J. Iran. Chem. Soc., Vol. 8, No. 3, September 2011, pp. 727-733.

JOURNAL OF THE
Iranian
Chemical Society

Synthesis, X-Ray Characterization and Antimicrobial Activity of Iron(II) and Cobalt(III) Complexes with the Schiff Base Derived from Pyridoxal and Semicarbazide or S-methylisothiosemicarbazide

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(Received 17 July 2010, Accepted 25 November 2010)

The synthesis, structural analysis and antibacterial reactivity of two octahedral complexes, namely $[Fe(PLSC)_2](NO_3)_2.H_2O$, **1** (PLSC is pyridoxal semicarbazone), and $[Co(PLITSC\text{-}2H)(PLITSC\text{-}H)].CH_3OH$, **2** (PLITSC is pyridoxal S-methylisothiosemicarbazone) are reported.

Keywords: Pyridoxal-semicarbazone, Pyridoxal-S-methylisothiosemicarbazone Fe(II) complex, Co(III) complex, Structure, Antimicrobial activity

INTRODUCTION

Isothiosemicarbazones (ITSC) and semicarbazones (SC) can act as biologically active antibacterial agents [1] and are excellent chelating ligands of different denticity resulting in the synthesis of a great number of transition metal complexes containing these ligands [2,3]. Several of these complexes, due to their stability and intense color, have been suggested as analytical reagents [4]. Furthermore, complexes incorporating either SC- or ITSC-based ligands exhibit a wide variety of biologically important properties, such as antiviral, antitumor and anti-inflammatory activities [5,6]. Dehydration of SC or ITSC with pyridoxal moiety (3-hydroxy-5-hydroxymethyl-2-methyl-pyridine-4-carbaldehyde) results in the formation of Schiff base ligands PLSC and PLITSC, respectively [7]. The synthesis, physical properties, structural analysis, as well as the biological activities of several transition metal complexes incorporating PLSC [8,9,10,11,12,13,14] or PLITCS [15,16, 17,18] have already been described. The tridentate coordination mode is predominant as regards both PLSC and PLITSC which can adopt three different forms in the coordination sphere of a transition metal, namely *neutral* (but zwitterionic), *monoanionic* (hydrazine deprotonation) and *dianionic* (both pyridinium and hydrazine deprotonation) forms (see Fig. 1).

Complexes containing a single PLSC (L) ligand in its neutral form, such as $LCuBr_2$ [10], $LFe\ Cl_2(H_2O)$ [11] and $LNi(NCS)_2$ [13], are the most predominant complexes characterized thus far. Several complexes containing PLSC ligand in its anionic (*e.g.* $(L\text{-}H)PtCl_3$ [9]) and dianionic (*e.g.* $[Ni(L\text{-}2H)(NH_3)].1.5H_2O$ [13]) forms are known. Moreover, there is the form $[Ni(L\text{-}H)_2].2H_2O$ [8] which represents the

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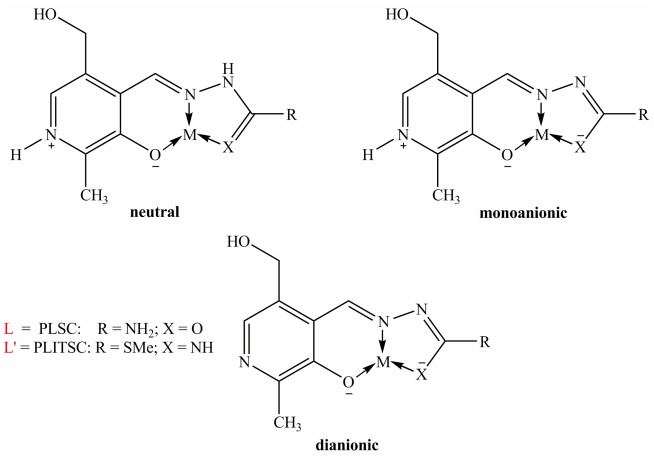
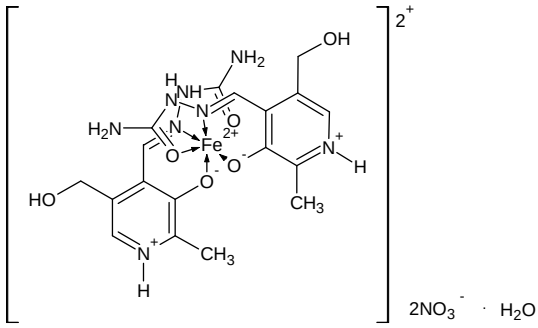
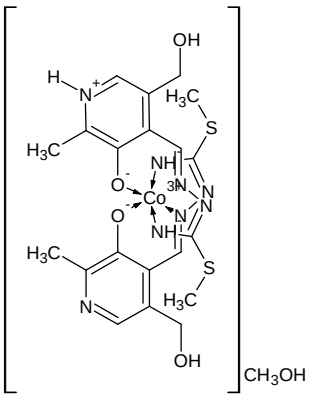


Fig. 1. Ligand forms for PLSC and PLITSC.

only complex containing two L ligands which, in this case, are monoanionic. As for the PLSC-base complexes, the complexes incorporating the neutral form of PLITSC (L'), such as $[Fe(ITSCPL)Cl_3].H_2O$ [16], are most predominant, while several examples in which the ligand is found in monoanionic (*e.g.* $[Fe(L'\text{-}H)_2]OAc.2H_2O$ [16]) and dianionic (*e.g.* $[Cu(L'\text{-}2H)NH_3].H_2O.MeOH$ [7]) forms are also reported. Thus, we wish to report $[Fe(L)_2](NO_3)_2.H_2O$, **1**, which is the only second structurally characterized complex containing two PLSC ligands, although it is the first one in which both ligands are in their neutral form, and $[Co(L'\text{-}2H)(L'\text{-}H)].CH_3OH$, **2**, which represents the first structurally characterized complex that incorporates two PLITSC ligands (Fig. 2).



(1)



(2)

Fig. 2. Schematic representations for **1** and **2**.

EXPERIMENTAL

Reagents

All commercially obtained reagent-grade chemicals were used without further purification, except for the ligands [7].

Synthesis of $[Fe(L)_2](NO_3)_2.H_2O$, 1. 0.26 g (1 mmol) of $L.2H_2O$ was dissolved in EtOH (10 cm^3) by heating followed by the addition of 0.20 g (0.5 mmol) of $Fe(NO_3)_2.9H_2O$ into the warm solution. To the resulting brown solution, 0.06 g (1 mmol) of LiOAc was added. After a couple of hours, separation of brown-colored crystals suitable for the X-ray analysis was observed. The crystals were filtered and washed with EtOH. Yield: 0.19 g (78%).

Synthesis of complex $[Co(L'\text{-}2H)(L'\text{-}H)].CH_3OH$, 2. 0.27 g (1 mmol) of L' and 0.28 g (1 mmol) of $CoCl_2.6H_2O$ was dissolved in 10 cm^3 MeOH and warmed up until all of the reactants dissolved. The warm mixture was filtrated and set aside for 10 h at room temperature, until the separation of violet, single crystals was compleded. The crystalls were filltered and wahsed with EtOH. Yield: 0.16 g (65%).

Crystal Structure Determination

Data for complexes **1** and **2** were collected on a Philips PW1100 diffractometer with MoKα radiation [λ = 0.7107 Å].

The structure was solved using direct method SIR 92 [19] and refined using SHELXL 97 [20] on F^2 by full-matrix least-squares with anisotropic displacement parameters for all non-hydrogen atoms.

Details concerning crystal data and refinement are given in

Table 1. Crystal Data and Structure Refinement Details for **1** and **2**

Identification code	**1**		**2**	
Empirical formula	$C_{18}H_{26}FeN_{10}O_{13}$		$C_{21}H_{29}CoN_8O_5S_2$	
Formula weight	664.32		596.57	
Temperature	293(2) K		293(2) K	
Wave length	0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Monoclinic	
Space group	P-1		P21/c	
Unit cell dimensions	a = 8.8925(9)	A = 72.538(8)	a = 11.375(3)	
in Å and °	b = 12.1639(12)	B = 87.904(8)	b = 14.263(5)	B = 99.63(2)
	c = 13.3999(12)	γ = 72.312(9)	c = 15.854(6)	
Volume	1314.9(2) $Å^3$		2535.9(15) $Å^3$	
Z	2		4	
Density (calculated)	1.632 mg m^{-3}		1.563 mg m^{-3}	
Absorption coefficient	0.659 mm^{-1}		0.892 mm^{-1}	
F(000)	668		1240	
Crystal size	$0.21 \times 0.16 \times 0.09$ mm^3		$0.19 \times 0.12 \times 0.08$ mm^3	
Theta range for data collection	2.97 to 29.24°		1.82 to 25.99°	
Index ranges	-11 <= h <= 11, -14 <= k <= 16,		0 <= h <= 14, 0 <= k <= 17,	
	-18 <= l <= 17		-19 <= l <= 19	
Reflections collected	10960		5221	
Independent reflections	5941 [R(int.) = 0.0388]		4966 [R(int.) = 0.0372]	
Completeness to theta =25.29 (= 29.24°)	82.9%		99.8%	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data/restraints/parameters	5941/0/389		4966/0/356	
Goodness-of-fit on F^2	0.916		1.028	
Final R indices [I > 2sigma(I)]	R1 = 0.0631, wR2 = 0.1394		R1 = 0.0567, wR2 = 0.1403	
R indices (all data)	R1 = 0.1161, wR2 = 0.156		R1 = 0.1137, wR2 = 0.1630	
Largest diff. peak and hole	0.799 and -0.488 e.$Å^{-3}$		0.903 and -0.430 e.$Å^{-3}$	

Table 1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Base as CCDC reference number 735523 for **1** and 725162 for **2**.

Bioassays

In order to obtain the quantitative data for the reported compounds, the micro dilution technique was used (NCCLS, 2000) [21]. The following bacteria were tested: *Escherichia coli* (ATCC 10526), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 11632), and *Bacillus cereus* (ATCC 10876). Cultures of the test bacteria were growing overnight in Müller-Hinton agar (Institute of Immunology and Virology, Torlak, Belgrade, Serbia) at 37 °C and then transferred to sterile saline. The bacterial suspension was adjusted with sterile saline to a concentration of approximately 1.0×10^7 cells/ml. The 1 ml of bacterial suspension was homogenized with 9 ml of melted (45 °C) Müeller-Hinton agar. Minimum inhibitory concentrations (MICs)

determination was performed by a serial dilution technique, using 96-well microtitre plates. The inocula applied contained approximately 1.0×10^5 cells in a final volume of 100 µl/well. The compounds tested were dissolved in H_2O (compounds L, $[Fe(L)_2](NO_3)_2.H_2O$, L'; conc. 5×10^{-3}/10 ml H_2O and DMSO ($[Co(L'-2H)(L'-H)].CH_3OH$; conc. 5×10^{-3}/10 ml DMSO) and added to the broth medium with bacterial inocula in a volume of 100 µl/well. The covered plates were incubated under aerobic conditions at 37 °C for 24 h. The lowest concentrations without visible growth (at the binocular microscope) were defined as concentrations which completely inhibited bacterial growth (MICs). DMSO was used as a negative control, while chloramphenicol was used as a positive control. Dilutions of the inocula were also cultured on solid MH to verify the absence of contamination and to check their validity. All tests were performed in triplicate.

RESULTS AND DISCUSSION

The molecular structure for **1** is shown in Fig. 3. It crystallizes in P-1 space group and it contains one discrete dicationic unit $[Fe(H_2L)_2]^{2+}$, two NO^{3-} anions and one H_2O molecule bond together with an extensive hydrogen-bonding network. The environment around the central cobalt atom in **1** can be best described as a distorted octahedral geometry. In fact, the N(3A)-Fe-N(3B) angle (172,17(2)°) is to a certain extent similar to the theoretical 180°, whereas the other two symmetry-related, O(1A)-Fe-O(2A) (155,80(11)º) and O(1B)-Fe-O(2B) (156,61 (11)º) angles greatly deviate from linearity due to the chelation rings strain. Furthermore, the angles formed by the carbonyl and phenolic O atoms and Fe (O(1A)-Fe-O(1B) and O(2A)-Fe-O(2B)) differ from 90º (87.02 and 95.35º, respectively) confirming a distorted octahedral geometry around the central Fe cation (Table 2). Furthermore, the phenolic Fe-O (1.895(2) to 1.942(2) Å for Fe-O2(A) and Fe-O2(B), respectively), the carbonic Fe-O (2.002(3) and 2.025(2) Å for Fe-O1(A) and Fe-O(1B), respectively) and hydrazine Fe-N (2.091(3) and 2.184(3) Å for Fe-N3(A) and Fe-N3(B), respectively) bond lengths fall within the range for the analogous bond distances found in the reported complexes.

It is also worth mentioning that the bond lengths of these three bond distance sets for **1** are longer than the analogous bond distances found in the other reported complexes with two L ligands due to the monoanionic nature of PLSC ligand in $[Ni(PLSC-H)_2].2H_2O$.

The values for certain bond lengths and angles of the ligand backbone (O(phenolic)-C-C-C-N(hydrazine)-N-C-O(carbonyl)) are crystallographic evidences used to determine which form (L, $[L-H]^-$ or $[L-2H]^{2-}$) the coordinated ligand L adopts. For example, the first deprotonation of L, forming

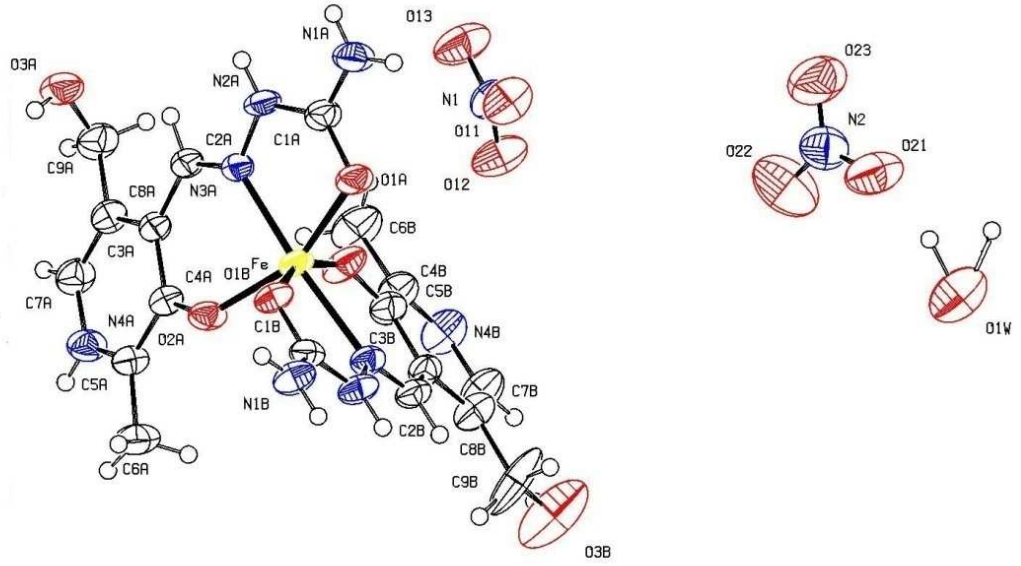


Fig. 3. The molecular structure for **1**.

Table 2. Selected Bond Lengths [Å] and Angles [°] for **1**

Fe-O(2B)	1.898(3)	O(2B)-Fe-O(2A)	95.34(12)
Fe-O(2A)	1.942(2)	O(2B)-Fe-O(1A)	98.34(13)
Fe-O(1A)	2.002(3)	O(2A)-Fe-O(1A)	155.80(11)
Fe-O(1B)	2.025(2)	O(2B)-Fe-O(1B)	156.61(11)
Fe-N(3A)	2.091(3)	O(2A)-Fe-O(1B)	88.28(11)
Fe-N(3B)	2.184(3)	O(1A)-Fe-O(1B)	87.03(11)
		C(5A)-N(4A)-C(7A)	123.7(3)
		C(5B)-N(4B)-C(7B)	124.3(4)

Table 3. Selected Bond Lengths [Å] and Angles [°] for **2**

Co-N(1)	1.884(3)	N(1)-Co-N(1´)	171.44(16)
Co-N(1´)	1.888(3)	N(1)-Co-N(3)	81.71(17)
Co-N(3)	1.890(4)	N(1´)-Co-N(3)	91.59(17)
Co-N(3´)	1.898(4)	N(1)-Co-N(3´)	92.27(16)
Co-O(1)	1.945(3)	N(1´)-Co-N(3´)	82.28(16)
Co-O(1´)	1.909(3)	N(1)-Co-O(1´)	90.30(15)
		C(8)-N4-C(6)	118.67(4)
		C(8´)-N(4´)-C(6´)	124.27(4)

monoanionic form $[L\text{-}H]^-$, changes the carbonyl C-O bond from a double to a single bond and the hydrazine N-N from a single to a double bond. Further deprotonation to form $[L\text{-}2H]^{2-}$ leads to the change in the C-N-C angle of the pyridine ring from about 125 to about 118º (*e.g.* $[Ni(L\text{-}H)_2].2H_2O$ [8]). Thus, in complex **1** the carbonyl C-O (1.257 Å, 1.287 Å) and N-N (1.360, 1.347 Å) bond lengths, and the pyridine C-N-C angles (123.7(3)º, 124.3(4)º) confirm that the PLSC ligand is in its neutral (zwitterionic) form H_2L.

The title complex **2** crystallizes in the space group $P2_1/c$ and incorporates two PLITSC ligands resulting in mer-octahedral geometry (expected due to the planarity of the ligands) around the metal cation (Fig. 4). Table 2 shows that the geometry around the central Co ion is slightly disordered as most of the angles are close to the theoretical values 90 or 180°, while only two angles N(1)-Co-N(1´) (171.44(16)°) and N(1)-Co-N(3) (81.71(17)°) deviate by more than 6° from their respected theoretical values. The Co-N (av. 1.89 Å) and Co-O (av. 1.93 Å) bond lengths fall within the range found for other complexes incorporating L' [17]. One of the interesting features of **2** that should be mentioned relates to the different forms of the two chelating ligands. One of the ligands is in the monoanionic form as is seen from the shortening of the C(1´)-N(2´) (1.334(6) Å) compared to the analogous bond in the neutral form (~1.37 Å [17,18]). The other ligand is in the dianionic form as is seen from the C(6)-N(4)-C(8) angle value 118.67(4)°, indicative of the second deprotonation.

The summary of the antimicrobal activities of the ligands (L and L') and complexes (1 and 2) are given in Table 4. From this table, it can be concluded that complex **2** shows the greatest antibacterial activity in comparison to the other tested substances. The fact that complex **2** showed activity towards both Gram negative (*Escherichia coli*, *Pseudomonas aeruginosa*) and Gram positive (*Staphylococcus aureus*, *Bacillus cereus*) bacteria, revelas that the antibacterial mechanism of **2** is not dependant on the structural features of the bacterial cell wall. Additionally, complex **2** showed antibacterial activity towards *Pseudomonas aeruginosa* (MIC

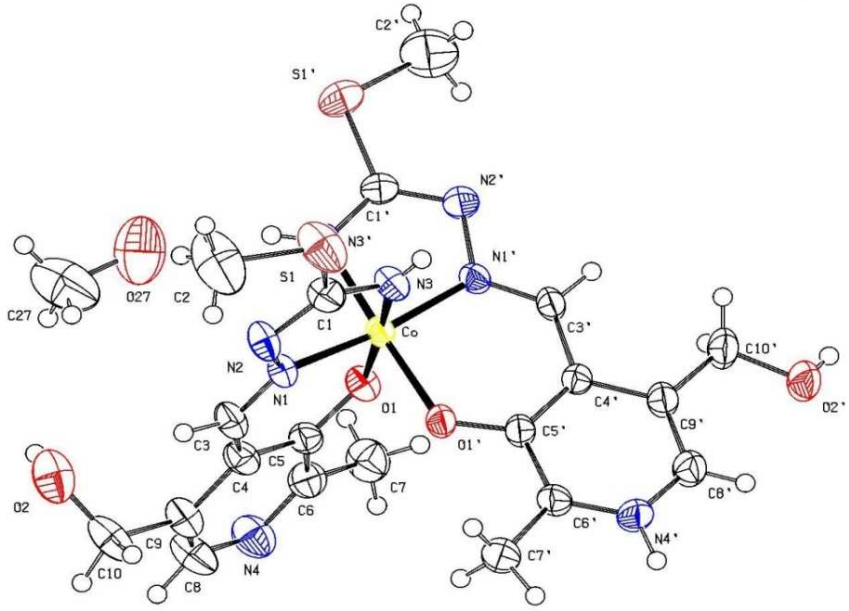


Fig. 4. The molecular structure for **2**.

Table 4. Minimum Inhibitory Concentrations of the Compaunds Tested (mg ml^{-1})

Organism	L	**1**	L'	**2**	Chloramphenicol
P. aeruginosa	>0.25	>1	>0.25	0.060	0.050
E. coli	>0.25	>1	>0.25	0.060	0.005
S. aureus	>0.25	>1	>0.25	0.125	0.005
B. cereus	>0.25	>1	>0.25	0.060	0.010

0.06 mg ml^{-1}) bacteria, which has been reported to show the least amount of susceptiveness towards antibiotic chloramphenicol (MIC 0.05 mg) [22]. It is also worth noting that these are typical soil and water bacteria which are widely distributed among fresh foods, especially vegetables, meats, poultry, and seafood products [22] and that complex **2** showed activity against *Staphylococcus aureus* (MIC 0.125 mg ml^{-1}), one of the common Gram positive bacteria causing food poisoning.

CONCLUSIONS

Octahedral complexes of Fe and Co incorporating pyridoxal substituted Schiff base ligands have been synthesized. The Co complex **2** shows a broad spectrum of antibacterial activity towards the most common types of bacteria and is significantly more active than complex **1**. This implies that the ligand pyridoxal S-methylisothio-semicarbazone can be used in synthesizing other complexes having the potential of being biologically active. The significant biological activity of the synthesized complex **2** may have wide practical applications in medicine, pharmacy and food technology.

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