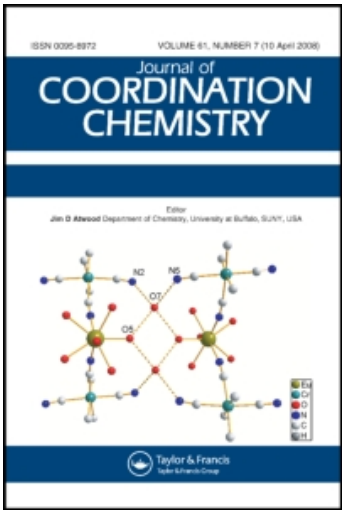

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Synthesis, crystal structure and antibacterial activity of a new binuclear copper(II) complex with N,N'-bis(N-hydroxyethylaminopropyl)oxamido as a bridging ligand

Chun-Yuan Zhu[a]; Yan-Tuan Li[a]; Zhi-Yong Wu[a]; Yu-Lan Song[a]
[a] Marine Drug and Food Institute, Ocean University of China, Qingdao, Shandong 266003, P. R. China

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Synthesis, crystal structure and antibacterial activity of a new binuclear copper(II) complex with *N*,*N*′-*bis*(*N*-hydroxyethyl-aminopropyl)oxamido as a bridging ligand

CHUN-YUAN ZHU, YAN-TUAN LI*, ZHI-YONG WU and YU-LAN SONG

Marine Drug and Food Institute, Ocean University of China, Qingdao, Shandong 266003, P. R. China

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A new μ-oxamido-bridged dicopper(II) complex, $[Cu_2(heap)](ClO_4)_2 \cdot 2H_2O$ [$H_2heap = N,N'$-*bis*(*N*- hydroxyethylaminopropyl)oxamido], has been synthesized and structurally characterized by elemental analyses, molar conductance, IR and single-crystal X-ray diffraction. The single crystal X-ray analysis reveals that the asymmetric unit of the complex is composed of half a binuclear cation $[Cu_2(heap)]^{2+}$, one perchlorate anion, and one lattice water molecule. Each copper(II) atom is tetracoordinate in a distorted square-planar geometry and the bridging ligand (H_2heap) adopts the *trans* conformation with an inversion centre at the middle of the C2–C2^i bond. The structure cohesion is ensured by hydrogen bonding interactions, which form a two-dimensional supramolecular framework. The antibacterial assay indicates that the complex showed better activity than the ligand.

Keywords: μ-Oxamido-bridge; Dicopper(II); Crystal structure; *trans* Conformation; Antibacterial activity

1. Introduction

Dicopper(II) complexes with multi-atom bridges are of interest in connection with spin-exchange and charge-transfer between metal ions, and in the domain of metalloenzymes and homogeneous catalysis [1, 2]. It is known that *N*,*N*′-bis(substituent)oxamides could be good candidates in forming polynuclear complexes because their coordinating ability toward transition-metal ions can be modified and tuned by changing the nature of the amide substituents [3]. An attribute of these ligands is the easy transformation of *cis-trans* conformations, which makes it practical to design tunable molecular materials with desired properties [4]. Hence this family of ligands has played an important role in coordination chemistry [3, 5]. Many complexes bridged by oxamido groups have been synthesized and their properties studied extensively [4, 6–13]. However, to the best of our knowledge, few complexes with hydroxyl coordinating in the *N*,*N*′-bis(substituent)oxamides bridging ligand have been reported. Therefore, it is of considerable interest to synthesize and study the oxamido-bridged

*Corresponding author. Email: yantuanli@ouc.edu.cn

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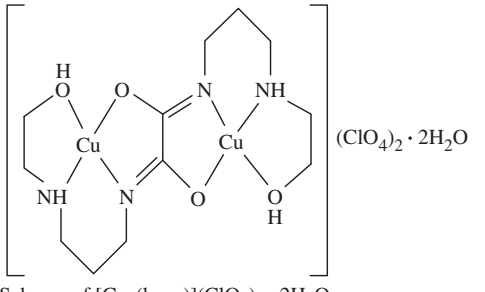
complexes with hydroxyl participating in coordination in order to gain insight into the structure and character of this kind of complex.

As part of our study on the synthesis and magnetism of the complexes bridged by oxamido groups [6–10], here we report the synthesis and crystal structure of a new μ-oxamido-bridged binuclear copper(II) complex, $[Cu_2(heap)](ClO_4)_2 \cdot 2H_2O$, by using *N*,*N*′-*bis*(*N*-hydroxyethylaminopropyl)oxamide (H_2heap) as bridging ligand. The antibacterial activities of the ligand and the complex were also studied.



Scheme of $[Cu_2(heap)](ClO_4)_2 \cdot 2H_2O$

2. Experimental

The ligand *N*,*N*′-*bis*(*N*-hydroxyethylaminopropyl)oxamide (H_2heap) was synthesized according to the reported method [3]. The C, H, and N microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. Molar conductance was measured with a Shanghai DDS-11A conductometer. Infrared spectra were recorded on a Nicolet-470 spectrophotometer in the spectral range 4000–400 cm^{-1} as KBr pellets.

Caution Although we have not encountered any problems, perchlorate compounds are potentially explosive and should be handled with care.

2.1. *Preparation*

A solution of copper(II) perchlorate hexahydrate (18.55 mg, 0.05 mmol) dissolved in methanol (5 mL) was added dropwise to a methanol (6 mL) solution containing the ligand (7.25 mg, 0.025 mmol) and piperidine (4.26 mg, 0.05 mmol). The mixture was heated under reflux with stirring for 1 h. The resulting blue solution was filtered and then an equal volume of benzene was added. Blue crystals (yield 9.43 mg, 58%) suitable for X-ray analysis were obtained from the solution after 10 d by slow evaporation at room temperature. Anal. Calcd for $C_{12}H_{28}Cl_2Cu_2N_4O_{14}$ (%): C, 22.16; H, 4.34; N, 8.61. Found: C, 22.02; H, 4.21; N, 8.50.

2.2. *Crystal structure determination*

Diffraction data were collected on a Bruker APEX area-detector diffractometer, using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The crystal structure was

solved by the heavy atom method followed by Fourier syntheses. Structure refinement was performed by full matrix least-squares procedures using SHELXL-97 on F^2 [14]. H atoms of water molecules were located in a difference Fourier map and included in the structure-factor calculation with fixed positional and displacement parameters (0.08 Å^2); all other H atoms were placed in calculated positions, with C–H = 0.97 Å and N–H = 0.91 Å, and included in the final cycles of refinement in the riding mode, with Uiso(H) = 1.2 Ueq of the carrier atoms. Crystal data and refinement conditions are summarized in table 1.

2.3. *Antibacterial assay*

The used bacteria were *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris* and *Pseudomonas aeruginosa*. The antibacterial activities of the ligand and its complex were determined qualitatively using the paper disc method. A lawn of microorganisms was prepared by pipetting and evenly spreading 100 µL of inoculum (adjusted turbidometrically to 10^5–10^6 CFU mL^{-1} [CFU = colony forming units]) onto nutrient agar set in Petri dishes. Paper discs of 6 mm diameter were impregnated with the stock solution of the complexes (100 mg mL^{-1} DMSO solution) and dried under sterile conditions. The dried discs were then placed on the previously inoculated agar surface. The plates were inverted and incubated at 37 ± 2°C. After 24 h the inhibition diameters were measured. The experiments were repeated three times and the results were expressed in average values.

In order to understand quantitatively the magnitude of the antibacterial activities, the antibacterial activities of the ligand and its complex were evaluated for their minimum inhibitory concentrations (MIC) by the microdilution broth method. Complex solution (100 mg mL^{-1}) was added to broth for different concentrations (range from 50 µg mL^{-1} to 1000 µg mL^{-1}). Suspensions of the bacterial strains, with an optical density of

Table 1. Crystal data and details of the structure determination.

Formula	$C_{12}H_{28}Cl_2Cu_2N_4O_{14}$
Formula weight	650.38
Crystal system	Monoclinic
Space group	$P21/c$
a, b, c (Å)	10.844(2), 8.7417(17), 12.723(3)
α, β, γ, (°)	90.00, 101.90(3), 90.00
V (Å^3)	1180.2(4)
Z	2
D(Calcd) (g cm^{-3})	1.830
μ (Mo-Kα) (mm^{-1})	2.102
Scan-mode	φ and ω scan
F(000)	664
Crystal size (mm^3)	0.22 × 0.14 × 0.12
θ range	1.92–25.12
Limiting indices	$-9 \le h \le 12$, $-10 \le k \le 9$, $-15 \le 1 \le 12$
Tot., uniq. data, R(int)	5973, 2107, 0.0200
Observed data [$I > 2\sigma(I)$]	1768
R, wR_2	0.0368, 0.1048
S	1.092
Max., av. shift/error	0.000, 0.000

McFarland 0.5 (10^7–10^8 CFU), were made in isotonic sodium chloride solution. Samples measuring 25 μL of each bacterial suspension were added to the serial dilution of the test substances. The inoculated test tubes were incubated at 37 ± 2°C under aerobic conditions. After 72 h the turbidity was evaluated. The MIC is defined as the lowest antimicrobial concentration of the test compounds, which completely inhibits bacterial growth. The experiments were repeated three times.

3. Results and discussion

3.1. *Synthetic route and solubility of the binuclear complex*

A promising method to design and synthesize homobinuclear complexes is to use binucleating ligands [11–13]. We obtained Cu(II)–Cu(II) homobinuclear complex by this synthetic method. As the binucleating ligand, we chose H_2heap, which can coordinate to metal ions through not only carbonyl oxygens and nitrogens of oxamido but also oxygens of hydroxyl. Indeed, elemental analyses, molar conductance, IR and single-crystal X-ray diffraction indicate that the reaction of H_2heap and $Cu(ClO_4)_2 \cdot 6H_2O$ in 1 : 2 mole ratio yielded the binuclear complex of formula $[Cu_2(heap)](ClO_4)_2 \cdot 2H_2O$, as expected. The binuclear complex is very soluble in water, methanol, ethanol, acetonitrile, DMF and DMSO to give stable solutions at room temperature, moderately soluble in acetone, and practically insoluble in THF, chloroform and benzene.

3.2. *Molar conductance and infrared spectra*

The molar conductance value ($\Lambda = 255\ \Omega^{-1}\,cm^2\,mol^{-1}$ in 1×10^{-3} mol L^{-1} acetonitrile solution) of the binuclear copper(II) complex falls in the expected range for 1 : 2 electrolytes [15], indicating that the two perchlorate anions are situated outside the metal coordination sphere. The IR spectrum of the free ligand show a sharp band at 1701 cm^{-1}, which is attributed to N=C–O vibration. However, in the IR spectrum of binuclear complex, the band shifts considerably toward lower wavenumber (1633 cm^{-1} indicating that oxygen and nitrogen atoms of the N=C–O are coordinated to the metal ions to form oxamido-bridged binuclear complex. In addition, a broad and intense band centered at 1092 cm^{-1}, and a strong sharp band at 625 cm^{-1}, typical for a non-coordinated perchlorate group [16], were observed for the binuclear complex. The conductance data and the IR spectrum are consistent with the crystal structure of this binuclear complex (*vide infra*).

3.3. *Description of the crystal structure*

The asymmetric unit of the complex is composed of half a binuclear cation $[Cu_2(heap)]^{2+}$, one perchlorate anion, and one lattice water molecule. An ORTEP view of the binuclear cation is illustrated in figure 1. Selected geometric parameters are summarized in table 2. The copper atom is in a distorted square-planar environment and the plane is defined by two nitrogen atoms (N3, N7) and two oxygen atoms

($O1^i$, O10). The maximum displacement of the four atoms from this plane is 0.0703(15) Å ($O1^i$ and O10) and the copper atom lies 0.0347(15) Å out of this mean plane. The Cu–N3 (amido) bond [1.930(3) Å] is shorter than the Cu–N7 (imine) bond [1.977(3) Å], which is consistent with the stronger donor ability of the deprotonated amido nitrogen compared with the imine nitrogen [17]. The bond distances of O1–C2 [1.280(4) Å] and N3–C2 [1.292(4) Å] indicate that the bond order of O1–C2 is almost single whereas that of N3–C2 is double, suggesting that the ligand is an enol form as coordinated with copper(II) [18, 19].

The dinuclear unit is deprotonated at the oxamido group, and the bridging ligand adopts the *trans* conformation with an inversion center at the middle of the C2–$C2^i$ bond. It forms two five- and one six-membered chelate rings around each metal ion. Whereas the five-membered Cu–$O1^i$–$C2^i$–C2–N3 cycle is almost planar, another five-membered Cu–O10–C9–C8–N7 cycle takes on the envelope form and the six-membered Cu–N3–C4–C5–C6–N7 cycle adopts the chair form conformation. The oxamido bridge is planar as observed in other oxamido-bridged copper(II) complexes [12, 20] and the Cu···Cu separation within the binuclear unit is 5.1244(11) Å.

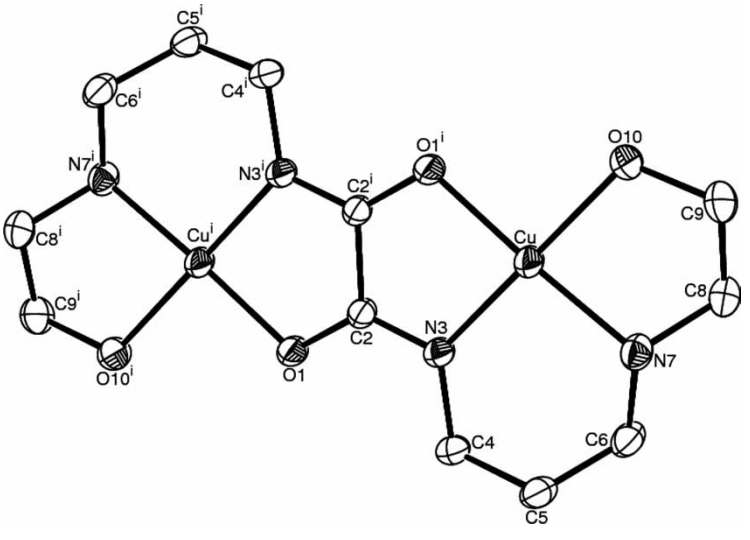


Figure 1. An ORTEP view of the binuclear cation. H atoms are omitted; displacement ellipsoids are drawn at the 30% probability level. [Symmetry code: (i) $-x$, $-y+1$, $-z+1$.]

Table 2. Selected bond distance and angles (Å, °) for the complex.

Cu–N3	1.930(3)	Cu–O10	1.967(3)
Cu–N7	1.977(3)	O1–C2	1.280(4)
Cu–$O1^i$	1.938(2)	N3–C2	1.292(4)
N3–Cu–$O1^i$	86.38(10)	$O1^i$–Cu–O10	92.77(10)
N3–Cu–O10	173.81(12)	$O1^i$–Cu–N7	176.29(11)
N3–Cu–N7	96.84(12)	O10–Cu–N7	84.23(12)

Symmetry code: (i) $-x$, $-y+1$, $-z+1$.

The distance (Å) and angles (°) of the hydrogen bonds for the complex are shown in table 3. A perspective view of the hydrogen bonding observed in this structure is depicted in figure 2. The perchlorate anions and the lattice water molecules are linked to each other *via* hydrogen bonds of O1W–H2W···O14A ($A = -x, -y+1, -z+1$) and O1W–H1W···O11B ($B = x, -y+3/2, z-1/2$) forming an infinite alternative chain, $-ClO_4^- - H_2O - ClO_4^-$–. Meanwhile, each dinuclear unit is joined to two ClO_4^- and two H_2O by means of hydrogen bonds of N7–H7···O12B and O10–H10···O1WC

Table 3. Distance (Å) and angles (°) of the hydrogen bonds for the complex.

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠(D–H···A)
O1W–H2W···O14A	0.86	2.11	2.944(5)	164.0
O1W–H1W···O11B	0.86	2.49	3.318(7)	161.3
O10–H10···O1WD	0.98	1.75	2.693(4)	160.9
N7–H7···O12B	0.91	2.31	3.087(5)	143.6

Symmetry codes: (A) $-x, -y+1, -z+1$; (B) $x, -y+3/2, z-1/2$; (D) $-x, -y+2, -z+1$.

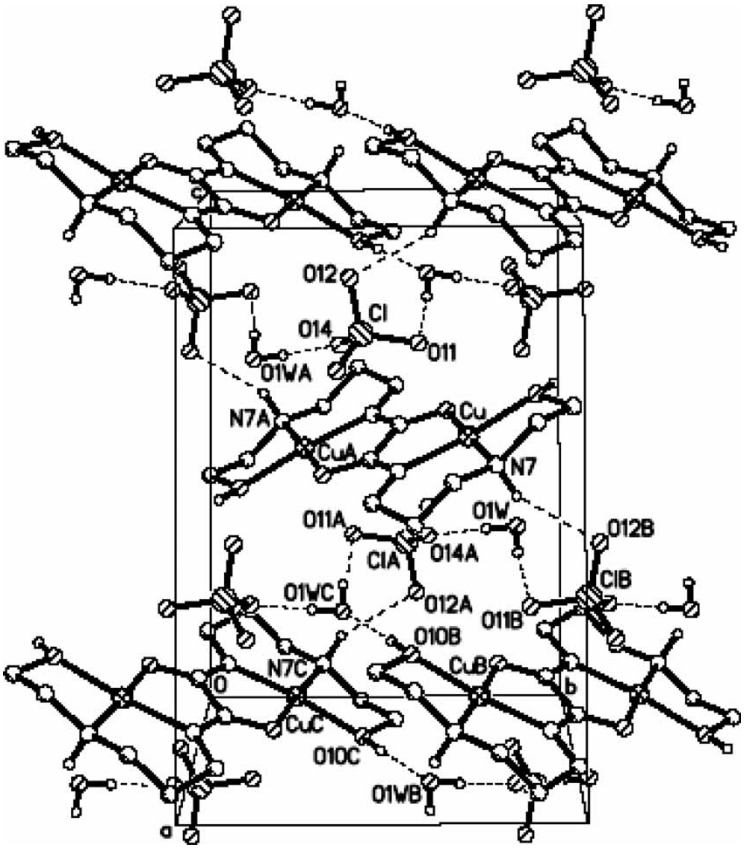


Figure 2. A packing diagram showing the intermolecular hydrogen bonding. [Symmetry codes: (A) $-x, -y+1, -z+1$; (B) $x, -y+3/2, z-1/2$; (C) $-x, y-1/2, -z+1/2$.]

Table 4. Qualitative antibacterial assay (100 mg mL^{-1}) .

	Diameter of inhibition zone (mm)				
Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. vulgaris*	*Ps. aeruginosa*
Ligand	13	–	12	–	–
Complex	16	12	14	–	–

Table 5. Quantitative antibacterial assay (MIC value, μg mL^{-1}).

Compound	*S. aureus*	*B. subtilis*	*E. coli*
Ligand	800	–	900
Complex	100	600	300

MIC = minimum inhibitory concentration, i.e. the lowest concentration to completely inhibit microbial growth.

($C = -x,\ y - 1/2,\ -z + 1/2$) respectively, which contribute to a two dimensional hydrogen-bonding supramolecular array.

3.4. *Antibacterial activity*

Preliminary antibacterial screening of the compounds using the paper disc method is given in table 4. The ligand showed activity against *S. aureus*, *E. coli* (inhibition zones less than 15 mm) and inactivity against *B. subtilis*, *P. vulgaris*, *Ps. aeruginosa*. The complex showed activity against *S. aureus*, *E. coli*, *B. subtilis* and inactivity against *P. vulgaris*, *Ps. aeruginosa*. The MIC values of the compounds by the microdilution broth method are given in table 5. The results indicated that the complex showed better activity than the ligand against the same bacteria and under identical experimental conditions. The increase in antibacterial activity of the complex may be due to the effect of the metal ion on the normal cell process. Complexation considerably reduces the polarity of the metal ion because of partial sharing of its positive charge with the donor groups. Such complexation could enhance the lipophilic character of the central metal atom, which subsequently favors its permeation through the lipid layers of cell membrane [21].

Supplementary material

Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with the Cambridge Crystallographic Data Center and allocated the deposition number: CCDC 287983.

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