

Design, Synthesis and Characterization of a Bicompartamental bithiosemicarbazone Ligand [†]

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Abstract: In this work, we present the design and synthesis of the *bithiosemicarbazone* ligand H_3L^{Me} by means of an imine condensation reaction between 2-hydroxyisophthalaldehyde and 4-methyl-3-thiosemicarbazide. This ligand is bicompartamental, pentadentate $[N_2S_2O]$ and potentially trianionic. The presence of a spacer constituted by a phenol group facilitates the coordination of transition metal ions, giving rise to a great variety of structures. To confirm the purity of the ligand, different characterization techniques were employed, including elemental analysis, mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance. The acquisition of suitable crystals of H_3L^{Me} allowed us to analyze its structure through X-ray diffraction studies.

Keywords: ligand; *bithiosemicarbazone*; coordination chemistry



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1. Introduction

Thiosemicarbazones and *bithiosemicarbazones* are organic ligands whose skeletons have donor atoms such as nitrogen and sulfur. These compounds are obtained by the reaction of a thiosemicarbazide with aldehydes or ketones [1]. The design and synthesis of this type of ligands has been extensively studied in recent decades due to their important properties: ion sensing [2], catalytic [3], magnetic [4], pharmaceutical, and biological (antiviral, radioprotective, anti-inflammatory, antibacterial, antifungal and antitumoral) [5].

With all this in mind, the coordination chemistry of these types of compounds and, therefore, their biological applications have been of great interest. Thus, in this work we report the design, synthesis, and characterization of a *bithiosemicarbazone* ligand, H_3L^{Me} , a potential precursor of dinuclear metal-derived complexes.

2. Experimental Section

The *bithiosemicarbazone* ligand H_3L^{Me} synthesis was carried out by means of an imine condensation reaction between 2-hydroxyisophthalaldehyde and 4-methyl-3-thiosemicarbazide in ratio 1:2, using absolute ethanol as a solvent (Figure 1). To promote the formation of the imine bond, acid catalysis was used by adding *p*-toluenesulfonic acid. The reaction mixture was refluxed for 4 h using a Dean–Stark trap to remove the released water.

Finally, the *bithiosemicarbazide* ligand was isolated as a yellow solid, which was characterized by the usual techniques in the solid state and in solution.

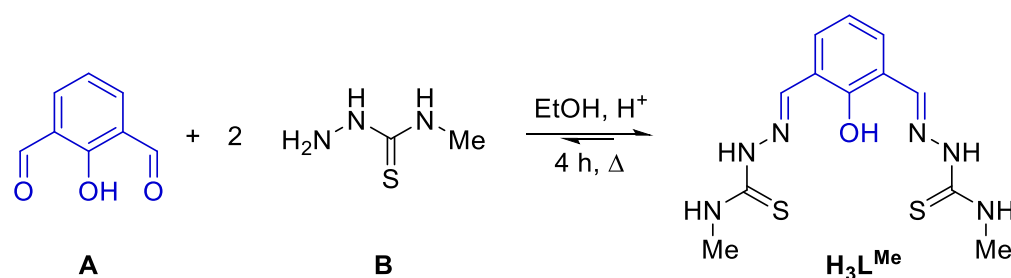


Figure 1. Synthesis of the *bisthiosemicarbazone* ligand $\text{H}_3\text{L}^{\text{Me}}$.

$\text{H}_3\text{L}^{\text{Me}}$: Yield 0.722 g, (90%). Elemental analysis, Calc. for $\text{C}_{12}\text{H}_{16}\text{N}_6\text{OS}_2$: C, 44.4; H, 5.0; N, 25.9; S, 19.8. Found: C, 44.5; H, 5.0; N, 25.7; S, 19.9%. MS ESI+ (m/z): 325.1 [$\text{H}_3\text{L}^{\text{Me}} + \text{H}$]. IR (KBr, cm^{-1}): $\nu(\text{O-H})$ 3360 (m), $\nu(\text{N-H})$ 3163 (m), $\nu(\text{C=N} + \text{C-N})$ 1611 (m), 1541 (mf), 1497 (m), $\nu(\text{C-O})$ 1231 (f) $\nu(\text{C=S})$ 1094 (m), 800 (mf), $\nu(\text{N-N})$ 1051 (d) RMN ^1H (400 MHz, dmsO-d_6) δ 11.51 (s, 2H), 9.95 (s, 1H), 8.51 (d, $J = 4.7$ Hz, 2H), 8.37 (s, 2H), 7.80 (d, $J = 7.8$ Hz, 2H), 6.98 (t, $J = 7.7$ Hz, 1H), 3.02 (s, 6H). RMN ^{13}C (400 MHz, DMSO-d_6): δ/ppm , 178.50 (C=S), 155.40 (C-O), 141.59 (C=N), 130.78–120.73 (C-Ar), 31.80 (CH_3).

Crystallographic Data

$\text{H}_3\text{L}^{\text{Me}} \cdot \text{CH}_3\text{OH}$: $\text{C}_{12}\text{H}_{16}\text{N}_6\text{OS}_2$; MW: 356.47 $\text{g} \cdot \text{mol}^{-1}$; crystal dimensions: $0.12 \times 0.03 \times 0.02$ mm; monoclinic; $\text{P2}_1/\text{c}$; $a = 13.2462$ (7), $b = 19.1436$ (9), $c = 6.8852$ (4) Å; $\alpha = 90$; $\beta = 99.102$ (4), $\gamma = 90$ °; $V = 1723.96(16)$ Å³; $z = 2$; $\mu = 2.96$ mm^{−1}; measured reflections = 28545; independent reflections [R_{int}] = 3149 [0.165]; $R = 0.078$; $wR = 0.191$.

3. Results and Discussion

The *bisthiosemicarbazone* ligand $\text{H}_3\text{L}^{\text{Me}}$ can be described as bicompartamental, potentially trianionic, and pentadentate [$\text{N}_2\text{S}_2\text{O}$], showing two [NS] binding domains separated by a short spacer with an oxygen donor atom. The ligand $\text{H}_3\text{L}^{\text{Me}}$ was fully characterized by the usual techniques for organic compounds.

3.1. IR Spectroscopy

Infrared spectra were obtained in the solid state using the KBr pellet transmission technique in the range 4000–500 cm^{-1} (Figure 2). Band assignments were carried out based on the literature [6].

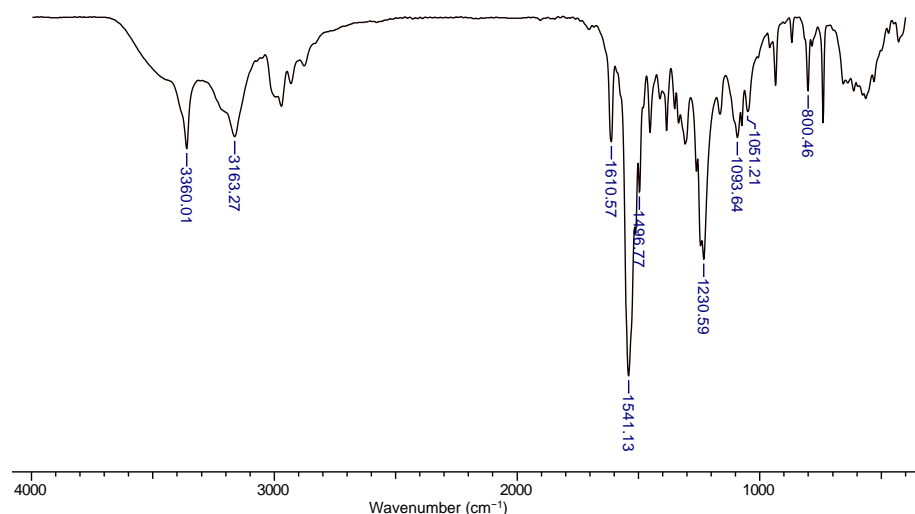


Figure 2. IR spectrum (cm^{-1}) of the *bisthiosemicarbazone* ligand $\text{H}_3\text{L}^{\text{Me}}$.

In these spectra, the absence of the band corresponding to the carbonyl group, $\nu(\text{C}=\text{O})$ of the precursor 2-hydroxyisophthalaldehyde around 1700 cm^{-1} , and the appearance of new bands around 1610 cm^{-1} attributed to the imine $\nu(\text{C}=\text{N})$ bonds, confirming the formation of the ligand $\text{H}_3\text{L}^{\text{Me}}$, should be highlighted.

3.2. X-ray Diffraction

The recrystallization in methanol of solid $\text{H}_3\text{L}^{\text{Me}}$ allowed us to obtain yellow crystals suitable for X-ray diffraction studies. The asymmetric unit of the $\text{H}_3\text{L}^{\text{Me}}$ ligand consists of a ligand molecule solvated by a methanol molecule (Figure 3). The main bond distances and angles given in Tables 1 and 2 are in the expected range for *bisthiosemicarbazone* ligands [7].

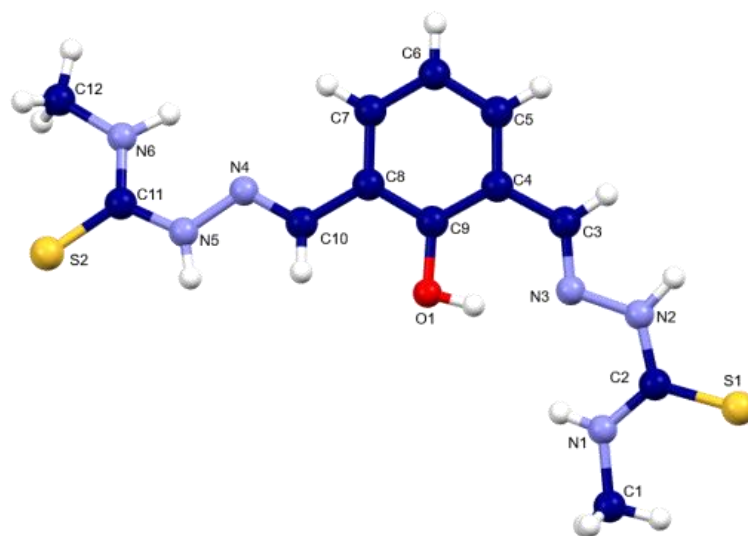


Figure 3. Crystal structure of the *bisthiosemicarbazone* ligand $\text{H}_3\text{L}^{\text{Me}} \cdot \text{CH}_3\text{OH}$. The solvent molecule was omitted for clarity.

Table 1. Selected bond length (Å) for $\text{H}_3\text{L}^{\text{Me}}$.

Main Bond Distances (Å)			
C3=N3	1.291	C10=N4	1.278
N2-N3	1.387	N4-N5	1.383
C2=S1	1.682	C11=S2	1.694
C2-N1	1.333	C11-N6	1.326
C9-O1	1.353		

Table 2. Selected bond angles ($^\circ$) for $\text{H}_3\text{L}^{\text{Me}}$.

Main Bond Angles ($^\circ$)			
N1-C2-N2	117.2	N6-C11-N5	116.6
N1-C2=S1	124.4	N6-C11=S2	124.8
N2-C2=S1	118.4	N5-C11=S2	118.6
N3=C3-C4	123.3	N4=C10-C8	120.3
C2-N2-N3	122.1	C11-N5-N4	119.3
C3=N3-N2	114.5	C10=N4-N5	115.5

The ligand shows an *E* configuration with respect to the imine bonds and an *anti* conformation with both branches arranged on opposite sides. This arrangement is conditioned by the existence of intramolecular hydrogen bonds between the imine nitrogen and the hydroxyl group of the spacer. In addition, there are intramolecular hydrogen

bonds between the phenolic hydrogen and the oxygen of the solvating molecule, as well as between the thioamide NH and the methanol oxygen atom, and between the OH group of the solvation molecule and the thioamide sulfur of an adjacent ligand. These interactions result in the ligand molecules being connected throughout the crystal lattice (Figure 4).

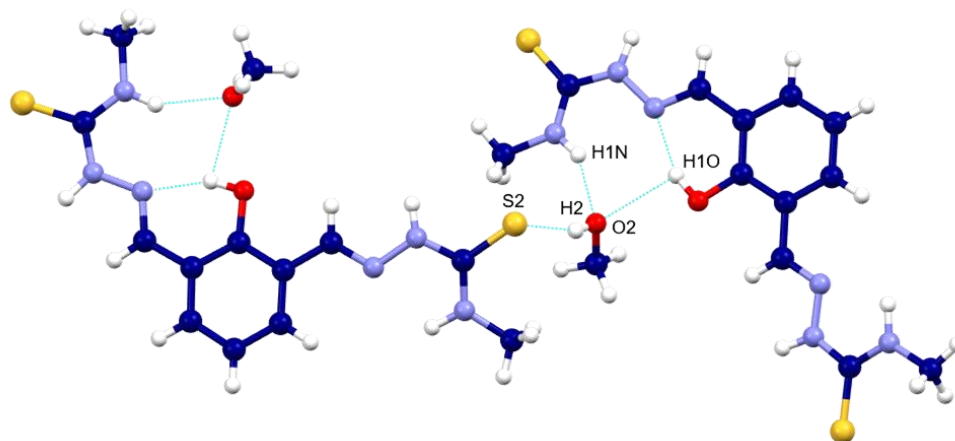


Figure 4. Intra- and intermolecular hydrogen bonds established in the crystal lattice of the ligand $H_3L^{Me} \cdot CH_3OH$ ($N3 \cdots H10$ 2.717 Å, $O1-H10 \cdots O2$ 2.756 Å, $N1-H1N \cdots O2$ 2.833 Å, $O2-H2 \cdots S2$ 3.172 Å).

4. Conclusions

The new *bisthiosemicarbazone* ligand H_3L^{Me} has been synthesized and isolated with high purity and yield. The X-ray diffraction study of the crystals that were obtained allowed us to know the structure of the ligand. The crystallographic studies revealed that the [NS] donor atoms are oriented in different directions in both ligand branches, indicating a conformational rotation to obtain metal-derived complexes.

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References

- Doğan, M.; Koçyiğit, U.M.; Gürdere, M.B.; Ceylan, M.; Budak, Y. Synthesis and biological evaluation of thiosemicarbazone derivatives. *Med. Oncol.* **2022**, *39*, 157. [[CrossRef](#)] [[PubMed](#)]
- Mahajan, R.K.; Walia, T.P.S.; Sumanjit; Lobana, T.S. Cyclopentanone Thiosemicarbazone, a New Complexing Agent for Copper Determination in Biological Samples by Adsorptive Stripping Voltammetry. *Anal. Sci.* **2006**, *22*, 389. [[CrossRef](#)] [[PubMed](#)]
- Güveli, Ş.; Çınar, S.A.; Karahan, Ö.; Aveyente, V.; Ülküseven, B. Nickel(II)–PPh₃ Complexes of S,N-Substituted Thiosemicarbazones—Structure, DFT Study, and Catalytic Efficiency. *Eur. J. Inorg. Chem.* **2016**, *4*, 538. [[CrossRef](#)]
- Jiménez-Pérez, A.; Marcos-Gómez, S.; Madariaga, G.; Zapico, M.; Vitoria, P.; Tercero, J.; Torres, M.B.; Lezama, L.; Cuevas, J.V.; Etxebarria, I.; et al. Thiosemicarbazonecopper/Halido Systems: Structure and DFT Analysis of the Magnetic Coupling. *Inorganics* **2023**, *11*, 31. [[CrossRef](#)]

5. Alcaraz, R.; Muñiz, P.; Cavia, M.; Palacios, O.; Samper, K.G.; Gil-Garcia, R.; Jiménez-Pérez, A.; García-Tojal, J.; García-Girón, C. Thiosemicarbazone-metal complexes exhibiting cytotoxicity in colon cancer cell lines through oxidative stress. *J. Inorg. Biochem.* **2020**, *206*, 110993. [[CrossRef](#)] [[PubMed](#)]
6. Pretsch, E.; Bühlmann, P.; Affolter, C.; Herrera, A.; Martínez, R. *Determinación Estructural de Compuestos Orgánicos*, 1st ed.; Elsevier: Madrid, Spain, 2002.
7. Romero, M.J.; Suárez, V.; Fernández-Fariña, S.; Maneiro, M.; Martínez-Núñez, E.; Zaragoza, G.; González-Noya, A.M.; Pedrido, R. Effect of the metal ion on the enantioselectivity and linkage isomerization of thiosemicarbazone helicates. *Chem. Eur. J.* **2017**, *23*, 4884. [[CrossRef](#)] [[PubMed](#)]

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