chemistry proceedings

MDPI

Proceeding Paper

Designing a Phosphino-Thiosemicarbazone Ligand Capable of Stabilizing Coinage Metal Ions †

Isabel Velo-Heleno [1], Sandra Fernández-Fariña [1], Lara Rouco [2], Miguel Martínez-Calvo [1,*] and Rosa Pedrido [1,*]

[1] Departamento de Química Inorgánica, Facultade de Química, Campus Vida, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain
[2] Departamento de Química Inorgánica, Facultade de Ciencias, Universidade de Santiago de Compostela, 27002 Lugo, Spain
* Correspondence: miguel.martinez.calvo@usc.es (M.M.-C.); rosa.pedrido@usc.es (R.P.)
† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2022; Available online: https://sciforum.net/event/ecsoc-26.

Abstract: Thiosemicarbazones are interesting organic skeletons due to their great coordinative versatility and their interesting biological and pharmacological properties, as well as their structural diversity. However, the isolation of their monovalent coinage metal complexes, such as Cu(I), Ag(I) and Au(I), is a partially studied field, since co-ligands with soft donor atoms such as phosphines are required. In this context, our research group has been studying a new family of ligands capable of stabilizing coinage complexes without the need for auxiliary co-ligands. To this end, it was decided to incorporate a phosphorus atom into the structure of a thiosemicarbazone kernel. This work presents the design, synthesis and structural characterization of a new phosphino-thiosemicarbazone ligand.

Keywords: ligand; thiosemicarbazone; phosphine; coinage metal ions

Citation: Velo-Heleno, I.; Fernández-Fariña, S.; Rouco, L.; Martínez-Calvo, M.; Pedrido, R. Designing a Phosphino-Thiosemicarbazone Ligand Capable of Stabilizing Coinage Metal Ions. *Chem. Proc.* **2022**, *12*, 44. https://doi.org/10.3390/ecsoc-26-13638

Academic Editor: Julio A. Seijas

Published: 16 November 2022

1. Introduction

Among the wide variety of organic skeletons reported to date, thiosemicarbazone ligands must be highlighted due to their interesting biological and pharmacological properties, as well as their structural diversity [1–5]. Nevertheless, in order to obtain their monovalent metal complexes, such as Cu(I) [6], Ag(I) and Au(I) [7–9], auxiliary co-ligands incorporating soft donor atoms were needed.

At this point, in the last few years we have designed and prepared a new family of thiosemicarbazone ligands featuring a phosphine unit [10–14]. The phosphine-thiosemicarbazone ligands were capable of stabilizing M(I) complexes without the need for auxiliary co-ligands. For further study, we report herein the design, synthesis and structural characterization of a new phosphino-thiosemicarbazone ligand functionalized with a nitro-phenyl ring (Figure 1).

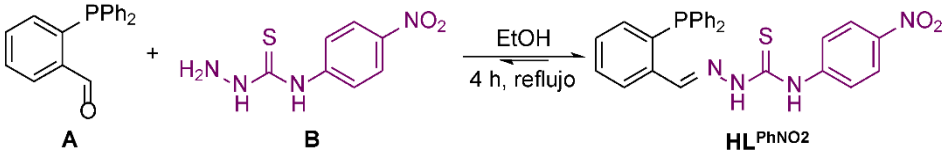

Figure 1. Synthesis of the phosphino-thiosemicarbazone ligand $\mathbf{HL^{PhNO2}}$.

2. Experimental Section

The new phosphino-thiosemicarbazone ligand $\mathbf{HL^{PhNO2}}$ has been created by means of an imine condensation reaction (Figure 1). First, 2-diphenylphosphinobenzaldehyde (A) (0.50 g, 1.7 mmol) and 4-(4-Nitrophenyl)thiosemicarbazide (B) (0.72 g, 3.4 mmol) were

mixed and dissolved in absolute ethanol. Then, a catalytic amount of p-toluensulfonic acid was added to promote imine bond formation. The reaction mixture was refluxed for 4 h using a Dean−Stark trap to remove the released water. The final white crystalline precipitate was isolated via concentration and filtration and washed with diethyl ether, giving rise to the required $\mathbf{HL^{PhNO2}}$.

$\mathbf{HL^{PhNO2}}$: yield 1.498 g, (91%). Elemental analysis, calc. for $C_{26}H_{21}N_4O_2PS$: C, 64.5; H, 4.4; N, 11.6; S, 6.6. Found: C, 64.3; H, 4.4; N, 11.4; S, 6.3 %. MS ESI+ (m/z): 483.1 [HL-H]-. IR (KBr, cm^{-1}): ν IR (KBr, cm^{-1}): ν(N-H) 3302 (d), ν(C=N + C-N) 1539 (mf), 1514 (f), 1435 (m), ν(NO2) 1333 (mf) ν(C=S) 1111 (m), 748 (m). RMN 1H (300 MHz, DMSO-d6): δ/ppm, 12.30 (s, 1H, -NH), 10.33 (s, 1H, -NH), 8.87 (d, J= 4.9 Hz, 1H), 8.48–6.82 (m, 18H, Ar-H). RMN 13C (126 MHz, DMSO-d6): δ/ppm, 175.24 (C=S), 145.22 (C=N), 143.47–123.76 (C-Ar). RMN 31P (202 MHz, DMSO-d6): δ/ppm, −12.76.

3. Results and Discussion

$\mathbf{HL^{PhNO2}}$ was characterized using the usual techniques for organic compounds. Analytical data are consistent with the ligand stoichiometry. An IR spectrum shows the bands corresponding to the NH group at 3302 cm^{-1}, to the imine bond at 1539, 1514 and 1435 cm^{-1} (Figure 2) and to the C=S thioamide group at 1111 and 748 cm−1. MS ESI+ exhibits a peak at 483.1(m/z) consistent with the monodeprotonated ligand molecule. Suitable crystals for X-ray diffraction were also obtained. The crystal structure corresponds with the oxidized $\mathbf{HL^{PhNO2}}$ ligand, that is shown in Figure 3. The main crystallographic data are summarized in Table 1, whereas bond lengths and angles are listed in Table 2. All bond distances and angles are in the order of those found in the literature for thiosemicarbazone and phosphine ligands and do not merit further discussion [10–14].

The asymmetric unit of the $\mathbf{HL^{PhNO2}}$ ligand consists of a ligand molecule showing an E conformation with respect to the imine group. In addition, the phosphine skeleton and the thiosemicarbazone branch are oriented towards the same side giving rise to a *syn* conformer (Figure 3).

The $\mathbf{HL^{PhNO2}}$ ligand crystallized with the oxidized phosphorus atom. This fact causes intramolecular hydrogen bonds to be established (Figure 4) involving the hydrogen in the thioamide position [N2-H2N···O1 2.795 Å], which possibly conditions the *syn* arrangement adopted by the phosphine skeleton and the thiosemicarbazone branch. In addition, intermolecular hydrogen bonds established by the thioamide sulfur and the hydrazide hydrogen atoms allow an interaction between two neighboring ligand molecules [N3-H3N···S1 3.461(2) Å].

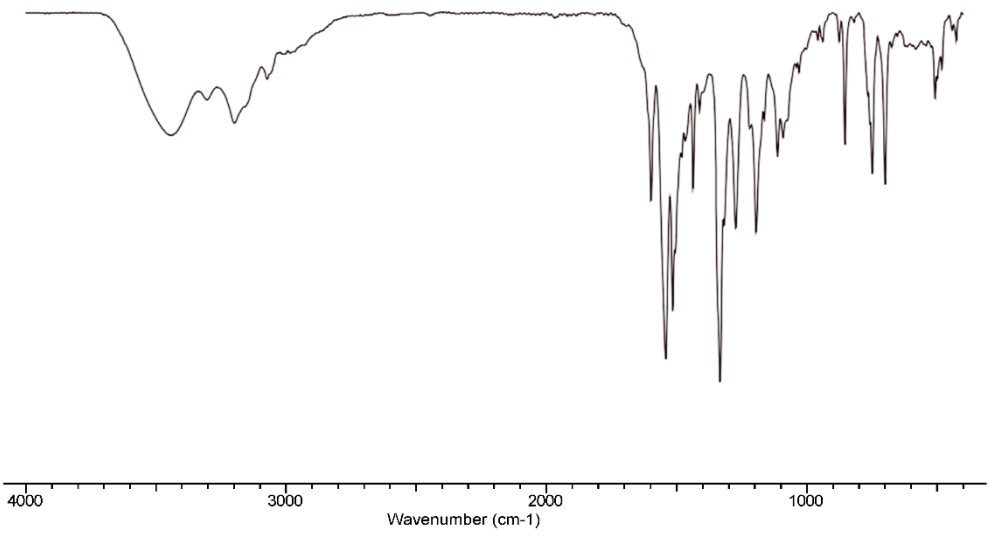

Figure 2. IR spectrum (cm^{-1}) of the phosphino-thiosemicarbazone ligand $\mathbf{HL^{PhNO2}}$.

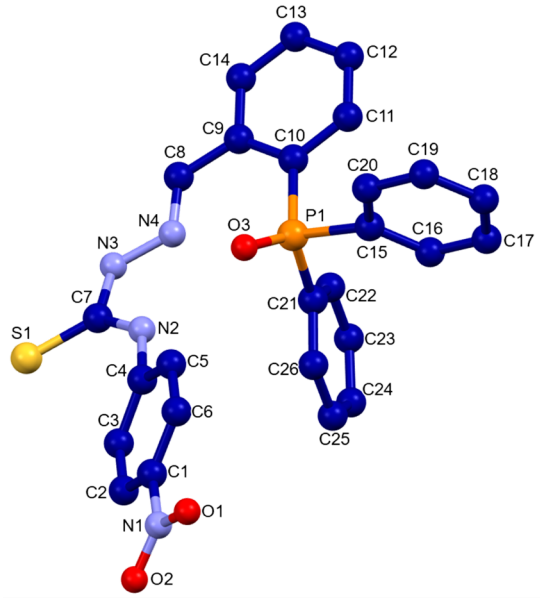

Figure 3. Crystal structure of the phosphino-thiosemicarbazone ligand $\mathbf{HL^{PhNO2}}$.

Table 1. Main crystallographic data for $\mathbf{HL^{PhNO2}}$.

Crystallographic Data	
Formula	C26H21N4O2.30PS
Molecular weight	489.3
Crystal system	Monoclinic
Crystal size/mm	0.70 × 0.11 × 0.03
Volume/Å^3	2327.1(3)
Space group	$P2_1/n$
Z	4
a/Å	13.7284(8)
b/Å	7.2366(5)
c/Å	23.5622(14)
α/°	90
β/°	96.214(3)
γ/°	90
d/g·cm^{-3}	1.383
μ/mm^{-1}	0.191
F(000)	432
Interval θ/°	2.41–28.13
Measured reflexions	33,552
Independent reflexions [R_{int}]	5787 [0.0396]
Residues/e·Å^{-3}	0.58 and −0.29
R	0.0392
wR	0.0889

The $\mathbf{HL^{PhNO2}}$ structure in the solid state is worthy of analysis for comparative purposes between the free ligand or when it is bound to different metal ions. By observing its arrangement, it should be noted that the O/S donor atoms are oriented in opposite directions. For this reason, a previous conformational rotation would be necessary to achieve both atoms' coordination to the same metal ion.

Table 2. Selected bond length (Å) and angles (°) for $\mathbf{HL^{PhNOs2}}$.

Main Bond Distances (Å)			
C8-N4	1.271(2)	C10-P1	1.843(1)
N4-N3	1.376(2)	P1-C21	1.823(1)
N3-C7	1.356(2)	C8-C9	1.452(2)
C7-S1	1.683(2)	P1-C15	1.826(2)
N1-O1	1.227(2)	P1-O3	1.377(4)
C7-N2	1.346(2)	C1-N1	1.463(2)
N4-C8	1.271(2)	N1-O2	1.229(2)
Main Bond Angles (º)			
C8-N4-N3	117.7(1)	O2-N1-O1	123.6(2)
N4-N3-C7	119.2(1)	C10-P1-C15	101.27(7)
N3-C7-S1	118.7(1)	C21-P1-C10	103.88(7)
N2-C7-N3	114.0(1)	C21-P1-C15	102.48(7)
N2-C7-S1	127.3(1)		

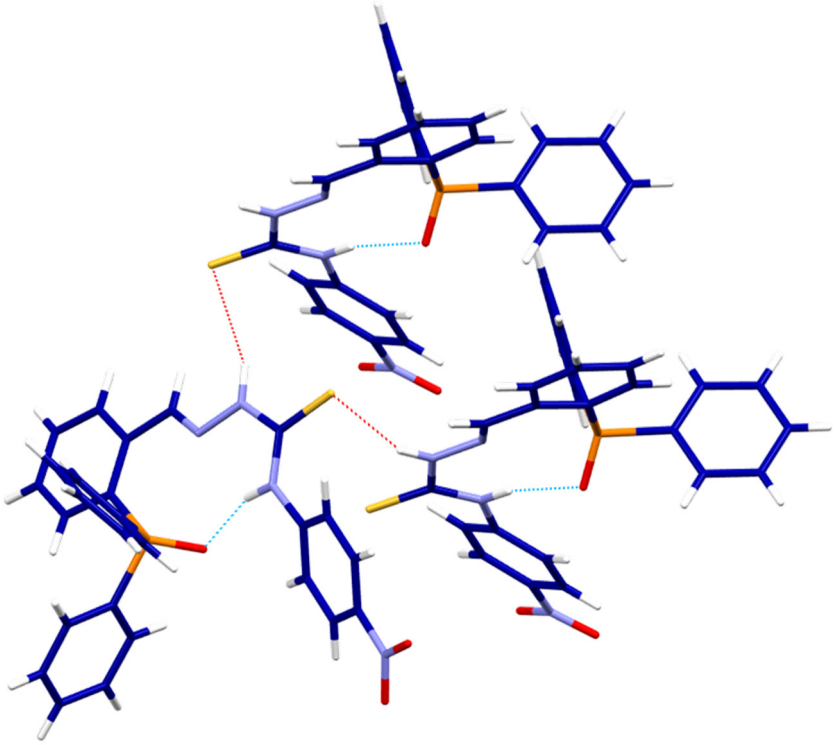

Figure 4. Intra- (light blue) and intermolecular (red) hydrogen bonds $\mathbf{HL^{PhNO2}}$.

4. Conclusions

The new phosphine-thiosemicarbazone ligand $\mathbf{HL^{PhNO2}}$ has been isolated in high purity and yield. Its crystal structure shows an opposite orientation of oxygen and sulfur donor atoms, which would imply a conformational rotation prior to coordination to the same metal ion.

Author Contributions: Conceptualization, S.F.-F., M.M.-C. and R.P.; methodology, I.V.-H., S.F.-F., M.M.-C. and R.P.; formal analysis, S.F.-F. and I.V.-H.; investigation, I.V.-H., S.F.-F., L.R., M.M.-C. and R.P.; resources, M.M.-C. and R.P.; data curation, S.F.-F., I.V.-H., L.R., M.M.-C. and R.P.; writing—original draft preparation, S.F.-F., I.V.-H., M.M.-C. and R.P.; writing—review and editing, I.V.-H., S.F.-F., L.R., M.M.-C. and R.P.; supervision, M.M.-C. and R.P.; project administration, M.M.-C. and R.P.; funding acquisition, R.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the following FEDER co-funded grants. From Consellería de Cultura, Educación e Ordenación Universitaria, Xunta de Galicia, 2017GRCGI-1682 (ED431C2017/01), 2018GRCGI-1584 (ED431C2018/13), MetalBIONetwork (ED431D2017/01). From Ministerio de Ciencia, Innovación y Universidades, METALBIO (CTQ2017-90802-REDT). From Ministerio de Ciencia e Innovación, MultiMet- DRUGS (RED2018-102471-T) and Project PID2021-127531NB-I00 (AEI/10.13039/501100011033/FEDER, UE).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Liberta, A.E.; West, D.X. Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: Current status. *BioMetals* **1992**, *5*, 121–126. [CrossRef] [PubMed]
2. Hu, W.X.; Zhou, W.; Xia, C.N.; Wen, X. Synthesis and anticancer activity of thiosemicarbazones. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2213–2218. [CrossRef] [PubMed]
3. Bal, T.R.; Anand, B.; Yogeeswari, P.; Sriram, D. Synthesis and evaluation of anti-HIV activity of isatin β-thiosemicarbazone deriva-tives. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4451–4455. [CrossRef] [PubMed]
4. Bajaj, K.; Buchanan, R.M.; Grapperhaus, C.A. Antifungal activity of thiosemicarbazones, bis(thiosemicarbazones), and their metal complexes. *J. Inorg. Biochem.* **2021**, *225*, 111620. [CrossRef] [PubMed]
5. Gonçalves, A.C.R.; Carneiro, Z.A.; Oliveira, C.G.; Danuello, A.; Guerra, W.; Oliveira, R.J.; Ferreira, F.B.; Veloso-Silva, L.L.W.; Batista, F.A.H.; Borges, J.C.; et al. Pt(II), Pd(II) and Au(III) complexes with a thiosemicarbazone derived from diacethylmonooxime: Structural analysis, trypanocidal activity, cytotoxicity and first insight into the antiparasitic mechanism of action. *Eur. J. Med. Chem.* **2017**, *141*, 615–631. [CrossRef] [PubMed]
6. Lobana, T.S.; Rekha; Butcher, R.J.; Castiñeiras, A.; Bermejo, E.; Bharatam, P.V. Bonding Trends of Thiosemicarbazones in Mononuclear and Dinuclear Copper(I) Complexes: Syntheses, Structures, and Theoretical Aspects. *Inorg. Chem.* **2006**, *45*, 1535–1542. [CrossRef] [PubMed]
7. Casas, J.S.; Castellano, E.E.; Couce, M.; Ellena, D.J.; Sánchez, A.; Sordo, J.C.; Taboada, J. A gold(I) complex with a vitamin K3 derivative: Characterization and antitumoral activity. *Inorg. Biochem.* **2006**, *100*, 1858–1860. [CrossRef] [PubMed]
8. Lobana, T.S.; Khanna, S.; Butcher, R.J. Synthesis of a fluorescent gold(I) complex with a thiosemicarbazone, [Au2(3-NO2-Hbtsc)4]Cl2 · 2CH3CN. *Inorg. Chem. Commun.* **2008**, *11*, 1433–1435. [CrossRef]
9. Molter, A.; Rust, J.; Lehmann, C.W.; Deepa, G.; Chiba, P.; Mohr, F. Synthesis, structures and anti-malaria activity of some gold(I) phos- phine complexes containing seleno- and thiosemicarbazonato ligands. *Dalton Trans.* **2011**, *40*, 9810–9820. [CrossRef] [PubMed]
10. Castiñeiras, A.; Pedrido, R.; Pérez-Alonso, G. A Convenient Mode to Stabilize MI Metal Ions by Using Thiosemicarbazones. *Eur. J. Inorg. Chem.* **2008**, *32*, 5106–5111. [CrossRef]
11. Castineiras, A.; Pedrido, R. Novel Fluorescent Cationic Silver Thiosemicarbazone Clusters Containing Different Eight-Membered Ag_4S_4 Metallacycles. *Inorg. Chem.* **2009**, *48*, 4847–4855. [CrossRef] [PubMed]
12. Castiñeiras, A.; Pedrido, R. A thiosemicarbazone ligand functionalized by a phosphine group: Reactivity toward coinage metal ions. *Dalton Trans.* **2010**, *39*, 3572–3584. [CrossRef] [PubMed]
13. Castiñeiras, A.; Pedrido, R. Aurophilicity in gold(I) thiosemicarbazone clústers. *Dalton Trans.* **2012**, *41*, 1363–1372. [CrossRef] [PubMed]
14. González- Barcia, L.M.; Romero, M.J.; González Noya, A.M.; Bermejo, M.R.; Maneiro, M.; Zaragoza, G.; Pedrido, R. The Golden Method Electrochemical Synthesis Is an Efficient Route to Gold Complexes. *Inorg. Chem.* **2016**, *55*, 7823–7825. [CrossRef] [PubMed]