Contribution from the Inorganic Chemistry Laboratory, University of Athens, Navarinou 13A, Athens, Greece, and the Department of Chemistry, University of Montreal, Montreal, Québec H3C 3V1, Canada

Complexes of Inosine, Cytidine, and Guanosine with Palladium(II)

G. PNEUMATIKAKIS, N. HADJILIADIS, and T. THEOPHANIDES*

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The reactions of Pd(II) with inosine (InoH) and guanosine (GuoH) have been studied in aqueous solutions. The complexes isolated from these reactions have the following formulas: *cis*- and *trans*-$[Pd(NuclH)_2Cl_2]$, *cis*- and *trans*-$[Pd(Nucl)_2]$, *cis*- and *trans*-$[Pd(InoH)_2(NuclH)_2]Cl_2$, *cis*- and *trans*-$[Pd(GuoH)_2(NuclH)_2]Cl_2$, *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$, *cis*-$[Pd(GuoH)_2(Guo)]Cl$, *cis*-$[Pd(GuoH)_2(Ino)]Cl$, $[Pd(GuoH)_3Cl]Cl$, and $[Pd(GuoH)_2(InoH)Cl]Cl$, where NuclH = inosine and guanosine. The compounds have been identified by elemental analyses, conductivity measurements, and IR and ^1H NMR spectra. In this case, i.e., with palladium, both cis and trans isomers have been isolated and characterized, in contrast to the platinum analogues. The diaquo *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ complex and the trinucleosides, $[Pd(GuoH)_3Cl]Cl$ and $[Pd(GuoH)_2(InoH)Cl]Cl$, are ionic and novel in this series of complexes. The trans effect of nucleosides follows the order Nucl < Cl^-, Br^-. N_7O_6 chelation has been found here, comparable to that proposed for the analogous platinum complexes. This N_7O_6 chelation is discussed with relation to the mode of action and the antitumor activity of *cis*-$[Pt(NH_3)_2Cl_2]$.

Introduction

The interaction of metals with purine and pyrimidine bases and their derivatives is of great biological importance. Both metal ions and certain nucleotides serve as cofactors for various enzymatic reactions.[1] Many investigations concerning these interactions have been carried out in recent years.[2,3]

The discovery of the antitumor activity of platinum inorganic salts by Rosenberg and his collaborators and the suggestion that platinum complexes attack DNA *in vivo*[4] prompted us to study the interaction of purine and pyrimidine bases with Pt(II).[5-7]

The antitumor properties of metals are not limited to Pt(II) complexes.[8] Recently, Kirschner et al.[9] reported some Pt(II) and Pd(II) complexes with sulfur and nitrogen ligands with potential antitumor activity. Therefore, the interaction of Pd(II) with purine and pyrimidine bases is interesting. The interactions of Pd(II) with certain purine and pyrimidine bases have been recently investigated in solution by ^1H and ^{13}C NMR spectroscopy.[10,11] The aquation of *cis*-$[Pd(en)Cl_2]$ has also been reported.[11b] In addition, the reactions of 6-mercaptopurine with Pd(II) and the stability constants of the complexes formed,[12] together with the crystal structure of (dimethylacetamide)bis(6-mecapto-9-benzylpurine)palladium(II), have been reported.[13]

The present work was undertaken in order to see if Pd(II) reacts in a similar way to Pt(II) with inosine and guanosine[7b,c] and to compare the behavior of Pd(II) complexes which undergo ligand-exchange reactions 10^5 faster than those of Pt(II)[11b] and easily form aquo derivatives.[10]

Experimental Section

Materials. The nucleosides were purchased from Raylo Chemicals, Ltd., and were used without further purification. Potassium tetrachloropalladate(II) and palladous chloride were from Fluka A.G.

Methods. The IR spectra were recorded with a Beckman Model 2050 spectrophotometer. The positions of the bands are given within ±2 cm^{-1}. The ^1H NMR spectra were recorded with a Varian T60 high-resolution spectrometer. Me_4Si was used as an external reference in the spectra recorded in D_2O. Conductivity measurements were performed using an E365B conductoscope, Metrohm Ltd., Herisau, Switzerland. The melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The microanalyses were performed in the Laboratories of The National Hellenic Research Foundation (N.H.R.F.) in Athens.

Preparation of the Complexes. (1) *cis*-[Bis(inosine)dichloropalladium(II)], *cis*-$[Pd(InoH)_2Cl_2]$. Palladous chloride (0.3546 g, 2 mmol) was dissolved in 10 mL of 1 N HCl by heating at 50 to 60 °C. Inosine (1.0728 g, 4 mmol) was dissolved in 20 mL of 1 N HCl. The two solutions were mixed and stirred for 2 h. The yellow precipitate that formed was filtered, washed with acetone and ether, and dried at 110 °C under vacuum (yield ~80%).

(2) *cis*-[Bis(inosinato)palladium(II)], *cis*-$[Pd(Ino)_2]$. *cis*-[Bis(inosine)dichloropalladium(II)] (0.7137 g, 1 mmol) was suspended and stirred in 50 mL of water. Immediately the compound was dissolved, and a yellow precipitate was formed. The stirring was continued for 2 h for completion of the reaction. It was then filtered, washed with water, ethanol, and ether, and dried at 110 °C under vacuum. The yield was quantitative.

(3) *trans*-[Bis(inosinato)palladium(II)], *trans*-$[Pd(Ino)_2]$. Potassium tetrachloropalladate(II) (0.6524 g, 2 mmol) was dissolved in 20 mL of 0.5 N HCl by heating and the pH adjusted to ~6 with 0.5 N KOH. Inosine (1.0728 g, 4 mmol) was dissolved in 80 mL of water. The two solutions were mixed, and the pH of the mixture decreased from about 6 to about 2 with subsequent precipitation. The precipitate was filtered, washed with water, ethanol, and ether, and dried at 110 °C under vacuum. The yield was quantitative.

(4) *trans*-[Bis(inosine)dichloropalladium(II)], *trans*-$[Pd(InoH)_2Cl_2]$. *trans*-[Bis(inosinato)palladium(II)] (1.2816 g, 2 mmol) was dissolved in 5 mL of 1 N HCl and filtered. Excess acetone/ether 1:1 was then added to the filtrate. The complex precipitated quantitatively, was filtered, and was washed with small quantities of acetone and ether.

(5) [Tetrakis(inosine)palladium(II)] Dichloride, $[Pd(InoH)_4]Cl_2$. *cis*- or *trans*-[Bis(inosine)dichloropalladium(II)] (0.3569 g, 0.5 mmol) was mixed with 0.2682 g (1 mmol) of inosine in the solid state, and to this mixture was added 4 mL of D_2O. After stirring for 5 to 10 min at room temperature, the materials were completely dissolved. ^1H NMR spectra indicate formation of the complex in solution, which was then precipitated by adding excess acetone. The precipitate was filtered, washed with acetone and ether, and dried at 110 °C under vacuum. The yield was quantitative.

(6) *cis*-[Bis(inosine)bis(guanosine)palladium(II)] Dichloride, *cis*-$[Pd(InoH)_2(GuoH)_2]Cl_2$. *cis*-[Bis(inosine)dichloropalladium(II)] (0.3569 g, 0.5 mmol) was mixed with 0.2833 g (1 mmol) of guanosine in the solid state, and then 4 mL of D_2O was added. After stirring for about 10 min at 50 °C, complete dissolution was achieved. ^1H NMR spectra show the end of the reaction, and the complex was then precipitated with acetone, filtered, washed with acetone and ether, and dried at 110 °C under vacuum. The yield was quantitative. The same product was obtained starting with *cis*-$[Pd(GuoH)_2Cl_2]$ and inosine.

(7) *trans*-[Bis(inosine)bis(guanosine)palladium(II)] Dichloride, *trans*-$[Pd(InoH)_2(GuoH)_2]Cl_2$. Using stoichiometric amounts of *trans*-[bis(inosine)dichloropalladium(II)] and guanosine, the product was isolated as in (5) or (6). The same product was obtained starting with *trans*-$[Pd(GuoH)_2Cl_2]$ and inosine. The yield was quantitative.

(8) *cis*-[Bis(inosine)bis(cytidine)palladium(II)] Dichloride, *cis*-$[Pd(InoH)_2(Cyd)_2]Cl_2$. By mixing 0.3569 g (0.5 mmol) of *cis*-[bis(inosine)dichloropalladium(II)] and 0.2432 g (1 mmol) of cytidine and using the same procedure as in (7), *cis*-$[Pd(InoH)_2(Cyd)_2]Cl_2$ was isolated in quantitative yield.

(9) *trans*-[Bis(inosine)bis(cytidine)palladium(II)] Dichloride, *trans*-$[Pd(InoH)_2(Cyd)_2]Cl_2$. This complex was obtained in quantitative yield as in (8), starting with *trans*-[bis(inosine)dichloropalladium(II)].

(10) *cis*-[Bis(inosine)bis(xanthosine)palladium(II)] Dichloride, *cis*-$[Pd(InoH)_2(XaoH)_2]Cl_2$. By using stoichiometric amounts of

* To whom correspondence should be addressed at the Physical Chemistry & Spectroscopy Centre, The National Hellenic Research Foundation, Athens 501/1, Greece.

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cis-[bis(inosine)dichloropalladium(II)] and xanthosine and heating in a water bath for 15 min at 65 °C, the above compound was isolated in quantitative yield.

(11) ***trans*-[Bis(inosine)bis(xanthosine)palladium(II)] Dichloride, *trans*-$[Pd(InoH)_2(XaoH)_2]Cl_2$.** This product was isolated as in (10), starting with *trans*-[bis(inosine)dichloropalladium(II)] and xanthosine.

(12) ***cis*-[Bis(guanosine)(diaquo)palladium(II)] Dichloride, *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$.** Potassium tetrachloropalladate(II) (0.6524 g, 2 mmol) was dissolved in 10 mL of water. Guanosine (1.1332 g, 4 mmol) was suspended in 20 mL of water. The pH of both solutions was brought to about 2.5 with 0.1 N HCl. The two solutions were then mixed and stirred until complete dissolution of the guanosine. The solution was then rotoevaporated to a small volume, and the compound precipitated with excess of equal volumes of acetone and ether. The dried precipitate was dissolved in 5 mL of DMF, filtered from the insoluble KCl, and then reprecipitated with excess of equal volumes of acetone and ether. The precipitate was filtered, washed with ether, and dried under high vacuum in the presence of $CaCl_2$ (yield ~80%).

(13) ***trans*-[Bis(guanosine)dichloropalladium(II)], *cis*-$[Pd(GuoH)_2Cl_2]$.** Palladous chloride (0.3546 g, 2 mmol) was dissolved in 10 mL of 0.5 N HCl by heating to about 50 °C. Guanosine (1.1332 g, 4 mmol) was dissolved in 20 mL of 0.5 N HCl. The two solutions were mixed and stirred for 2 h. The yellow precipitate that formed was filtered, washed with acetone and ether, and dried at 110 °C under vacuum (yield ~80%). **Note:** *cis*-$[Pd(GuoH)_2Cl_2]$ can also be prepared in quantitative yield by dissolution of *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ in 0.5 N HCl, where upon stirring for 2 h the compound precipitates (see eq 12).

(14) ***trans*-[Bis(guanosinato)palladium(II)], *trans*-$[Pd(Guo)_2]$.** Guanosine (1.1332 g, 4 mmol) was suspended in 80 mL of water and mixed with 0.6524 g (2 mmol) of potassium tetrachloropalladate(II) dissolved in 20 mL of water. The mixture was stirred at room temperature for 2–3 h, during which time the yellow complex precipitated and the pH decreased. The precipitate was filtered, washed with water, ethanol, and ether, and dried at 110 °C under vacuum. The yield was quantitative.

(15) ***cis*-[Bis(guanosinato)palladium(II)], *cis*-$[Pd(Guo)_2]$.** This complex was prepared in quantitative yield by suspending *cis*-$[Pd(GuoH)_2Cl_2]$ in water and stirring at room temperature for 1 h. During the reaction, the pH decreased and the precipitate that formed was filtered, washed with small quantities of ethanol and ether, and dried at 110 °C under vacuum.

(16) ***trans*-[Bis(guanosine)dichloropalladium(II)], *trans*-$[Pd(GuoH)_2Cl_2]$.** This compound was prepared quantitatively by dissolving *trans*-[bis(guanosinato)palladium(II)] in the minimum amount of 1 N HCl, followed by precipitation with excess of equal volumes of acetone and ether.

(17) [Tetrakis(guanosine)palladium(II)] Dichloride, $[Pd(GuoH)_4]Cl_2$. *cis*- or *trans*-[Bis(guanosine)dichloropalladium(II)] (0.3755 g, 0.5 mmol) was mixed with 0.2833 g (1 mmol) of guanosine in the solid state, and 4 mL of D_2O was added. The same procedure as in (6) was then followed to isolate the compound quantitatively.

(18) ***cis*-[Bis(guanosine)bis(cytidine)palladium(II)] Dichloride, *cis*-$[Pd(GuoH)_2(Cyd)_2]Cl_2$.** Using stoichiometric amounts of *cis*-$[Pd(GuoH)_2Cl_2]$ and cytidine, the complex was isolated quantitatively following the usual procedure.

(19) ***trans*-[Bis(guanosine)bis(cytidine)palladium(II)] Dichloride, *trans*-$[Pd(GuoH)_2(Cyd)_2]Cl_2$.** This complex was prepared as in (18), starting with *trans*-$[Pd(GuoH)_2Cl_2]$.

(20) ***cis*-[Bis(guanosine)bis(xanthosine)palladium(II)] Dichloride, *cis*-$[Pd(GuoH)_2(XaoH)_2]Cl_2$.** This complex was prepared as in (10) from *cis*-$[Pd(GuoH)_2Cl_2]$ and xanthosine in stoichiometric amounts.

(21) ***trans*-[Bis(guanosine)bis(xanthosine)palladium(II)] Dichloride, *trans*-$[Pd(GuoH)_2(XaoH)_2]Cl_2$.** Here the starting materials were *trans*-$[Pd(GuoH)_2Cl_2]$ and xanthosine. The procedure was as in (10).

(22) ***cis*-[Bis(guanosine)(guanosinato)palladium(II)] Chloride, *cis*-$[Pd(GuoH)_2(Guo)]Cl$.** *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ (0.3773 g, 0.5 mmol) was mixed with 0.2833 g (1 mmol) of guanosine, and 20 mL water was added. The mixture was heated until complete dissolution and then cooled in an ice bath. The unreacted guanosine precipitated and was filtered off. During the reaction, the pH decreased from an initial value of ~5.5 to the final value of ~2.5. The filtrate was concentrated to a small volume, and the *cis*-$[Pd(GuoH)_2(Guo)]Cl$ was precipitated with excess acetone. The precipitate was then filtered, washed with acetone and ether, and dried at 110 °C under vacuum.

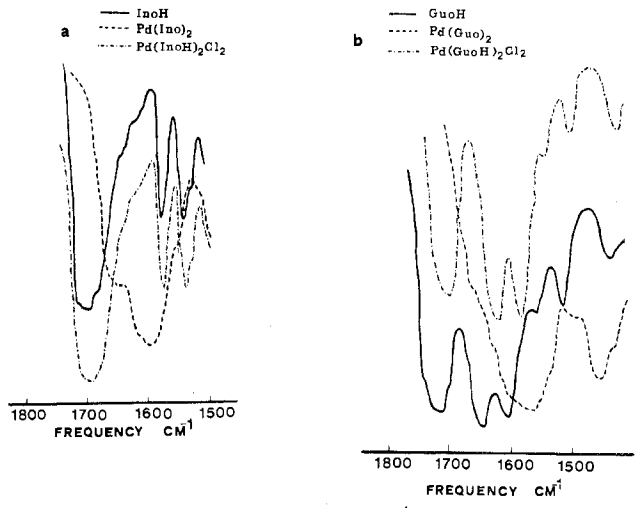


Figure 1. IR spectra in the 1500–1800 cm^{-1} region of (a) InoH, *cis*- or *trans*-$[Pd(Ino)_2]$, *cis*- or *trans*-$[Pd(InoH)_2Cl_2]$ and (b) GuoH, *cis*- or *trans*-$[Pd(Guo)_2]$, *cis*- or *trans*-$[Pd(GuoH)_2Cl_2]$.

(23) [Tris(guanosine)monochloropalladium(II)] Chloride, $[Pd(GuoH)_3Cl]Cl$. *cis*-$[Pd(GuoH)_2(Guo)]Cl$ (0.4989 g, 0.5 mmol) was dissolved in 5 mL of 0.5 N HCl and filtered. The $[Pd(GuoH)_3Cl]Cl$ was precipitated from the filtrate with excess of acetone. The precipitate was filtered, washed with acetone and ether, and dried at 110 °C under vacuum. The yield was quantitative.

(24) ***cis*-[Bis(guanosine)(inosinato)palladium(II)] Chloride, *cis*-$[Pd(GuoH)_2(Ino)]Cl$.** *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ (0.3773 g, 0.5 mmol) and 0.1341 g (0.5 mmol) of inosine were mixed, and 20 mL of water was added. The mixture was stirred at 50 °C for 1 h, and the pH decreased from ~5.5 to ~2.5. The *cis*-$[Pd(GuoH)_2(Ino)]Cl$ was precipitated with excess acetone, filtered, washed with ether, and dried at 110 °C under vacuum. The yield was quantitative.

(25) [Bis(guanosine)(inosine)monochloropalladium(II)] Chloride, $[Pd(GuoH)_2(Ino)Cl]Cl$. This compound was prepared quantitatively from *cis*-$[Pd(GuoH)_2(Ino)]Cl$ following the procedure in (23) by dissolving it in 0.5 N HCl.

(26) ***cis*-[Bis(cytidine)dichloropalladium(II)], *cis*-$[Pd(Cyd)_2Cl_2]$.** Potassium tetrachloropalladate(II) (0.3262 g, 1 mmol) was dissolved in 10 mL of water. Cytidine (0.4864 g, 2 mmol) was dissolved in 20 mL of water. The two solutions were mixed and stirred overnight. The yellow precipitate that formed was filtered, washed with water, ethanol, and ether, and dried at 110 °C under vacuum (yield ~90%).

(27) [Tetrakis(cytidine)palladium(II)] Dichloride, $[Pd(Cyd)_4]Cl_2$. *cis*-$[Pd(Cyd)_2Cl_2]$ (0.3319 g, 0.5 mmol) and 0.2432 g (1 mmol) of cytidine were suspended in 3 mL of D_2O and stirred at 50 °C until complete dissolution. The $[Pd(Cyd)_4]Cl_2$ product was first detected by ^1H NMR in solution and was then precipitated with excess acetone, filtered, washed with ether, and dried at 110 °C under vacuum. The yield was quantitative.

Results

Inosine. Direct interaction of K_2PdCl_4 or H_2PdCl_4 with inosine at pH ~5.5–6 and a 1:2 molar ratio resulted in the immediate quantitative precipitation of the *trans*-bis(inner complex) $Pd(Ino)_2$ with subsequent pH decrease, as in eq 1.

$$K_2[PdCl_4] + 2InoH \rightarrow trans\text{-}[Pd(Ino)_2] + 2HCl + 2KCl \quad (1)$$

Analytical data are consistent with the product formula (see Table I).

The ~1700 cm^{-1} IR ν(C=O) stretching band of the free inosine shifted to ~1625 cm^{-1} for the $[Pd(Ino)_2]$ complex, indicating Pd–O interaction (see Figure 1). Similar behavior has always been observed in the IR spectra of metal complexes of inosine and guanosine with the formation of M–O bonds.[7c] The $[Pd(Ino)_2]$ complex was not soluble in most organic solvents, but it reacted easily with 1 N HCl to form the *trans*-$[Pd(InoH)_2Cl_2]$ complex (eq 2). Reaction 2 was re-

$$trans\text{-}[Pd(Ino)_2] + 2HCl \underset{H_2O}{\overset{1\ N\ HCl}{\rightleftharpoons}} trans\text{-}[Pd(InoH)_2Cl_2] \quad (2)$$

Table I. Analytical and Physical Data of the Complexes

Compound		% C	% H	% N	% Pd	% Cl	Λ_M, Ω^{-1} cm^2 mol^{-1}	Mp,[a] °C
cis-[Pd(InoH)$_2$Cl$_2$]	Calcd	33.62	3.36	15.69	14.91	9.95	5 (DMF)	185 D
	Found	33.10	3.40	16.10	15.20	9.70		
cis-[Pd(Ino)$_2$]	Calcd	37.45	3.43	17.48	16.60			160 D
	Found	37.20	3.35	17.10	16.20			
trans-[Pd(Ino)$_2$]	Calcd	37.45	3.43	17.48	16.60			158 D
	Found	37.80	3.50	17.80	16.50			
trans-[Pd(InoH)$_2$Cl$_2$]	Calcd	33.62	3.36	15.69	14.91	9.95	6 (DMF)	180 D
	Found	33.20	3.50	16.10	15.20	10.20		
[Pd(InoH)$_4$]Cl$_2$	Calcd	38.39	3.84	17.92	8.51		270 (H$_2$O)	210 D
	Found	37.90	3.60	18.30	8.10			
cis-[Pd(InoH)$_2$(GuoH)$_2$]Cl$_2$	Calcd	37.49	3.91	19.68	8.31		310 (H$_2$O)	220 D
	Found	37.90	4.10	20.10	8.60			
trans-[Pd(InoH)$_2$(GuoH)$_2$]Cl$_2$	Calcd	37.49	3.91	19.68	8.31		305 (H$_2$O)	215 D
	Found	37.10	3.70	19.10	8.50			
cis-[Pd(InoH)$_2$(Cyd)$_2$]Cl$_2$	Calcd	37.99	4.17	16.33	8.87		280 (H$_2$O)	200 D
	Found	38.20	4.35	16.81	9.15			
trans-[Pd(InoH)$_2$(Cyd)$_2$]Cl$_2$	Calcd	37.99	4.17	16.33	8.87		270 (H$_2$O)	205 D
	Found	37.31	4.40	16.70	8.50			
cis-[Pd(InoH)$_2$(XaoH)$_2$]Cl$_2$	Calcd	37.44	3.74	17.47	8.30		310 (H$_2$O)	230 D
	Found	37.90	3.90	17.83	8.00			
trans-[Pd(InoH)$_2$(XaoH)$_2$]Cl$_2$	Calcd	37.44	3.74	17.47	8.30		310 (H$_2$O)	215 D
	Found	37.10	3.50	17.80	8.50			
cis-[Pd(H$_2$O)$_2$(GuoH)$_2$]Cl$_2$	Calcd	30.77	3.85	17.95	13.64	9.10	90 (DMF)	220 D
	Found	30.41	4.02	18.35	13.60	9.50		
cis-[Pd(GuoH)$_2$Cl$_2$]	Calcd	32.26	3.49	18.82	14.30	9.54	5 (DMF)	195 D
	Found	32.60	3.70	19.20	14.00	9.80		
trans-[Pd(GuoH)$_2$Cl$_2$]	Calcd	32.26	3.49	18.82	14.30	9.54	6 (DMF)	180 D
	Found	32.70	3.63	18.20	14.80	10.00		
trans-[Pd(Guo)$_2$]	Calcd	35.77	3.58	20.86	15.86			160 D
	Found	36.00	3.70	21.00	15.50			
cis-[Pd(Guo)$_2$]	Calcd	35.77	3.58	20.86	15.86			165 D
	Found	35.10	3.70	20.10	16.25			
[Pd(GuoH)$_4$]Cl$_2$	Calcd	36.62	3.97	21.36	8.12		280 (H$_2$O)	225 D
	Found	37.10	4.20	20.80	8.50			
cis-[Pd(GuoH)$_2$(Cyd)$_2$]Cl$_2$	Calcd	37.06	4.23	18.21	8.65		310 (H$_2$O)	210 D
	Found	37.50	4.50	17.80	8.15			
trans-[Pd(GuoH)$_2$(Cyd)$_2$]Cl$_2$	Calcd	37.06	4.23	18.21	8.65		305 (H$_2$O)	205 D
	Found	36.60	4.00	18.60	9.00			
cis-[Pd(GuoH)$_2$(XaoH)$_2$]Cl$_2$	Calcd	36.57	3.81	19.20	8.11			230 D
	Found	37.10	4.10	19.80	7.80			
trans-[Pd(GuoH)$_2$(XaoH)$_2$]Cl$_2$	Calcd	36.57	3.81	19.20	8.11		275 (H$_2$O)	220 D
	Found	37.00	3.60	18.50	8.50			
cis-[Pd(GuoH)$_2$(Guo)]Cl	Calcd	36.37	3.84	21.22	10.75	3.59	40 (DMF)	180 D
	Found	35.90	3.50	20.90	11.00	3.90		
[Pd(GuoH)$_2$Cl]Cl	Calcd	35.04	3.80	20.44	10.36	6.91	45 (DMF)	215 D
	Found	34.70	3.50	19.70	10.80	7.25		
cis-[Pd(GuoH)$_2$(Ino)]Cl	Calcd	36.90	3.79	20.09	10.90	3.64	42 (DMF)	183 D
	Found	37.30	4.00	20.90	11.30	3.93		
[Pd(GuoH)$_2$(InoH)Cl]Cl	Calcd	35.57	3.75	19.36	10.51	7.01	44 (DMF)	210 D
	Found	35.00	3.42	19.95	11.00	7.52		
cis-[Pd(Cyd)$_2$Cl$_2$]	Calcd	32.54	3.92	12.65	16.03			195 D
	Found	32.44	3.95	12.80	16.50			
[Pd(Cyd)$_4$]Cl$_2$	Calcd	37.56	3.65	14.61	9.25		290 (H$_2$O)	210 D
	Found	37.80	3.80	14.20	10.00			

[a] D = decomposition.

versible in water, producing the initial [Pd(Ino)$_2$] immediately.

In the IR spectrum of *trans*-[Pd(InoH)$_2$Cl$_2$], the ~1700-cm^{-1} band of free C=O stretching reappears together with the band at ~330 cm^{-1}, attributed to the Pd–Cl stretching vibration (see Figure 1). A Kurnakoff test showed trans geometry for the complex. This suggests a monomer character for the initial [Pd(Ino)$_2$] complex with N_7O_6 chelation.

The N_7 coordination in *trans*-[Pd(InoH)$_2$Cl$_2$] can be followed from the NMR spectrum (see Table II and Figure 2). The H_8 proton near the binding site (N_7) is shifted downfield and is shown at 9.03 ppm, while the H_2 proton remains unshifted. The above shift of H_8 is shown in the NMR spectrum of *trans*-[Pd(InoH)$_2$Cl$_2$] in the presence of excess thiourea (Kurnakoff's test) because the NMR spectrum was taken after mixing the *trans*-[Pd(InoH)$_2$Cl$_2$] and thiourea in the solid state and adding D_2O. We observe the spectrum of the *trans*-[Pd(InoH)$_2$Tu$_2$]Cl$_2$ complex.

cis-[Pd(InoH)$_2$Cl$_2$] could only be prepared by carrying out the reaction in 0.5–1 N HCl, where the trans influence of InoH is comparable to that of pyridine and produces the cis analogue[7c] (eq 3). The *cis*-[Pd(InoH)$_2$Cl$_2$] was precipitated

$$H_2[PdCl_4] + 2InoH \xrightarrow{0.5\text{–}1\ N\ HCl} cis\text{-}[Pd(InoH)_2Cl_2] + 2HCl \quad (3)$$

quantitatively. In the IR spectrum of this complex, the ~1700-cm^{-1} C=O stretching was again observed together with the ~330-cm^{-1} Pd–Cl stretching, indicating no Pd–O interaction[7c] (see Figure 1). The NMR spectrum of this complex could only be taken in strongly acidic solutions (see Table II and Figure 2) and indicates only Pd–N_7 interaction. In water the complex was unstable, decomposing according to reaction 4. The C=O stretching in this complex shifted

$$cis\text{-}[Pd(InoH)_2Cl_2] \underset{1\ N\ HCl}{\overset{H_2O}{\rightleftharpoons}} cis\text{-}[Pd(Ino)_2] + 2HCl \quad (4)$$

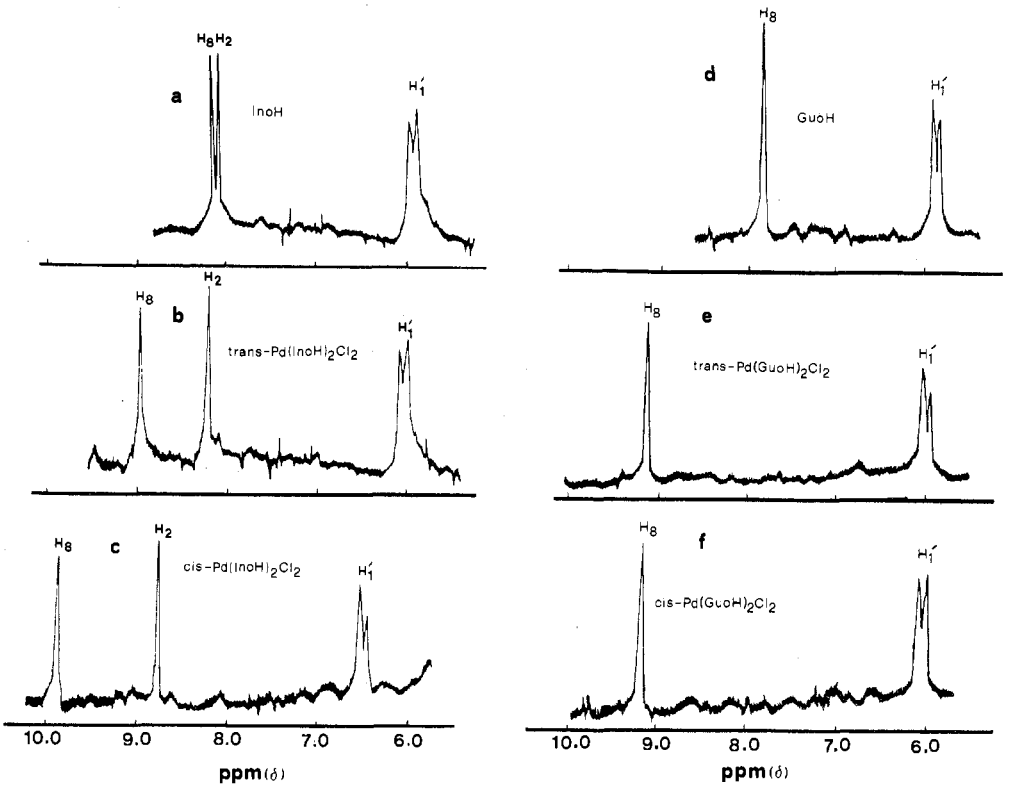


Figure 2. NMR spectra in the aromatic proton region of (a) InoH in D_2O, (b) *trans*-$[Pd(InoH)_2Cl_2]$ in the presence of excess thiourea, in D_2O, (c) *cis*-$[Pd(InoH)_2Cl_2]$ in 3 N DCl, (d) GuoH in Me_2SO-d_6, (e) *trans*-$[Pd(GuoH)_2Cl_2]$ in the presence of excess thiourea, in D_2O, and (f) *cis*-$[Pd(GuoH)_2Cl_2]$ in 3 N HCl.

Table II. NMR Chemical Shifts (ppm) of Palladium(II)-Inosine Complexes

Compound	Inosine			Guanosine		Xanthosine		Solvent
	H_2	H_8	H_1'	H_8	H_1'	H_8	H_1'	
InoH	8.11	8.22	6.03[a]					D_2O
			5.93					
cis-$[Pd(InoH)_2Cl_2]$	8.83	9.97	6.63[a]					3 N DCl
			6.57					
trans-$[Pd(InoH)_2Tu_2]Cl_2$	8.13	9.03	6.10[a]					D_2O
			6.00					
$[Pd(InoH)_4]Cl_2$	8.16	8.87	5.83[a]					D_2O
			5.77					
cis-$[Pd(InoH)_2(GuoH)_2]Cl_2$	8.17	8.87	6.00[a]	8.47	5.78[a]			D_2O
			5.93		5.72			
trans-$[Pd(InoH)_2(GuoH)_2]Cl_2$	8.15	8.82	5.73[a]	8.53	5.53[a]			D_2O
			5.67		5.43			
cis-$[Pd(InoH)_2(XaoH)_2]Cl_2$	8.13	8.83	6.00[a]			8.47	5.80[a]	D_2O
			5.93				5.67	

[a] Doublet.

from 1700 cm^{-1} to 1625 cm^{-1}, indicating carbonyl involvment in bonding. The reaction was reversible in 1 N HCl. The cis geometry of the above complex was again shown by a Kurnakoff test. The complex was mixed with excess thiourea in the solid state and the mixture was dissolved in D_2O. The NMR spectrum of the mixture showed the presence of free inosine.

Both *cis*-$[Pd(InoH)_2Cl_2]$ and *trans*-$[Pd(InoH)_2Cl_2]$ reacted readily with other bases like guanosine, xanthosine, cytidine, and inosine to form mixed complexes of the type *cis*- and *trans*-$[Pd(InoH)_2(NuclH)_2]Cl_2$. These reactions were carried out by mixing stoichiometric amounts of the initial cis and trans complexes and the bases in the solid state. The mixture was dissolved in D_2O to obtain the complexes and observe their NMR spectra. It is readily seen from Table II and Figures 2 and 3 that all the bases are bonded to Pd(II) through their N_7 atom because the H_8 protons are shifted downfield by 0.6–1 ppm compared to the free bases.[5-7] The shifts are higher in strongly acidic solutions.

cis-$[Pd(Cyd)_2Cl_2]$ was prepared by direct interaction of K_2PdCl_4 and cytidine in water (eq 5). Two more cytidine

$$K_2[PdCl_4] + 2Cyd \rightarrow cis\text{-}[Pd(Cyd)_2Cl_2] + 2KCl \quad (5)$$

molecules could be added to *cis*-$[Pd(Cyd)_2Cl_2]$ as in eq 6.

$$cis\text{-}[Pd(Cyd)_2Cl_2] + 2Cyd \rightarrow [Pd(Cyd)_4]Cl_2 \quad (6)$$

Coordination takes place here through the N_3 atom (see Table III and Figure 3). The same has also been shown from ^{13}C NMR studies of *cis*-$[Pd(en)Cl_2]$ and cytidine interactions[10] and in the *cis*-$[Pt(NH_3)_2Cl_2]$–cytidine interactions.[6b] The overall reactions of inosine with Pd(II) can be summarized as shown in Scheme I.

Guanosine. Unlike inosine, guanosine is not soluble in water at pH ~6. A suspension of guanosine in water was mixed

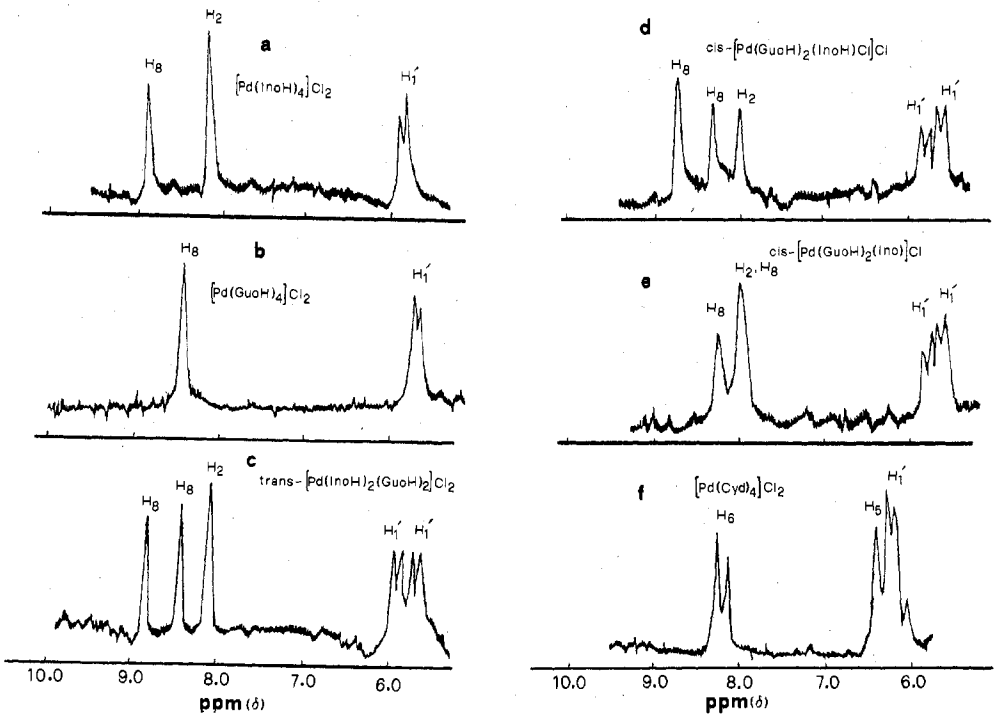


Figure 3. NMR spectra in the aromatic proton region of (a) $[Pd(InoH)_4]Cl_2$ in D_2O, (b) $[Pd(GuoH)_4]Cl_2$ in D_2O, (c) *trans*-$[Pd(InoH)_2(GuoH)_2]Cl_2$ in D_2O, (d) *cis*-$[Pd(GuoH)_2(InoH)Cl]Cl$ in Me_2SO-d_6, (e) *cis*-$[Pd(GuoH)_2(Ino)]Cl$ in Me_2SO-d_6, and (f) $[Pd(Cyd)_4]Cl_2$ in D_2O.

Table III. NMR Chemical Shifts (ppm) of Palladium(II)–Guanosine Complexes

Compound	Guanosine		Inosine			Cytidine			Solvent
	H_8	H_1'	H_8	H_2	H_1'	H_5	H_6	H_1'	
GuoH	7.80	5.74[a] 5.68							Me_2SO-d_6
cis-$[Pd(H_2O)_2(GuoH)_2]Cl_2$	8.43	5.73[a] 5.67							D_2O
cis-$[Pd(GuoH)_2Cl_2]$	9.17	6.07[a] 6.00							3 N DCl
trans-$[Pd(GuoH)_2Tu_2]Cl_2$	9.10	6.03[a] 5.97							D_2O
cis-$[Pd(GuoH)_2(Guo)]Cl$	8.49	5.77[a] 5.70							Me_2SO-d_6
$[Pd(GuoH)_3Cl]Cl$	8.50	5.79[a] 5.72							Me_2SO-d_6
$[Pd(GuoH)_4]Cl_2$	8.40	5.87[a] 5.80							D_2O
cis-$[Pd(GuoH)_2(Ino)]Cl$	7.95	5.65[a] 5.72	8.30	7.95	5.80[a] 5.88				Me_2SO-d_6
cis-$[Pd(GuoH)_2(InoH)Cl]Cl$	8.70	5.70[a] 5.75	8.30	7.95	5.78[a] 5.76				Me_2SO-d_6
$[Pd(Cyd)_4]Cl_2$						8.15[a] 8.23	6.40	6.24[a] 6.17	D_2O

[a] Doublet.

with H_2PdCl_4 or K_2PdCl_4 in a metal/ligand ratio of 1:2 and produced a yellow precipitate corresponding to the formula *trans*-$[Pd(Guo)_2]$ (eq 7) (see Table I).

$$K_2[PdCl_4] + 2GuoH \rightarrow trans\text{-}[Pd(Guo)_2] + 2KCl + 2HCl \quad (7)$$

The ν(C=O) band in the IR spectrum of free guanosine at ~1700 cm^{-1} is shifted to ~1625 cm^{-1}, while the Pd–Cl stretching band was absent,[7c] suggesting the N_7O_6 chelate structure. *trans*-$[Pd(Guo)_2]$, which is insoluble in the usual organic solvents, is dissolved in 1 N HCl, producing *trans*-$[Pd(GuoH)_2Cl_2]$ (eq 8) similar to inosine; the reaction is

$$trans\text{-}[Pd(Guo)_2] \underset{H_2O}{\overset{1\ N\ HCl}{\rightleftharpoons}} trans\text{-}[Pd(GuoH)_2Cl_2] \quad (8)$$

reversible in water (see Figure 1). The *trans*-$[Pd(GuoH)_2Cl_2]$ shows both free ν(C=O) at ~1700 cm^{-1} and ν(Pd–Cl) at ~330 cm^{-1}. The trans geometry of the above compound is again suggested by the Kurnakoff test as in the case of inosine. The NMR spectra (Table III and Figure 2) also indicate the Pd–N_7 interaction of guanosine in the *trans*-$[Pd(GuoH)_2Cl_2]$ complex, implying N_7O_6 chelation in the initial *trans*-$[Pd(Guo)_2]$.

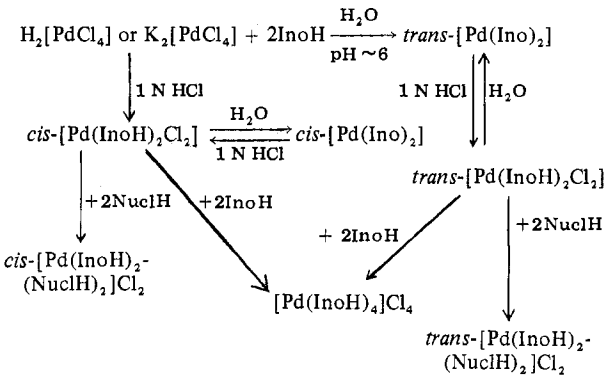
cis-$[Pd(GuoH)_2Cl_2]$ was prepared from H_2PdCl_4 and guanosine in acidic solutions (0.5–1 N HCl) as the analogous inosine complex (eq 9). The cis geometry was again suggested

$$H_2[PdCl_4] + 2GuoH \xrightarrow{0.5\text{–}1\ N\ HCl} cis\text{-}[Pd(GuoH)_2Cl_2] + 2HCl \quad (9)$$

here by a Kurnakoff test. The corresponding *cis*-$[Pd(Guo)_2]$ complex was prepared easily from *cis*-$[Pd(GuoH)_2Cl_2]$ (eq 10).

$$cis\text{-}[Pd(GuoH)_2Cl_2] \underset{0.5\text{–}1\ N\ HCl}{\overset{H_2O}{\rightleftharpoons}} cis\text{-}[Pd(Guo)_2] + 2HCl \quad (10)$$

Scheme I



In the *cis*-$[Pd(Guo)_2]$ complex the chelate is formed between N_7O_6 as in the other cases. During the precipitation of the *cis*- and *trans*-$[Pd(Nucl)_2]$ complexes, where Nucl = inosinate or guanosinate, the pH of the supernatant liquid decreased from pH ~6 to ~2, indicating 2HCl liberation in all cases, which was also shown from conductivity measurements.

If the reaction of H_2PdCl_4 and guanosine was carried out at an initial pH ~2.5, no precipitate was obtained, but the color of the solution turned to yellow, producing the diaquo complex (eq 11). Analytical data and conductivity measurements confirmed the formula of the product in eq 11 (see Table I). The two water molecules of the aquated complex could easily be removed in acid solutions (0.5–1 N HCl) in a reversible manner, producing *cis*-$[Pd(GuoH)_2Cl_2]$ (eq 12).

$$H_2[PdCl_4] + 2GuoH \xrightarrow[pH \sim 2.5]{H_2O} cis\text{-}[Pd(H_2O)_2(GuoH)_2]Cl_2 + 2HCl \quad (11)$$

$$cis\text{-}[Pd(H_2O)_2(GuoH)_2]Cl_2 \underset{pH \sim 2.5}{\overset{0.5\ N\ HCl}{\rightleftharpoons}} cis\text{-}[Pd(GuoH)_2Cl_2] \quad (12)$$

cis-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ is a 1:2 electrolyte in water (Λ_M = 240 Ω^{-1} cm^2) in the beginning, attaining a value of 350 Ω^{-1} cm^2 after 24 h, due to the ionization of the imino protons of guanosine and formation of N_7O_6 chelates. *cis*-$[Pd(Guo)_2]$ could also be produced from *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ in water at pH ~6 in a reversible manner (eq 13).

$$cis\text{-}[Pd(H_2O)_2(GuoH)_2]Cl_2 \underset{pH \sim 2.5}{\overset{pH \sim 6}{\rightleftharpoons}} cis\text{-}[Pd(Guo)_2] + 2HCl + 2H_2O \quad (13)$$

In water *cis*-$[Pd(GuoH)_2Cl_2]$ was very unstable, reacting according to eq 10 and giving a molar conductance of ~400 Ω^{-1} cm^2, in agreement with the liberation of two HCl molecules. The same was true for the trans analogue and the inosine complexes. In DMF solutions *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ was a 1:2 electrolyte, while *cis*-$[Pd(GuoH)_2Cl_2]$ was not conducting. The presence of the two water molecules in *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ was also confirmed from the reaction of the complex with both inosine and guanosine in water to form 1:1 complexes (eq 14). The pH of the mixture decreases during the reaction from an initial value of ~5.5 to ~2.7, indicating imino proton liberation for both bases and formation of N_7O_6 chelates. The latter two complexes are 1:1 electrolytes in DMF, and their analytical results confirm the assigned formulas (see Table I). In the NMR spectrum of *cis*-$[Pd(GuoH)_2(Guo)]Cl$, there is only one resonance at 8.49 ppm due to H_8 protons of both chelated and nonchelated guanosine.

$$cis\text{-}[Pd(H_2O)_2(GuoH)_2]Cl_2 \xrightarrow{+NuclH} cis\text{-}[Pd(GuoH)_2(NuCl)]Cl + HCl + 2H_2O \quad (14)$$

(NuCl = Ino, Guo)

The NMR spectrum of *cis*-$[Pd(GuoH)_2(Ino)]Cl$ in Me_2SO-d_6 shows two resonances in the aromatic proton region at 7.95 and 8.30 ppm (see Figure 3). The first is due to both H_2 of chelated inosine and H_8 of guanosine, while the second is due to the H_8 of inosine. The low value of the guanosine H_8 indicates that the guanosine molecules in this complex have been displaced by the solvent Me_2SO-d_6. The NMR spectrum of *cis*-$[Pd(GuoH)_2(InoH)Cl]Cl$ in Me_2SO-d_6 shows three resonances in this region at 8.70, 8.30, and 7.95 ppm, assigned to the H_8 of guanosine, H_8 of inosine, and H_2 of inosine, respectively (see Figure 3). The H_8 of guanosine is twice as intense as that of H_8 and H_2 protons of inosine, in conformity with the above formula. These assignments were based on the NMR spectra of the complexes with inosine deuterated at the 8 position, where the resonances at 8.30 ppm in both spectra disappeared. The compounds $[Pd(GuoH)_3Cl]Cl$ and $[Pd(GuoH)_2(InoH)Cl]Cl$ were prepared by dissolving $[Pd(GuoH)_2(Guo)]Cl$ and $[Pd(GuoH)_2(Ino)]Cl$ in 0.5 N HCl, respectively. In the first case the reaction is reversible, while in the second a mixture of complexes such as $[Pd(GuoH)(InoH)(Guo)]Cl$ and $[Pd(GuoH)_2(Ino)]Cl$ could be obtained by dissolving $[Pd(GuoH)_2(InoH)Cl]Cl$ in water (eq 15 and 16).

$$[Pd(GuoH)_2(Guo)]Cl \underset{H_2O}{\overset{0.5\ N\ HCl}{\rightleftharpoons}} [Pd(GuoH)_3Cl]Cl \quad (15)$$

$$[Pd(GuoH)_2(Ino)]Cl \xrightarrow{0.5\ N\ HCl} [Pd(GuoH)_2(InoH)Cl]Cl \quad (16)$$

Finally, both *cis*- and *trans*-$[Pd(GuoH)_2Cl_2]$ complexes reacted with two extra molecules of other nucleosides as in the inosine complexes according to the general reaction:

$$cis\text{- and } trans\text{-}[Pd(GuoH)_2Cl_2] \xrightarrow{NuclH} cis\text{- and } trans\text{-}[Pd(GuoH)_2(NuclH)_2]Cl_2 \quad (17)$$

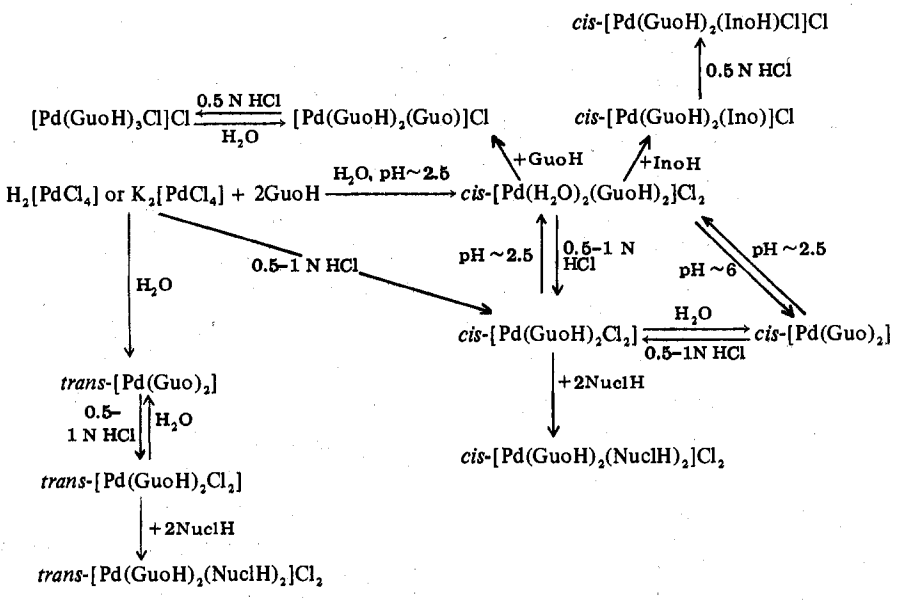
The overall reactions of guanosine may be represented as in Scheme II.

Discussion

It is known that Pd(II) undergoes faster ligand exchange reactions than Pt(II).[11] In this respect, it is worth comparing the reactions of both metals with the ligands inosine and guanosine. Both ligands have a ketone oxygen atom at the 6 position which can be enolized, making possible the formation of five-membered chelate rings with the metal through N_7. The possibility of formation of such a chelate has been proposed[14] to explain the mechanism of action of *cis*-$[Pt(NH_3)_2Cl_2]$ as an antitumor agent reacting with DNA. Maquet and Theophanides[14] suggested a bidentate interaction of *cis*-$[Pt(NH_3)_2Cl_2]$ with guanosine in DNA in vitro on the basis of titration, chlorine determination,[14b] and photoelectron spectroscopy.[14c] According to these authors,[14] the first attack occurs at the N_7 site of guanosine by *cis*-$[Pt(NH_3)_2Cl_2]$, followed by ring closure and formation of a five-membered chelate ring with a subsequent pH decrease due to the imino proton ionization. This could explain the antitumor activity of *cis*-$[Pt(NH_3)_2Cl_2]$, causing a permanent damage in the DNA by preventing the ability of O_6 to form hydrogen bonds with the opposite cytidine base.[14c,15]

The ability of O_6 to coordinate with metals through a chelate involving N_7 has been a matter of controversy in recent years. Sletten[16] excluded N_7O_6 chelation with Cu(II) on the basis of a crystal-structure determination of bis(9-methyl-6-oxopurine)copper(II) due to steric effects. Neumann et al.[17] agreed with this explanation. Kelman et al.[18] supported the idea of *cis*-$[Pt(NH_3)_2Cl_2]$ binding to two adjacent guanine bases in DNA. Mansy et al.[19] excluded a metal–oxygen interaction of guanosine in DNA on the basis of Raman

Scheme II



spectra. On the other hand, there is enough evidence from other investigations that an N_7O_6 chelation may actually exist under certain conditions. Ogawa and Sakaguchi[20] found O_6–Hg interaction in Hg–IMP complexes. Tu et al.[21] proposed N_7O_6 chelate complexes in Ag(I) and Cu(II) complexes of inosine and guanosine. Berger and Eichhorn[22] found N_7O_6 chelation in Cu(II)–IMP interactions. Recently, Dehand and Jordanov[23] reported a guanosine chelate of Pt(II) without ionization of the imino proton. Five-membered chelation is known to take place in the 6-mercaptopurine and 6-mercaptopurine ribosides with Pt(II) and Pd(II).[7,12] Heitner and Lippard,[13] in the crystal structure of (dimethylacetamide)bis(6-mercapto-9-benzylpurine)palladium(II), stated that chelation of the metal through N_7 and the substituent at the 6 position of the purine base may exist when the ligand undergoes the proper distortion to accommodate the metal ion.

Our results[7] show that Pt(II) can react with O_6, N_7, and N_1 sites of guanosine and inosine with possible chelate formation at pH values higher than the pK_a values of the free bases, although the reactions are slow. Pt(II) reacts quantitatively in aqueous solutions with thioinosine and thioguanosine with chelate formation,[7a] this is due to the strong tendency of sulfur to bind with Pt(II). *cis*-$[Pt(InoH)_2Cl_2]$[7c] could only be isolated pure in the presence of 2 M NaCl in the reaction mixture of K_2PtCl_4 and InoH, preventing the removal of HCl.[24] The tendency of the N_1 proton to ionize increases on platinum coordination at N_7 by lowering the pK_a value of the proton, and this facilitates the ring closure.[7c]

The results with Pd(II) further substantiate the formation of five-membered chelate complexes of inosine and guanosine. Both bases react quantitatively with Pd(II) to form the bis(inner complexes) $[Pd(Nucl)_2]$. Palladous chloride has been used as a reagent for the isolation and estimation of purine derivatives by Gulland and Macrae,[25] and it was found that it gave almost quantitative precipitation of the purines tested. These reactions are comparable to the reactions of Pt(II) with thiopurine bases.[7a,12] In aqueous solution the obtained $[Pd(Nucl)_2]$ products were of trans geometry, as were the analogous 8-hydroxyquinoline metal complexes.[26] The cis complexes were obtained in 0.5–1 N HCl solutions as *cis*-$[Pd(NuclH)_2Cl_2]$, and the bases were immediately deprotonated in water, yielding *cis*-$[Pt(Nucl)_2]$. In this way both cis and trans isomers have been isolated (see Figure 4). The reaction of the bases with palladium definitely indicates that N_7O_6 ring closure is much easier in this case than with platinum. These reactions also show that the trans effect of

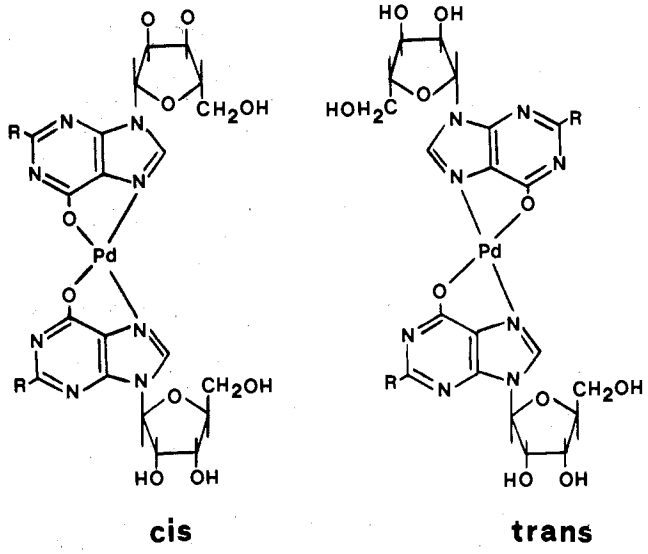


Figure 4. Proposed structures of *cis*- and *trans*-$[Pd(NuclH)_2Cl_2]$, where NuclH = nucleoside (inosine for R = H and guanosine for R = NH_2), are shown.

nucleosides is comparable to that of pyridine[7b,c] and smaller than that of the halogens (nucleoside < Cl^-, Br^-) and that the Kurnakoff test is operative in this case.

cis- and *trans*-$[Pd(NuclH)_2Cl_2]$ reacted with other nucleosides to yield complexes of the *cis*- and *trans*-$[Pd(NuclH)_4]Cl_2$ type. These reactions were always carried out by mixing stoichiometric amounts of the initial complexes and bases in the solid state. The mixture was dissolved in D_2O to obtain the complexes and observe their NMR spectra. These experiments also indicate that the initial compounds, although unstable in water and tending to ionize their imino protons and form chelates, are stabilized in the presence of four bases or thiourea. The diaquo complex *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$ was also isolated in these reactions since the Cl^- substitution by water is easier in Pd(II) complexes than in Pt(II).[10]

Conclusion

The strong reactivity of Pd(II) toward inosine and guanosine and the tendency of formation of N_7O_6 chelates by ionization of the imino protons of the bases have been found to be operative in this study. The differences in reactivity of Pd(II)

and Pt(II) toward inosine and guanosine are mainly due to their difference in ligand-exchange reactions. Thus, Pt(II), being less reactive than Pd(II), reacts slower with the bases. Both metals in aqueous solution first react with the N_7 site of the base and subsequently chelate with O_6. Coordination of Pt at N_7 does not introduce significant geometrical perturbations in the base as was shown[27] in the $[PtCl_3(9\text{-MeAdeH})]$ complex. In addition, the N_7O_6 distance is suitable for closure of the ring with the metal.

Acknowledgment. We wish to thank Dr. Mantzos of The National Hellenic Research Foundation for the microanalyses and the National Research Council of Canada and the Ministère de l'Education of Quebec for financial assistance.

Registry No. *cis*-$[Pd(InoH)_2Cl_2]$, 64715-03-3; *cis*-$[Pd(Ino)_2]$, 64715-04-4; *trans*-$[Pd(Ino)_2]$, 64753-38-4; *trans*-$[Pd(InoH)_2Cl_2]$, 64753-39-5; $[Pd(InoH)_4]Cl_2$, 64715-05-5; *cis*-$[Pd(InoH)_2(GuoH)_2]Cl_2$, 64715-06-6; *trans*-$[Pd(InoH)_2(GuoH)_2]Cl_2$, 64753-40-8; *cis*-$[Pd(InoH)_2(Cyd)_2]Cl_2$, 64715-07-7; *trans*-$[Pd(InoH)_2(Cyd)_2]Cl_2$, 64753-41-9; *cis*-$[Pd(InoH)_2(XaoH)_2]Cl_2$, 64715-08-8; *trans*-$[Pd(InoH)_2(XaoH)_2]Cl_2$, 64753-42-0; *cis*-$[Pd(H_2O)_2(GuoH)_2]Cl_2$, 63251-58-1; *cis*-$[Pd(GuoH)_2Cl_2]$, 62800-79-7; *trans*-$[Pd(GuoH)_2Cl_2]$, 64753-34-0; *trans*-$[Pd(Guo)_2]$, 64753-35-1; *cis*-$[Pd(Guo)_2]$, 62850-22-0; $[Pd(GuoH)_4]Cl_2$, 64727-96-4; *cis*-$[Pd(GuoH)_2(Cyd)_2]Cl_2$, 64714-96-1; *trans*-$[Pd(GuoH)_2(Cyd)_2]Cl_2$, 64753-36-2; *cis*-$[Pd(GuoH)_2(XaoH)_2]Cl_2$, 64714-97-2; *trans*-$[Pd(GuoH)_2(XaoH)_2]Cl_2$, 64753-37-3; *cis*-$[P(GuoH)_2(Guo)]Cl$, 62800-80-0; $[Pd(GuoH)_3Cl]Cl$, 62800-81-1; *cis*-$[Pd(GuoH)_2(Ino)]Cl$, 64714-98-3; $[Pd(GuoH)_2(InoH)Cl]Cl$, 64714-99-4; *cis*-$[Pd(Cyd)_2Cl_2]$, 64715-00-0; $[Pd(Cyd)_4]Cl_2$, 64715-01-1; *trans*-$[Pd(InoH)_2Tu_2]Cl_2$, 64715-02-2; *trans*-$[Pd(GuoH)_2Tu_2]Cl_2$, 64714-95-0; $K_2[PdCl_4]$, 10025-98-6.

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Contribution No. 3079 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401

Reactions of $MoO(S_2CNR_1R_2)_2$ with Azide

E. A. MAATTA and R. A. D. WENTWORTH*

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When an alkylammonium salt of N_3^- is partitioned between water and $CHCl_3$ containing $MoO(S_2CNEt_2)_2$, the slow formation of N_2, NH_3, and $MoO_2(S_2CNEt_2)_2$ occurs. Significant enhancement of the rate of evolution of N_2 occurs when the aqueous layer is acidified and the reaction no longer requires the alkylammonium cation. There are no indications that significant quantities of a protonated Mo(IV) complex occur under the experimental conditions. The results are interpreted in terms of the reaction between HN_3 and $MoO(S_2CNEt_2)_2$ with the formation of a nitrene and N_2. Subsequent hydrolysis of the nitrene produces NH_4^+ and the Mo(VI) complex. Variation of the organic substituents of the dithiocarbamate ligand produces changes in $\nu(C{\cdots}N)$ and $\nu(MoO)$ and decreases in the rate of evolution of N_2 as the complexity of these substituents is increased. An explanation in terms of electronic effects rather than steric hindrance is offered. The decrease in the rate of the reaction of $Mo_2O_3(S_2CNEt_2)_4$ when compared to that of $MoO(S_2CNEt_2)_2$ is rationalized in terms of the disproportionation of the dinuclear complex prior to the reaction with HN_3. The possible biological significance of these reactions as they pertain to the functioning of the nitrogenases is discussed.

Introduction

The dialkyldithiocarbamate complexes of oxomolybdenum(IV), $MoO(S_2CNR_1R_2)_2$, and particularly the derivative with $R_1 = R_2 = C_2H_5$ (Et), have received considerable attention because they are possible models for molybdoenzymes.[1-5] While their reactions with certain activated molecules appear to be reasonably fast in certain instances,[2] reactions with real biological substrates tend to be very slow or even nonexistent under the experimental conditions which have been described. Neither N_2, N_3^-, nor N_2O,[1,5] all of which are substrates for nitrogenases,[6] bind to $MoO(S_2CNEt_2)_2$ or react with it in anhydrous $CHCl_3$. The possibility that this

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