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# A multiprotic ditopic thiocarbohydrazone ligand in the formation of mono- and di-nuclear organotin(IV) complexes: Crystal structure, antibacterial activity and DNA cleavage

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ABSTRACT

Three organotin(IV) complexes, $Ph_4Sn_2L$ (**1**), $Me_2Sn(H_2L)$ (**2**) and $Bu_2Sn(H_2L)$ (**3**) have been formed from reaction of $R_2SnCl_2$ (R = Ph, Me and Bu) with a multiprotic dihydrazone, 1,5-bis((2-hydroxynaphthaldehyde) thiocarbohydrazone ($H_4L$). The synthesized compounds have been investigated by elemental analysis, IR, $^1H$ NMR, and $^{119}Sn$ NMR spectroscopy. The structure of **1** has been also confirmed by X-ray crystallography. The results show **1** is binuclear and fully deprotonated thiocarbohydrazone supplies two different tridentate dianionic domains, NNO and ONS, for coordination to two diphenyltin(IV) moieties. Coordination number of both tin(IV) center is five and it is maintain in solution. In **1** and **2** only one part of ligand as doubly deprotonated ONS donor was coordinated with tin and a mononuclear organotin complex with coordination number of five was formed. The *in vitro* antibacterial activity of ligand and complexes has been evaluated against Gram-positive (*B. subtilis* and *S. aureus*) and Gram-negative (*E. coli* and *P. aeruginosa*) bacteria and compared with standard drugs. The synthesized compounds also have been investigated for the chromosomal and plasmid DNA cleavage activity. All complexes significantly inhibited bacterial growth and completely degrade the treated DNA.


## 1. Introduction

Metal complexes of multidentate ligands having oxygen, nitrogen and sulfur as donor atoms, such as thiosemicarbazones, have attracted great and growing interest due to their structural considerations, potential biological activity and practical application. Thiocarbohydrazones are homologues of thiosemicarbazones with a possible extra metal binding domain. The chelating ability of thiocarbohydrazones plays an important role for serving as analytical reagents. Thiocarbohydrazones also have recently attracted special attention due to their antimicrobial, antiproliferative and anticarcinogenic activity [1–6].

Thiocarbohydrazones are easily prepared by condensation of thiocarbohydrazide with two molecules of carbonyl compounds. The most interesting features of these ligands are that they contain hard and soft donor atoms and are conformationally flexible. The tautomerism in these ligands and also the tendency of oxygen and sulfur donors to act as bridging sites allows various structural possibilities for the corresponding metal complexes. Thiocarbohydrazones have served as chelating ligands to form mono-, di- or multi-nuclear complexes. These compounds also be able to act as building blocks in the self-assembly structures [7–14].

To our knowledge, despite the several reports about chelating behavior of thiocarbohydrazones with transition metals, there are very little work on their organotin(IV) complexes [15,16]. In these reports only one part of the thiocarbohydrazone in doubly deprotonated O,N,S-manner was used in coordination with tin and a mononuclear organotin complex was formed. In view of the structural variety and the potential applications of organotins in medicinal chemistry and biotechnology, it was considered worthwhile to synthesize the organotin complexes with thiocarbohydrazones and investigate the interaction of these compounds with biological systems. In continuation of our studies on synthesis and characterization of organotin(IV) complexes, we have recently reported the synthesis, structural and antibacterial properties of a series of dinuclear organotin(IV) complexes with dihydrazones

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[17–19]. Although organotin complexes of monohydrazones have been studied in detail, these complexes with dihydrazones have been less widely studied. Among the organotin(IV) complexes of dihydrazones only a few are binuclear and in all of them coordination sphere around two tin center are equivalent [17–22]. In this research work we report the results of our investigations on the ligating properties of one thiocarbohydrazone derivative, 1,5-bis((2-hydroxynaphthaldehyde)thiocarbohydrazone ($H_4L$), with diorganotin(IV) dichlorides, $R_2SnCl_2$ (R = Me, Bu and Ph). This ligand is a multiprotic dihydrazone with two different tridentate donor part, ONS and ONN, and therefore structural investigation and biological properties of its organotin complexes will be interesting. The results of these studies are reported herein.

## 2. Experimental

### 2.1. Materials and methods

All starting materials were purchased from Merck while diphenyltin dichloride was supplied from Acros Company and were all used as received. All solvents were of reagent grade and used without further purification. 1,5-bis((2-hydroxynaphthaldehyde) thiocarbohydrazone ($H_4L$) has been prepared according to the procedure described in the literature from the reaction of thiocarbohydrazide and 2-hydroxynaphthaldehyde in ethanol [4] (note: structure of this compound drawn in ref. 4 is wrong). IR spectra were obtained using a FT BOMEM MB102 spectrophotometer. The $^1H$ and $^{119}Sn$ NMR spectra were recorded with Bruker Avance Ultrashield spectrometers using TMS and $SnMe_4$ as references, respectively. The elemental analyses for C, H, N and S were performed on a Costech-ECS 4010 CHNSO analyzer.

### 2.2. Synthesis of $Ph_4Sn_2L$ (**1**)

$H_4L$ (0.103 g, 0.25 mmol) was dissolved in ethanol (10 mL) at 55–60 °C and triethylamine (0.13 mL, 1 mmol) was added. This solution was stirred for 20 min and then $Ph_2SnCl_2$ (0.172 g, 0.5 mmol) in ethanol (5 mL) was added. The solution was refluxed for 4 h. A red precipitate was formed during the reaction. This precipitate was collected, washed with ethanol (5 mL) and dried in vacuum over $CaCl_2$. Yield: 0.174 g (73.3%). Red cubic single crystals suitable for X-ray diffraction studies were obtained by slow evaporation of an ethanol/chloroform (4:1) solution after 3 days. Anal. Calcd. for $C_{47}H_{34}N_4O_2SSn_2$: C, 59.0; H, 3.6; N, 5.9; S, 3.3%. Found: C, 58.8; H, 3.2; N, 6.3; S, 3.6%. FT-IR (KBr, $cm^{-1}$): ν(C=N–N=C), 1616, 1596; ν(C–S), 777; ν(Sn–O), 571, 534; ν(Sn–N), 482, 447; ν(Sn–S), 423. $^1H$ NMR (250 MHz, DMSO-$d_6$): 6.56–8.17 (m, 32H, ArH), 8.70 [s, 1H, HC=N––Sn, $^3J(^{119}Sn\text{-}^1H)$ = 36.0 Hz], 9.24 [s, 1H, HC=N–Sn, $^3J(^{119}Sn\text{-}^1H)$ = 48.5 Hz], $^{119}Sn$ NMR (149 MHz, DMSO): δ = −344.1, −440.2.

### 2.3. Synthesis of $Me_2Sn(H_2L)$ (**2**)

Complex **2** was synthesized as described for **1** from $H_4L$ (0.103 g, 0.25 mmol), triethylamine (0.07 mL, 0.5 mmol) and $Me_2SnCl_2$ (0.055 g, 0.25 mmol). The product was obtained as red solid. Yield: 0.088 g (63%). Anal. Calcd for $C_{25}H_{23}N_4O_2SSn$: C, 53.4; H, 4.1; N, 10.0; S, 5.7%. Found: C, 53.9; H, 4.4; N, 10.4; S, 5.4%. FT-IR (KBr, $cm^{-1}$): ν(OH), 3410; ν(NH), 3199; ν(C=N–N=C), 1618, 1597; ν(C–S), 776; $\nu_{as}$(Sn–C), 643; $\nu_s$(Sn–C),560; ν(Sn–O), 520; ν(Sn–N), 475; ν(Sn–S), 423. $^1H$ NMR (250 MHz, DMSO-$d_6$): δ = 0.86 [s, 6H, $Me_2Sn$, $^2J(^{119}Sn\text{-}^1H)$ = 82.5 Hz], 6.93 (d, 1H, $H_1$, $^3J_{HH}$ = 9.5 Hz), 7.22 (d, 1H, $H_{1'}$, $^3J_{HH}$ = 9.5 Hz), 7.35 (t, 1H, $H_4$, $^3J_{HH}$ = 7.6 Hz), 7.44 (t, 1H, $H_{4'}$, $^3J_{HH}$ = 7.6 Hz), 7.57 (t, 1H, $H_5$, $^3J_{HH}$ = 7.2 Hz), 7.63 (t, 1H, $H_{5'}$, $^3J_{HH}$ = 7.3 Hz), 7.78–7.90 (m, 4H, $H_{2,\ 2',\ 3,\ 3'}$), 8.03 (d, 1H, $H_6$, $^3J_{HH}$ = 7.5 Hz), 8.15 (d, 1H, $H_{6'}$, $^3J_{HH}$ = 7.5 Hz), 9.24 (s, 1H, HC=N), 9.37 [s, 1H, HC=N–Sn, $^3J(^{119}Sn\text{-}^1H)$ = 35.0 Hz], 11.74 (s, 1H, NH), 12.43 (s, 1H, OH). $^{119}Sn$ NMR (149 MHz, DMSO): δ = −206.1.

### 2.4. Synthesis of $Bu_2Sn(H_2L)$ (**3**)

Complex **3** was synthesized as described for **1** from $H_4L$ (0.103 g, 0.25 mmol), triethylamine (0.07 mL, 0.5 mmol) and $Bu_2SnCl_2$ (0.076 g, 0.25 mmol). The product was obtained as red solid. Yield: 0.095 g (59%). Anal. Calcd for $C_{31}H_{35}N_4O_2SSn$: C, 57.6; H, 5.5; N, 8.7; S, 5.0%. Found: C, 57.4; H, 5.6; N, 8.6; S, 4.6%. FT-IR (KBr, $cm^{-1}$): ν(OH), 3421; ν(NH), 3180; ν(C=N–N=C), 1620, 1598; ν(C–S), 776; ν(Sn–O), 517; ν(Sn–N), 463; ν(Sn–S), 423. $^1H$ NMR (250 MHz, DMSO-$d_6$): δ = 0.88 (t, 6H, $H_d$, $^3J_{HH}$ = 7.7 Hz), 1.35–1.39 (m, 4H, $H_c$), 1.51–1.63 (m, 8H, $H_{a,b}$), 7.02–7.17 (m, 2H, $H_{1,1'}$), 7.26–7.32 (m, 2H, $H_{6,6'}$), 7.39–7.50 (m, 2H, $H_{5,\ 5'}$), 7.70 (d, 2H, $H_{3,3'}$, $^3J_{HH}$ = 9.5 Hz), 8.88 (d, 2H, $H_{2,2'}$, $^3J_{HH}$ = 9.5 Hz), 9.26 (s, 1H, HC=N), 9.50 (s, 1H, HC=N–Sn), 12.51 (s, H, NH), 13.75 (s, H, OH). $^{119}Sn$ NMR (149 MHz, DMSO): δ = −197.7.

### 2.5. Antibacterial tests

In order to evaluate the antibacterial activity of ligand and complexes four different concentrations including 2.5, 5, 10 and 20 mg/mL were prepared in DMSO and sterile blank discs (6.4 mm) were saturated by these solutions. So, the effective dose per disc was as 0.1, 0.2, 0.4 and 0.8 mg, respectively. Then their effects against *Escherichia coli* ATCC25299, *Pseudomonas aeruginosa* ATCC9027, *Bacillus subtilis* ATCC6633 and *Staphylococcus aureus* ATCC6538 were surveyed according to the Kirby-Bauer standard disc diffusion method. Bacterial suspension equal to 0.5 McFarland was lawn cultured on Muller-Hinton agar (MHA, Merck, Germany), the prepared discs were placed on these cultures and plates were incubated at 37 °C for 24 h. A DMSO saturated disc was also used as negative control and standard antibiotic discs as positive control were tested against each species. Finally, the inhibition zone diameter (mm) of each disc was measured and recorded. In order to compare the results, the effect of standard antibiotic discs including Vancomycin, Streptomycin, Penicillin, Nalidixic acid and Gentamicin were studied as previously mentioned.

### 2.6. Gel electrophoresis assay

The DNA of *Bacillus subtilis* and *Escherichia coli* was extracted by boiling method. One mL of each bacterial suspension was centrifuged at 10000 rpm for 10 min. The precipitates were dissolved in 1 mL of sterile distilled water and boiled for 15 min. The mixture was centrifuged at 5000 rpm for 1 min and the supernatant was harvested and mixed with cold ethanol (2.5 v/v) and stored overnight at −20 °C. Finally, centrifugation at 13000 rpm for 10 min was done and the precipitate was dissolved in 100 μL of DNase free sterile water and stored at −20 °C. Plasmid DNA was also extracted by plasmid extraction kit (Qiagen, Germany). A 20 mg/mL solution of each compound in DMSO was prepared. 10 μL of this solution was mixed with 10 μL of DNA and incubated at 37 °C for 2 h. A positive control was also prepared by mixing 10 μL of $H_2O_2$ with 10 μL of DNA and untreated DNA was regarded as negative control. These DNA samples were electrophoresed in 1% agarose containing DNA safe stain at 100 V for 50 min. A 1 Kb DNA ladder was used as size marker. The gel was documented with UVI-Tec gel documentation system.

### 2.7. X-ray structure determination

The X-ray diffraction measurement for complex **1** was made on