**Department of Chemistry, Faculty of Science**

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February 25, 2020

**Dear Prof. Ivan Oskar Juranić**

Thank you very much for your email on 26 November, 2019 concerning our manuscript entitled “(E)-4-(((2-amino-5-chlorophenyl)imino)methyl)-5-(hydroxymethyl)-2-methylpyridin-3-ol and its Cu(II) complex: Synthesis, DFT calculations and AIM analysis" (Ms. Ref. No.:  **8693**).

I’d also like to express my appreciation to reviewers who have reviewed the manuscript and made their valuable comments. For more clarification, many changes demanded by the respectable referees have been included in the manuscript. Now, the corrected manuscript and answer to questions are being sent to you.

1. **Answers to questions:**

**Q1)** The main objective I have is the level of theory used - authors employed

B3LYP functional. However, it is well known that for problems involving weak

interactions - i.e. hydrogen bonding, classical functional (like b3lyp) are

not the perfect choice. One should use either dispersion correction (like

Grimme's D3) or functionals that incorporate dispersion (like Minnesota

functionals). Therefore, B3LY-D3 or M062X should be methods of choice.  In

particular, this should be important for the tautomerization reaction

studied here - the structure and energetics of TS with proton transfer

involving N-H-O hydrogen bonding.

**A1)** As requested, all the DFT calculations have been performed again by using the M062X functional. All results have been corrected in the text.

**Q2)** When discussing the structure of [CuLCL] square-planar complex, authors

should use tau\_4 index (Dalt. Trans. 2007, 9, 955−964)- tau4=360 −

(alpha + beta)/141, where alpha and beta are the two largest angles around

the central metal ion). These values are between zero (perfect square

planar) and 1.00 (perfect tetrahedral) with intermediate structures (e.g.

trigonal pyramidal or seesaw) in between.

**A2) These sentences have been included in text:**

**"** Yang and co-workers [1] proposed a geometry index (τ4) for four-coordinate complexes. The τ4 index is obtained fromτ4=(360−(α+β))/141 equation, where α and β are the two largest θ angles around the central metal ion. The value of τ4 varies from zero for the perfect square planar geometry to 1.00 for the perfect tetrahedral one, with intermediate structures (e.g. trigonal pyramidal or seesaw) in between. To explore geometry of the [Cu**L**CL] complex, its τ4 index was calculated. In the [Cu**L**CL] complex, the N3-Cu-Cl and N1-Cu-O1 angles are 170.3 and 174.0°, respectively. These angles are considered as the alpha and beta angles. Since, the τ4 index of the complex is 0.11, which confirms that geometry of the [Cu**L**CL] complex is very close to square planar.**"**

(1) Yang, L.;Powell, D. R.;Houser, R. P. Structural variation in copper (I) complexes with pyridylmethylamide ligands: structural analysis with a new four-coordinate geometry index, τ 4. *Dalton Transactions* **2007**, 955-964.

Q3) How can authors be sure that there is no formation of binuclear species -

[CuL2Cl2]? There is a possibility that two CuLCl, with L being NNO donor,

complexes are connected via bridging Cl ions  (e.g. Crystal Growth & Design,

2019, 19, 4810-4821; Polyhedron 2013, 57, 118−126; Polyhedron 2018, 141,

60−68; Eur. J. Inorg. Chem. 2015, (5), 882−895; Polyhedron 2019, 165,

22−30, etc.).

A3) It is possible that the Cl ligand acts as a bridging ligand. However, it is notable that in the above references, oxygen atom of the carbonyl group is coordinated to the metal ion. But, in the investigated [CuLCl] complex, deprotonated phenolate oxygen is coordinated to the metal ion. Many tridentate Schiff bases involving the phenolate oxygen as a donor atom form a mononuclear complex with the Cu2+ ion (For example: [2-9]). In these complexes, there is a weak interaction between the Cl ligand of a complex and Cu2+ ion of adjacent complex may. This interaction is not strong as a Cu-Cl bond and account as a weak interaction.

(1) Yang, L.;Powell, D. R.;Houser, R. P. Structural variation in copper (I) complexes with pyridylmethylamide ligands: structural analysis with a new four-coordinate geometry index, τ 4. *Dalton Transactions* **2007**, 955-964.

(2) Ribeiro, N.;Roy, S.;Butenko, N.;Cavaco, I.;Pinheiro, T.;Alho, I.;Marques, F.;Avecilla, F.;Costa Pessoa, J.;Correia, I. New Cu(II) complexes with pyrazolyl derived Schiff base ligands: Synthesis and biological evaluation. *J. Inorg. Biochem.* **2017**, 174, 63-75.

(3) Pradhan, R.;Banik, M.;Cordes, D. B.;Slawin, A. M. Z.;Saha, N. C. Synthesis, characterization, X-ray crystallography and DNA binding activities of Co(III) and Cu(II) complexes with a pyrimidine-based Schiff base ligand. *Inorg. Chim. Acta* **2016**, 442, 70-80.

(4) Saheb, V.;Sheikhshoaie, I.;Setoodeh, N.;Rudbari, H. A.;Bruno, G. A new tridentate Schiff base Cu(II) complex: Synthesis, experimental and theoretical studies on its crystal structure, FT-IR and UV–Visible spectra. *Spectrochim. Acta, Part A* **2013**, 110, 124-129.

(5) Adhikary, C.;Banerjee, S.;Chakraborty, J.;Ianelli, S. Copper(II) azide complexes with NNO donor ligands: Syntheses, structure, catalysis and biological studies. *Polyhedron* **2013**, 65, 48-53.

(6) Saha, S.;Jana, S.;Gupta, S.;Ghosh, A.;Nayek, H. P. Syntheses, structures and biological activities of square planar Ni(II), Cu(II) complexes. *Polyhedron* **2016**, 107, 183-189.

(7) Manimohan, M.;Pugalmani, S.;Sithique, M. A. Biologically active novel N, N, O donor tridentate water soluble hydrazide based O-carboxymethyl chitosan Schiff base Cu (II) metal complexes: Synthesis and characterisation. *International Journal of Biological Macromolecules* **2019**, 136, 738-754.

(8) Ammar, R. A.;Alaghaz, A.-N. M. A.;Zayed, M. E.;Al-Bedair, L. A. Synthesis, spectroscopic, molecular structure, antioxidant, antimicrobial and antitumor behavior of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of O2N type tridentate chromone-2-carboxaldehyde Schiff's base ligand. *J. Mol. Struct.* **2017**, 1141, 368-381.

(9) Hueso-Ureña, F.;Illán-Cabeza, N. A.;Moreno-Carretero, M. N.;Peñas-Chamorro, A. L.;Faure, R. Ni(II) and Cu(II) complexes with the dianionic N,N,O-tridentate Schiff base 6-amino-5-formyl-1,3-dimethyluracil-benzoylhydrazone: Crystal structure of the monodimensionally hydrogen-bonded aqua-(6-amino-1,3-dimethyl-uracilato-benzoylhydrazone(2-)-N6,N51,O52]-copper(II) hydrate. *Polyhedron* **2000**, 19, 689-693.

Q4) p. 9, line 2019 - "the experimental chemical shifts have been recorded in

DMSO solution, while the DFT values are calculated for the isolated molecule

in a vacuum" Why DFT calculations have not been performed in DMSO (with

PCM)? Tautomerization on the other hand was explored with PCM(methanol). How

do the results depend on the PCM/vacuum calculations performed? Would

PCM(DMSO) calculations improve calculated chemical shifts? The authors

should give those results. Authors should also clearly specify in

Computational details which calculations were performed in vacuum and which

with PCM.

A4) There are two types of solvent effects between a solute and molecules of the solvent: implicit and explicit effects. In this work, the implicit effects have been only considered in evaluation of energy values and NMR chemical shifts. But, intermolecular interactions between two molecules of the **HL** Schiff base as well as between molecule of the **HL** Schiff base and molecules of the solvent have been omitted. Since, the DFT-calculated chemical shifts for the H5 atom. The mentioned sentences in section 4.1.3 (pages 10 and 11) have been corrected as “The DFT-chemical shift for the H5 proton of the –CH2OH group is considerably lower than its experimental value. The experimental chemical shifts have been recorded in DMSO solution, while the DFT-values have been calculated for an isolated **HL** molecule. The alcoholic H5 proton can engage in intermolecular hydrogen bonds with other **HL** molecules as well as the molecules of solvent. The intermolecular interactions affect the chemical shift of the H5 atom.”

Q5) Figures should be more of higher resolution/more clear - in particular Figs 1-3, Figs S1, S2, S4

A5) These figures have been improved.

Q6) Why the labeling in Fig 2, N2/N3 is not the same in meta and para isomer?

A6) Labales of atoms have been corrected.

Q7) Caption in Fig S4 should include description of critical points (differently colored spheres).

A7) Fig. 4 has been corrected.

Q8) Table S4, units of electron density missing

Q9) - p.12, line 290, line 295 - "C.Bobhr-3"?

A8,A9) Unit of electron density (e-/a03) has been included in text and Table S4.

1. **The text of the manuscript has been reviewed and revised with the aim of removing the literary problems. As a result, many improvements have been made on the text, the most important of which are as follows:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| row | section | page | paragraph | Line(s) | **Incorrect text** | **Corrected text** |
| 1 | 3 | 3 | 4 | 2 | The B3LYP functional and | The M062X functional and |
| 2 | 3 | 4 | 1 | 1 | Optimized geometries showed no | The gas phase optimized geometries showed no |
| 3 | 3 | 4 | 1 | 5 | was explored in both methanol solution | was explored in both of the gas phase and methanol solution |
| 4 | 3 | 4 | 2 | 3 | NMR chemical shifts of the **HL** Schiff base were predicted with | NMR chemical shifts of the **HL** Schiff base were predicted in DMSO solution with |
| 5 | 4.1.2.1 | 5 | 2 | 6,7 | But, in the *meta* isomer, the *meta* –NH2 group of the pyridoxal to form the C4=N3 azomethine group. | But, in the *meta* isomer, the *meta* –NH2 group with respect to chloro substitution reacts with the –CHO group of the pyridoxal. |
| 6 | conclusion | 16 | 2 | 3 | The 4th coordination position of the square complex | The fourth coordination position of the square planar complex |

**All of the corrections have highlighted with the blue color in the text.**

Sincerely,

S. Ali Beyramabadi