ISSN 1070-3284, Russian Journal of Coordination Chemistry, 2020, Vol. 46, No. 9, pp. 600–607. © Pleiades Publishing, Ltd., 2020.
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The authors congratulate Academician I.L. Eremenko on his 70th birthday

Copper(II) Complexes with N,O-Hybrid Ligands Based on Pyridyl-Containing Phospholane Oxides

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Received January 10, 2020; revised February 4, 2020; accepted February 26, 2020

Abstract—New water-soluble copper(II) bis-N,O-chelate complexes $[Cu(L^2)_2Cl_2]$ (**I**), $[Cu_2(L^1)_2Cl_4]$ (**II**), and $[Cu(L^1)_2Cl]_2[CuCl_4]$ (**III**) (L^1, L^2 = pyridyl-containing phospholane oxides) were prepared from N,O-ligands. The complexes were characterized by physicochemical methods (mass spectrometry, IR spectroscopy, elemental analysis, and X-ray diffraction (CIF files CCDC nos. 1976723 (**I**), 1976724 (**II**), and 1974303 (**III**)). The physicochemical properties of the products were studied and the molecular and crystal structures were established. The cytotoxicity against M-HeLa cancer cell lines and Chang liver normal cell lines was determined for the binuclear complex $[Cu_2(L^1)_2Cl_4]$.

Keywords: tertiary phosphine oxides, pyridyl-containing phosphine oxides, N,O-chelating ligands, Cu(II) complexes, cytotoxicity, molecular structure, X-ray diffraction

DOI: 10.1134/S1070328420090055

INTRODUCTION

Chelating ligands containing N and O donor atoms exhibit various biological and catalytic activities [1]. For example, Ru(II) complexes $[(\eta^6\text{-areno})Ru(XY)Cl]PF_6$, where XY = N,O-chelating amino acidates, exhibit cytotoxic action against pancreatic and lung cancer cells [2]. Metal chelate complexes $LMX_n \cdot H_2O$ and L_2MX_n (where M = Ag^+, Mn^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} or Fe^{3+}; X = NO_3^-, Br^-, or Cl^-; L is a Schiff base containing a phosphate group) have considerable antibacterial and antifungal activities [3]. Studies in vitro of Cu(II) complexes of bis(imidazol-1-yl)methane scorpionate heterocyclic ligands demonstrated the potential of these compounds as antitumor agents against human breast (MCF-7), cervical (HeLa), and lung (A549) adenocarcinoma cells [4].

Apart from the biological activity found for copper(II) complexes with N,O-chelating ligands (anti-inflammatory [5], anti-tuberculosis [6], and antioxidant agents [7]), alternative applications of these complexes, for example, in selective catalysis have been considered [8].

The N,O-ligands containing donor centers of different types can be used to stabilize metal ions and to design mono- and polynuclear homo- or heterometallic complexes [9, 10]. An examination of published data demonstrated that N,O-chelating ligands are mainly represented by Schiff bases [11], amino acids [12], amino alcohols [13], enamino ketones [14], and amidates [15]. Of particular interest are pendant-armed N,O-containing macrocyclic ligands, i.e., those in which various functional groups are attached to the ring atoms. In these ligands, a carbonyl, hydroxyl, or carboxyl group is usually the source of O-coordination [16–22]; however, there is a small and, therefore, less studied class of N,O-ligands in which the oxygen coordination site is incorporated in a phosphorus-containing functional group, e.g., phosphoryl [23–27] or phosphate [28] group. In view of the above, extension of the N,O-ligand library by introducing an alternative source of an oxygen coordination site such as a phosphoryl group appears to be a relevant task. In this regard, of particular interest are phosphine oxides that have an N-heterocyclic moiety (in this case, a pyridyl substituent), since transition metal complexes of pyridyl-containing phosphine oxides can be applied as oxidants in olefin epoxidation [29], radiopharma-

ceuticals [23], emitters for organic light-emitting diodes [30], molecular magnets [31], antibacterial and antifungal agents [3], etc.

In order to expand the range of Cu(II) complexes and obtain structural data on these compounds, we present here the synthesis of new copper(II) complexes based on phosphorus-containing N,O-ligands: pyridyl-containing phospholane oxides.

EXPERIMENTAL

All solvents were purified and dried prior to use. The starting ligands, pyridyl-containing phospholane oxides (L^1, L^2) and (pyridin-2-yl)phospholane (L^3), were synthesized by reported procedures [32, 33].

IR spectra were measured on a Tensor 27 spectrometer (Bruker) in the 4000–400 cm^{-1} range with an optical resolution of 4 cm^{-1} and acquisition of 32 scans (the samples were prepared as KBr pellets or mineral oil mulls). MALDI mass spectra were recorded on a Bruker Ultraflex III TOF/TOF mass spectrometer in the positive ion mode. *p*-Nitroaniline was used as the matrix. Elemental analysis was performed on a EuroVector-3000 instrument (C, H, N) and manually by pyrolysis of a sample in an oxygen flow (P).

Synthesis of the complex $[Cu(L^2)_2Cl_2]$ (I). A suspension of copper chloride (0.32 g, 1.85 mmol) in ethanol (4 mL) was added with stirring to phosphine oxide L^2 (0.72 g, 3.70 mmol) dissolved in ethanol (4 mL). The reaction mixture was stirred for 12 h. The remaining copper(II) chloride was filtered off, and the filtrate was concentrated at a reduced pressure. The residue was washed first with diethyl ether and then with acetone and dried at a reduced pressure (2×10^{-2} mbar). The yield was 0.71 g (73%). T_m = 162°C. MALDI mass spectrum (*m/z*): 453 $[M\text{-}2Cl]^+$, 582 $[M + 2H_2O + Na]^+$.

For $C_{20}H_{28}N_2O_2P_2Cl_2Cu$

Anal. calcd., %	C, 45.77	H, 5.38	N, 5.34	P, 11.80	Cu, 12.11
Found, %	C, 45.87	H, 5.34	N, 5.14	P, 11.97	Cu, 12.34

IR (vaseline oil; ν, cm^{-1}): 2959, 2921, 1605, 1452, 1404, 1263, 1164, 1027, 842, 713, 534, 453.

Synthesis of the complex $[Cu_2(L^1)_2Cl_4]$ (II). A solution of copper(II) chloride dihydrate (0.16 g, 1.19 mmol) in EtOH (4 mL) was added to a solution of ligand L^1 (0.43 g, 1.19 mmol) in EtOH (5 mL). The reaction mixture was stirred for 12 h, which gave a light green precipitate. The precipitate was separated on a filter, washed with diethyl ether, and dried at a reduced pressure (2×10^{-2} mbar). The yield was 0.43 g (60%); T_m = 245°C. MALDI mass spectrum (*m/z*): 460 $[M\text{-}Cu\text{-}3Cl]^+$.

For $C_{18}H_{24}N_2O_2P_2Cl_4Cu_2$

Anal. calcd., %	C, 34.25	H, 3.83	N, 4.44	P, 9.81	Cu, 20.13
Found, %	C, 34.31	H, 3.81	N, 4.34	P, 9.86	Cu, 20.17

IR (vaseline oil; ν, cm^{-1}): 2925, 2854, 1590, 1453, 1377, 1261, 1165, 1128, 1100, 886, 857, 767, 739, 717, 537, 488, 448.

Synthesis of the complex $[Cu(L^1)_2Cl]_2[CuCl_4]$ (III). Copper(I) chloride (0.64 g, 6.4 mmol) was added to a solution of ligand L^3 (0.53 g, 3.2 mmol) in THF (7 mL). The reaction mixture was stirred for 12 h. On storage of the solution under aerobic conditions for a week, yellow crystals of complex **III** were formed. They were separated on a filter, washed with diethyl ether, and dried at a reduced pressure (2×10^{-2} mbar). The yield was 0.7 g (60%).

For $C_{36}H_{48}N_4O_4P_4Cl_6Cu_3$

Anal. calcd., %	C, 38.37	H, 4.31	N, 4.89	P, 10.35	O, 5.62	Cu, 16.86
Found, %	C, 38.33	H, 4.29	N, 4.97	P, 10.28	O, 5.67	Cu, 16.90

IR (KBr; ν, cm^{-1}): 2930, 2860, 1588, 1450, 1380, 1270, 1163, 1130, 1105, 880, 860, 765, 740, 720, 535, 490, 450.

Slow evaporation of a saturated solution of complex **III** in THF at room temperature gave single crystals of $[Cu(L^1)_2Cl]_2[CuCl_4] \cdot 2THF$ (**III** · 2THF) as a solvate.

X-ray diffraction study of polycrystalline samples was carried out on a Bruker D8 Advance X-ray diffractometer equipped with a Vario attachment and a Vantec linear detector. Cu$K_{\alpha 1}$ radiation (λ = 1.54063 Å) monochromatized with a Johansson curved monochromator was used. The experiments were carried out at room temperature in the Bragg–Brentano geometry with a planar sample. Polycrystalline samples were deposited on a single crystalline silicon wafer. Powder X-ray diffraction patterns were recorded in the 2θ range from 5° to 50° with a step of 0.016° and acquisition time of 0.5–5 s at a point with sample spinning at 15 rpm.

Single crystal X-ray diffraction study was carried out on a Bruker KAPPA APEX II automated diffractometer for **I** and **II** and a Rigaku Gemini diffractometer for **III** · 2THF. In all cases, monochromatic MoK_α radiation (λ = 0.71073 Å) was used. The data collection and indexing, determination and refinement of unit cell parameters, absorption corrections and taking account of systematic errors were carried out using an APEX3 (v2019.1-0) or CrysAlisPro (v1.171.37.35) program package. Interestingly, the monoclinic unit cell of of **I** has a β angle close to 90°. The structures were solved by direct methods using the SHELXT-2018/2 program package [34] (for **I** and **II**) or

Table 1. Crystallographic data and structure refinement parameters for **I**, **II**, and **III** · 2THF

Parameter	Value		
	I	**II**	**III** · 2THF
Molecular formula	$C_{20}H_{28}N_2O_2P_2Cl_2Cu$	$C_{18}H_{24}N_2O_2P_2Cl_4Cu_2$	$C_{44}H_{64}N_4O_6P_4Cl_6Cu_3$
Crystal color	Greenish blue	Green	Yellow
M	524.82	631.21	1272.19
Temperature	100(2) K	293(2) K	130(2) K
System	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$	$C2/c$
a, Å	8.0406(4)	10.0287(4)	27.2122(7)
b, Å	13.6498(7)	8.8328(3)	18.4528(4)
c, Å	10.1145(6)	13.2044(5)	10.9918(2)
β, deg	90.007(2)	96.0378(17)	102.230(2)
V, Å^3	1110.09(10)	1163.18(8)	5394.2(2)
Z/Z'	2/0.5	2/0.5	4/0.5
ρ(calcd.), g cm^{-3}	1.570	1.802	1.567
μ, mm^{-1}	1.389	2.445	1.636
F(000)	542	636	2612
θ_{min}–θ_{max}, deg	3.564–33.199	3.081–27.094	2.187–29.248
Range of indices	$-12 \le h \le 12$, $-21 \le k \le 21$, $-15 \le l \le 15$	$-12 \le h \le 12$, $-10 \le k \le 11$, $-16 \le l \le 15$	$-31 \le h \le 34$, $-24 \le k \le 22$, $-14 \le l \le 14$
Total number of reflections	29116	20869	22763
Number of unique reflections	4232	2543	6391
R_{int}	0.0324	0.0356	0.0595
R_σ	0.0250	0.0251	0.0691
Completeness of data to θ_{max}, %	99.6	99.4	87.0
T_{max}/T_{min}	0.4667/0.3574	0.3854/0.2261	1.0000/0.9502
Number of observed reflections ($I > 2\sigma(I)$)	3720	2150	4419
Number of refined parameters	134	136	348
GOOF	1.074	1.066	1.021
R ($I > 2\sigma(I)$)	$R_1 = 0.0277$, $wR_2 = 0.0644$	$R_1 = 0.0271$, $wR_2 = 0.0617$	$R_1 = 0.0518$, $wR_2 = 0.1179$
R (for all reflections)	$R_1 = 0.0349$, $wR_2 = 0.0674$	$R_1 = 0.0356$, $wR_2 = 0.0646$	$R_1 = 0.0873$, $wR_2 = 0.1345$
Residual electron density (max/min), e/Å^3	0.652/–0.451	0.41 8/–0.341	0.947/–0.811

SHELXS-2013/1 program package (for **III** · 2THF) [35] and refined by the full-matrix least squares method on F^2 using the SHELXL-2018/3 software [36]. The non-hydrogen atoms were refined in the anisotropic approximation. The hydrogen atoms of methyl groups were placed into calculated positions and refined by rotation of a group with idealized bond angles. The other hydrogen atoms were placed into geometrically calculated positions and included in the refinement in the riding model. The calculations were mainly carried out using the WinGX-2018.3 program package [37]. The crystallographic data and structure refinement details for **I**–**III** are summarized in Table 1.

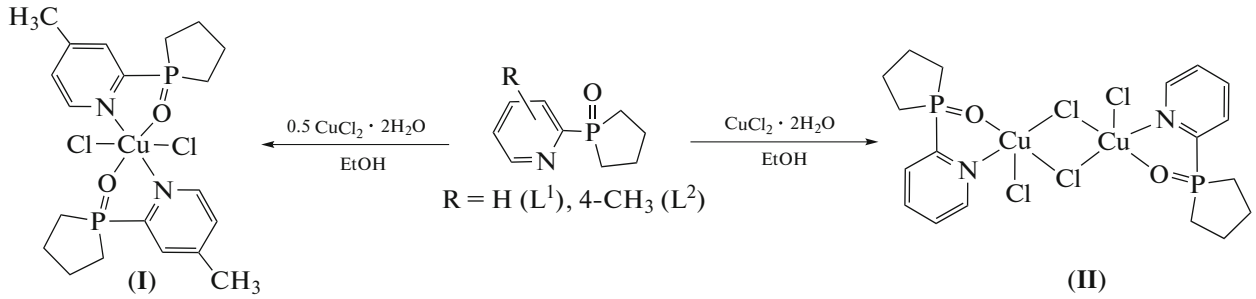
The full set of X-ray diffraction parameters for **I**, **II**, and **III** · 2THF are deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 1976723

(**I**), 1976724 (**II**), and 1974303 (**III** · 2THF); https://www.ccdc.cam.ac.uk/structures/).

Biological activity assays. The cytotoxic action of test compounds on human cancer and normal cells was assessed using a Cytell multifunctional cell imaging system (GE Healthcare Life Science, Sweden) and a Cell Viability Bio application, which counts the number of cells and assesses the cell viability from the fluorescence intensity data. In experiments, two fluorescence dyes were used, which selectively penetrate cell membranes and fluoresce at different wavelengths. Low-molecular-weight 4',6-diamidine-2-phenylindole (DAPI) dye can penetrate intact membranes of living cells and color the nuclei blue. A high-molecular-weight dye, propidium iodide, penetrates only dead cells with damaged membranes, which are thus colored yellow. As a result, living cells are colored blue and dead cells are colored yellow. DAPI and propidium iodide were purchased from Sigma-Aldrich. For the experiments, we used a tumor cell culture M-Hela clone 11 (epithelioid carcinoma of the cervix uteri, subline Hela, clone M-Hela) from the collection of typical cultures at the Institute of Cytology, Russian Academy of Sciences, and a culture of normal liver cells (Chang liver) from the Gamaleya National Research Institute of Epidemiology and Microbiology were used in experiments. The cells were cultured in the standard Eagle culture medium manufactured at the Chumakov Institute of Poliomyelitis and Viral Encephalitis (PanEco company), with addition of 10% fetal bovine serum and 1% replaceable amino acids. The cells were inoculated into a 96-well plate (Eppendorf) in the concentration of 100000 cells/mL, 150 μL of the medium per well, and cultured in a CO_2 incubator at 37°C. 24 h after cell inoculation, the test compound was added at a pre-established dilution in 150 μL amount per well. The compound dilutions in culture media were prepared immediately prior to use; for better solubility, 5% dimethyl sulfoxide, which does not induce cell inhibition at this concentration, was added. The experiments were repeated 3 times. Intact cells cultured in parallel with experimental cells were used as the control [38].

RESULTS AND DISCUSSION

Phosphine oxides L^1 and L^2 containing pyridyl substituents at the phosphorus atom were prepared by a procedure that we developed previously [32]. The reactions of ligands L^2 and L^1 with $CuCl_2 \cdot 2H_2O$ in metal to ligand ratio of 1 : 2 and 1 : 1 in ethanol gave complexes **I** and **II**, respectively, in good yields (Scheme 1).



Scheme 1.

Complexes **I** and **II** are readily soluble in most organic solvents and in water. Mass spectrometry and elemental analysis data confirmed the composition of the complexes. The IR spectra of the complexes were compared with those of free ligands to identify the donor sites involved in coordination. It was found that the positions and intensities of spectral bands change upon chelation. The lower-frequency position of the P=O stretching modes in the IR spectra of complexes **I** and **II** (1158 and 1161 cm^{-1}, respectively) compared to those of free ligands (1181–1183 cm^{-1}) confirms the coordination of the phosphoryl group [32]. The absence of the $\nu(H_2O)$ mode attests to replacement of the coordinated water molecules in the starting $CuCl_2 \cdot 2H_2O$ by the phosphine oxide ligand.

The structures of the complexes were ultimately established by X-ray diffraction. The single crystals of compounds **I** and **II** were obtained by slow evaporation of saturated solutions of complexes in acetonitrile at room temperature. The powder diffraction patterns of the polycrystalline **I** and **II** samples are in good agreement with the ones simulated based on the single crystal X-ray diffraction study, which confirms their purity and polymorphic identity.

According to X-ray diffraction data, complex **I** crystallizes in the monoclinic space group $P2_1/c$ and represents a centrosymmetrical neutral mononuclear Cu(II) complex, in which the coordination center has a distorted octahedral configuration (Fig. 1).

The first coordination sphere of the complex is composed of the heteroatoms of two N,O-ligands, which form the tetragonal base of the octahedron, and two chloride ions in apical positions. The ligand L^2 coordinates the metal center, thus forming a five-membered N,O-chelate metallacycle. The attention is drawn by the considerably elongated Cu···O=P coor-

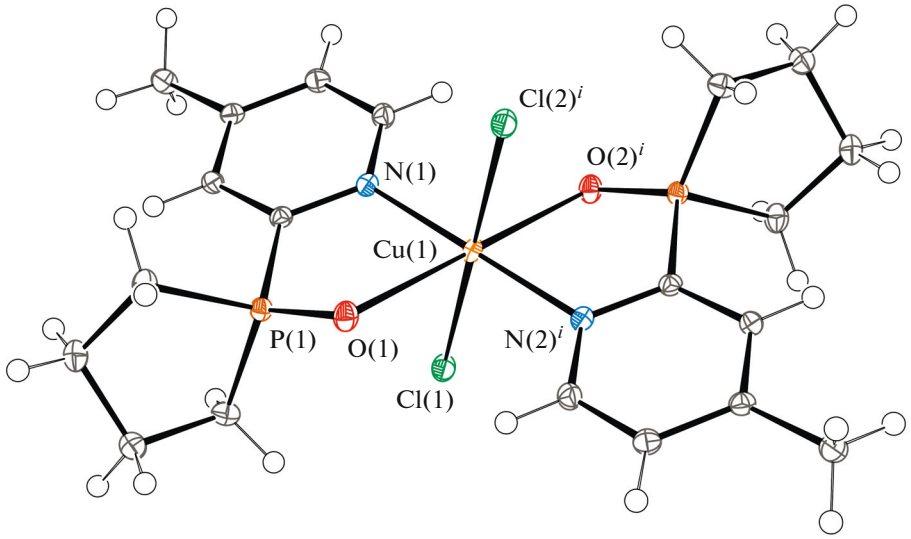


Fig. 1. Geometry of complex **I** in the crystal. Thermal ellipsoids are drawn at 50% probability level. The superscript *i* designates equivalent atoms connected by symmetry codes (1 – *x*, 1 – *y*, 1 – *z*). Selected bond lengths: Cu(1)–Cl(1), 2.3515(3); Cu(1)–O(1), 2.4390(9); Cu(1)–N(1), 1.9887(10), P(1)–O(1), 1.4969(9) Å.

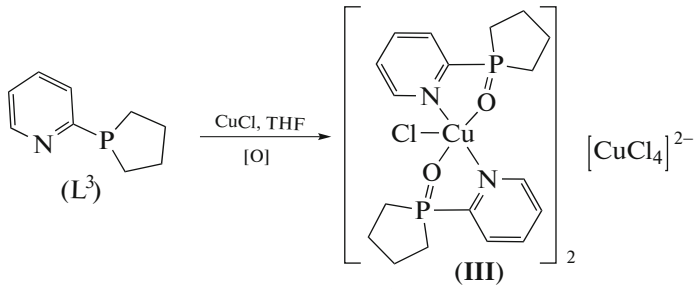
dination bond, which is likely due to the Jahn–Teller effect, inherent in the copper(II) complexes. The interatomic distances for the Cu(1)–O(1) and Cu(1)–N(1) coordination bonds are 2.4390(9) and 1.9887(10) Å, respectively. The distance for the Cu(1)–Cl(1) bond is 2.3515(3) Å.

Complex **II** crystallizes in the monoclinic space group $P2_1/n$. According to X-ray diffraction experiment (Fig. 2), this compound is a centrosymmetrical neutral binuclear Cu(II) complex with the Cu_2Cl_4 core, in which two of the four coordinated chloride ions occupy bridging positions (Cu(1)–Cl(2), 2.2680(6); and Cu(1)–Cl(2)^i, 2.7456(7) Å), thus inducing proximate positions of two formally charged metal centers (Cu(1)···Cu(1)^i 3.5215(6) Å).

It is of interest that the coordination bond with a non-bridging chloride ion, Cu(1)–Cl(1), is somewhat shorter, being 2.2318(6) Å. The Cu^{2+} ion with C.N. of 5 has a distorted square pyramidal geometry with the structural parameter τ_5 = 0.23, where the pyramid base is formed by the N(1) and O(1) atoms of the ligand and two chloride co-ligands, Cl(1) and Cl(2). The apical position is occupied by the Cl(2)^i chloride ion. Note that the extreme values of τ_5 are 0 and 1, corresponding to the ideal tetragonal pyramid and trigonal bipyramid, respectively [39]. In complexes **I** and **II**, the ligand coordinates the metal thus forming a five-membered N,O-chelate ring.

The interatomic distances for the P(1)=O(1) bond of **I** and **II** are 1.4969(9) and 1.5069(16) Å, respectively, which is similar to the P=O bond lengths in Cu(II) complexes of phosphine oxides containing aromatic (1.4979(17) [40], 1.488(1) [41]) and aliphatic (1.5176(19) [42], 1.5155(13) Å [43]) substituents at the phosphorus atom. The P=O bond lengths in the complexes are also comparable with similar bonds in uncoordinated phosphoryl compounds with aromatic (1.477(3) Å [44]) or aliphatic P-substituents (1.518(2) Å [45]).

It was found that the reaction of non-oxidized L^3 ligand with copper(I) chloride in 1 : 2 ratio in THF under aerobic conditions results in oxidation of both the ligand to L^1 and the metal ion, with only complex **III**-$[Cu(L^1)_2Cl]_2[CuCl_4]$ being detected in the reaction mixture after a week (Scheme 2).



Scheme 2.

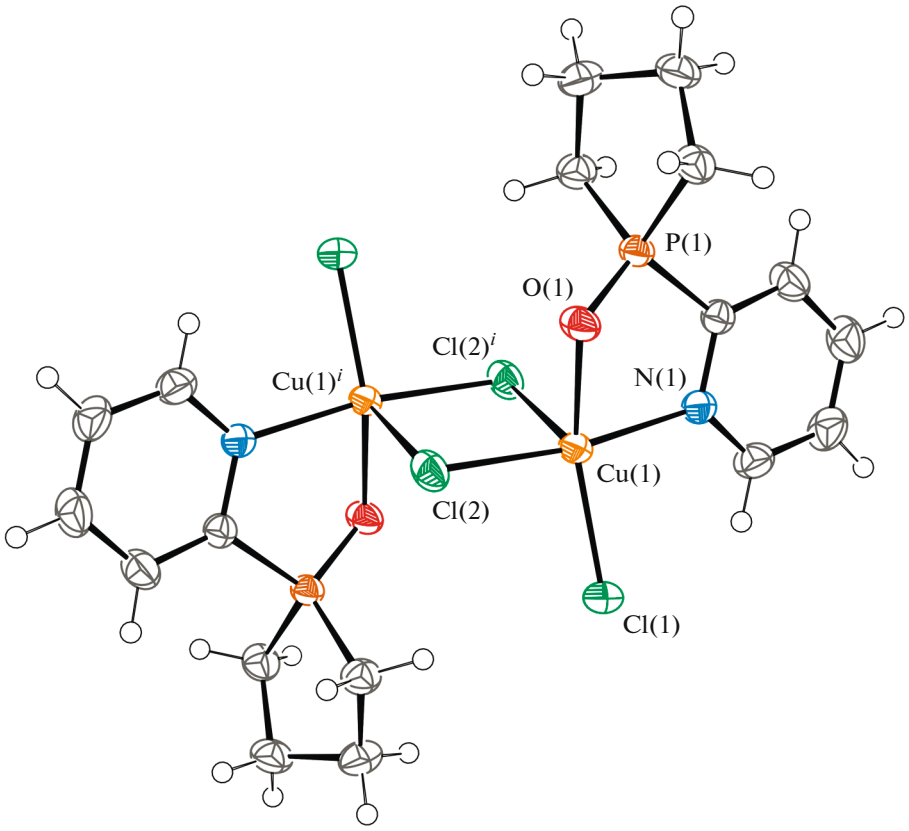


Fig. 2. Geometry of complex **II** in the crystal. Thermal ellipsoids are drawn at 50% probability level. The superscript *i* designates equivalent atoms connected by symmetry codes ($1 - x$, $1 - y$, $1 - z$). Selected bond lengths: Cu(1)–Cl(1), 2.2318(6); Cu(1)–Cl(2), 2.2680(6); Cu(1)–Cl(2)^i, 2.7456(7); Cu(1)–O(1), 1.9756(15); Cu(1)–N(1), 2.0805(19); P(1)–O(1), 1.5069(16) Å.

Unlike diamagnetic copper(I) complexes with phosphine ligands, which exhibit characteristic signals of the coordinated ligands in the ^{31}P NMR spectra, in the case of paramagnetic copper(II) complexes, this method provides little information. The absence of a signal and a broad baseline in the ^{31}P NMR spectrum of complex **III** indicate that the complex is paramagnetic and, hence Cu(I) has been oxidized to Cu(II). In addition, yellow color of the complex also indicates the oxidation of the copper ion. The ligand oxidation is confirmed by the characteristic P=O absorption band at 1165 cm^{-1} in the IR spectrum, similar to the band observed in complexes **I** and **II**.

The structure of complex **III** was ultimately confirmed by X-ray diffraction. The single crystals of **III** · 2THF were obtained by slow evaporation of a saturated THF solution of the complex at room temperature. Complex **III** with the general formula $[Cu(L^1)_2Cl]_2[CuCl_4]$ crystallizes as a solvate with two THF molecules in the monoclinic space group $C2/c$, with the copper atom of the $[CuCl_4]^{2-}$ anion being located in a special position. This anion has a distorted tetrahedral configuration. As shown in Fig. 3, the $[CuL^1_2Cl]^+$ cation is a mononuclear charged Cu(II) complex with a highly distorted trigonal bipyramidal geometry, which is confirmed by the geometric index $\tau_5 = 0.47$. The bipyramid base is formed by the coordinated chloride anion and oxygen atoms of two pyridyl-containing phosphine oxide ligands. The apical positions are occupied by the nitrogen atoms of these ligands. Like in two above-described structures **I** and **II**, the N,O-ligand formed in situ during the reaction coordinates the metal center, thus forming the five-membered N,O-chelate ring. The interatomic distances for coordination bonds are listed in the caption to Fig. 3.

Among metal ions, copper is widely encountered in biological systems, and copper complexes are known to show a broad range of biological action, in particular, coordination compounds of copper proved to be promising candidates for the treatment of cancer [46]. The cytotoxicity mediated by copper(II) complexes may be due to their ability to bind and cleave DNA molecules. It was found that copper complexes have high antitumor activities, which was tested in vitro on several cancer cell lines, and some of them were tested in vivo [47].

In view of the foregoing, water-soluble compound **II** was tested for cytotoxicity against normal and can-

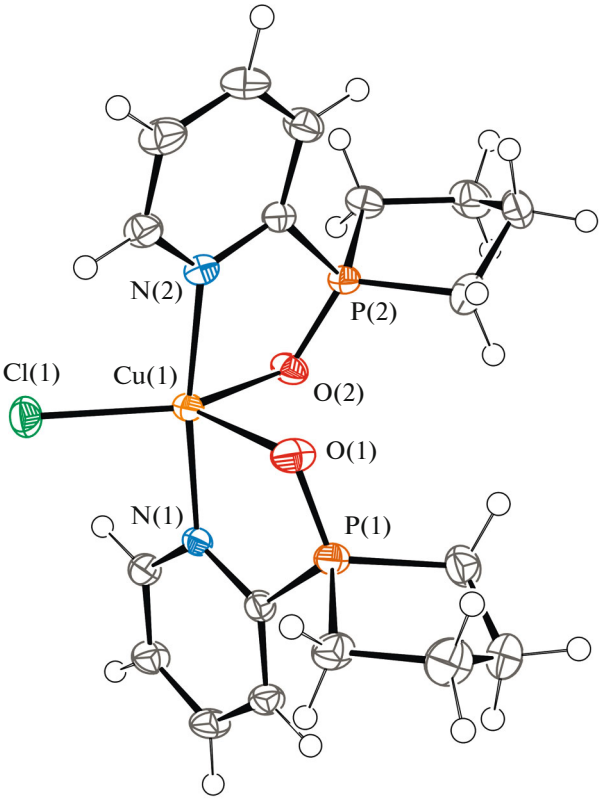


Fig. 3. Geometry of the cation of complex **III** in the crystal. Thermal ellipsoids are drawn at 50% probability level. The $[CuCl_4]^{2-}$ counter-ion and disordered THF molecules are not shown for clarity. Selected bond lengths: Cu(1)–Cl(1), 2.2348(10); Cu(1)–O(1), 2.155(3); Cu(1)–O(2), 2.052(3); Cu(1)–N(1), 1.999(3); Cu(1)–N(2), 2.000(3); P(1)–O(1), 1.500(3); P(2)–O(2), 1.509(3) Å.

cer human cell lines. The IC^{50} value for complex **II** towards M-HeLa cancer cell line is 38.0 ± 2.9 μM, which is inferior to that of tamoxifen used as the reference (28.0 ± 2.5 μM). However, it proved to be less toxic towards the Chang liver normal cell lines than the standard anticancer drug (IC^{50} is 53.0 ± 4.6 μM versus 46.2 ± 3.5 μM for tamoxifen). It should be noted that free ligand L^1 showed no cytotoxic activity.

Thus, phospholane oxides containing pyridyl groups at phosphorus are complexed with copper(II) chloride as classical chelating N,O ligands, forming, depending on the reaction stoichiometry, a charged mononuclear bis-chelate complex **I** or neutral binuclear Cu(II) complex **II** with bridging chlorine atoms and monochelated metal coordination. The synthetic possibility of preparation of copper(II) complexes from phosphine ligands and copper(I) derivatives via aerobic oxidation of both the ligand and the metal ion was demonstrated in relation to the preparation of **III**. Complex **II** showed a moderate cytotoxicity against the M-HeLa cancer cells, which makes promising the preparation of analogous complexes and studying of their biological activities.

CONFLICT OF INTEREST

The authors declare than they have no conflicts of interest.

ACKNOWLEDGMENTS

The authors are grateful to the Center of Collective Use for Physicochemical Studies of Structure and Properties, Kazan Scientific Center, Russian Academy of Sciences, for the technical support of the research.

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Translated by Z. Svitanko