Synthesis, Crystal Structures and Characterization of a New Antitumor Cu(II) Complex with N-sulfonamide Ligand

ADRIANA CORINA HANGAN¹, ALEXANDRU TURZA¹, ROXANA LIANA STAN²*, LUMINITA SIMONA OPREAN²
¹University of Medicine and Pharmacy Iuliu Haieganu Cluj Napoca, Faculty of Pharmacy, Department of Inorganic Chemistry, 400010, Cluj Napoca, Romania
²National Institute for R&D of Isotopic and Molecular Technologies, 67-103 Donat Str., 40093 Cluj, Romania
³University of Medicine and Pharmacy Iuliu Haieganu Cluj Napoca, Faculty of Pharmacy, Department of Pharmaceutical biochemistry and Clinical laboratory, 6 Pasteur Str., 400349, Cluj Napoca, Romania

A new Cu(II) complex with N-sulfonamide ligand, (Cu(N-(5-(4-methylphenyl)-[1,3,4]-thiadiazole-2-yl)-toluenesulfonamidate)]((CH₃)₂NH₂)₂complex has been synthesized and characterized. The X-ray crystal structure of the complex has been determined. The Cu(II) ion is four-coordinated, forming a CuN₄ chromophore. The ligand acts as monodentate, coordinating the metal ion through a single N-thiadiazole atom. The complex has a square planar geometry. The characterization of the complex has been studied by FT-IR, electronic, EPR spectroscopic and magnetic methods.

Keywords: copper complex, N-substituted sulphonamides, crystal structure, ERP spectrum

Metal ions are important for the course of the vital functions of the living organisms where they occur under the form of complex or chelate combinations, as well as for the methods of analysis and control of the medical substances by forming complexes [1-5].

The synthesis of Cu(II) complexes with N-sulfonamides ligands greatly increased in the past twenty years due to the diversity of biological activity of the resulting compounds: antimicrobial, anti-inflammatory, SOD mimetic, nuclease and antitumor activity. Studies have shown that Cu(II) complexes with different types of ligands can be used as potential chemical nucleases[6-8].

In this context, we have described the nuclease activity of several copper-sulfonamide complexes[9-12]. In the present paper we report the synthesis and the physicochemical characterization of a new Cu(II) complex with N-substituted heterocyclic sulfonamide: HL=N-(5-(4-methylphenyl)-[1,3,4]-thiadiazole-2-yl)-toluenesulfonamide. Its structure was determined by X-ray diffraction. Their IR, EPR, electronic spectra and its magnetic susceptibility were investigated and discussed, along with the structural and spectral comparisons with those of the analogous complexes. Antitumor activity of this complex will be the subject of a future article.

Experimental part
Materials and physical measurements
Copper sulfate pentahydrate, copper acetate monohydrate, N,N-dimethylamine and methanol were purchased from commercial sources and used as received.
Elemental analyses (C, N, H, S) were performed with a Vario EL analyser. IR spectra were recorded with a Jasco FT/IR-4100 spectrophotometer using diffuse reflectance of incident radiation focused on a sample, in the 4000-400 cm⁻¹ range. All melting points were determined in open capillaries with an Electrothermal IA 9100 apparatus and were uncorrected. Diffuse reflectance spectra were carried out on a Jasco V-550 spectrophotometer. Magnetic susceptibilities were measured at room temperature with the Faraday MSB-MKI balance. Hg[Co(NCS)₄] was used as susceptibility standard. Electronic paramagnetic resonance (EPR) spectra were performed at room temperature with a Bruker ELEXSYS spectrometer operating at the X-band frequency.

The synthesis, structure and properties of the ligand HL have been reported [13].

Synthesis of the complex \(\text{[Cu(N-(5-(4-methylphenyl)-[1,3,4]-thiadiazole-2-yl)-toluenesulfonamidate)]}((\text{CH}_3\text{)}_2\text{NH}_2)\) complex

\(\text{Cu(CH}_3\text{COO)}_2 \cdot \text{H}_2\text{O} (0.690\text{g}, 2 \text{ mmol})\) was added under continuous stirring to a solution of \((0.690\text{g}, 2 \text{ mmols})\) HL ligand dissolved in a mixture of 50 mL methanol and 10 mL N, N'-dimethylamine. The resulting green solution was stirred for two hours and was then left to stand at room temperature. After one month by the slow evaporation of the solvent, brown crystals suitable for X-ray diffraction were obtained.

Data for compound (yield 65%).

Anal. Calcd. mass fractions of elements, w/ %, for Cu₄H₂CuN₁₂O₂₈ (Mr = 1533.33) are: C 53.21, H 4.69, N 12.78, S 16.69; found: C 53.09; H 4.25; N 11.84; S 17.02. IR (KBr) \(\nu\) cm⁻¹: 1442 (thiadiazole); 1278(S=O⁻), 1140 (S=O⁻), 1117 (S-N). UV/Vis (solid) \(\lambda\) nm: 300 (π→π⁺), 396 (LMCT), 510 (d-d). \(\epsilon = 70 \text{ cm}^{-1}\text{M}^{-1}\) (Yield ca. 58%).

X-ray crystallography
A brown crystal of the complex was mounted on a glass fiber and used for data collection. Crystal data were collected at 293(2) K using a dual microsource SuperNova Diffractometer and Cu Kα radiation (λ = 1.54184 Å).

Using Olex 2 [14], the structure was solved with the Superflip [15] structure solution program using Charge Flipping and refined with the ShelXL [16] refinement package using Least Squares minimisation. A summary

* email: roxanaluc@yahoo.com

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of the crystal data, experimental details and refinement results is listed in table 1.

Results and discussions

Crystal structures of \([\text{Cu}(L)_4]((\text{CH}_3)_2\text{NH}_2)^+\)_2 complex

Relevant bond distances and angles for the complex are collected in table 2.

The molecular structure and crystallographic numbering scheme for the complex are illustrated in figure 1.

The crystal structure of the complex contains a CuN_4 entity in a square planar geometry. In this complex, the Cu(II) ion is coordinated by four molecules of ligand. Each ligand acting as monodentate and coordinates the metal ion through one N-thiadiazole atom of the thiadiazole rings. The Cu1-N_\text{thiadiazole} distances (1.988(2) - 2.002(2) Å) are similar to those reported for other complexes with ligands containing a thiadiazole ring [17, 18]. The coordination bond angles ranging from 89.10(9)° [N22-Cu1-N33] to 90.89(9)° [N22-Cu1-N33], confirm the regular square-planar geometry of the complex.

The distortion of the square-planar geometry (commonly known as tetrahedrality) can be determined from the angle subtended by two planes, each encompassing the copper and two adjacent atoms. The dihedral angle between the planes N22Cu1N33 and N22Cu1N33 (the tetrahedrality) equal to 0° confirms that the five atoms (Cu1 and the four N_\text{thiadiazole} atoms) are in the same plane so the regular square-planar geometry of the CuN_4 chromophore. For the complex, the crystalline packing of the symmetrical unit also includes a (CH_3)_2NH_2^+ molecules from the reaction medium, that does not coordinate the Cu(II) ion.

The complex also presents the C-H...π interactions, involving the H4 and H7 atoms which points towards the center of the methylphenyl ring in the same complex molecule. Intramolecular C-H...π interactions contribute to the stabilization of the \([\text{Cu}(L)_4]((\text{CH}_3)_2\text{NH}_2)^+\)_2 complex (fig. 2).

Also, the complex is stabilised by intermolecular strong and weak hydrogen interraactions [19], implicating hydrogen atoms from the N, N'- dimethylamine, N sulfonamido or O sulfonamido atoms. The geometric
parameters defining the hydrogen interactions are collected in table 3.

In the complex, the sulfonamidate ligand (HL) acting as monodentate through a nitrogen atom of the thiadiazole heterocycle. The sulfonamide molecules of this type can behave as bidentate ligands as well through the N atom from the thiadiazole moiety and through one of the O atoms and even through the N$_{\text{sulfonamido}}$ atom from the sulfonamido moiety [20].

The presence of aromatic rings like methylphenyl in the structure of the sulfonamides is probably the main variable determining their capacity to destroy DNA. Their complexes have a higher capacity to destroy DNA than the non-coordinated sulfonamide ligand. These plane aromatic rings allow the complex molecule to come closer to DNA through intercalation between neighboring base pairs of the DNA chains, and then link with them through π-stacking bonds [12].

**Spectroscopic and magnetic properties**

The IR spectrum of the complex present a similar pattern with the other Cu(II) complexes with N-substituted sulfonamide. The most remarkable difference occurring in the band corresponding to the stretching vibration of the thiadiazole ring, which is shifted from 1542 cm$^{-1}$ (HL) in the free ligand to 1442 cm$^{-1}$ (1) in the complex. The characteristic band corresponding to the ν(S–N) appears at 917 cm$^{-1}$ shifted to higher frequencies with respect to those of the uncoordinated ligands (906 cm$^{-1}$ (HL)). These modifications in the thiadiazole heterocycle and in the sulfonamide group are attributed to the involvement to the N$_{\text{thiadiazole}}$ atom in coordination of Cu(II) and to the deprotonation of the sulfonamido moiety for the both complexes [21]. Bands due to the antisymmetric and symmetric vibration modes of the S=O bond appear at 1278 and 1140 cm$^{-1}$, ca. 20 cm$^{-1}$ lower than those corresponding to the free ligand; [22, 23] such a decrease can be related to the electron transfer from the deprotonated, negatively charged N atom to the sulfonamide oxygen atoms, which results in partial single-bond character for the S-O bonds [24]. Such electron transfer increases the bond order of the S=O moiety, thus accounting for the 25 cm$^{-1}$ shift towards higher wave numbers of the band due to the stretching mode of this bond. The lack of bands close to 3200 cm$^{-1}$, which were originally present in the spectra of the free ligands confirms deprotonation of the sulfonamido moiety for the both complexes (906 cm$^{-1}$ (HL)).

According to the Bertini classification, the value of $A_e$ can be correlated with the geometry of the complex [28]. Thus, values between 160 and 200 x 10$^{-4}$ cm$^{-1}$ correspond to a square-planar geometry. As $g_\parallel > g_\perp$ in the complexes, the unpaired electron must be in the $d_z^2$ (or $d_{xy}$) orbital [29].

The room temperature magnetic moment of the complex ($\mu_{\text{eff}} = 1.73$ MB) is consistent with the presence of a single unpaired electron.

**Table 3**

<table>
<thead>
<tr>
<th>D-H - A</th>
<th>d(D-H) (Å)</th>
<th>d(H...A) (Å)</th>
<th>d(D...A) (Å)</th>
<th>&lt;(DHA) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N49-H19A-..N11 (strong)</td>
<td>0.906</td>
<td>2.093</td>
<td>2.897</td>
<td>172.38</td>
</tr>
<tr>
<td>N49-H49B-..N36 (strong)</td>
<td>0.900</td>
<td>2.084</td>
<td>2.981</td>
<td>173.73</td>
</tr>
<tr>
<td>N49-H49B-..O39 (weak)</td>
<td>0.990</td>
<td>2.426</td>
<td>3.000</td>
<td>121.89</td>
</tr>
</tbody>
</table>

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**Fig. 3.** X-band polycrystalline powder EPR spectrum of the complex

**Conclusions**

A new Cu(II) complex with N-sulfonamide ligand, Cu(N(5-(4-methylphenyl)-[1,3,4]-thiadiazole-2-yl)-toluene-sulfonamidate)$(\text{CH}_3)\text{NH}_2$ was synthesized and characterized. The crystalline structure of the complex was attributed using X-ray diffraction and was confirmed by the data obtained from elemental analysis, spectral (IR, UV-Vis, EPR) and magnetic determinations.

Crystallographic data without structure factors for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-1519070. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; www.ccdc.cam.ac.uk/data/request/cif).

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