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INVESTIGATION OF SOME WATER-SOLUBLE BINUCLEAR COMPLEXES OF COPPER(II) BASED ON*BIS*-ISOTHIOSEMICARBAZONES

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Abstract

It has been studied interaction of known water-soluble copper(II) dimer $[Cu_2(H_2Q)$-μ-$Cl]Cl_2 \cdot H_2O$ with some chloride salts, where H_3Q representsbinucleating 2,6-diformyl-4-methylphenol bis(*S*-methyl-isothiosemicarbazone). It was obtainedthree new polynuclear coordination dimers, including one heterometallic containing Cu_2-Zn. The complexes were characterized by elemental analysis, IR spectroscopy and XRD analysis. In contrast to other copper dimers in $[Cu_2H_2Q$-μ-Cl-μ-$(ZnCl_4)] \cdot H_2O$ the both chloride anions coordinate to copperin cis-apical fashion, as well as being part of a new formed tetrachlorzincate anion which function as additional triatomic bridge between copper centers: Cu_1-Cl-Zn-Cl-Cu_2. The EPR spectra of the starting compound recorded at 300 K reveals seven lines of hyperfine structure with g= 2.006 ± 0.001 of the central component and the constant of hyperfine interaction A= $(126.9 \pm 0.1) \cdot 10^{-4}$ cm^{-1}. It was found that this dimer manifests a pronounced selective antibacterial activity against pathogen Gram(+) bacteria (MMC= 1-2 μg/mL), as well as against fungal strains (MMC= 4-8 μg/mL), while the free ligand H_3Q does not reveal significant antimicrobial activity.

Keywords: copper, binuclear, isothiosemicarbazone, X-ray, EPR, antimicrobial.

STUDIUL UNOR COMPLECȘI HIDROSOLUBILI AI CUPRULUI(II) PE BAZĂ DE BIS-IZOTIOSEMICARBAZONE

Rezumat

A fost studiată interacțiunea dimerului hidrosolubil cunoscut $[Cu_2(H_2Q)$-μ-$Cl]Cl_2 \cdot H_2O$ cu unele săruri de clorură, unde H_3Q reprezintă bis(S-metilizotiosemicarbazona) binucleabilă a 2,6-diformil-4-metilfenolului. În rezultat au fost sintetizați trei noi dimeri ai cuprului(II), inclusiv unul heterometallic Cu_2-Zn. Compușii coordinativi au fost caracterizați prin analiza elementală, spectroscopia IR, studiul cu raze X. Spre deosebire de ceilalți dimeri de cupru, în$[Cu_2H_2Q$-μ-Cl-μ-$(ZnCl_4)] \cdot H_2O$ ambii anioni de clorură se coordonează cis-apical la ionii de cupru, totodată făcând parte dintrun anion de nou format tetraclorzincat, care funcționează ca o punte suplimentară triatomică dintre centrele de cupru: Cu_1-Cl-Zn-Cl-Cu_2. Spectrele RES înregistrate la 300K ale compusului initial, denotă o strucură hiperfină din șapte liniicu g= 2.006 ± 0.001ale componentei centrale și constanta interacțiunei hiperfine A= $(126.9 \pm 0.1) \cdot 10^{-4}$ cm^{-1}. S-a depistat că dimerul acesta manifestă o activitate antimicrobiană pronunțată și selectivăcontra bacteriilor patogene Gram (+) (MMC=1-2 μg/mL), de asemenea și contra tulpinilor de fungi(MMC=4-8 μg/mL), totodată ligandul liber H_3Q nu posedă o activitate antimicrobiană semnificativă.

Cuvinte-cheie: cupru, binuclear, isotiosemicarbazone, raze-X, RES, antimicrobian.

Introduction

Thiosemicarbazone derivatives and especially their polynuclear coordination complexes reveal interesting chemical, physical and biological properties [1-4]. For example, it has been found significant antiferromagnetic interaction between copper centers in binuclear complexes of compartmental 2,6-diformyl-4-methylphenol bis(thiosemicarbazones) [5,6]. The properties of thiosemicarbazones and their coordination compounds varies widely in dependence of the nature of the metal, the structure of the ligand or complex, the nature of the substituents in both the carbonyl and the thiosemicarbazide fragments. The latter can be derivatized by substitution to nitrogen or sulphur atoms from the thiocarbonyl group, which can be alkylated to give *S*-alkylisothiosemicarbazides. Alkylation of the sulphur atom drastically reduces the coordination capacity of the thioether atom formed with most transition metals. As a result, the sulphur atom in the isothiosemicarbazide moiety no longer participates in coordination with most metals, and its place in the isothiosemicarbazide donor set is occupied by the N4 terminal atom [7].

The effect of alkylation of the thiosemicarbazide sulphur atom, as well as of metal coordination on biological activity may be divergent. From the literature data it appears that the alkylation of sulphur in the thiosemicarbazide moiety in many cases does not increase the biological activity of the ligands or respective coordination compounds (vide infra).

The general disadvantage of biologically active thiosemicarbazone coordination compounds is that many of them are insoluble in water, which is the most suitable solvent from a biological and ecological point of view. One method to confer the water solubility is to introduce hydrophilic groups such as sulphonic (-SO_3H) or carboxylic (-COOH) groups into the organic ligand. These groups are easily ionized in the basic medium with the formation of the respective alkali metal or ammonium salts, which usually renders water solubility to the respective ligands and complexes.

Previously it was synthesized the binuclear complex [$Cu_2(H_2Q)$-μ-Cl]$Cl_2 \cdot H_2O$ (**1**), where H_3Qrepresents a compartmental ligand based on 2,6-diformyl-4-methylphenol *bis*(*S*-methylisothiosemicarbazone). The complex**1** has been tentatively assigned the following structure (Figure 1) [5].

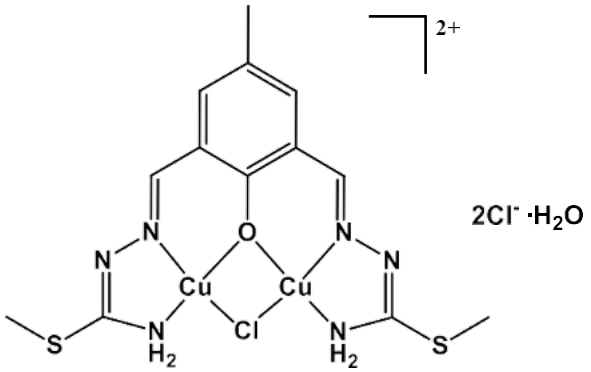


Figure 1. Proposed structure for binuclear complex *1*

The remarkable property of this dicopper complex is the water solubility with formation of dark-green solutions at relatively low concentrations. This water solubility for this compound is rather unusual, since an analogous dimer with non-alkylated thiosemicarbazone, also containing three chloride ions, is insoluble in water [5]. This water-soluble complex as well manifests some antimicrobial properties [8].

Proceeding from the mentioned properties of the binuclear copper complex **1**, the aim of the present work was the synthesis of new coordination compounds of copper(II) with thiosemicarbazone and investigation of physico-chemical properties including the biological activity.

Experimental

Materials

Thiosemicarbazide, iodomethane, 2,6-diformyl-4-methylphenol, 3-formylsalicylic acid, methanol, ethanol, dimethylsulfoxide (DMSO), dimethylformamide (DMF) and starting chlorides of ammonium, potassium, copper and zinc have been purchased from Aldrich and used without further purification.

Synthesis of ligand and derived complexes

2,6-diformyl-4-methylphenol bis(S-methylisothiosemicarbazone) (H_3Q)

Starting ligand H_3Q was obtained by condensation of *S*-methylisothiosemicarbazide hydroiodide with 2,6-diformyl-4-methylphenol in ethanol-water solvents, in the presence of sodium carbonate [5]. Yield 93%. Elemental analysis for $C_{13}H_{18}N_6OS_2$ (338.33): calcd., %: C 57.03, H 5.67, N 4.93; found, %: C 56.92, H 5.70, N 4.89. The ligand is insoluble in water, but is soluble in DMSO and DMF. M.p. 208-211°C. IR spectrum (KBr, cm^{-1}): 3484 w, 3404 w, sharp, 3081 w, 1636 s, sharp, 1607 s, 1517 v.s., sharp, 1299 s, sharp, 1016 m, sharp, 757 s, sharp, 691 m, sharp.

$[Cu_2(H_2Q\text{-}\mu\text{-}Cl]Cl_2\cdot H_2O$ (1)

The coordination compound 1 was obtained by slightly modified method described in [5]. To a suspension of H_3Q (1.70 g, 5.0 mmol) in methanol (100 mL) at room temperature was added $CuCl_2\cdot 2H_2O$ (1.70 g, 10.0 mmol). The slurry was magnetically stirred about 15 min until the disappearance of solid starting yellow ligand, then the solution was heated at 50-60°C for 0.5 h. After standing for 4-6 h at the room temperature, the green crystalline product was filtered out, washed with methanol, followed by diethyl ether and dried on air. Yield 2.86 g (97%) as green microneedles.Elemental analysis for $C_{13}H_{19}Cu_2Cl_3N_6O_2S_2$ (588.12) calcd., %: C 57.03, H 5.67, N 4.93; found, %: C 56.92, H 5.70, N 4.89.The complex is soluble in water (about 1%), DMSO and DMF, forming dark-green clear solutions. After 24 h the aqueous solution starts to acquire a very nuanced shade without forming any precipitate within 3 months.

The complex is stable for at least five years on storing in tightly closed dark vessels.IR spectra (KBr, cm^{-1}): 3503 w, 3419 w, sharp, 3300 w, 2797 m, 1555 vs, sharp, 1315 s, sharp, 1144 s, sharp, 904 m, sharp, 713 m.

$[(Cu\text{-}Cl)_2H_2Q\text{-}\mu\text{-}Cl]\cdot 3CH_3OH$ (2)

To a solution of H_3Q, (0.068 g, 0.2 mmol) in methanol (50 mL) at room temperature was added $CuCl_2\cdot 2H_2O$ (0.070 g, 0.4 mmol), packaged in dense filter paper bag. The tightly closed flask with reagents was left to stand at room temperature. After about one week it was formed a long thin green needle suitable for XRD study. The green crystalline needles were filtered out, washed with methanol, followed by diethyl ether and dried on air. Yield 0.021 g (30%). Elemental analysis for $C_{16}H_{29}Cu_2Cl_3N_6O_4S_2$ (1137.18) calcd., %: C 57.03, H 5.67, N 4.93%; found, %: C 56.92, H 5.70, N 4.89%.

$[(Cu\text{-}Cl)_2H_2Q\text{-}\mu\text{-}Cl]\cdot 4H_2O$ (3)

To a solution of $[Cu_2H_2Q\text{-}\mu\text{-}Cl]Cl_2\cdot H_2O$ (1) (0.29 g 0.5 mmol) in water (50 mL) was added the solid KCl (2.0 g) under constant mixing at room temperature. Very quickly it was formed a voluminous light-green suspension. After a few hours the suspension began to being compacted. Within a week practically all initial suspension has been transformed into the dark-green crystalline rod-shape product.

The dark-green crystals have been isolated by filtration on large pore glass filter and washed with ethanol. Yield 0.21 g (60%). Elemental analysis for $C_{13}H_{25}Cu_2Cl_3N_6O_5S_2$(642.95) calcd., %: C24.28, H 3.92, N 13.07, S 9.97; found, %: C 24.60, H 3.55, N 13.36, S 11.25. IR spectra (KBr, cm^{-1}): 3418 m, 3261 m, 2921 w, 2758 m, 1628 w, 1608 w, 1552 vs, 1436 w, 1391 w, 1376 w, 1309 s, 1242 m, 1146s, 904 m, sh, 760 w, 713 w.

$[Cu_2H_2Q$-μ-Cl-μ-$(ZnCl_4)]\cdot H_2O$(4)

The solid $ZnCl_2$ (1.0 g) to the slurry of $[Cu_2(H_2Q$-μ-$Cl]Cl_2\cdot H_2O$ (1) (0.29 g 0.5 mmol) in methanol (50 mL) was added with constant mixing and moderate heating on water-bath until solid phase was completely dissolved. Then the dark-green solution was set to store in closed vessel at room temperature. After several weeks the obtained dark-green rod-shape crystals were isolated by filtration, washed with ethanol and dried on air. Yield 0.14 g (40%). Elemental analysis for $C_{13}H_{19}Cl_5Cu_2N_6O_2S_2Zn$ (725.21) calcd, %: C21.53, H 2.64, N 11.59, S 8.84;found, %: C 17.78, H 2.77, N 9.62, S 8.15. IR spectra (nujol, cm^{-1}): 3536 w, 3464 w, 3422 w, 1625 w, 1608 w, 1560 vs, 1532 m, 1436 vs, 1378 s, 1308s, 1243 w, 1152m, 1132 m, 946 w, 758 w, 721 w, 667 w, 615 m, 478 m.

$K_3[Cu((FSA)_2T)]\cdot 4H_2O$ (5)

Precursor ligand 3-formylsalicylic acid thiosemicarbazone (H_3FSAT), m.p. 211°C, has been described earlier [9]. Recorded IR spectra (KBr pellets, cm^{-1}): 3677 w, 3442 m sh., 3287 m, 3168 s, 2974 w, 2902 w, 1663 s (ν_{as}COOH), 1611 s, 1600 s, 1549 s, 1450 m, 1412 s, 1380 m, 1225 vs, 1151 vs, 1108 s, 1079 s, 1064 s, 946 m, 754 s, 702 m, 672 m sh.

Water soluble complex $K_3[Cu((FSA)_2T)]\cdot 4H_2O$ has been synthesized by template condensation on Cu(II) of H_3FSAT with 3-formylsalicylic acid (H_2FSA) in strong basic media, where $H_3((FSA)_2T)$ represents N_1,N_4-bis(3-caboxysalicyliden) thiosemicarbazide. The solution of $CuCl_2\cdot 2H_2O$ (1.70 g, 10 mmol) in methanol (100 mL) was added dropwise under magnetic stirring to a methanol-water solution (7:3, 100 mL), containing H_3FSA-T (2.50 g, ~10.1 mmol), H_2FSA (2.00 g, ~12 mmol) and KOH (12.0 g, ~214 mmol) heated at 50-60°C. After addition of solution the resulted brown-red crystalline suspension was being maintained for about 0.5 h and the slurry was left to cool for about 24 h. The deep brown reddish sediment (micro needles) was filtered out, then was washed with methanol and diethyl ether and dried on air. Yield 5.05-5.39 g (79-84%). The complex is soluble in water, DMSO and DMF, is insoluble in ethanol and acetonitrile. Aqueous solutions have a very-intense brown-red colour and are stable at least for one month. Elemental analysis for $C_{17}H_{16}CuK_3N_3O_{10}S$ (635.23) calcd., %: Cu 10.00, C 32.14, H 2.54, N 6.61; found, %: Cu 10.45, C 31.22, H 2.28, N 6.70. IR spectra (KBr pellet, cm^{-1}): 3203 m, v. broad, 1601 vs, 1535 vs, 1418 s, 1374 s, 1305 s, 1222 m sh, 1122 s, 1083 s, 1035 m, 986 m, 881 w sh, 870 w, 830 w, 798 w, 745 m. v. sh, 671 w.

$K[Cu((FSAT^1)Cl]\cdot 2H_2O$ (6)

Starting ligand 3-formylsalicylic acid *S*-methylisothiosemicarbazone–hemihydrate ($H_3FSAT^1\cdot 0.5H_2O$) was obtained according the previously described method [9].

IR spectra (KBr pellets, cm^{-1}): 3541 w, 3480 w, 3241 m, 2888 m, 2681 m, 1653 s (ν_{as}COOH), 1628 s, 1615 s, 1598 s, 1553 m, 1475 s sh, 1432 vs sh, 1393 vs sh, 1353 m, 1289 vs, 1188 m, 1141 m sh, 1066 m, 956 w, 940 w, 842 s sh, 811 s, 762 m sh, 737 w, 664 w sh.

Copper complex 6 was prepared according to following method: the solution of $CuCl_2\cdot 2H_2O$ (0.87 g, 5 mmol) in ethanol (30 mL) was added at room temperature by dropping and magnetic stirring to an ethanol-water solution (20:8; 28 mL), containing $H_3FSAT^1\cdot 0.5H_2O$ (1.31 g, ~10.1 mmol) and KOH (1.12 g, ~20 mmol). The obtained green-kaki crystalline slurry was stirred for one hour. The green-khaki crystalline sediment (micro needles) was washed with ethanol, then with diethyl ether and dried in air. Yield 1.10 g (54%) of green-grayish crystalline powder. The complex is soluble in water, DMSO and DMF, is insoluble in ethanol and acetonitrile. Elemental analysis for $C_{10}H_{13}ClCuKN_3O_5S$ (425.39) calcd., %: Cu 14.94, C 28.23,

H 3.08, N 9.88; found, %: Cu 15.35, C 29.59, H 3.06, N 9.40. IR spectra (KBr pellet, cm^{-1}): 1604 m, 1590 m, 1540 s, 1487 vs, 1418 s, 1357 s, 1283 m, 1133 m, 916 m sh, 870 m sh, 754 m sh, 673 m.

Physical measurements

Elemental analysis of the complexes for C, H, and N, was carried out on a Vario EL (III) Elemental Analyzer.

The IR spectra of the ligand and the complexes were recorded using a Perkin Elmer Spectrum 100 FT-IR spectrometer in the range 4000-650 (KBr pellets) or 4000-400 (nujol) cm^{-1}.

X-ray crystallography: Suitable crystals for single crystal X-ray diffraction study were grown by synthesis in dilute reaction media. X-ray diffraction measurements for compound ***4*** were performed at room temperature using Oxford-Diffraction XCALIBUR E CCD diffractometer with graphite-monochromated Mo-Kα radiation. The data integration and unit cell determination were performed using CrysAlisPro package from Oxford Diffraction [10].The structures were solved with ShelXT [11]by intrinsic phasing methods and refined with ShelXL-2015 [12] using least-squares minimization. The Olex2 program was used as a graphical interface for ShelX programmes [13]. The hydrogen atoms attached to carbon were placed geometrically and constrained to ride with d_{CH} = 0.96 Å and U_{iso} of 1.2Ueq of the parent atoms. The hydrogen atoms attached to nitrogen were localized from difference Fourier maps and their positional parameters were verified according to hydrogen bonds geometry. CCDC 2218209 contains the supplementary crystallographic data for compound **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystallographic information is summarized in Tables 1.

Table 1. Crystal data and details of data collection for $[Cu_2H_2Q\text{-}\mu\text{-}Cl\text{-}\mu\text{-}(ZnCl_4)]\cdot H_2O$ (4).

Empirical formula	$C_{13}H_{19}Cu_2Cl_5N_6O_2S_2Zn$
Fw	725.16
Space group	$P2_1/c$
a [Å]	12.0561(5)
b [Å]	11.6057(4)
c [Å]	18.7412(8)
β [°]	108.790(5)
V [$Å^3$]	2482.51(18)
Z	4
r_{calcd} [g cm^{-3}]	1.940
Crystal size [mm]	0.40 × 0.30 × 0.20
T [K]	297
μ [mm^{-1}]	3.387
2Θ range [°]	3.568 to 50.054
Reflections collected	14179
Independent reflections, R_{int}	4375, 0.0314
Data/restraints/parameters	4375/0/286
R_1	0.0407
wR_2	0.1009
GOF	1.035
Largest diff. peak/hole [e $Å^{-3}$]	1.52/-1.05

Electron Paramagnetic Resonance measurements: The X-band EPR spectra of the polycrystalline dicopper complex **1** at a room temperature has been recorded by using spectrometer SE/X-2544 (9.5 GHz).

Antimicrobial activity assays

The strains of microorganisms selected for microbiological testing were provided by the National Collections of Pathogenic Microorganisms. The following Gram-positive pathogenic strains were used: *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 11778, and as Gram-negative pathogenic strains - *Escherichia coli* ATCC 25922 and *Acinetobacter baumannii* ATCC BAA-747. *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019, *Cryptococcus neoformans* CECT 1043 were used as fungal strains. *Erwinia amylovora, Erwinia carotovora* and *Xanthomonas campestris* strains were selected as phytopathogenic microorganisms for the evaluation of antimicrobial activity. To confirm the possibility of extending the antibacterial activity, the non-pathogenic strains of *Bacillus subtilis* CNMN BB-01, *Pseudomonas fluorescens* CNMN-PFB-01 offered by the National Collection of Non-pathogenic Microorganisms were also included in the tests.

The starting thiosemicarbazone ligands (initially dissolved in DMSO) and complexes have been tested *in vitro* as water solutions for antimicrobial activity against different bacteria and fungi by serial dilution method according standard protocol [14].

Results and discussion

Synthesis of complexes

The tripotasium salt of mononuclear copper complex5 has been synthesized on copper template condensation in basic media of 3-formylsalicylic acid thiosemicarbazone with 3-formylsalicylic acid. The monopotasium salt6 was prepared on interaction of copper(II) chloride with 3-formylsalicylic acid S-methylisothiosemicarbazone in ethanol in the presence of 2 equivalents of potassium hydroxide.

The proposed structures of 5 and 6 are in accordance with elemental analysis, IR spectra and the properties, namely a good solubility in water due to presence of deprotonated carboxyl groups. During attempts to grow up crystals of 1 from very dilute solutions instead of 1 has been isolated compound 2 with formula $[(Cu\text{-}Cl)_2H_2Q\text{-}\mu\text{-}Cl]\cdot 3CH_3OH$ which has a very close structure to complex 3.

The synthesis of 3 and 4 has been carried out on the action of excess of simple chloride salts (NH_4Cl or KCl) and $ZnCl_2$, respectively, on $[Cu_2(H_2Q\text{-}\mu\text{-}Cl]Cl_2\cdot H_2O$(1). All complexes are soluble in water, DMSO and DMF forming dark-green solutions. These solutions, especially water ones, tend to slowly change their colour in olive brown tones on standing for some days due to oxidation of isothiosemicarbazone ligand.

Attempts were run to substitute chloride ions in1 to sulphate anion, while it was smoothly obtained much dispersed hardly characterized light-green microcristaline sediments.

IR spectroscopic characterization

The spectra of all complexes contain a large number of bands which are rather difficult to be attributed with certainty due to combination and overlapping of different type of vibrations of organic compartmental ligand. Nevertheless, the very strong band that appears in all complexes at 1552-1560 cm^{-1} can be attributed to skeletal vibrations of bridge phenoxide ν(C-O), conjugated with both adjacent imine chelates. This intense band is a strong characteristic or indication to binuclear structure containing 2,6-bis(imine)-μ-phenoxide moiety [15,16]. In the region 3100-3600 cm^{-1} there are present bands that may assigned to stretching vibrations of ν(OH), ν(NH) of solvate water (methanol) molecules or NH_2 groups.

For complexes 5 and 6 IR spectra univocally demonstrates the deprotonation of carboxyl group by disappearing of strong stretching band of free carboxyl group ν_{as}(COOH) present in starting ligands,at 1663 and1653 cm^{-1} respectively.

X-ray diffraction results

The result of the X-ray diffraction study for compound 4 is shown in Figure 2, while the values of bond distances and angles are summarized in Table 2 and 3. According to X-ray crystallography data compound 4 represents a neutral hetero-trinuclear complex where the H_2Q^- mono-anion acts as a compartmental pentadentate ligand bridging two cooper atoms so that the charge balance is in agreement with the determined composition of the species: [Cu_2H_2Q-μ-Cl-μ-($ZnCl_4$)].The Cu1···Cu2 distance is of 3.0177(8) Å. Each Cu(II) atom is five-coordinated in distorted square-pyramidal geometry. The basal coordination is provided by μ-O, μ-Cl bridging atoms and two nitrogen atoms of the *S*-methylisotiosemicarbazide fragment. The apical position is occupied by chloride atom of $ZnCl_4^-$ anion coordinated in a bidentate-bridging fashion. As the result, the molecular complex exhibits the presence of two distinguished cyclic hetero-trinuclear: {$Cu_2Zn(\mu\text{-}Cl)_2(\mu\text{-}O_{ph})$}and {$Cu_2Zn(\mu\text{-}Cl)_3$} cores. The Cu1···Zn1 and Cu2···Zn1 distances are of 4.2546(8) Å and 4.1743(8) Å, respectively. As a whole, the molecular structure and geometric parameters of compound 4 are consistent with that of earlier reported analogue dicopper complex having deprotonated isothiosemicarbazone arms [6].



Figure 2. X-ray molecular structure of [Cu_2H_2Q-μ-Cl-μ-($ZnCl_4$)] (*4*) with atom labelling and thermal ellipsoids at 50% level.

In the crystal the trinuclear complexes and interstitial water molecules are associated through numerous O-H···Cl N-H···Cl and N-H···O hydrogen bonding (Table 3) to form a two-dimensional supramolecular layer oriented parallel to 101 plane, as shown in Figure 6. The further analysis of the crystal structure has shown the presence of a tree-dimensional supramolecular network which is built-up from the 2D layers interconnected through N-H···O interlayer hydrogen bonds. A fragment of 3D network is represented in Figures 3 and 4.

According to Cambridge Structural Data Base (CSD version 5.43, November 2022), there are registered 18 hits with tetrachlorozincate moiety bridging to other transitional metal ions (mainly to other zinc ions). Only one of them, namely dicopper(I) π-complex based on 5-thioallyl-1,2,4-triazole (refcode: ROKGIK),includes tetrachlorozincate bridge for monovalent copper ions[17]. Thus, the structure of **4** is rather unusual for compartmental dicopper(II) complexes. Moreover, as a consequence of formation of a new additional intramolecular bridge Cu-Cl-Zn-Cl-Cu by tetrachlorozincate involving both apical chlorides is that the apical ligands

are imposed to adopt a *cis* mutual arrangement relative to compartmental ligand plane.This is in contrast to usually *trans* arrangement in μ-chloro-dicopper(II)-dichloro groups of 2,6-bis(imino)-phenoxy chelates. According to Cambridge Structural Data Base (CSD version 2022.3.0) there are registered such 5 chelates, all of them reveals mutually *trans* arrangement of apical chlorides. These reciprocal *trans* arrangement of apical chloride ions being also confirmed for both complexes **2** and **3** (vide infra).

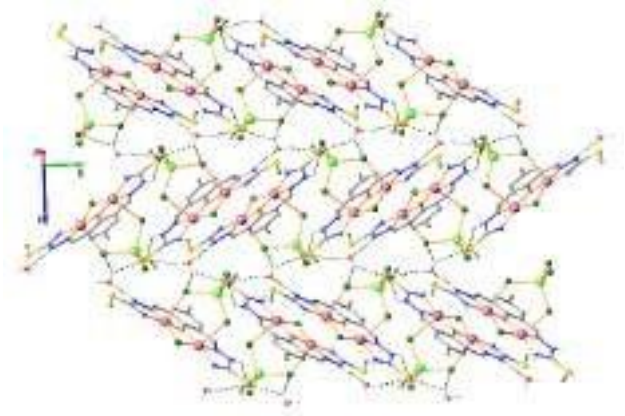


Figure 3. Partial view of the crystal structure packing along *a* crystallographic axis of 4 showing the formation of 2D supramolecular layer. H-bonds are drown as dashed-black lines.

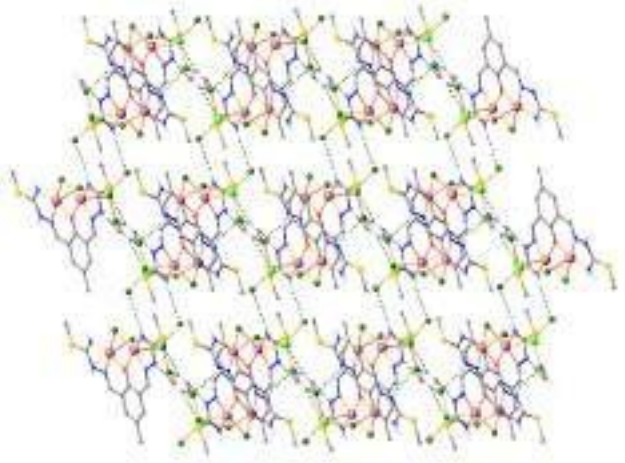


Figure 4. Crystal structure of 4 viewed along *b* axis.

In order to determine the crystal structure of **2** and **3** the X-ray diffraction experiments for these compounds has been also performed. Unfortunately, all tested crystalls were of low quality, giving weak diffracting and the resolution of the collected X-ray data was very low. Both structures could be solved and electron density of the molecule was well defined allowing for the determination of the atomic connectivity. The resulted structural models have unequivocally demonstrated both compounds to have a similar phenolato bridged dinuclear structures, as shown in Figures 5 and 6. As a result, due to the low quality of the structural parameters, in particular high R_1 values in the range between 13-18%, the structural investigation for compound **2** and **3** are not discussed.

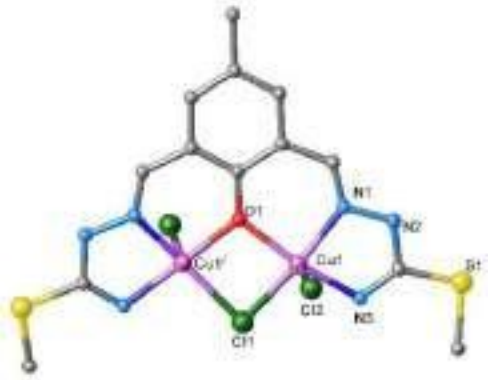


Figure 5. X-ray molecular structure of 2. Unit cell Parameters: a=9.002, b=23.117, c=14.882, α=90, β=105.48, γ=90; Sp. Gr.*I*2/a.

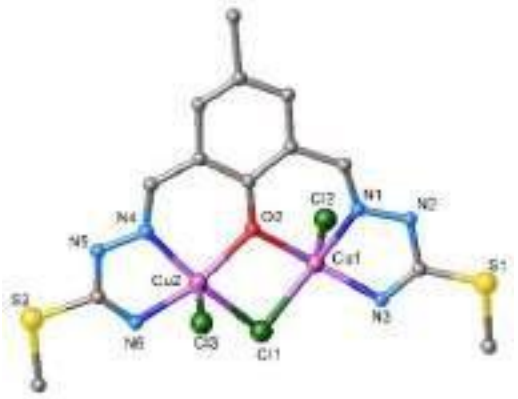


Figure 6. X-ray molecular structure of 3. Unit Cell Parameters:*a*=14.670, *b*=22.954, *c*=8.893, α=90, β=103.62, γ=90; Sp. Gr. $P2_1/c$.

Table 2. Bond distances (Å) for $[Cu_2H_2Q\text{-}\mu\text{-}Cl\text{-}\mu\text{-}(ZnCl_4)]\cdot H_2O$ (4).

Bond	d,(Å)	Bond	d,(Å)	Bond	d,(Å)	Bond	d,(Å)
Zn1-Cl2	2.2780(13)	O1-C1	1.336(6)	Cu2-Cl1	2.2827(17)	C1-C2	1.421(6)
Zn1-Cl3	2.2608(13)	N1-N2	1.377(5)	Cu2-Cl3	2.8606(15)	C1-C6	1.420(7)
Zn1-Cl4	2.3002(13)	N1-C8	1.274(6)	Cu2-O1	1.950(3)	C2-C3	1.399(7)
Zn1-Cl5	2.2297(14)	N2-C9	1.350(6)	Cu2-N4	1.937(4)	C2-C11	1.457(7)
Cu1-Cl1	2.2910(17)	N3-C9	1.289(6)	Cu2-N6	1.934(4)	C3-C4	1.384(7)
Cu1-Cl2	2.6946(14)	N4-N5	1.383(5)	S1-C9	1.749(5)	C4-C5	1.390(7)
Cu1-O1	1.969(3)	N4-C11	1.281(6)	S1-C10	1.781(6)	C4-C7	1.494(7)
Cu1-N1	1.943(4)	N5-C12	1.364(6)	S2-C12	1.739(5)	C5-C6	1.395(7)
Cu1-N3	1.943(4)	N6-C12	1.284(6)	S2-C13	1.790(6)	C6-C8	1.450(7)

Table 3. Angles (°) for $[Cu_2H_2Q\text{-}\mu\text{-}Cl\text{-}\mu\text{-}(ZnCl_4)]\cdot H_2O$ (4).

Angle	ω, (°)	Angle	ω, (°)	Angle	ω, (°)
Cl2-Zn1-Cl4	104.09(5)	N6-Cu2-Cl1	98.50(13)	O1-C1-C2	121.2(4)
Cl3-Zn1-Cl2	110.18(5)	N6-Cu2-Cl3	84.94(13)	O1-C1-C6	121.6(4)
Cl3-Zn1-Cl4	107.86(5)	N6-Cu2-O1	166.64(17)	C6-C1-C2	117.2(4)
Cl5-Zn1-Cl2	109.50(6)	N6-Cu2-N4	81.99(17)	C1-C2-C11	124.4(4)
Cl5-Zn1-Cl3	114.14(6)	Cu2-Cl1-Cu1	82.57(6)	C3-C2-C1	120.1(4)
Cl5-Zn1-Cl4	110.57(6)	Zn1-Cl2-Cu1	122.04(5)	C3-C2-C11	115.5(4)
Cl1-Cu1-Cl2	103.33(6)	Zn1-Cl3-Cu2	108.62(5)	C4-C3-C2	123.2(5)
O1-Cu1-Cl1	87.42(10)	C9-S1-C10	101.9(3)	C3-C4-C5	116.1(5)
O1-Cu1-Cl2	89.33(10)	C12-S2-C13	101.2(3)	C3-C4-C7	122.8(5)
N1-Cu1-Cl1	167.69(12)	Cu2-O1-Cu1	100.71(15)	C5-C4-C7	121.1(5)
N1-Cu1-Cl2	88.83(11)	C1-O1-Cu1	128.8(3)	C4-C5-C6	123.6(5)
N1-Cu1-O1	90.87(15)	C1-O1-Cu2	130.1(3)	C1-C6-C8	124.2(4)
N1-Cu1-N3	81.95(16)	N2-N1-Cu1	111.4(3)	C5-C6-C1	119.8(4)
N3-Cu1-Cl1	98.12(12)	C8-N1-Cu1	128.5(3)	C5-C6-C8	115.9(4)
N3-Cu1-Cl2	97.36(12)	C8-N1-N2	120.0(4)	N1-C8-C6	125.2(4)
N3-Cu1-O1	170.05(16)	C9-N2-N1	115.1(4)	N2-C9-S1	112.6(3)
Cl1-Cu2-Cl3	96.16(6)	C9-N3-Cu1	113.2(3)	N3-C9-S1	129.1(4)
O1-Cu2-Cl1	88.11(10)	N5-N4-Cu2	110.8(3)	N3-C9-N2	118.3(4)
O1-Cu2-Cl3	106.00(10)	C11-N4-Cu2	129.4(3)	N4-C11-C2	124.1(4)
N4-Cu2-Cl1	176.76(13)	C11-N4-N5	119.8(4)	N5-C12-S2	113.1(4)
N4-Cu2-Cl3	87.07(12)	C12-N5-N4	114.5(4)	N6-C12-S2	129.1(4)
N4-Cu2-O1	90.78(15)	C12-N6-Cu2	113.4(4)	N6-C12-N5	117.7(4)

EPR study of complex 1

The EPR spectra of the compound 1 at a temperature of 300 K, confirms the existence of an antiferromagnetic type exchange interaction in binuclear clusters of Cu(II) ions. Although the EPR spectra were investigated only at one temperature, a conclusion about the nature of the exchange interaction between Cu(II) ions could be made based on the fact that the energy of thermal vibrations at T= 300 K, that is equal to 210 cm^{-1}, exceeds the singlet-triplet splitting ($2|J|= (148 \pm 1)$ cm^{-1} [5]). This leads to the thermal population of the spin levels E_{-1}, E_0 and E_1 of the binuclear cluster in an external magnetic field that is sufficient to recording the EPR spectrum. In the region of low magnetic fields, the EPR spectrum of the complex *1* contains one asymmetric line with the g-factor g= 4.34 ± 0.20 calculated taking into account the corrections of its spectral position as well as the position of the zero line (Figure 7.).

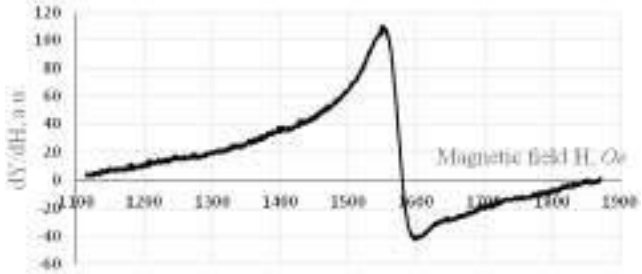


Figure 7. The single EPR line of 1 at T= 300 K and low magnetic field.

At higher magnetic fields and a sufficient increase in the gain of EPR spectrometer a group of seven spectral lines is recorded (Figure 8). This is conditioned by hyperfine interaction of

Cu(II) ions included in binuclear clusters with Cu nuclei: [2(2I) + 1 = 7] for two copper ions. The g-factor of the central component of this group of spectral lines calculated taking into account the above corrections is g= 2,006 ± 0,001. Based on experimental data (Figure 8) it was found that the constant of hyperfine interaction is A= (126.9 ± 0.2) $\cdot 10^{-4}$ cm^{-1}. The seven-component hyperfine structure of the EPR spectrum (Figure 8) is an additional confirmation that Cu(II) ions form binuclear clusters in **1**.

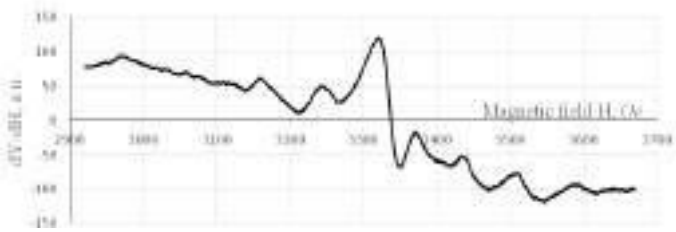


Figure 8. Hiperfine structure of the EPR spectrumof 1 atT= 300 K and high magnetic field.

Antimicrobial activity evaluation

In order to compare antimicrobial activity of complex 1 with other water soluble copper isothiosemicarbazone complexes it has been synthesized mononuclear complexes 5 and 6 with aromatic thiosemicarbazones containing free carboxyl group, which may render water solubility to respective copper complex on deprotonation to form alkali metal salts of these complexes (Figures 9 and 10).

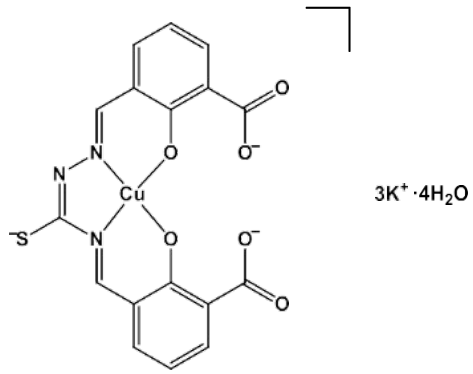


Figure 9. Water-soluble tripotasium salt of mononuclear complex 5.

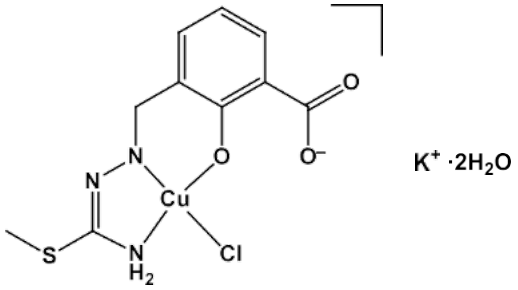


Figure 10. Water-soluble monopotasium salt of complex 6.

From the data presented in the Table 4, results that compound **1** possess a superior antifungal activity, being approximately 10 times higher, compared to other water-soluble complexes of copper (II) with hydroxyaromatic *S*-methylisotiosemicarbazones, being nonalkylated and alkylated on sulphur, respectively **5** and **6**. Compound **1**, being soluble in DMSO, may be used in special cases and in the form of solutions in DMSO for subsequent dilution with water, and in highly dilute aqueous solutions any interference with DMSO will be negligible. In conclusion, the copper dimer compound ***1*** has a potential application in pharmaceuticals and agriculture in the form of aqueous solutions in concentrations of the order of percentages (0.001%= 10μg/mL), for combating various microorganisms.

Table 4. Antimicrobial activity of complexes 1, 5 and 6.

Strains	MIC/MMC (μg/mL)		
	1	**5**	**6**
Staphylococcus aureus	1/2	125/250	31/63
Bacillus cereus	0.5/1	250/500	31/63
Bacillus subtilis	0.5/1	125/250	31/63
Escherichia coli	250/500	l.a.	l.a.
Acinetobacter baumannii	250/500	l.a.	l.a
Candida albicans	4/8	l.a	31/63
Candida parapsilosis	4/8	l.a	125/250
Cryptococcus neoformans	2/4	63/125	31/63
Erwinia carotovora	70/70	300/600	1200/1200
Erwinia amylovora	70/70	300/600	1200/1200
Xanthomonas campestris	70/70	300/600	1200/1200
Pseudomonas fluorescens	300/300	150/300	1200/1200

Notes: MIC– minimum inhibitory concentrations; MMC– minimum microbicidal concentrations; l.a. – low activity.

The biological activity of **1** is rather nonobvious, because the effect of alkylation of the thiosemicarbazide sulfur atom on biological activity as was mentioned earlier may be divergent. For example, S-alkylation of 1,4-benzoquinone-isothiosemicarbazone-guanylhydrazone decreases the antibacterial activity compared to nonalkylated thiosemicarbazone [18]. In the case of benzoic aldehyde thiosemicarbazone, which has an antituberculosis activity - the S-substituted derivative is no longer active against the tuberculous bacillus [19]. A comparative study of the antiproliferative activity of metal complexes, including copper, with unalkylated hydroxyaromatic thiosemicarbazones and S-methylisotiosemicarbazones shows that sulphur alkylation drastically reduces the complexes' ability to inhibit cancer cell proliferation [20]. At the same time, the coordination compounds of copper (II) with 4-allyl-S-methyl-isothiosemicarbazone of salicylic aldehyde show pronounced antimicrobial properties [21].

The biological activity of binuclear compounds, especially of copper with compartmental ligands, has been studied relatively less, where a varied influence on the activity is observed depending on the nature of the ligand and coordination with metals. For example, in the case of hybrid ligands with thiosemicarbazones – the S-methyl analogy is more cytotoxic than the non-alkylated ligand. While for the respective copper dimers the situation is reversed – complexes with alkylated ligand reveals a lower activity than the dimer with the non-alkylated ligand [22]. On the other hand, the binuclear copper(II) complex with ligand based on the non-alkylated thiosemicarbazone - bis(4-phenylthiosemicarbazone)-2,6-diformyl-4-methylphenol, is inactive against various species of fungi or bacteria [23].

Conclusions

Four new coordination compounds of copper(II) containing binucleating Schiff base have been synthesized starting from the copper dimer **1** based on 2,6-diformyl-4-methylphenol bis(S-methylisothiosemicarbazone H_3Q. The complexes were characterizedby IRspectroscopy and XRD analysis. By the action of a large excess of NH_4Cl or $ZnCl_2$ on compound **1**was obtained compounds **3** and **4** respectively. The structures reveal that for the first complex two chloride ligands are coordinated to copper ions in *trans* apical fashion. In the second copper dimer, both chloride anions coordinated in *cis*-apical fashion to the copper dimer, being part of a newly formed tetrachlorzincate anion which functions as an additional triatomic bridge between copper centers: Cu-Cl-Zn-Cl-Cu. Anyway, all chloride anions are located in the inner coordination sphere of binucleating complexes, being coordinated to copper or zinc ions. The geometry of the compartmental monodeprotonated ligand remains practically unchanged for all studied complexes.

It has been shown that EPR spectra of dimer **1** at 300 K consist of a single asymmetric EPRline with theg-factor g= 4.34 ± 0.02 in the region of low magnetic fields and a group of seven equidistant spectral lines in the region of high magnetic fields at a sufficient increase in the gain of EPR spectrometer in the last case. This group of spectral lines with the g-factor of central component g= 2.006 ± 0.001 is due to the hyperfine interaction of Cu(II) ions from binuclear clusters with copper nuclear spins.

It was found that dicopper compound **1** does manifest a pronounced antimicrobial activity, also being selective against pathogen Gram(+) bacteria, namely it manifested in aqueous solutions at MMC up to 1-2 μg/mL and against fungal strains up to 4-8 μg/mL. The similar hydrosoluble mononuclear copper complexes of binucleating thio- or S-methylisothiosemicarbazone of 3-formylsalicylic acid, as well as the free ligands, including H_3Q, do not reveal any significant activity.

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