ELSEVIER

www.elsevier.nl/locate/carres

Carbohydrate Research 328 (2000) 425–429

CARBOHYDRATE RESEARCH

Note

Cu, Pt, and Pd complexes of the 3-deoxy-1,2-bis(thiosemicarbazone) derived from D-glucose

Derek Horton [a,*], Oscar Varela [b]

[a] *Department of Chemistry, American University, 4400 Massachusetts Avenue, NW, Washington, DC 20016-8014, USA*

[b] *CIHIDECAR (CONICET)–Departamento Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón II, Ciudad Universitaria, 1428 Buenos Aires, Argentina*

Received 28 February 2000; accepted 13 April 2000

Abstract

3-Deoxy-D-*erythro*-hexos-2-ulose bis(thiosemicarbazone) (**1**) acts as a tetradentate ligand of the N_2S_2 type which forms stable coordination complexes with metal(II) cations. The Cu(II), Pt(II), and Pd(II) chelates (**2**, **4**, and **6**, respectively) of **1** were synthesized and characterized by elemental analysis and NMR spectroscopy. The NMR spectra of the Pt complex (**4**) showed the coupling of H-1 and C-1, C-2 of the bis(thiosemicarbazone) with ^{195}Pt (33.7% naturally occurring), which supports the structure proposed for the chelate. The complexes **2**, **4**, and **6** were acetylated to give the corresponding tri-*O*-acetyl derivatives **3**, **5**, and **7**. Elimination of Cu(II) from **3** with hydrogen sulfide afforded **8**, the tri-*O*-acetyl derivative of **1**. Preliminary studies have shown antiviral activity of chelates **2**, **4**, and **6** against poliovirus type 1.

Keywords: Bis(thiosemicarbazone); Chelates; Copper; Platinum; Palladium

Thiosemicarbazones have found varied applications in industry and analytical chemistry, and some derivatives have shown antiparasitic, antimicrobial, antineoplastic, and antiviral activities [1]. In many cases, the biological activities of thiosemicarbazones have been related to their chelating properties [2], as these compounds can coordinate in vivo to metal ions. However, the high hydrophobicity and low water solubility of most thiosemicarbazones and their chelates make their administration difficult and restrict the studies on their biological properties. The introduction of a carbohydrate moiety into the thiosemicarbazone should increase the water solubility and the cell-membrane permeability. With that aim, we have reported [3] the synthesis of 3-deoxyaldos-2-ulose bis(thiosemicarbazones) starting from aldoses, and more recently the preparation of *O*-(β-D-glycopyranosyl)-2-hydroxyacetaldehyde thiosemicarbazones has been described [4]. These bis(thiosemicarbazones) are particularly interesting as the thiosemicarbazone groups are positioned in such a way that they are capable of coordinating with metal cations to form

* Corresponding author. Tel.: +1-202-8851767; fax: +1-202-8851095.

E-mail address: carbchm@american.edu (D. Horton).

0008-6215/00/$ - see front matter
PII: S0008-6215(00)00118-X

stable complexes. Thus, the copper(II) complex of 3-deoxy-D-*erythro*-hexos-2-ulose bis(thiosemicarbazone) was prepared, and it showed in vivo antitumor activity in the murine L-1210 assay [3]. We expected that other metal complexes of this type could display higher antitumor activity, and we were particularly interested in the platinum compounds. Many platinum complexes have been examined since cisplatin was introduced as an anticancer drug [5]. It has been stated that Pt(II) complexes of diamino sugars [6] and dithiocarbamic acids [7] have shown cytostatic activity. We report here the synthesis, characterization and derivatization of Cu(II), Pt(II), and Pd(II) chelates of a bis(thiosemicarbazone) derived from D-glucose.

3-Deoxy-D-*erythro*-hexos-2-ulose bis(thiosemicarbazone) (**1**), readily obtained from D-glucose, reacts with copper acetate hydrate to give the corresponding chelate **2** as a red–brown solid [3]. Similarly, the platinum and palladium chelates (**4** and **6**, respectively) were prepared from **1** by applying the same procedure as that described for the synthesis of **2**. These complexes were obtained in very good yields ($>80\%$) as solids of defined melting point. The elemental analyses of compounds **2**, **4**, and **6** indicated a 1:1 ratio of metal(II) to bis(thiosemicarbazone). Wolfrom et al. [8] proposed that bis(semicarbazones) can act as tetradentate ligands in the formation of Cu(II) coordination complexes. Further studies based mainly on IR, UV, and some NMR spectroscopic data [7,9,10] seem to confirm that the bis(thiosemicarbazone) group coordinates with the metal to form three five-membered chelate rings. X-Ray crystallographic studies of **2** revealed a square-planar coordination geometry in the solid state, with retention of the metal-center geometry upon dissolution [11]. The crystal structure of the Ni(II) complex of 2,3-butanedione 3-*N*-methyl-phenylthiosemicarbazone has been determined, and it showed the same arrangement for the coordination site [10].

We have now recorded the ^{1}H and ^{13}C NMR spectra of chelates **4** and **6**, and these studies give further support to the structure proposed for such complexes in solution. The proton spectra (Table 1) were performed using pyridine-d_5 or dimethyl-d_6 sulfoxide as sol-

Table 1
^{1}H NMR data for compounds **1** and **4**–**8**

Compound	H-1	H-3	H-3′	H-4	H-5	H-6	H-6′	N-*H*
		$J_{3,4}$	$J_{3',4}$ $J_{3,3'}$	$J_{4,5}$	$J_{5,6}$	$J_{6,6'}$	$J_{5,6'}$	
1 [a]	8.00	3.80	3.23	4.59	4.96	4.31	4.31	13.00, 12.11, 9.76
		1.7	8.1, 13.7	6.4				9.67, 8.82, 8.76
4 [a]	7.80 [c]	3.32	3.07	4.47	4.12	4.34	4.20	9.26, 9.20
		3.4	8.1, 14.3	6.0	3.8	10.4	5.8	
4 [b]	7.29 [c]	2.67	2.46	3.67–3.20	3.67–3.20	3.67–3.20	3.67–3.20	7.90, 7.80
		3.3	9.1, 14.5					
5 [a]	7.66 [c]	2.98	2.98	5.69	5.57	4.0	4.39	9.41, 9.28
				5.6	3.5	12.1	6.0	
5 [b]	7.32 [c]	2.74	2.69	5.19	5.09	4.27	4.12	7.93
		4.2	8.8, 14.7	5.5	3.0	12.3	7.0	
6 [a]	7.47	3.31	3.08	4.47	4.11	4.34	4.21	9.10, 9.02
		3.5	8.0, 14.2	7.0	4.0	10.7	5.8	
7 [a]	7.29	2.96	2.96	5.65	5.55	4.49	4.37	9.19, 9.04
				7.0	3.5	12.2	6.0	
8 [a]	8.14	3.54	3.54	5.84	5.57	4.68	4.49	
				6.2	4.0	12.0	6.2	
8 [b]	7.64	3.18	3.18	5.24	5.24	4.47	4.16	11.70, 10.50
					2.0	12.5	6.5	

[a] Recorded in pyridine-d_5.
[b] Recorded in dimethyl-d_6 sulfoxide.
[c] Singlet overlapped with a doublet (see text).

Table 2
^{13}C NMR data for compounds **1** and **4**–**8**

Compound	*C*S	C-1	C-2	C-3	C-4,5	C-6	CH_3CO
1 [a]	178.6, 178.2	142.0	149.3	28.6	74.3, 70.7	62.8	
4 [a]	184.3, 182.1	148.8	159.4	31.3	74.9, 69.1	62.9	
5 [a]	184.4, 182.8	147.5	155.0	27.5	70.9, 68.5	61.4	170.1, 169.6, 169.4, 20.6, 20.5, 20.4
6 [b]	185.1, 183.3	148.3	158.7	32.8	75.9, 71.3	64.8	
7 [b]	185.5, 183.9	146.3	153.6	28.3	72.1, 69.6	62.3	170.5, 170.1, 169.9, 20.9, 20.6, 20.5
8 [a]	178.8, 178.2	141.6	144.2	25.3	71.6, 69.5	61.2	169.8, 169.3, 169.2, 20.4 (×2), 20.3
8 [b]	180.4	141.0	144.7	26.4	72.4, 70.3	61.7	170.3, 170.0 (×2), 20.7 (×2), 20.5

[a] Recorded in dimethyl-d_6 sulfoxide.
[b] Recorded in pyridine-d_5.

vents, as in some cases the change of solvent improved the resolution. The ^{1}H NMR spectrum of **4** was particularly interesting, as the H-1 resonance gave two signals: a singlet and a doublet, both centered at 7.80 ppm, and which represented about 0.7 and 0.3 of the integral. The doublet corresponded to the H–C=N–^{195}Pt coupling (J 59.6 Hz) with an area determined by the abundance of the naturally occurring isotope ^{195}Pt (33.7%, $I = 1/2$). This doublet was superimposed upon the singlet due to H-1 in molecules having Pt with $I = 0$ (66.3%). Our observations were in agreement with other studies on Pt(II) complexes [12]. These results confirmed that the nitrogen bonded to C-1 is involved in an N–Pt bond in the chelate. Furthermore, the strongly downfield shifted N*H* signals in **1** ($\sim$12–13 ppm), probably due to hydrogen bonding with the pyridine-d_5, disappear in the complexes, indicating the dissociation of these protons on coordination to give a $N_2S_2^{2-}$ type of ligand. Also, the four signals of the two NH_2 groups in **1** collapsed into two broad singlets in the complexes **4** and **6**. The Ni(II) chelates of bis(thiosemicarbazones) have shown a similar behavior [9].

The chemical shifts of the signals in the ^{13}C NMR spectra of compounds **4** and **6** (Table 2) were only slightly afected by changing the solvent from dimethyl-d_6 sulfoxide to pyridine-d_5. As with the results for other thiosemicarbazone complexes [9,10], compounds **4** and **6** exhibited in their spectra a downfield shift for C-1 and C-2, as compared to the same signals in the spectrum of **1**. This effect is attributed to deshielding by coordination via the azomethine nitrogens. This was confirmed in the ^{13}C NMR spectrum of **4**, as the C-1 and C-2 signals showed the satellite bands due to coupling with ^{195}Pt. Thus, a singlet superimposed with a doublet ($J \approx 92$ Hz) was observed for the resonances of these carbons. A broadening of the signals corresponding to the carbons bonded to sulfur was also detected, although no coupling constants could be measured in this instance.

To perform definitive structural studies on these chelates, crystals of good quality were required. Unfortunately, all our attempts to date to grow crystals have been unsuccessful. We considered that, as is commonly found with sugars, some simple derivatives of the complexes might have better crystalline properties. Therefore, acetylation of compounds **2**, **4**, and **6** was conducted under standard conditions, to afford respectively the acetyl derivatives **3**, **5**, and **7** (see Scheme 1). They were characterized by elemental analysis and NMR spectroscopy. The NMR spectra of **5** and **7** followed the same pattern of signals observed in the spectra of their precursors **4** and **6**, respectively. The acetylated complexes crystallized from mixtures of alcohol and water, but we failed to grow crystals suitable for X-ray studies. The preparation of other derivatives of the complexes is in progress.

It has been reported that acetylation of thiosemicarbazone derivatives led to 2,3-dihydro-1,3,4-thiodiazoles as the main products [13,14]. Depending on the reaction conditions, different diastereoisomers of such compounds could be obtained [13]. In order to obtain a bis(thiosemicarbazone) derivative having the thiosemicarbazone moiety intact and the hydroxyl groups protected, a solution of **4** was

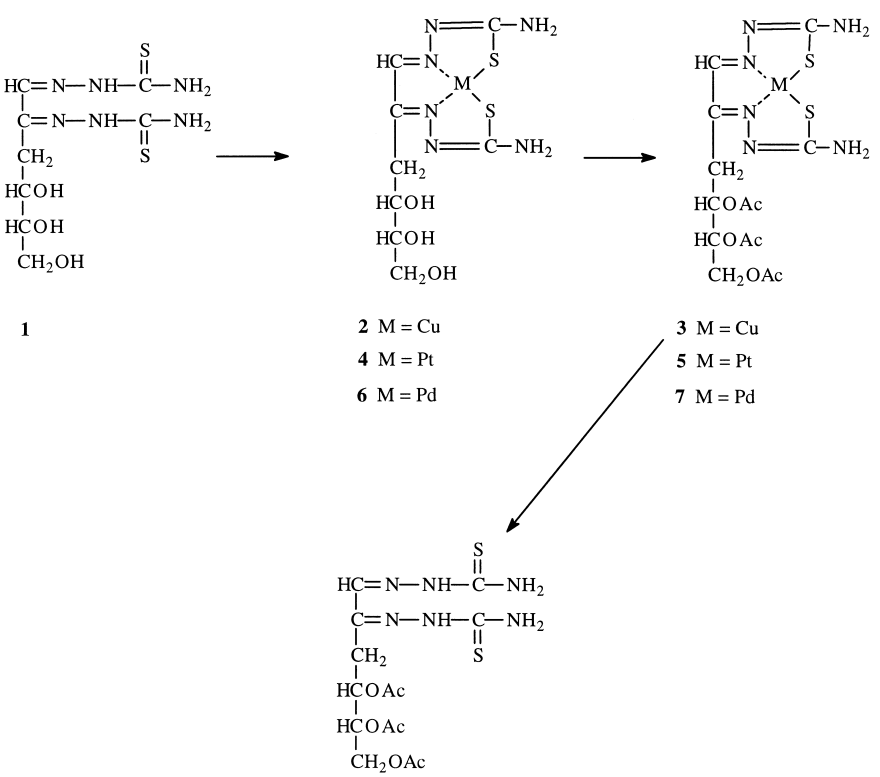
subjected to treatment with hydrogen sulfide. While the gas was bubbled into the solution a black precipitate of copper(II) sulfide formed. From the mother liquors the desired compound **8** was obtained. The ^{1}H NMR spectrum of **8** greatly resembles that of **1**, except for the downfield shift of the sugar-chain protons, due to acetylation of the OH groups. The ^{13}C NMR spectrum of **8** was also very similar to that of **1**, but it showed the signals of the three acetyl groups.

Chelates **2**, **4**, and **6**, and the ligand **1** were tested for antiviral activity against poliovirus type 1 on monkey kidney vero cells, by the plaque-reduction method. Preliminary results have shown that complexes **2**, **4**, and **6** were virus inhibitors with effective concentration 50% (EC_{50}) values of 5.8, 10.5, and 14.4 μg/mL, respectively. The solubility in water of ligand **1** and the chelates was higher than 50 μg/mL. Compound **1** showed no viral inhibition for a concentration of 30 μg/mL.

1. Experimental

General methods.—Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm Silica Gel 60 F_{254} (E. Merck) aluminum-supported plates. Detection was effected by dipping the plates in 5% H_2SO_4 (v/v) in EtOH, followed by charring. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker AC 200 spectrometer (^{1}H at 200 MHz, ^{13}C at 50 MHz). For NMR data see Tables 1 and 2. Microanalyses were performed by Atlantic Microlab, Atlanta, Georgia.

3-Deoxy-D-erythro-*hexos-2-ulose bis(thiosemicarbazone) platinum chelate* (**4**).—To a boiling solution of **1** (0.31 g, 1.0 mmol) in 1:1 EtOH–water (40 mL), K_2PtCl_4 (0.42 g, 1.0 mmol) dissolved in hot water (5 mL) was added. The deep green solution was boiled for 5 min and then it was maintained at room temperature (rt) for 20 h. The green solid formed was filtered to afford **4** (0.41 g, 85%).



Scheme 1.

Recrystallized from water, **4** had mp 220–222 °C. Anal. Calcd for $C_8H_{14}N_6O_3PtS_2$ (501.46): C, 19.16; H, 2.81; N, 16.76; S, 12.79. Found: N, 16.56; H, 2.85; N, 16.76; S, 12.61.

3-Deoxy-D-erythro-*hexos-2-ulose bis(thiosemicarbazone) palladium chelate* (**6**).—This compound was prepared as described for **4**, starting from **1** (0.92 g, 3.0 mmol) and $PdCl_2$ (0.53 g, 3.0 mmol). After 20 h at rt, the deep-blue precipitate was filtered to afford **6** (1.03 g, 82%), mp 157–160 °C. Anal. Calcd for $C_8H_{14}N_6O_3PdS_2 \cdot H_2O$ (420.77): C, 22.81; H, 3.80; N, 19.96. Found: C, 22.49; H, 3.56; N, 20.10.

Acetylation of the complexes **2**, **4**, *and* **6**: *general procedure*.—The metal complex (1.0 mmol) was suspended in dry pyridine (5 mL) and acetic anhydride (3 mL) was slowly added. The mixture was stirred at rt for 16 h, and then slowly poured into ice–water. The solid formed was filtered, dried and recrystallized from 1:1 MeOH–water.

Chelates of 4,5,6-tri-O-*acetyl-3-deoxy*-D-erythro-*hexos-2-ulose bis(thiosemicarbazone)*

Copper chelate (**3**). Compound **3** was obtained in 68% yield after recrystallization; mp 190–192 °C. Anal. Calcd for $C_{14}H_{20}CuN_6O_6S_2$ (496.02): C, 33.90; H, 4.06; N, 16.94; S, 12.93. Found: C, 33.72; H, 4.09; N, 16.85; S, 12.86.

Platinum chelate (**5**). Obtained in 63% yield; mp 168–171 °C. Anal. Calcd for $C_{14}H_{20}N_6O_6PtS_2$ (627.57): C, 26.79; H, 3.21; N, 13.39; S, 10.22. Found: C, 26.84; H, 3.22; N, 13.29; S, 10.15.

Palladium chelate (**7**). The acetylated derivative **7** was obtained in 67% yield; mp 198–200 °C. Anal. Calcd for $C_{14}H_{20}N_6O_6PdS_2$ (538.88): C, 31.20; H, 3.74; N, 15.60; S, 11.90. Found: C, 31.33; H, 3.74; N, 15.58; S, 11.82.

4,5,6-Tri-O-*acetyl-3-deoxy*-D-erythro-*hexos-2-ulose bis(thiosemicarbazone)* (**8**).—Through a solution of compound **2** (1.11 g, 3.0 mmol) in 1:1 MeOH–water (200 mL) H_2S was bubbled. The progress of the reaction was monitored by TLC employing EtOAc as solvent. The starting material (R_f 0.48) was gradually converted into a faster migrating product (R_f 0.63). After 2 h the black precipitate [Cu(II) sulfide] that formed was removed by filtration, and the solution was concentrated to a final volume of about 20 mL. On refrigeration, compound **8** crystallized slowly. After 20 h the crystals were filtered off and recrystallized from 2:1 water–MeOH to give **6** (0.71 g, 55%); mp 188–190 °C. Anal. Calcd for $C_{14}H_{22}N_6O_6S_2$ (434.5): C, 38.70; H, 5.10; N, 19.34, S, 14.73. Found: C, 38.94; H, 5.38; N, 19.10; S, 14.45.

Acknowledgements

We thank Professor Celia Coto and Dr Graciela Andrei, from the Laboratory of Virology, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires for performing the preliminary biological tests. O.V. is a Research Member of the National Research Council of República Argentina (CONICET).

References

[1] S.R. Turk, C. Shipman Jr., C.J. Drack, *Biochem. Pharmacol.*, 35 (1986) 1539–1545 and Refs. cited therein.
[2] D.T. Minkel, D.H. Petering, *Cancer Res.*, 38 (1978) 117–123.
[3] D. Horton, R.G. Nickol, O. Varela, *Carbohydr. Res.*, 168 (1987) 295–300.
[4] A. Díaz, A. Fragoso, R. Cao, V. Vérez, *J. Carbohydr. Chem.*, 17 (1998) 293–303.
[5] (a) L.S. Hollis, A.R. Amundsen, E.W. Stern, *J. Am. Chem. Soc.*, 107 (1985) 274–276. (b) M.P. Hacker, E.B. Douple, I.H. Krakoff (Eds.), *Platinum Coordination Complexes in Cancer Chemotherapy*, M. Nijhoff, Boston, MA, 1984.
[6] T. Tsubomura, S. Yano, K. Kobayashi, T. Sakurai, S. Yoshikawa, *J. Chem. Soc., Chem. Commun.*, (1986) 459–460.
[7] G. Faraglia, L. Sindellari, L. Trincia, A. Furlani, V. Scarcia, *Inorg. Chim. Acta*, 106 (1985) 31–35.
[8] M.L. Wolfrom, H. El Khadem, H. Alfes, *J. Org. Chem.*, 29 (1964) 3074–3076.
[9] A. Díaz, I. García, R. Cao, H. Beraldo, M.M. Salberg, D.X. West, L. Gonzalez, E. Ochoa, *Polyhedron*, 16 (1997) 3549–3555.
[10] D.X. West, J.S. Ives, G.A. Bain, A.E. Liberta, J. Valdés-Martínez, K.H. Ebert, S. Hernández-Ortega, *Polyhedron*, 16 (1997) 1895–1905.
[11] S. Signorella, C. Palopoli, A. Frutos, G. Escandar, T. Tanase, L.F. Sala, *Can. J. Chem.*, 77 (1999) 1492–1497.
[12] P. Haake, P. Cronin Turley, *J. Am. Chem. Soc.*, 89 (1967) 4611–4616.
[13] L. Somogyi, *Corbohydr. Res.*, 75 (1979) 324–330.
[14] M.A. Martins Alho, N.B. D'Accorso, *J. Heterocyclic Chem.*, 34 (1997) 1415–1419.