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Palladium Reactions with Guanosine. Definitive Evidence of O_6N_7 Chelation

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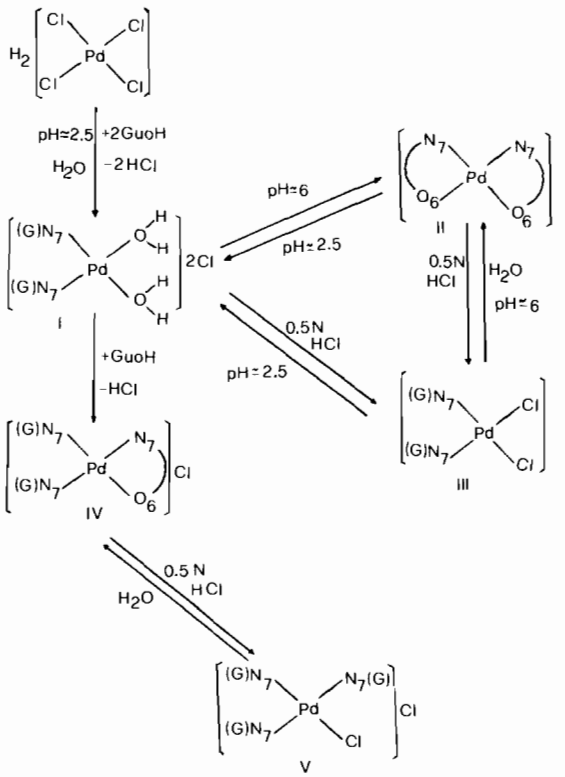
The reactions of palladium with the purine base Guanosine have been investigated and it has been found that the palladium reactions are much faster than the corresponding platinum reactions [1, 2]. Using this nucleoside it has been found that it is susceptible to attack by the palladium salts at the N_7 atom first, and subsequently chelation O_6N_7 has been obtained under certain conditions. Evidence of O_6N_7 chelation has been reported previously [2–5] with platinum.

A number of reaction products were identified in this report indicating that beside a single attack at N_7, bidentate O_6N_7 chelation involving one base could also occur. This purine base forms complexes of the type *cis*- and *trans*-$Pd(O_6N_7)_2$ [6]. The following scheme shows the reactions and the products



obtained starting from H_2PdCl_4 or K_2PdCl_4 and Guanosine. H_2PdCl_4 or K_2PdCl_4 reacts with 2 mol of Guanosine in water at a pH ~ 2.5 (HCl) and produces immediately the ionic diaquo monomer I which has been isolated and characterized (Scheme). In this compound Guanosine is a monofunctional ligand linked to palladium through N_7 only. This is confirmed by ^1H nmr and ir spectra, which indicate a shift [1, 2] of the proton H_8 and that the free ketone carbonyl, *i.e.*, the C_6=O stretching is not perturbed at all by complexation. In addition, the compound is a 1:2 electrolyte in water (Λ_m = 240 ohm^{-1} cm^2 mol^{-1}). The reaction processes shown in the scheme support the monomer nature of this diaquo complex. The diaquo monomer, if left in water for 24 hr, forms the non ionic zero charged bis chelate complex II, in which the C_6=O stretching frequency is shifted to lower frequencies [2] by about 75 cm^{-1} (from 1700 cm^{-1}, which is the free carbonyl C_6=O stretching frequency to 1625 cm^{-1} on chelation). At a pH ~ 6, the N_7O_6 chelate complex II precipitates immediately. The complex bis-chelate, $Pd(O_6N_7)_2$, is a non electrolyte and does not contain chloride, also the Pd–Cl stretching frequency is absent from the ir spectra. The formation of HCl in solution during this reaction is shown from conductivity and pH data. This compound is transformed reversibly into compound III in which the palladium–oxygen bonds break and in the presence of 0.5N HCl form Pd–Cl bonds with the opening of the chelate rings and the formation of the *cis*-dichlorodiguanosinepalladium (II). Compound III can be also prepared from I directly with 0.5N HCl and in a reversible fashion (see scheme).

It has been also found that the diaquo monomer of palladium reacts with excess guanosine and gives the extremely interesting compound IV in which we have two guanosine molecules linked through N_7 to palladium and the third base forms a chelate ring with O_6N_7. The compound is ionic with ionic chloride and analysis, isolation and characterization of the complex strongly suggest the presence of a 1:1 electrolyte in DMF. The compound reacts with 0.5N HCl and forms V which now has again three guanosine molecules in the inner sphere but they are all coordinated as monofunctional ligands, *i.e.*, only through N_7. The ir of this 1:1 electrolyte shows only free C_6=O stretching at 1700 cm^{-1} and a Pd–Cl stretching at 325 cm^{-1}, indicating the breaking of the Pd–O bonds and the attack of palladium by chloride ions to form Pd–Cl bonds (see Table for analytical data).

The reactions of palladium with guanosine compared to platinum show two distinct differences: 1) faster reactivity of palladium towards oxygen, and 2) the competitive effect of making and breaking

TABLE. Analytical and Physical Data for Palladium–Guanosine Complexes.[a]

	Complex	Color	M.P. (°C)	%	H	C	Pd	$\nu(C_6=O)$ cm^{-1}	$\nu(Pd-Cl)$ cm^{-1}	Nmr Shifts in ppm	Solvent
I	*cis*-$[Pd(GuoH)_2(H_2O)_2]Cl_2$	Yellow	220 °C, D	calcd	3.85	30.77	13.64	1700	–	8.43	D_2O
				found	4.02	30.41	13.60				
II	*cis*-$[Pd(GuoH)_2]$	Light Yellow	165 °C, D	calcd	3.58	35.77	15.86	1625	–	–	
				found	3.70	36.00	15.50				
III	*cis*-$[Pd(GuoH)_2Cl_2]$	Yellow	195 °C, D	calcd	3.49	32.26	14.30	1700	325	9.17	2N DCl
				found	3.70	32.60	14.00				
IV	*cis*-$[Pd(GuoH)_2Guo]Cl$	Light Yellow	180 °C, D	calcd	3.84	36.37	10.75	–	–	8.49	D_2O
				found	3.50	35.90	11.00				
V	$[Pd(GuoH)_3Cl]Cl$	Light Yellow	215 °C, D	calcd	3.80	35.04	10.36	1700	325	8.50	D_2O
				found	3.50	34.70	10.80				

[a]D = decomposition, GuoH = Guanosine.

Pd–O bonds is again faster with palladium than with platinum. As a result, ring formation and ionization take place much faster with palladium than with platinum. Furthermore, these experiments support the proposed mechanism of the antitumor activity of *cis*-$Pt(NH_3)_2Cl_2$ interacting with DNA [3, 4] at the GC planes and forming O_6N_7 chelates.

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