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Interaction of zinc cation with some acetyl-substituted-D-penicillamines

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Abstract

In the present treatment, interaction of zinc cation with N-, O- or S-acetyl substituted amino-D-penicillamines are considered within the restrictions of density functional theory and the basis set employed (at the level of B3LYP/6-31++G(d,p)). N-acetyl-D-penicillamine has some medical use as a chelating agent for many metal poisoning cases such as mercury, copper (Wilson's disease), etc. However, affinity of the aforementioned molecule depends on various factors, such as pH, and has some adverse side effects. On the other hand, zinc is very important metabolic functions in living bodies acting as cofactor in many enzyme systems. The collected data have revealed presently that the optimized structures of the composites have exothermic heats of formation and favorable Gibbs free energy of formation values. They are thermally favored and electronically stable at the standard states. Various structural and quantum chemical data have been collected and discussed, including IR and UV-VIS spectra. The data also revealed that there exists a certain complex formation between the zinc cation and the substituted amino-D-penicillamines considered.

1. Introduction

Penicillamine is a potent chelating agent that binds to heavy metals—including copper, gold, mercury, and zinc—to increase their excretion, while zinc salts are used to induce metallothione in the gut to reduce copper absorption [1]. Bhushan and Kumar, worked on enantio-resolution of dl-penicillamine [2].

Domingo et al., examined in rats whether the combined use of D-penicillamine (DPA) and a zinc salt, or the administration of a DPA/Zn complex could have some advantages over the use of either single agent on the excretion of copper [3].

Chong and Auld investigated carboxypeptidase-A and the differences in the mechanisms of ester and peptide hydrolysis D-penicillamine (D-PEN) catalyzes zinc(II) transfer from carboxypeptidase-A to chelators such as thionein and EDTA at a rate constant up to 400-fold faster than the uncatalyzed release. Once D-PEN releases zinc(II) from enzyme stronger chelators can tightly bind zinc(II) leading to complete and essentially irreversible inhibition. D-PEN is the first drug to inhibit a zinc protease by catalyzing metal removal, and the name "catalytic chelation" is proposed for this mechanism [4].

Tang et al., interested the comparison of the effectiveness and safety of D-penicillamine and zinc salt treatment for symptomatic Wilson disease. Their analysis suggests that symptomatic WD patients treated with D-penicillamine have higher incidence of adverse effects and neurological deterioration than that of zinc salts. The therapeutic effectiveness of these two regimens does not seem to be significantly different, and these results must be interpreted with caution [5]. Their analysis suggests that symptomatic WD patients treated with D-penicillamine have higher incidence of adverse effects and neurological deterioration than that of zinc salts. The

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therapeutic effectiveness of these two regimens does not seem to be significantly different, and these results must be interpreted with caution [4]. Penicillamine treatment may be associated with a wide spectrum of adverse effects [6].

Habib et al., interested penicillamine and nephrotic syndrome [7], Phelps et al., and Tandon et al., investigated D-Penicillamine effect on retinopathy [8,9]. Peters et al., investigated D-Penicillamine metabolism in neurodegenerative diseases [10]. In the last couple of decades numereous articles appeared in the literature, published on diverse fields of medicine [11-23].

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 [24-26]. 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) [27,28]. 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 [29]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [30] and Lee, Yang, Parr (LYP) correlation correction functional [31]. In the present study, the normal mode analysis for each structure 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 program [32].

3. Results and Discussion

In the present treatment interaction of zinc dication with the perturbed N-acetyl amino-D-penicillamines are investigated at the molecular level. The parent structure, N-acetyl amino-D-penicillamine has been subjected to certain intra molecular perturbations by changing the position of the acetyl moiety from the amino site to OH oxygen of the acid (COOH) moiety and then sulfur (SH) sites. Presently, the resultant assembly of the zinc cation and the parent structure is called composite, although bond density maps revealed the occurrence of certain complexation.

Figure 1 shows the optimized structures as well as the directions of the dipole moments vectors of the composites presently considered.

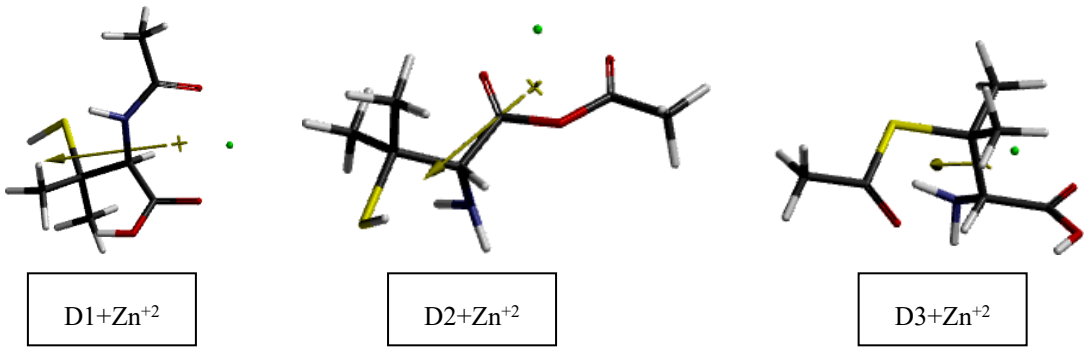


Figure 1. Optimized structures of the composites considered.

Table 1 lists some thermochemical properties of the composites considered. The data in the table reveal that the standard heat of formation (H°) values of the composites are exothermic and they are favored according to their G° (Gibbs free energy of formation) values. The algebraic order of H° and G° values is the same as D1+Zn^{+2}< D3+Zn^{+2}< D2+Zn^{+2}, whereas the order of S° values is D3+Zn^{+2} < D1+Zn^{+2}< D2+Zn^{+2}.

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

Composite	H°	S° (J/mol°)	G°
D1+Zn^{+2}	-7171711.736	471.46	-7171852.307
D2+Zn^{+2}	-7171585.606	483.56	-7171729.773
D3+Zn^{+2}	-7171666.551	463.39	-7171804.732

Energies in kJ/mol.

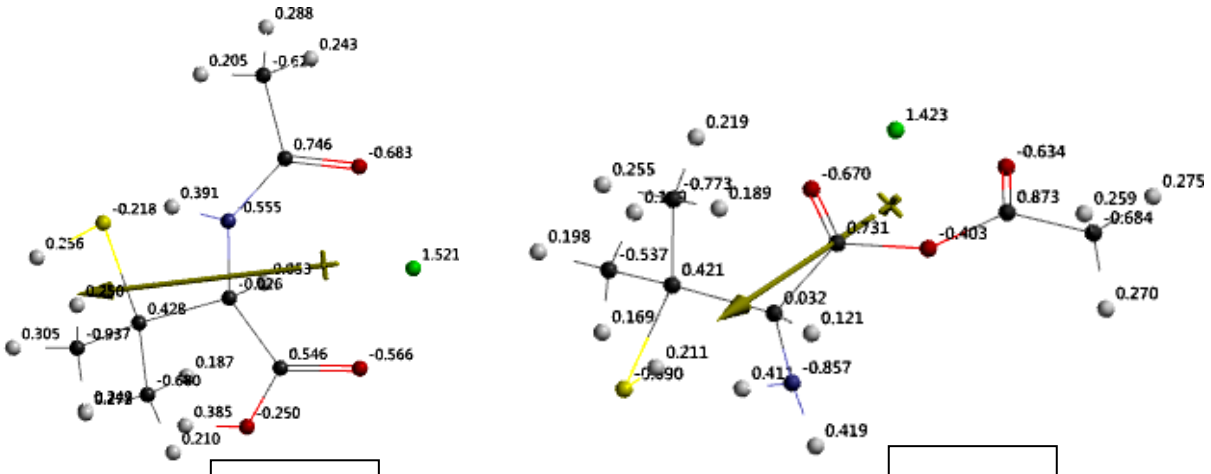
Table 2 shows some energies of the composites considered. Note that E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively [32]. The data in the table reveal that N-acetyl derivatives are electronically more stable than the O- and S-acetyl substituted forms (namely, N-> S-> O-).

Table 2. Some energies of the composites considered.

Composite	E	ZPE	E_C
D1+Zn^{+2}	-7172215.38	532.53	-7171682.85
D2+Zn^{+2}	-7172084.16	525.90	-7171558.26
D3+Zn^{+2}	-7172175.69	538.90	-7171636.79

Energies in kJ/mol.

Figure 2 shows the electrostatic potential (ESP) charges on atoms of the composites. The ESP charges are obtained by the program which uses a numerical method that generates charges, thus reproducing the electrostatic potential field from the entire wavefunction [32]. As seen in the figure in all the cases, the charge of zinc component is no longer +2 but a partial charge less than 2 which indicates that some electron population has been transferred to zinc from the organic component. Thus, the organic component gets some over all positive charge (see Figure 3).



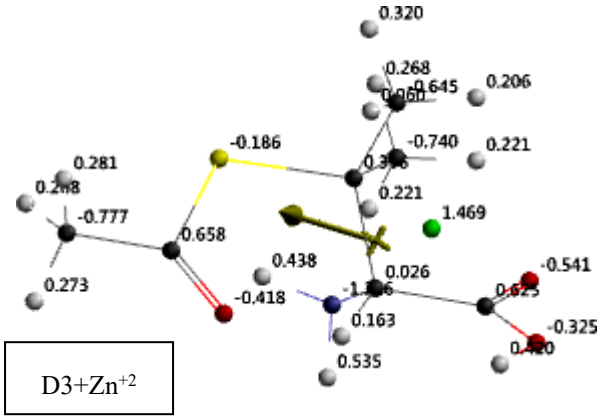


Figure 2. The ESP charges on atoms of the composites.

Figure 3 shows the electrostatic potential maps of the composites. As seen in the figure the positive potential covers all over the systems. The map is the over all aspect of potential field of attractive and repulsive forces. The interaction energies (repulsive and attractive) have mainly contributions from charge-charge and orbital interactions [33].

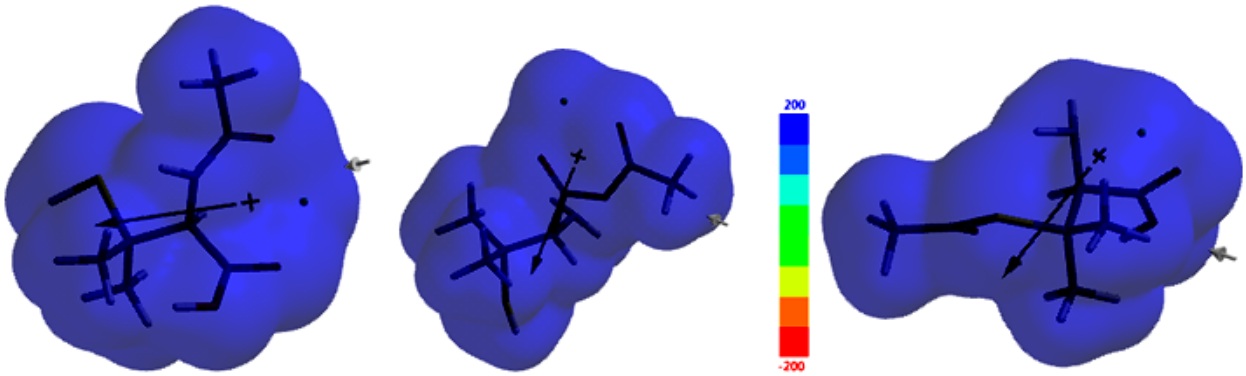


Figure 3. Electrostatic potential maps of the composites.

Figure 4 displays the calculated IR spectra of the composites. In the case of D1+Zn^{+2} a strong stretching occurs at 3580 cm^{-1} which is assigned to O-H vibration. Another strong peak occurs at 1655 cm^{-1} which is the acid carbonyl stretch coupled with some bendings. Composite D2+Zn^{+2} has the symmetrical and asymmetrical N-H stretching vibrations at 3641 cm^{-1} and 3526 cm^{-1}, respectively. The C-O-C bending happens at 1670 cm^{-1}. The spectrum of D3+Zn^{+2} possesses very many strong peaks, these are 3711 cm^{-1} COO-H stretching; 3480 cm^{-1} and 3312 cm^{-1} N-H (asym. and sym) stretchings; 2685 cm^{-1} CH_2-H stretch; 1805 cm^{-1} S-CH_3 bending and 1670 cm^{-1} stands for C-COO-H bending.

Figure 5 stands for the bond densities of the composites considered. The figure clearly indicates that in each case a complex formation occurs between the zinc cation and the organic component through the hetero atoms around the zinc cation. In the first two cases carbonyl oxygens (amido and ester groups) are involved whereas in D3+Zn^{+2} case the amino group and acid carbonyl oxygen atom take place. Organic component is acting as a bidentate ligand. Note that the maximum coordination number of zinc is four [34]. Note that in living systems zinc cation is mostly in the hydrated form and therefore to form a complex with penicillamine species there should exist competing equilibria [34].

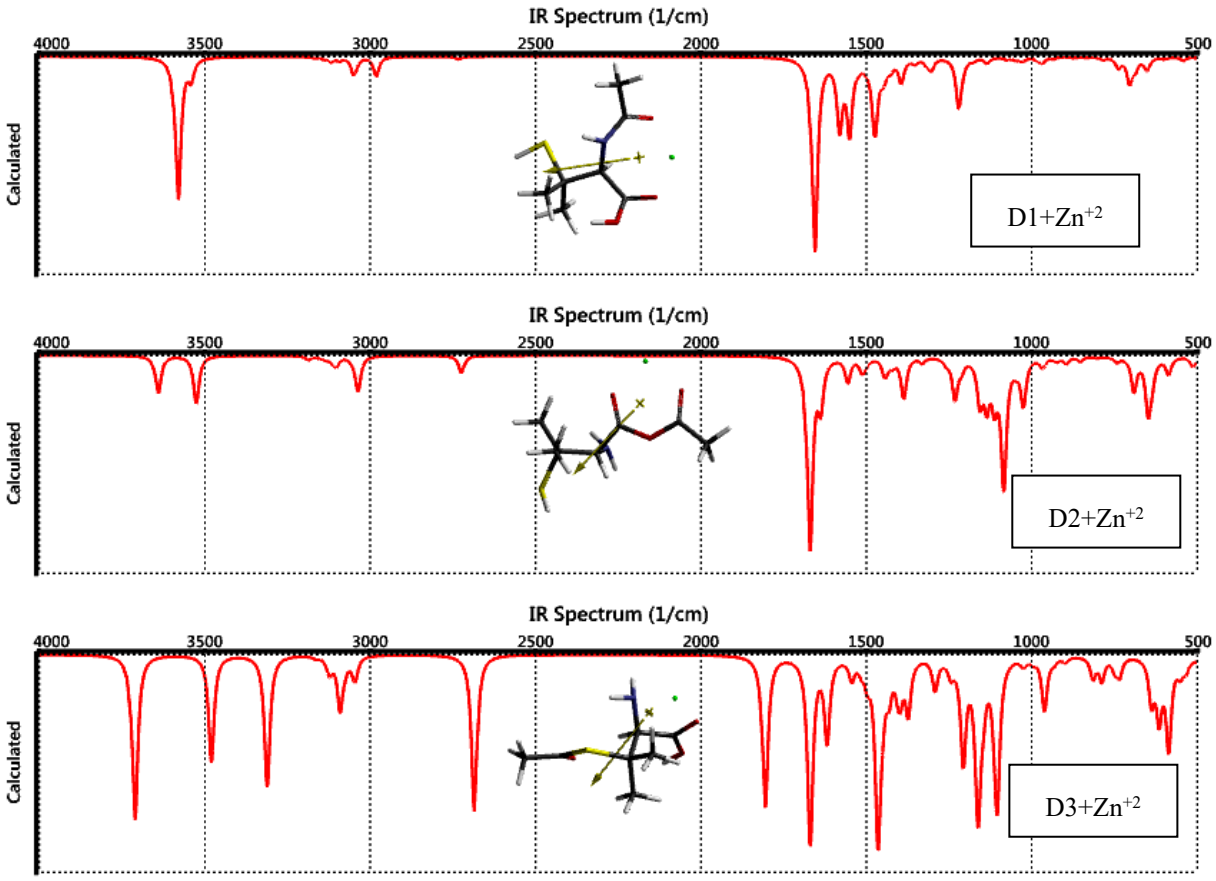


Figure 4. Calculated IR spectra of the composites.

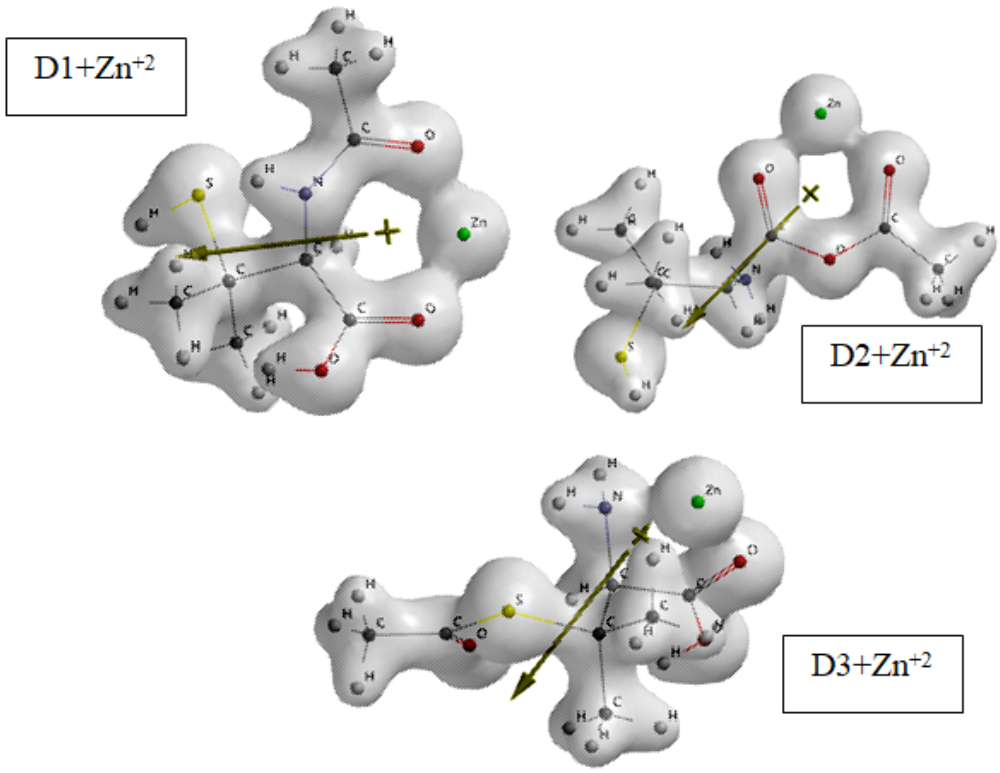


Figure 5. Bond densities of the composites considered.

Figure 6 presents the calculated bond lengths of the composites considered. Those distances between the zinc ion and the interacting sites of the organic components are 1.84 and 1.86 Å in D1+Zn^{+2}, 1.918 Å and 1.922 Å in D2+Zn^{+2} and in D3+Zn^{+2} case 1.988 and 1.034 Å.

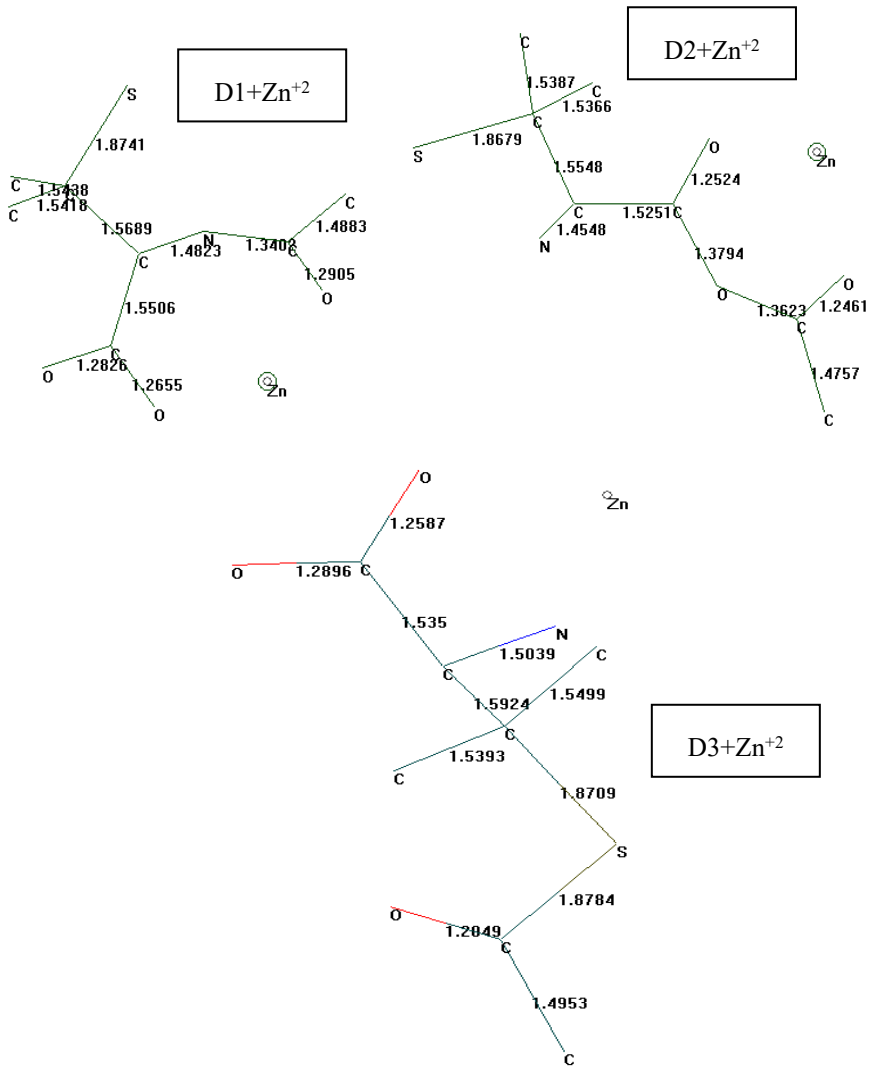


Figure 6. The calculated bond lengths of the composites considered (hydrogens omitted).

Figure 7 shows some of the molecular orbital energy levels of the composites considered. Within the group of composites, D2+Zn^{+2} differs from the others having a very narrow interfrontier molecular orbital energy gap value $\Delta\varepsilon$ ($\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$). In classical terms it possesses much greater extended conjugation compared to the others (See Table 3). The acetyl group on oxygen atom raises the HOMO but lowers the LUMO energy with respect to other composites which are isomers. The net result is a narrow molecular orbital energy level for D2+Zn^{+2} composite.

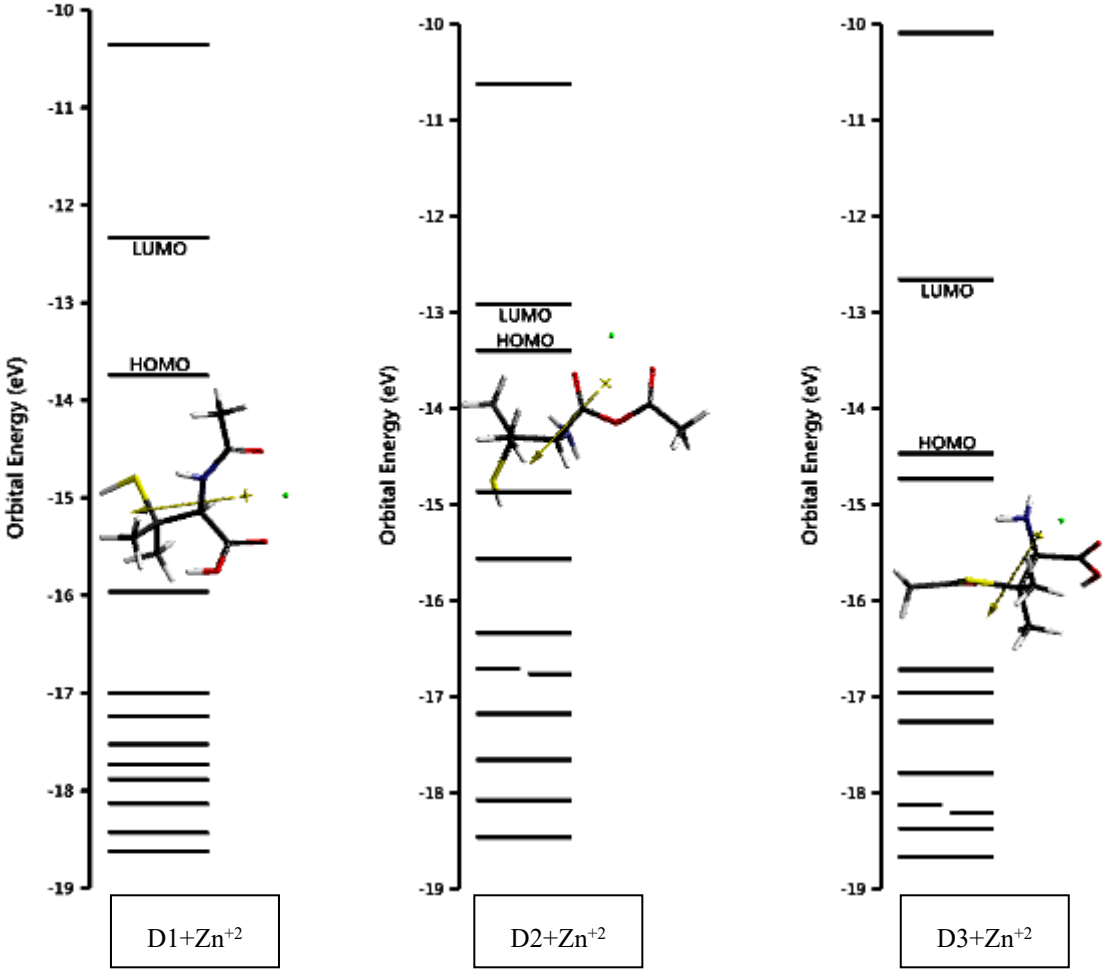


Figure 7. Some of the molecular orbital energy levels of the composites considered.

Table 3 tabulates the HOMO, LUMO energies and Δε values of the composites. The algebraic orders of the HOMO and LUMO energies are $D3+Zn^{+2}$< $D1+Zn^{+2}$< $D2+Zn^{+2}$ and $D2+Zn^{+2}$< $D3+Zn^{+2}$< $D1+Zn^{+2}$, respectively. Note that these composites are structural isomers of each other. So, variations arise from the differences of σ- and π-topologies. The over all apparent outcome is that the acetyl moiety on the sulfur lowers the HOMO energy better than it is on the nitrogen or oxygen atom.

Table 3. The HOMO, LUMO energies and Δε values of the composites.

Composite	HOMO	LUMO	Δε
$D1+Zn^{+2}$	-1326.11	-1189.86	136.24
$D2+Zn^{+2}$	-1293.15	-1246.17	46.98
$D3+Zn^{+2}$	-1396.10	-1221.61	174.49

Energies in kJ/mol.

As for the LUMO energies, this time the acetyl group attached to oxygen atom lowers the LUMO energy more pronounced than it is on the sulfur or nitrogen atom. Consequently, Δε value follow the order of $D3+Zn^{+2}$ > $D1+Zn^{+2}$> $D2+Zn^{+2}$.

Figure 8 shows the HOMO and LUMO patterns of the composites. As seen from the figure, the zinc cation does not contribute to the HOMO except D2+Zn^{+2} case. The contribution of zinc, as expected, is very high as compared to other atomic orbitals. Note that the frontier molecular orbitals, HOMO and LUMO, play a crucial role in chemical reactions [33].

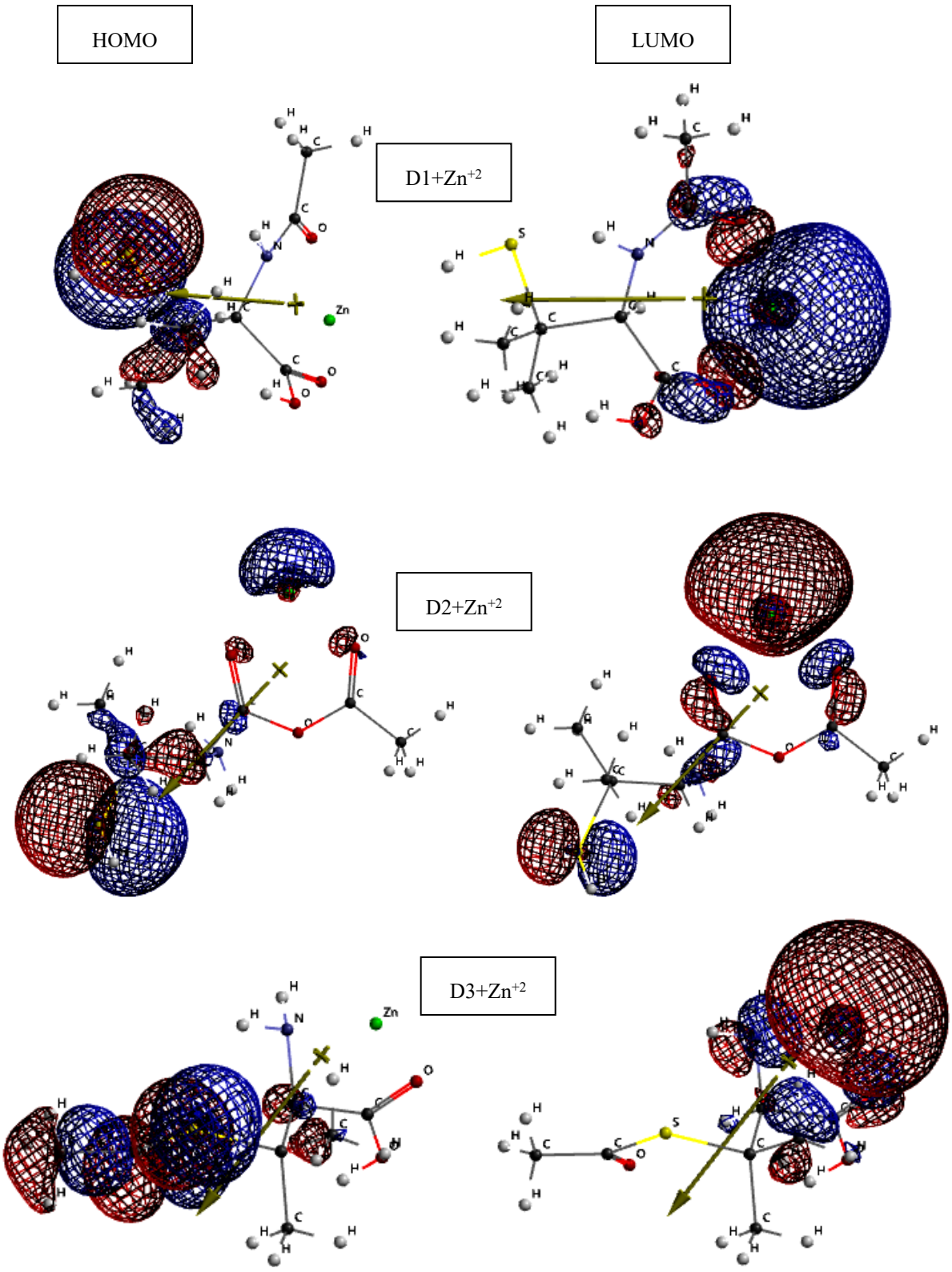


Figure 8. The HOMO and LUMO patterns of the composites.

Figure 9 displays the calculated UV-VIS (time dependent, TDDFT) spectra of the composites. In the case of N-acetyl substituted composite ($D1+Zn^{+2}$) the spectrum spreads over the UV and VIS regions with a comparatively strong absorption peak with a strong shoulder. The peak in the visible region is also strong.

When the acetyl group is attached to carboxyl OH moiety ($D2+Zn^{+2}$ case) the whole spectra shows an effective bathochromic effect due to emergence of more extended conjugation which narrows the interfrontier molecular orbital gap.

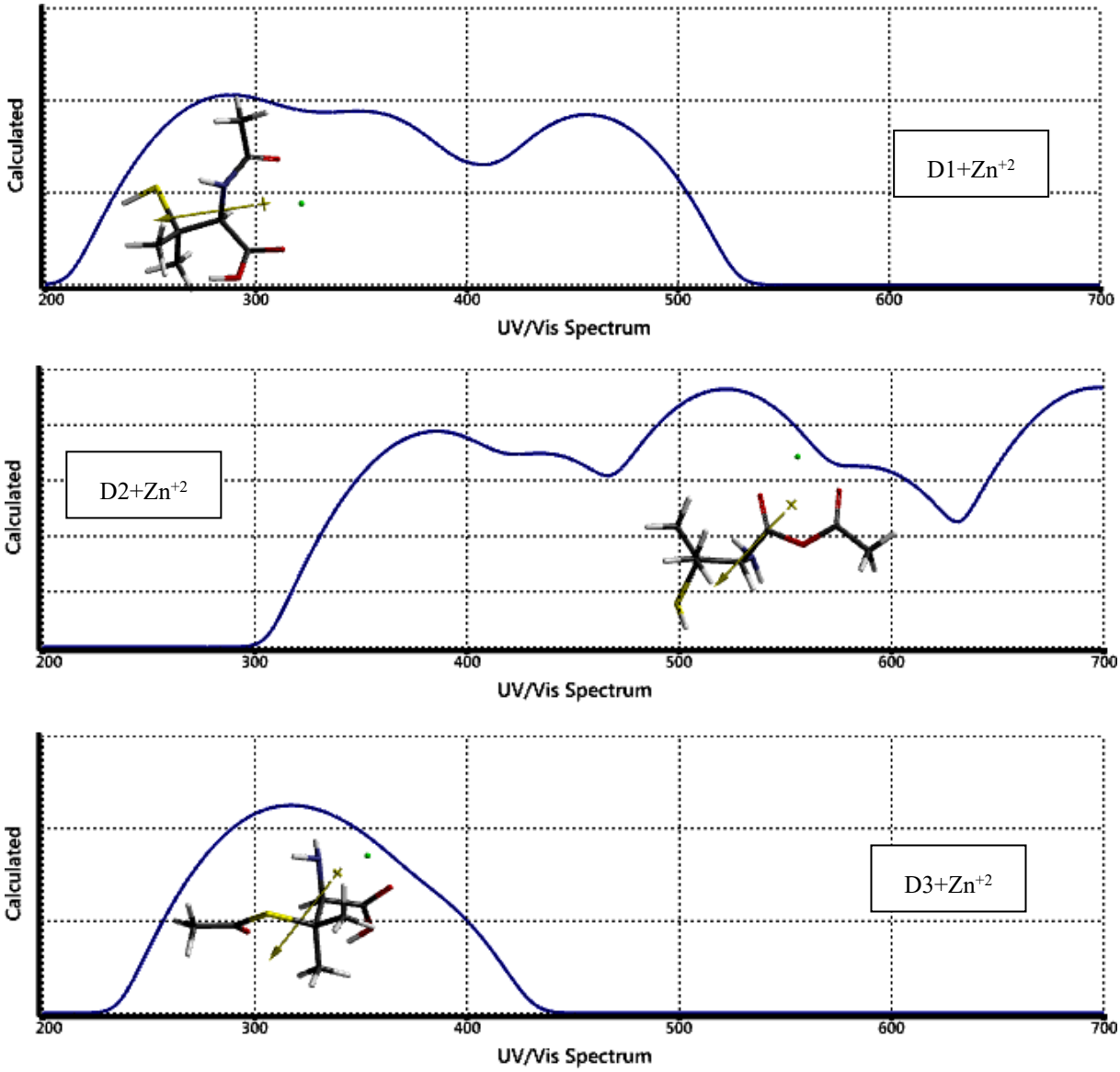


Figure 9. Calculated UV-VIS spectra of the composites.

The spectrum of $D3+Zn^{+2}$, where the acetyl moiety is linked to sulfur, shrinks to almost completely to UV region (hypsochromic shift). Note that hypsochromic shift occurs due to structural modifications, such as reduced conjugation/size mismatch between the orbitals or decreased electron-donating group, or through environmental changes like changing solvent polarity [35]. A skirt of the peak of $D3+Zn^{+2}$ appears in the visible region as a feeble shoulder. Note that intensities of the peaks are related to magnitudes of the transition moments between the orbitals involved which vary from structure to structure [35-37].

Figure 10 shows the LUMO maps of the composites considered. A LUMO map displays the absolute value of the LUMO on the electron density surface. The blue color stands for the maximum value of the LUMO and the color red, the minimum value. The zinc cation lies in the blue region of the maps. Thus, nucleophiles may attack to form various complexes of zinc depending on the competing equilibria between the ligands.

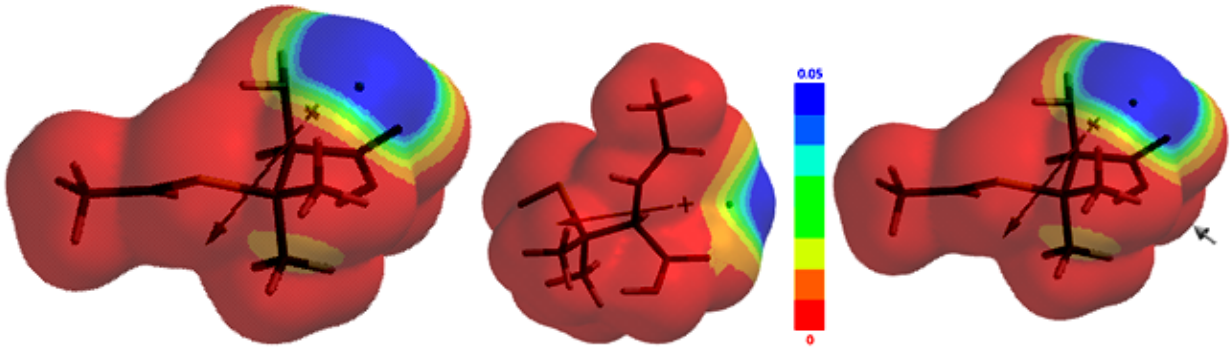


Figure 10. The LUMO maps of the composites.

4. Conclusion

The present DFT treatment, within the restrictions of density functional theory, at the level of B3LYP/6-31++G(d,p) reveals that in vacuum conditions the zinc composites of isomeric N-, O- or S-acetyl substituted-D-penicillamines have exothermic heat of formation values and favorable Gibbs free energy of formation values. All the composites considered are electronically stable. Some electron population is transferred from the organic component of the composites to the zinc cation so it possesses some partial charge less than the initial formal charge of two. Variation of the linkage position of the acetyl moiety, affects configurational and topological characteristics so that many quantum chemical properties of the composites are highly different from each other, especially the molecular orbital energy levels and the spectral properties. Depending on very many perturbing factors in the living environment the composites may exhibit some unexpected adverse effects.

References

[1] Delville, A., & Detellier, C. (1986). Zn(II)–D-(−)penicillamine complexes in aqueous solution: Zn-67 nuclear magnetic resonance study. *Canadian Journal of Chemistry, 64*(9), 1845–1849. https://doi.org/10.1139/v86-303

[2] Bhushan, R., & Kumar, R. (2010). Enantioresolution of DL-penicillamine. *Biomedical Chromatography, 24*(1), 66–82. https://doi.org/10.1002/bmc.1355

[3] Domingo, J. L., Gómez, M., & Jones, M. M. (1998). Concurrent administration of D-penicillamine and zinc has no advantages over the use of either single agent on copper excretion in the rat. *Toxicology, 126*(3), 195–205. https://doi.org/10.1016/s0300-483x(98)00017-1

[4] Chong, C. R., & Auld, D. S. (2007). Catalysis of zinc transfer by D-penicillamine to secondary chelators. *Journal of Medicinal Chemistry, 50*(22), 5524–5527. https://doi.org/10.1021/jm070803y

[5] Tang, S., Bai, L., Hou, W., Hu, Z., Chen, X., Zhao, J., Liang, C., Zhang, W., Duan, Z., & Zheng, S. (2022). Comparison of the effectiveness and safety of D-penicillamine and zinc salt treatment for symptomatic Wilson disease: A systematic review and meta-analysis. *Frontiers in Pharmacology, 13*, Article 847436. https://doi.org/10.3389/fphar.2022.847436

[6] Ishak, R., & Abbas, O. (2013). Penicillamine revisited: Historic overview and review of the clinical uses and cutaneous adverse effects. *American Journal of Clinical Dermatology, 14*(3), 223–233. https://doi.org/10.1007/s40257-013-0022-z

[7] Habib, G. S., Saliba, W., Nashashibi, M., & Armali, Z. (2006). Penicillamine and nephrotic syndrome. *European Journal of Internal Medicine, 17*(5), 343–348. https://doi.org/10.1016/j.ejim.2006.03.001

[8] Phelps, D. L., Lakatos, L., & Watts, J. L. (2001). D-penicillamine for preventing retinopathy of prematurity in preterm infants. *Cochrane Database of Systematic Reviews,* (1), CD001073. https://doi.org/10.1002/14651858.CD001073

[9] Tandon, M., Dutta, S., Dogra, M. R., & Gupta, A. (2010). Oral D-penicillamine for the prevention of retinopathy of prematurity in very low birth weight infants, a randomized placebo controlled trial. *Acta Paediatrica, 99*(9), 1324–1328. https://doi.org/10.1111/j.1651-2227.2010.01837.x

[10] Peters, L., Steventon, G. B., Green, S., Sturman, S., Waring, R. H., & Williams, A. C. (1994). D-penicillamine metabolism in neurodegenerative diseases: An in vivo/in vitro sulphydryl methylation study. *Xenobiotica, 24*(10), 1013–1020. https://doi.org/10.3109/00498259409043298

[11] Klingenberg, S. L., & Chen, W. (2006). D-penicillamine for primary sclerosing cholangitis. *Cochrane Database of Systematic Reviews*, (1), CD004182. https://doi.org/10.1002/14651858.CD004182.pub3

[12] Corrigan, J. J., Jr., Damiano, M. L., Leissinger, C., & Wulff, K. (2003). Treatment of chronic haemophilic synovitis in humans with D-penicillamine. *Haemophilia, 9*(1), 64–68. https://doi.org/10.1046/j.1365-2516.2003.00676.x

[13] Kaya, T. I., Kokturk, A., Tursen, U., Ikizoglu, G., & Polat, A. (2002). D-penicillamine treatment for lipoid proteinosis. *Pediatric Dermatology, 19*(4), 359–362. https://doi.org/10.1046/j.1525-1470.2002.00104.x

[14] Nagler, R., Cohen, S., Savulescu, D., Leschiner, S., Otradnov, I., & Gavish, M. (2010). Penicillamine as a potent protector against injurious effects of cigarette smoke in aerodigestive tract cancer. *Oncology, 78*(1), 12–19. https://doi.org/10.1159/000287967

[15] Gupte, A., & Mumper, R. J. (2009). Elevated copper and oxidative stress in cancer cells as a target for cancer treatment. *Cancer Treatment Reviews, 35*(1), 32–46. https://doi.org/10.1016/j.ctrv.2008.07.004

[16] Brem, S., Grossman, S. A., Carson, K. A., New, P., Phuphanich, S., Alavi, J. B., Mikkelsen, T., & Fisher, J. D. (2005). Phase 2 trial of copper depletion and penicillamine as antiangiogenesis therapy of glioblastoma. *Neuro-Oncology, 7*(3), 246–253. https://doi.org/10.1215/S1152851704000869

[17] Squitti, R., Rossini, P. M., Cassetta, E., Moffa, F., Pasqualetti, P., Cortesi, M., Colloca, A., Rossi, L., & Finazzi-Agrò, A. (2002). D-penicillamine reduces serum oxidative stress in Alzheimer's disease patients. *European Journal of Clinical Investigation, 32*(1), 51–59. https://doi.org/10.1046/j.1365-2362.2002.00933.x

[18] Sharifian, M., Sari-Aslani, F., Hemmatinejad, B., Fallahzadeh, M. K., Kasraee, B., Khoshandish, M., Miri, R., Mohammadi-Samani, S., Jowkar, F., & Namazi, M. R. (2011). D-penicillamine, a potent melanogenesis inhibitor, lacks any depigmenting effect on black guinea pig skin: The first randomized, evaluated blinded vehicle-controlled, in vivo study. *Acta Dermatovenerologica Alpina, Pannonica et Adriatica, 20*(2), 51–53.

[19] Qiao, S., Cabello, C. M., Lamore, S. D., Lesson, J. L., & Wondrak, G. T. (2012). D-penicillamine targets metastatic melanoma cells with induction of the unfolded protein response (UPR) and Noxa (PMAIP1)-dependent mitochondrial apoptosis. *Apoptosis, 17*(10), 1079–1094. https://doi.org/10.1007/s10495-012-0746-x

[20] Manzini, C. U., Sebastiani, M., Giuggioli, D., Manfredi, A., Colaci, M., Cesinaro, A. M., & Ferri, C. (2012). D-penicillamine in the treatment of eosinophilic fasciitis: Case reports and review of the literature. *Clinical Rheumatology, 31*(1), 183–187. https://doi.org/10.1007/s10067-011-1866-3

[21] Bienaimé, F., Clerbaux, G., Plaisier, E., Mougenot, B., Ronco, P., & Rougier, J. P. (2007). D-penicillamine-induced ANCA-associated crescentic glomerulonephritis in Wilson disease. *American Journal of Kidney Diseases, 50*(5), 821–825. https://doi.org/10.1053/j.ajkd.2007.05.026

[22] Sharma, R., Jain, S., & Kher, V. (2012). ANCA-associated Goodpasture's syndrome in a patient with rheumatoid arthritis on penicillamine. *Indian Journal of Nephrology, 22*(1), 45–47. https://doi.org/10.4103/0971-4065.83743

[23] Poulas, K., Koutsouraki, E., Kordas, G., Kokla, A., & Tzartos, S. J. (2012). Anti-MuSK- and anti-AChR-positive myasthenia gravis induced by D-penicillamine. *Journal of Neuroimmunology, 250*(1–2), 94–98. https://doi.org/10.1016/j.jneuroim.2012.05.011

[24] Stewart, J. J. P. (1989). Optimization of parameters for semi-empirical methods I. *Journal of Computational Chemistry, 10*(2), 209–220. https://doi.org/10.1002/jcc.540100208

[25] Stewart, J. J. P. (1989). Optimization of parameters for semi-empirical methods II. *Journal of Computational Chemistry, 10*(2), 221–264. https://doi.org/10.1002/jcc.540100209

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

[27] Kohn, W., & Sham, L. J. (1965). Self-consistent equations including exchange and correlation effects. *Physical Review, 140*(4A), 1133–1138. https://doi.org/10.1103/PhysRev.140.A1133

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

[29] Becke, A. D. (1988). Density-functional exchange-energy approximation with correct asymptotic behavior. *Physical Review A, 38*(6), 3098–3100. https://doi.org/10.1103/PhysRevA.38.3098

[30] 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*(8), 1200–1211. https://doi.org/10.1139/p80-159

[31] 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*(2), 785–789. https://doi.org/10.1103/PhysRevB.37.785

[32] Wavefunction Inc. (2006). SPARTAN 06. Wavefunction Inc.

[33] Fleming, I. (1976). *Frontier orbitals and organic reactions*. Wiley.

[34] Bard, A. J. (1966). *Chemical equilibrium*. Harper & Row.

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

[36] Barrow, G. M. (1962). *Introduction to molecular spectroscopy*. McGraw-Hill/Kogakusha.

[37] Harris, D. C., & Bertolucci, M. D. (1978). *Symmetry and spectroscopy*. Oxford University Press.