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Original Scientific Paper

Synthesis and Characterization of Fatty Acid Copper(II) Carboxylates with *N,N*-Diethylnicotinamide

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A series of new fatty acid copper(II) carboxylates of the composition $[(Cu_2(O_2CC_nH_{2n+1})_4(Et_2nia)_2)]$ (Et_2nia = *N,N*-diethylnicotinamide; n = 6 to 11) were synthesized, characterized and tested for fungicidal activity. The compounds were synthesized and crystallized from aqueous solution only because their solubility in organic solvents is too high. Dimeric structure for all compounds was proposed (μ_{eff} at room temperature = 1.43–1.48 BM; UV-Vis λ_{max} at 350–400 nm; IR, $\Delta\nu(COO^-)$ = 185–199 cm^{-1}). A binuclear paddle-wheel cage structure was found for the compound $[(Cu_2(O_2CC_7H_{15})_4(Et_2nia)_2)]$ by X-ray diffraction. Screening for fungicidal activity against the wood-rotting fungi *Trametes versicolor* and *Antrodia vaillantii* shows that the compounds dissolved in DMSO stop mycelium growth completely at a concentration of 1.0×10^{-3} mol L^{-1}. Some of them show strong activity also in more diluted solutions; however, stronger retardation for *Antrodia vaillantii* was noticed for all substances.

Key words: copper(II) carboxylates, fatty acids, diethylnicotinamide, crystal structure, fungicidal activity.

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INTRODUCTION

Our interest in copper(II) carboxylates of saturated carboxylic (fatty) acids originates from their use as wood preservatives.[1] During investigations with the wood destroying fungus *Trametes versicolor,* it was found that dimeric complexes, with the carboxylic – fatty – acids of different length are especially interesting.[2–4] The coordination sphere around Cu(II) in the dimers is fulfilled by an apical ligand, which may also have influence on the biological system. For a better understanding of this type of influence, synthesis and standard characterization of fatty acid copper(II) carboxylates with *N,N*-diethylnicotinamide (Et_2nia) and the crystal structure for copper(II) octanoate compound are reported. Screening for their activity in the biological system, *e.g.* the widespread wood destroying fungi *Trametes versicolor* and *Antrodia vaillantii,* is also presented herein.

EXPERIMENTAL

Synthesis

Diethylnicotinamide (Et_2nia) and all solvents were purchased from commercial sources and used without further purification. Sodium carboxylates were synthesized from sodium hydroxide and the corresponding fatty acid in an aqueous solution.

Sodium carboxylate was dissolved in a minimal volume of water. To dissolve the compounds with longer fatty acid chains, heating was also necessary. The obtained solution was cooled and then slowly added to the blue transparent solution of copper sulphate dissolved in water mixed with diethylnicotinamide. The product started to precipitate very soon as green needle-like crystals or as green liquid droplets that crystallized after two days. To avoid precipitation of copper(II) carboxylates, an excess of the ligand Et_2nia and a smaller amount of sodium carboxylate were used for undecanoate and dodecanoate compounds. The precipitate was filtered off after a day and dried in a desiccator over KOH for another day or under high vacuum. Satisfactory purity of the complexes (elemental analysis) was reached only by slow suction with paper that was replaced several times. Dissolution in water or DMSO resulted in removal of the ligand Et_2nia from the starting compound, while recrystallization in other organic solvents was not successful. Average yield is over 50% for all compounds. Single crystals of X-ray quality for the octanoate compound were obtained by the above procedure, however a lower concentration was used.

Metal analysis was carried out electrogravimetrically with Pt electrodes. C, H, N analysis was performed in the Department of Organic Chemistry, Faculty of Chemistry and Chem. Technology, University of Ljubljana, Slovenia. The results of elemental analysis are available from the authors upon request.

Physical Measurements

Infrared spectra were measured on mineral oil mulls between CsI plates using a Perkin-Elmer FT-IR 1720X spectrometer in the range 4000–400 cm^{-1}. Electronic spectra were recorded as Nujol mulls (200–860 nm) with a Perkin-Elmer UV/VIS/NIR Spectrometer Lambda 19. Magnetic susceptibility of the substances was determined at room temperature by the Evans method using powdered samples and a Sherwood Scientific MSB-1 balance with Hg[Co(NCS)$_4$] as calibrant. Diamagnetic corrections were estimated from Pascal's constants and the effective magnetic moments were calculated using the equation $\mu_{\text{eff}} = 2.828\ (\chi_M\ T)^{1/2}$. Thermograms were recorded by the instrument Mettler TA 2000 in an argon atmosphere (flux: 35 mL min^{-1}) in the temperature range 15 to 500 °C. Crucible material was Pt with reference substance α-Al$_2$O$_3$. Sample weighed 20 mg and the heating rate was 2 K min^{-1}. Compounds were tested for fungicidal activity of the wood-rotting fungi *Trametes versicolor* (L. ex Fr.) Pilat and *Antrodia vaillantii* (DC. ex Fr.) Ryv., as described earlier.[5]

*X-ray Crystallography of Tetrakis(μ-octanoato-*O,O'*)-bis(*N,N*-diethylnicotinamide)dicopper(II)*

Room temperature data were collected on an Enraf-Nonius CAD-4 diffractometer with Mo-Kα radiation, using a graphite monochromator. Common data corrections for variations in reference reflections and Lorentz-polarization effects were applied. An absorption correction was done by Gaussian integration using ABSORP (in NRCVAX).[6] The crystallographic data are summarized in Table I. The structure was solved by direct methods using SHELXS-86.[7] The figures were drawn using ORTEP[8] and PLUTON.[9]

Refinements were by full-matrix least squares based on F^2 (all data) using SHELXL-97.[10] The extinction correction was performed using the standard technique of SHELXL-97.[10] Hydrogen atoms were placed at the calculated positions and refined as riding atoms with isotropic displacement parameters taken from those of the attached heavy atoms and multiplied by 1.5 for methyl and phenyl groups and by 1.2 for methylenic moieties.

RESULTS AND DISCUSSION

Crystal Structure

The X-ray analysis of [Cu$_2$(O$_2$CC$_7$H$_{15}$)$_4$(Et$_2$nia)$_2$] reveals a centrosymmetric tetracarboxylate dimeric core structure with the two diethylnicotinamide ligands on apical positions (Figure 1), being very similar to that observed in acetate[11] and benzoate[12] compounds. Similar dimeric complexes with fatty acid copper carboxylates are rare[13] and only structures with pyridine[14] and nicotinamide (nia)[1] as apical positioned ligands are reported.

The coordination sphere around each copper atom is square-pyramidal with Cu atoms displaced 0.2008(9) Å from the basal O$_4$ plane and with *N,N*-diethylnicotinamide as an apical ligand, coordinated through pyridine N atom (Cu–N 2.169(2) Å). The Cu–Cu distance is 2.6273(7) Å and equatorial Cu–O (octanoate) distances vary from 1.957(2) to 1.983(2) Å, which is considered normal for this type of system.[15] One pair of hydrocarbon chains

TABLE I

Crystal data, data collection and structure refinement parameters for the compound [$Cu_2(O_2CC_7H_{15})_4(Et_2nia)_2$]

Molecular formula	$Cu_2(O_2CC_7H_{15})_4(Et_2nia)_2$
Molecular weight	1056.34
Crystal colour	Dark green
Crystal dimensions / mm	0.17 × 0.50 × 0.34
Crystal system	Triclinic
Space group	P–1
a/Å	9.987(2)
b/Å	10.801(2)
c/Å	14.867(2)
α/°	74.36(2)
β/°	70.80(2)
γ/°	80.48(2)
V/Å^3	1453.2(3)
Density (calc.) / g cm^{-3}	1.207
Z	1
λ/Å	0.71073
Scan mode	ω / 2θ
θ_{max}/°	27.91
Data measured	13966
Unique data	6984
Observed data $\|F_o\| > 4\sigma(\|F_o\|)$	4063
Goodness of fit on F^2	0.962
Final R_1 indices $\|F_o\| > 4\sigma(\|F_o\|)$	0.0427
wR_2 indices $\|F_o\| > 4\sigma(\|F_o\|)$	0.1021
R_1 indices (all data)	0.1055
wR_2 indices (all data)	0.1217
Extinction coefficient	0.0043(11)
Max., min. residue / eÅ^{-3}	0.302, –0.347
Mean, max. shift / error	0.004, 0.067
Absorption coefficient / cm^{-1}	7.86

$R_1 = \sum \left| |F_o| - |F_c| \right| / \sum |F_o|$

$wR_2 = \left\{ \sum \left[w(F_o^2 - F_c^2)^2 \right] / \sum \left[w(F_o^2)^2 \right] \right\}^{1/2}$

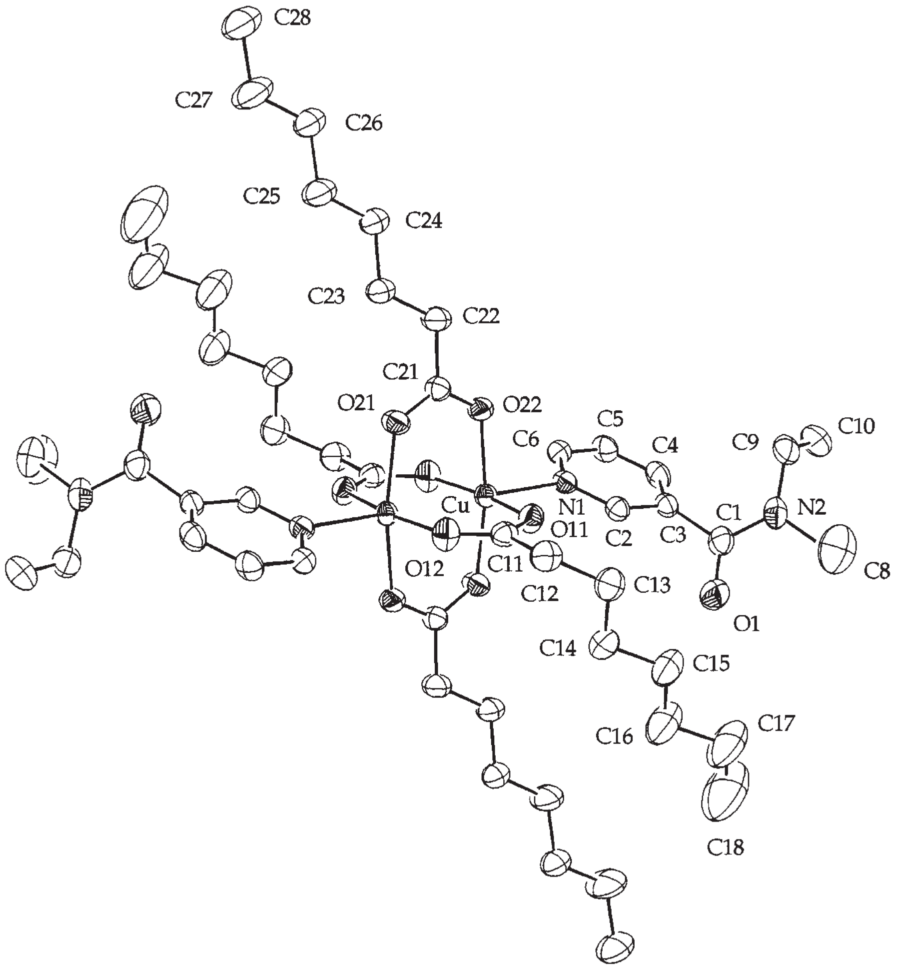

Figure 1. An ORTEP[8] plot of the $[Cu_2(O_2CC_7H_{15})_4(Et_2nia)_2]$ molecule with thermal ellipsoids shown at the 30% probability level. Hydrogen atoms are omitted for clarity.

in each dimer is in the common zigzag conformation, while the other pair is distorted by rotation about the C(11)–C(12) bond. Distortion of hydrocarbon chains facilitates efficient packing (Figure 2). Similar situation was observed for anhydrous copper(II) heptanoate,[16] octanoate,[17] decanoate[18] and for $[Cu_2(O_2CC_7H_{15})_4(py)_2]$,[14] which also crystallize in *P*-1 space group.

In the family of fatty acid copper(II) carboxylates, nicotinamide complexes[1] ($[Cu_2(O_2CC_nH_{2n+1})_4(nia)_2]$; $n = 6$(a,b), 8) are in composition very related to the title compound. However, although nia and Et₂nia are related

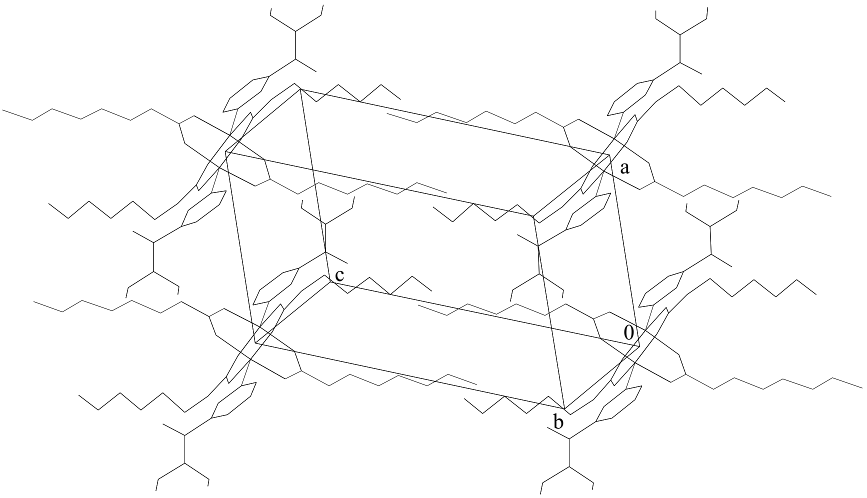

Figure 2. A view of the molecular packing for octanoate compound (PLUTON).[9]

molecules, they as well as their tertracarboxylates differ significantly. Copper(II) carboxylates with nicotinamide crystallize in monoclinic space system and only one heptanoate modification is with the crystallographic center of inversion between the two copper atoms. Amide group in the nia moiety is free, which enables extensive intermolecular hydrogen bonding among isolated dimers. In contrast ethyl groups in $\mathrm{Et_2}$nia block nitrogen atoms and thus disable this type of bonding. Significant decrease of the melting point (T_m/° C for nonanoate and dodecanoate, respectively: nia 178, 159; $\mathrm{Et_2}$nia 53, 65) also agrees with this. An increase of the angle between the planes of amide (CON) and pyridine ring (nia, 16–24°; $\mathrm{Et_2}$nia, 54°) in apical ligand was also observed.

Spectroscopic and Magnetic Measurements

The values of room temperature magnetic moments for all compounds lie in the range between 1.43 and 1.48 BM, that is below the spin-only-value for one uncoupled electron. The electronic spectra reveal the presence of three bands at 272 nm (strong), 380 nm (shoulder) and 700 nm (broad). The results for both methods are in agreement with the dimeric tetracarboxylate nature of the compounds. Similar observations were also noticed in the vibrational spectra where the average difference (Δ) between symmetric (ν_s) and asymmetric (ν_as) stretching vibrations is at 191 $\mathrm{cm^{-1}}$. The slight increase of Δ compared to the observed value in nicotinamide complexes[1] is the consequence of the ν_as shift to higher energies. An even stronger decrease of amide CO vibration (nia, 1666 $\mathrm{cm^{-1}}$; $\mathrm{Et_2}$nia, 1640 $\mathrm{cm^{-1}}$) is observed.

Biological Activity

The synthesized compounds were tested for fungicidal activity against the wood-rotting fungus *Trametes versicolor* and *Antrodia vaillantii*. Dissolved in DMSO, the complexes completely stop mycelium growth for both fungus species at a concentration of 1.0×10^{-3} mol L^{-1}. Among all compounds, mycelium growth of *Trametes versicolor* was observed only for undecanoate and dodecanoate. Maximal retardation for *Antrodia vaillantii* culture was observed also in more diluted solutions (5.0×10^{-4} mol L^{-1} and 1.0×10^{-4} mol L^{-1}), however for *Trametes versicolor* the mycelium growth for both lower concentrations was noticed (Table II). Nonanoate and decanoate compounds showed the smallest decrease of retardation. It is interesting to note that also Et_2nia showed strong activity in the first days of testing, the retardation significantly decreasing during a week. The results show possible biological decomposition of the compound by fungus or by its instability under the experimental conditions. Similar time dependent changes were also noticed for some other substances, however the extent was not so obvious.

Interestingly, stronger activity on *Trametes versicolor* at the concentration 1.0×10^{-4} mol L^{-1} was reported for the fatty acid copper carboxylates with nicotinamide.[1] Both homologous series of compounds are dimeric copper(II) tetracarboxylates, which differ in the apical ligand, which is in both cases a biologically interesting molecule. Therefore lower fungicidal activity

TABLE II

Fungicidal activity for species *Trametes versicolor* (T.v.) and *Antrodia vaillantii* (A.v.) at different concentrations, seven days after inoculation[a]

c/mol L^{-1}:	1.0×10^{-3}		5.0×10^{-4}		1.0×10^{-4}	
Compound	T.v.	A.v.	T.v.	A.v.	T.v.	A.v.
Et_2nia	4	4	3	4	3	3
$Cu_2(O_2CC_6H_{13})_4(Et_2nia)_2$	5	5	4	5	3	5
$Cu_2(O_2CC_7H_{15})_4(Et_2nia)_2$	5	5	4	5	3	5
$Cu_2(O_2CC_8H_{17})_4(Et_2nia)_2$	5	5	5	5	3	5
$Cu_2(O_2CC_9H_{19})_4(Et_2nia)_2$	5	5	4	5	4	5
$Cu_2(O_2CC_{10}H_{21})_4(Et_2nia)_2$	4	5	3	5	3	5
$Cu_2(O_2CC_{11}H_{23})_4(Et_2nia)_2$	3	5	3	5	2	5

[a] The numbers in the table have the following meaning: 1, normal growth, no retardation; 2, slightly visible signs of retardation; 3, significant retardation; 4, retardation is very strong; 5, no fungal growth.
The values for the control without dissolved compounds: water 1, DMSO 2–3.

of the Et_2nia complexes compared to nia series for *Trametes versicolor* is obviously a consequence of the apically positioned ligands that differ in amide group. The ethyl groups make a barrier to the nitrogen, which may play an important role in fungal metabolism.

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Supplementary Materials. – Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44–1223–336033; e-mail: deposit@ccdc.cam.ac.uk) and can be obtained on request, free of charge, by quoting the publication citation and the deposition number 124878.

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SAŽETAK

Sinteza i karakterizacija mješovitih kompleksa bakra(II) s alifatskim kiselinama i s *N,N*-dietilnikotinamidom

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Opisana je priprava i karakterizacija novih mješovitih kompleksa bakra(II) s alifatskim kiselinama i biološki važnim ligandima sastava $[Cu_2(O_2CC_nH_{2n+1})_4(Et_2nia)_2]$ (Et_2nia = *N,N*-dietilnikotinamid, n = 6 do 11), i testirana njihova fungicidna aktivnost. Spojevi su sintetizirani i kristalizirani samo iz vodene otopine, jer je njihova topljivost u organskim otapalima prevelika. Predložena je dimerna struktura za sve sintetizirane spojeve, μ_{eff} pri sobnoj temperaturi = 1,43–1,48 BM; UV–Vis, λ_{max} = 350–400 nm; IR, $\Delta\nu(COO^-)$ = 185–199 cm^{-1}. Difrakcijom X-zraka nađeno je da spoj $[Cu_2(O_2CC_7H_{15})_4(Et_2nia)_2]$ ima binuklearnu, kavezastu strukturu mlinskog kola. Provjeravanje fungicidne aktivnosti prema gljivicama drvne truleži *Trametes versicolor* i *Antrodia vaillantii* pokazuje da spojevi otopljeni u DMSO potpuno zaustavljaju rast micelija pri koncentraciji $1{,}0 \times 10^{-3}$ mol L^{-1}. Neki od njih pokazuju visoku aktivnost i u razrjeđenijim otopinama; ipak, za sve spojeve jače usporavanje opaženo je za *Antrodia vaillantii*.