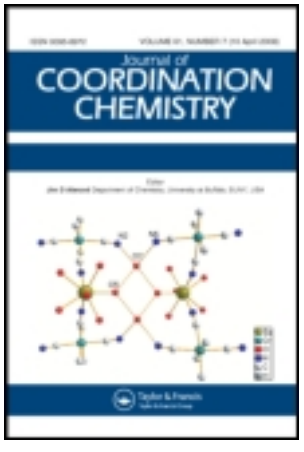

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Synthesis, characterization, and antimicrobial activities of a dinuclear copper(II) complex with bis(2-[(2-hydroxy-ethylimino)-methyl]-4,6-diiodo-phenol)

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Synthesis, characterization, and antimicrobial activities of a dinuclear copper(II) complex with bis(2-[(2-hydroxy-ethylimino)-methyl]-4,6-diiodo-phenol)

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A dinuclear copper(II) complex with a newly synthesized tridentate Schiff-base ligand 2-[(2-hydroxy-ethylimino)-methyl]-4,6-diiodo-phenol (**HL**), of formula $[Cu_2L_2Cl_2 \cdot C_4H_8O]$ (**1**), was prepared. Both the ligand and the complex were characterized by X-ray crystallography, confirming that the Schiff base is tridentate and its dinuclear copper(II) complex is five-coordinate from one nitrogen and two oxygens from L and two chlorides. The complex was assayed for antibacterial (*Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterobacter cloacae*) activities by the MTT method. Complex **1** exhibited better antimicrobial activity than the ligand.

Keywords: Schiff-base ligand; Dinuclear copper(II) complex; Antibacterial activity

1. Introduction

Salicylaldehyde Schiff bases and their metal complexes have a wide spectrum of antimicrobial properties [1–5]. Many researchers have studied the synthesis, characterization, and structure–activity relationship (SAR) of Schiff bases [6–9]. Salicylaldehyde derivatives, with one or more halogens in the aromatic ring, show antibacterial and antifungal activities [10], suggesting that the complexes of such Schiff bases would possess potential biological properties [11].

In this article, a new dinuclear copper complex, $[Cu_2L_2Cl_2 \cdot C_4H_8O]$ (**1**), was prepared from a newly synthesized tridentate Schiff-base ligand 2-[(2-hydroxy-ethylimino)-methyl]-4,6-diiodo-phenol (**HL**). This complex was assayed for antibacterial activities against three Gram-positive bacterial strains (*Bacillus subtilis*, *Staphylococcus aureus*, and *Streptococcus faecalis*) and three Gram-negative bacterial strains (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*) by the MTT method.

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2. Experimental

2.1. *Materials and instruments*

All chemicals were reagent grade and used as received. The 3,5-diiodosalicylalidene was synthesized with salicylaldehyde, KI, and KIO_3 [12]. Carbon, hydrogen, and nitrogen assays were carried out with a CHN–O-Rapid instrument and were within ±0.4% of the theoretical values. Infrared (IR) spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs from 4000 to 400 cm^{-1}. UV spectra were recorded on a U-3000 Spectrophotometer. ^1H NMR spectra were recorded on a Bruker AV 400 spectrometer with TMS as internal standard. Solid-state fluorescence spectra were obtained using an F-2500 fluorescence spectrophotometer.

2.2. *Synthesis of HL*

3,5-Diiodosalicylalidene (0.374 g, 1 mmol) and 2-aminoethanol (0.061 g, 1 mmol) were dissolved in ethanol (15 mL) and refluxed for 1 h. Excess ethanol was removed under reduced pressure to afford yellow solid. Single crystals of the title compound were obtained by evaporating slowly in EtOAc/ethyl ether. Yield 86%, m.p.: 171–173°C. UV (λ nm): 433.5; 257.0. IR data (cm^{-1}, KBr): 3264.7(m), 2877.1(m), 1645.4(s), 1481.9(s), 1424.7(m), 1232.4(m), 1199.9(s), 1133.4(s), 1076.3(s), 1027.5(m), 1014.4(m), 918.0(m), 867.7(m), 697.1(m). MS (ESI): 418.98 ($C_9H_{10}I_2NO_2^+$, $[M+H]^+$). Anal. Calcd for $C_9H_9I_2NO_2$ (%): C, 25.92; H, 2.18; N, 3.36. Found (%): C, 25.95; H, 2.19; N, 3.34. ^1H NMR ($CDCl_3$) δ (ppm): 14.706 (s, 1H), 8.178 (s, 1H), 8.054 (d, $J = 2.0$ Hz, 1H), 7.523 (d, $J = 2.0$ Hz, 1H), 3.929 (d, $J = 9.7$ Hz, 2H), 3.780 (d, $J = 10.1$ Hz, 2H).

2.3. *Synthesis of [$Cu_2L_2Cl_2 \cdot C_4H_8O$] (1)*

HL (0.208 g, 0.5 mmol) with $CuCl_2 \cdot 2H_2O$ (0.085 g, 0.5 mmol) was dissolved in tetrahydrofuran (THF) (6 mL) and stirred at room temperature for 10 min to give a clear solution. After standing for 5–7 days, the precipitate was separated by filtration, washed with methanol three times, and dried. Single crystals of the title complex were obtained by evaporating slowly in methanol/ethyl ether. Yield 81%, m.p.: 228–229°C. UV (λ nm): 386.5; 258.0. IR data (cm^{-1}, KBr): 3134.4(m), 2917.2(m), 1627.0(s), 1431.2(m), 1405.0(m), 1229.6(m), 1150.8(s), 1070.0(m), 1029.3(m), 879.0(m), 752.1(m), 681.3(m). MS (MALDI-TOF): 1104.02 ($C_{22}H_{25}I_4N_2O_5Cl_2Cu_2^+$, $[M+H]^+$). Anal. Calcd for $C_{22}H_{24}I_4N_2O_5Cl_2Cu_2$ (%): C, 23.98; H, 2.20; N, 2.54. Found (%): C, 23.95; H, 2.19; N, 2.51.

2.4. *Crystal structure determination and refinement*

The crystallographic data for **HL** and **1** were collected on a Bruker Smart 1000 CCD area detector diffractometer equipped with Mo-Kα (λ = 0.71073 Å) radiation using ω-scan mode. Empirical absorption correction was applied to the data. The structures were solved by direct methods and refined by full-matrix least-squares on F^2. All non-hydrogen atoms were located from the trial structure and then refined anisotropically. All hydrogens were generated in idealized positions. All calculations were performed

with SHELXL-97 programs. Other relevant parameters of the crystal structure are listed in table 1.

2.5. *Antimicrobial activity*

The antibacterial activity of the synthesized complex was tested against *B. subtilis*, *S. aureus*, *S. faecalis*, *P. aeruginosa*, *E. coli*, and *E. cloacae* using MTT medium. The minimum inhibitory concentrations (MICs) of the test complexes were determined by a colorimetric method using the dye MTT [13]. A stock solution of the synthesized complex (50 μg mL^{-1}) in DMSO was prepared and quantities of the test complexes were incorporated in a specified quantity of sterilized liquid medium. A specified quantity of the medium containing the complex was poured into microtitration plates. Suspension of the microorganism was prepared to contain 10^5 cfu mL^{-1} and applied to microtitration plates with serially diluted complexes in DMSO and incubated at 37°C for 24 h. After the MICs were visually determined on each of the microtitration plates, 50 μL of phosphate buffered saline (PBS 0.01 mol L^{-1}, pH 7.4: $Na_2HPO_4 \cdot 12H_2O$ 2.9 g, KH_2PO_4 0.2 g, NaCl 8.0 g, KCl 0.2 g, distilled water 1000 mL) containing 2 mg mL^{-1} 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 μL of isopropanol containing 5% 1 mol L^{-1} HCl was added to extract the dye. After 12 h of incubation at room

Table 1. Crystallographic and experimental data for **HL** and **1**.

	HL	**1**
Empirical formula	$C_9H_9I_2NO_2$	$C_{22}H_{24}Cl_2Cu_2I_4N_2O_5$
Formula weight	416.97	1102.01
Temperature (K)	298(2)	298(2)
Crystal system	Monoclinic	Monoclinic
Space group	*P2(1)/c*	*C2/c*
Unit cell dimensions (Å, °)		
a	16.0265(17)	27.886(3)
b	8.6930(11)	8.6890(12)
c	8.4063(10)	26.598(2)
α	90	90
β	102.0010(10)	105.521(2)
γ	90	90
Volume (Å^3), *Z*	1145.6(2), 4	6233.1(12), 8
Calculated density (g cm^{-3})	2.418	2.349
Absorption coefficient μ (mm^{-1})	5.466	5.533
F(000)	768	4112
Max. and min. transmission	0.2369 and 0.1748	0.3065 and 0.1765
Data/restraints/parameters	2017/0/128	5486/0/344
θ range for data collection (°)	2.60–25.02	1.58–25.01
Limiting indices	$-19 \le h \le 15$; $-10 \le k \le 8$; $-10 \le l \le 9$	$-33 \le h \le 18$; $-10 \le k \le 9$; $-30 \le l \le 31$
Reflections collected/unique	5542/2017	15,157/5486
R_{int}	0.0314	0.0487
R^a ($I > 2\sigma(I)$)	0.0270	0.0486
wR^b ($I > 2\sigma(I)$)	0.0580	0.1175
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ (e Å^{-3})	0.854 and −0.646	1.542 and −1.277

[a] $R = \sum||F_o| - |F_c||\sum|F_o||$; [b] $wR = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

temperature, the optical density (OD) was measured with a microplate reader at 570 nm. The observed MICs are presented in table 2.

3. Results and discussion

IR spectra of the complexes (KBr pellets) display an intense absorption at *ca* 1617–1629 cm^{-1} attributable to the $\nu_{(C=N)imine}$ stretching frequency. This band shifts *ca* 17–29 cm^{-1} to lower wavenumbers compared to 1645 cm^{-1}, attributable to $\nu_{(C=O)imine}$ of $C_9H_9I_2NO_2$. UV spectra of the complexes display an intense absorption at 257–258 nm ($\pi \rightarrow \pi^*$) and 380–406 nm ($n \rightarrow \pi^*$).

HL crystallizes in monoclinic with space group *P2(1)/c*. As shown in figure 1, the two iodines are on the benzene ring. The I(1)–C(4), I(2)–C(6), N(1)–C(1), N(1)–C(8), O(1)–C(3), and O(2)–C(9) bonds are 2.093(4), 2.092(4), 1.302(5), 1.453(5), 1.281(5), and 1.406(5) Å, respectively. The bond angles of N(1)–C(1)–C(2), C(1)–N(1)–C(8), and N(1)–C(8)–C(9) are 123.3(4)°, 122.9(4)°, 112.3(4)°, respectively.

Table 2. MICs of the synthetic complex.

	MICs ($\mu g\,mL^{-1}$)					
	Gram positive			Gram negative		
Compounds	*B. subtilis*	*S. aureus*	*S. faecalis*	*P. aeruginosa*	*E. coli*	*E. cloacae*
1	3.125	6.25	6.25	12.5	3.125	6.25
HL	6.25	12.5	25	12.5	6.25	12.5
Penicillin	1.562	1.562	1.562	6.25	6.25	3.125
Kanamycin	0.39	1.562	3.125	3.125	3.125	1.562

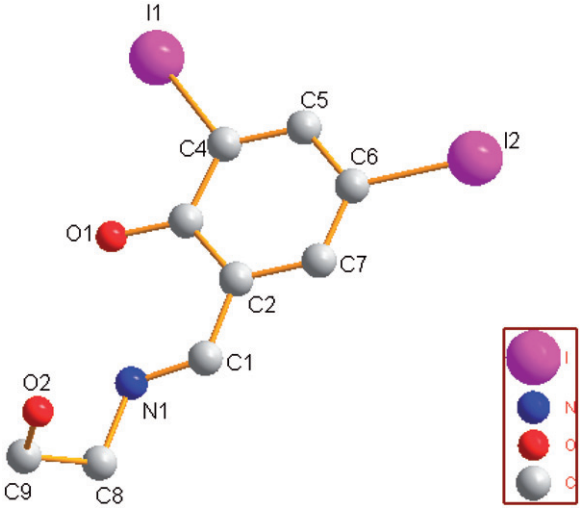

Figure 1. Crystal structure of **HL** showing 30% probability displacement ellipsoids (all hydrogens have been omitted for clarity).

The molecular structure of **1** is shown in figure 2 and the selected bond lengths and angles are given in table 3. Compound **1** is dinuclear with two unique copper(II) ions in the asymmetric unit. Both Cu(II)s adopt a distorted trigonal bipyramidal geometry coordinated by one nitrogen and two oxygens from **HL** and two chlorides. The distance

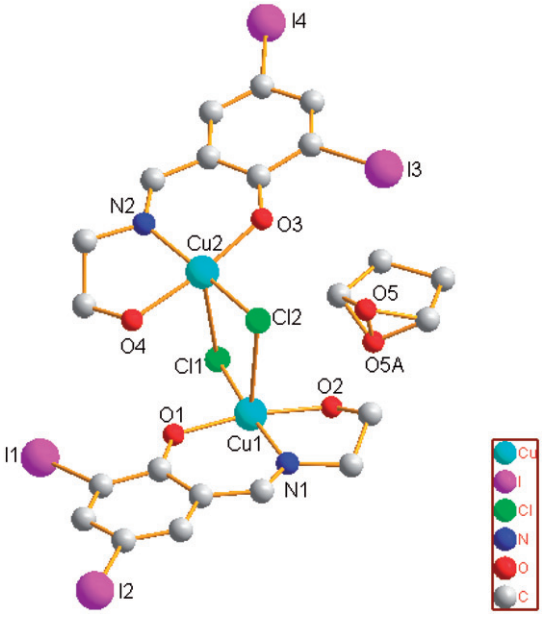

Figure 2. Crystal structure of **1** showing 30% probability displacement ellipsoids (all hydrogens have been omitted for clarity).

Table 3. Selected bond lengths (Å) and angles (°) of **HL** and **1**.

HL			
C1–N1	1.301	C8–N1	1.454
C9–O2	1.406	C3–O1	1.282
C4–I1	2.093	C6–I2	2.091
O2–C9–C8	113.3	C8–N1–C1	122.9
C2–C3–O1	122.0	C4–C3–O1	122.3
C3–C4–I1	117.9	C5–C4–I1	119.3
C5–C6–I2	119.3	C7–C6–I2	121.2
1			
Cu1–O1	1.921	Cu1–O2	1.985
Cu1–N1	1.944	Cu1–Cl1	2.271
Cu1–Cl2	2.732	Cu2–O3	1.892
Cu2–O4	2.031	Cu2–N2	1.935
Cu2–Cl1	2.799	Cu2–Cl2	2.256
O1–Cu1–N1	93.8	O1–Cu1–Cl1	92.6
O1–Cu1–Cl2	94.7	O1–Cu1–O2	170.0
O2–Cu1–N1	81.1	O2–Cu1–Cl1	91.9
O2–Cu1–Cl2	94.0	Cl1–Cu1–Cl2	92.4
O3–Cu2–N2	92.6	O3–Cu2–Cl1	103.7
O3–Cu2–Cl2	92.4	O3–Cu2–O4	172.4
O4–Cu2–N2	81.9	Cl1–Cu2–Cl2	90.9
Cu1–Cl1–Cu2	85.8	Cu1–Cl2–Cu2	87.7

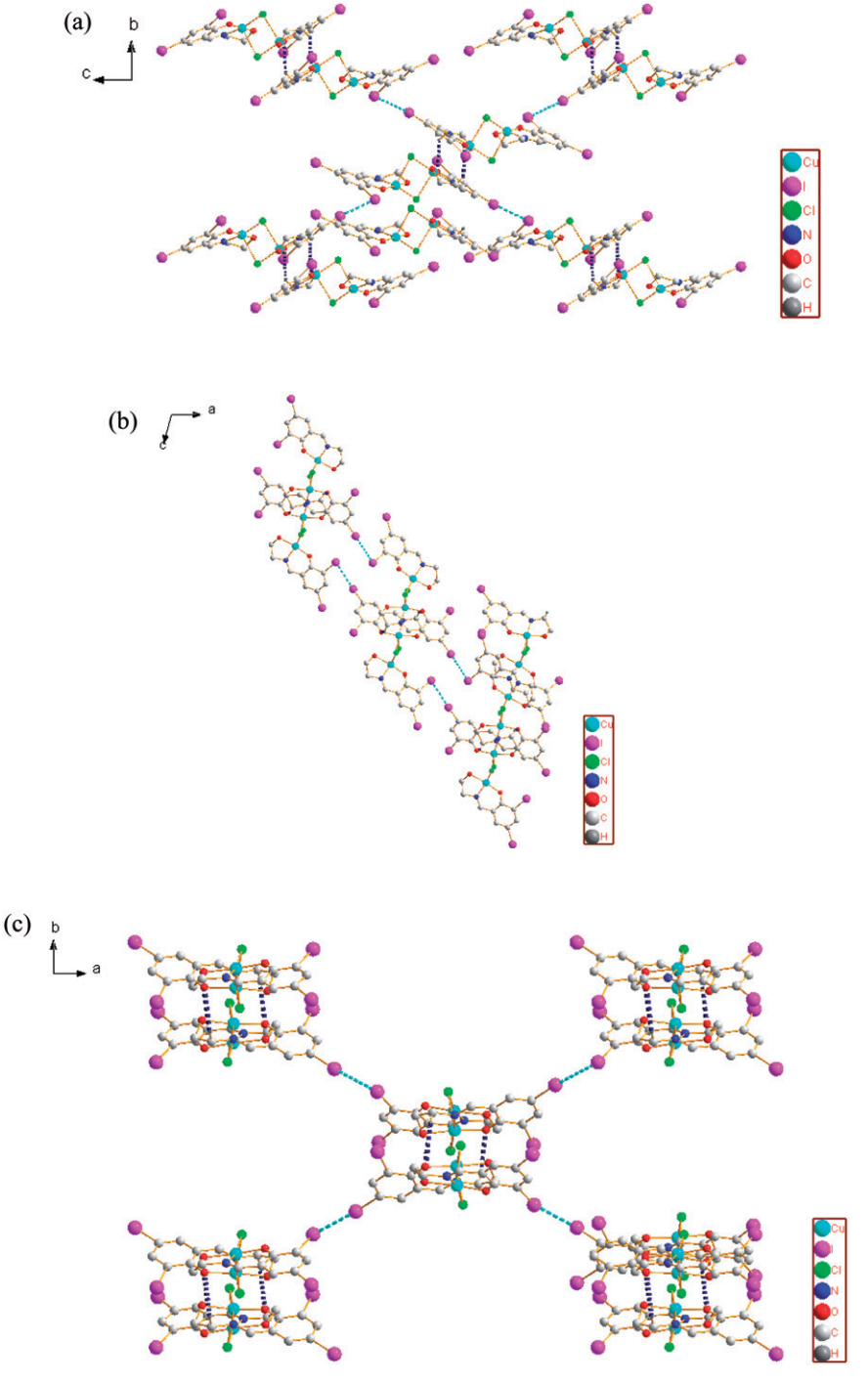

Figure 3. (a) The packing structure of **1** along the *a*-axis, (b) the packing structure of **1** along the *b*-axis, and (c) the packing structure of **1** along the *c*-axis. All hydrogens and THF have been omitted for clarity.

between coppers (3.472 Å) is much longer than that in complex $[Cu_2(dppm)_2L(NO_3)(CH_3OH)]$ (L = 2-(9H-carbazol-9-yl)acetic acid), indicating that there is no weak metal–metal interaction [14]. Furthermore, the complex also contains a THF. As shown in figure 3, intermolecular H-bonds (O–H $\cdots$ O) and weak I $\cdots$ I interactions formed between adjacent molecules generate a 3-D supramolecular network. The H $\cdots$ O distance is 2.686 Å and the OH $\cdots$ O angle is 138.1°.

Complex **1** was screened for antibacterial activity against three Gram (+) bacterial strains (*B. subtilis*, *S. aureus*, and *S. faecalis*) and three Gram (−) bacterial strains (*E. coli*, *P. aeruginosa*, and *E. cloacae*) by the MTT method. The MICs of the complex against six bacterial strains are presented in table 3. Complex **1** exhibits better antimicrobial activity than **HL**. The enhanced bactericidal activity on complexation with copper(II) may be explained by chelation theory, according to which chelation reduces the polarity of the central metal because of the partial sharing of its positive charge with the donor groups and possible π-electron delocalization within the whole chelate ring [15, 16]. This chelation increases the lipophilic nature of the central atom, which favors the permeation of the complexes through the lipid layer of the cell membrane.

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