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Solvent-influenced syntheses and crystal structures of two azido-bridged polynuclear copper(II) complexes derived from 2-[(3-methylaminopropylimino)methyl]phenol with urease inhibitory activities

Li-Li Ni · Zhong-Lu You · Lin Zhang · Che Wang · Kun Li

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Abstract An end-on azido-bridged dinuclear Cu(II) complex, $[Cu_2L_2(\mu_{1,1}\text{–}N_3)_2]\cdot CH_3OH$, and an end-on azido-bridged polynuclear Cu(II) complex, $[CuL(\mu_{1,1}\text{–}N_3)]_n$, derived from the Schiff base 2-[(3-methylaminopropylimino)methyl]phenol (HL), were synthesized and characterized by physico-chemical and spectroscopic methods. The two complexes were synthesized and crystallized with different solvents, methanol for $[Cu_2L_2(\mu_{1,1}\text{–}N_3)_2]\cdot CH_3OH$ and ethanol for $[CuL(\mu_{1,1}\text{–}N_3)]_n$. The Cu atom in each complex is five-coordinate in a square pyramidal geometry with one O and two N atoms of L, and one N atom of an azide ligand defining the basal plane, and with one N atom of another azide ligand occupying the apical position. The urease inhibitory activities of both complexes were evaluated.

Introduction

Polynuclear complexes play an important role in coordination chemistry due to their versatile structures and wide applications [1–3]. An efficient way to construct such polynuclear complexes is to use suitable bridging ligands, such as N_3^-, NCS^-, and CN^- [4–6]. Among the bridging ligands, azide is particularly interesting, which coordinates to the metal through end-on, end-to-end, and many other modes. However, we can hardly predict which coordination mode will be adopted by the azide group [7]. Urease (urea amidohydrolase; EC 3.5.1.5) is a nickel-containing metalloenzyme that catalyzes the hydrolysis of urea to form ammonia and carbon dioxide [8, 9]. High concentrations of ammonia arising from this reaction has undesirable consequences in medicine and agriculture [10]. Control of the activity of urease through the use of inhibitors could decrease the negative effects. Recently, a few metal complexes show urease inhibitory activities [11, 12]. In this paper, two azido-bridged polynuclear complexes, $[Cu_2L_2(\mu_{1,1}\text{–}N_3)_2]\cdot CH_3OH$ and $[CuL(\mu_{1,1}\text{–}N_3)]_n$, where L denotes an anionic form of 2-[(3-methylaminopropylimino)methyl]phenol (HL, Scheme 1), have been synthesized and characterized. The urease inhibitory activities were evaluated.

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

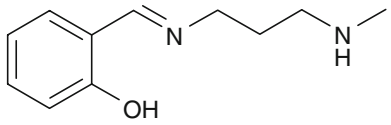
Experimental

Materials and methods

Salicylaldehyde and N-methylpropane-1,3-diamine of AR grade were purchased from Lancaster. Sodium azide and solvents were purchased from Beijing Chemical Reagent Company and were used as received. Copper(II) perchlorate was prepared by reaction of $Cu_2(OH)_2CO_3$ with perchlorate acid in water. Elemental analyses for C, H, and N were performed on a Perkin–Elmer 240C elemental analyzer. IR spectra were recorded on a Nicolet AVATAR 360 spectrophotometer as KBr pellets in the 4,000–400 cm^{-1} region.

Preparation of HL

To a methanol solution (20 mL) of salicylaldehyde (122.1 mg, 1.0 mmol), a methanol solution (20 mL) of *N*-methylpropane-1,3-diamine (88.1 mg, 1.0 mmol) was added with stirring. The mixture was stirred for 30 min at room temperature to give a yellow solution. Then, the



Scheme 1 Ligand HL

methanol was evaporated to give yellow oil of HL. Yield: 186 mg (97%). Anal. Calcd (%) for $C_{11}H_{16}N_2O$: C, 68.7; H, 8.4; N, 14.6. Found (%): C, 68.4; H, 8.5; N, 14.8. Characteristic IR data (cm^{-1}): 1645 (s).

Preparation of $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$

To a methanol solution (5 mL) of HL (19.2 mg, 0.1 mmol) and sodium azide (6.5 mg, 0.1 mmol), a methanol solution (5 mL) of copper(II) perchlorate (37.0 mg, 0.1 mmol) was added with stirring. The mixture was stirred for 10 min at room temperature and filtered. Upon keeping the filtrate in air for a week, blue block-shaped crystals of the complex, suitable for X-ray diffraction, were formed on slow evaporation of the solvent. Yield: 14.1 mg (45%). Anal. Calcd (%) for $C_{23}H_{34}Cu_2N_{10}O_3$: C, 44.2; H, 5.5; N, 22.4. Found (%): C, 44.9; H, 5.2; N, 23.3. Characteristic IR data (cm^{-1}): 3427 (b, w), 3218 (m), 2039 (s), 1618 (s).

Preparation of $[CuL(\mu_{1,1}–N_3)]_n$

$[CuL(\mu_{1,1}–N_3)]_n$ was prepared in ethanol solution by a similar procedure as that described for $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$. Blue block-shaped crystals of the complex were obtained after 5 days. Yield: 20.8 mg (70%). Anal. Calcd (%) for $C_{11}H_{15}CuN_5O$: C, 44.5; H, 5.1; N, 23.6. Found (%): C, 44.3; H, 5.3; N, 23.9. Characteristic IR data (cm^{-1}): 3232 (m), 2037 (s), 1617 (s).

Caution: Azide salts and perchlorate salts are potentially explosive and should be handled with small quantities with care.

X-ray crystallography

Diffraction intensities for the two complexes were collected at 298(2) K using a Bruker SMART 1000 CCD area detector with MoKα radiation ($\lambda = 0.71073$ Å). The collected data were reduced using the SAINT program [13], and multi-scan absorption corrections were performed using the SADABS program [14]. Both structures were solved by direct methods. The complexes were refined against F^2 by full-matrix least-squares methods using the SHELXTL program [15]. All of the non-hydrogen atoms were refined anisotropically. The amino H atoms in the complexes were located in difference Fourier maps and refined isotropically, with N–H distances restrained to 0.90(1) Å. All other H atoms were placed in calculated positions and constrained to ride on their parent atoms. The crystallographic data for the complexes are summarized in Table 1. Selected bond lengths and angles are given in Table 2. Hydrogen bonds are listed in Table 3. Crystallographic data for the complexes have been deposited with the Cambridge Crystallographic Data Center (CCDC 638055 for $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$, and 731413 for $[CuL(\mu_{1,1}–N_3)]_n$).

Table 1 Crystal data for the complexes

Complex	$[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$	$[CuL(\mu_{1,1}–N_3)]_n$
Chemical formula	$C_{23}H_{34}Cu_2N_{10}O_3$	$C_{11}H_{15}CuN_5O$
Fw	625.68	296.82
Crystal shape/color	Block/blue	Block/blue
Crystal size (mm)	0.31 × 0.27 × 0.22	0.22 × 0.16 × 0.11
T (K)	298(2)	298(2)
λ (MoKα) (Å)	0.71073	0.71073
Crystal system	Triclinic	Monoclinic
Space group	$P-1$	Cc
a (Å)	7.901(1)	12.427(2)
b (Å)	9.957(2)	17.568(3)
c (Å)	18.245(3)	6.876(2)
α (°)	86.966(2)	90
β (°)	78.953(2)	122.749(2)
γ (°)	74.586(2)	90
V (Å^3)	1358.1(4)	1262.4(4)
Z	2	4
μ (MoKα) (cm^{-1})	1.611	1.726
T (min)	0.635	0.703
T (max)	0.718	0.833
D_c (g cm^{-3})	1.530	1.562
Reflections/parameters	5451/353	2545/167
Unique reflections	3388	2229
Goodness of fit on F^2	0.975	0.975
R_{int}	0.0559	0.0297
R_1 [$I \geq 2\sigma(I)$]	0.0656	0.0356
wR_2 [$I \geq 2\sigma(I)$]	0.1563	0.0704
R_1 (all data)	0.1060	0.0416
wR_2 (all data)	0.1819	0.0729

Urease inhibitory test

The measurement of urease inhibitory activities was carried out according to the method reported by Tanaka [16]. Acetohydroxamic acid was used as a reference. Generally, the assay mixture, containing 25 μL of jack bean urease (10 kU/l) and 25 μL of the tested compounds of various concentrations (dissolved in DMSO/H_2O = 1:1 (v/v)), was

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

$[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$			
Bond lengths			
Cu1–O1	1.917(4)	Cu1–N1	1.958(4)
Cu1–N2	2.037(5)	Cu1–N5	2.342(5)
Cu1–N8	2.018(4)	Cu2–O2	1.910(4)
Cu2–N3	1.963(5)	Cu2–N4	2.007(5)
Cu2–N5	2.048(5)	Cu2–N8	2.356(5)
Bond angles			
O1–Cu1–N1	91.4(2)	O1–Cu1–N8	89.9(2)
N1–Cu1–N8	176.7(2)	O1–Cu1–N2	161.7(2)
N1–Cu1–N2	93.0(2)	N8–Cu1–N2	84.9(2)
O1–Cu1–N5	102.3(2)	N1–Cu1–N5	101.4(2)
N8–Cu1–N5	81.3(2)	N2–Cu1–N5	94.2(2)
O2–Cu2–N3	90.8(2)	O2–Cu2–N4	165.9(2)
N3–Cu2–N4	93.1(2)	O2–Cu2–N5	87.6(2)
N3–Cu2–N5	173.0(2)	N4–Cu2–N5	86.8(2)
O2–Cu2–N8	97.4(2)	N3–Cu2–N8	106.6(2)
N4–Cu2–N8	94.4(2)	N5–Cu2–N8	80.4(2)
$[CuL(\mu_{1,1}–N_3)]_n$			
Bond lengths			
Cu1–O1	1.926(4)	Cu1–N1	1.982(4)
Cu1–N2	2.048(4)	Cu1–N3	2.012(4)
$Cu1–N3^{\#1}$	2.524(4)		
Bond angles			
O1–Cu1–N1	90.5(2)	O1–Cu1–N3	88.6(2)
N1–Cu1–N3	158.4(2)	O1–Cu1–N2	173.8(2)
N1–Cu1–N2	95.5(2)	N3–Cu1–N2	86.3(2)
$O1–Cu1–N3^{\#1}$	87.3(2)	$N1–Cu1–N3^{\#1}$	92.0(2)
$N2–Cu1–N3^{\#1}$	91.2(2)	$N3–Cu1–N3^{\#1}$	109.5(2)

Table 3 Hydrogen bond distances (Å) and bond angles (°)

D–H···A	d(D–H)	d(H···A)	d(D···A)	Angle (D–H···A)
$[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$				
O3–H3A···O1	0.82	1.93	2.699(7)	156
N4–H4A···O3	0.89(5)	2.07(5)	2.958(8)	170(7)
N2–H2···O2	0.90(6)	2.12(4)	2.905(6)	145(6)
$[CuL(\mu_{1,1}–N_3)]_n$				
$N2–H2···N5^{\#1}$	0.899(10)	2.55(3)	3.216(6)	132(4)
$N2–H2···O1^{\#1}$	0.899(10)	2.42(3)	3.133(5)	137(4)

Symmetry transformation used to generate the equivalent atoms: #1: $x, -y, 1/2 + z$

preincubated for 1 h at 37 °C in a 96-well assay plate. Then, 0.2 mL of 100 mM N-(2-hydroxyethyl)piperazine-N′-(2-ethanesulfonic acid) buffer at pH 6.8 containing 500 mM urea and 0.002% phenol red were added and incubated at 37 °C. The reaction time, which was required to produce enough ammonium carbonate to raise the pH of the buffer from 6.8 to 7.7, was measured by a micro-plate reader (570 nm) with the end-point being determined by the color of phenol red indicator. The results are listed in Table 4.

Table 4 Inhibitory activities of urease

Tested material	IC_{50} (μM)
$[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$	61.3 ± 0.13
$[CuL(\mu_{1,1}–N_3)]_n$	63.2 ± 0.15
HL	>100
Copper(II) perchlorate	12.80 ± 0.27
Acetohydroxamic acid	42.12 ± 0.08

Results and discussion

The influence of the hydrogen bonds on the coordination modes of the azide groups has been discussed in a recent report [17]. In this paper, the two complexes were synthesized following the same procedures and starting materials, except for the solvents used in the synthesis and crystallization. The polarity of methanol is stronger than that of ethanol, which made the methanol molecules readily reside in the crystal structures of the complexes through hydrogen bonds [18, 19]. For $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$, there are three intramolecular N–H···O and O–H···O hydrogen bonds between the two CuL units, while for $[CuL(\mu_{1,1}–N_3)]_n$, there is one N–H···O hydrogen bond between the adjacent two CuL units, and one N–H···N hydrogen bond between the ligand L and the azide group. The tighter hydrogen linkage in $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ than that in $[CuL(\mu_{1,1}–N_3)]_n$ makes the distance of the adjacent Cu atoms in $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ shorter than that in $[CuL(\mu_{1,1}–N_3)]_n$. Thus, there are two end-on azide bridges between the adjacent Cu atoms in

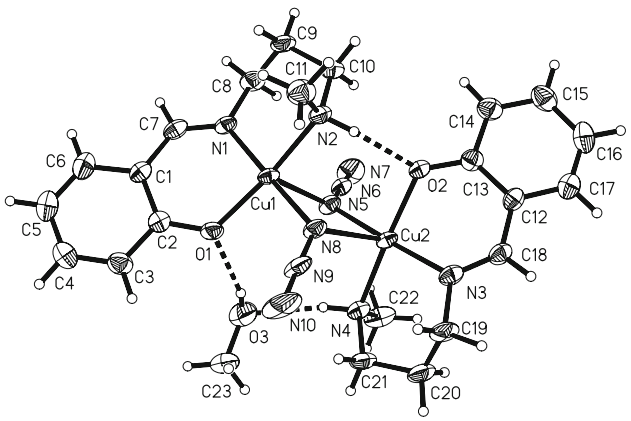


Fig. 1 Molecular structure of $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ at 30% probability ellipsoids. *Hydrogen bonds* are shown as *dashed lines*

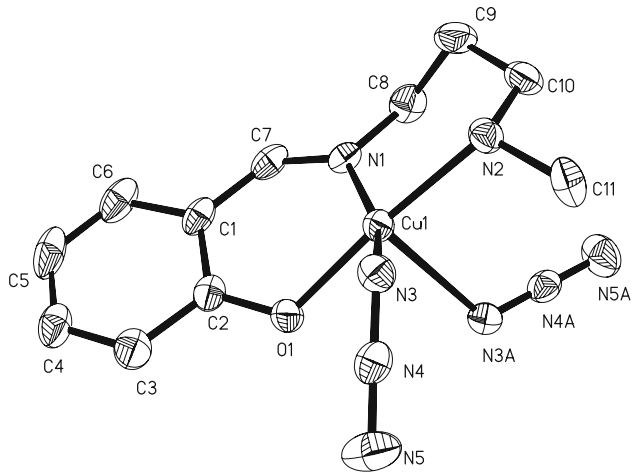


Fig. 2 The unit of $[CuL(\mu_{1,1}–N_3)]_n$ at 30% probability ellipsoids

$[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$, and one end-on azide bridge between those in $[CuL(\mu_{1,1}–N_3)]_n$.

Structures of $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ and $[CuL(\mu_{1,1}–N_3)]_n$

Figure 1 gives the perspective view of the complex $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$, and Fig. 2 gives the perspective view of the unit of the complex $[CuL(\mu_{1,1}–N_3)]_n$, respectively, together with the atomic-labeling systems. $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ is a double end-on azido-bridged dinuclear copper(II) complex, while $[CuL(\mu_{1,1}–N_3)]_n$ is a single end-on azido-bridged polynuclear copper(II) complex. $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ contains a methanol solvate, whereas $[CuL(\mu_{1,1}–N_3)]_n$ contains no solvent molecules of crystallization. The methanol molecule in $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ is linked to the complex molecule through N–H···O and O–H···O hydrogen bonds. With the exception of the methanol content in the case of $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$, the composition of the two compounds is the same, $[CuL(N_3)]$.

Each Cu atom in the complexes has square pyramidal coordination and is coordinated by one O and two N atoms of L, and by one N atom of a bridging azide ligand, defining the base plane, and by one N atom of another bridging azide ligand, occupying the apical position. The apical coordinate bond lengths in $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ are much shorter than those in $[CuL(\mu_{1,1}–N_3)]_n$, which is caused by the hydrogen bonds in the complexes. In $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$, there is one intramolecular O–H···O and two N–H···O hydrogen bonds between the two CuL units, while in $[CuL(\mu_{1,1}–N_3)]_n$, there is only one N–H···O hydrogen bond between the two CuL units, and one N–H···N hydrogen bond between the CuL and the adjacent azide ligand. All other bond lengths are comparable to each other and comparable with those observed in other Schiff base copper(II) complexes [20, 21]. As expected, the coordinate bonds involving amine N atoms are longer than those involving imine N atoms. Each bridging azide ligand is nearly linear and shows bent coordination mode with the metal atoms. The Cu···Cu distances are 3.306(2) Å in $[Cu_2L_2(\mu_{1,1}–N_3)_2]\cdot CH_3OH$ and 3.599(2) Å in $[CuL(\mu_{1,1}–N_3)]_n$.

In the crystal structure of $[CuL(\mu_{1,1}–N_3)]_n$, the $[CuL(\mu_{1,1}–N_3)]$ units are linked by Cu–N bonds and intermolecular N–H···O and N–H···N hydrogen bonds,

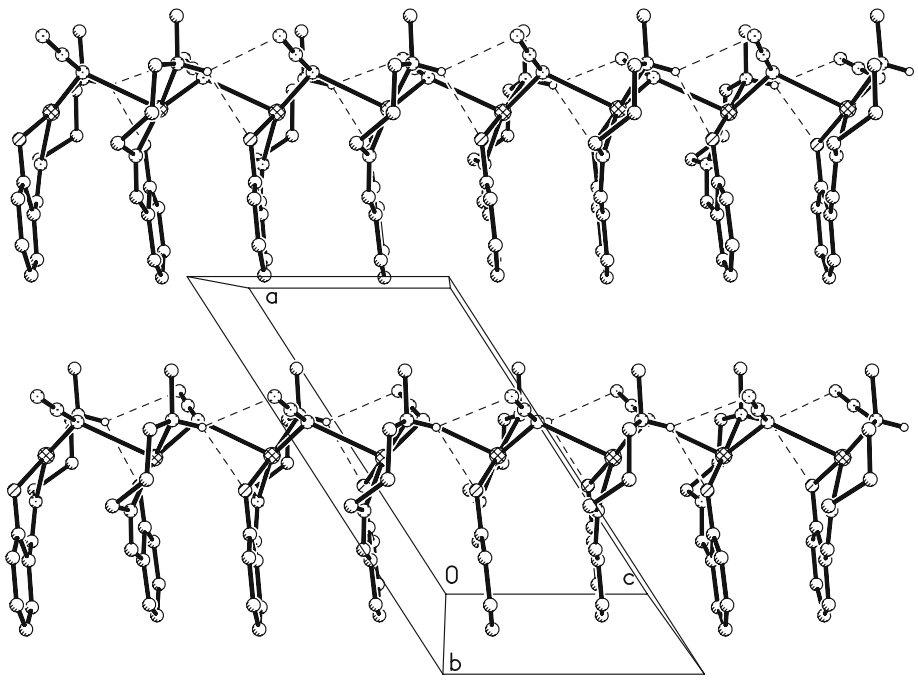


Fig. 3 The molecular packing of $[CuL(\mu_{1,1}–N_3)]_n$ viewed along the *b* axis. *Hydrogen bonds* are shown as *dashed lines*

forming an infinite one-dimensional chain running along the *c* axis (Fig. 3).

Urease inhibitory activities

The urease inhibitory activities of both complexes are comparable to each other, and slightly weaker than that of the acetohydroxamic acid co-assayed as a positive reference against the urease. The Schiff base HL shows no activity. As a comparison, the urease inhibitory activities of the two complexes are slightly lower than those we reported previously [21, 22].

Summary

It is evident from this discussion that the solvents used in the synthesis and crystallization can influence the composition and the hydrogen bonding pattern of the complexes. The urease inhibitory activities show that such complexes could be potential urease inhibitors.

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