

Synthesis and Crystal Structure of a Polymeric Copper(II) Complex Derived from 2-Hydroxy-5-methylbenzaldehyde Oxime with Antibacterial Activities

Ya-Li Sang* and Xue-Song Lin

Department of Chemistry and Chemical Engineering, Chifeng University, Chifeng 024001, P. R. China

* Corresponding author: E-mail: sangyali0814@126.com

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Abstract

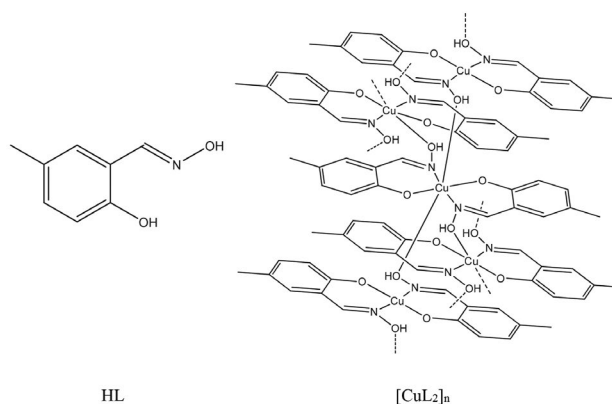
A centrosymmetric O-bridged polynuclear copper(II) complex, $[\text{CuL}_2]_n$, where L is the deprotonated form of the Schiff base ligand 2-hydroxy-5-methylbenzaldehyde oxime, has been prepared and characterized by IR, UV and single-crystal X-ray determination. There is a crystallographic inversion center in the complex. The Cu atom in the complex is coordinated by the phenolate oxygen, imino nitrogen and hydroxyl oxygen atoms from two Schiff base ligands, forming octahedral geometry. The complex was tested *in vitro* for its antibacterial activity.

Keywords: Schiff base; copper complex; synthesis; crystal structure; antibacterial activity

1. Introduction

Schiff bases are readily synthesized by the condensation reaction of carbonyl compounds with primary amines.¹ Schiff bases have been widely investigated for their biological activities, such as antibacterial and antitumor activities,² biomimetic catalytic properties, *etc.*³ Metal complexes of Schiff bases have also been received much attention. These complexes not only play an important role in the development of coordination chemistry related to catalysis and enzymatic reactions, magnetism and molecular architectures,⁴ but also exhibit interesting biological activities.⁵

In recent years, a number of Schiff bases derived from salicylaldehyde and its derivatives with various amines, and their complexes have been reported.⁶ Most of the compounds show versatile biological properties especially antibacterial activities.⁷ In addition, copper complexes show effective biological activities.⁸ In the present work, we choose 2-hydroxy-5-methylbenzaldehyde oxime (HL) as ligand, to prepare a novel polymeric copper complex $[\text{CuL}_2]_n$. To our knowledge, there have been no complexes derived from HL reported so far. The antibacterial activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas fluorescens*, were evaluated for the Schiff base and the copper complex.



Scheme 1. The Schiff base HL and the copper complex

2. Experimental

2. 1. Materials and Measurements

2-Hydroxy-5-methylbenzaldehyde, hydroxylamine hydrochloride, and copper perchlorate hexahydrate with AR grade were obtained from Aldrich and were used as received. Elemental analyses were performed using a Perkin-Elmer 240C analytical instrument. Infrared spectra were recorded on a Nicolet 5DX FT-IR spectrophotometer

with KBr pellets. ^1H NMR spectrum was recorded on a Bruker instrument at 300 MHz. UV-Vis spectra were recorded on a JASCO V-570 spectrophotometer. Molar conductance was measured with a Shanghai DDS-11A conductometer.

Caution! Although no problems were encountered in our work, perchlorate salts are potentially explosive. Therefore, only a small amount of copper perchlorate should be used at a time and handled with proper care.

2. 2. Synthesis of HL

Hydroxylamine hydrochloride (0.70 g, 0.010 mol) and NaOH (0.40 g, 0.010 mol) were reacted in absolute ethanol (30 mL). The solid was removed by filtration. To the filtrate an ethanol solution of 2-hydroxy-5-methylbenzaldehyde (1.36 g, 0.01 mol) was added with stirring. The mixture was stirred at room temperature for 30 min to give yellow solution. The solution was evaporated to give yellow powder, which was recrystallized from methanol and dried in air. Yield: 87%. Anal. Calcd. for $\text{C}_8\text{H}_9\text{NO}_2$ (%): C, 63.56; H, 6.00; N, 9.27. Found (%): C, 63.45; H, 6.12; N, 9.15. ^1H NMR (d^6 -DMSO): δ : 2.32 (s, 6H, CH_3), 6.87 (d, 1H, ArH), 7.14 (d, 1H, ArH), 7.53 (s, 1H, ArH), 8.28 (s, 1H, $\text{CH}=\text{N}$), 11.71 (s, 1H, OH), 12.23 (s, 1H, OH). ^{13}C NMR (d^6 -DMSO): δ : 21.2, 116.7, 118.1, 130.5, 131.3, 133.0, 146.7, 157.2.

2. 3. Synthesis of $[\text{CuL}_2]_n$

To an ethanolic solution (15 mL) of HL (15.1 mg, 0.10 mmol) an ethanolic solution (10 mL) of copper perchlorate hexahydrate (37.1 mg, 0.10 mmol) was added with stirring. The mixture was stirred for half an hour and filtered. The filtrate was kept undisturbed at room temperature to slowly evaporate for a few days, generating blue crystals suitable for X-ray diffraction. Crystals were isolated by filtration and dried in air. Yield 37% with respect to HL. Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{CuN}_2\text{O}_4$ (%): C, 52.82; H, 4.43; N, 7.70. Found (%): C, 52.63; H, 4.55; N, 7.81.

2. 4. X-ray Crystallography

A suitable single crystal with high quality of the complex was selected and mounted on a Bruker Smart 1000 CCD area-detector diffractometer with graphite monochromatized Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$). Diffraction data for the complex were collected by ω scan mode at 298(2) K. Data reduction and cell refinement were performed by the SMART and SAINT programs.⁹ Empirical absorption correction was applied by using SADABS.¹⁰ The structure was solved by direct methods and refined with the full-matrix least-squares technique using the SHELXL97 package.¹¹ The non-H atoms in the structure were subjected to refined anisotropic refinement. Hydrogen atoms were located in geometrically and treated with

the riding mode. Crystallographic data and experimental details for the complex are summarized in Table 1. Selected bond lengths and angles for the complex are listed in Table 2.

Table 1. Crystallographic and experimental data for the copper complex

Parameter	Value
Chemical formula	$\text{C}_{16}\text{H}_{16}\text{CuN}_2\text{O}_4$
Formula weight	363.85
T (K)	298(2)
Crystal system	orthorhombic
Space group	$Pbca$
a ($\text{\AA}$)	7.5170(5)
b ($\text{\AA}$)	6.4796(4)
c ($\text{\AA}$)	32.076(2)
V ($\text{\AA}^3$)	1562.3(2)
Z	4
ρ (g/cm^3)	1.547
μ (Mo-K α) (mm^{-1})	1.419
$F(000)$	748
No. of measured reflections	12412
No. of unique reflections	1440
No. of observed reflections	1269
Parameters/restraints	107/0
R_{int}	0.0234
Goodness of fit on F^2	1.300
R_1, wR_2 [$I \geq 2\sigma(I)$] ^a	0.0397, 0.0859
R_1, wR_2 (all data) ^a	0.0450, 0.0884
$\Delta\rho_{\text{max}}/\Delta\rho_{\text{min}}$, e $\text{\AA}^{-3}$	0.269, -0.254

$$^a R_1 = \Sigma |F_o| - |F_c| / \Sigma |F_o|, wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}.$$

Table 2. Selected bond lengths ($\text{\AA}$) and angles ($^\circ$) for the copper complex

Bond	$d, \text{\AA}$	Bond	$d, \text{\AA}$
Cu(1)–O(1)	1.921(2)	Cu(1)–N(1)	1.934(2)
Cu(1)–O(2A)	2.571(3)		
Angle	$\omega, ^\circ$	Angle	$\omega, ^\circ$
O(1)–Cu(1)–O(1A)	180	O(1)–Cu(1)–N(1A)	88.36(9)
O(1)–Cu(1)–N(1)	91.64(9)	N(1)–Cu(1)–N(1A)	180
O(1)–Cu(1)–O(2A)	98.85(9)	N(1)–Cu(1)–O(2A)	84.28(9)
O(1)–Cu(1)–O(2B)	81.15(9)	N(1)–Cu(1)–O(2B)	95.72(9)

Symmetry codes: A: $1 - x, 1 - y, -z$; B: $\frac{1}{2} + x, \frac{1}{2} - y, -z$.

2. 5. Antibacterial test

Antibacterial activities of the Schiff base and the complex were tested *in vitro* against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas fluorescens* using MH medium (Mueller–Hinton medium: casein hydrolysate 17.5 g, soluble starch 1.5 g, beef extract 1000 mL). The minimum inhibitory concentrations (MIC)

of the test compounds were determined by a colorimetric method using the dye MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide).¹² A solution of the compounds ($50 \mu\text{g mL}^{-1}$) in DMSO were prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. A specified quantity of the medium containing the compound was poured into microtitration plates. Suspension of the microorganism was prepared to contain about 10^5 colony forming units cfu mL^{-1} and applied to microtitration plates with serially diluted compounds in DMSO to be tested and incubated at 37°C for 24 h. After the MICs were visually determined on each of the microtitration plates, $50 \mu\text{L}$ of PBS (Phosphate Buffered Saline $0.01 \text{ mol}\cdot\text{L}^{-1}$, pH 7.4: $\text{Na}_2\text{HPO}_4\cdot 12\text{H}_2\text{O}$ 2.9 g, KH_2PO_4 0.2 g, NaCl 8.0 g, KCl 0.2 g, distilled water 1000 mL) containing 2 mg of MTT was added to each well. Incubation was continued at room temperature for 4–5 h. The content of each well was removed, and $100 \mu\text{L}$ of isopropyl alcohol containing 5% $1.0 \text{ mol}\cdot\text{L}^{-1}$ HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density (OD) was measured with a microplate reader at 550 nm. The observed MICs are presented in Table 3.

Table 3. Antibacterial activities of the compounds

	MIC ($\mu\text{g mL}^{-1}$)			
	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Pseudomonas fluorescens</i>	<i>Staphylococcus aureus</i>
HL	> 100	12.5	> 100	25
$[\text{CuL}_2]_n$	3.12	1.56	12.5	1.56
Penicillin B	1.3	> 100	> 100	2.1
Kanamycin G	0.78	3.12	3.12	0.78

3. Results and Discussion

The Schiff base HL was readily prepared by the reaction of 2-hydroxy-5-methylbenzaldehyde with hydroxylamine in ethanol. The copper complex was prepared by reaction of equimolar quantities of the Schiff base ligand and copper perchlorate hexahydrate in ethanol. The molar conductivities of the copper complex measured in acetonitrile at concentration of 10^{-3} and 10^{-4} M are 25 and $7.0 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$, indicating the dissociation of the polymeric complex to form single $[\text{CuL}_2]$ units in such solution.¹³

3. 1. Crystal structure Description

Figure 1 gives the perspective view of the copper complex. The molecule of the complex possesses crystallographic inversion center symmetry, with the inversion center located at the Cu atom. The smallest repeat unit of the complex contains $[\text{CuL}_2]$ unit. The adjacent $[\text{CuL}_2]$

units are bridged by hydroxyl groups, with Cu...Cu separation of $4.962(2) \text{ \AA}$. The Schiff base ligand forms one six-membered chelate ring with bite angle of $91.64(9)^\circ$. The Cu atom is in an octahedral coordination, with the two phenolate oxygen and two imino nitrogen donor atoms from two Schiff base ligands defining the equatorial plane, and with two hydroxyl oxygen donor atoms from symmetry related Schiff base ligands occupying the axial positions. The axial coordinate bonds are much longer than those in the equatorial plane, which is caused by the Jahn-Teller distortion. The *cis* bond angles are in the range $88.36(9)–91.64(9)^\circ$. The Cu–O and Cu–N bond lengths in the complex are comparable to the values observed in Schiff base copper(II) complexes.¹⁴ The molecules are linked by hydroxyl groups to form two-dimensional network (Figure 2).

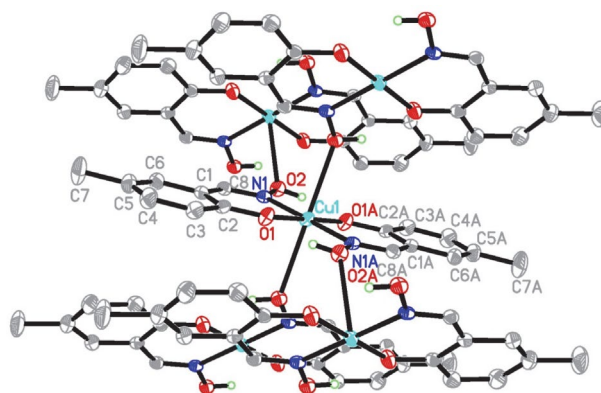


Figure 1. Molecular structure of the copper complex. Displacement is drawn at the 30% probability level. Atoms labeled with the suffix A are at the symmetry position $1 - x, 1 - y, -z$. Hydrogen atoms of the carbon atoms were omitted for clarity.

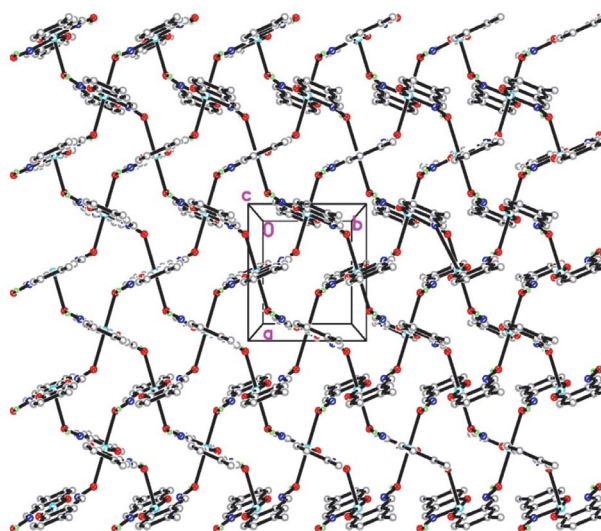


Figure 2. Molecular packing diagram of the copper complex, viewed along the *c* axis. Hydrogen atoms of the carbon atoms were omitted for clarity.

3. 2. IR and UV-Vis Spectra

The IR spectra of the free Schiff base and the copper complex provide information about the metal-ligand bonding. The weak and broad absorptions at 3350–3500 cm^{-1} are assigned to the stretching vibrations of the phenolic O–H group of the compounds. Several bands in the range of 2900–3150 cm^{-1} are assigned to the characteristic absorption of CH groups. The phenolic $\nu(\text{C}=\text{O})$ in the spectrum of the Schiff base is observed as a medium band at 1278 cm^{-1} . However, in the spectrum of the complex, the absorption appears at 1287 cm^{-1} . The strong band at 1639 cm^{-1} of the free Schiff base is assigned to the azomethine group, $\nu_{\text{C}=\text{N}}$,¹⁵ which is observed at low wave number of 1627 cm^{-1} for the complex, indicating the coordination of the imino nitrogen atom to the Cu atom. The newly observed bands in the region 450–650 cm^{-1} can be assigned to the Cu–O and Cu–N bonds.

The electronic spectra of the compounds in acetonitrile were recorded in the range of 200–800 nm. The intense absorption band at 270 nm may be assigned to intra-ligand π – π transitions in the complex. The weak absorptions centered at 350 nm may be assigned to the phenolate of Schiff base ligand to Cu center charge transfer band (LMCT). Unlike the spectrum of the free ligand, much weaker and less well-defined broad band found in the spectrum of the complex at 605 nm which is assigned to the d – d transition. The transition is typical for square-planar copper(II) complexes,¹⁶ which indicates that the complex dissociated to form $[\text{CuL}_2]$ units with square planar geometry in such solution.

3. 3. Antibacterial Activity

The Schiff base HL and the complex were screened *in vitro* for antibacterial activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas fluorescens* by the MTT method. The MICs of the compounds against the bacteria are presented in Table 3. Penicillin B was used as a reference.

The Schiff base HL shows medium antibacterial activities against *Escherichia coli* and *Staphylococcus aureus*, and no activity against *Bacillus subtilis* and *Pseudomonas fluorescens*. In general, the copper complex has stronger activities against the bacteria than the free Schiff base. The complex has strong activity against *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*, and medium activity against *Pseudomonas fluorescens*. The present complex has stronger activities against *Bacillus subtilis* and *Escherichia coli* than the copper complex we reported recently.¹⁷ It is quite interesting that the complex has better activity against *Staphylococcus aureus* than Penicillin B, and better activity against *Escherichia coli* than Kanamycin G, which deserve further study and to explore new antibacterial drugs.

4. Conclusion

A new centrosymmetric O-bridged polynuclear copper(II) complex derived from 2-hydroxy-5-methylbenzaldehyde oxime has been prepared and characterized. The Cu atom in the complex is in octahedral coordination. The antibacterial activities of the Schiff base and the complex were assayed. The results indicated that the complex is a potential antibacterial material.

5. Supplementary Material

CCDC reference number 1445981 for the copper complex contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk, or from Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.

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Povzetek

Sintetizirali smo centrosimetrični O-premosteni polimerni bakrov(II) kompleks, $[\text{CuL}_2]_n$, kjer je L deprotonirana oblika Schiffove baze 2-hidroksi-5-metilbenzaldehyd oksim, ter ga okarakterizirali z IR, UV in monokristalno rentgensko difrakcijo. Kompleks vsebuje kristalografski center inverzije. V kompleksu je Cu atom koordiniran s fenolnimi kisikovimi atomi, imino dušikovim atomom in hidroksilnim kisikovim atomom dveh ligandov Schiffove baze in ima oktaedrično geometrijo. Kompleks smo testirali *in vitro* za antibakterijsko aktivnost.