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# DESIGN, SYNTHESIS AND CHARACTERIZATION OF NEW Cu(II) COMPLEXES WITH *N*-SUBSTITUTED SULFONAMIDE LIGANDS

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**ABSTRACT.** Three new Cu(II) complexes with potential biological activity with *N*-substituted sulfonamide-type ligands (one new - HL1 and one - $H_2L2$ previously reported by our research group) were synthesized and characterized. The aromatic nucleus and the N-heterocyclic nuclei found in the ligands' structures could facilitate an efficient interaction between the complexes and DNA, as a preliminary step in exerting their nuclease activity. The HL1 ligand was characterized by elemental analysis, IR spectroscopy and mass spectrometry. The binary complexes, $[Cu(L1)_2]$ and $[Cu(L2)(H_2O)_2]$ and the ternary Cu(II)-sulfonamide-1,10-phenanthroline complex $[Cu(L1)_2(phen)]$ were characterized by elemental analysis and spectral methods (IR, UV-Vis, EPR). Complex $[Cu(L2)(H_2O)_2]$ was characterized by X-ray diffraction, the data suggesting a severely distorted square-planar geometry.

***Keywords:*** *N-substituted sulfonamides, copper(II) complexes, IR, UV-Vis and EPR spectroscopy, X-ray diffraction*

## INTRODUCTION

Sulfonamides were the first effective chemotherapeutic agents employed systematically to treat bacterial infections[1]. Due to the fact that they possess a variety of biological activities, they are widely used in ophthalmic, urinary and gastrointestinal infections [2], but also as anti-hypertensive and diuretic

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drugs [3]. Many sulfonamide-type compounds with interesting biological activities and promising therapeutic potential have recently been synthesized, such as antitumor agents [4, 5], carbonic anhydrase inhibitors [6, 7], antidiabetics [8] and antiviral drugs [9-11].

Another research direction involving sulfonamides is represented by the use of these structures as ligands in coordination chemistry. N-substituted sulfonamides are suitable candidates for coordination chemistry primarily because of the presence of N and O donor atoms in the sulfonamide moiety. According to specific needs, the functional groups of N-substituted sulfonamides may bear additional donor atoms increasing their potential as ligands for metal ions coordination. Also, the sulfonamide structure may be designed to exhibit particular features that allow for a certain coordination pattern of the metallic center or that are correlated with particular desired functions of the final product [12, 13].

1,10-Phenanthroline (phen) is a well-known motif used to obtain a large range of ligands for various metal ions. Its chelating properties allowed researchers to develop copper(II) complexes with very interesting features, like the capacity to cleave the DNA double helix [14-16].

Transition metal complexes obtained with ligands with therapeutic properties have attracted much attention due to the fact that they show enhanced biological activity compared to the free ligands, including antibacterial and antitumor activity [17-19].

It is well known that DNA is very resistant to spontaneous hydrolysis, due to the negatively charged phosphate backbone that prevents attack by nucleophiles[20]. Nature resolved this matter with the help of hydrolytic enzymes, such as restriction endonucleases and topoisomerases, which reduce the hydrolysis time significantly [21]. Although natural nucleases have been very useful in many applications, they also present disadvantages, such as large size and limited range of sequence selectivity [22], which led scientists to conceive the so-called chemical or artificial nucleases. Chemical nucleases are small molecules that are able to bind to DNA, cleave the nucleic acid and be potentially used as gene regulators, mapping of protein and DNA interactions, probing of DNA specific structures and cancer therapy [23].

Copper ions, constituents of numerous enzymes’ active centers are particularly appealing for the design of complexes acting as chemical nucleases, as they possess biologically accessible redox potentials and relatively high nucleobase affinity.Copper ions have been extensively studied as models for generating reactive oxygen species [24]. It has been shown that in the presence of hydrogen peroxide, copper ions produce highly reactive DNA-damaging species and induce more DNA base damage than the iron ions and other biologically relevant transition metal ions [25].

The copper(II) ion coordinates to a large range of organic structures with N, O and S donor atoms.

With this in mind, we designed a new *N*-substituted sulfonamide and synthesized three copper(II) complexes, one of them containing a 1,10-phenanthroline molecule as coligand. The evaluation of the complexes' ability to interact with DNA and their nuclease activity are currently being studied.

## RESULTS AND DISCUSSION

### Crystal structure of complex [Cu(L2)($H_2O$)$_2$]

Figure 1 shows the molecular structure of complex [Cu(L2)($H_2O$)$_2$] as well as the atomic labeling scheme adopted. The structural parameters for the coordination polyhedron are listed in Table 1.

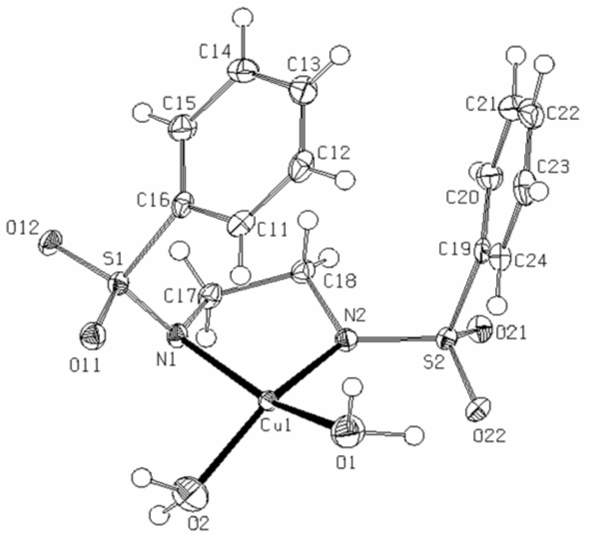


**Figure 1.** Molecular structure of complex [Cu(L2)($H_2O$)$_2$] showing the atom labeling scheme

**Table 1.** Selected bonds and angles for complex [Cu(L2)($H_2O$)$_2$]

| Selected Bond lengths (Å) | | Selected Angles (°) | |
|---|---|---|---|
| Cu(1)-N(2) | 1.968(2) | N(2)-Cu(1)-N(1) | 84.83(10) |
| Cu(1)-N(1) | 1.975(2) | N(2)-Cu(1)-O(2) | 151.89(10) |
| Cu(1)-O(2) | 1.991(2) | N(1)-Cu(1)-O(2) | 93.00(10) |
| Cu(1)-O(1) | 1.995(2) | N(2)-Cu(1)-O(1) | 101.20(10) |
| | | N(1)-Cu(1)-O(1) | 154.60(10) |
| | | O(2)-Cu(1)-O(1) | 92.73(10) |

N,N'-(ethane-1,2-diyl)dibenzenesulfonamide ($H_2L2$) acts as a bidentate ligand through the two $N_{sulfonamido}$ atoms, forming a stable five-member ring with the metal ion. The coordination process is associated with the deprotonation of the two sulfonamide moieties.

Copper(II) is surrounded by two $N_{sulfonamido}$ atoms and two O atoms belonging to two water molecules, in a severely distorted square-planar local environment.

The Cu-$N_{sulfonamido}$ bond lengths of 1.968(2) Å and 1.975(2) Å are in the range observed for similar reported sulfonamidato complexes [14, 26]. The two Cu-O bond lengths are slightly larger, of 1.991(2) Å and 1.995(2) Å. The angles that describe the coordination polyhedron, in the range 84.83(10) – 101.20(10)$^o$, deviate significantly from 90$^o$. As it is to be expected considering the bidentate nature of the sulfonamide ligand, the angle formed by the central ion and the two $N_{sulfonamido}$ atoms is the smallest. The deviations of N(1), N(2), O(1) and O(2) atoms are from the mean plane are 0.484, -0.454, 0.404 and -0.454 Å respectively and Cu1 is practically included in the mean plane. These values, together with the bond angles and the tetrahedrality value of 37.75$^o$, are indicative of the severe distortion of the square-planar geometry.

The structure of complex $[Cu(L2)(H_2O)_2]$ is stabilized by both intra- and inter-molecular hydrogen bonds of moderate strength [27]. The hydrogen bonds involve the hidrogen atoms in the coordinated water molecules and the oxygen atoms of the sulfonamide moieties belonging to the same complex molecule or to adjacent ones. The geometric parameters defining the hydrogen bonds are listed in Table 2.

**Table 2.** Hydrogen bonds for complex $[Cu(L2)(H_2O)_2]$

| ***D-H...A*** | ***d(D-H) (Å)*** | ***d(H...A) (Å)*** | ***d(D...A) (Å)*** | ***<[9] ($^o$)*** |
|---|---|---|---|---|
| O(1)-H(1A)...O(22) | 1.07 | 2.02 | 2.859(3) | 132.9 |
| O(1)-H(1B)...O(12)#1 | 1.07 | 1.98 | 3.035(3) | 168.8 |
| O(2)-H(2A)...O(21)#2 | 1.05 | 2.00 | 3.050(3) | 175.6 |
| O(2)-H(2B)...O(21)#3 | 1.06 | 2.19 | 2.994(3) | 130.4 |
| O(2)-H(2B)...O(11) | 1.06 | 2.44 | 3.112(3) | 119.9 |

Symmetry transformations used to generate equivalent atoms:
#1 x,-y+5/2,z+1/2 #2 -x,-y+2,-z #3 x,y+1,z

## Infrared spectroscopy

The IR spectra were interpreted according to literature data concerning the absorption bands of the functional groups found in the structure of the sulfonamides. The spectra of the complexes were interpreted by comparison with the IR spectra of the free ligands and according to literature data concerning similar structures [14, 15, 28-30].

The bands assigned to the ligand vibrations are slightly shifted as compared to those that appear in the IR spectra of the uncoordinated sulfonamide, as the electronic structure and the energy of the ligands is modified upon coordination [28].

An important aspect to be noted on the IR spectra of all the Cu(II) complexes is the disappearance of the band assigned to the N-H stretching vibration, indicating the deprotonation of the sulfonamides upon coordination.

In the case of complex $[Cu(L1)_2]$,the bands characteristic of the antisymmetric and symmetric vibration modes of S=O bonds are 21 $cm^{-1}$ (for $[\nu(SO_2)_{asym}]$),11 $cm^{-1}$(for $[\nu(SO_2)_{sym}]$) and 17 $cm^{-1}$ (for [v(S-N)]) higher than those corresponding to the free ligands, indicating that the sulfonamide moiety is directly involved in the formation of the complex.

The displacements of the characteristic bands attributed to $[\nu(SO_2)_{asym}]$ and $[\nu(SO_2)_{sym}]$ are slightly shifted towards lower frequencies in complex $[Cu(L1)_2(phen)]$ (from 1360 $cm^{-1}$ to 1332 $cm^{-1}$ and from 1120 $cm^{-1}$ to 1103 $cm^{-1}$, respectively), with respect to the uncoordinated ligand, meanwhile the band corresponding to the S-N bond appears at a higher frequency (966 $cm^{-1}$).

In complex $[Cu(L2)(H_2O)_2]$, as a result of the coordination process taking place through the $N_{sulfonamido}$ atoms in both sulfonamide moieties, the bands assigned to $[\nu(SO_2)_{asym}]$ and $[\nu(SO_2)_{sym}]$ are shifted towards lower frequencies of the spectrum, from 1322 $cm^{-1}$ to 1266 $cm^{-1}$ and from 1155 $cm^{-1}$ to11133-1088 $cm^{-1}$, respectively. The band corresponding to the stretching vibrations of the S-N bond from the same group, [v(S-N)], is, too, subjected to a rather significant shift towards a lower frequency (from 1055 $cm^{-1}$ to 966 $cm^{-1}$).

All modifications mentioned above are due to deprotonation of the sulfonamide moiety. The proton loss induces a weak conjugation effect between the N, S and O atoms in the sulfonamide group and an electron transfer to the copper(II) ion via the nitrogen atom [13-15].

The bands corresponding to the characteristic vibrations of 1,10-phenanthroline are rather difficult to assign in the IR spectra of the $[Cu(L1)_2(phen)]$ complex, as they partly overlap the bands characteristic of the bound sulfonamide. However, the high intensity bands at 1459 $cm^{-1}$ and 855 $cm^{-1}$ could be assigned to the coordinated 1,10-phenanthroline molecule.

The bands in the range 1595-1491 $cm^{-1}$ must include the stretching vibrations of the C=C and C=N bonds in the 1,10-phenanthroline structure but also the similar v(C=C) vibrations in the aromatic rings present in the structure of the sulfonamide.

### Diffuse reflectance spectroscopy

The diffuse reflectance spectrum of complex $[Cu(L1)_2]$ (Figure 3) shows a broad band at around 22624 $cm^{-1}$ (442 nm), assigned to a charge-transfer transition, and a wide asymmetric band centered around 16129 $cm^{-1}$ (620 nm), corresponding to the d-d transitions in the $CuN_4$ chromophore [31].

In the diffuse reflectance spectrum of complex [Cu(L1)$_2$(phen)] (Figure 4) a broad band at around 22472 cm$^{-1}$ (445 nm), assigned to a charge-transfer transition is identified, as well as a wide asymmetric band centered around 15823 cm$^{-1}$ (632 nm), attributed to the d-d transitions characteristic of a CuN$_6$ chromophore with the copper ion in a distorted octahedral environment [31].

The fact that the differences in the diffuse reflectance spectra of the [Cu(L1)$_2$] and [Cu(L1)$_2$(phen)] complexes are not significant seem to indicate that the octahedral complex shows an important degree of tetragonal distortion, adopting an elongated tetragonal-octahedral geometry [31].

The d – d transitions in complex [Cu(L2)(H$_2$O)$_2$] generate a wide band with a maximum at 17241 cm$^{-1}$ (582nm) (Figure 5), in agreement with the distorted square-planar geometry of a CuN$_2$O$_2$ chromophore.

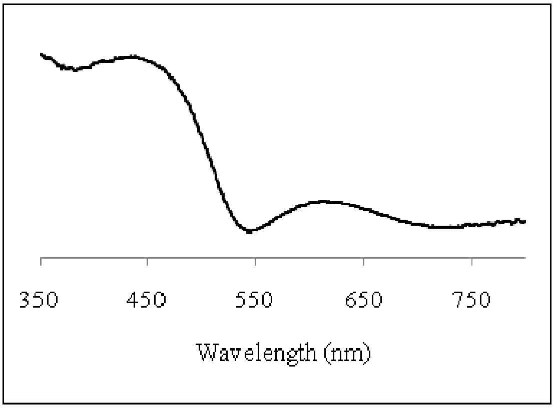


**Figure 3.** Diffuse reflectance spectrum of complex [Cu(L1)$_2$]

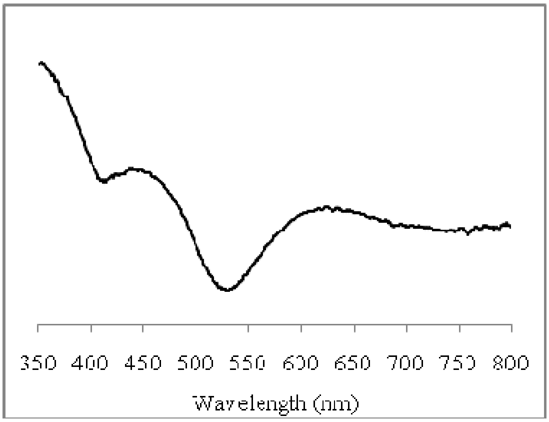


**Figure 4.** Diffuse reflectance spectrum of complex [Cu(L1)$_2$(phen)]

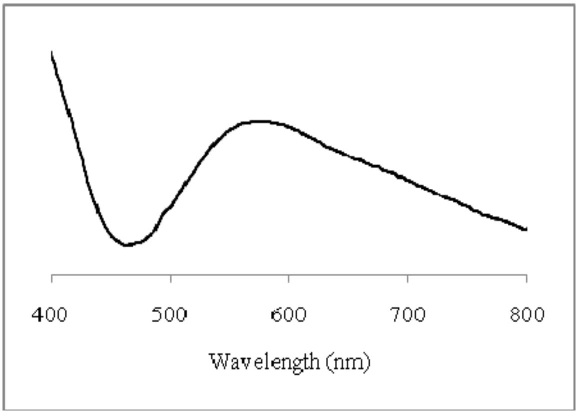


**Figure 5.** Diffuse reflectance spectrum of complex [Cu(L2)($H_2O$)$_2$]

## Electronic paramagnetic resonance spectroscopy

The EPR spectrum of [Cu(L1)$_2$(phen)] is axial (Figure 6). The EPR parameters obtained by simulation [32] are $g_{||} = 2.340$ and $g_{\perp} = 2.063$. The values $g_{||} > g_{\perp}$ are indicative of a mainly copper(II) $d_{x2-y2}$ ground state.

The EPR spectrum of [Cu(L2)($H_2O$)$_2$] is rhombic (Figure 7) with the calculated g parameters as follows: $g_x = 2.04$, $g_y = 2.066$ and $g_z = 2.190$. The R value of 0.161 indicates the presence of the unpaired electron of copper(II) in a $d_{x2-y2}$ orbital.

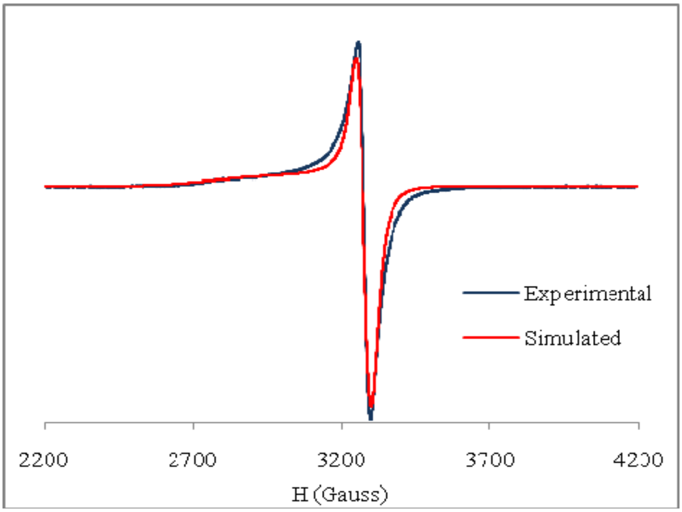


**Figure 6.** EPR spectra (X-band) of complex [Cu(L1)$_2$(phen)]

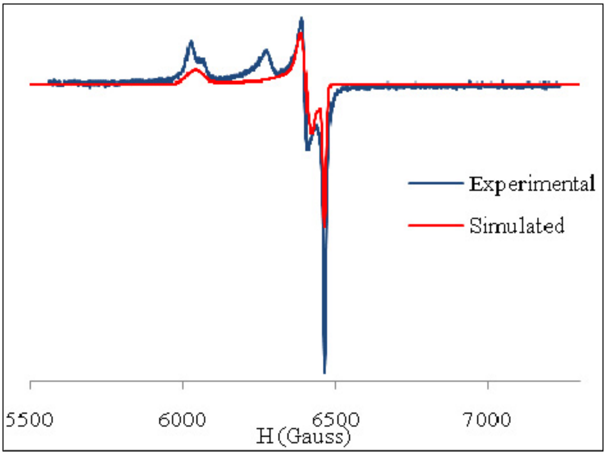


**Figure 7.** EPR spectra (X-band) of complex [Cu(L2)($H_2O$)$_2$]

# CONCLUSIONS

A new N-substituted sulfonamide (HL1) was synthesized, as well as three Cu(II) complexes, with different coordination environments and geometries. The obtained compounds were characterized by various physico-chemical methods. The [Cu(L2)($H_2O$)$_2$] complex was characterized by X-ray diffraction, while the proposed formulas for the other two Cu(II) complexes are supported by the spectroscopic data.

# EXPERIMENTAL SECTION

## Materials and methods

All chemicals and solvents were commercially available (Sigma, Alfa Aesar, Panreac) and used without further purification.

Elemental analyses (C, H, N, S) were performed on a Carlo Erba AAS instrument. Infrared spectra were recorded with a Thermo Scientific Nicolet iS10 FT-IR spectrophotometer from 4000 to 400 cm$^{-1}$ using the Smart iTR ATR accessory. Electrospray ionization-mass spectra (+ mode) analyses were performed on a Brucker Esquire 3000 plus liquid chromatography-mass spectrometry (LC-MS) system. Electronic paramagnetic resonance (EPR) spectra were collected at the X-band frequency at room temperature with a Brucker ELEXSYS spectrometer. The diffuse reflectance spectra of the copper(II) complexes were recorded on an Jasco V-550 instrument, in the interval 300 - 800 nm.

## Synthesis of the ligands

For the synthesis of *N*-(pyridin-2-yl) quinoline-8-sulfonamide, HL1 (see scheme 1), 8.8 mmol (2 g) of solid quinoline-8-sulfonyl chloride were added to a solution containing 8.8 mmol (0.82 g) of pyridin-2-amine in 6 mL of pyridine. The reddish-orange suspension was stirred at 0°C for 1 hour, and then at room temperature for another 2 hours and 30 minutes. 50 mL of cold water were added to the orange suspension and the mixture was stirred for another 2 hours in an ice bath. The resulting light orange solid was filtered and recrystallized with 50 mL of ethanol at 40°C. The purified ligand was a white solid, obtained with a yield of 50%.

Compound *N,N'*-(ethane-1,2-diyl)dibenzenesulfonamide, $H_2L2$ (Figure 2), was synthesized and characterized as previously reported by our research group [14].

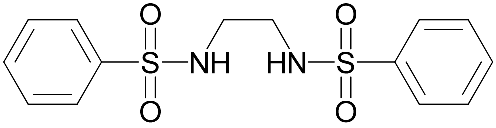


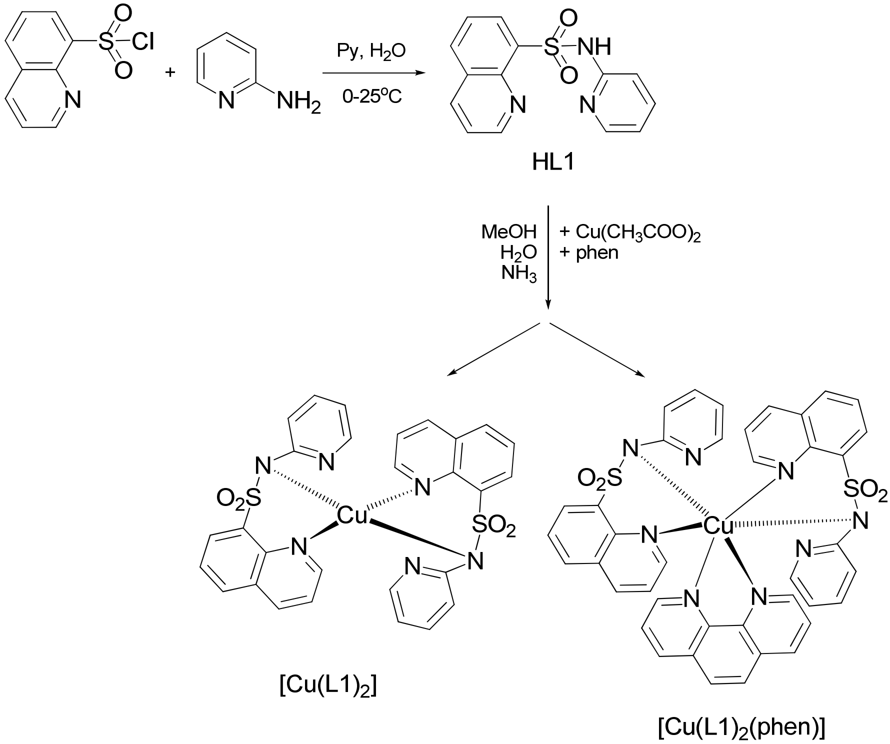
**Figure 2.** Ligand $H_2L2$ structure

## Synthesis of [Cu(L1)$_2$] and [Cu(L1)$_2$(phen)]

0.25 mmol (0.045 g) of solid 1,10-phenanthroline was added to a solution containing 0.25 mmol (0.05 g) of $Cu(CH_3COO)_2 \cdot H_2O$ in 5 mL of $H_2O$. The resulting blue mixture was added dropwise to a solution of 0.5 mmol (0.142 g) of HL1 in 30 mL of methanol containing 2 mL of $NH_3$ 25% and stirred at room temperature for 1 hour. The green solid obtained ([Cu(L1)$_2$]) was removed and after a few days, a green microcrystalline deposit ([Cu(L1)$_2$(phen)]) formed in the filtrate. The synthetic route used to obtain the [Cu(L1)$_2$] and [Cu(L1)$_2$(phen)] complexes can be depicted as in Scheme 1.

Synthesis of [Cu(L2)($H_2O$)$_2$]

A ligand solution was prepared by dissolving 1 mmol (0.34 g) of $H_2L2$ in 30 mL of methanol containing 2 mL $NH_3$ 30%. To this solution, a mixture of 1 mmol (0.241 g) $Cu(NO_3)_2 \cdot 3H_2O$ in 20 mL methanol was added dropwise, under continuous stirring. The resulting blue-purple precipitate, possibly a copper(II) complex with $NH_3$, was removed from the reaction mixture. After approximately 48 h, blue plate crystals, suitable for X-ray diffraction, formed in the filtrate.



**Scheme 1.** Synthetic route for the HL1 ligand and its copper(II) complexes

## Elemental analysis

The results of the C, H, N, S elemental analysis of the N-substituted sulfonamide and of the Cu(II) complexes are shown in Table 3.

**Table 3.** Elemental analysis results for the sulfonamide ligand and for the copper(II) complexes

| | Molecular formula | Molecular weight (g/mol) | Elemental analysis Experimental % (Calculated %) | | | |
|---|---|---|---|---|---|---|
| | | | C | H | N | S |
| HL1 | $C_{14}H_{11}N_3O_2S$ | 285.32 | 58.57 (58.93) | 3.76 (3.89) | 14.45 (14.73) | 11.13 (11.24) |
| [Cu(L1)$_2$] | $C_{28}H_{20}CuN_6O_4S_2$ | 634.1 | 53.8 (53.03) | 3.37 (3.15) | 13.3 (13.25) | 10.31 (10.11) |
| [Cu(L1)$_2$(phen)] | $C_{40}H_{28}CuN_8O_4S_2$ | 812.42 | 59.05 (59.08) | 3.39 (3.44) | 13.58 (13.78) | 7.74 (7.87) |
| [Cu(L2)(H$_2$O)$_2$] | $C_{14}H_{18}CuN_2O_6S_2$ | 437.96 | 39.19 (38.39) | 3.86 (4.14) | 5.72 (6.39) | 13.12 (14.64) |

## Infrared spectroscopy

The bands corresponding to the valence vibrations characteristic to various groups are shown in Table 4.

**Table 4.** Characteristic frequencies ($cm^{-1}$) of the sulfonamide ligands and of the Cu(II) complexes in the IR spectra

| | ν(N-H) | $ν_{asym}(SO_2)$ | $ν_{sym}(SO_2)$ | ν(S-N) |
|---|---|---|---|---|
| HL1 | 3120 | 1360 | 1120 | 958 |
| $[Cu(L1)_2]$ | - | 1381 | 1131 | 975 |
| $[Cu(L1)_2(phen)]$ | - | 1332 | 1103 | 966 |
| $[Cu(L2)(H_2O)_2]$<br>$(H_2L2)$ | -<br>(3322, 3266d) | 1266<br>(1322) | 1133-1088d<br>(1155) | 966<br>(1055) |

d - doublet

## Mass spectrum of HL1

Positive mode ionization ESI experiment was run using a DMF ligand solution. In the mass spectrum of the HL1 ligand, the peak at m/z 286.07 corresponds to the pseudomolecular ion $[HL1 + H]^+$.

## X-ray crystallography for complex $[Cu(L2)(H_2O)_2]$

A blue plate crystal of complex $[Cu(L2)(H_2O)_2]$, measuring 0.15 x 0.08 x 0.04 mm, was mounted on a glass fiber and used for data collection. Crystal data were collected at a temperature of 100.0(2) K, using a Bruker X8 Kappa APEXII diffractometer. Graphite monochromated MoK(alpha) radiation (lambda = 0.71073 angstrom's) was used throughout. The data were processed with APEX2 [33] and corrected for absorption using SADABS (transmissions factors: 1.000 - 0.863) [34]. The structure was solved by direct methods using the program SHELXS-97 [35] and refined by full-matrix least-squares techniques against $F^2$ using SHELXL-97 [36]. Positional and anisotropic atomic displacement parameters were refined for all nonhydrogen atoms. Hydrogen atoms were located in difference maps and included as fixed contributions riding on attached atoms with isotropic thermal parameters 1.2 times greater than those of their carrier atoms. Criteria of a satisfactory complete analysis were the ratios of "rms" shift to standard deviation less than 0.001 and no significant features in final difference maps. Atomic scattering factors were from "International Tables for Crystallography" [37]. Programs PLATON [38] and SCHAKAL [39] were used to obtain the molecular graphics. A summary of the crystal data, experimental details and refinement results for complex $[Cu(L2)(H_2O)_2]$ are listed in Table 5.

**Table 5.** Crystal and structure refinement for complex [Cu(L2)($H_2O$)$_2$]

| | |
|---|---|
| Empirical formula | $C_{14}H_{18}CuN_2O_6S_2$ |
| Formula weight | 437.96 |
| Temperature (K) | 100(2) K |
| Wavelength (Å) | 0.71073 |
| Crystal system, space group | Monoclinic, P2(1)/c (No. 14) |
| a [Å] | 15.8938(3) |
| b [Å] | 8.7865(2) |
| c [Å] | 13.7732(3) |
| α [º] | 90 |
| β [º] | 113.33(10) |
| γ [º] | 90 |
| Volume [$Å^3$] | 1766.18(6) |
| Z, calculated density [Mg $m^{-3}$] | 4, 1.647 |
| Absorbtion coefficient [$mm^{-1}$] | 1.506 |
| F(000) | 900 |
| Crystal size [mm] | 0.15 x 0.08 x 0.04 |
| θ range for data collection [º] | 1.40 to 26.39 |
| Limiting indices | $-19 \le h \le 18$,<br>$0 \le k \le 10$,<br>$0 \le l \le 17$ |
| Reflections collected/unique | 20236 / 3609 [R[41] = 0.0408] |
| Data/restraints/parameters | 3609 / 0 / 226 |
| Completeness to θ=26.39 [%] | 99.8% |
| Final *R* indices [$I > 2\sigma(I)$] | R1 = 0.0388, wR2 = 0.0985 |
| R indices (all data) | R1 = 0.0495, wR2 = 0.1039 |

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