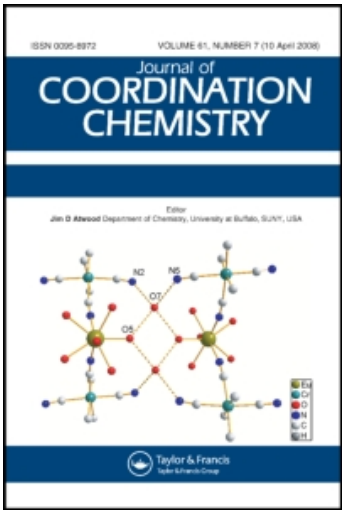

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Synthesis, spectral properties, crystal structures and biological activity of copper(II) pyridinecarboxylates with N-heterocyclic ligands

Peter Segl'a[a]; Dušan Mikloš[a]; Jana Jašková[a]; Jozef Miklovič[b]; Barbora Kaliňáková[c]; Daniela Hudecová[c]; Jozef Švorec[a]; Tadeusz Lis[d]; Milan Melník[a]
[a] Department of Inorganic Chemistry, [b] Faculty of Natural Sciences, Department of Inorganic Chemistry, University of St. Cyril and Methodius 917 01 Trnava, Slovakia [c] Department of Biochemistry and Microbiology, Slovak Technical University, 812 37 Bratislava, Slovakia [d] Faculty of Chemistry, University of Wroclaw, 50 383 Wroclaw, Poland

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Synthesis, spectral properties, crystal structures and biological activity of copper(II) pyridinecarboxylates with *N*-heterocyclic ligands

PETER SEGL'A*†, DUŠAN MIKLOŠ†, JANA JAŠKOVÁ†, JOZEF MIKLOVIČ§, BARBORA KALIŇÁKOVÁ‡, DANIELA HUDECOVÁ‡, JOZEF ŠVOREC†, TADEUSZ LIS¶ and MILAN MELNÍK†

†Department of Inorganic Chemistry,
‡Department of Biochemistry and Microbiology, Slovak Technical University, Radlinského 9, 812 37 Bratislava, Slovakia
§Faculty of Natural Sciences, Department of Inorganic Chemistry, University of St. Cyril and Methodius 917 01 Trnava, Slovakia
¶Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50 383 Wroclaw, Poland

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Synthesis and characterization of four new 2,6-dimethoxynicotinate (2,6-$(MeO)_2$nic) copper(II) monomeric complexes $[Cu(2,6\text{-}(MeO)_2nic)_2(py)_2]$ (py is pyridine), $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ (Etnic is ethylnicotinate), $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$ (Et_2nia is *N*,*N*-diethylnicotinamide) as well as of the polymeric complex $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ (ron is ronicol) are reported. The characterizations were based on elemental analysis, infrared, electronic and EPR spectra. Crystal structures of two of the complexes have been determined. The copper(II) of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$ has a distorted tetragonal-bipyramidal (4 + 2) coordination environment. Both 2,6-$(MeO)_2$nic anions are asymmetrically chelating. The Cu(II) of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ is pentacoordinate in a slightly distorted tetragonal-pyramidal arrangement by two *trans* nitrogens, each of one Etnic, by two oxygens, each of the carboxyl group of one unidentate 2,6-$(MeO)_2$nic and the axial position occupied by water at a longer distance. Antimicrobial effects of the complexes have been tested on various strains of bacteria, yeasts and filamentous fungi. While the 2,6-$(MeO)_2$nicH alone did not influence the model bacteria growth, dimeric $[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ and polymeric $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ have pronounced influence on the growth of *Staphylococcus aureus*, *Escherichia coli* and *Candida parapsilosis*.

Keywords: Crystal structure; *N*-Heterocyclic ligands; Antimicrobial agent; Pyridinecarboxylate; Copper(II) complexes

*Corresponding author. Email: peter.segla@stuba.sk

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1. Introduction

Endogenous copper plays an important role in many biochemical processes and pyridinecarboxylic acids and their derivatives play important roles in the metabolism of all living cells. For example, nicotinic acid (pyridine-3-carboxylic acid) is converted to nicotinamide adenine nucleotide (NAD) which serves as an intermediate in two-electron transfer in organisms [1]. The effect of insulin in the body is optimized by glucose tolerance factor (GTF), formed by two nicotinic acid ligands coordinated to Cr(III) [2]. Moreover, nicotinic acid is used in clinical applications as a lipid-altering agent preventing atherosclerosis and significantly reducing cardiovascular risks [3]. Nicotinic acid is also applied in the skin following topical applications as vasodilator of the peripheral blood capillaries [4] or in the treatment of pellagra [5, 6].

Synthesis, spectral and magnetic properties, antimicrobial effects and crystal structures of various $CuX_2 \cdot nH_2O$ complexes (where X is nicotinate – nic, isonicotinate – isonic, 2-methylthionicotinate – 2-MeSnic; 2,6-dimethoxynicotinate and *trans*-3-(3-pyridyl)-acrylate, $n = 0$–4) as well as of their molecular adducts with chelating or *N*-heterocyclic ligands have been reported [7–15].

It is well documented that heterocyclic compounds, especially *N*-donor ligand systems, play a significant role in biological systems, being a component of several vitamins and drugs [16, 17]. Therefore, many authors have investigated heterocyclic compounds as ligands in coordination compounds of various central atoms, since metal complexes of biologically important ligands are often more effective than the free ligands [18].

N,*N*-diethylnicotinamide (Et_2nia) is a derivative of nicotinamide (vitamin B) used as exhalation agent in respiratory systems in medicine [19]. Some copper(II) carboxylates with Et_2nia were also studied by X-ray diffraction showing dimeric [20, 21] (similarly as for copper(II) acetate monohydrate [22]), polymeric [23] or monomeric [24–26] structures, where carboxylate anions are unidentate [24, 26] or bidentate [25], and Et_2nia is a monodentate nitrogen donor.

One non-steroid anti-inflammatory agent in current use is 3-pyridylmethanol (ronicol – ron), which can be used as a bridging ligand for construction of coordination polymers. One-dimensional (1D) or two-dimensional (2D) coordination polymers of the composition $[CuX_2(ron)_2]_n$ (X = carboxylato anion), as well as a complex $[Cu_3(2\text{-Clnic})_6(ron)_6]_n$ (where 2-Clnic is 2-chloronicotinato anion) forming 1D "accordian chains", have been prepared and characterized [27]. In $[Cu_3(2\text{-Clnic})_6(ron)_6]_n$, ron is a terminal ligand (coordinated via oxygen of hydroxymethyl group) and a bridging ligand (coordinated also by nitrogen of the pyridine) [27].

In this article, we describe synthesis, spectral properties, crystal structures and antimicrobial activities of 2,6-dimethoxynicotinatecopper(II) adducts with *N*-heterocyclic ligands, namely $[Cu\{2\text{-MeSnic})_2(py)_2]$, $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$, $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$. The crystal and molecular structure of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ have also been studied by X-ray structure analysis.

Topological structures and abbreviations of pyridinecarboxylates and heterocyclic ligands are given in figure 1.

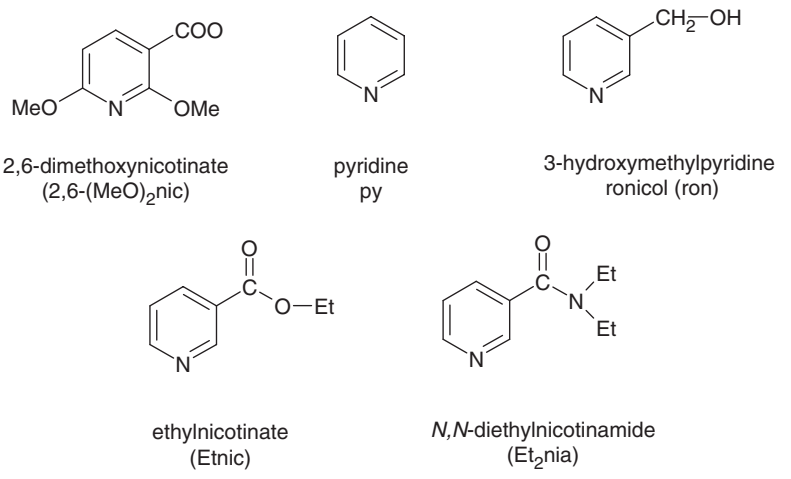

Figure 1. Structures and abbreviations of 2,6-dimethoxynicotinate and heterocyclic ligands.

2. Experimental

2.1. *Chemical reagents, analysis and physical measurements*

All the chemicals used were reagent grade (Aldrich or Sigma) and used without further purification. All organic reagents were purchased from Aldrich; their purity was checked by IR spectra.

Copper was determined by electrolysis after mineralization of the complexes; carbon, hydrogen and nitrogen were determined by microanalytical methods (Thermo Electron Flash EA 1112). Analytical data for the solid complexes are given in table 1.

Electronic spectra (9,000–50,000 cm^{-1}) of the powdered samples in nujol mulls were recorded at room temperature (RT) on a Specord 200. IR spectra in the region of 400−4000 cm^{-1} were recorded on a Magna 750 spectrometer at RT. Spectra of the solid samples were obtained in nujol mulls and KBr pellets (1 wt%).

The EPR spectra were measured in polycrystalline form at room temperature using field-modulated X-band EPR CW Bruker EMX spectrometer. All EPR spectra were simulated using the shareware program Simfonia, developed by Bruker [28].

2.2. *Crystallography*

Crystal data collection procedures and refinement results for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ are given in table 2. Data collection and cell refinement were carried out using Siemens P4 and Kuma KM-4 CCD diffractometers. The diffraction intensities were corrected for Lorentz, polarization and absorption effects.

The structures of the complexes were solved with SHELXS-97 [29] using direct methods, while further refinement with full-matrix least squares on F^2 was carried out with SHELXL-97 [30]. Geometrical analysis was performed using SHELXL-97 [30]. The structures of the complexes were drawn by ORTEP-3 [31] (figures 2 and 3). Selected bond distances and angles for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ are given in tables 3 and 4, respectively.

Table 1. Analytical data[a] for the complexes.

Complex	Calculated (%) Found (%) Cu	C	H	N
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$	10.8	53.3	4.5	9.6
	10.5	53.7	4.5	9.3
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$	7.9	53.9	6.0	0.5
	8.2	53.5	6.2	10.6
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$	8.7	52.6	5.0	7.7
	9.1	52.4	5.1	7.5
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$	9.8	52.1	4.7	8.7
	9.5	52.4	5.0	9.0

[a]Microanalysis results obtained with maximum deviations: Cu, ±0.4; C, ±0.4; H, ±0.3; N, ±0.3.

Table 2. Crystal data and structure refinement for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$.

Compound	$[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$	$[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$
Empirical formula	$C_{26}H_{26}Cu_2N_7O_{21}$	$C_{32}H_{36}CuN_4O_{13}$
Formula weight	586.05	748.19
Crystal system	Monoclinic	Monoclinic
Space group	$P2(1)/n$	$P2(1)/c$
Unit cell dimensions (Å,°)		
a	13.1490(10)	32.456(4)
b	8.2950(10)	14.369(3)
c	13.784(2)	7.333(2)
α	90	90
β	116.550(10)	95.45(3)
γ	90	90
Volume (Å^3)	1344.9(3)	3404.4(1)
Z	2	4
D_{Calcd} (Mgm^{-3})	1.447	1.460
μ (mm^{-1})	0.868	1.529
$F(000)$	606	1556
Diffractometer	Siemens P4	KUMA KM4
Radiation type	Mo-Kα, $\lambda = 0.71073$ Å	Cu-Kα, $\lambda = 1.54180$ Å
Temperature (K)	293(2)	100(2)
Reflections collected	4938	23787
Independent reflections	3922	6548
Refinement method	Full matrix, least-squares on F^2	Full matrix, least-squares on F^2
Data/restraints/parameters	3922/0/230	6548/0/505
Goodness-of-fit on F^2	0.984	1.084
Final R indices ($I > 2\sigma(I)$)	$R = 0.0486$, $R_w = 0.1172$	$R = 0.0537$, $R_w = 0.1462$
Largest diff. peak and hole (e Å^{-3})	0.506 and −0.523	0.609 and −0.776

2.3. *Preparation of the complexes*

The dimeric complex $[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ was prepared as described [13]. The complex $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$ was formed in a methanolic solution (20 cm^3) of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ (2.5 mmol) by adding pyridine in excess (1 cm^3). The mixture was refluxed for 3 h. The blue crystals of the above complex were deposited after several days when the filtrate was left to slowly evaporate at room temperature.

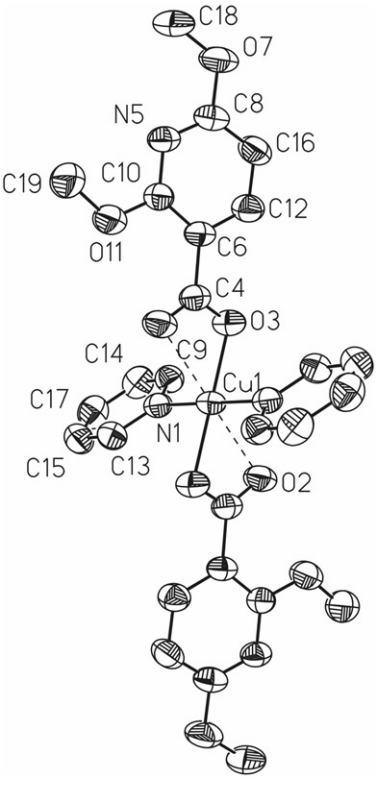

Figure 2. An ORTEP view of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$.

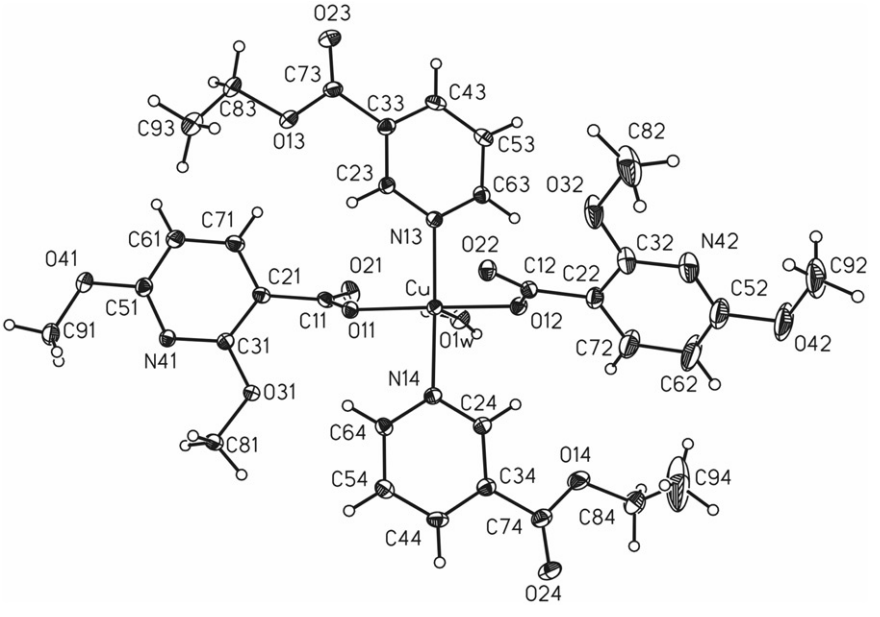

Figure 3. An ORTEP view of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$.

Table 3. Selected bond lengths (Å) and angles (°) for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$.

Cu1–O3	2.003(2)	N1–C13	1.338(3)
Cu1–N1	2.019(2)	N1–C9	1.341(3)
Cu1–O2	2.443(2)	C9–C14	1.370(4)
		C14–C17	1.370(5)
O3–C4	1.270(3)	C15–C17	1.368(5)
C4–O2#1	1.242(3)	C13–C15	1.368(4)
C4–C6	1.504(3)		
C6–C12	1.390(4)	O3–Cu1–N1	90.87(7)
C6–C10	1.390(4)	N1–Cu1–O2	86.9(1)
C12–C16	1.372(4)	O3–Cu1–O2	121.7(1)
C8–C16	1.382(4)	O3–Cu1–N1#1	89.13(7)
N5–C8	1.319(3)	N1–Cu1–O2#1	93.1(1)
N5–C10	1.336(3)	O3–Cu1–O2#1	58.3(1)
O7–C8	1.353(3)		
O7–C18	1.440(4)		
C10–O11	1.343(3)		
O11–C19	1.440(4)		

Symmetry transformations used to generate equivalent atoms: #1 $-x+1, -y, -z$.

Table 4. Selected bond lengths (Å) and angles (°) for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$.

Cu–O11	1.9380(18)	O11–Cu–O12	169.92(7)
Cu–O12	1.9603(19)	O11–Cu–N13	90.57(8)
Cu–N13	2.031(2)	O12–Cu–N13	91.50(8)
Cu–N14	2.035(2)	O11–Cu–N14	88.38(8)
Cu–O1w	2.235(2)	O12–Cu–N14	89.02(8)
O11–C11	1.284(3)	N13–Cu–N14	176.84(8)
O21–C11	1.233(3)	O11–Cu–O1w	98.74(8)
O31–C31	1.352(3)	O12–Cu–O1w	91.11(8)
O31–C81	1.442(3)	N13–Cu–O1w	90.46(8)
O41–C51	1.360(3)	N14–Cu–O1w	92.64(8)
O41–C91	1.428(4)		
O12–C12	1.285(3)		
O22–C12	1.246(3)		
O32–C32	1.336(4)		
O32–C82	1.452(4)		
O42–C52	1.359(4)		
O42–C92	1.425(6)		
C73–O23	1.212(3)		
C73–O13	1.335(4)		
O13–C83	1.453(3)		
C74–O24	1.198(4)		
C74–O14	1.332(4)		
O14–C84	1.459(4)		

The well-shaped crystals were collected by filtration, washed with ethanol and dried *in vacuo*. The blue complexes $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$, $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ were formed by reaction of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ (2.5 mmol) with an excess of Et_2nia or Etnic (3 cm^3) and ron (5 cm^3), respectively. Crystals of the complexes were filtered off, washed with ethanol and finally dried *in vacuo*.

We were unable to prepare crystals of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ suitable for single crystal X-ray structure analysis. Therefore, powder sample has been used for structure determination from X-ray powder diffraction data [15].

2.4. *Antimicrobial assay*

Antibacterial and anti-yeast activities of the tested compounds were evaluated by a micro-dilution method [11] using bacteria G^+ *Staphylococcus aureus* CCM 3953 and G^- *Escherichia coli* CCM 3988 (both from the Czech Collection of Microorganisms, Masaryk University, Brno, Czech Republic) and the yeast *Candida parapsilosis* (from the Laboratory of Medical Mycology, Postgraduate Medical Institute, Bratislava, Slovakia). The efficiency of the prepared derivatives on filamentous fungi *Rhizopus oryzae*, *Alternaria alternata*, *Fusarium nivale* (all from the Collection of Microorganisms of Department of Biochemistry and Microbiology, Faculty of Chemical and Food Technology STU, Bratislava, Slovakia) and *Microsporum gypseum* (from the Laboratory of Medical Mycology, Postgraduate Medical Institute, Bratislava, Slovakia) was observed by macro-dilution technique on solidified broth medium during static culturing [12].

The antimicrobial activity was characterized by the IC_{50} values (concentration of a derivative which in comparison to the control inhibits the growth of microorganisms to 50%) and MIC values (minimal inhibitory concentration of a derivative which inhibits microbial growth by 100%). The IC_{50} and MIC values were read from toxicity curves. At concentrations when no growth of microorganisms had been observed in the presence of tested compounds, the microorganisms were transferred into appropriate fresh agar medium and incubated at 30°C for 48 h (bacteria, yeasts) and at 25°C for 96 h (filamentous fungi). The tested concentration was considered microbicidal (MMC) if no growth was observed and microbistatical (MMS) if there was some growth after the transfer. Chromatographically pure compounds were dissolved in dimethylsulfoxide (DMSO); its final concentration never exceeded 1.0% vol. in either control or treated samples. Concentration of tested compounds was in the range of 0.1 to 10.0 mmol L^{-1} in all experiments.

3. Results and discussion

3.1. *Crystal structure description of [Cu{2,6-(MeO)$_2$nic}$_2$(py)$_2$]*

An ORTEP diagram of [Cu{2,6-$(MeO)_2$nic}$_2$$(py)_2$] is shown in figure 2 and selected bond distances and angles are given in table 3.

The Cu(II) in [Cu{2,6-$(MeO)_2$nic}$_2$$(py)_2$] (figure 2) is six-coordinate in a distorted centrosymmetrical tetragonal-bipyramidal (4 + 2) arrangement. The equatorial plane is formed by two oxygens of two 2,6-dimethoxynicotinate anions (Cu1–O3 = 2.003(2) Å) and two nitrogens of pyridine (Cu1–N1 = 2.019(2) Å) *trans*. The other oxygens of 2,6-dimethoxynicotinate carboxyl groups are coordinated in axial positions (Cu–O2 distance being 2.443(2) Å, the angles N1–Cu1–O2 and O3–Cu1–O2 are 86.9° and 121.7°, respectively). Therefore, both 2,6-$(MeO)_2$nic anions are coordinated to the Cu(II) atom in an asymmetrically chelating manner. No hydrogen bonds have been detected in the structure.

3.2. *Crystal structure description of [Cu{2,6-(MeO)$_2$nic}$_2$(Etnic)$_2$(H$_2$O)]*

An ORTEP diagram of [Cu{2,6-$(MeO)_2$nic}$_2$$(Etnic)_2$$(H_2O)$] is shown in figure 3 and selected bond distances and angles are given in table 4.

The Cu(II) in $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ (figure 3) is five-coordinate in a slightly distorted tetragonal-pyramidal arrangement. The equatorial plane is formed by two carboxyl oxygens of two 2,6-dimethoxynicotinate anions (the distances Cu–O11 and Cu–O12 being 1.938(2) and 1.960(2) Å, respectively) and two nitrogens of ethylnicotinates (Cu–N13 and Cu–N14 being 2.031(2) and 2.035(2) Å, respectively). Contrary to $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$, the distances of the other oxygens of the two 2,6-dimethoxynicotinate carboxyl groups from Cu(II) (Cu–O22 and Cu–O21 are 2.874(2) and 3.170(2) Å, respectively) are too long to be considered bonding distances. Hydrogens of the water are involved in hydrogen bonds, one an intramolecular hydrogen bond to O21 with the distance O1w–O21 of 2.703(2) Å, the other one in a bifurcated hydrogen bond to oxygens O22 and O32 in a neighboring molecule with the corresponding distances O1w–O22′ and O1w–O32′ of 2.725(2) and 3.158(2) Å, respectively.

3.3. *Spectroscopic data*

All typical features of IR spectra are clearly compatible with the structures of the complexes under study; some characteristic IR bands are given in table 5. The IR spectra of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$ show one or two absorption bands in the region from 3200 to 3500 cm^{-1}, which correspond to the antisymmetric and symmetric OH stretches and confirm the presence of water in the compounds.

The carboxylate stretching frequencies $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ for each of the complexes under study are given in table 5. The broad bands assigned to antisymmetric and symmetric stretching vibration for complexes which contain 2,6-$(MeO)_2$nic anions are in the expected regions about 1600 and 1400 cm^{-1}, respectively [32]. The broad bands at about 1600 cm^{-1} (assigned to the antisymmetric stretch $\nu_{as}(COO^-)$) are often overlapped with the stretching vibration of C=N of the pyridine ring. The difference between the antisymmetric stretch and symmetric stretch gives information on carboxylate bonding for complexes after comparison with Δ values of compounds with ionic carboxylic groups. For sodium 2,6-dimethoxynicotinate the Δ value is 204 cm^{-1}. Greater Δ values from 221 to 233 cm^{-1} for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$, $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ are typical for unidentate carboxylate of pyridinecarboxylate. The suggested unidentate O-coordination of the

Table 5. Spectral data (in cm^{-1}) for the copper(II) 2,6-dimethoxynicotinate adducts with *N*-heterocyclic ligands.

	Infrared data[a]				Electronic data[a]		EPR data		
	Carboxyl group			py ring					
Compound	$\nu_{as}(COO^-)$	$\nu_s(COO^-)$	Δ[b]	δ(py)	Band I	Band II	$g_{\|\|}$	$g_\perp$	$A_{\|\|}$
$2,6\text{-}(MeO)_2nicNa$	1602vs,br[c]	1398vs,br	204	597m					
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$	1599vs,br[c]	1367s	232	642m	16500br		2.33	2.08	
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$	1600vs,br[c]	1367s	233	656m	16100br	29000sh	2.41	2.07	156
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$	1597vs,br[c]	1371s	226	644m	16100br	28500sh	2.29	2.06	
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$	1597vs,br[c]	1376vs,br	221	658m	16900br	28500sh	2.32	2.03	

[a]vs, very strong; s, strong; m, medium; sh, shoulder; br, broad. [b]$\Delta = \nu_{as}(COO^-) - \nu_s(COO^-)$. [c]Mixed bands.

carboxyl group of 2,6-$(MeO)_2$nic in complex [Cu{2,6-$(MeO)_2$nic}$_2$(Etnic)$_2$(H_2O)] is also in agreement with the structure determined by X-ray analysis.

In polymeric [Cu{2,6-$(MeO)_2$nic}$_2$(ron)$_2$]$_n$ ronicol is a bridging ligand coordinated via the oxygen of the hydroxyl group (band at 1028 cm^{-1} assigned to ν(C–O) of free ronicol is shifted to higher wavenumber at 1074 cm^{-1}). Very close positions of the strong or very strong bands assigned to ν(C=O) of the carbonyl group of Et_2nia ([Cu{2,6-$(MeO)_2$nic}$_2$(Et_2nia)$_2$(H_2O)$_2$]) and Etnic ([Cu{2,6-$(MeO)_2$nic}$_2$(Etnic)$_2$(H_2O)]) to positions of bands in corresponding free molecules are typical for non-coordination of the carbonyl group in the amide or ester complexes.

In [Cu{2,6-$(MeO)_2$nic}$_2$(py)$_2$] (Δ is 232 cm^{-1}), carboxylates of pyridinecarboxylates are probably asymmetric chelating (see the crystal structure). In this case Δ values are comparable to those of unidentate complexes [33].

Non-coordination of the nitrogen atom of the pyridine ring of 2,6-$(MeO)_2$nic (in position 2 and 6, there are bulky substituents) in all complexes is in agreement with the positions of absorption bands at about 600 cm^{-1}, due to in-plane deformation of the uncoordinated pyridine ring [32]. Positions of bands which correspond to pyridine ring deformation of py, Etnic, Et_2nia or ron (bands due to in-plane pyridine ring deformation at about 600 cm^{-1} for free molecules are shifted to higher wavenumbers at about 650 cm^{-1} – table 5) show that the *N*-heterocyclic ligand is coordinated through the nitrogen, consistent with other copper(II) carboxylates containing Et_2nia or ron [20–27]. Moreover, ron in complex [Cu{2,6-$(MeO)_2$nic}$_2$(ron)$_2$]$_n$ is simultaneously coordinated through oxygen of the hydroxymethyl group. However, coordination or non-coordination of the pyridine ring is also indicated from IR spectra by other typical bands of the pyridine ring.

The solid state electronic spectra of the copper(II) complexes under study exhibit a broad asymmetrical ligand field (LF) band with a maximum range of 16,900 to 16,100 cm^{-1} (table 5). These types of $d-d$ spectra are typical for tetragonal arrangement about copper(II), corresponding to electron transfer from the one-electron orbital ground state $d_{x^2-y^2}$ [34]. For [Cu{2,6-$(MeO)_2$nic}$_2$(Etnic)$_2$(H_2O)], [Cu{2,6-$(MeO)_2$nic}$_2$(Et_2nia)$_2$(H_2O)$_2$] and [Cu{2,6-$(MeO)_2$nic}$_2$(ron)$_2$]$_n$, there is also a shoulder at about 29,000 cm^{-1} (band II), attributed to a charge transfer band of the LMCT transition pyridinecarboxylate anion $\rightarrow$ Cu(II) ($p_\Pi \rightarrow d_{x^2-y^2}$) [34, 35]. Maxima for the complexes are consistent with the assignments for other copper(II) carboxylates with a *trans*-Cu(II)N2O2$\cdots$O2 chromophore [36–38]. Moreover, the suggested stereochemistry has been confirmed by X-ray structure analysis for [Cu{2,6-$(MeO)_2$nic}$_2$(py)$_2$] and [Cu{2,6-$(MeO)_2$nic}$_2$(Etnic)$_2$(H_2O)], respectively.

The solid state EPR spectra are of monomeric type, exhibiting allowed transitions ($\Delta M_S = 1$) characteristic of species with $S = 1/2$. The EPR spectra show axial symmetry with axial g-tensor, where $g_{||} > g_\perp$, which is in agreement with elongated pseudo-octahedral geometry having a $d_{x^2-y^2}$ ground state. [Cu{2,6-$(MeO)_2$nic}$_2$(Etnic)$_2$(H_2O)] also shows a well-resolved copper hyperfine splitting in the parallel part of the signal due to the interaction of the unpaired electron with copper nuclei ($I^{Cu} = 3/2$). The EPR data of the presented complexes are typical for compounds with tetragonal distortion around Cu(II) atom.

3.4. *Antimicrobial activities*

The antimicrobial activity (characterized by IC_{50} and MIC values; mmol L^{-1}) of [Cu{2,6-$(MeO)_2$nic}$_2$(H_2O)]$_2$, [Cu{2,6-$(MeO)_2$nic}$_2$(Et_2nia)$_2$(H_2O)$_2$], [Cu{2,6-$(MeO)_2$nic}$_2$

Table 6. Antimicrobial activity[a] of tested compounds characterized by IC_{50} and MIC (mmol L^{-1}).

	Bacteria				Yeasts		Filamentous fungi							
	S. aureus		*E. coli*		*C. parapsilosis*		*R. oryzae*		*A. alternata*		*F. nivale*		*M. gypseum*	
Compound	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ (**1**)	4.7	10s	5.8	10s	1.5	7.5s	1.3	2.5s	1.6	2.5s	1.8	2.5s	1.6	2.5s
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$ (**2**)	>10	>10	4.9	7.5s	2.6	5.0s	1.5	2.5s	1.8	2.5s	1.7	2.5s	1.6	2.5s
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ (**3**)	>10	>10	6.3	7.5s	9.5	>10	1.1	2.5s	1.7	2.5s	1.8	2.5s	1.6	2.5s
$[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ (**4**)	4.1	10s	1.9	>10	2.4	7.5s	2.6	5.0s	3.4	5.0s	3.5	5.0s	7.5	>10
$2,6\text{-}(MeO)_2nicH$ (acid)	>10	>10	>10	>10	6.9	>10	2.0	2.5s	1.6	2.5s	1.8	2.5s	1.8	2.5s
3-hydroxymethylpyridine (ron)	>10	>10	>10	>10	6.0	>10	>10	>10	>10	>10	>10	>10	>10	>10
N,*N*-diethylnicotinamide (Et_2nia)	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10
Ethylnicotinate (Etnic)	>10	>10	>10	>10	6.3	>10	>10	>10	>10	>10	>10	>10	>10	>10
$CuSO_4$	8.1	>10	>10	>10	2.8	>10	3.0	5.0s	9.4	>10	5.9	10s	8.8	>10
Dichloro-oxodicopper(II) (Kuprikol 50)	–	–	–	–	–	–	8.4	>10	>10	>10	>10	>10	9.0	>10

[a]s – microbistatical effect (MMS).

$(Etnic)_2(H_2O)]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ as well as 2,6-dimethoxynicotinic acid, *N*,*N*-diethylnicotinamide, ethylnicotinate, 3-hydroxymethylpyridine (ronicol), kuprikol 50 (dichloro-oxodicopper(II)) and Cu^{2+} ions alone are summarized in table 6.

While the 2,6-dimethoxynicotinic acid (2,6-$(MeO)_2$nicH) alone in tested concentrations did not influence bacteria growth ($IC_{50} > 10\,mmol\,L^{-1}$), in the presence of copper(II) dimeric $[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ and polymeric $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ have shown the most pronounced influence on the growth of *Staphylococcus aureus* ($IC_{50} = 4.7$ and $4.1\,mmol\,L^{-1}$, respectively). Although based on comparison of IC_{50} values we might state that the greatest inhibitory activity on the growth of *Escherichia coli* was shown by $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ ($IC_{50} = 1.9\,mmol\,L^{-1}$), 100% growth inhibition was observed for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$ and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ already at MIC of $7.5\,mol\,L^{-1}$, while for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$ at a concentration of $10\,mol\,L^{-1}$ the growth inhibition for *Escherichia coli* was only 85%. All tested compounds exhibited higher inhibitory activity against *Escherichia coli* than $CuSO_4$.

From all tested compounds, the greatest inhibitory activity against *Candida parapsilosis* was observed for $[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ ($IC_{50} = 1.5\,mmol\,L^{-1}$, $MIC = 7.5\,mmol\,L^{-1}$) and $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Et_2nia)_2(H_2O)_2]$ ($IC_{50} = 2.6\,mmol\,L^{-1}$, $MIC = 5.0\,mmol\,L^{-1}$). Addition of the bioactive ligand Etnic into the complex $[Cu\{2,6\text{-}(MeO)_2nic\}_2(H_2O)]_2$ decreased the anti-yeast activity of copper(II) complex $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ ($IC_{50} = 9.5\,mmol\,L^{-1}$, $MIC > 10\,mmol\,L^{-1}$). Comparison with $CuSO_4$ ($IC_{50} = 2.8\,mmol\,L^{-1}$) showed that the activity against *C. parapsilosis* was probably due to copper cation, a consequence of the presence of bulky methoxy substituents in positions 2 and 6 of nic, resulting in easy dissociation of the complex.

The complexes show inhibitory activity against *Rhizopus oryzae*, *Alternaria alternata*, *Fusarium nivale* and *Microsporum gypseum* at the same level ($IC_{50} = 1.1 - 1.8\,mmol\,L^{-1}$), except for lower antifungal activity of $[Cu\{2,6\text{-}(MeO)_2nic\}_2(ron)_2]_n$, for which the values observed were five times (for *M. gypseum*) or two times (for the rest of the micromycetes) greater in comparison with those for other complexes of this group; the activity is comparable to the activity of 2,6-dimethoxynicotinic acid alone, indicating that the acid plays the decisive role in this case. The standard used, Kuprikol (dichloro-oxodicopper(II)) ($IC_{50} \geq 8.4\,mmol\,L^{-1}$), exhibited lower inhibitory activity than the most active copper(II) complexes. The bioactive ligands Et_2nia, ron and Etnic did not substantially inhibit the growth of tested bacteria and filamentous fungi ($IC_{50} > 10\,mmol\,L^{-1}$ – table 6).

Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 669208 for compound $[Cu\{2,6\text{-}(MeO)_2nic\}_2(py)_2]$ and CCDC No. 669209 for compound $[Cu\{2,6\text{-}(MeO)_2nic\}_2(Etnic)_2(H_2O)]$ CCDC. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; Email: deposit@ccdc.cam.ac.uk; www: http:/www.ccdc.ac.uk).

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