. (1945). "O-Heterohkrtin" a biologically active oxygen analog of biotin. *Arch. Biochem*., *6*, 480-481.

[3] Krueger, K.K., & Peterson, W.H.I. (1948). Metabolism of biotin and oxybiotin by *Lactobacillus pentosus* 124-2. *J. Bact*., *55*, 693-703.

[4] Shull, G.M., & Peterson, W.H. (1948). The nature of the "spprogenes vitamin" and other factors in the nutrition of *Clostridium sporogenes*. *Arch. Biochem*., *18*, 69-83.

[5] Hofmann, K., McCoy, R.H., Felton, J.R., Axelrod, A.E., & Pilgrim, F.J. (1945). The biological activity of oxybiotin for the rat and the chick. *Arch. Biochem.*, *7*, 393-394. PMID: 21015707.

[6] Axelrod, A.E., Pilgrim, F.J., & Hofmann, K.J. (1946). The activity of dl-oxybiotin for the rat. *J. Biol. Chem., 163*, 191-194. PMID: 21023639.

[7] Hofmann, K.J. (1945). Furan and tetrahydrofuran derivatives. VI. The total synthesis of dl-oxybiotin. *J. Am. Chem. Soc., 67*, 1459-1462. https://doi.org/10.1021/ja01225a013

[8] Ohrui, H., Kuzuhara, H., & Emoto, S. (1971). Syntheses with azido-sugars Part III. Preparation of d-oxybiotin. *Agric. Biol. Chem*., 35, 752-755. https://doi.org/10.1080/00021369.1971.10859969

[9] Reddy, L.V.R., Swamy, G.N., & Shaw, A.K. (2008). A versatile route for the stereoselective synthesis of oxybiotin. *Tetrahedron: Asymmetry, 19*(11), 1372-1375. https://doi.org/10.1016/j.tetasy.2008.05.008

[10] Shelke, A.M., Rawat, V., Sudalai, A., & Suryavanshi, G. (2014). A short, enantioselective synthesis of 3-epi-jaspine B and (+)-oxybiotin via an intramolecular tandem desilylation oxa-Michael addition strategy. *RSC Adv*., *4*, 49770-49774. https://doi.org/10.1039/C4RA08698H

[11] Hofmann, K., & Winnick, T. (1945). The determination of oxybiotin in the presence of biotin. *J. Biol. Chem*., *160*, 449-463.

[12] Rubin, S.H., Flower, D., Rosen, F., & Drekter, L. (1945). The biological activity of O-heterobiotin. *Arch. Biochem*., *8*, 79-90.

[13] Bender, D. (2003). *Nutritional biochemistry of the vitamins*. Cambridge: Cambridge University Press.

[14] Zempleni, J., Wijeratne, S.S.K., & Hassan, Y.I. (2009). Biotin. *BioFactors*, *35*(1), 36-46. https://doi.org/10.1002/biof.8

[15] McMahon, R.J. (2002). Biotin in metabolism and molecular biology. *Annual Review of Nutrition*, *22*, 221-239. https://doi.org/10.1146/annurev.nutr.22.121101.112819

[16] Perrin, C.L., & Dwyer, T.J. (1987). Proton exchange in biotin: a reinvestigation, with implications for the mechanism of carbon dioxide transfer. *J. Am. Chem. Soc.*, *109*(17), 5163-5167. https://doi.org/10.1021/ja00251a020

[17] Yi, L., Li, H., Zhang, R., & Han, S. (2007). Theoretical study of cooperativity in biotin. *J. Phys. Chem. B*, *111*(51), 14370-14377. https://doi.org/10.1021/jp076914q

[18] Yi, L., Li, H., Zhang, R., & Han, S. (2004). Molecular dynamics simulations of biotin in aqueous solution. *J. Phys. Chem. B*, *108*(28), 10131-10137. https://doi.org/10.1021/jp049207v

[19] Abyar, F., & Novak, I. (2018). Electronic structure of biotin conformers studied with SAC-CI and OVGF methods. *J. Phys. Chem. A*, *122*(8), 2079-2085. https://doi.org/10.1021/acs.jpca.7b12631

[20] Emami, M., Teimouri, A., & Chermahini, A.N. (2008). Vibrational spectra and assignments using *ab initio* and density functional theory analysis on the structure of biotin. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *71*(4), 1516-1524. https://doi.org/10.1016/j.saa.2008.05.020

[21] Stewart, J.J.P. (1989). Optimization of parameters for semi empirical methods I. *J. Comput. Chem.*, *10*, 209-220. https://doi.org/10.1002/jcc.540100208

[22] Stewart, J.J.P. (1989). Optimization of parameters for semi empirical methods II. *J. Comput. Chem.*, *10*, 221-264. https://doi.org/10.1002/jcc.540100209

[23] Leach, A.R. (1997). *Molecular modeling*. Essex: Longman.

[24] Kohn, W., & Sham, L.J. (1965). Self-consistent equations including exchange and correlation effects. *Phys. Rev.*, *140*, 1133-1138. https://doi.org/10.1103/PhysRev.140.A1133

[25] Parr, R.G., & Yang, W. (1989). *Density functional theory of atoms and molecules*. London: Oxford University Press.

[26] Becke, A.D. (1988). Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A*, *38*, 3098-3100. https://doi.org/10.1103/PhysRevA.38.3098

[27] Vosko, S.H., Wilk, L., & Nusair, M. (1980). Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.*, *58*, 1200-1211. https://doi.org/10.1139/p80-159

[28] Lee, C., Yang, W., & Parr, R.G. (1988). Development of the Colle-Salvetti correlation energy formula into a functional of the electron density. *Phys. Rev. B*, *37*, 785-789. https://doi.org/10.1103/PhysRevB.37.785

[29] SPARTAN 06 (2006). Wavefunction Inc. Irvine CA, USA.

[30] Dewar, M.J.S., & Dougherty, R.C. (1975). *The PMO theory of organic chemistry*. New York: Plenum/Rosseta.

[31] Durant, P.J., & Durant, B. (1972). *Introduction to advanced inorganic chemistry*. London: Longman.