The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM)
ISSN: 2602-3199

The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM), 2023

Volume 23, Pages 548-555

ICRETS 2023: International Conference on Research in Engineering, Technology and Science

DFT Study of a Schiff Base Ligand and Its Nickel and Copper Complexes: Structure, Vibration, Chemical Reactivity and in Silico Biological

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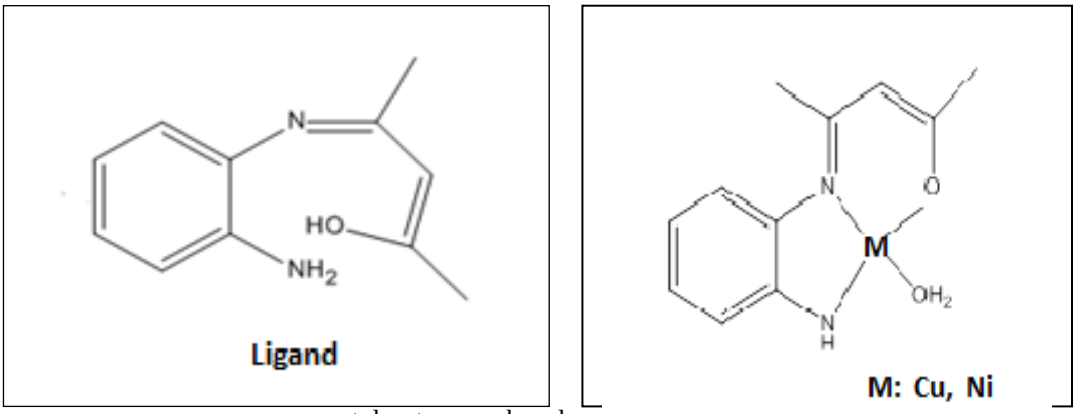
Abstract: Schiff base complexes are extensively studied because of their affinity, selectivity, and sensitivity to a wide variety of metals. They have been found to be very useful in catalysis, medicine as antibiotics, anti-inflammatory agents and also in industry as compounds with anti-corrosive properties. In this work, we will focus on the study of some Schiff base ligands and their complexes based on nickel and copper. An energetic, structural, spectral (IR, UV) and electronic study was carried out, using the density functional theory method. All the calculations have been made with density functional theory (DFT) using Becke's three parameters hybrid method and the Lee-Yang-Parr correlation functional (B3LYP) with LANL2DZ basis set for heavy metals and 6-31G** for all others atoms in gas phase using Gaussian 03 program package. We used the GaussView program to draw the optimized geometries and to visualize the the normal modes vibrations. The stability of the considered complexes has been studied in the basis of the binding energies. A study of reactivity indices will be highlighted in order to predict attack sites. The in-silico biological properties of compounds studied have been calculated and discussed. The theoretical results will be compared with the available experimental ones.

Keywords: Schiff base, Complexes, Reactivity, ADMET properties, Drug likeness properties.

Introduction

Schiff's base derivatives are excellent chelating ligands (Munde, 2010). They present very varied potential interests for a large number of interdisciplinary fields (Ramana, 2009). This is due to the simplicity of their preparation, the diversity of their application through the relative stability of their complexes with the majority of transition metals.They have been found to be very useful in medicine as antibiotics, anti-inflammatory, antibacterial, and anticarcinogenic agents (Brodowska, 2014). The condensation of substituted o-phenylenediamine with various diketones is used in the preparation of a variety of pharmaceuticals (Carvalho, 2014). And also in industry as compounds with anti-corrosive properties. Indeed, Schiff's bases (o-PDA) are involved in the synthesis of insecticides, corrosion inhibitors and pigments (Verma, 2014). In coordination chemistry, phenylenediamine (o-PDA) is an important ligand precursor. Oxidation of metal-phenylenediamine complexes yields the imine derivatives, which are intensely colored and often exist in multiple stable oxidation states (Abu Dief, 2015). The resistance of bacteria to antibiotics poses serious problems in therapy. This has caused a growing need to develop new antibacterial agents (Massai, 2013).

In this work, we are interested in the study of a Schiff-based ligand and its complexes based on nickel and copper (Figure 1). An energetic, structural, spectral and electronic study was carried out using the density functional theory method. A study of reactivity indices will be highlighted in order to predict attack sites. A biological study was also carried out in order to study the pharmacokinetic profile and to determine the interactions of the ligand and its complexes with DNA.



mono acetylacetone-o-phenylene

Figure 1. Ligand and complexes structures

Computational Method

Quantum Mechanical Analysis

Full geometry optimization have been made with density functional theory (DFT) using Kohn–Sham's Density Functional Theory subjected to the gradient-corrected hybrid density functional B3LYP [36-38 affa]. This functional is the combinaison of Becke's three parameters hybrid method and the Lee-Yang-Parr correlation functional (B3LYP) (Lee, 1988) with LANL2DZ basis set for heavy metals (Ni and Cu atoms), and 6-31G (d,p), for all others atoms (H, N, C, O) (Pearson, 1985) in gas phase, as implemented by Gaussian 09 program (Frisch, 2009). Without any constraint of symmetry, followed by a calculation of the normal modes of vibration, to make sure that the stationary points were minima. Our complexes are all minima in their potential energy surface. Indeed, the analysis of the frequencies of the normal modes of vibration gives no imaginary frequency. We used the GaussView program to draw the optimized geometries and to visualize the the normal modes vibrations (Fresch, 2009).

We have determined the structure, the electronic parameters, the energies and the gaps E_{HOMO}/E_{LUMO}. Natural bond orbitals (NBO) atomic charges were also reported. The theoretical results obtained are compared with the available experimental data. In order to study the chemical reactivity of the ligand and its optimized complexes, we calculated the following parameters of several global reactivity descriptors by means of DFT, such as: the ionization potential (I), the electron affinity (A), electronic chemical potential (μ), the absolute hardness (η), the global softness (S) and the global electrophilicity (ω) (Azquez, 2008). The electronic chemical potential (μ) is defined by Parr and Pearson (Parr, 1983):

$$\mu = -\frac{1}{2}(I + A) = -\chi \quad (1)$$

Were χ is the electronegativity given by Mulliken.

The global hardness is defined by (Parr, 1991):

$$\eta = \frac{1}{2}(I - A) \quad (2)$$

The global softness *S* is obtained from:

$$S = \frac{1}{2\eta} \quad (3)$$

The global electrophilicity (ω) measures the affinity of compounds given by Parr (Parr, 1999) is calculated by:

$$\omega = \frac{\mu^2}{2\eta} \quad (4)$$

The nucleophilicity index equal to the negative of the ionization potential:

$$Nu = -I \quad (5)$$

A high value of the nucleophilicity index Nu characterizes a good nucleophile, while a low value indicates a good electrophile.

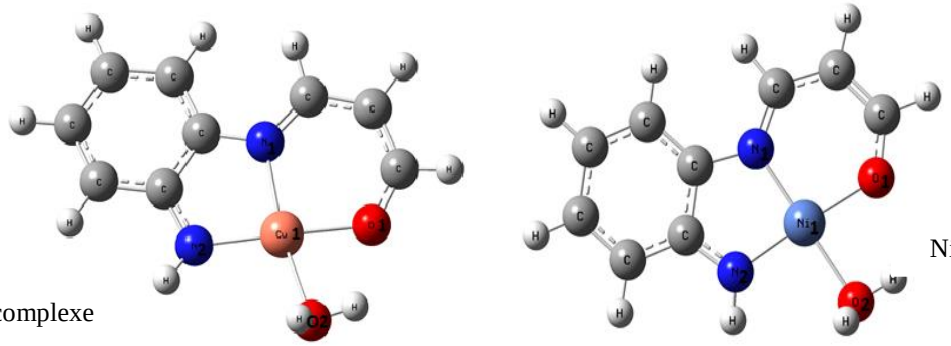
ADMET and Drug-Likeness Analysis

ADMET in silico analysis is performed to predict which the mono acetylacetone-o-phenylenediamine Schiff base ligand and its corresponding Ni(II) and Cu(II) complexes produce toxicity after administration into the body or exhibit a pharmacokinetic profile. For this, the servers admetSAR (Cheng, 2012) and SwissADME (Daina, 2017) were used. Drug-likeness is a qualitative concept that evaluates the bioavailability of a compound in accordance with its physicochemical properties. Thus, compounds with good bioavailability can be considered as oral drug candidates (Pires, 2015). Thus, blood brain barrier (BBB) penetration, human intestinal absorption (HIA), Caco-2 permeability, AMES toxicity and carcinogenicity were calculated. Drug similarity properties of compounds with acceptable physicochemical properties were determined using several filter rules, namely Lipinski's rule (Lipinski, 2001), Veber's rule (Verber, 2002).

Results and Discussion

Geometry

Figure 2 shows the optimized structures of complexes and all geometric parameters are depicted in Table 1.



Cu(II) complexe Ni(II) complexe

Figure 2. Optimized structures at DFT level

Table 1. Optimized structural parameters at DFT

Parameters	Ni(II) Complex	Cu(II)
Bond length (Å)		
M-N1	1.847	1.914
M-N2	1.873	2.010
M-O1	1.861	1.94
M-O2	1.988	2.168
Bond angles(°)		
N1-M-N2	97.4	84.1
N1-M-O1	93.6	94.6
N2-M-O2	97.4	104.1
O1-M-O2	78.4	82.8

Hydrogen Bonds

The complexes under consideration exhibit multiple hydrogen bonds, which contribute to their stability. Table 2 illustrates the hydrogen bonds involved in intramolecular interactions.

Table 2. Theoretical hydrogen bonds at DFT

Hydrogen bonds (Å)	Ni(II) Complex	Cu(II) Complex
O2…HO	2.096	2.041
N2…HO	2.874	2.981
O1…HN	2.744	2.885

Infrared Spectra

To facilitate the assignment of observed experimental peaks for the copper(II) and nickel (II) complexes, we conducted a theoretical analysis of the IR spectrum (Table 3) and compared it with the experimentally obtained results (SOAYED, 2013). Based on this analysis, we assigned the normal modes of vibration for both the ligand and its complexes. This allowed us to deduce the new vibrational modes that arise after complexation and to observe the influence of the metal change on the vibrational behavior.

Table 3. Selected theoretical and experimentall IR frequencies (cm^{-1}).

Compound	ν O-H cm^{-1}	ν C=N cm^{-1}	ν C-O cm^{-1}	ν N-H bending cm^{-1}	ν M-O or M-N
Ligand	3451	1529	1300	1499	-
	3449[a]	1523[a]	1298[a]	1504[a]	-
Cu Complex	3396	1630	1322	1512	356 -440
	3460[a]	1634[a]	1298[a]	1518[a]	364[a], 393[a]
Ni Complex	3457	1660	1259	1520	368, 397
	3448[a]	1654[a]	1256[a]	1518[a]	364[a], 393[a]

a: experimental data

Theoretical spectra of the Cu(II) and Ni(II) complexes displayed broad bands at 3396 cm-1 and 3457 cm-1, respectively. These bands were experimentally appear at 3460 cm-1 and 3448 cm-1 and they have been assigned to the coordination of water molecules (Table 3). The displacement of the ν N-H bending band from 1504 cm-1 in the ligand to 1512 cm-1 and 1520 cm-1, during complexation indicates the participation of the NH group in the formation of the complex. In the Cu and Ni complexes, new bands ranging from 356 to 440 cm-1 were detected, and these bands were attributed to the vibrations of ν M-N and ν M-O.

Binding Energy Calculation

To conduct a comparative analysis of the complexes' stability, we calculated the Binding Energy (BE) using the following formula:

$$E_{binding} = E_{complex} - (E_{metal} + E_{Ligand}) \quad (6)$$

Here, $E_{complex}$ represents the energy of the optimized complex, while E_{Ligand} and E_{metal} denote the single point energies of the ligand and metal in their respective optimized states. The complex with the highest BE corresponds to the most stable complex. The calculated BE values for the complexes are presented in Table 4.

The order found is as follows:

Cu(II) < Ni(II). The nickel complex is the most stable

Table 4. Binding energies (Kcal/mol) obtained at DFT.

Parameters	Ni(II) Complex	Cu(II) Complex
Binding Energy (Kcal/mol)	-823.775	-776.920

Energetic Properties

The calculated dipole moment, NBO charge, HOMO, LUMO and gap energy are listed in Table 5.

Table 5. Energetic properties of the synthesized complexes at DFT.

Parameters	Ni(II) Complex	Cu(II) Complex
Energy (a.u.)	-778.3008	-
HOMO (eV)	-6.748	805.1151
LUMO (eV)	-2.608	-6.646
ΔE(eV)	4.140	-3.499
Dipole moment (Debye)	3.25	3.147
Charges NBO (e)		3.47
M	0.706	0.916
N_1	-0.425	-0.503
N_2	-0.560	-0.592
O_1	*-0.585*	-0.751

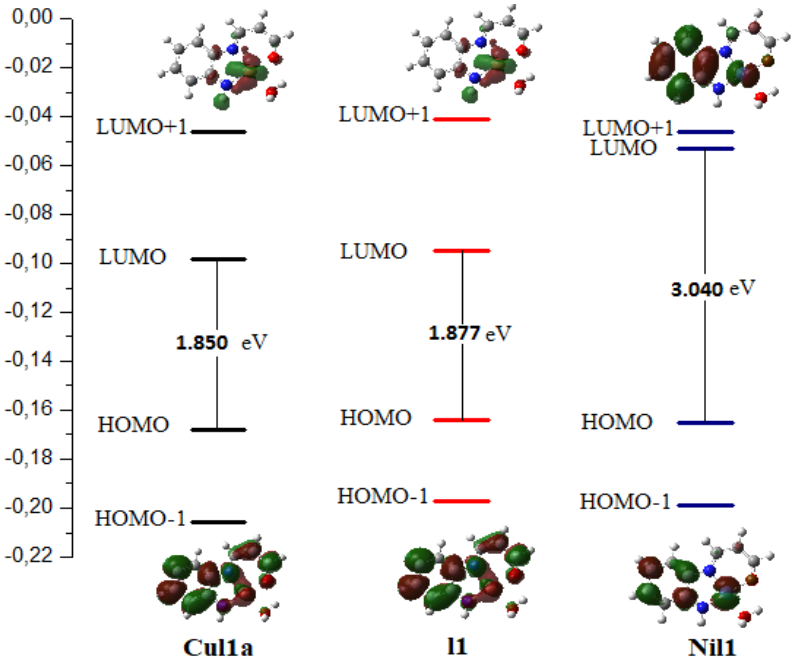


Figure 3. FMO and gap |HOMO–LUMO| for the studied structures

NBO charges are good predictors of electrophilic and nucleophilic attack sites (Chen, 2012). The values obtained for the metal atoms show a Ligand Metal Charge Transfer (LMCT). We find that the covalent character of the metal-ligand bonds decreases as follows:

Ni(II) > Cu(II).

The oxygen atoms possess a greater negative charge compared to the nitrogen atoms. Our results validate that oxygen exhibits higher reactivity when forming bonds with metals than nitrogen atoms.

Frontier Molecular Orbital (FMO)

For the ligand, the HOMO is located practically on all the atoms constituting it . n the case of Cu(II), the HOMO is fully localized on all the complex. While, it covers metal, and phenyl rings in nickel complex. The LUMO is mainly localized on nitrogen and oxygen atoms in ligand and copper complex the LUMO is located on the metal and phenyl ring in nickel complex (Figure 3).

Reactivity

The parameters μ, η, S, ω and Nu were calculated using the equations 1-5. The results are summarized in the Table 6.

Table 6. The reactivity parameters of two molecules.

Molecules	E_H	E_L	μ	η	ω
Cul1a	-4.510	-2.660	-3.585	0.462	13.9
L1	-4.460	-2.584	-3.522	0.938	6.60
Nil1	-4 .489	-1.442	-2.965	1.523	2.88

The values of ω *and* μ indicate that the copper complex is the most electrophilic and Ni(II) complex is the most nuceophilic. The decrease in energy gap explains the charge transfer (CT) taking place in the molecule, which can be responsible for their biological reactivity (Chen, 2012). As can be seen from Figure 3, Cu(II) complex has the lowest energy gap and appear the most reactive.

ADMET and Drug-Likeness

The predicted pharmacokinetic profiles of the Schiff base ligand and its Ni(II) and Cu(II) complexes are listed in Table 7. The obtained results show that all the compounds present high values of intestinal absorption and human adenocarcinoma cells (Caco-2) permeability (log Papp> 0.9). These results suggest that the compounds would easily reach their target in the body. Moreover, the negative values of logBB indicate that the studied compounds are poorly distributed to the brain, which suggests their safety for the central nervous system. In addition, the ligand and its nickel (II) and copper (II) complexes are non-inhibitors of the isoenzymes CYP2C9 and CYP3A4. On the other hand, the compounds were tested for their compliance with Lipinski's rule (Lipinski, 2001), and Veber's rule (Verber, 2002). These rules evaluate the bioavailability and the oral administration efficacy of drugs according to their physicochemical properties. The ligand and its complexes are compliant with Lipinski's rule (molecular weight ≤500 g/mol, number of hydrogen bond donors and acceptors ≤5 and ≤10, respectively, and octanol-water partition coefficient LogP ≤5) and Veber's rule (polar surface area (PSA) < 140 Å² and a number of rotatable bonds < 10) (Table 8). Which indicates that the compounds show favorable drug-like properties.

Table 7. Predicted pharmacokinetic properties of the ligand complexes

Compounds	Caco-2 permeability (cm/s)	HIA (%)	BBB (LogBB)	CYP450 CYP2C9 İnhibitor	CYP3A4 inhibitor	Total clearance
L1	1.192	83.91	-0.353	No	No	0.716
NiL1	1.185	97.38	-0.217	No	No	1.076
CuL1	1.185	97.38	-0.21	No	No	1.095

Table 8. Prediction of the physicochemical properties of the studied compounds.

Compounds	Molecular Weight (g/mol)	PSA (A^2)	HBD	HBA	Rotatable bonds	LogP	Lipinski rule	Veber rule
L1	162.11	58.61	2	2	2	2.05	Yes	Yes
NiL1	236.79	42.85	2	2	2	1.24	Yes	Yes
CuL1	241.64	42.85	2	2	0	1.24	Yes	Yes

Table 9. Toxicity prediction of the studied compounds.

Compounds	Skin sensitization	AMES toxicity (mutagenicity)	hERG inhibitor	Oral Rat Acute Toxicity (LD50) (mol/kg)	Maximum tolerated dose (mg/kg/day)	Hepatoxicity
L1	No	No	No	2.045	1.452	No
niL1	No	Yes	No	2.837	-0.412	No
CuL1	No	No	No	2.837	0.439	No

Furthermore, the prediction of toxicity revealed that the ligand and the complexes are not inhibitors of the hERG (human Ether-a-go-go-Related Gene) potassium channels. The inhibition of the hERG potassium channels may cause arrhythmia (Garrido , 2020). Additionally, according to Table 9, all the compounds don't show skin sensitization and hepatotoxicity. Additionally, the acute oral toxicity of the complexes shows a lethal dosage

value (LD50) of 2.837 mol/kg. Consequently, the complexes show less toxicity than the ligand. The prediction of the pharmacokinetic properties and toxicity (ADMET), along with drug-likeness of the studied ligand and its corresponding nickel (II) and copper (II) complexes reveals that the compounds could be interesting oral drug candidates.

Conclusion

In this work, structural and energy parameters, spectroscopic analysis, electronic properties and reactivity descriptors and *in silico*-biological activities of the mono acetylacetone-o-phenylenediamine Schiff base ligand and its corresponding Ni(II) and Cu(II) complexes were calculated using the DFT methods. The aim is to investigate if these compounds could be interesting oral drug candidates. The results revealed that:

- The nickel complex is the most stable one, While, Cu(II) complex has the lowest gap energy and it's the most reactive one, which is in good consistent with the results of the OMF study.
- Our complexes exhibit multiple hydrogen bonds, which contribute to their stability.
- All the compounds studied present good absorption in the intestine which could help them to reach their target.
- Toxicity prediction shows that, in general, the compounds are not hERG inhibitors and don't show skin sensitization and hepatotoxicity.

The ligand and its complexes respect the rules of Lipinski and Viber. Thus, they present favorable drug-like properties.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

Acknowledgements or Notes

* This article was presented as an oral presentation at the International Conference on Research in Engineering, Technology and Science (www.icrets.net) held in Budapest/Hungary on July 06-09, 2023.

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To cite this article:

Guechtouli, N., Kichou N., Bouzaheur, A., & Adjal, C. (2023). DFT study of a Schiff base ligand and its nickel and copper complexes: Structure, vibration, chemical reactivity and in silico biological. *The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM), 23*, 548-555.