Interaction of Pd(II) with Thiazolidine-4-carboxylic Acid and its 4-Acetyl Derivative

BARBARA RADOMSKA, TOMASZ TATAROWSKI, JAN P. MORAWIEC and HENRYK KOZŁOWSKI

Institute of Chemistry, University of Wrocław, Joliot-Curie 14, 50-383 Wrocław, Poland

Received November 14, 1984

Thiaproline (thiazolidine-4-carboxylic acid) is believed to be able to induce the restoration of 'contact inhibition' to tumor cells and its interaction with metal ions seems to be of critical importance [1–3]. Recent studies on the coordination ability of thiaproline have shown that for metal ions like Zn(II), Mn(II), Ni(II), Co(II) and Cu(II) the main binding sites are a nitrogen donor and a carboxylic group [4–6]. A sulfur donor competes in the binding of such metal ions as Pd(II) or Pt(II) but recent studies concerning these systems have not reached clear conclusions [7, 8].

In this communication we present the ^{13}C NMR and CD results for the Pd(II)–thiaproline and Pd(II)–N-acetyl-thiaproline systems which may clarify some doubts.

Experimental

L-thiazolidine-4-carboxylic acid was used as obtained from Merck. N-acetyl-thiaproline was synthesized according to Ratner and Clarke [9]. K_2PdCl_4 was used as a metal ion source. ^{13}C NMR spectra were recorded on a JEOL JNM-PS-100 spectrometer with dioxane as internal standard in D_2O. CD spectra were recorded on an automatic recording spectropolarimeter JASCO-J-20.

The solid state complex of Pd(II) with thiaproline was obtained according to the procedure given earlier [8]. The precipitate was washed out with water and dissolved in a hot ethanol–water mixture. The crystals obtained after cooling analyzed as Pd, 36.5; C, 17; S, 11; N, 4.5; Cl, 8.7; H, 3.7%. These data suggest a partly hydrolyzed complex $PdLCl_{0.7}(OH)_{0.3}\cdot H_2O$ (Pd, 37.1; Cl, 16.8; S, 11.2; N, 4.9; Cl, 8.7; H, 2.9%), which is considerably different from that proposed earlier [8].

Results and Discussion

Pd(II)–N-acetyl-L-thiaproline Solutions

^{13}C NMR spectra clearly indicate Pd(II) binding to the sulfur donor of the N-acetyl-thiaproline ligand. The ^{13}C signals most affected by Pd(II) binding are those of the C_β and C_δ carbons of the thiaproline ring which are just next to sulfur (Table I, Fig. 1). Neither COO^- nor blocked nitrogen interacted with the metal ion in all solutions studied.

The CD spectra usually indicate very clearly Pd–S bond formation due to S → Pd(II) charge transfer transition seen in the UV region [10]. The CD spectra (Table II) show in the d–d region a negative band at 402 nm. Three other complex transitions are observed in the 275–330 nm region (Table II, Fig. 2). Though the 330 nm band could still be assigned as a d–d transition E, see *e.g.* [10], the other two bands at 302 and 275 nm can only be attributed to the S → Pd(II) charge transfer bands. Thus the CD spectra are really diagnostic for S → Pd(II) bond formation and for the N-acetyl-L-thiaproline ligand.

Pd(II)–L-thiaproline Solutions

The pattern of the CD spectra of the Pd(II)–thiaproline solutions is very close to that found for Pd(II)–N-acetyl-thiaproline (Table II) though there are shifts in energy of the respective bands of about 20 nm. The very intensive transitions at 312, 284 and 253 nm which are clearly complex transitions can

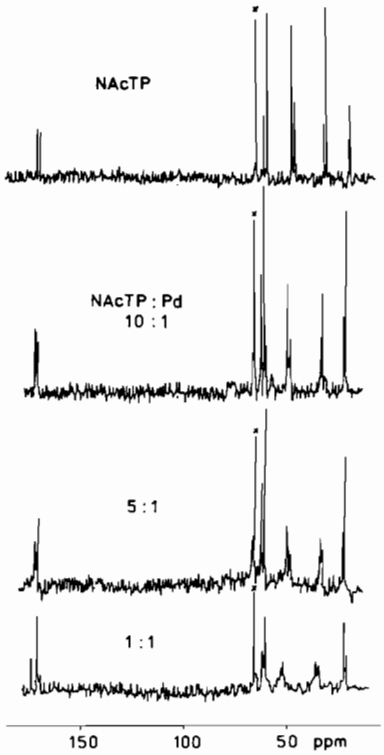

Fig. 1. ^{13}C NMR spectra of N-acetyl-thiaproline with different ligand to palladium molar ratios (x = dioxane as an internal standard).

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TABLE I. ^{13}C NMR Data of N-Acetyl-thiaproline and the N-Acetyl-thiaproline Complex with Palladium(II)

	pH = 0.5	pH = 1.8	pH = 2.5	pH = 3.6	pH = 6.5	Pd:AcTP 1:1 pH = 0.2
*C*OO	174.42	174.6	176.1 175.5	177.2	177.6	175.8
*C*OCH$_3$	173.21	173.2	173.0	173.6[b] 172.7[c]	173.5[b] 172.6[c]	173.0
C	63.76[b] 62.3[c]	63.9[b] 62.3[c]	65.0[b] 63.0[c]	65.8[b] 64.4[c]	65.9[b] 64.7[c]	63.0[b] 61.8[c]
C	50.5[c] 49.3[b]	50.5[c] 49.3[b]	50.7[c] 49.6[b]	50.8[c] 49.7[b]	50.7[c] 49.7[b]	53.2[a]
C	34.4[b] 33.5[c]	34.8[b] 33.6[c]	35.4[b] 33.8[c]	35.7[b] 34.3[c]	35.7[b] 34.4[c]	37.9[b] 36.7[c]
COC*H*$_3$	22.0[b] 22.5[c]	23.0[b] 22.5[c]	23.0[b] 22.5[c]	23.0[b] 22.8[c]	22.9[b] 22.6[c]	22.7[b] 21.9[c]

All chemical shifts given in ppm from TMS.
[a] Signal too broad to assign the isomer type, $c_{AcTP} = 0.3$ M. [b] s-*cis* isomer. [c] s-*trans* isomer [11].

TABLE II. Circular Dichroism of Pd(II): Thiaproline, Pd(II): N-Acetyl-thiaproline and Pd(II): Thiaproline: Glycine Solutions. $c_{Pd} = 0.001$ M; $c_{Cl^-} = 0.014$ M.

Pd:AcTP 1:1 pH = 2.0 λ_{max} nm		Pd:AcTP:Gly 1:1:1 pH = 2.6 λ_{max} nm		Pd:TP 1:1 pH = 1.7 λ_{max} nm	
540	+0.02	550	+0.01		
402	−0.46	421	−0.33	431	+0.25
				385	−0.49
330	+1.30	320	+1.00		
				312	+5.1
302	+0.61	300	+0.80		
275	−2.1	272	−0.91	284	−12.5
				253	+5.3
230	+2.0	235	−2.0	225sh	+1.5

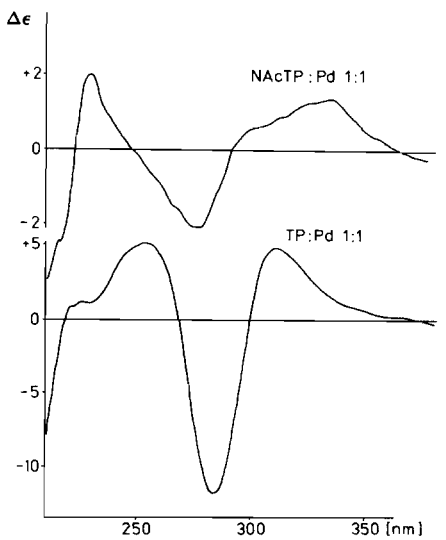

Fig. 2. UV part of CD spectra of N-acetyl-thiaproline and thiaproline complexes with palladium.

easily be assigned as charge transfer transitions from S to Pd(II). Thus also in the Pd(II)–thiaproline system the sulfur donor is a major binding site for the metal ion. The behaviour of the Pd(II)–L-thiaproline system is, however, considerably different from that of the Pd(II)–N-acetyl-L-thiaproline one. The addition of equimolar amounts of glycine to a 1:1 molar ratio solution of Pd(II)AcTP distinctly changes the CD spectra (Table II) indicating that Gly binds the Pd(II) ion. In the Pd(II)TP solutions even excess of Gly (or other chelating agents like en) does not cause any change in the CD spectra which suggests that TP occupy more than one binding site of the coordination sphere. The binding of sulfur and nitrogen (see also [7]) or COO^- must lead to the formation of polynuclear species. The latter result may explain the much lower solubility of the PdTP complex ($< 10^{-3}$ M/dm^3) compared to PdAcTP (~ 0.3 M/dm^3). The formation of polymer $(PdTP)_n$ is also suggested by the primary X-ray data showing that one of the lattice constants is above 30 Å.

The formation of polymer species may also explain the fact that the analogous Pt(II) complex was showing only a minor anticancer effect [8] probably derived from the monomer impurities. Thus thiaproline binds the Pd(II) ion via sulfur as well as amino acid donors with the formation of polymer species. The N-acetyl-thiaproline having blocked the nitrogen donor may use only sulfur as a binding site. This indicates that a nitrogen is a second donor used in complex formation.

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