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Synthesis, crystal structures and xanthine oxidase inhibitory activities of two copper(II) complexes with Schiff bases

Yan-Qin Cui · Zhong-Lu You · Xiao-Fang Li · Xiao-Ling Wang · Yu-Ping Ma · Che Wang · Cheng-Lu Zhang

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Abstract Two azido-coordinated Schiff base Cu(II) complexes with the formulae $[Cu(L1)(N_3)]\cdot MeOH$ and $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$, where L1 is the deprotonated form of 2-chloro-2-[(2-ethylaminoethylimino)methyl]phenol, and L2 is the deprotonated form of 2,4-dibromo-6-[(2-dimethylaminoethylimino)methyl]phenol, have been synthesized and characterized by physico-chemical and spectroscopic methods. The X-ray crystal structures of both complexes have been determined. The Cu atom in $[Cu(L1)(N_3)]\cdot MeOH$ is four-coordinate in a square planar geometry, while $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ is five-coordinate with a square pyramidal geometry. The molecules in $[Cu(L1)(N_3)]\cdot MeOH$ are linked by intermolecular O–H···O and N–H···O hydrogen bonds, forming dimers. The molecules in $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ are linked through end-on azido bridges, forming one-dimensional chains. The xanthine oxidase inhibitory activities of both complexes were evaluated.

Introduction

Xanthine oxidase (EC 1.1.3.22; XO) catalyses the hydroxylation of hypoxanthine and xanthine to yield uric acid and superoxide anions. These superoxide anions have been linked to post-ischemic tissue injury and edema as well as to vascular permeability [1]. XO can also oxidize synthetic purine drugs, such as the antileukemic 6-mercaptopurine, with loss of their pharmacological properties [2]. Hence, control of the action of XO may help the therapy of some diseases. Nowadays, the treatment of gout makes use of allopurinol, a potent inhibitor of XO, which has been known for a long time [3]. However, given its side effects and its inability to prevent the formation of free radicals by the enzyme [4], research on new XO inhibitors is needed. Recently, we have reported some azido-bridged Schiff base complexes with urease inhibitory activities [5, 6] and a Schiff base zinc complex with XO inhibitory activity [7]. In this paper, two azido-coordinated copper(II) complexes, $[Cu(L1)(N_3)]\cdot MeOH$ and $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$, where L1 is the deprotonated form of 2-chloro-2-[(2-ethylaminoethylimino)methyl]phenol, and L2 is the deprotonated form of 2,4-dibromo-6-[(2-dimethylaminoethylimino)methyl]phenol, were synthesized and evaluated for their XO inhibitory activities (Scheme 1).

Experimental

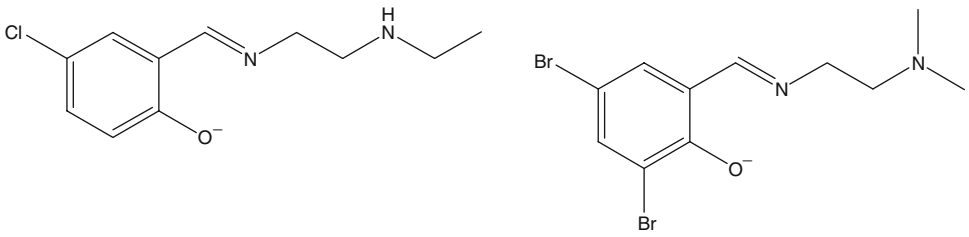
AR grade 5-chlorosalicylaldehyde, 3,5-dibromosalicylaldehyde, *N*-ethylethane-1,2-diamine and *N*,*N*-dimethylethane-1,2-diamine were purchased from Lancaster. Copper(II) acetate, sodium azide and solvents were purchased from Beijing Chemical Reagent Company and were used as received. Elemental analyses for C, H and N were performed on a Perkin–Elmer 240C elemental analyzer. IR spectra were recorded on a Jasco FT-IR/420 spectrophotometer as KBr pellets in the 4,000–200 cm^{-1} region.

Preparation of 2-chloro-2-[(2-ethylaminoethylimino) methyl]phenol (HL1)

To a methanol solution (20 mL) of 5-chlorosalicylaldehyde (156.6 mg, 1.0 mmol) was added a methanol solution

Y.-Q. Cui · Z.-L. You (✉) · X.-F. Li · X.-L. Wang · Y.-P. Ma · C. Wang · C.-L. Zhang
Department of Chemistry and Chemical Engineering, Liaoning Normal University, 116029 Dalian, People's Republic of China
e-mail: youzhonglu@yahoo.com.cn

Scheme 1 The deprotonated form of the Schiff bases



L1 L2

(20 mL) of *N*-ethylethane-1,2-diamine (88.2 mg, 1.0 mmol), with stirring. The mixture was stirred for 30 min at room temperature to give a yellow solution. Most of the methanol was evaporated to give a yellow precipitate. Yield: 99%. Anal. Found (%): C, 58.0; H, 6.9; N, 12.7. Calcd (%) for $C_{11}H_{15}ClN_2O$: C, 58.3; H, 6.7; N, 12.4.

Preparation of 2,4-dibromo-6-[(2-dimethylaminoethylimino)methyl]phenol (HL2)

To a methanol solution (20 mL) of 3,5-dibromosalicylaldehyde (280.0 mg, 1.0 mmol) was added a methanol solution (20 mL) of *N*,*N*-dimethylethane-1,2-diamine (88.2 mg, 1.0 mmol), with stirring. The mixture was stirred for 30 min at room temperature to give a yellow solution. Most of the methanol was evaporated to give a yellow precipitate. Yield: 98%. Anal. Found (%): C, 37.5; H, 4.1; N, 8.3. Calcd (%) for $C_{11}H_{14}Br_2N_2O$: C, 37.7; H, 4.0; N, 8.0.

Preparation of $[Cu(L1)(N_3)]\cdot MeOH$

To a methanol solution (5 mL) of 2-chloro-2-[(2-ethylaminoethylimino)methyl]phenol (22.7 mg, 0.1 mmol) and sodium azide (6.5 mg, 0.1 mmol) was added a methanol solution (5 mL) of copper(II) acetate (19.9 mg, 0.1 mmol), with stirring. The mixture was stirred for 10 min at room temperature and then filtered. Upon keeping the filtrate in air for 3 days, blue block-shaped crystals of the complex, suitable for X-ray diffraction, were formed at the bottom of the vessel on slow evaporation of the solvent. Yield: 63%. Anal. Found (%): C, 39.3; H, 5.3; N, 19.7. Calcd (%) for $C_{12}H_{18}ClCuN_5O_2$: C, 39.7; H, 5.0; N, 19.3.

Preparation of $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$

$[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ was prepared in methanol solution by a similar procedure as that described for $[Cu(L1)(N_3)]\cdot MeOH$ with 2-chloro-2-[(2-ethylaminoethylimino)methyl]phenol replaced by 2,4-dibromo-6-[(2-dimethylaminoethylimino)methyl]phenol (35.0 mg, 0.1 mmol). Blue block-shaped crystals of the complex were obtained after 7 days. Yield: 71%. Anal. Found (%): C, 29.4; H, 3.2; N, 15.0. Calcd (%) for $C_{11}H_{13}Br_2CuN_5O$: C, 29.1; H, 2.9; N, 15.4.

X-ray crystallography

Diffraction intensities for the two complexes were collected at 298(2) K using a Bruker SMART 1000 CCD area-detector with Mo-$K\alpha$ radiation ($\lambda = 0.71073$ Å). The collected data were reduced with the SAINT program [8], and multi-scan absorption corrections were performed using the SADABS program [9]. Both structures were solved by direct methods. The complexes were refined against F^2 by full-matrix least-squares methods using the SHELXTL package [10]. All of the non-hydrogen atoms were refined anisotropically. H2A attached to N2 in $[Cu(L1)(N_3)]\cdot MeOH$ was located from a difference Fourier map and refined isotropically, with N–H distance restrained to 0.90(1) Å, and with $U_{iso}(H)$ value constrained to 0.08 Å^2. Other hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. The crystallographic data for both complexes are summarized in Table 1. Selected bond lengths and angles are given in Table 2. Crystallographic data for the complexes have been deposited with the Cambridge Crystallographic Data Center (CCDC 638042 for $[Cu(L1)(N_3)]\cdot MeOH$ and 638051 for $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$).

XO inhibitory test

The XO inhibition tests were carried out in triplicate. Xanthine oxidase from cow's milk was purchased from Sigma–Aldrich (St. Louis, MO, USA). The XO activities with xanthine as the substrate were measured spectrophotometrically, based on the procedure reported by Kong et al. [11], with modification. The activity of XO was measured by uric acid formation monitored at 295 nm. The assay was performed in a final volume of 1 mL 50 mM K_2HPO_4 pH 7.8 in a quartz cuvette. The reaction mixture contained 200 μL of 84.8 μg/mL xanthine in 50 mM K_2HPO_4. The reaction was started by addition of 66 μL 37.7 mU/mL XO. The reaction was monitored for 6 min at 295 nm, and the product is expressed as μmol uric acid per minute. The kinetics of the reactions were linear during the 6 min of monitoring. The test compounds dissolved initially in DMSO were incorporated in the enzyme assay to assess their inhibitory activity at different concentrations, in

Table 1 Crystallographic data for the complexes

Complex	$[Cu(L1)(N_3)]\cdot MeOH$	$[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$
Chemical formula	$C_{12}H_{18}ClCuN_5O_2$	$C_{11}H_{13}Br_2CuN_5O$
Fw	363.3	454.6
Crystal shape/color	Block/blue	Block/blue
Crystal size (mm)	0.25 × 0.12 × 0.05	0.22 × 0.20 × 0.10
T (K)	298(2)	298(2)
λ (Mo*Kα*) (Å)	0.71073	0.71073
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/n$	*Pbca*
a (Å)	11.892(2)	7.104(1)
b (Å)	7.159(1)	19.035(1)
c (Å)	18.410(3)	22.532(2)
β (°)	100.997(2)	
V (Å^3)	1538.6(4)	3046.9(5)
Z	4	8
μ (Mo*Kα*) (cm^{-1})	1.604	6.681
T_{min}	0.690	0.321
T_{max}	0.924	0.555
D_c (g cm^{-3})	1.569	1.982
No. of measured reflections	11,961	24,459
No. of unique reflections and R_{int}	3,183 and 0.0877	3,509 and 0.0486
No. of observed reflections	1,914	2,597
Data/restraints/parameters	3,183/1/196	3,509/0/183
Goodness of fit on F^2	1.049	1.027
R_1 [$I \geq 2\sigma(I)$]	0.0663	0.0312
wR_2 [$I \geq 2\sigma(I)$]	0.1369	0.0671
R_1 (all data)	0.1185	0.0510
wR_2 (all data)	0.1557	0.0748
Large diff. peak and hole (e Å^{-3})	0.389, −0.398	0.579, −0.390

Table 2 Selected bond lengths (Å) and angles (°) for the complexes

$[Cu(L1)(N_3)]\cdot MeOH$			
Bond lengths			
Cu1–O1	1.913(3)	Cu1–N1	1.950(4)
Cu1–N2	2.017(4)	Cu1–N3	2.054(5)
Cu1–N3^{i}	2.914(4)		
Bond angles			
O1–Cu1–N1	91.6(2)	O1–Cu1–N2	176.2(2)
N1–Cu1–N2	84.8(2)	O1–Cu1–N3	91.0(2)
N1–Cu1–N3	176.0(2)	N2–Cu1–N3	92.6(2)
O1–Cu1–N3^{i}	90.1(2)	N1–Cu1–N3^{i}	87.2(2)
N2–Cu1–N3^{i}	88.7(2)	N3–Cu1–N3^{i}	95.8(2)
$[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$			
Bond lengths			
Cu1–O1	1.917(2)	Cu1–N1	1.950(2)
Cu1–N2	2.053(2)	Cu1–N3	1.978(2)
Cu1–N5^{ii}	2.761(3)		
Bond angles			
O1–Cu1–N1	92.6(1)	O1–Cu1–N3	89.7(1)
N1–Cu1–N3	174.2(1)	O1–Cu1–N2	177.3(1)
N1–Cu1–N2	84.7(1)	N3–Cu1–N2	92.9(1)
O1–Cu1–N3^{ii}	89.9(1)	N1–Cu1–N3^{ii}	83.5(1)
N2–Cu1–N3^{ii}	90.2(1)	N3–Cu1–N3^{ii}	101.8(1)

Symmetry codes: (i) $1 - x, -1/2 + y, 1 - z$; (ii) $1/2 - x, 1/2 + y, z$

Table 3 Average IC_{50} values of the tested compounds against XO

Tested materials	IC_{50} (μM)
$[Cu(L1)(N_3)]\cdot MeOH$	25.33
$[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$	21.27
HL1	>100
HL2	>100
Allopurinol	10.30

comparison with allopurinol as the standard reference. The final concentration of DMSO in the assay was 5%. Control experiments showed that DMSO, at a final concentration of 5%, did not affect the enzyme assay. XO inhibitory activity was expressed as the percentage inhibition of XO in the above-mentioned assay mixture system or as the concentration resulting in half-maximal enzyme velocity (IC_{50}). The average results are summarized in Table 3.

Results and discussion

The Schiff bases HL1 and HL2 were readily prepared in excellent yields in methanol solution. Both compounds are stable in air at room temperature. They are soluble in methanol, ethanol and acetonitrile, but insoluble in water. The blue crystals of both copper(II) complexes are stable in air at room temperature, and soluble in DMF, DMSO, methanol, ethanol and acetonitrile, but insoluble in water. The UV–Vis spectra of the complexes show weak absorption bands at 380 and 367 nm, respectively, indicating that both complexes are stable in solution ($DMSO:H_2O = 1:20$) at a concentration of 10^{-4} mol/L. The molar conductance values of the complexes measured in solution at concentrations of 10^{-3} mol/L are 17.8 and 15.3 μS/cm, indicating the non-electrolytic nature of the complexes in solution [12].

Structures of the complexes

Figures 1 and 2 give perspective views of the complexes. $[Cu(L1)(N_3)]\cdot MeOH$ is a mononuclear copper complex,

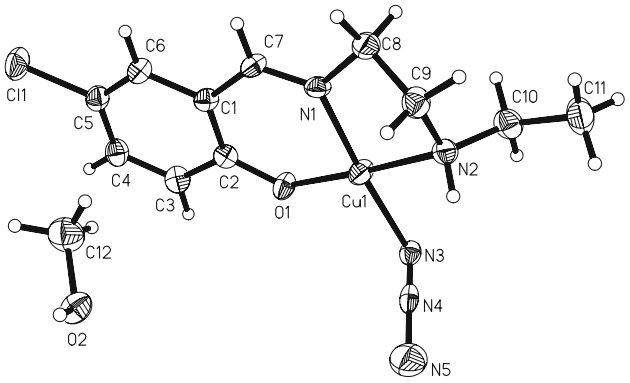


Fig. 1 Molecular structure of $[Cu(L1)(N_3)]\cdot MeOH$ at 30% probability ellipsoids

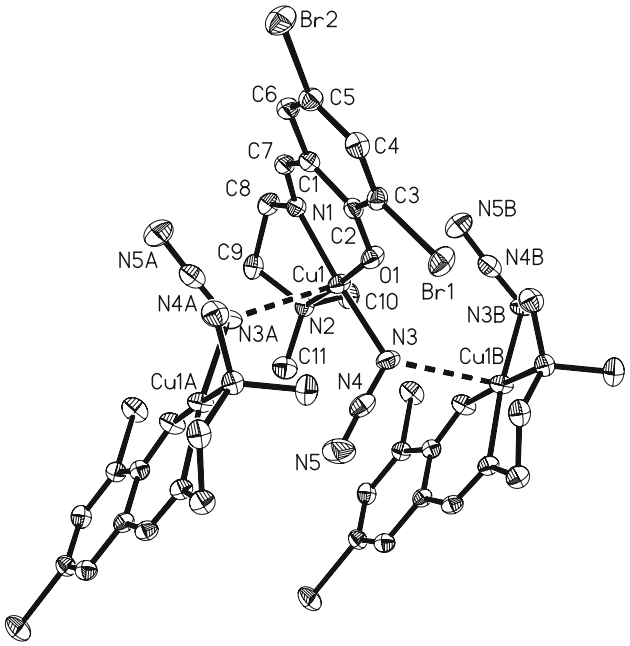


Fig. 2 Molecular structure of $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ at 30% probability ellipsoids. Atoms labeled with the suffix A and B are at the symmetry positions $-1/2 + x,\ 1/2 - y,\ 1 - z$ and $1/2 + x,\ 1/2 - y,\ 1 - z$, respectively. H atoms have been omitted for clarity

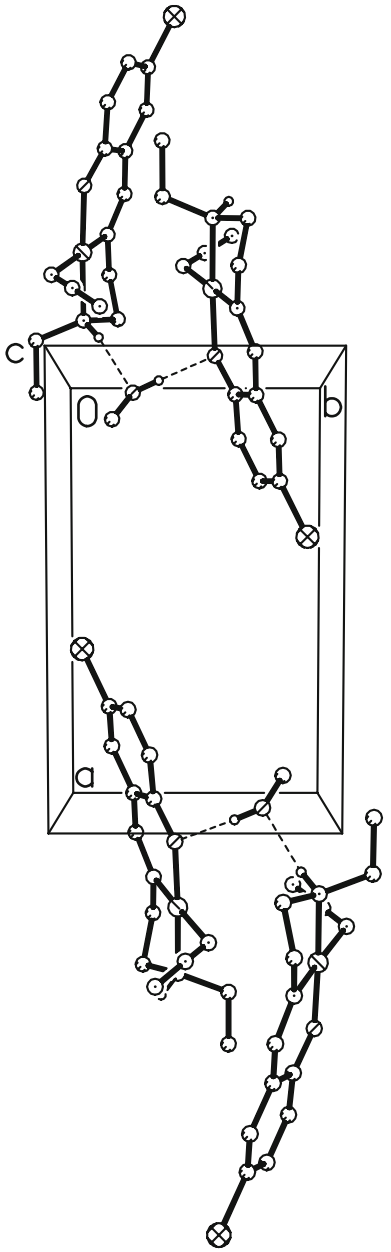


Fig. 3 The molecular packing of $[Cu(L1)(N_3)]\cdot MeOH$ viewed along the *c* axis. Intermolecular hydrogen bonds are shown as dashed lines

which consists of a methanol solvate, while $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ is an azido-bridged polymeric complex, which has no solvates.

The Cu atom in $[Cu(L1)(N_3)]\cdot MeOH$ has a square planar coordination geometry and is coordinated by one phenolic O, one imine N and one amine N atoms of L1, and by one N atom of an azide ligand. The Cu atom in $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ has square pyramidal coordination and is coordinated by one phenolic O, one imine N and one amine N atoms of L2, and by the terminal N atom of one bridging azido ligand, defining the base plane. The terminal N atom of another bridging azido ligand occupies the apical position.

The coordinate bond lengths and angles in the complexes are comparable to each other, and also comparable to those observed in other similar Schiff base copper(II) complexes [13–15]. The apical bond length of 2.761(3) Å in $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ is also comparable to those seen for other Schiff base copper(II) complexes with square pyramidal coordination [16–18]. As expected, the bonds involving the amine atom N2 (2.017(4) Å for $[Cu(L1)(N_3)]\cdot MeOH$ and 2.053(2) Å for $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$) are a little longer than those involving imine atom N1 (1.950(4) Å for $[Cu(L1)(N_3)]\cdot MeOH$ and 1.950(2) Å for $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$). Each

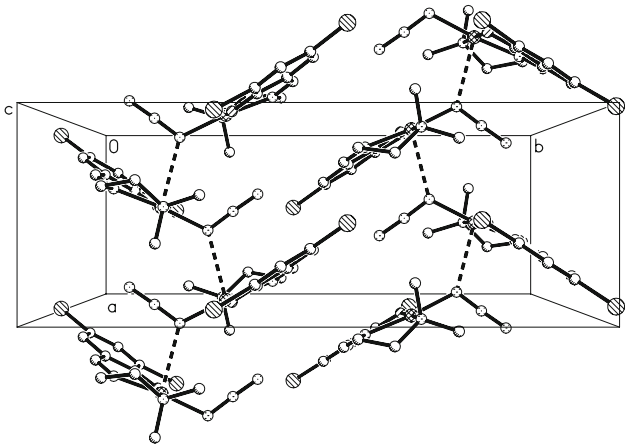


Fig. 4 The molecular packing of $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$ viewed along the *c* axis

azido ligand is nearly linear and shows bent coordination mode with the metal atoms. The Cu···Cu distances are 4.509(3) Å in $[Cu(L1)(N_3)]\cdot MeOH$ and 4.325(2) Å in $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$, respectively.

In the crystal structure of $[Cu(L1)(N_3)]\cdot MeOH$, adjacent molecules are linked by methanol molecules through intermolecular O–H···O and N–H···O hydrogen bonds, forming dimers (Fig. 3). In the crystal structure of $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$, the molecules are linked through end-on azido bridges, forming polymeric chains running along the *a* axis (Fig. 4).

IR spectra

The IR spectra of the Schiff bases and their complexes provide information about the metal–ligand bonding. Assignments are based on typical group frequencies. The weak and broad absorptions at about 3,420 cm^{-1} substantiate the presence of phenol groups in the Schiff bases, which are absent from the spectra of the complexes. The strong absorption bands at 1,643–1,645 cm^{-1} in the spectra of the Schiff bases are assigned to the azomethine groups, ν(C=N). These bands are shifted to lower wave numbers (1,636 cm^{-1}) in both complexes, consistent with coordination of the nitrogen atom of the azomethine to the copper atoms. The strong absorption bands arising from the Ar–O bonds in the Schiff bases are at about 1,200 cm^{-1}, which are located at higher frequencies (1,217 cm^{-1}) for both complexes. The strong absorption bands indicative of the bridging azide ligands appear at 2,045 cm^{-1} for $[Cu(L1)(N_3)]\cdot MeOH$ and at 2,047 cm^{-1} for $[Cu(L2)(\mu_{1,1}\text{-}N_3)]_n$.

XO inhibitory activities

The IC_{50} values for these compounds are given in Table 3. Both complexes show stronger XO inhibitory activity than those of the corresponding free Schiff bases, but less activity than the allopurinol used as a reference which has an IC_{50} value of 10.30 μM. When compared with the zinc(II) complex we reported previously [7], it can be seen that the XO inhibitory activities of the present two copper(II) complexes are much weaker.

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