Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry, 41:229–233, 2011

ISSN: 1553-3174 print / 1553-3182 online
DOI: 10.1080/15533174.2011.555851

Synthesis, Crystal Structures, and Cytotoxicity Studies of Two Cobalt(III) and Zinc(II) Complexes Derived from 2-Ethoxy-6-[(3-methylaminopropylimino)methyl]phenol

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A new cobalt(III) complex, $[CoL_2]\cdot ClO_4$ (1), and a new zinc(II) complex, $[Zn(HL)_2(NCS)]\cdot NCS$ (2) (HL = 2-ethoxy-6-[(3-methylaminopropylimino)methyl]phenol), have been synthesized and characterized by elemental analysis, IR spectra, and single crystal X-ray diffraction. In (1), the Co atom, lying on the inversion center, is six-coordinate in an octahedral coordination, with two phenolate O, two imine N, and two amine N atoms from two Schiff base ligands. In (2), the Zn atom is five-coordinate in a trigonal-bipyramidal coordination, with two imine N atoms from two Schiff base ligands and one thiocyanate N atom defining the basal plane, and with two phenolate O atoms from two Schiff base ligands occupying the axial positions. The cytotoxic activities of both complexes were evaluated.

Keywords cobalt, crystal structure, cytotoxicity, Schiff base, synthesis, zinc

INTRODUCTION

Schiff bases are kinds of versatile ligands in coordination chemistry due to their easy synthesis and wide applications.[1–4] The biological properties of Schiff bases and their metal complexes have been widely investigated.[5–7] Recent research indicates that the Schiff base complexes have potent antitumor activities.[8,9] In this paper, a new cobalt(III) complex, $[CoL_2]\cdot ClO_4$ (**1**), and a new zinc(II) complex, $[Zn(HL)_2(NCS)]\cdot NCS$ (**2**) (HL = 2-ethoxy-6-[(3-methylaminopropylimino)methyl]phenol), were synthesized and structurally characterized. The cytotoxic activities of the complexes were investigated.

EXPERIMENTAL

Materials and Measurements

All chemicals were available commercially as AR grade and were used without further purification. C, H, and N elemental analyses were performed on a Vario-EL-III analyzer. The IR spectra were recorded on a Perkin Elmer 2000 spectrophotometer with KBr pellets in the region 4000–400 cm^{-1}.

Synthesis of HL

3-Ethoxysalicylaldehyde (1.0 mmol, 166.2 mg) and *N*-methylpropane-1,3-diamine (1.0 mmol, 88.2 mg) were mixed in 50 mL methanol solution and then stirred and refluxed for 30 min. The solvent was removed by distillation to give orange product. The product was washed with methanol and dried in air. Yield: 93%. Anal. calcd. for $C_{13}H_{20}N_2O_2$: C, 66.1; H, 8.5; N, 11.8. Found: C, 65.7; H, 8.6; N, 12.1%.

Synthesis of $[CoL_2]\cdot ClO_4$ (1)

A methanol solution (10 mL) of cobalt(II) perchlorate hexahydrate (0.1 mmol, 36.6 mg) was added to the methanol solution (10 mL) of HL (0.1 mmol, 23.6 mg), and refluxed for 1 h. The resulting clear brown solution was allowed to evaporate slowly in air at room temperature for a week, affording red crystals which were collected by filtration, washed with methanol, and dried in air. Yield: 73% (based on HL). Anal. calcd. for $C_{26}H_{38}ClCoN_4O_8$: C, 49.6; H, 6.1; N, 8.9. Found: C, 49.1; H, 6.3; N, 8.7%.

Synthesis of $[Zn(HL)_2(NCS)]\cdot NCS$ (2)

A methanol solution (10 mL) of zinc(II) acetate dihydrate (0.1 mmol, 22.0 mg) was added to the methanol solution (10 mL) of HL (0.1 mmol, 23.6 mg) and ammonium thiocyanate (0.1 mmol, 7.6 mg), and refluxed for 1 h. The resulting clear colorless solution was allowed to evaporate slowly in air at room temperature for a few days, affording colorless crystals which were collected by filtration, washed with methanol and dried in air. Yield: 61% (based on HL). Anal. calcd. for $C_{28}H_{40}N_6O_4S_2Zn$: C, 51.4; H, 6.2; N, 12.8. Found: C, 51.7; H, 6.1; N, 12.5%.

Cytotoxicity Assay

The cytotoxicity assay was carried out according to the literature method.[10] Two human leukemia cell lines, promyelocytic

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Received 9 July 2010; accepted 6 October 2010.

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HL-60 and lymphoblastic *NALM-6,* were used as targets. Carboplatin was used as a reference. Cells were cultured in an RPMI 1640 medium supplemented with 10% fetal calf serum in a 5% CO_2/95% air atmosphere. Exponentially growing cells were seeded at 3×10^5 per well of 24-well plate (Nunc), and cells were then exposed to the tested compounds for 48 h. Stock solutions were freshly prepared in DMSO, and then dilutions from 10^{-3} to 10^{-7} M in complete culture medium were made.

The number of viable cells was counted in a Bûrker hemocytometer using the trypan-blue exclusion assay. The values of IC_{50} (the concentration of test compounds required to reduce the cell survival fraction to 50% of the control) were calculated from dose-response curves and used as a measure of cellular sensitivity to a given treatment. All data are expressed as mean ± standard deviation.

Crystal Structure Determination

The suitable single crystals of the complexes were mounted on glass fibers for data collection performed on a Bruker SMART 1000 CCD area diffractometer equipped with a graphite-monochromatic Mo Kα radiation (λ = 0.71073 Å) at 298 K. The unit cell dimensions were obtained with the least-squares refinements and the structures were solved by direct methods using SHELXTL-97 program.[11] The final refinement was performed by full-matrix least-squares methods with anisotropic thermal parameters for the non-hydrogen atoms on F^2. H atoms were placed in calculated positions and constrained to ride on their parent atoms. Multi-scan absorption correction was applied by using the SADABS program.[12] The N2-C13 group in (**1**) is disordered over two distinct sites, with occupancies of 0.410(3) and 0.590(3), respectively. The crystallographic data and experimental details for structural analysis of 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 complex has been deposited with the Cambridge Crystallographic Data Centre (CCDC 738696 for (**1**) and 738697 for (**2**)).

RESULTS AND DISCUSSION

The red crystals of (**1**) and the colorless crystals of (**2**) are stable in air at room temperature, soluble in most polar organic solvents, such as MeOH, EtOH and MeCN, but insoluble in water and non-polar organic solvents such as Et_2O.

IR Spectra of the Complexes

Both complexes show two bands above 3000 cm^{-1} at 3317 and 3233 cm^{-1}, what can be attributed to the ν_{NH} frequency. The strong and sharp bands at 1613 cm^{-1} for (**1**) and 1615 cm^{-1} for (**2**) are assigned to the –C=N– stretching vibrations.[13] The strong absorption band at 1093 cm^{-1} in (**1**) is assigned to the perchlorate anion. The occurrence of the strong peaks at 2064 cm^{-1} and 2077 cm^{-1} in (**2**) are ascribed to the stretching vibrations of the coordinate and dissociative thiocyanate groups.[14]

TABLE 1
Crystal data for the complexes

Complex	(**1**)	(**2**)
Formula	$C_{26}H_{38}ClCoN_4O_8$	$C_{28}H_{40}N_6O_4S_8Zn$
FW	628.98	654.15
Crystal shape/colour	block/red	block/colorless
Crystal size /mm^3	$0.20 \times 0.18 \times 0.17$	$0.23 \times 0.20 \times 0.20$
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbcn*	$P2_1/c$
a /Å	17.759(2)	9.851(2)
b /Å	8.537(1)	27.252(3)
c /Å	19.238(2)	12.737(2)
β /^{o}	90	105.534(3)
V /Å^3	2916.7(6)	3294.5(9)
Z	4	4
λ (Mo$K\alpha$) /Å	0.71073	0.71073
T /K	298(2)	298(2)
μ (Mo$K\alpha$) /cm^{-1}	0.734	0.913
T_{min}	0.867	0.817
T_{max}	0.885	0.838
Reflections/parameters	2813/212	7121/374
Goodness of fit on F^2	1.081	1.012
R_1, wR_2 $[I \geq 2\sigma(I)]^a$	0.0567, 0.1590	0.0440, 0.0846
R_1, wR_2 (all data)^a	0.0808, 0.1798	0.0923, 0.0997

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

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

(**1**)			
Co1-O1	1.895(3)	Co1-N1	1.929(3)
Co1-N2	2.001(4)		
O1-Co1-O1A	180	O1-Co1-N1A	89.85(14)
O1-Co1-N1	90.15(14)	N1-Co1-N1A	180
O1-Co1-N2	88.66(17)	O1-Co1-N2A	91.34(17)
N1-Co1-N2	87.46(17)	N1-Co1-N2A	92.54(17)
N2-Co1-N2A	180		
(**2**)			
Zn1-O1	2.0654(18)	Zn1-O3	2.0619(18)
Zn1-N1	2.078(2)	Zn1-N3	2.068(2)
Zn1-N5	2.018(3)		
N5-Zn1-O3	89.19(8)	N5-Zn1-O1	91.41(8)
O3-Zn1-O1	178.06(7)	N5-Zn1-N3	114.29(9)
O3-Zn1-N3	88.88(8)	O1-Zn1-N3	92.55(8)
N5-Zn1-N1	116.33(10)	O3-Zn1-N1	90.17(8)
O1-Zn1-N1	87.91(7)	N3-Zn1-N1	129.34(9)

TABLE 3
Hydrogen-bond geometry (Å, °) for the complexes

D–H···A	D–H	H···A	D···A	D–H···A
(**1**)				
N2–H2···O3	0.91	2.48	3.302(11)	150
(**2**)				
N4–H4B···N6^{i}	0.90	2.01	2.852(4)	156
N4–H4A···O2	0.90	2.31	2.831(3)	117
N4–H4A···O1	0.90	1.91	2.792(3)	165
N2–H2B···O4	0.90	2.31	2.793(3)	113
N2–H2B···O3	0.90	1.88	2.770(3)	170
N2–H2A···S2^{ii}	0.90	2.46	3.286(3)	152

Symmetry codes: (i) $1 - x, -1/2 + y, 3/2 - z$; (ii) $x, -1 + y, z$.

The typical bridging acetate vibrations are at 1571 and 1450 cm^{-1}, respectively.[15]

Structure Description of (1)

Complex (**1**) is a perchlorate salt of a centrosymmetric mononuclear cobalt(III) complex cation (Figure 1). All the bond lengths and angles are comparable to those observed in the similar Schiff base cobalt(III) complex.[16] The Co^{III} atom, lying on an inversion center, is six-coordinate in an octahedral coordination, with two phenolate O, two imine N, and two amine N atoms from two Schiff base ligands. The coordination around the Co atom displays somewhat distortion. The bond lengths around the Co atom are range from 1.895(3) to 2.001(4) Å, and, the greatest deviation of the bond angles from those expected for an ideal octahedral geometry is found for N1-Co1-N2 with 87.5(2)° and N1-Co1-N2A with 92.5(2)°. The conformation of the six-membered ring containing the Co, azomethine N (N1), amine N (N2) and three C atoms (C10, C11 and C12) is a twisted chair. The perchlorate anion in the complex is disordered about an inversion center.

In the crystal structure, molecules are linked through intermolecular hydrogen bonds of types N–H· · ·O, forming chains running along the *c* axis as shown by Figure 2.

Structure Description of (2)

Complex (**2**) is a thiocyanate salt of a mononuclear zinc(II) complex cation (Figure 3). All the bond lengths and angles are comparable to those observed in the similar Schiff base zinc(II) complex.[17] The coordination of the Zn atom may be regarded as midway between trigonal–bipyramidal and square–pyramidal as described by the τ parameter, an index of the degree of trigonality.[18] The τ value calculated for the complex is 0.813. Thus, the coordination of the Zn atom in the complex is close to distorted trigonal-bipyramidal. The basal plane of the trigonal–bipyramid is furnished by two imine N atoms from two Schiff base ligands and one thiocyanate N atom, and the axial positions are occupied by two phenolate O atoms from two Schiff base ligands. The amine N atoms are protonated, and not coordinate to the metal atom.

In the crystal structure, molecules are linked through intermolecular hydrogen bonds of types N–H· · ·N and N–H· · ·S, forming chains running along the *b* axis as shown by Figure 4.

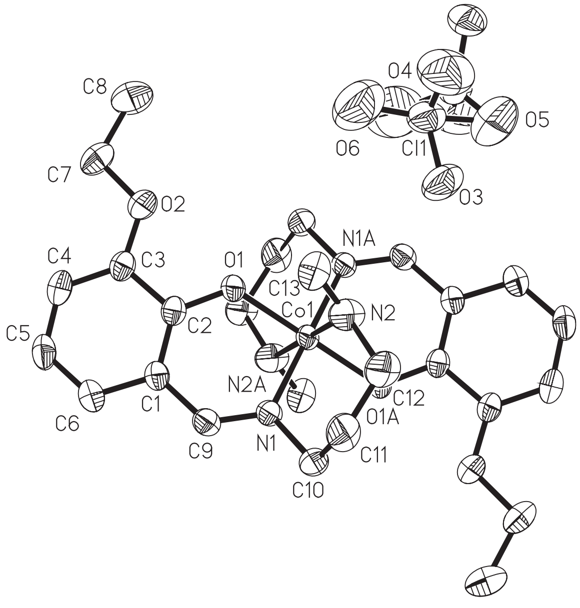

FIG. 1. The molecule of (**1**), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity. Atoms labeled with the suffix A or unlabeled are at the symmetry position –*x*, 1 – *y*, 1 – *z*.

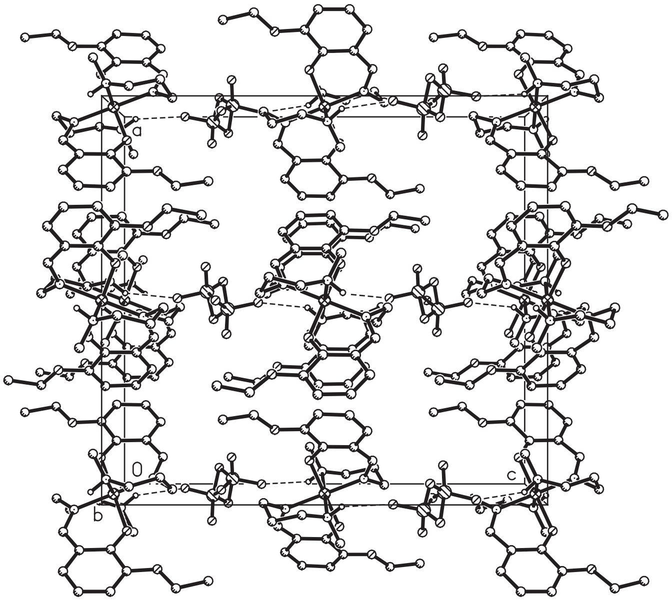

FIG. 2. The molecular packing of (**1**), viewed along the *b* axis. Intermolecular hydrogen bonds are shown as dashed lines.

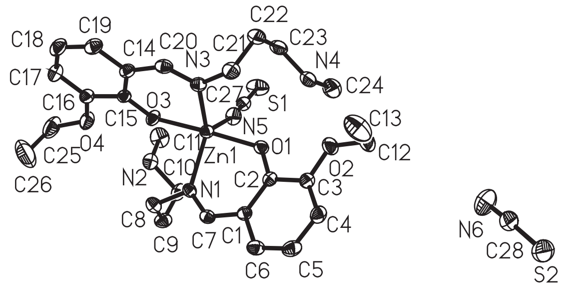

FIG. 3. The molecule of (**2**), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity.

Cytotoxic Activity

The cytotoxic activities of the complexes were evaluated on two human leukemia cell lines *HL-60* and *NALM-6*. The cytotoxic activity is expressed as the concentration required reducing the cell survival fraction to 50% after 48 h of exposure to the compounds (IC_{50}). The results are summarized in Table 4. It can be seen that the Schiff base HL has no cytotoxic activity against both cell lines. Complex (**1**) has stronger activities than those of (**2**). However, both complexes have much less activities than the carboplatin which was used as a reference.

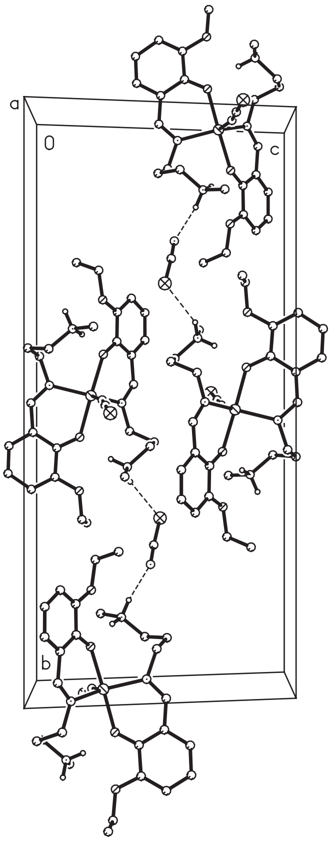

FIG. 4. The molecular packing of (**2**), viewed along the *a* axis. Intermolecular hydrogen bonds are shown as dashed lines.

TABLE 4
Cytotoxic activities (IC_{50}, μM)

Compound	*HL-60*	*NALM-6*
HL	>1000	>1000
(**1**)	113.0 ± 23.6	127.3 ± 21.9
(**2**)	>1000	783.5 ± 63.3
Carboplatin	5.4 ± 1.1	1.3 ± 0.5

CONCLUSIONS

In this paper, a new cobalt(III) complex (**1**) and a new zinc(II) complex (**2**) have been synthesized and structurally characterized. The cytotoxicity studies indicate that complex (**1**) has stronger activities than those of (**2**). Both complexes show much less activity than the carboplatin.

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