Synthesis, Crystal Structures, and Antimicrobial Activity of Zinc(II) and Manganese(II) Complexes Derived from \(N'-(1-(\text{Pyridin-2-yl})\text{Ethylidene})\text{Isonicotinohydrazide}\)

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Abstract

Two mononuclear zinc(II) and manganese(II) compounds, \([\text{ZnL}_2]\) (1) and \([\text{MnL(HL)}]\text{ClO}_4\) (2), where \(L\) is the mono-anionic form of \(N'-(1-(\text{pyridin-2-yl})\text{ethylidene})\text{isonicotinohydrazide}\) (HL), and HL is the zwitterionic form of HL, have been prepared and characterized by elemental analyses, IR and UV-Vis spectroscopy, and single-crystal X-ray crystallographic determination. Compound 1 contains a neutral \([\text{ZnL}_2]\) complex molecule. Compound 2 contains a \([\text{MnL(HL)}]\)⁴⁺ complex cation and one perchlorate anion. The metal atoms in the complexes are in octahedral coordination. The hydrazine ligands coordinate to the metal atoms through the pyridine N, imine N, and enolate O atoms. The compounds were investigated for their antimicrobial activity against \(\text{Staphylococcus aureus}\), \(\text{Escherichia coli}\), and \(\text{Candida albicans}\).

Keywords: Hydrazine, Zinc complex, Manganese complex, Crystal structure, Antimicrobial activity

1. Introduction

Schiff bases bearing characteristic C=N bonds are a kind of versatile ligands in coordination chemistry.¹ In recent years, metal complexes of Schiff bases have attracted considerable attention due to their interesting biological activity, such as antifungal, antibacterial and antitumor.² Schiff base complexes derived from salicylaldehyde and its derivatives with primary amines, bearing the \(N_2O, N_2S, NO_2\) or \(NSO\) donor sets, have particular biological activities.³ Hydrazine is a kind of special Schiff base compound, which possess interesting biological activities.⁴ Metal complexes usually show stronger biological activities than the hydrazine ligands.⁵ Chang and coworkers have reported that some transition metal complexes derived from \(N'-(1-(\text{pyridin-2-yl})\text{ethylidene})\text{isonicotinohydrazide}\) (HL; Scheme 1) have interesting antitumor and antioxidant activities.⁶ However, no report on the antimicrobial activity of complexes derived from HL has been reported so far. As an extension of our work on Schiff base complexes,⁷ a new zinc(II) compound, \([\text{ZnL}_2]\) (1), and a new manganese(II) compound, \([\text{MnL(HL)}]\text{ClO}_4\) (2), are reported.

2. Experimental

2.1. Material and Methods

2-Acetylpyridine and pyridine-4-carbohydrazide were purchased from Fluka. Other reagents and solvents were analytical grade and used without further purification. Elemental (C, H, and N) analyses were made on a Perkin-Elmer Model 240B automatic analyzer. Infrared (IR) spectra were recorded on an IR-408 Shimadzu 568 spectrophotometer. UV-Vis spectra were recorded on a Lambda 35 spectrometer. X-ray diffraction was carried out on a Bruker SMART 1000 CCD area diffractometer. The ligand HL was prepared according to the literature method.⁸

Caution! Perchlorate salts are potentially explosive. Only a small amount of material should be prepared, and they should be handled with great care.

2.2. Synthesis of Compound 1

The hydrazine (48.0 mg, 0.20 mmol) was dissolved by methanol (10 mL) and then a methanol solution (10 mL) of \(\text{Zn(ClO}_4\) (37.2 mg, 0.10 mmol) was added with stir-
ring. The mixture was stirred for 1 h at ambient temperature to give a colorless solution. Colorless block-shaped single crystals suitable for X-ray diffraction were formed by slow evaporation of the solution in air for several days. The yield is 45% (based on Zn). IR data (KBr, cm\(^{-1}\)): 1595 (C=N), 1498, 1451, 1363, 1160, 1072, 947, 854, 543, 522. UV-vis data in methanol [\(\lambda_{\text{max}}\) (nm), \(\varepsilon\) (L mol\(^{-1}\) cm\(^{-1}\))]: 277, 6450; 362, 15510. Anal. Calcd. (%) for C\(_{26}\)H\(_{22}\)N\(_8\)O\(_2\)Zn: C, 57.42; H, 4.08; N, 20.60. Found (%): C, 57.61; H, 4.17; N, 20.45.

2. 3. Synthesis of Compound 2

The hydrazone (48.0 mg, 0.20 mmol) was dissolved by methanol (10 mL) and then a methanol solution (10 mL) of Mn(ClO\(_4\))\(_2\) 6H\(_2\)O (36.2 mg, 0.10 mmol) was added with stirring. The mixture was stirred for 1 h at ambient temperature to give a brown solution. Brown block-shaped single crystals suitable for X-ray diffraction were formed by slow evaporation of the solution in air for several days. The yield is 33% (based on Mn). IR data (KBr, cm\(^{-1}\)): 1596 (C=N), 1499, 1450, 1365, 1160, 1079 (ClO\(_4\)), 945, 855, 756, 696, 622, 546, 518. UV-vis data in methanol [\(\lambda_{\text{max}}\) (nm), \(\varepsilon\) (L mol\(^{-1}\) cm\(^{-1}\))]: 271, 7270; 366, 16480. Anal. Calcd. (%) for C\(_{26}\)H\(_{22}\)ClMnN\(_8\)O\(_6\): C, 49.34; H, 3.50; N, 17.70. Found (%): C, 49.16; H, 3.62; N, 17.83.

2. 4. X-ray Structure Determination

Data were collected from selected crystals mounted on glass fibres. The data were collected with Mo K\(_\alpha\) radiation (0.71073 Å) at 298(2) K with a Bruker SMART 1000 CCD area diffractometer. The data for the two complexes were processed with SAINT9 and corrected for absorption using SADABS.10 Multi-scan absorption corrections were applied with \(\psi\)-scans.11 The structures were solved by direct methods using the program SHELXS-97 and were refined by full-matrix least-squares techniques on \(F^2\) using anisotropic displacement parameters.12 All hydrogen atoms were placed at the calculated positions. Idealized H atoms

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>2</th>
</tr>
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<tr>
<td>Habit, color</td>
<td>Block, colorless</td>
<td>Block, brown</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C(<em>{26})H(</em>{22})N(_8)O(_2)Zn</td>
<td>C(<em>{26})H(</em>{23})ClMnN(_8)O(_6)</td>
</tr>
<tr>
<td>Formula weight</td>
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<td>633.91</td>
</tr>
<tr>
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<td>Orthorhombic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>Aba2</td>
<td>P2(_1)/n</td>
</tr>
<tr>
<td>Unit cell dimensions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a), Å</td>
<td>12.363(2)</td>
<td>11.755(2)</td>
</tr>
<tr>
<td>(b), Å</td>
<td>20.251(2)</td>
<td>9.437(2)</td>
</tr>
<tr>
<td>(c), Å</td>
<td>9.595(2)</td>
<td>26.198(2)</td>
</tr>
<tr>
<td>(a)(^\circ)</td>
<td>90</td>
<td>90</td>
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<tr>
<td>(\beta)(^\circ)</td>
<td>90</td>
<td>98.197(2)</td>
</tr>
<tr>
<td>(\gamma)(^\circ)</td>
<td>90</td>
<td>90</td>
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<tr>
<td>(V), Å(^3)</td>
<td>2402.7(7)</td>
<td>2876.5(8)</td>
</tr>
<tr>
<td>(Z)</td>
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<td>4</td>
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<tr>
<td>(\rho_{\text{calc}}, \text{g cm}^{-3})</td>
<td>1.504</td>
<td>1.464</td>
</tr>
<tr>
<td>(F(000))</td>
<td>1120</td>
<td>1300</td>
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<tr>
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<td>1.065</td>
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<tr>
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<tr>
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<tr>
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<td>1</td>
<td>0</td>
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<tr>
<td>(R_1, wR_2) ([I &gt; 2\sigma(I)])</td>
<td>0.0333, 0.0634</td>
<td>0.0879, 0.2408</td>
</tr>
<tr>
<td>(R_1, wR_2) (all data)</td>
<td>0.0538, 0.0718</td>
<td>0.1133, 0.2583</td>
</tr>
<tr>
<td>Goodness-of-fit on (F^2)</td>
<td>1.020</td>
<td>1.070</td>
</tr>
</tbody>
</table>

| Table 2. Selected bond lengths (Å) and bond angles (º) for complexes 1 and 2 |
|------------------|------------------|
|                  |                  |

| Parameters       | 1               | 2               |
|------------------|------------------|
| Zn(1)–N(3)       | 2.069(3)         | 2.149(3)        |
| Zn(1)–N(4)       | 2.193(4)         |                 |
| N(3)–Zn(1)–N(3A) | 173.3(3)         | 101.34(13)      |
| N(3)–Zn(1)–O(1)  | 74.22(13)        | 100.30(17)      |
| N(3)–Zn(1)–N(4)  | 75.14(14)        | 109.70(15)      |
| O(1)–Zn(1)–N(4A) | 91.47(13)        | 142.58(14)      |
| N(4)–Zn(1)–N(4A) | 93.19(19)        |                 |

| Parameters       | 1               | 2               |
|------------------|------------------|
| Mn(1)–O(1)       | 2.144(4)         | 2.151(4)        |
| Mn(1)–N(7)       | 2.191(4)         | 2.193(4)        |
| Mn(1)–N(4)       | 2.314(5)         | 2.326(4)        |
| O(1)–Mn(1)–O(2)  | 107.34(16)       | 122.05(15)      |
| O(2)–Mn(1)–N(7)  | 72.27(15)        | 72.01(14)       |
| O(2)–Mn(1)–N(3)  | 125.51(15)       | 155.58(17)      |
| O(1)–Mn(1)–N(4)  | 142.00(15)       | 90.69(16)       |
| N(7)–Mn(1)–N(8)  | 90.90(15)        | 90.90(15)       |
| N(4)–Mn(1)–N(8)  | 93.19(19)        |                 |

Symmetry code for A: –x, –y, z.
2.5. Antimicrobial Assay

Qualitative determination of antimicrobial activity was done using the disk diffusion method as described in the literature. Suspensions in sterile peptone water from 24-h cultures of microorganisms were adjusted to 0.5 McFarland. Muller–Hinton Petri dishes of 90 mm were inoculated using these suspensions. Paper disks (6 mm in diameter) containing 10 μL of the substance to be tested (at a concentration of 2048 μg/mL in DMSO) were placed in a circular pattern in each inoculated plate. Incubation of the plates was done at 37 °C for 18–24 h. Reading of the results was done by measuring the diameters of the inhibition zones generated by the test substance. Tetracycline was used as a reference substance. Determination of MIC was done using the serial dilutions in liquid broth method. The materials used were 96-well plates, suspensions of microorganism (0.5 McFarland), Muller-Hinton broth (Merck) and stock solutions of each substance to be tested (2048 μg/mL in DMSO). The following concentrations of the substances to be tested were obtained in the 96-well plates: 1024, 512, 256, 128, 64, 32, 16, 8, 4 and 2 μg/mL. After incubation at 37 °C for 18–24 h, the MIC for each tested substance was determined by microscopic observation of microbial growth. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited.

3. Results and Discussion

3.1. Chemistry

The hydrazone compound HL was prepared by the condensation of equimolar quantities of 2-acetylpyridine with pyridine-4-carbohydrazide in methanol at ambient temperature. The hydrazone compound prepared in this way was formed in nearly quantitative yield and of high purity. The compounds 1 and 2 were readily synthesized by reaction of the hydrazone compound HL with zinc perchlorate and manganese perchlorate in methanol at ambient temperature. All the compounds are very stable at room temperature in the solid state, and soluble in common organic solvents, such as methanol, ethanol, and acetonitrile. The results of the elemental analyses are in accord with the composition suggested for the hydrazone and the complexes.

### Table 3 Distances (Å) and angles (°) involving hydrogen bonding of the complexes

<table>
<thead>
<tr>
<th>D–H--A</th>
<th>d(D–H)</th>
<th>d(H--A)</th>
<th>d(D--A)</th>
<th>Angle(D–H--A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(9)–H(9)--O(1)</td>
<td>0.93</td>
<td>2.36(5)</td>
<td>3.180(5)</td>
<td>148(6)</td>
</tr>
<tr>
<td>C(10)–H(10)--N(1)</td>
<td>0.93</td>
<td>2.54(5)</td>
<td>3.455(5)</td>
<td>170(6)</td>
</tr>
<tr>
<td>C(13)–H(13A)--N(2)</td>
<td>0.96</td>
<td>2.43(5)</td>
<td>2.811(5)</td>
<td>103(6)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N(1)–H(1)–N(5)</td>
<td>0.93</td>
<td>2.39(3)</td>
<td>3.284(4)</td>
<td>161(7)</td>
</tr>
<tr>
<td>C(10)–H(10)--O(5)</td>
<td>0.93</td>
<td>2.39(3)</td>
<td>3.284(4)</td>
<td>161(7)</td>
</tr>
<tr>
<td>C(13)–H(13C)--N(2)</td>
<td>0.96</td>
<td>2.40(3)</td>
<td>2.778(4)</td>
<td>103(5)</td>
</tr>
<tr>
<td>C(23)–H(23)--O(6)</td>
<td>0.93</td>
<td>2.48(4)</td>
<td>3.258(5)</td>
<td>142(6)</td>
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<tr>
<td>C(26)–H(26A)--N(6)</td>
<td>0.96</td>
<td>2.37(3)</td>
<td>2.788(4)</td>
<td>106(5)</td>
</tr>
</tbody>
</table>

Symmetry codes: #1: ½ + x, −y, −½ + z; #2: ½ − x, −½ + y, −1 + z; #3: ½ + x, −½ − y, −1/2 + z; #4: ½ − x, ½ + y, ½ − z; #5: −x, 1 − y, −z.
range from 74.22(13) to 109.70(15)° and from 148.77(11) to 173.3(3)°, respectively, indicating the distortion of the octahedral coordination from ideal geometry. In the crystal structure of the compound, the complex molecules are linked through hydrogen bonds (Table 3), to form a three-dimensional network (Fig. 2).

3. 4. Structure Description of Compound 2

The molecular structure of compound 2 is shown in Fig. 3. Selected bond distances and angles are listed in Table 2. The compound contains a [MnL(HL)]⁺ complex cation and a perchlorate anion. The Mn atom in the [MnL(HL)]⁺ complex cation is coordinated by two pyridine N, two imine N, and two enolate O atoms from one deprotonated form of the hydrazone ligand and one zwitterionic form of the hydrazone ligand, forming an octahedral geometry. The hydrazones act as tridentate ligands, forming two five-membered chelate rings with the Mn atom. The bond distances subtended at the Mn atom are comparable to those observed in the similar manganese(II) complexes with Schiff bases. The cis and trans coordinate bond angles are range from 70.38(15) to 125.52(15)° and from 141.99(14) to 155.58(17)°, respectively, indicating the distortion of the octahedral coordination from ideal geometry. In the crystal structure of the compound, the [MnL(HL)]⁺ complex cations and the perchlorate anions are linked through hydrogen bonds (Table 3), to form a three-dimensional network (Fig. 4).

3. 5. Antimicrobial Activity

The results are summarized in Table 4. A comparative study of minimum inhibitory concentration (MIC) values of the hydrazone and the metal complexes indicates that the complexes have better activity than the free hy-
drazone. Generally, this is caused by the greater lipophilic nature of the complexes than the ligand. Such increased activity of the metal chelates can be explained on the basis of chelating theory. On chelating, the polarity of the metal atoms will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of positive charge of the metal atoms with donor atoms. Further, it increases the delocalization of \( p \)-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membrane and blocks the metal binding sites on enzymes of microorganisms.

From Table 4, it is obvious that the two complexes have higher antibacterial and antifungi activities against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* when compared to the free hydrazone. Complex 1 has strong activity against *Escherichia coli*, with MIC value of 0.20 \( \mu \)g/mL, which is comparable to Tetracycline. Complex 1 has medium activity against *Staphylococcus aureus* and weak activity against *Candida albicans*. Complex 2 has effective activity against *Escherichia coli*, and weak activity against *Staphylococcus aureus* and *Candida albicans*. In general, the zinc complex has stronger activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* than the manganese complex. So, the metal type of the complexes can influence the antimicrobial activity.

<table>
<thead>
<tr>
<th>Compounds</th>
<th><em>Staphylococcus aureus</em></th>
<th><em>Escherichia coli</em></th>
<th><em>Candida albicans</em></th>
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<tbody>
<tr>
<td>The hydrazone</td>
<td>64</td>
<td>32</td>
<td>&gt;512</td>
</tr>
<tr>
<td>1</td>
<td>8.0</td>
<td>2.0</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>16.0</td>
<td>8.0</td>
<td>128</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.32</td>
<td>2.12</td>
<td>&gt;1024</td>
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### 4. Supplementary Material

CCDC 1871743 for 1, and 1871744 for 2 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from http://www.ccdc.cam.ac.uk/const/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or email: deposit@ccdc.cam.ac.uk.

### 5. Acknowledgments

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### 6. References


Xue et al.: *Synthesis, Crystal Structures, and Antimicrobial Activity* ...

Povzetek
Sintetizirali smo dve enojedrni cinkovi(II) in manganovi(II) spojin, [ZnL₂] (1) in [MnL(HL)]ClO₄ (2), kjer je L monoanionska oblika N’-(1-(piridin-2-il)etiliden)izonikotinohidrazida (HL) in HL ion dvojček HL, ter ju okarakterizirali z elementno analizo, IR in UV-Vis spektroskopijo ter monokristalno rentgensko strukturno analizo. Spojina 1 je nevtralen [ZnL₂] kompleks. Spojina 2 je zgrajena iz [MnL(HL)]⁺ kompleksnega iona in enega perkloratnega aniona. Kovinski ion v obeh kompleksih so oktaedrično koordinirani. Hidrazonski ligand se koordinira na kovinski ion preko piridinskega N, iminskega N in enolatnega O atoma. Spojinama smo določili antimikrobno aktivnost proti Staphylococcus aureus, Escherichii coli in Candidi albicans.