ISSN 1070-3632, Russian Journal of General Chemistry, 2013, Vol. 83, No. 9, pp. 1673–1677. © Pleiades Publishing, Ltd., 2013.
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Synthesis, Structure, and Properties of the Cu(II) Coordination Compounds with the Pyruvic Acid Nicotinoyl and Isonicotinoyl Hydrazones

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Received October 8, 2012

Abstract—New coordination compounds of Cu(II) and hydrazones of nicotinic and isonicotinic acids have been prepared. The complexes isolated have been studied by elemental analysis, thermogravimetric analysis, magnetic susceptibility measurements, IR, diffuse reflectance, and EXAFS spectroscopy. The geometry of the compounds has been determined and the type of the ligands coordination has been revealed. Antibacterial activity of the complexes has been studied.

DOI: 10.1134/S1070363213090089

Earlier [1] were obtained the copper(II) complexes via the spontaneous self-assembly of isonicotinic acid hydrazide, copper(II) chloride or bromide, and pyruvic acid in ethanol. The complexes structure and composition were determined basing on elemental analysis data and physico-chemical characteristics.

It is known that by altering the conditions and methods of the synthesis, the same starting compounds can give coordination products of different composition and structure, and hence differing in properties, particularly in biological activity, which is important as the complexes contain biologically active components [1].

Previously, a modification of stepwise synthesis was tested to prepare the complexes of bivalent cobalt and nickel with hydrazones of nicotinic (HNpv) and isonicotinic (HIpv) acids, the products of corresponding hydrazides condensation with pyruvic acid. Composition, structure, and properties of the following complexes were determined: $[NiCl(HNpv)(H_2O)_2]$, $[NiCl(HIpv)(H_2O)_2]$, $[CoCl(HNpv)(H_2O)_2]$, $[CoCl(HIpv)\cdot(H_2O)_2]$, $[Ni(HNpv)_2]\cdot 2CH_3OH$, $[Ni(HIpv)_2]\cdot 2CH_3OH$, $[Co(HNpv)_2]\cdot CH_3OH$, and $[Co(HIpv)_2]\cdot CH_3OH$ [2].

The objectives of this work were: to prepare CuX_2 complexes ($X = Cl^-$, CH_3COO^-, and NO_3^-) with H_2Npv (H_2Ipv) via stepwise synthesis developed for the above-mentioned complexes of Co and Ni [2]; to characterize the complexes by using elemental analysis, thermogravimetry and a set of physico-chemical methods; to elucidate the influence of the complex forming metal on the composition, structure and properties of the prepared complexes.

Elemental analysis (Table 1) revealed that the composition of the complexes **I**–**VI** was independent of the position of the pyridine nitrogen in the hydrazide moiety of the ligand and the Cu^{2+}: hydrazone ratio in the reaction medium. The complexes were formed with the molar ratio of $Cu^{2+}:H_2Npv\ (H_2Ipv):X^- = 1:1:1$, X^- being the anion of the initial Cu^{2+} salt: $[CuCl(HNpv)]\cdot H_2O$ (**I**), $[CuCl\ (HIpv)]\cdot H_2O$ (**II**), $[Cu(CH_3COO)(HNpv)]$ (**III**), $[Cu(CH_3COO)(HIpv)]$ (**IV**), $[Cu(NO_3)(HNpv)]$ (**V**), and $[Cu(NO_3)(HIpv)]$ (**VI**).

In contrast with the earlier prepared Co(II) and Ni(II) analogues [1], the compounds **I**–**VI** were fine-crystalline, insoluble in alcohols, acetonitrile, nitrobenzene, chloroform, acetic acid, dimethylformamide, and dimethylsulfoxide. Thermogravimetric study of complexes **I**–**VI** (Table 2) showed that they were stable in air. The thermolysis proceeded stepwise, similarly for all the compounds. Complexes **I** and **II** were crystal hydrates: in the temperature range of 70–120°C, the endothermic effect was observed, with the mass loss corresponding to one water molecule per complex

Table 1. Elemental analysis of coordination compounds **I**–**VI**

Comp. no.	Color	Found, %					Formula	Calculated, %				
		C	H	Cl	N	Cu		C	H	Cl	N	Cu
I	Green	33.00	3.08	11.00	12.98	19.10	$C_9H_{10}ClN_3O_4Cu$	33.44	3.10	10.99	13.00	19.66
II	Light green	33.10	3.06	11.20	13.05	19.20	$C_9H_{10}ClN_3O_4Cu$	33.44	3.10	10.99	13.00	19.66
III	Blue	46.10	3.80		14.60	21.65	$C_{11}H_{11}N_3O_5Cu$	46.07	3.84		14.66	22.16
IV	Blue	46.12	3.76		14.71	21.75	$C_{11}H_{11}N_3O_5Cu$	46.07	3.84		14.66	22.16
V	Green	32.60	2.38		16.80	19.80	$C_9H_8N_4O_6Cu$	32.58	2.41		16.89	19.16
VI	Blue	32.62	2.42		16.75	20.10	$C_9H_8N_4O_6Cu$	32.58	2.41		16.89	19.16

Table 2. Thermogravimetric analysis of coordination compounds **I**–**VI**

Comp. no.	ΔT (t_{max}), °C	Δm (TG), %	Δm_{theor}, %	Thermal decomposition product (CuO)	
				m_{theor}, %	m_{exp}, %
I	75–120 (100)↓ 120–270 (260)↑ 270–580 (320)↑ 580–880 (600)↑	5.8 17.5 32.5 20.2	5.6 ($-H_2O$)	24.6	24.0
II	70–120 (100)↓ 290–300 (300)↑ 300–570 (360)↑ 570–850 (620)↑	5.9 17.5 27.5 25.0	5.6 ($-H_2O$)	24.6	24.1
III	206–300 (250)↑ 300–400 (350)↑	53.0 22.0		27.8	27.0
IV	200–288 (230)↑ 288–380 (350)↑	55.1 20.2		27.8	27.2
V	210–320 (300)↑ 320–400 (350)↑	52.4 23.6		24.0	24.0
VI	208–330 (280)↑ 330–410 (370)↑	50.7 25.6		24.0	23.7

molecule; this was confirmed by annealing of the samples at the thermolysis onset temperature. In contrast to **I** and **II**, compounds **III**–**VI** did not contain solvate water. Further thermolysis of the complexes was accompanied by a number of exothermic effects due to destruction and burning out of the organic parts of the molecules. The final product of the thermal decomposition of **I-VI** was copper(II) oxide, as confirmed by the mass loss in the thermogravimetric experiments and by X-ray diffraction analysis.

The type of hydrazone coordination in complexes **I**–**VI** was determined by infrared spectroscopy. In the spectra of complexes as compared with those of the ligands three amide bands at 1690 (I), 1548 (II), and 1269 cm^{-1} (III) were shifted: to lower frequency by ~60 cm^{-1} (amide I), to lower frequency by 35–40 cm^{-1} (amide II), and to higher frequency by 20 cm^{-1} (amide III). Instead of the bands characteristic of –COOH (ν_{as} = 1766 cm^{-1}, ν_s = 1425 cm^{-1}), the corresponding bands of carboxylate COO^- groups (ν_{as} = 1614 cm^{-1}, ν_s = 1383 cm^{-1}) appeared; $\Delta\nu = [\nu_{as}(COO^-)–\nu_s(COO^-)]$ = 1614–1383 = 231 cm^{-1}. Those changes indicated the binding of metal with mono-deprotonated ligand via the oxygen atoms of pyruvic acid carboxylate group [3] and via the carbonyl group of the hydrazide fragment.

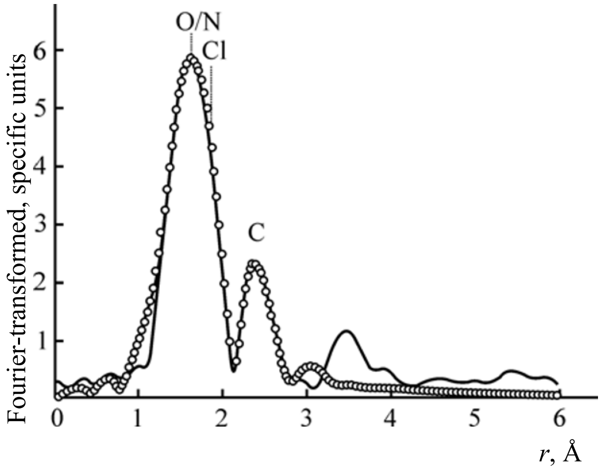
Taking into account the energetically favored formation of conjugated five-membered rings, azomethine nitrogen was evidently involved in the coordination as well. Unfortunately, we could not observe a shift of the ν(C=N) band as it overlapped with $\nu_{as}(COO^-)$ at 1610–1614 cm^{-1}. However, the appearance of the ν(M–N) bands (510–540 cm^{-1}) and the ν(M–O) bands (422–450 cm^{-1}) supported the assumption. In the spectra of **I** and **II** a band at ~3440 cm^{-1} was also detected, assigned to vibrations of the water molecules, which was consistent with thermogravimetric data.

In contrast to **I**–**IV,** IR spectra of complexes **V** and **VI** contained the bands of $\nu(NO_3^-)$ at 840, 1415 and 845, 1418 cm^{-1}, respectively, typical of the monodentate binding of nitrate ion [3].

Cu^{2+} coordination polyhedron in the studied complexes was determined from diffuse reflectance spectra and μ_{eff} data. In the diffuse reflectance spectra of **I**–**VI,** no intense band at ~16000 cm^{-1} was found, thus the complexes octahedral structure was rejected [4]. The following bands were observed: 5104 and 13417 cm^{-1} (**I**), 5208 and 12390 cm^{-1} (**II**), 5112 and 13428 cm^{-1} (**III**), 5128 and 12364 cm^{-1} (**IV**), 5110 and 13320 cm^{-1} (**V**), and 5106 and 12450 cm^{-1} (**VI**); those bands were characteristic of a pseudotetrahedron distorted by oblateness along the second order axis [5]. Such distortion was additionally supported by the absence of the $^2B_{2g}\rightarrow{}^2B_{1g}$ transition band (~7500 cm^{-1}) in the reflectance spectra.

For the complexes **II** and **V,** the magnetic susceptibility as function of temperature (77.4–297 K) was studied by Faraday method. The analysis showed that μ_{eff} of 1.79 MB and 1.91 MB, respectively, did not change over the studied temperature range. Consequently, those compounds were monomeric ones.

To determine the quantitative parameters of the local atomic environment in metal complex **II**, the Fourier-transformed EXAFS χ-spectra were analyzed by multispheric nonlinear approximation.



EXAFS-spectrum (CuK edge) of the $[CuCl(HIpv)]\cdot H_2O$ (**II**) metal complex. (Solid line) experiment, (circles) calculation.

The figure shows the EXAFS spectrum Cu*K* absorption edge for the studied metal complex. The specific feature of the spectrum was the main peak at $r = 1.51$ Å, corresponding to the first nearest coordination sphere consisting of nitrogen and oxygen atoms of the ligand. A series of weaker peaks at large *r* distances, corresponding to further coordination spheres, were observed as well. Quantitative characteristics of the first coordination sphere as elucidated by multispheric nonlinear fitting are shown in Table 3. In the EXAFS spectrum of **II,** the asymmetry of the main peak was evident, associated with appearance of the coordination sphere at somewhat longer distance. The best fit corresponded to the first coordination sphere consisting of three N/O atoms and one Cl atom at a distance of 2.25 Å. The obtained Debye-Waller factors for the first coordination sphere of **II** were typical of such complexes [6].

Based on the set of the data obtained for the complexes **I**–**VI**, we proposed the schematic structures (see bellow).

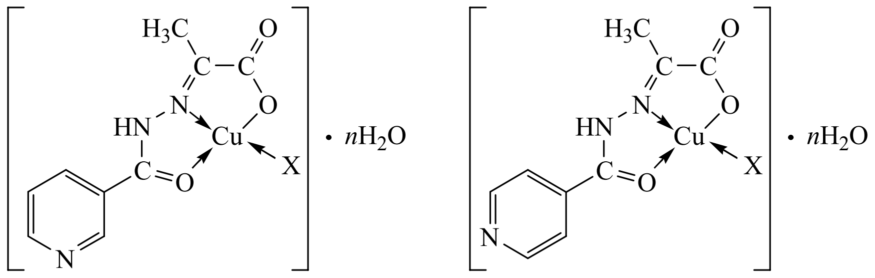
The study of antimicrobial activity revealed that *S. aureus* cells were the most sensitive to the complexes **I** and **II**.

The highest growth inhibition, 88.3% and 76.2% in the cases of **I** and **II**, respectively, was observed at concentrations of 100 μmol (**I**) and 50 μmol (**II**). Both of the complexes effectively suppressed reproduction of *M. luteus* and *P. aeruginosa*. At 50 μmol of **II** or

Table 3. Structural data from EXAFS-fitting for the copper complexes $[CuCl(HIpv)]\cdot H_2O$ (**II**)[a]

N	*R*, Å	σ^2, $Å^2$	Atom	*Q*, %
1	1.87	0.0030	N/O	4.7[b]
2	1.96	0.0030	N/O	
1	2.25	0.0035	Cl	

[a] (*R*) is the interatomic distance, (*N*) is the coordination number, (σ^2) is Debye-Waller factor, (*Q*) is a quality of the fitting. [b] Fit with window of $\Delta r = 1.1–2.7$ Å.



n = 1 (**I, II**), 0 (**III,** VI); X = Cl^- (**I, II**), CH_3COO^- (**III, IV**), NO_3^- (**V, VI**).

100 μmol of **I**, *M. luteus* biomass was 36.6% and 25.6%, respectively, of that in the control experiment. The growth of *P. aeruginosa* culture was depressed by 78.4% and 58.6%, respectively, with 50 μmol of **I** and 100 μmol of **II**.

Addition of **II** to the *B. subtilis* culture did not cause any significant changes: the growth inhibition did not exceed 30%. Noticeable suppression of the same culture biomass growth (43.5%) was observed in the presence of 100 μmol of **I**. The activity of **I** and **II** with respect to *P. vulgaris* was about the same.

To conclude, the set of various physico-chemical data proved that by using the proposed procedure the similar pseudotetrahedral complexes **I-VI** were formed regardless of the copper(II) salt anion; the complexes were alike to those obtained earlier by self-assembly method [2].

The coordination polyhedron of the complex changed depending on the complex forming metal, being octahedron in the cases of Co^{2+} and Ni^{2+} and tetrahedron in the case of Cu^{2+}.

The remarkably high activity of **I** against pseudomonades, naturally resistant to known antimicrobial agents, should inspire further study of the biological activity of similar compounds to extend a very limited arsenal of modern antipseudomonade agents.

EXPERIMENTAL

The prepared complexes were analyzed for carbon, hydrogen, nitrogen with a CHN-analyzer, chlorine content was determined by mercurimetry [7], and copper content was determined by atomic emission spectroscopy with inductively coupled plasma (ICP) with Perkin-Elmer Optima-2100 DV instrument.

Thermogravimetric analysis was performed with Paulik-Paulik-Erdei Q-derivatograph. The samples were heated in air from 20 to 1000°C at a rate of 10°C/min. The sample mass was of 60–80 mg, a platinum open pot was used to hold the sample, the reference was calcinated aluminum oxide.

IR absorption spectra (4000–400 cm^{-1}) of ligands and complexes were recorded with Perkin-Elmer Spectrum BX$^-$II FI-IR and Shimadzu FTIR-8400S spectrophotometers in KBr tablets.

Magnetic susceptibility was measured by the Gouy and Faraday methods. The calibration was performed using $CuSO_4 \cdot 5H_2O$. Magnetic measurements of **II** and **V** were made with Quantum Design SQUID magnetometer at 77.4–297 K in 5 kOe magnetic field of [8].

The local atomic environment in the metal complexes was probed by extended X-ray absorption fine structure (EXAFS) spectroscopy, with EXAFS spectrometer at the Kurchatov Synchrotron Center (Moscow). The X-ray synchrotron radiation source was the electron beam of 2.5 GeV energy, at a current of 60–80 mA. The double-crystal Si(III) X-ray monochromator was used.

The samples were thoroughly mixed with apiezon and placed between thin lavsan films. The sample thickness was adjusted so that the intensity of the transmitted X-rays was 2.5–3.0 times lower than that of the incident beam. After the common procedures of background subtraction, normalization by the value of the K-edge jump, and isolation of atomic absorption μ_0 [9], the experimental EXAFS (χ)-spectra were obtained.

Antimicrobial activity of **I** and **II** was determined by serial dilution, in a Hiss glucose medium using the following bacterial strains from the Museum of microorganism cultures of the Gromashevskiy Epidemiology and Infectious Diseases Institute, Academy of Medical Sciences of Ukraine: *Staphylococcus aureus* ATCC 25923, *Proteus vulgaris* ATCC 6896, *Pseudomonas aeruginosa* ATCC 27853, *Bacillus subtilis* ATCC 6633, and *Micrococcus luteus* ATCC 4698.

The content of substances in the medium was 25, 50 or 100 μmol. Each experiment was performed in 5 parallel repeats. The tubes with the medium were sterilized in an autoclave at 0.5 atm [10]. All the experiments were performed in 3 replicates. The cultures were incubated at 37°C for 24 h. The growth rate of the test strains was determined from the culture optical density measured with "Spekol-10" spectrophotometer at a wavelength of 540 nm. The reference samples were the same cultures grown in a parallel experiment using the Hiss medium without the tested complex.

Starting pyruvic acid nicotinoyl and isocotinoyl hydrazones were prepared as previously described [2].

Preparation of complexes I–VI. Methanol solution of a crystalline salt $CuCl_2 \cdot 2H_2O$ (**I**, **II**), $Cu(CH_3COO)_2 \cdot H_2O$ (**III**, **IV**), or $Cu(NO_3)_2 \cdot 3H_2O$ (**V**, **VI**) was added upon stirring to solution of 0.002 mol of H_2Npv (**I**, **III**, **V**) in 50 ml of methanol or to suspension of 0.002 mol of H_2Ipv (**II**, **IV**, **VI**) in 20 ml of methanol; different molar ratios of Cu^{2+} to H_2Npv or H_2Ipv were used, 1:1, 1:2, 2:1. The precipitates of **I**, **III**, and **V** were instantly formed. In the cases of **II**, **IV**, and **VI**, the reaction mixture was refluxed until the suspension turned into the precipitate. After cooling and isothermal evaporation, the **I–VI** precipitates were filtered off, washed with methanol, and dried at T = 80°C to constant mass.

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