

Study of the Influence of a Solvent on the Crystal Structure of an Ethyl-Substituted *Bisthiosemicarbazone* Ligand †

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Abstract: A potentially dianionic symmetric *bisthiosemicarbazone* ligand H_2L^{Et} has been prepared by a condensation reaction between two equivalents of 4-N-ethyl-3-thiosemicarbazide and one equivalent of 4,4'-methylenebis(acetophenone). The crystal structures obtained from solvents with different donor abilities were studied. The recrystallization of H_2L^{Et} from methanol and dimethylsulfoxide enables the isolation of single crystals suitable for the X-ray diffraction studies of $[H_2L^{Et}]$ **1** and $[H_2L^{Et}] \cdot CH_3SOCH_3$ **2**, respectively. This study shows that the solvent does not affect the macrostructure but influences the microstructure of the ethyl-substituted *bisthiosemicarbazone* ligand H_2L^{Et} .

Keywords: *bisthiosemicarbazone*; X-ray diffraction; solvent



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1. Introduction

To date, a vast family of thiosemicarbazone ligands has been synthesized because of their high versatility in coordination chemistry and their interesting properties related to biomedical and pharmacological activities [1,2]. These ligands can be easily obtained by a condensation reaction between an appropriate carbonyl compound and a thiosemicarbazide [3], giving rise to the formation of an imine bond and the liberation of a water molecule.

In the case of thiosemicarbazone ligands, the influence of different factors such as the presence of metal ions [4], the pH of the medium [5] or the solvent [6], among others, can lead to a desulfurization process, giving rise to the loss of the sulfur atom. Having this in mind, in this work, we decided to study the influence of the recrystallization solvent on the desulfurization process and the concomitant modification of the macrostructure of the *bisthiosemicarbazone* ligand H_2L^{Et} . For this reason, we have again prepared the ethyl-substituted *bisthiosemicarbazone* published [7] and recrystallized it in solvents with different donor abilities.

2. Experimental Section

2.1. Reactants and Solvents

All solvents, 4,4'-methylenebis(acetophenone) and 4-N-ethyl-3-thiosemicarbazide are commercially available and they were used without further purification.

2.2. Preparation of the *Bisthiosemicarbazone* Ligand H_2L^{Et}

The $[N_2S_2]$ *bisthiosemicarbazone* ligand H_2L^{Et} was obtained by means of a condensation reaction between two equivalents of 4-N-ethyl-3-thiosemicarbazide and one equivalent of 4,4'-methylenebis(acetophenone) using absolute ethanol as a solvent (ca. 50 mL) and

p-toluenesulfonic acid as a catalyst [7]. The recrystallization of $\text{H}_2\text{L}^{\text{Et}}$ from dimethylsulfoxide yielded yellow needle-shaped crystals that were suitable for monocrystal X-ray-crystallographic studies.

2.3. Crystallographic Data

$[\text{H}_2\text{L}^{\text{Et}}]\cdot\text{CH}_3\text{SOCH}_3$ **2**: $\text{C}_{23}\text{H}_{30}\text{N}_6\text{S}_2\cdot\text{C}_2\text{H}_6\text{OS}$, MW: 532.78; crystal dimensions: $0.53 \times 0.14 \times 0.1$; monoclinic; $P2_1/c$; $a = 17.8816(15)$; $b = 14.0286(11)$; $c = 10.9880(9)$ Å; $\alpha = 90$; $\beta = 91.617(3)$; $\gamma = 90^\circ$; $V = 2755.3(4)$ Å³; $Z = 4$; $\mu = 0.30$ mm⁻¹; measured reflexions = 21262678; independent reflexions $[\text{R}_{\text{int}}] = 5642$ [0.040]; $R = 0.048$; $wR = 0.131$.

3. Results and Discussion

The ethyl-substituted *bisthiosemicarbazone* ligand $\text{H}_2\text{L}^{\text{Et}}$ was prepared by means of a condensation reaction between 4-N-ethyl-3-thiosemicarbazide and 4,4'-methylenebis(acetophenone), as previously reported [7].

The recrystallization of $\text{H}_2\text{L}^{\text{Et}}$ from methanol allows discrete molecules of $\text{H}_2\text{L}^{\text{Et}}$ **1** to be isolated [7]. In the ligand, both thiosemicarbazone arms adopt an *E* configuration with respect to the imine bonds and an *anti* conformation, with the two thiosemicarbazone arms facing different sides.

With the aim of exploring if the solvent of recrystallization influences in the macro- and microstructure of the ligand $\text{H}_2\text{L}^{\text{Et}}$, we used dimethylsulfoxide to recrystallize the solid obtained from the synthesis. The recrystallization of the ligand solid in dimethylsulfoxide allowed us to obtain yellow needle-shaped crystals suitable for X-ray diffraction studies. The crystal structure of $[\text{H}_2\text{L}^{\text{Et}}]\cdot\text{CH}_3\text{SOCH}_3$ **2** is shown in Figure 1.

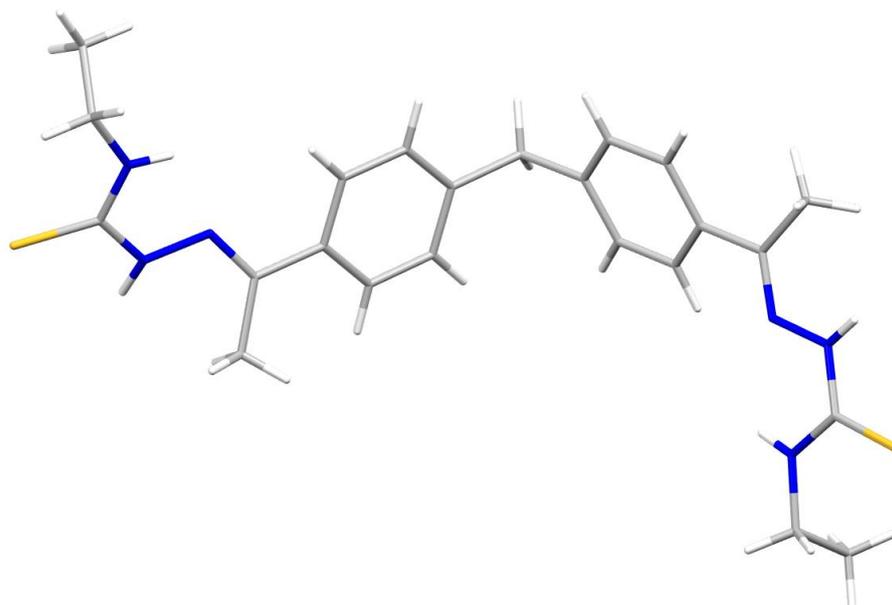


Figure 1. Crystal structure of the ethyl-substituted *bisthiosemicarbazone* ligand $[\text{H}_2\text{L}^{\text{Et}}]\cdot\text{CH}_3\text{SOCH}_3$ **2**. The solvent molecule was omitted for clarity.

Compound $[\text{H}_2\text{L}^{\text{Et}}]\cdot\text{CH}_3\text{SOCH}_3$ **2** (Figure 1) crystallize solvated by one molecule of dimethylsulfoxide. The crystal structure consists of discrete molecules in which both thiosemicarbazone arms adopt an *E* configuration with respect to the imine bonds and an *anti* configuration with the two thiosemicarbazone arms oriented on opposite sides, similar to the previously published ethyl-substituted *bisthiosemicarbazone* ligand crystal structure obtained using methanol as a solvent [7]. The main C=N, N-N and C-S bond distances and angles given in Table 1 are very similar to $\text{H}_2\text{L}^{\text{Et}}$ **1** being in the expected range for thiosemicarbazone ligands and need no further discussion [7].

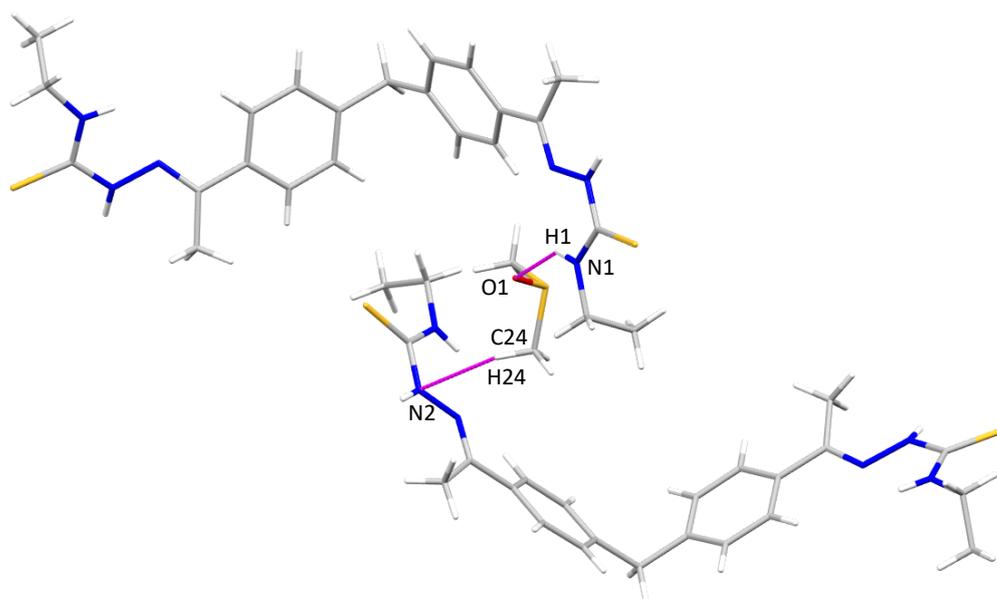
Table 1. Selected bond lengths (Å) for $[\text{H}_2\text{L}^{\text{Et}}]\cdot\text{CH}_3\text{SOCH}_3$ **2**.

Main Bond Distances (Å)			
C3—S1	1.685 (2)	C21—S2	1.387 (3)
C5—N3	1.290 (3)	C22—N8	1.288 (4)
N2—N3	1.381 (3)	N4—N7	1.383 (3)

However, the comparison of **1** and **2** shows that there are some differences related to the hydrogen bonds established in the crystal lattice.

In the case of $\text{H}_2\text{L}^{\text{Et}}$ **1**, moderate intermolecular hydrogen bonds are observed between the thioamidic sulfur atom of one of the ligand arms and one of the thioamidic NH groups of the adjacent unit ligand, connecting the molecules along the crystal lattice. Also, intramolecular hydrogen bonds between the iminic nitrogen and the thioamidic nitrogen atom of one branch are observed [7].

On the other hand, in the case of $\text{H}_2\text{L}^{\text{Et}}\cdot\text{CH}_3\text{SOCH}_3$ **2**, the ligand establishes a moderate intermolecular hydrogen bond between the thioamidic nitrogen atom of one of their branches and the oxygen atom of the solvation dimethylsulfoxide molecule. Also, a weak intermolecular hydrogen bond exists between one methyl group of the dimethylsulfoxide molecule and the hydrazidic nitrogen of another ligand unit (Figure 2). However, in this case there are no intramolecular hydrogen bonds.

**Figure 2.** Intermolecular hydrogen bonds [N1–H1...O1 2.924 Å; C24–H24...N2 3.516] in $\text{H}_2\text{L}^{\text{Et}}\cdot\text{CH}_3\text{SOCH}_3$ **2**.

4. Conclusions

The recrystallization of the ethyl-substituted bithiosemicarbazone ligand $\text{H}_2\text{L}^{\text{Et}}$ in methanol [7] and in dimethylsulfoxide allowed to explore the influence of solvents with different donor abilities in the structure of the compound. It is clear from the crystal data obtained that the solvents used do not have an influence on the macrostructure of the bithiosemicarbazone compound, confirming that there is no evidence of a desulfurization process. However, the solvent affects the microstructure showing a higher number of hydrogen bonds in the case of the crystal structure obtained in methanol, $\text{H}_2\text{L}^{\text{Et}}$ **1**, compared with the crystal structure obtained in dimethylsulfoxide, $\text{H}_2\text{L}^{\text{Et}}\cdot\text{CH}_3\text{SOCH}_3$ **2**.

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References

1. Parrilha, G.L.; dos Santos, R.G.; Beraldo, H. Applications of radiocomplexes with thiosemicarbazones and bis(thiosemicarbazones) in diagnostic and therapeutic nuclear medicine. *Coord. Chem. Rev.* **2022**, *458*, 214418. [[CrossRef](#)]
2. Fernández-Fariña, S.; Velo-Helena, I.; Carballido, R.; Martínez-Calvo, M.; Barcia, R.; Palacios, Ò.; Capdevila, M.; González-Noya, A.M.; Pedrido, R. Exploring the Biological Properties of Zn(II) Bisthiosemicarbazone Helicates. *Int. J. Mol. Sci.* **2023**, *24*, 2246. [[CrossRef](#)]
3. Singh, R.B.; Ishii, H. Analytical potentialities of thiosemicarbazones and semicarbazones. *Crit. Rev. Anal. Chem.* **1991**, *22*, 381–409. [[CrossRef](#)]
4. Da S Maia, P.I.; Nguyen, H.H.; Ponader, D.; Hagenbach, A.; Bergemann, S.; Gust, R.; Deflon, V.M.; Abram, U. Neutral gold complexes with tridentate SNS thiosemicarbazide ligands. *Inorg. Chem.* **2012**, *51*, 1604–1613. [[CrossRef](#)]
5. Gil-García, R.; Madariaga, G.; Jiménez-Pérez, A.; Herrán-Torres, I.; Gago-González, A.; Ugalde, M.; Januskaitis, V.; Barrera-García, J.; Insausti, M.; Galletero, M.S.; et al. Perchlorate-induced structural diversity in thiosemicarbazone-copper(II) complexes provides insights to understand the reactivity in acid and basic media. *CrystEngComm* **2023**, *25*, 2213–2226. [[CrossRef](#)]
6. Fernández-Fariña, S.; González-Barcia, L.M.; Romero, M.J.; García-Tojal, J.; Maneiro, M.; Seco, J.M.; Zaragoza, G.; Martínez-Calvo, M.; González-Noya, A.M.; Pedrido, R. Conversion of a double-tetranuclear cluster silver helicate into a dihelicate via a rare desulfurization process. *Inorg. Chem. Front.* **2022**, *9*, 531–536. [[CrossRef](#)]
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*, 4884–4892. [[CrossRef](#)]

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