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Copper(II) perchlorate complexes with antipyrine: synthesis, structure, cytotoxicity and DFT calculations

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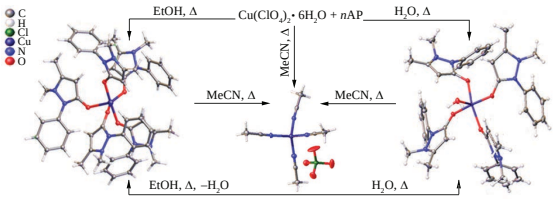
The synthesis, structure and properties of copper(II) perchlorate complexes with antipyrine (AP), $[Cu(AP)_4(H_2O)](ClO_4)_2$ and $[Cu(AP)_5](ClO_4)_2$, are described and compared with those of alternative compounds containing different AP ligands.



Keywords: antipyrine, copper(II) perchlorate, crystal structure, cytotoxicity, reactive oxygen species.

With this growing global burden, prevention of cancer is one of the most significant public health challenges of the 21st century.[1,2] To overcome side effects of platinum drugs, numerous approaches have been adopted,[3] namely, studies on metal–drug synergism[4,5] as well as complexes of essential transition elements that participate in enzymatic processes.[3,6,7] Palladium and copper complexes with derivatives of natural chlorins are prospective as diagnostic and therapeutic radiopharmaceuticals,[8] while tetraazacyclododecane–chlorin conjugates and their complexes with palladium and gadolinium are promising as theranostics for non-invasive diagnostics and therapy in oncology.[9]

Copper complexes exhibit cytotoxic properties within the mechanism of action different from that of cisplatin.[3,6,10] It consists in generation of intracellular reactive oxygen species (ROS) by reduction of Cu^{II} to Cu^{I}.[11–13] On the other hand, antipyrine (1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one) and its derivatives are known for their pharmaceutical activities.[14–16] Antipyrine complexes of copper(II) and cobalt(II) chlorides were found to strongly bind to CT-DNA *via* intercalation which is maximized by the active compounds with planar structure.[10,17] Complexes of zinc(II), cadmium(II) and copper(II) with antipyrine and caffeine have been documented.[14,15,18–21] Structural features of $[Cu(AP)_5](ClO_4)_2$ and $[Cu(AP)_5](ClO_4)_2 \cdot AP$ have been hypothesized indirectly,[22–26] however their bioactivity was not investigated.

The present work is devoted to the synthesis of copper(II) perchlorate complexes with antipyrine, their identification, and cytotoxicity studies. Compounds $[Cu(AP)_4(H_2O)](ClO_4)_2$ **1** and $[Cu(AP)_5](ClO_4)_2$ **2** were prepared by the treatment of $Cu(ClO_4)_2 \cdot 6H_2O$ with antipyrine taken in the molar ratio of $Cu(ClO_4)_2$/AP = 1:2, 1:4 and $Cu(ClO_4)_2$/AP = 1:5, 1:6, respectively, in an aqueous or ethanolic medium (the yields were 70–85%). Carrying out the reaction in acetonitrile at the Cu/AP molar ratio of 1 : 5 gave known[27,28] light yellow crystals of $[Cu(MeCN)_4](ClO_4)$ **3**† (Scheme 1, for details, see Online Supplementary Materials).

† Single crystals of **1** were obtained as light-green prisms after 5–7 days of isothermal evaporation of the solvent, those of **2** appeared as green blocks from the vitreous mass, prepared after heating the $Cu(ClO_4)_2$/AP = 1:5 mixture in aqueous medium (recrystallization from ethanol).

Crystal data for $[Cu(AP)_4(H_2O)](ClO_4)_2$ **1**. $C_{44}H_{50}Cl_2CuN_8O_{13}$, M = 1033.36, monoclinic, space group $P2_1/c$, a = 27.4806(7), b = 25.2199(6) and c = 13.7206(4) Å, β = 94.7110(10)°, V = 9477.0(4) Å^3, Z = 8, μ(MoKα) = 0.646 mm^{-1}, F(000) = 4296.0, d_{calc} = 1.448 g cm^{-3} (see Online Supplementary Materials, Tables S2 and S3).

Crystal data for $[Cu(AP)_5](ClO_4)_2 \cdot 0.25H_2O$ **2**. $C_{55}H_{60}Cl_2CuN_8O_{13.25}$, M = 1207.57, monoclinic, space group $C2/c$, a = 37.0018(11), b = 15.2340(5) and c = 23.9586(7) Å, β = 122.8220(10)°, V = 11349.1(6) Å^3, Z = 8, μ(MoKα) = 0.552 mm^{-1}, F(000) = 5032, d_{calc} = 1.413 g cm^{-3} (see Tables S4 and S5).

Crystal data for $[Cu(CH_3CN)_4](ClO_4)$ **3**. $C_8H_{12}ClCuN_4O_4$, M = 327.21, orthorhombic, $Pan2_1$, a = 23.8013(13), b = 8.3216(4) and c = 20.3492(12) Å, $\alpha = \beta = \gamma$ = 90°, V = 4030.5(4) Å^3, Z = 12, μ(MoKα) = 1.836 mm^{-1}, F(000) = 1992, d_{calc} = 1.618 g cm^{-3} (see Tables S6 and S7).

Reflections were measured at 150 K (for **1**) or 100 K (for **2** and **3**) under a stream of cooled nitrogen on a CCD area diffractometer by Bruker D8 Venture (graphite monochromatized MoKα radiation, ω scan mode). The primary processing of the experimental data was performed by the SAINT program.[34] The absorption correction was applied by the use of SADABS program. The crystal structure was solved by direct methods and refined on F^2 by full-matrix least-squares in anisotropic approximation for non-hydrogen atoms. Positions of hydrogen atoms were calculated geometrically and refined by the riding model. All calculations were performed using Olex-2[35] and SHELXTL-Plus[36] program software (see Online Supplementary Materials, Tables S2–S7). Visualization of the compounds structure was performed using the MERCURY program.[37]

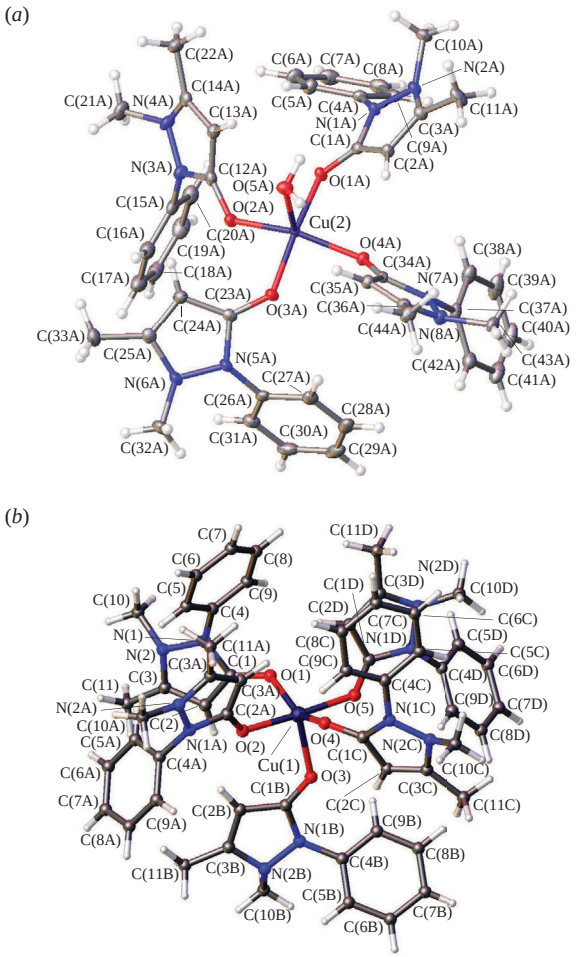


Figure 1 Molecular structures of (*a*) complex $[Cu(AP)_4(H_2O)](ClO_4)_2$ **1** and (*b*) complex $[Cu(AP)_5](ClO_4)_2$ **2** (only complex cations are shown).

EPR spectrum for the powder **1** is characteristic for the polycrystalline magneto-diluted mononuclear complex $[Cu(AP)_4(H_2O)](ClO_4)_2$ similar to the related compounds.[24,29,30] EPR spectrum for the powder **2** is characterized by the presence of broad signals with unresolved hyperfine structure peculiar to polycrystalline mononuclear copper(II) complexes with rhombic distortions[31–33] associated with asymmetric disposition of the coordinated ligands (see Online Supplementary Materials).

According to the pXRD data (see Online Supplementary Materials), the compounds were isolated in a pure form, and the single-crystal structure is representative of the sample bulk. Copper atoms in **1** and **2** are located in the center of distorted square pyramid (Figure 1), the Cu–O (H_2O or axial AP) bond length being significantly longer than the other Cu–O bonds.†

DFT calculations were performed using the Priroda program[38] the PBE exchange-correlation functional,[39] and TZDP Gaussian-type basis sets. The basis set has the following contraction schemes: (17s13p8d)/[12s9p4d] for Cu, (11s6p2d)/[6s3p2d] for C, N and O, (5s1p)/[3s1p] for H. Geometry optimization was started from the single crystal X-ray experimental atomic positions and was performed without restrictions on the molecular symmetry. Vibrational harmonic frequency analysis of the optimized geometries was utilized to ensure that it was true local minimum having no imaginary frequencies. Solvent effects (water) were considered using the Gaussian 09 program[40] and the integral equation formalism variant of polarizable continuum model (PCM).[41,42]

Bond lengths (calculated and experimental values) for $[Cu(AP)_4(H_2O)]^{2+}$ and $[Cu(AP)_5]^{2+}$ (see Online Supplementary Materials, Table S8) demonstrate the same tendency: one longer axial Cu–O bond. Consideration of $\Delta_r G_{298}$ for the reactions of complex formation and taking into account solvent effects $\Delta_r G_{298}$(PCM) allow us to write the following order of the complex formation priority:

$$[Cu(AP)_4]^{2+} > [Cu(AP)_4(H_2O)]^{2+} \approx [Cu(AP)_4(MeCN)]^{2+} > > [Cu(AP)_5]^{2+} > [Cu(AP)_5]^{2+}\cdot AP,$$

the unsaturated $[Cu(AP)_4]^{2+}$ being the most stable, so axial ligands are readily removed with the formation of $[Cu(AP)_4]^{2+}$. The existence of near planar $[Cu(AP)_4]^{2+}$ in solution has been confirmed by ESI-MS spectroscopy (see Online Supplementary Materials).

Cytotoxicity effects of both compounds [MTT[43] assay, postnatal dental pulp stem cells (DPSC), human breast cancer cell line MCF-7, 24 h] demonstrate dose-dependent behaviour and suppress the cellular survival of DPSC and MCF-7 cells at $c = 1\times10^{-4}$–5×10^{-4} mol dm^{-3} (Figure 2) to a greater extent than the stoichiometric mixtures. Cytotoxicity effects for **1** and **2** were higher for DPSC than for MCF-7; at $c = 5\times10^{-4}$ mol dm^{-3}, toxic action of **1** on MCF-7 exceeds that of **2**; at $c = 1\times10^{-4}$ mol dm^{-3}, these values are approximately equal (see Figure 2, Tables S9 and S10). Both complexes **1** and **2** demonstrate moderate or weak antiproliferative activity against ten cell lines, the highest toxicity being found for IMR32 human neuroblastoma cell line (see Online Supplementary Materials).

All samples are moderate ROS generators[44] (Figure S7), compound **2** being more toxic than **1** towards DPSC, while **1** is non-significantly more toxic for MCF-7. This is in agreement with the plot of ROS formation (see Figure S7), confirming ability of copper-containing compounds to generate ROS.[45]

To conclude, we have examined the structural features of $[Cu(AP)_4(H_2O)](ClO_4)_2$ and $[Cu(AP)_5](ClO_4)_2$ and compared their cytotoxic effect for stem cells and cancer cell lines.

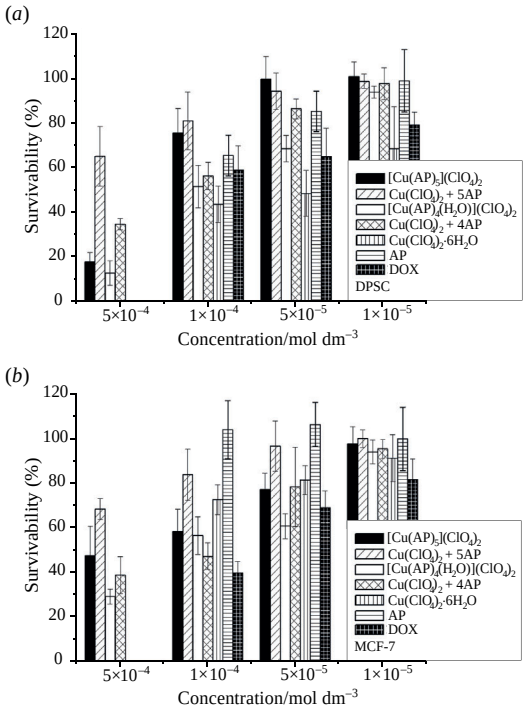
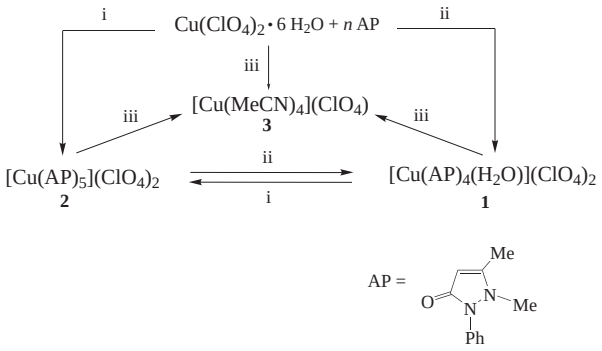


Figure 2 Effect of different compounds on survivability of: (*a*) DPSC and (*b*) MCF-7 cell line.

CCDC 2058676, 2083390, 2091016 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk.



Scheme 1 *Reagents and conditions*: i, EtOH, Δ; ii, H_2O, Δ; iii, MeCN, Δ.

Analytical studies, IR spectroscopy, ESI-MS spectrometry were performed using equipment of the Center of Joint Use 'Scientific Analytical Center of the NRC Kurchatov Institute-IREA'. X-ray diffraction studies and investigations using the EPR method were performed at the User Facilities Center of IGIC RAS within the State Assignment on Fundamental Scientific Researches to the Kurnakov Institute of General and Inorganic Chemistry of the Russian Academy of Sciences and with the financial support of the Council for Grants of the President of the Russian Federation MK-5992.2021.1.3. Studies *in vitro* were performed in the framework of the State Assignment on Fundamental Scientific Researches no. 075-00381-21-00.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.01.040.

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