Earthline Journal of Chemical Sciences
E-ISSN: 2581-9003; CODEN: EJCSB4
Volume 13, Number 1, February 2026, Pages 75-86
https://doi.org/10.34198/ejcs.13126.06.075086

Effect of Mg^{+2} or Zn^{+2} ion on melatonin – 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

Effects of dications of magnesium and zinc atom(s) on melatonin, a nocturnal hormone, have been investigated within the constraints of density functional theory at the level of B3LYP/ 6-31++G(d,p). The results revealed that the composites considered (like melatonin and its dication) are exothermic and favorable in terms of H^o and G^o values. Also they are electronically stable. Various structural, quantum chemical and spectral (IR and UV-VIS) data are collected and discussed. In each case, interaction with melatonin, the cations possessed less positive charge than the initial charge of +2 that means some electron population has been transferred from melatonin to the cation. However, in the case of zinc dication composite, some bond density exists between the organic and inorganic components.

1. Introduction

Melatonin, a nocturnal hormone, (known as circadian rhythm hormone) which is secreted by pineal gland in brain is a highly ubiquitous biomaterial [1]. Some evidence accumulated so far indicates that melatonin is also synthesized in the hypothalamus and in other parts of the body, however the melatonin in the circulation originates from the pineal [1]. Also, it has been found that its concentration in cerebrospinal fluid is higher than that in plasma [1]. Moreover, it has been proved that the melatonin level circulating is interestingly dependent on the incident light, so that high levels are attained in darkness. Thus, melatonin is a nocturnal (sleep-related) hormone and inter-related with circadian rhythm [2, 3].

However, it has been clinically demonstrated that melatonin treatment adversely affects the symptoms of rheumatoid arthritis [2]. Recently, a review article has reported some anticarcinogenic activity of melatonin [4]. Also, it has been quite recently shown that of serum melatonin level determination is a valuable methodology to define body circadian phase in lung cancer patients [5]. It has been reported that melatonin reverses the darkening effect of melanin-releasing hormone (MRH) by stimulating aggregation, causing lightening of skin color [6]. It has been also proved that melatonin exerts a certain retarding action on the esterus cycle. Since, melatonin also exists in hypothalamic tissue and peripheral nerve, it might possess some yet unknown functions in the metabolism of several neural and endocrine processes [1, 6, 7]. Considerable experimental evidence piled up so far suggests that melatonin prevents accumulation of amyloid β (Aβ) peptide in the brain which is supposed to be a cause of Alzheimer's disease [8]. Very recently, many articles accumulated in the literature displaying its role in diverse fields of biology and medicine [9-17].

The melatonin biosynthesis originates from 5-hydroxy tryptophan which undergoes by decarboxylation in vivo to produce serotonin (5-hydroxytryptamine). N-Acetylation of serotonin, followed by O-methylation in the pineal body forms melanotonin (melatonin, N-acetyl-5-methoxyserotonin) [1, 6]. Recent years also evidenced some biological, physical and theoretical investigations on melatonin [18-26].

Received: December 10, 2025; Accepted: January 3, 2026; Published: January 5, 2026

Keywords and phrases: melatonin, magnesium, zinc, density functional calculation, spectra.

2. Method of Calculations

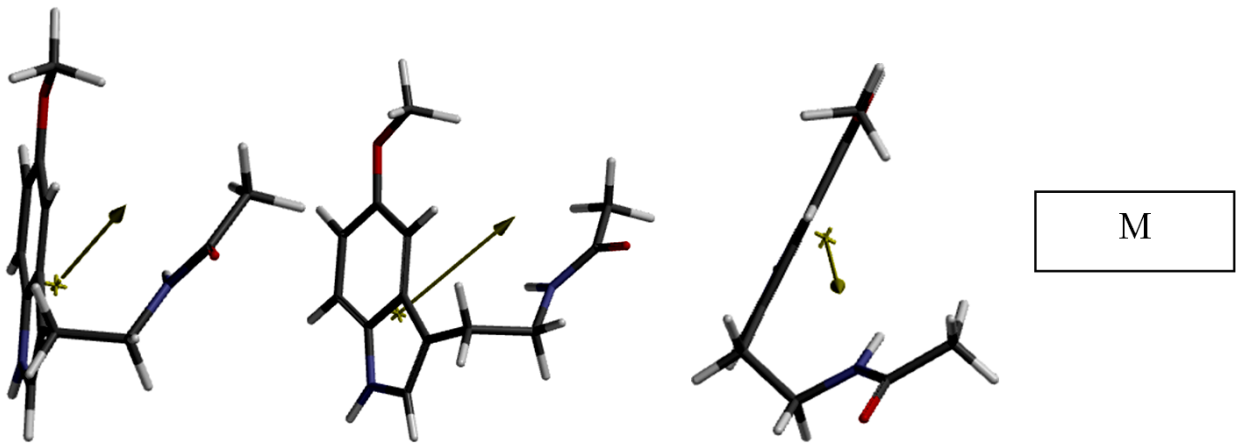
In the present study, all the initial optimizations of the structures leading to energy minima have been achieved, first by using MM2 method which is then followed by semi empirical PM3 self consistent fields molecular orbital method [27-29]. Afterwards, the structure optimizations have been achieved within the framework of Hartree-Fock and finally by using density functional theory (DFT) at the level of B3LYP/6-31++G(d,p) [30,31]. 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 [32]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [33] and Lee, Yang, Parr (LYP) correlation correction functional [34]. In the present study, the normal mode analysis for each structure yielded no imaginary frequencies for the 3*N*–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 program [35].

3. Results and Discussion

Figure 1 shows the optimized structures of the systems of consideration, where M, stands for melatonin whereas M^{+2} is the product of static charging of melatonin. Other symbols are self indicative. The arrows in the figure stand for the direction of calculated dipole moment vectors. It is worth remembering that a resultant dipole moment vector is the vectorial sum of the individual bond dipoles, thus location/orientation of the heteroatoms in the organic component greatly affects both the magnitudes and the directions. In the case of composites considered, also the cations of Mg or Zn, exert their influence.

Some thermo chemical properties of the structures considered are listed in Table 1. The data presented in the table reveal that the standard thermo chemical formation data of all the species considered are exothermic (H^o values) and they are favored according to their G^o (Gibbs free energy of formation) values.

Some energies of the structures considered are included in Table 2, where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. According to the data, all the structures are electronically stable.



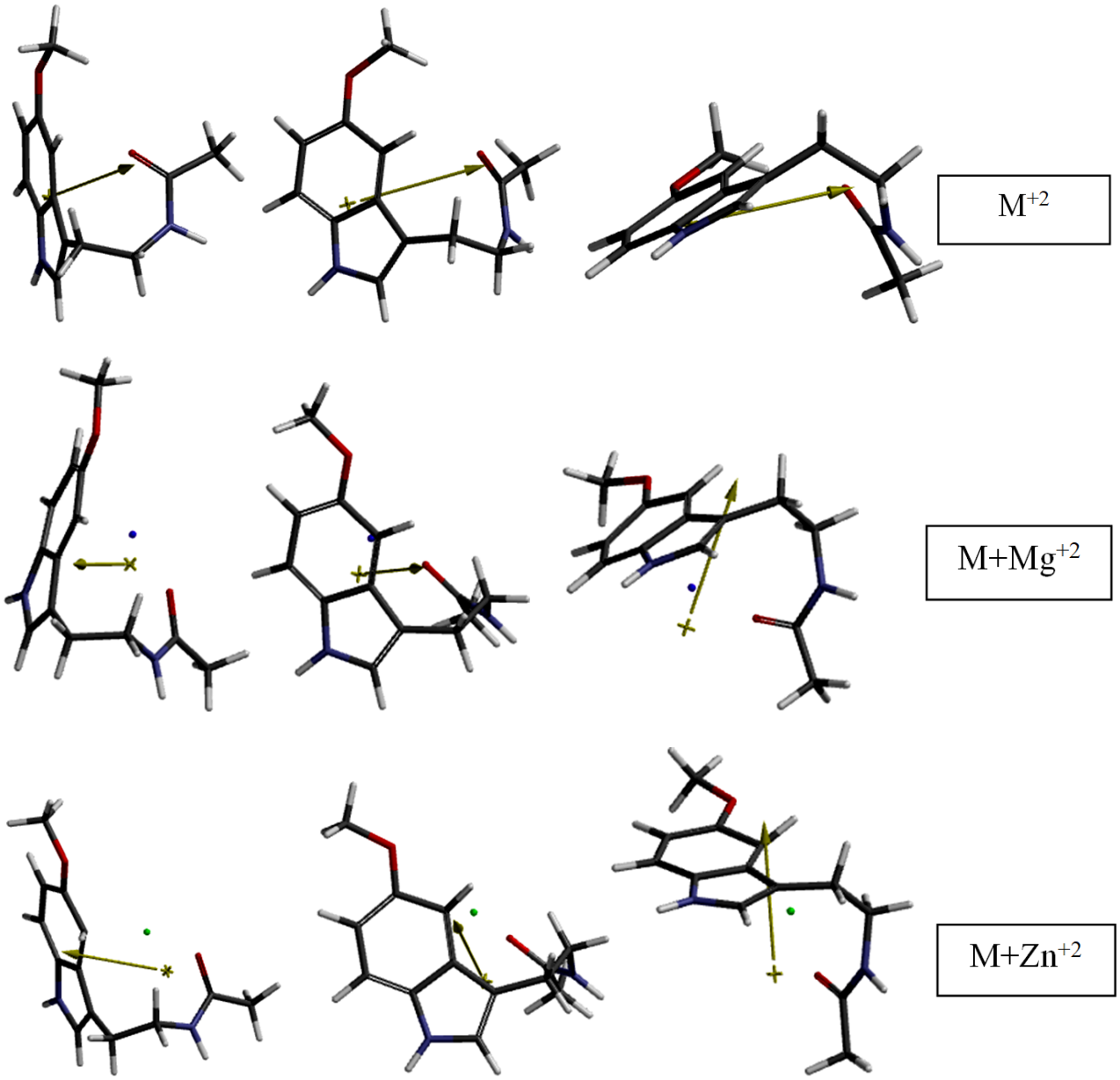


Figure 1. Optimized structures of the systems of consideration (Three different views).

Table 1. Some thermo chemical properties of the systems considered.

Systems	Hº	Sº (J/molº)	Gº
M	-2007870.247	479.68	-2008013.268
M^{+2}	-2006085.756	479.23	-2006228.641
$M+Mg^{+2}$	-2531898.865	493.32	-2532045.950
$M+Zn^{+2}$	-6677601.167	495.90	-6677749.036

Energies in kJ/mol.

Table 2. Some energies of the systems considered.

Systems	E	ZPE	E_C
M	-2008608.99	718.46	-2007890.53
M^{+2}	-2006825.58	719.67	-2006105.91
$M+Mg^{+2}$	-2532646.72	730.35	-2531916.37
$M+Zn^{+2}$	-6678310.47	730.26	-6677580.21

Energies in kJ/mol.

Figure 2 shows the calculated bond lengths of the composite structures considered.

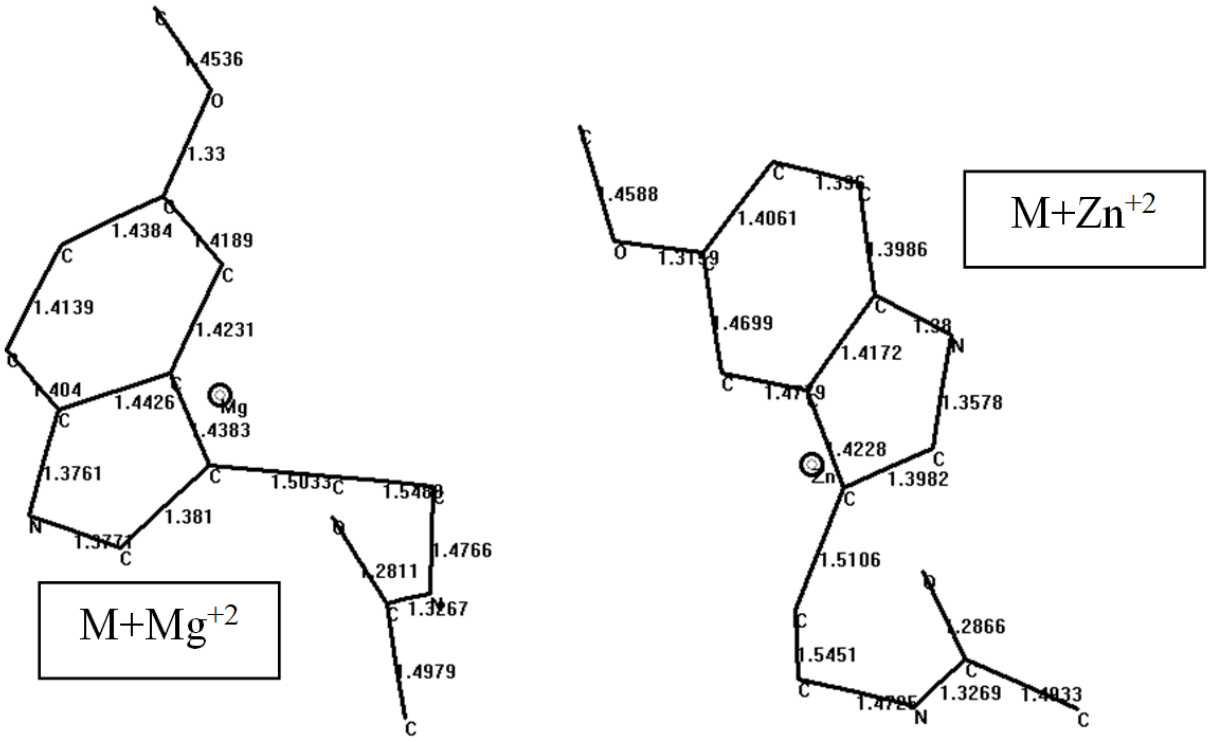


Figure 2. Calculated bond lengths (Å) of the composite systems considered (Hydrogens omitted).

Figure 3 shows the calculated IR spectra of the structures considered. In the spectrum of melatonin N-H stretching of 5-membered ring happens at 3684 cm^{-1}, followed by amide N-H stretching at 3627 cm^{-1}. The sharp peak at 1742 cm^{-1} is the C=O stretch. In the dication form N-H stretching occurs at 3581 cm^{-1} (amide) and 3540 cm^{-1} (5-membered ring). The amide C=O stretch takes play at 1651 cm^{-1}. In the magnesium dication composite the ring N-H vibration occurs at 3628 cm^{-1} whereas the amide N-H vibrates at 3589 cm^{-1}. The peak at 1635 cm^{-1} stands for the amide C=O stretch. In the zinc dication composite of melatonin, N-H stretchings occur at 3623 cm^{-1} (the ring) and 3584 cm^{-1}(amide) sequentially. The C=O stretching coupled with various bending vibrations occurs at 1592 cm^{-1}.

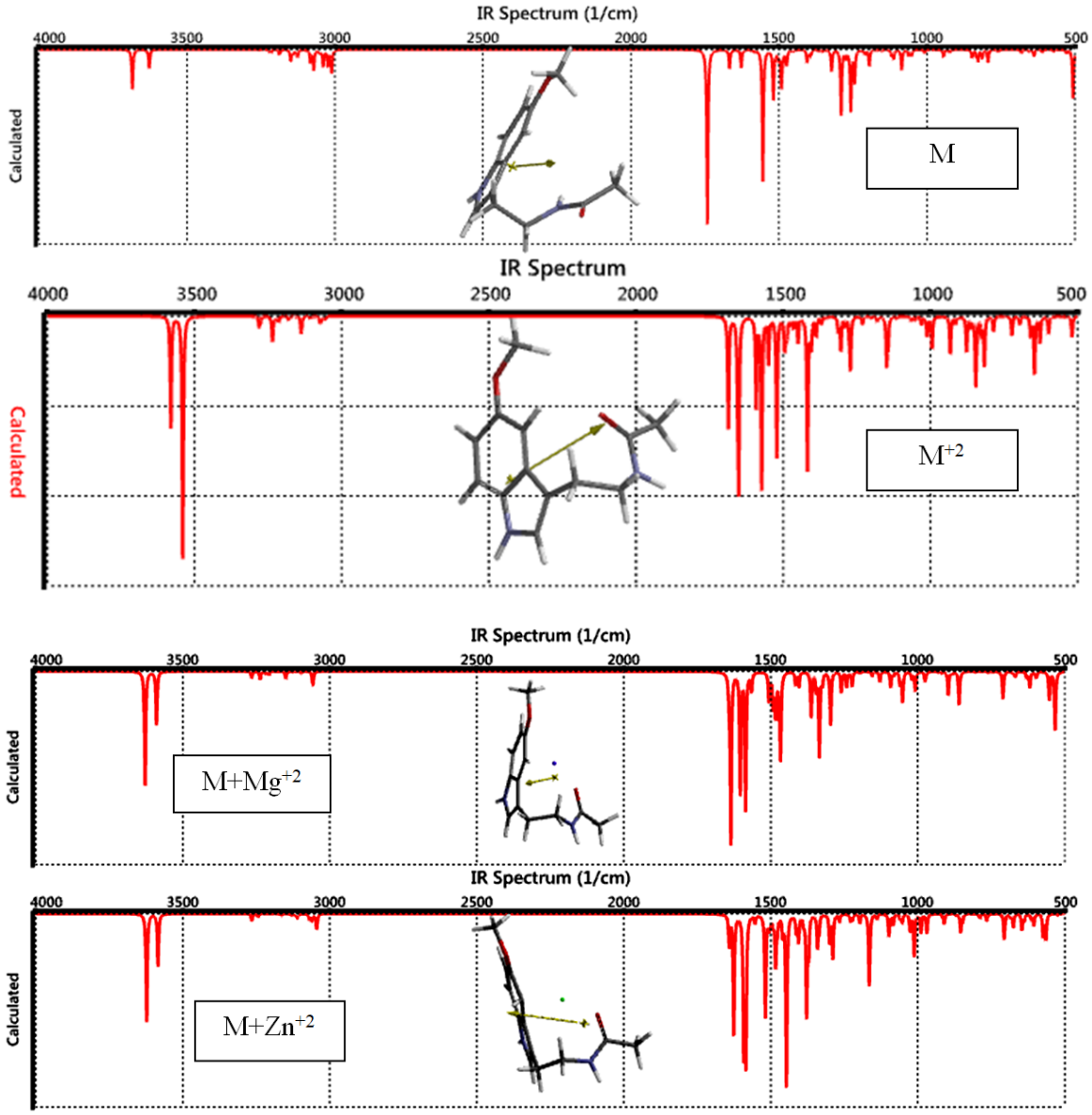


Figure 3. Calculated IR spectra of the systems considered.

Figure 4 displays the bond densities of the composite systems considered. It is clearly seen in the figure that although there is no bond density between melatonin and the magnesium cation in the case of $M+Mg^{+2}$, there is some for $M+Zn^{+2}$. It seems some electron population has been shared mutually between the components of $M+Zn^{+2}$ composite.

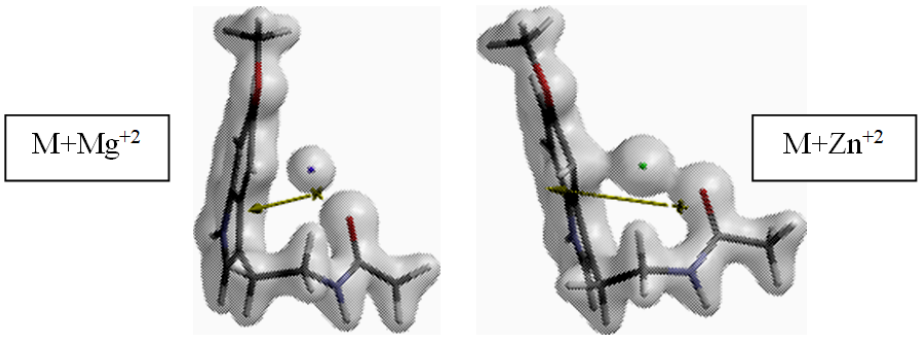


Figure 4. The bond densities of the composite systems considered.

Figure 5 shows the ESP charges on the atoms of the composite systems considered. 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 [35]. Note that the cations considered no longer possess the initial charge of +2 but some electron population has been transferred form the organic component, melatonin, to the cations hence the magnesium and zinc acquire 1.235 and 1.247 esu, respectively. Note that the first ionization energies of Mg and Zn atoms are 736 and 908 kJ/mol whereas and second ionization energies are 1450 and 1730 kJ/mol , respectively. Whereas electro negativities of Mg and Zn (Pauling electro negativity scale 0-4) are 1.2 and 16, respectively.

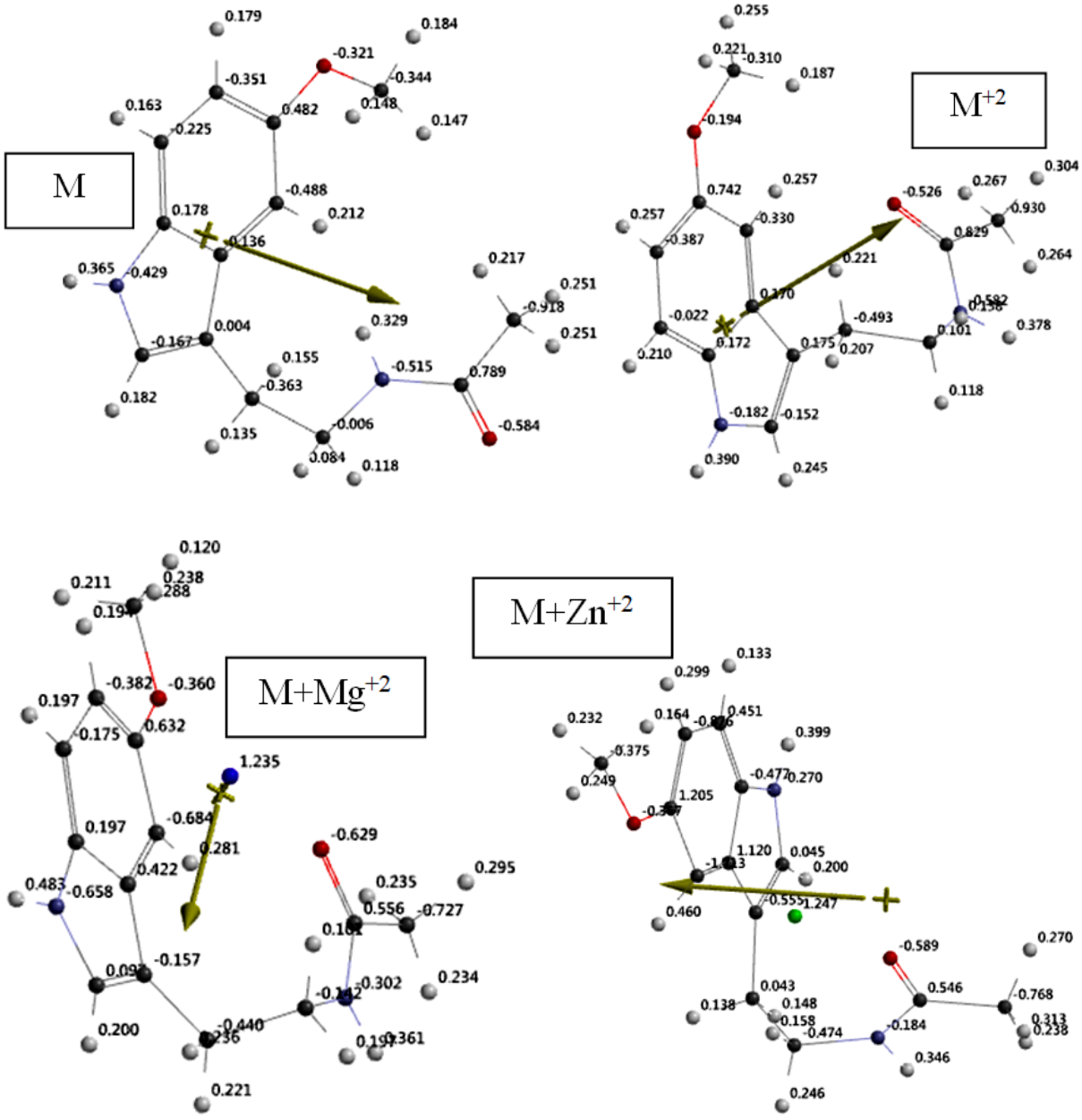


Figure 5. The ESP charges on the atoms of melatonin, its dication and the composite systems considered.

The natural charges on the atoms of the composite systems considered are shown in Figure 6. The charges of the cations in this case, are 1.812 and 1.536 esu, respectively for magnesium and zinc.

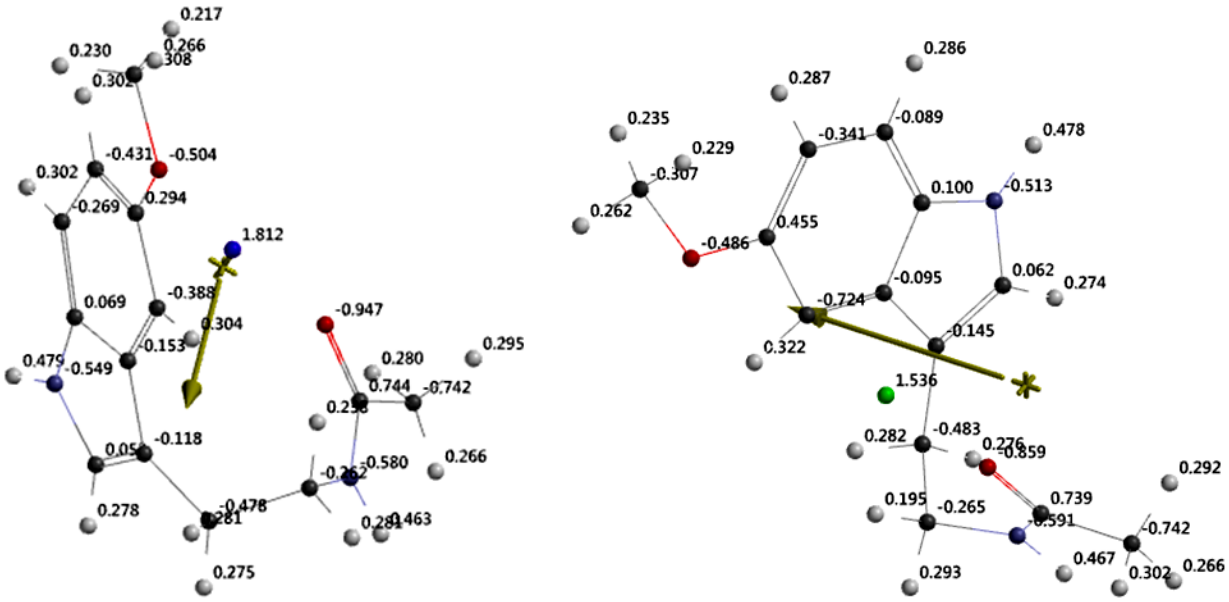


Figure 6. The natural charges on the atoms of the composite systems considered.

As the data reveal the cations considered affect the charge distribution of melatonin moiety at different extents. How all these ionic and molecular orbital interactions affect the free concentration of melatonin is a matter of question. However, just remember that decrease in melatonin can result in early puberty or in sex-gland problems [36].

Table 3 lists some properties of the species of interest. In the data one highly noticeable difference between the composites lies in the dipole moment values which is $M+Mg^{+2}$> $M+Zn^{+2}$.

Table 3. Some properties of the species of interest.

Species	Dipole (debye)	Polarizability	Area (Å²)	Volume (Å³)	PSA (Å²)	Ovality
$M+Mg^{+2}$	5.11	61.01	272.94	253.86	39.692	1.41
$M+Zn^{+2}$	2.38	61.13	277.76	253.41	40.755	1.43

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

Figure 7 shows some of the molecular orbital energy levels of the systems considered. Table 4 includes the HOMO, LUMO energies and interfrontier molecular orbital energy gap values, Δε, ($\Delta\varepsilon = \varepsilon_{LUMO}-\varepsilon_{HOMO}$) of the structures considered. As seen in the figure when melatonin acquires positive (2) charge, the HOMO and LUMO energies are considerably lowered but approach to each other. Consequently, Δε value decreases. Note the big gap exists between the LUMO and NEXT LUMO levels.

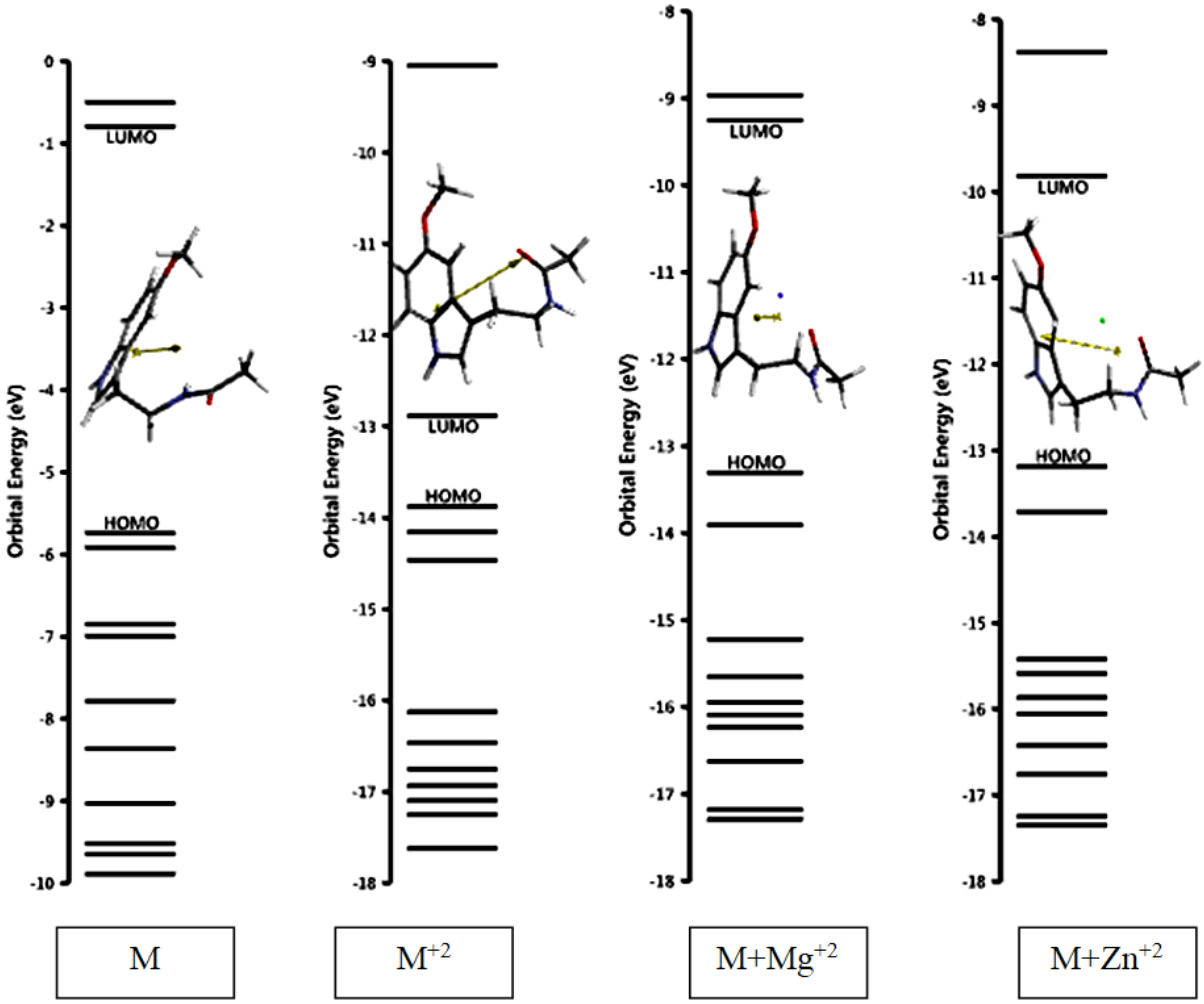


Figure 7. Some of the molecular orbital energy levels of the systems considered.

As for the composite systems of melatonin, the positive charge on them causes shuffling of the molecular orbital energies compared to melatonin and its dication. The algebraic orders order of HOMO and LUMO energies are $M^{+2}< M+Mg^{+2}< M+Zn^{+2}< M$ and, $M^{+2} < M+Zn^{+2}< M+Mg^{+2} < M$, respectively. Namely, the magnesium dication lowers the HOMO energy of melatonin more effectively than the zinc dication. On the other hand, the zinc dication is more effective on lowering of the LUMO energy of melatonin. Consequently, the order of Δε values become $M^{+2} < M+Zn^{+2} < M+Mg^{+2} < M$.

Table 4. The HOMO, LUMO energies and Δε values of the structures considered.

System	HOMO	LUMO	Δε
M	-553.89	-76.65	477.24
M^{+2}	-1338.52	-1242.95	95.57
$M+Mg^{+2}$	-1284.31	-892.55	391.76
$M+Zn^{+2}$	-1272.40	-946.91	325.49

Energies in kJ/mol.

Figure 8 displays the calculated UV-VIS spectra (time dependent density functional, TDDFT) of the structures considered. As seen in the figure melatonin absorption is confined to UV region of the spectrum. However, the present treatment predicts its spectrum of dication form to shift to visible side, implying the emergence of some longer conjugative path in the structure via charging. In the case of composite structures the spectra cover both the UV and the visible regions (extended to visible part having many shoulders). Since the calculated spectra involve not only the HOMO-LUMO excitations, some of the spectra possess shoulders or overlapped peaks. The calculated intensities of the peaks are related to magnitudes of the transition moments between the orbitals involved which vary from composite to composite [37,38].

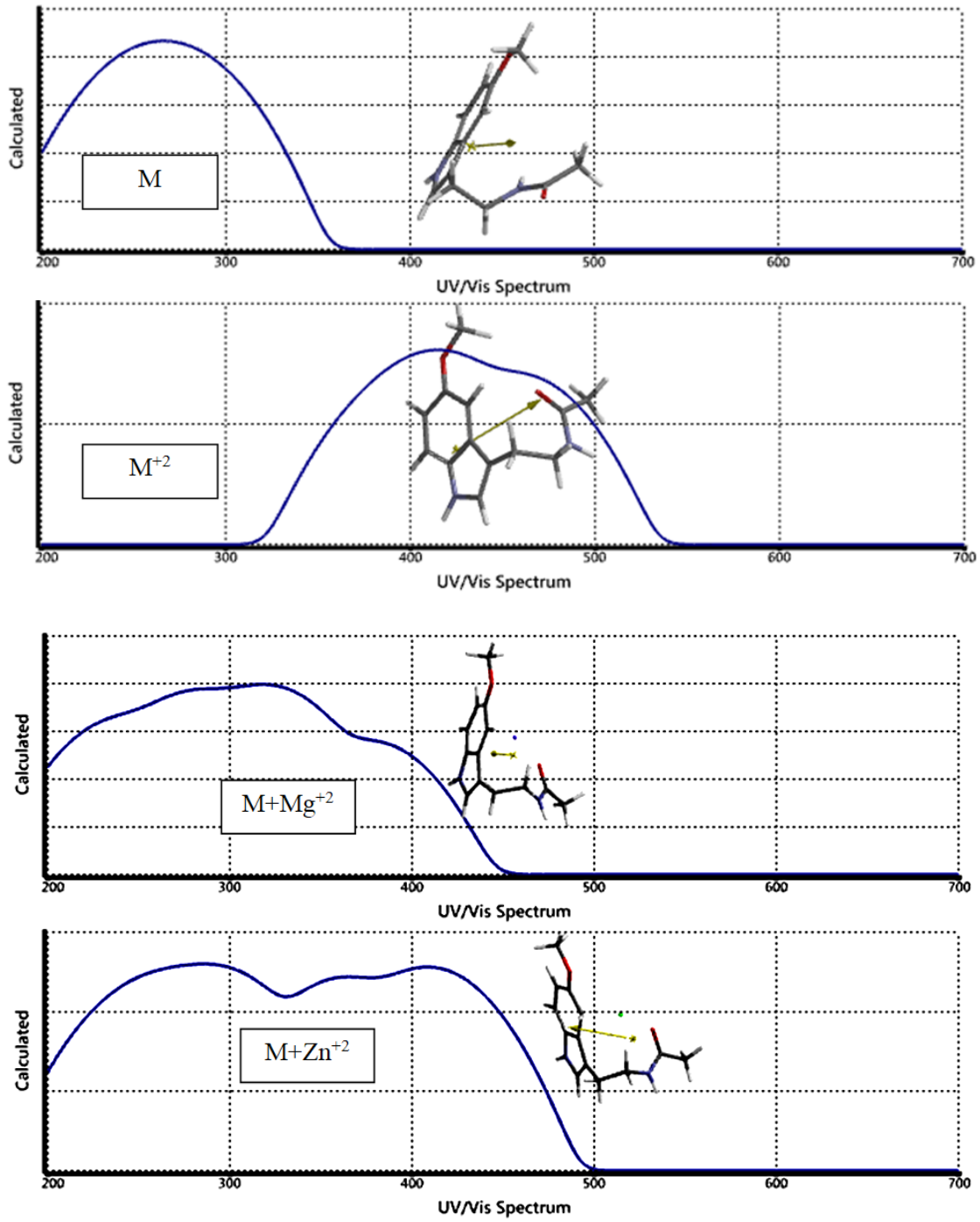


Figure 8. The calculated UV-VIS spectra of the structures considered.

4. Conclusion

The present computational study considered melatonin, its static charged dication and dication composites of magnesium and zinc with melatonin within the restrictions of density functional theory at the level of B3LYP/6-31++G(d,p). All of the species considered possess exothermic H^o and favorable G^o values and as well as they are electronically stable. In the composites, as most of the properties, their HOMO and LUMO energies are dictated by the fine topology of the structures considered. However, relatively larger inter frontier molecular orbital energy gap, $\Delta\varepsilon$, value possessed by $M+Mg^{+2}$. Compared with $\Delta\varepsilon$ value of melatonin, both of the dications considered lower it substantially. In the case of zinc dication composite, some bond density exists between the melatonin and zinc dication. Thus, some electron population has been shared mutually between the components of $M+Zn^{+2}$ composite which may affect free concentration of nocturnal hormone, melatonin (or adversely Zn^{+2}). All these points are to be investigated by clinical experiments.

References

[1] Greenspan, F. S., & Forsham, P. H. (1983). *Basic and clinical endocrinology* (p. 33). Lange Medical Publications.

[2] Cutolo, M., Straub, R., & Buttgereit, F. (2008). Circadian rhythms of nocturnal hormones in rheumatoid arthritis: Translation from bench to bedside. *Annals of the Rheumatic Diseases*, *67*, 905–908. https://doi.org/10.1136/ard.2008.088955

[3] Tagaya, H. (2008). Measurement of sleep-related hormones. *Biomedical Engineering, 46*(2), 169–176.

[4] Bukowska, A. (2011). Anticarcinogenic role of melatonin—Potential mechanisms. *Medycyna Pracy, 62*, 425–434.

[5] Mazzoccoli, G., Giuliani, F., & Sothern, R. B. (2012). Determination of whole body circadian phase in lung cancer patients: Melatonin vs. cortisol. *Cancer Epidemiology, 36*, 46–53. https://doi.org/10.1016/j.canep.2011.06.005

[6] White, A. W., Handler, P., & Smith, E. L. (1968). *Principles of biochemistry* (p. 985). McGraw-Hill.

[7] Murray, R. K., Granner, D. K., Mayes, P. A., & Rodwell, V. W. (1988). *Harper's biochemistry*. Lange Medical Publications.

[8] Pike, C. J., Burdick, D., Walencewitz, A. J., Glabe, C. G., & Cotman, C. W. (1993). Neurodegeneration induced by β-amyloid peptides in vitro: The role of peptide assembly state. *Journal of Neuroscience, 13*, 1676–1687. https://doi.org/10.1523/JNEUROSCI.13-04-01676.1993

[9] Foley, H. M., & Steel, A. E. (2019). Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. *Complementary Therapies in Medicine, 42*, 65–81. https://doi.org/10.1016/j.ctim.2018.11.003

[10] Xu, Z., Wu, Y., Zhang, Y., Zhang, H., & Shi, L. (2019). Melatonin activates BKCa channels in cerebral artery myocytes via both direct and MT receptor/PKC-mediated pathway. *European Journal of Pharmacology, 842*, 177–188. https://doi.org/10.1016/j.ejphar.2018.10.032

[11] Luo, C., Yang, Q., Liu, Y., Zhou, S., Jiang, J., Reiter, R. J., Bhattacharya, P., Cui, Y., Yang, H., Ma, H., Yao, J., Lawler, S. E., Zhang, X., Fu, J., Rozental, R., Aly, H., Johnson, M. D., Chiocca, E. A., & Wang, X. (2019). The multiple protective roles and molecular mechanisms of melatonin and its precursor N-acetylserotonin in targeting brain injury and liver damage and in maintaining bone health. *Free Radical Biology and Medicine, 130*, 215–233. https://doi.org/10.1016/j.freeradbiomed.2018.10.402

[12] Rafat, A., Roushandeh, A. M., Alizadeh, A., Hashemi-Firouzi, N., & Golipoor, Z. (2019). Comparison of the melatonin preconditioning efficacy between bone marrow and adipose-derived mesenchymal stem cells. *Cell Journal, 20*(4), 450–458.

[13] Mukherjee, S. (2019). Recent advancements in the mechanism of nitric oxide signaling associated with hydrogen sulfide and melatonin crosstalk during ethylene-induced fruit ripening in plants. *Nitric Oxide: Biology and Chemistry, 82*, 25–34. https://doi.org/10.1016/j.niox.2018.11.003

[14] Campos, C. N., Ávila, R. G., de Souza, K. R. D., Azevedo, L. M., & Alves, J. D. (2019). Melatonin reduces oxidative stress and promotes drought tolerance in young Coffea arabica L. plants. *Agricultural Water Management, 211*, 37–47. https://doi.org/10.1016/j.agwat.2018.09.025

[15] Abecia, J. A., Forcada, F., Vázquez, M. I., Blanco, T. M., Pérez-Ce, J. A., Pérez-Pé, R., & Casao, A. (2019). Role of melatonin on embryo viability in sheep. *Reproduction, Fertility and Development, 31*(1), 82–92. https://doi.org/10.1071/RD18308

[16] Hosseinzadeh, A., Javad-Moosavi, S. A., Reiter, R. J., Yarahmadi, R., Ghaznavi, H., & Mehrzadi, S. (2018). Oxidative/nitrosative stress, autophagy and apoptosis as therapeutic targets of melatonin in idiopathic pulmonary fibrosis. *Expert Opinion on Therapeutic Targets, 22*(12), 1049–1061. https://doi.org/10.1080/14728222.2018.1541318

[17] Kuznetsova, T. Y., Solovyova, N. V., Solovyov, V. V., & Kostenko, V. O. (2017). Antioxidant activity of melatonin and glutathione interacting with hydroxyl and superoxide anion radicals. *Ukrainian Biochemical Journal, 89*(6), 22–30. https://doi.org/10.15407/ubj89.06.022

[18] Pshenichnyuk, S. A., Modelli, A., Jones, D., Lazneva, E. F., & Komolov, A. S. (2017). Low-energy electron interaction with melatonin and related compounds. *Journal of Physical Chemistry B, 121*(16), 3965–3974. https://doi.org/10.1021/acs.jpcb.7b01408

[19] Kubota, M., & Kobayashi, T. (2003). Electronic structures of melatonin and related compounds studied by photoelectron spectroscopy. *Journal of Electron Spectroscopy and Related Phenomena, 128*(2–3), 165–178. https://doi.org/10.1016/S0368-2048(02)00279-7

[20] Vasilescu, D., & Broch, H. (1999). Quantum molecular modeling of melatonin. *Journal of Molecular Structure: Theochem, 460*(1–3), 191–205. https://doi.org/10.1016/S0166-1280(98)00317-0

[21] Lewis, D. F., Arendt, J., & English, J. (1990). Quantitative structure–activity relationships within a series of melatonin analogs and related indolealkylamines. *Journal of Pharmacology and Experimental Therapeutics, 252*(1), 370–373. https://doi.org/10.1016/S0022-3565(25)13357-0

[22] Türker, L., & Atalar, T. (2012). Interaction between TNT and melatonin: A DFT treatment. *Polycyclic Aromatic Compounds, 32*, 615–625. https://doi.org/10.1080/10406638.2012.667499

[23] Türker, L. (2019). Interaction of FOX-7 and melatonin: A DFT treatment. *Earthline Journal of Chemical Sciences, 1*(1), 19–35. https://doi.org/10.34198/ejcs.1119.1935

[24] Kamfar, W. W., Khraiwesh, H. M., Ibrahim, M. O., Qadhi, A. H., Azhar, W. F., Ghafouri, K. J., Alhussain, M. H., Aldairi, A. F., AlShahrani, A. M., Alghannam, A. F., Abdulal, R. H., Al-Slaihat, A. H., Qutob, M. S., Elrggal, M. E., Ghaith, M. M., & Azzeh, F. S. (2024). Comprehensive review of melatonin as a promising nutritional and nutraceutical supplement. *Heliyon, 10*(2), e24266. https://doi.org/10.1016/j.heliyon.2024.e24266

[25] Arendt, J., & Skene, D. J. (2005). Melatonin as a chronobiotic. *Sleep Medicine Reviews, 9*(1), 25–39. https://doi.org/10.1016/j.smrv.2004.05.002

[26] Pévet, P. (2002). Melatonin. *Dialogues in Clinical Neuroscience, 4*(1), 57–72. https://doi.org/10.31887/DCNS.2002.4.1/ppevet

[27] Stewart, J. J. P. (1989a). Optimization of parameters for semi-empirical methods I. *Journal of Computational Chemistry, 10*, 209–220. https://doi.org/10.1002/jcc.540100208

[28] Stewart, J. J. P. (1989b). Optimization of parameters for semi-empirical methods II. *Journal of Computational Chemistry, 10*, 221–264. https://doi.org/10.1002/jcc.540100209

[29] Leach, A. R. (1997). *Molecular modeling*. Longman.

[30] Kohn, W., & Sham, L. J. (1965). Self-consistent equations including exchange and correlation effects. *Physical Review, 140*, A1133–A1138. https://doi.org/10.1103/PhysRev.140.A1133

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

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

[33] Vosko, S. H., Wilk, L., & Nusair, M. (1980). Accurate spin-dependent electron liquid correlation energies for local spin density calculations: A critical analysis. *Canadian Journal of Physics, 58*, 1200–1211. https://doi.org/10.1139/p80-159

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

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

[36] Glanze, D. W., Anderson, K. N., & Anderson, L. E. (1987). *Medical encyclopedia*. Signet/Mosby.

[37] Turro, N. J. (1991). *Modern molecular photochemistry*. University Science Books.

[38] Anslyn, E. V., & Dougherty, D. A. (2006). *Modern physical organic chemistry*. University Science Books.