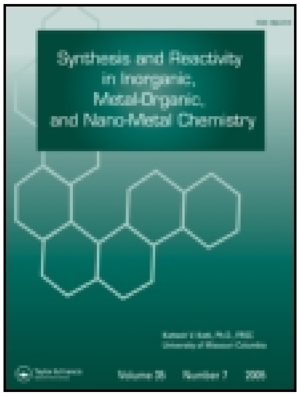

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Synthesis, Crystal Structures, and Antibacterial Activity of Cobalt and Copper Complexes With Tridentate Schiff Bases

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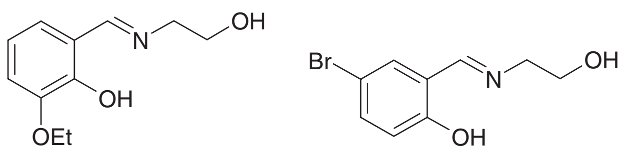
Three mononuclear cobalt and copper complexes, $[Co(HL^1)_2]\cdot[Co(L^1)_2]$ (1), $[Cu(HL^2)_2]$ (2), and $[CoL^2(HL^2)]_2$ (3), where HL^1 and HL^2 are the monoanionic form of 2-ethoxy-6-[(2-hydroxyethylimino)methyl]phenol (H_2L^1) and 4-bromo-2-[(2-hydroxyethylimino)methyl]phenol (H_2L^2), and L^1 and L^2 are the dianionic form of H_2L^1 and H_2L^2, have been synthesized and characterized by elemental analysis, FT-IR spectra, and single-crystal X-ray determination. The Co atoms in (1) and (3) are in octahedral coordination, and the Cu atom in (2) is in square planar coordination. The preliminary antibacterial activity of the complexes on the bacteria *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. typhi* was evaluated.

Keywords antibacterial activity, cobalt, copper, crystal structure, Schiff base

INTRODUCTION

The coordination chemistry of cobalt and copper complexes with multidentate ligands has received considerable attention in recent years for their biological and medicinal applications.[1–3] Among the multidentate ligands, Schiff bases are considered as a very important class of organic compounds that have wide applications in many biological aspects. Some Schiff bases were reported to possess antibacterial, antifungal, and antitumor activities.[4–7] Schiff base complexes have widely been used as drugs. Moreover, it is well known that some biological activities, when administered as metal complexes, are being increased.[8,9] We report herein the synthesis and characterization of three mononuclear cobalt and copper complexes, $[Co(HL^1)_2]\cdot[Co(L^1)_2]$ (**1**), $[Cu(HL^2)_2]$ (**2**), and $[CoL^2(HL^2)]_2$ (**3**), where HL^1 and HL^2 are the monoanionic form of 2-ethoxy-6-[(2-hydroxyethylimino)methyl]phenol (H_2L^1) and 4-bromo-2-[(2-hydroxyethylimino)methyl]phenol (H_2L^2; Scheme 1), and L^1 and L^2 are the dianionic form of H_2L^1 and H_2L^2. The preliminary antibacterial activity of the complexes on the bacteria *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. typhi* was evaluated.



SCH. 1. The Schiff bases HL^1 and HL^2.

EXPERIMENTAL

Materials and Measurements

3-Ethoxysalicylaldehyde, 5-bromosalicylaldehyde, and 2-aminoethanol were obtained from Lancaster (England). Other chemicals were obtained commercially and were used as received. Carbon, hydrogen, and nitrogen analyses were obtained on an Eager 300 NCH System Elemental Analyzer (Zhengzhou, College of Animal Husbandry, China). IR spectra of the complexes were recorded as KBr pellets on a Nicolet-5700 FT-IR spectrophotometer (Zhengzhou, College of Animal Husbandry, China).

Synthesis of $[Co(HL^1)_2]\cdot[Co(L^1)_2]$ (1)

H_2L^1 (1.0 mmol, 0.21 g) in methanol (30 mL) was added with stirring to cobalt nitrate hexahydrate (0.5 mmol, 0.15 g) in methanol (20 mL). The mixture was stirred at refluxed for 30 min to give a brown solution. The solution was left still at room temperature in air to give brown block-shaped single crystals, which were collected by filtration and dried in vacuum containing anhydrous $CaCl_2$. The yield is 0.16 g (67.5%). Anal. Calcd. for $C_{44}H_{54}Co_2N_4O_{12}$ (%): C, 55.7; H, 5.7; N, 5.9. Found (%): C, 55.5; H, 5.8; N, 5.8.

Synthesis of $[Cu(HL^2)_2]$ (2)

H_2L^2 (1.0 mmol, 0.24 g) in methanol (30 mL) was added with stirring to copper acetate monohydrate (0.5 mmol, 0.10 g) in methanol (20 mL). The mixture was stirred at refluxed for 30 min to give a blue solution. The solution was left still at room temperature in air to give blue block-shaped single crystals, which were collected by filtration and dried in vacuum

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TABLE 1
Crystal data and structural refinement details for the complexes

Complex	(**1**)	(**2**)	(**3**)
Chemical formula	$C_{44}H_{54}Co_2N_4O_{12}$	$C_{18}H_{18}Br_2CuN_2O_4$	$C_{18}H_{17}Br_2CoN_2O_4$
Formula weight	948.8	549.7	544.1
Color and habit	brown, block	blue, block	brown, block
T (K)	298(2)	298(2)	298(2)
radiation (λ, Å)	Mo Kα (0.71073)	Mo Kα (0.71073)	Mo Kα (0.71073)
Crystal system	Orthorhombic	Monoclinic	Hexagonal
Space group	*Pbca*	$P2_1/n$	*R*-3
a (Å)	14.343(12)	4.9943(11)	19.096(2)
b (Å)	16.019(13)	17.1869(18)	19.096(2)
c (Å)	38.11(3)	10.9889(13)	27.402(3)
α (°)	90	90	90
β (°)	90	94.513(2)	90
γ (°)	90	90	120
V (Å^3)	8756(12)	940.3(3)	8653.7(16)
Z	8	2	18
d_{calcd} (g cm^{-3})	1.439	1.941	1.879
μ (mm^{-1})	0.825	5.438	5.075
F(000)	3968	542	4824
Reflections collected	45457	7548	17825
Unique reflections	10762	2039	4203
Observed reflections [$I \geq 2\sigma(I)$]	4069	1475	2193
No. of parameters	569	125	287
No. of restraints	21	0	11
Goodness of fit on F^2	0.965	1.021	1.009
R_1 [$I \geq 2\sigma(I)$]^a	0.0733	0.0353	0.0422
R_1 (all data)^a	0.1362	0.0673	0.0720
$wR_2{}^b$ [$I \geq 2\sigma(I)$]	0.2188	0.0599	0.1192
$wR_2{}^b$ (all data)	0.1882	0.0751	0.0917

$^aR_1 = \sum||Fo| - |Fc||/\sum|Fo|$, $^b\ wR_2 = [\sum w(Fo^2 - Fc^2)^2/\sum w(Fo^2)^2]^{1/2}$.

containing anhydrous $CaCl_2$. The yield is 0.14 g (50.9%). Anal. Calcd. for $C_{18}H_{18}Br_2CuN_2O_4$ (%): C, 39.3; H, 3.3; N, 5.1. Found (%): C, 39.5; H, 3.3; N, 5.2.

Synthesis of $[CoL^2(HL^2)]_2$ (3)

H_2L^2 (1.0 mmol, 0.24 g) in methanol (30 mL) was added with stirring to cobalt nitrate hexahydrate (0.5 mmol, 0.15 g) in methanol (20 mL). The mixture was stirred at refluxed for 30 min to give a brown solution. The solution was left still at room temperature in air to give brown block-shaped single crystals, which were collected by filtration and dried in vacuum containing anhydrous $CaCl_2$. The yield is 0.19 g (69.9%). Anal. Calcd. for $C_{18}H_{17}Br_2CoN_2O_4$ (%): C, 39.7; H, 3.1; N, 5.1. Found (%): C, 39.6; H, 3.2; N, 5.2.

Crystal Structure Determination

Single crystals of the complexes were selected and mounted on glass fibers. The data were collected at 298(2) K on a Bruker SMART 1000 CCD area-detector (Liaocheng University, China) with MoKα radiation ($\lambda = 0.71073$ Å). Multiscan absorption corrections were applied using the SADABS program (Bruker, Germany).[10] The structures of the complexes were solved by direct method and were refined by full-matrix least-squares technique based on F^2 using the SHELXL97 package (Bruker, Germany).[11] All non-hydrogen atoms were refined anisotropically. The hydroxyl H atoms in the complexes (**1**) and (**3**) were located from difference Fourier maps and refined isotropically, with O−H distances restrained to 0.85(1) Å. The remaining hydrogen atoms were refined as riding model. One ethylene group of (**3**) is disordered over two sites with occupancies of 0.652(3) and 0.348(3). The crystallographic data and structure determination parameters for the complexes are given in Table 1. Selected bond lengths and angles are summarized in Table 2.

Antibacterial Test

The complexes and the free Schiff bases were determined against the bacteria *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. typhi*. Microorganisms were cultured on Müller–Hinton agar medium. After drilling wells on medium using a 6 mm cork

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

(**1**)			
Bond lengths			
Co1-N1	1.877 (5)	Co1-N2	1.880 (5)
Co1-O1	1.880 (4)	Co1-O2	1.934 (4)
Co1-O4	1.879 (4)	Co1-O5	1.917 (4)
Co2-N3	1.883 (4)	Co2-N4	1.884 (5)
Co2-O7	1.884 (4)	Co2-O8	1.900 (4)
Co2-O10	1.869 (4)	Co2-O11	1.929 (4)
Bond angles			
N1-Co1-O4	87.76 (18)	N1-Co1-N2	174.8 (2)
O4-Co1-N2	95.0 (2)	N1-Co1-O1	94.22 (19)
O4-Co1-O1	90.11 (16)	N2-Co1-O1	90.21 (18)
N1-Co1-O5	91.78 (18)	O4-Co1-O5	177.64 (16)
N2-Co1-O5	85.67 (19)	O1-Co1-O5	87.61 (16)
N1-Co1-O2	85.71 (19)	O4-Co1-O2	90.52 (16)
N2-Co1-O2	89.84 (18)	O1-Co1-O2	179.35 (17)
O5-Co1-O2	91.75 (15)	O10-Co2-N3	89.28 (18)
O10-Co2-N4	94.5 (2)	N3-Co2-N4	174.0 (2)
O10-Co2-O7	89.16 (17)	N3-Co2-O7	94.47 (19)
N4-Co2-O7	90.20 (19)	O10-Co2-O8	91.64 (17)
N3-Co2-O8	85.98 (19)	N4-Co2-O8	89.30 (19)
O7-Co2-O8	179.09 (18)	O10-Co2-O11	178.78 (17)
N3-Co2-O11	91.78 (17)	N4-Co2-O11	84.49 (19)
O7-Co2-O11	90.16 (17)	O8-Co2-O11	89.03 (17)
(**2**)			
Bond lengths			
Cu1-O1	1.943 (2)	Cu1-N1	1.997 (3)
Bond angles			
O1-Cu1-O1A	180	O1-Cu1-N1A	90.86 (11)
O1-Cu1-N1	89.14 (11)	N1-Cu1-N1A	180
(**3**)			
Bond lengths			
Co1-O1	1.878 (3)	Co1-O2	1.924 (3)
Co1-O3	1.869 (3)	Co1-O4	1.921 (3)
Co1-N1	1.881 (4)	Co1-N2	1.890 (4)
Bond angles			
O3-Co1-O1	90.82 (14)	O3-Co1-N1	86.11 (14)
O1-Co1-N1	94.58 (14)	O3-Co1-N2	94.83 (15)
O1-Co1-N2	87.84 (13)	N1-Co1-N2	177.39 (15)
O3-Co1-O4	178.48 (14)	O1-Co1-O4	90.35 (14)
N1-Co1-O4	92.83 (15)	N2-Co1-O4	86.18 (15)
O3-Co1-O2	88.27 (14)	O1-Co1-O2	178.77 (14)
N1-Co1-O2	86.18 (15)	N2-Co1-O2	91.41 (14)
O4-Co1-O2	90.57 (14)		

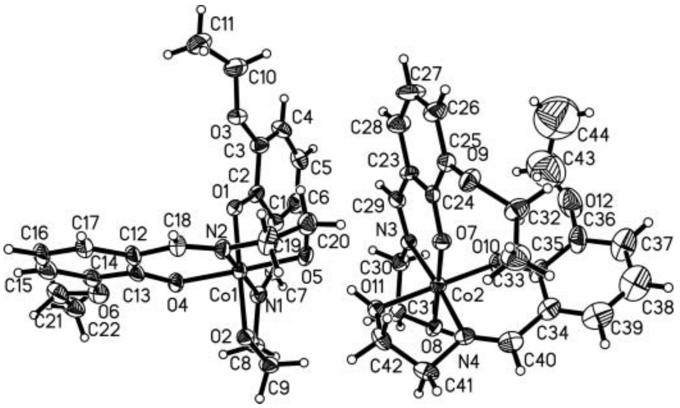

FIG. 1. Molecular structure of (**1**) at 30% probability displacement.

borer, 100 μL of solution from different compounds was poured into each well. The plates were incubated at 37°C overnight. The diameter of the inhibition zone was measured to the nearest. Each test was carried out in triplicate and the average was calculated for inhibition zone diameters. A blank containing only methanol showed no inhibition in a preliminary test. The macrodilution broth susceptibility assay was used for the evaluation of minimal inhibitory concentration (MIC). By including 1 mL Müller-Hinton broth in each test, and then adding 1 mL extract with concentration 100 μg mL^{-1} in the first tube, we made serial dilution of this extract from first tube to last tube. Bacterial suspension prepared to match the turbidity of 0.5 McFarland turbidity standards. Matching this turbidity provides a bacterial inoculum concentration of 1.5 × 10^{8} cfu mL^{-1}. Then 1 mL of bacterial suspension was added to each test tube. After incubation at 37°C for 24 h, the last tube was determined as the MIC without turbidity.

RESULTS AND DISCUSSION

The Schiff bases were prepared by the reaction of equimolar quantities of 2-aminoethanol with 3-ethoxysalicylaldehyde and 5-bromosalicylaldehyde in methanol. The cobalt and copper complexes were simply prepared by the reaction of the Schiff bases with cobalt nitrate and copper acetate in methanol at open air. The Co atom with +2 oxidation number in cobalt nitrate was oxidized to +3 in the complexes (**1**) and (**3**).

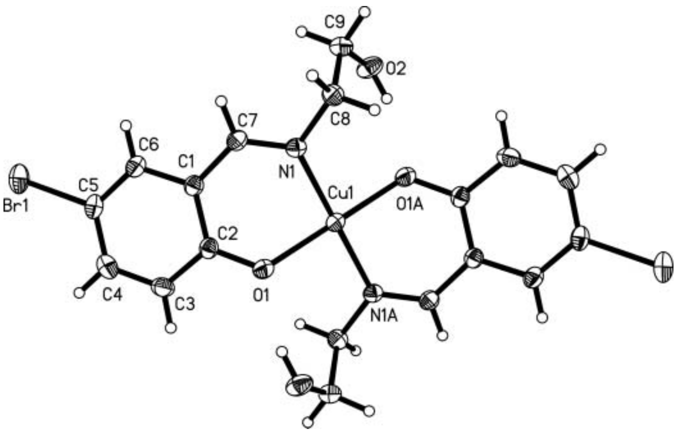

FIG. 2. Molecular structure of (**2**) at 30% probability displacement.

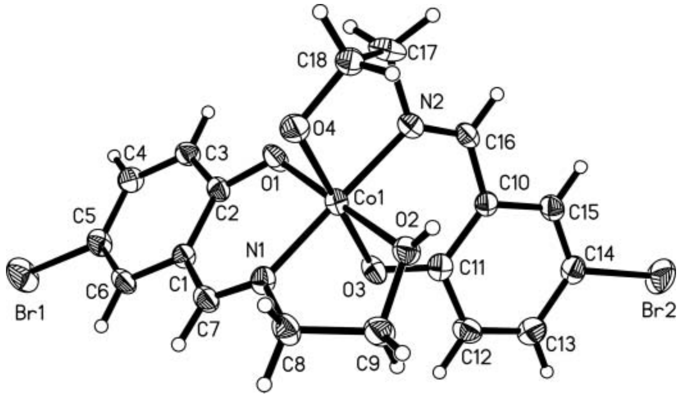

FIG. 3. Molecular structure of (**3**) at 30% probability displacement.

Structure Description of the Complexes

The molecular structures of the complexes (**1**), (**2**), and (**3**) are presented in Figures 1, 2, and 3, respectively. The asymmetric unit of the mononuclear complex (**1**) contains a $[Co(HL^1)_2]^+$ cation and a $[Co(L^1)_2]^-$ anion. The mononuclear complex (**2**) possesses a crystallographic inversion center symmetry, with the Cu atom located at the inversion center. The Co atoms in complexes (**1**) and (**3**) are coordinated by two phenolate O, two hydroxy O, and two imine N atoms from two Schiff base ligands, forming octahedral coordination. The Cu atom in complex (**2**) is coordinated by two phenolate O and two imine N atoms from two Schiff bases, forming square planar coordination. The Co-O and Co-N coordinate bond lengths in the complexes (**1**) and (**3**) are comparable to each other, and are also comparable to the corresponding values observed in other similar cobalt complexes with Schiff bases.[12–14] The Cu-O and Cu-N bond lengths in complex (**2**) are comparable to the corresponding values observed in other similar copper complexes with Schiff bases.[15–17]

Infrared Spectra

The weak and broad bands in the region 3250–3470 cm^{-1} are assigned to the streching vibration of the O-H groups of the Schiff bases and the complexes. In the IR spectra of the free Schiff bases, the ν(C=N) bands are at about 1637 cm^{-1} for HL^1 and 1651 cm^{-1} for HL^2, which are located at lower wave numbers for the complexes, 1619 cm^{-1} for (**1**), 1625 cm^{-1} for (**2**), and 1628 cm^{-1} for (**3**), indicating that the Schiff bases are coordinated to the V atoms through the azomethine N atoms. The middle ν(C-O) bands in the spectra of the complexes are located at 1170–1183 cm^{-1}. The weak bands in the low wave numbers 400–570 cm^{-1} can be assigned to the vibration of the M-O and M-N bonds.

TABLE 3
Zone of growth inhibition (mm)

Tested material	*S. aureus*	*E. coli*	*P. aeruginosa*	*S. typhi*
HL^1	7	10	6	8
HL^2	11	15	8	7
(**1**)	15	23	16	13
(**2**)	27	21	35	24
(**3**)	21	18	12	15
Imipenum	26	29	30	29

TABLE 4
MIC values (μg mL^{-1})

Tested material	*S. aureus*	*E. coli*	*P. aeruginosa*	*S. typhi*
HL^1	> 50	43.5	> 50	32.1
HL^2	38.2	27.3	> 50	40.3
(**1**)	18.9	12.3	15.5	21.0
(**2**)	5.3	15.2	2.7	17.9
(**3**)	14.0	19.0	10.1	15.3
Imipenum	8.2	3.7	5.1	8.5

Antibacterial Activity

Transition metal complexes, in particular biometals containing biologically important ligands, have significance as potential biologically relevant agents. The free Schiff bases and the three complexes were tested *in vitro* for their antibacterial activities against the bacteria *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. typhi* (Tables 3 and 4). The results were compared with the positive control Imipenum.

From the results, we can found that the antibacterial activities of the complexes are much more stronger than the free Schiff bases. The copper complex (**2**) is in general more effective than the cobalt complexes (**1**) and (**3**). It is interesting that complex (**2**) show stronger activities against *S. aureus* and *P. aeruginosa* than the reference drug Imipenum. The enhancement in the activity of the complexes in comparison to the free ligands may be due to the coordination of the Schiff bases to metal and an efficient diffusion of the metal complexes into bacterial cell.[18,19]

CONCLUSION

Three mononuclear cobalt and copper complexes have been prepared by the reaction of the tridentate Schiff bases 2-ethoxy-6-[(2-hydroxyethylimino)methyl]phenol and 4-bromo-2-[(2-hydroxyethylimino)methyl]phenol with cobalt nitrate and copper acetate, respectively. The structures of the complexes have been characterized by elemental analysis, IR spectra, and single-crystal X-ray diffraction. The Schiff bases coordinate to the Co and Cu atoms through the NNO donor atoms. The complexes show effective antibacterial activities against the bacteria *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. typhi*.

SUPPLEMENTARY MATERIALS

X-ray crystallographic data for the complexes have been deposited with the Cambridge Crystallographic Data Centre (The

Director, CCDC, 12 Union Road, Cambridge, CB2 1 EZ, UK; e-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk; fax: +44-(0)1223–336033) and are available free of charge on request, quoting the deposition number CCDC 846540 for (**1**), 846541 for (**2**), and 846542 for (**3**).

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