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Equilibria among Cytidine Complexes of Palladium(II)

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The binding modes of nucleic acid bases and nucleosides to palladium have been described recently [1, 2]. Cytosine and its N(1) derivatives have been established to bind monofunctionally to palladium(II) through the N(3) atom [2]. In this paper we report a study of the system cytidine–palladium(II)–chloride in aqueous solution.

The 60 MHz proton magnetic resonance spectra of solutions of K_2PdCl_4 (or $Pd(Cyd)_2Cl_2$) and cytidine (Cyd) in D_2O with varying metal to nucleoside ratio, r, have been analyzed to identify the complexes formed. Assignments of resonances are summarized in Table I. The small differences among quoted chemical shifts are significant, since different sets of resonances could be measured in the same spectrum.

TABLE I. ^{1}H NMR Chemical Shifts (δ).

Spectrum	Species	H(6)	H(5)
	Cyd[a]	7.88	6.11
	$CydH^{+}$[b]	8.11	6.21
"A"	$[PdCydCl_3]^-$	7.92	6.07
"B"	$Pd(Cyd)_2Cl_2$	7.96	6.12
"C"	$[Pd(Cyd)_3Cl]^+$	7.90	6.06
"D"	$[Pd(Cyd)_4]^{2+}$	7.84	5.99

[a]0.02 *M*. [b]0.07 *M*.

The spectrum of the base portion of cytidine in D_2O consists of a low field doublet due to H(6) coupled to a high field doublet due to H(5) ($|J_{H(5)-H(6)}| \simeq 7.5$ Hz). Addition of palladium at a ratio $r = 0.25$ causes the H(5) and H(6) doublets to shift upfield. The observed spectrum, "D", is assigned to the complex cation $[Pd(Cyd)_4]^{2+}$. With $r < 0.25$ signals due to free cytidine are observed besides those of the palladium complex. Identical chemical shift values for the tetrakis-cytidine adduct were measured for solutions with $r = 0.25$ containing cytidine hydrochloride. The upfield shift of H(5) and H(6) resonances of $[Pd(Cyd)_4]^{2+}$ relative to uncomplexed cytidine shows that effects of magnetic anisotropy within the complex overcome effects due to coordination to a positive centre. Coupling between H(5) and H(6) protons is not appreciably affected by complexation.

Palladium–cytidine systems with $r > 0.25$ were studied in the presence of excess sodium chloride (*ca.* 0.3 *M*) in order to prevent hydrolysis of palladium–chloride bonds. Signals H(5) and H(6) of free cytidine are unchanged upon addition of NaCl. With $r = 1$ two sets of resonances, "A" and "B", were observed with intensities in the ratio *ca.* 3:1. These are respectively assigned to the complexes $[PdCydCl_3]^-$ and $Pd(Cyd)_2Cl_2$, since it is found that the intensity of spectrum "A" realtive to total intensity is decreased upon decreasing r from 1 to 0.5, while the intensity of "B" is first increased on going from $r = 1$ to $r = 0.5$, and then decreased at $r = 0.33$.

The spectra of solutions with $r = 0.5$ consist of four partly overlapping sets of resonances, "A"–"D" (see Figure 1). Signals "A" and "C" appear very close together at 60 MHz, but they are confirmed as separate resonances by a spectrum measured at 270 MHz. None of the signals observed can be ascribed to uncomplexed cytidine, since in experiments carried out in the presence of cytidine hydro-

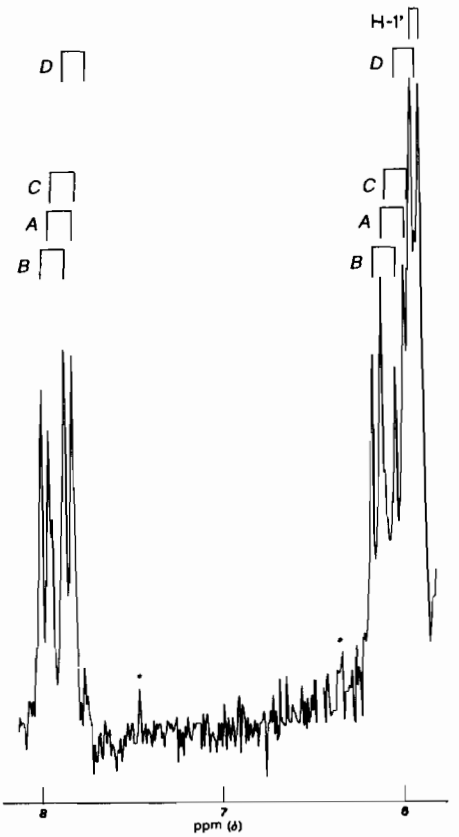

Figure 1. ^{1}H NMR (60 MHz) spectrum of 5×10^{-3} *M* $Pd(Cyd)_2Cl_2$ in D_2O at 25 °C in the presence of 0.35 *M* NaCl (asterisks denote spikes).

chloride no shift is observed for the resonances of cytidine monocation, $CydH^+$, relative to a solution of the acid alone. "A", "B" and "D" spectra are identified as the complexes $[PdCydCl_3]^-$, $Pd(Cyd)_2Cl_2$ and $[Pd(Cyd)_4]^{2+}$, respectively. Resonances "C" are assigned to the complex $[Pd(Cyd)_3Cl]^+$. Two sets of H(5) and H(6) signals may be expected in principle for the tris-cytidine complex, besides possible splittings due to different conformations around metal–ligand bonds. NMR spectra reported for palladium(II) complexes of formula $[PdL_3X]^+$ (where L = PR_3 or AsR_3; X = halogen) show signals for the two mutually *trans* L groups different from those of the L group *trans* to halogen [3]. It is likely that further resonances from $[Pd(Cyd)_3Cl]^+$ are superimposed on the signals of $[PdCydCl_3]^-$.

The observed equilibria among the complexes $[Pd(Cyd)_nCl_{4-n}]^{n-2}$ appear to be slow in the NMR time scale under the experimental conditions. However, ligand substitutions in these systems are rather fast reactions. For example, monitoring the reaction between $10^{-2}M$ K_2PdCl_4 and $10^{-2}M$ cytidine in the presence of 0.3 *M* NaCl (25 °C) by means of the stopped-flow technique at 500 nm shows that equilibrium is achieved within 10 seconds.

Data on the redistribution equilibria of $5 \times 10^{-3}M$ $Pd(Cyd)_2Cl_2$ at 25 °C (oversaturated solution) in the presence of 0.35 *M* NaCl are obtained from potentiometric and NMR measurements. For this solution a potential of 0.47 V at a palladium electrode was measured. Criteria indicating that the measured potential was an equilibrium potential were return to the initial value after brief cathodic and anodic polarization of the electrode and invariability with stirring rate. By contrast, poor response of the electrode was observed when measurements of solutions with low chloride to cytidine ratios were attempted. Using values for $Pd^{2+}(aq)/Pd$ standard potential [4] and cumulative formation constant of $[PdCl_4]^{2-}$ [5] taken from the literature and referred to 0.35 *M* ionic strength, the following concentrations are calculated: $[Pd(H_2O)_4^{2+}] \simeq 3 \times 10^{-15}M$; $[PdCl_4^{2-}] \simeq 10^{-5}M$. From reported stability constants [5] other chloro-aquo complexes, $[Pd(H_2O)_nCl_{4-n}]^{n-2}$, are calculated to amount to less than 20% of $[PdCl_4]^{2-}$. Therefore, the above results indicate quantitative complexation of palladium with cytidine. Measurements of H(6) NMR signal intensities and mass balance give the following concentrations for cytidine adducts: $[PdCydCl_3^-] \simeq 1.5 \times 10^{-3}$M; $[Pd(Cyd)_2Cl_2] \simeq 2.2 \times 10^{-3}M$; $[Pd(Cyd)_3Cl^+] \simeq 10^{-3}M$; $[Pd(Cyd)_4^{2+}] \simeq 2.5 \times 10^{-4}M$. Approximation of data mainly arises from uncertainty of "D" signal intensities and from the assumption that there is no contribution to resonances "A" from a bis-cytidine complex. The presence of both configurational isomers of $Pd(Cyd)_2Cl_2$ cannot be ruled out. However, the species giving rise to spectrum "B" is surely the dominating bis-cytidine isomer, most likely having *trans* structure. The *trans* arrangement of $Pd(Cyd)_2Cl_2$ in the solid state is consistent with the appearance in the IR spectrum (Nujol mull) of a single Pd–Cl stretching band at 353 cm^{-1}, assigned by comparison with the spectra of the complexes $Pd(Cyd)_2Br_2$ and $[Pd(Cyd)_4]Cl_2 \cdot 3H_2O$. The isolation of dichlorobis(cytidine)palladium(II) has been reported also in a recent paper, where a *cis* geometry is ascribed to the complex [2d]. Since arguments for the above assignment are not given, comparison with our results is not possible. It is pertinent to note, however, that a *trans* structure has been established for the complex dichlorobis(1-methylcytosine)palladium(II), similarly obtained from an aqueous solution of K_2PdCl_4 and the ligand [2b].

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