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Oxotechnetium(V) Complexes with a Novel Class of Tridentate Thiosemicarbazide Ligands

Hung Huy Nguyen,[†] Pedro I. da S. Maia,[‡] Victor M. Deflon,[‡] and Ulrich Abram*[,†]

Institute of Chemistry and Biochemistry, Freie Universität Berlin, Fabeckstrasse 34−36,
D-14195 Berlin, Germany, and Instituto de Química de São Carlos, Universidade de São Paulo,
CP 780, São Carlos, São Paulo, Brazil

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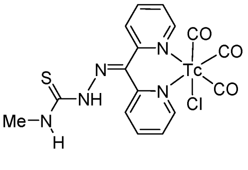
A novel tridentate thiosemicarbazide-type ligand class with an SNS donor set, H_2L^1, was prepared by reactions of *N*-[*N*′,*N*′-dialkylamino(thiocarbonyl)]benzimidoyl chlorides with thiosemicarbazides. H_2L^1 ligands readily react with $(NBu_4)[TcOCl_4]$ in MeOH under the formation of red oxotechnetium(V) complexes of composition $[TcOCl(L^1)]$. The monomeric, five-coordinate compounds are air-stable and bind $(L^1)^{2-}$ tridentate in the equatorial coordination sphere. The compounds represent the first examples of oxotechnetium(V) complexes with NS chelate-bonded thiosemicarbazones.

Thiosemicarbazones form stable complexes with many main-group and transition metals,[1] and some of the products possess remarkable biological and pharmaceutical properties such as antibacterial, antiviral, antineoplastic, or antimalarial activity.[2] However, surprisingly less is known about technetium complexes of this ligand class. The structural versatility of thiosemicarbazones early recommended them for applications in organ imaging, and several studies have been undertaken particularly with kethoxal bis(thiosemicarbazones) and glucosone bis(thiosemicarbazones).[3] However, no structural information about the composition of the complexes, which were mainly prepared with ^{99m}Tc at a concentration level of approximately 10^{-9} mol/L, could be given. The first structurally fully characterized technetium thiosemicarbazones were published in 2005.[4] Nevertheless, the mono- and binuclear tricarbonyltechnetium(I) compounds with 2,2′-dipyridylketone (**1**) and 4-acetylpyridine (**2**) thiosemicarbazones do not contain the ligands in the common NS chelating mode, and several attempts to isolate technetium compounds with intact, chelate-bonded thiosemicarbazones failed. Instead, some decomposition products that are mainly due to solvolysis of the Schiff base C═N double bond could be characterized.



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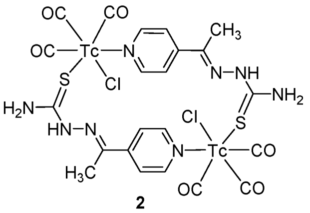

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Here, we present technetium complexes with new tridentate ligands (H_2L), which combine a thiosemicarbazide moiety with a thiourea building block. They can easily be modified by variation of either the residues R^1 and R^2 of the thiosemicarbazide or the alkyl substituents of the thiourea unit, as has been demonstrated previously for a number of benzoylthiourea and thiocarbamoylbenzamidine complexes of rhenium and technetium.[5] Reactions of appropriate *N*-[*N*′,*N*′-dialkylamino(thiocarbonyl)]benzimidoyl chlorides and 4,4-dialkylthiosemicarbazides in dry acetone give the novel benzamidine ligands H_2L in high yields (Chart 1). The products were isolated as colorless, analytically pure, microcrystalline solids directly from the reaction mixtures.[6] They were characterized by elemental analysis and spectroscopic methods such as IR, ^{1}H NMR, and ^{13}C NMR. H_2L^{1a} was additionally studied by X-ray analysis.[7] A representation of its molecular structure is given in Figure 1. The protonation of the nitrogen atoms N5 and N7 is experimentally

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* To whom correspondence should be addressed. E-mail: abram@chemie.fu-berlin.de.

[†] Freie Universität Berlin.

[‡] Universidade de São Paulo.

(1) (a) Campbell, M. J. M. *Coord. Chem. Rev.* **1975**, *15*, 279. (b) West, D. X.; Padhye, S. B.; Sonawane, P. A. *Struct. Bonding (Berlin)* **1991**, *76*, 1. (c) Casas, J. S.; García-Tasende, M. S.; Sordo, J. *Coord. Chem. Rev.* **2000**, *209*, 49.

(2) Klayman, D. L.; Scovill, J. B.; Bartosevich, J. F.; Bruce, J. *J. Med. Chem.* **1983**, *26*, 39.

(3) (a) Hosotani, T.; Yokoyama, A.; Arano, Y.; Horiuchi, K.; Wasaki, H.; Saji, H.; Torizuka, K. *Int. J. Nucl. Med. Biol.* **1986**, *12*, 431. (b) Yokoyama, A.; Terauchi, Y.; Horiuchi, K.; Tanaka, H.; Odori, T.; Morita, R.; Mori, T.; Torizuka, K. *J. Nucl. Med.* **1976**, *17*, 816. (c) Grases, F.; Genestar, C. *Radiochim. Acta* **1985**, *39*, 43. (d) Misra, M.; Sarkar, H. S.; Chatterjee, M.; Banerjee, S. *Nucl. Med. Biol.* **1988**, *15*, 409.

(4) Pereiras-Gabián, G.; Vázquez-López, E. M.; Braband, H.; Abram, U. *Inorg. Chem.* **2005**, *44*, 834.

(5) (a) Nguyen, H. H.; Abram, U. *Inorg. Chem.* **2007**, *46*, 5310. (b) Nguyen, H. H.; Grewe, J.; Schroer, J.; Kuhn, B.; Abram, U. *Inorg. Chem.* **2008**, *47*, 5136.

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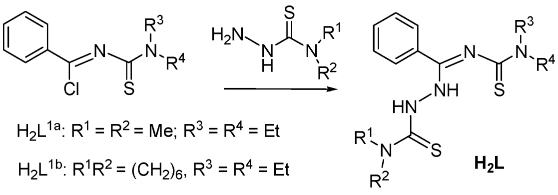
Chart 1. Synthesis of H_2L



justified by the detection of the corresponding hydrogen atoms and the fact that they are involved in hydrogen bonds (for details, see the Supporting Information). Thus, the bonding situation in the solid state of the compound recommends the treatment of H_2L^{1a} as a "thiosemicarbazide" rather than as a "thiosemicarbazone", as is indicated by the mesomeric formulas **A** and **B** in Chart 2. This is also supported by the bond length situation inside the C,N skeleton of the ligand with a C4−N5 bond length of 1.348(2) Å, which can be regarded as an (only slightly shortened) single bond, and the IR spectrum of the complex. The IR spectra of H_2L^{1a} and H_2L^{1b} are characterized by strong and broad NH absorptions around 3185 cm^{-1} and very strong and sharp absorptions at 1632 and 1635 cm^{-1}, which can be assigned to C═N stretches. In solution and in metal complexes of the new ligands, however, the other mesomeric forms should also be considered, particularly when chelate formation establishes an extended system of delocalized π-electron density. Thus, with regard to the conformations **C**−**F**, the formation of thiosemicarbazone-type complexes cannot be ruled out.

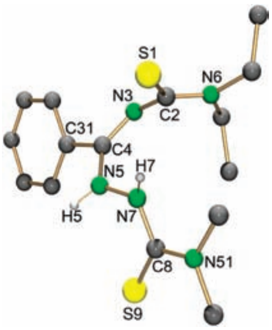
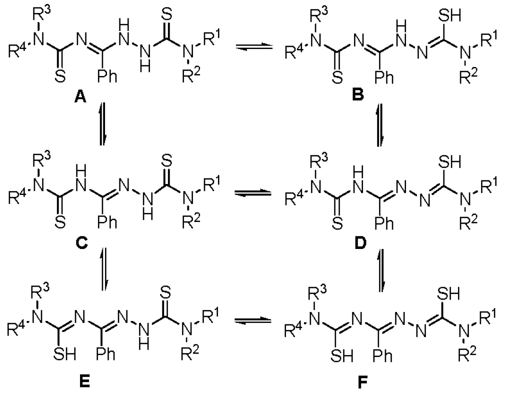


Figure 1. Molecular structure of H_2L^{1a}.[8] Hydrogen atoms at carbon atoms are omitted for clarity. Selected bond lengths (Å): S1−C2 1.701(2), C2−N6 1.332(2), C2−N3 1.367(2), N3−C4 1.285(2), C4−N5 1.348(2), N5−N7 1.380(2), N7−C8 1.372(2), C8−S9 1.669(2).

Chart 2. Possible Conformations of H_2L^1



The ^1H NMR spectra of the new ligands show two sets of well-separated signals corresponding to their ethyl residues, which are due to the hindered rotation around of the C−NEt_2 bonds of the thiourea moiety, as has already been observed for some other benzamidines.[5b,9] The rotation around the C−NR^1R^2 bonds of thiosemicarbazide sides is not restricted, as is indicated by a singlet at 3.28 ppm for the methyl protons in the spectrum of H_2L^{1a}, while fluctuation of the CH_2 groups in the seven-membered ring of H_2L^{1b} results in less resolved ^1H NMR signals of the corresponding protons. The signals of the two NH protons appear in a very broad singlet in the region between 9.5 and 9.8 ppm. In the ^{13}C NMR spectra, the C═N and C═S signals of thiourea residues appear around the 149 and 183 ppm regions, while the C═S resonances of the thiosemicarbazide parts appear around 179 ppm.

Reactions of H_2L^1 with $(NBu_4)[TcOCl_4]$ in MeOH at room temperature afford red solids of composition $[TcOCl(L^1)]$ (**3**) in excellent yields.[9] The compounds are stable both in solution and in the solid state. IR spectra of complexes **3** exhibit strong bands near 1520 cm^{-1}, which corresponds to

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(6) **General Procedure of the Synthesis of H_2L^1**: *N*-(*N*′,*N*′- Diethylaminothiocarbonyl)benzimidoyl chloride (5 mmol) was dissolved in 10 mL of dry acetone and slowly added to a stirred mixture of 4,4-dialkylthiosemicarbazide (5 mmol) and NEt_3 (1.51 g, 15 mmol) in 10 mL of dry acetone. The mixture was stirred for 4 h at room temperature. The formed precipitate of $NEt_3 \cdot HCl$ was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was redissolved in 5 mL of CH_2Cl_2, and the obtained solution was extracted with a brine solution (3 × 5 mL). After being dried with $MgSO_4$, the organic solvent was halved in volume under vacuum. Diethyl ether (10 mL) was added, and the mixture was stored at −20 °C. The colorless solid of H_2L^1, which deposited from this solution, was filtered off, washed with diethyl ether, and dried under vacuum. The compounds were used for the syntheses of complexes without further purification. For analytical and spectroscopic data, see the Supporting Information.

(7) **Structure Determination and Refinement of H_2L^{1a}**: STOE IPDS, $C_{15}H_{23}N_5S_2$, yellow block, triclinic, space group $P\bar{1}$, $a = 9.603(1)$ Å, $b = 10.227(1)$ Å, $c = 10.978(1)$ Å, $\alpha = 63.66(1)°$, $\beta = 65.23(1)°$, $\gamma = 83.92°$, $V = 873.3(2)$ Å^3, $Z = 2$, $D_{calc} = 1.284$ g/cm^3, $\theta = 2.78{-}29.57°$, 8476 reflections collected, 4488 independent [R(int) = 0.0298], $\mu = 0.309$, no absorption correction, solved b direct methods and refined by full-matrix least-squares procedures using *SHELXS* and *SHELXL* (Sheldrick, G. M. University of Göttingen, Göttingen, Germany), 207 parameters, R1 = 0.0399, wR2 = 0.0979. **Structure Determination and Refinement of [TcOCl(L^{1a})]**: STOE IPDS, $C_{15}H_{21}ClN_5OS_2Tc$, red block, monoclinic, space group $P2_1/c$, $a = 10.012(1)$ Å, $b = 21.742(2)$ Å, $c = 9.601(1)$ Å, $\beta = 109.41(1)°$, $V = 1971.1(3)$ Å^3, $Z = 4$, $D_{calc} = 1.637$ g/cm^3, $\theta = 2.71{-}29.30°$, 14 681 reflections collected, 5309 independent [R(int) = 0.0733], $\mu = 1.091$, no absorption correction, solved by direct methods and refined by full-matrix least-squares procedures using *SHELXS* and *SHELXL* (Sheldrick, G. M. University of Göttingen, Göttingen, Germany), 248 parameters, R1 = 0.0518, wR2 = 0.1213. **Structure Determination and Refinement of [TcOCl(L^{1b})]**: STOE IPDS, $C_{19}H_{27}ClN_5OS_2Tc$, red block, monoclinic, space group $P2_1$, $a = 9.213(1)$ Å, $b = 10.906(1)$ Å, $c = 11.792(1)$ Å, $\beta = 106.73(1)°$, $V = 1134.7(2)$ Å^3, $Z = 2$, $D_{calc} = 1.578$ g/cm^3, $\theta = 2.31{-}29.26°$, 8841 reflections collected, 6053 independent [R(int) = 0.0621], $\mu = 0.957$, no absorption correction, solved by direct methods and refined by full-matrix least-squares procedures using *SHELXS* and *SHELXL* (Sheldrick, G. M. University of Göttingen, Göttingen, Germany), 281 parameters, R1 = 0.0463, wR2 = 0.1300. Flack parameter: −0.11(5).

(8) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.

(9) (a) Hartung, J.; Weber, G.; Beyer, L.; Szargan, R. *Z. Anorg. Allg. Chem.* **1985**, *523*, 153. (b) del Campo, R.; Criado, J. J.; Garcia, E.; Hermosa, M. R.; Jimenez-Sanchez, A.; Manzano, J. L.; Monte, E.; Rodriguez-Fernandez, E.; Sanz, F. *J. Inorg. Biochem.* **2002**, *89*, 74. (c) Hernandez, W.; Spodine, E.; Richter, R.; Hallmeier, K.-H.; Schröder, U.; Beyer, L. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2559. (d) Schröder, U.; Richter, R.; Beyer, L.; Angulo-Cornejo, J.; Lino-Pacheco, M.; Guillen, A. *Z. Anorg. Allg. Chem.* **2003**, *629*, 1051.

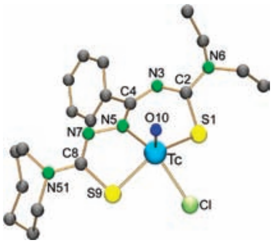

Figure 2. Structure of the complex **3b**.[7] Hydrogen atoms are omitted for clarity.

Table 1. Selected Bond Lengths (Å) and Angles (deg) in **3a** and **3b**

	3a/3b		3a/3b
Tc−O10	1.646(3)/1.650(4)	N3−C4	1.311(5)/1.324(7)
Tc−S1	2.303(1)/2.296(1)	C4−N5	1.365(5)/1.359(7)
Tc−N5	1.996(3)/2.024(4)	C2−N6	1.324(6)/1.340(7)
Tc−S9	2.276(1)/2.280(1)	N5−N7	1.414(5)/1.417(6)
Tc−Cl	2.373(1)/2.358(2)	N7−C8	1.290(5)/1.285(7)
S1−C2	1.749(5)/1.747(6)	C8−S9	1.773(4)/1.771(6)
C2−N3	1.328(6)/1.322(7)	C8−N51	1.348(6)/1.354(7)
O10−Tc−S1	112.5(1)/110.0(2)	N5−Tc−S9	80.5(1)/80.4(1)
O10−Tc−N5	105.9(2)/106.5(2)	S9−Tc−Cl	84.7(1)/82.9(1)
O10−Tc−S9	113.4(1)/110.5(2)	Cl−Tc−S1	80.5(1)/80.6(1)
O10−Tc−Cl	105.6(1)/109.2(2)	S1−Tc−S9	133.9(1)/139.4(1)
S1−Tc−N5	90.0(1)/91.8(1)	N5−Tc−Cl	148.3(1)/144.0(1)

a bathochromic shift of the $\nu_{C=N}$ stretches of about 115 cm^{-1} and indicates chelate formation with a large degree of π-electron delocalization within the chelate rings. The absence of ν_{NH} absorptions in the regions above 3100 cm^{-1} indicates the expected double deprotonation of the ligands during complex formation. Intense bands appearing at 957 and 961 cm^{-1} can be assigned to the Tc═O vibrations. In the ^1H NMR spectra of the complexes, expectedly two triplet signals of the thiosemicarbazide methyl groups are observed. Furthermore, the ^1H NMR spectra reflect the rigid structure of the tertiary amine nitrogen atoms of thiourea groups. The appearance of four proton signals of the methylene groups with the ABX_3 splitting pattern shows that they are magnetically not equivalent with respect to their axial and equatorial positions. No hindered rotation effects are observed for the CNR^1R^2 moiety of the thiosemicarbazide side.

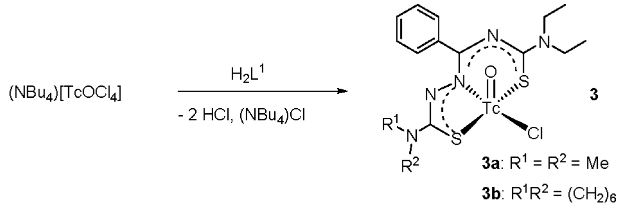

Figure 2 illustrates the molecular structure of **3b** as the prototype compound of the $[TcOCl(L^1)]$ complexes. A structural plot of **3a** with an identical atomic labeling scheme is given in the Supporting Information. Selected bond lengths and angles for both technetium complexes are compared in Table 1. The arrangement around the technetium atoms is best described as distorted square pyramids with the oxo ligands in apical positions. The basal planes are defined by the donor atoms of the tridentate ligand and a remaining chloro ligand. The technetium atoms are situated 0.742(1) Å for **3a** and 0.727(1) Å for **3b** above this plane toward the oxo ligands. All O10−Tc−X angles (X = equatorial donor atom) fall in the range between 105 and 113°. This corresponds to the typical bonding situation in square-pyramidal Tc^VO complexes.[11] The Tc═O distances of 1.646(4) and 1.650(4) Å are within the expected range for a Tc−O double bond.[11] A considerable delocalization of the π-electron density in the six-membered ring is indicated by the observed bond lengths. The C−S and C−N bonds inside the chelate rings are within the ranges between C−S and C−N single and double bonds. This bond-length equalization is even extended to the C2−N6 bonds, which are significantly shorter than expected for typical single bonds. The partial transfer of the electron density into this bond agrees with the ^1H NMR spectra of the compounds. In the five-membered rings, the C8−N7 bonds of 1.285(7) and 1.290(5) Å have more double-bond character. The C8−S9 bonds in the complexes are almost equal, which indicates a stronger lengthening of the C8−S9 bond with respect to the situation in H_2L^{1a}. Interestingly, the C4−N5 bond in H_2L^{1a} [1.348(2) Å] is only slightly influenced by the complex formation [1.365(5) Å] and indicates that also the bonding situation in the technetium complexes under study is mainly determined by the (deprotonated) borderline structure **A** in Chart 2, and the novel ligands are best discussed to be of the "thiosemicarbazide" type with some characteristics of "thiosemicarbazone".

This "zwitter" type of the new ligands might explain the high stability of the novel technetium complexes (with regard to the frequently observed decomposition of thiosemicarbazones during reactions with technetium complexes; see above) and will open the door to a new class of metal complexes of potential interest for medical applications, which combine the activity features of thiosemicarbazones and the stability of amine complexes. Related studies also involving rhenium and other transition metals are currently underway in our laboratories.

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Supporting Information Available: Syntheses, ellipsoid and cell plots, and lists of bond lengths and angles and of hydrogen bonds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **Synthesis of 3**: H_2L^1 (0.11 mmol) dissolved in 3 mL of MeOH was dropwise added to a stirred solution of $(NBu_4)[TcOCl_4]$ (50 mg, 0.1 mmol) in 2 mL of MeOH. The color of the solution immediately turned deep red, and a red precipitate deposited within a few minutes. The red powder was filtered off, washed with cold MeOH, and recrystallized from CH_2Cl_2/MeOH. For analytical and spectroscopic data, see the Supporting Information.

(11) Alberto, R. Technetium. In *Comprehensive Coordination Chemistry II*; McCleverty, J. A.; Mayer, T. J., Eds.; Elsevier: Amsterdam, The Netherlands, 2003; Vol. *5*, p 128.