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Equilibrium Studies of Cytidine for Chloride Substitution in Palladium Complexes

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Equilibrium constants for substitution of Cl^- by cytidine in $PdCl_4^{2-}$ and $Pd(en)Cl_2$ in aqueous solution were determined. Equilibrium constants for substitution of Cl^- by pyridine in $Pd(en)Cl_2$ were also measured. For unit ionic strength at 25 °C, log K values for the successive substitutions of two chlorides are: $PdCl_4^{2-}$–cytidine, log $K_1 = 4.49$, log $K_2 = 3.45$; $Pd(en)Cl_2$–cytidine, log $K_1 = 3.32$, log $K_2 = 2.56$; $Pd(en)Cl_2$–pyridine, log $K_1 = 4.31$, log $K_2 = 3.15$. Comparison of equilibrium constants indicates that intramolecular hydrogen bonding and steric interactions of the exocyclic substituents ortho to the binding site of cytidine do not contribute significantly to the stability of the palladium–nucleoside complexes. Coordination equilibria of deprotonated cytidine occur in alkaline solutions of $PdCl_4^{2-}$ and the ligand.

Introduction

Equilibria of palladium(II) complexes with nucleic acid derivatives are of interest particularly because these systems are rapidly reacting prototypes for platinum(II) [1]. We have reported preliminary studies on the coordination equilibria of the system $PdCl_4^{2-}$–cytidine [2]. This paper reports the equilibrium constants for the successive substitutions of two chlorides by cytidine from $PdCl_4^{2-}$ and $Pd(en)Cl_2$ in aqueous solution (eqn. 1–4; Cyd = cytidine, en = ethylenediamine). Coordination equilibria of pyridine have also been studied for comparison (eqn. 5–6; Py = pyridine). Binding of cytosines to palladium(II) has been shown to occur at N(3) [1, 3].

$$PdCl_4^{2-} + Cyd = Pd(Cyd)Cl_3^- + Cl^- \quad (1)$$

$$Pd(Cyd)Cl_3^- + Cyd = Pd(Cyd)_2Cl_2 + Cl^- \quad (2)$$

$$Pd(en)Cl_2 + Cyd = Pd(en)(Cyd)Cl^+ + Cl^- \quad (3)$$

$$Pd(en)(Cyd)Cl^+ + Cyd = Pd(en)(Cyd)_2^{2+} + Cl^- \quad (4)$$

$$Pd(en)Cl_2 + Py = Pd(en)(Py)Cl^+ + Cl^- \quad (5)$$

$$Pd(en)(Py)Cl^+ + Py = Pd(en)(Py)_2^{2+} + Cl^- \quad (6)$$

Experimental

Materials

K_2PdCl_4 was prepared from $PdCl_2$ and KCl. $Pd(en)Cl_2$ was prepared according to a literature method [4]. All other chemicals were reagent grade. All solutions for u.v.–visible spectroscopic measurements were prepared from deionized and distilled water.

Measurements

Proton n.m.r. spectra were recorded on a Bruker WP60 spectrometer. Integral intensities were obtained instrumentally or by weight. U.v.–visible spectra were recorded on a Perkin-Elmer 576 ST spectrophotometer equipped with a thermostatted cell compartment using 1 cm cells. The reference cell contained a suitable blank in each case. The solutions for measurement of equilibrium constants were equilibrated at 25 °C usually for 1 d. The reproducibility of the results at different times was occasionally checked. NaCl, D_2SO_4 or H_2SO_4 were used as sources of chloride and hydrogen ions. The ionic strength was maintained at 1 *M* with $NaNO_3$ or $NaClO_4$. Preliminary measurements showed that the complexes $PdCl_4^{2-}$ and $Pd(en)Cl_2$ obey the Lambert–Beer law under the experimental conditions.

Results

Equilibrium constants are concentration constants obtained for unit ionic strength at 25 °C. Slightly different ionic strengths were occasionally used, corresponding to negligible changes in activity coefficients. Values of equilibrium constants obtained for different concentrations in each system are available as supplementary material.

System $PdCl_4^{2-}$–Cytidine

The formation of the complexes $[Pd(Cyd)_nCl_{4-n}]^{n-2}$ (n = 1–4) in water has been shown previously by ^1H n.m.r. spectroscopy. The proton spectrum of cytidine in D_2O displays in the base region doublets at $\delta = 7.88$ (H6) and 6.11 (H5) ($J_{5-6} = 7.5$ Hz). Protonated cytidine shows the H6 signal at $\delta = 8.11$ and the H5 signal at 6.21. The spectra of N3

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bonded cytidine complexes of the type $[Pd(Cyd)_n Cl_{4-n}]^{n-2}$ show pyrimidine resonances in the ranges $\delta = 7.96–7.84$ (H6) and 6.12–5.99 (H5). The coupling constant J_{5-6} is not appreciably changed upon protonation or coordination to palladium(II).

Since complexation of palladium(II) with cytidine is quantitative even in the presence of excess chloride [2], K_1 and K_2 values for reactions (1) and (2) were obtained indirectly from equilibrium constants of reactions (7) and (8) in D_2O and (9) in H_2O, carried out in the presence of added acid.

$$PdCl_4^{2-} + CydD^+ = Pd(Cyd)Cl_3^- + D^+ + Cl^-, \quad K_1'(D) \tag{7}$$

$$Pd(Cyd)Cl_3^- + CydD^+ = Pd(Cyd)_2Cl_2 + D^+ + Cl^-, \quad K_2'(D) \tag{8}$$

$$PdCl_4^{2-} + CydH^+ = Pd(Cyd)Cl_3^- + H^+ + Cl^-, \quad K_1' \tag{9}$$

Equilibria (7) and (8) were studied by means of ^1H n.m.r. spectroscopy using experimental conditions where the concentrations of Cyd, $Pd(Cyd)_3Cl^+$ and $Pd(Cyd)_4^{2+}$ were negligible. The concentration ranges used are: $[PdCl_4^{2-}] = 1.0 \times 10^{-2}–7.1 \times 10^{-2}$ *M*, $[Cyd] = 1.0 \times 10^{-2}–7.0 \times 10^{-2}$ *M*, $[D^+] = 4 \times 10^{-2}–2.2 \times 10^{-1}$ *M*, $[Cl^-] = 0.23–0.74$ *M*. Equilibrium concentrations were calculated from measured relative intensities of H6 signals of $CydD^+$, $Pd(Cyd)Cl_3^-$ and $Pd(Cyd)_2Cl_2$ and from equations for mass balance of cytidine, palladium and hydrogen and chloride ions. In these calculations the formation of $Pd(H_2O)Cl_3^-$ was taken into account, whereas formation of other aquo-complexes from hydrolysis of tetrachloropalladate(II) was considered negligible at the chloride concentrations used. The stepwise equilibrium constants for substitution of Cl^- by H_2O in $PdCl_4^{2-}$ are log $K = -1.3$, -2.4, -3.3 and -4.3 [5]. The degree of hydrolysis of the complexes $Pd(Cyd)Cl_3^-$ and $Pd(Cyd)_2Cl_2$ was also assumed to be small at the chloride concentrations used by analogy with the corresponding amino-complexes $Pd(NH_3)Cl_3^-$ and $Pd(NH_3)_2Cl_2$, for which log K values for the first substitution of Cl^- by H_2O are -1.9 and -2.3, respectively [5]. The calculated mean value of $K_1'(D) = [Pd(Cyd)Cl_3^-][D^+][Cl^-]/[PdCl_4^{2-}][CydD^+]$ is 0.96 ± 0.02 *M*; the value of $K_2'(D) = [Pd(Cyd)_2Cl_2][D^+][Cl^-]/[Pd(Cyd)Cl_3^-][CydD^+]$ is 0.087 ± 0.005 *M*. In relation to the calculation of $K_1'(D)$ and $K_2'(D)$ the question of the possible association of $CydD^+$ could arise. Association of pyrimidine nucleosides through base stacking is known to occur in aqueous solution [6]. From reported equilibrium constants cytidine can be calculated to be 90% monomer in a 0.07 *M* solution and 99% in a 0.01 *M* solution. Information on the possible association of protonated cytidine is not available. However, studies on the intramolecular base stacking of the dinucleotide CpC and of its protonated derivatives have been reported [7]. The equilibrium ratio of stacked and unstacked species is $K = 0.72$ for CpC, 0.75 for $CpCH^+$ and *ca.* 0 for $HCpCH^{2+}$ (25 °C, I = 0.1 *M*). These data suggest that the concentration of species of the type $(CydD^+)_n$ is negligible. The formation of stacked species of the type $(CydD^+)(Cyd)_n$ or of hydrogen bonded base pairs $Cyd–CydD^+$ is not important due to the very low concentration of Cyd under the experimental conditions. Coordinated Cyd is not expected to form stacking interactions with $CydD^+$ more strongly than free Cyd. Therefore, the degree of association at metal bound Cyd should be small even at the highest concentrations used. The above deductions are confirmed by agreement of observed $K_1'(D)$ and $K_2'(D)$ values.

Equilibrium (9) was studied by difference spectra in the range 400–550 nm using experimental conditions where the concentrations of palladium complexes other than $PdCl_4^{2-}$, $Pd(H_2O)Cl_3^-$ and $Pd(Cyd)Cl_3^-$ and of unprotonated cytidine are negligible. The concentration ranges used are: $[PdCl_4^{2-}] = 4.6 \times 10^{-3}–5.9 \times 10^{-3}$ *M*, $[Cyd] = 4.2 \times 10^{-4}–1.2 \times 10^{-3}$ *M*, $[H^+] = 9.8 \times 10^{-3}–1.4 \times 10^{-2}$ *M*, $[Cl^-] = 0.3–1.0$ *M*. In each experiment changes of the absorption at 485 nm upon addition of increasing amounts of cytidine to a solution of $PdCl_4^{2-}$ were measured as long as an isosbestic point at *ca.* 450 nm was observed. This is consistent with the presence of $PdCl_4^{2-}$, $Pd(H_2O)Cl_3^-$ and $Pd(Cyd)Cl_3^-$, the concentration of the first two species being constant due to the presence of excess chloride. Equilibrium concentrations of the complexes were obtained by eqns. 10 and 11, where $[Pd]_T$ is the total palladium concentration, A is the optical

$$[PdCl_4^{2-}] = [Pd]_T(A - A_L)/(A_0 - A_L) \tag{10}$$

$$[Pd(Cyd)Cl_3^-] = [Pd]_T(A_0 - A)/(A_0 - A_L) \tag{11}$$

density of the equilibrium mixture, A_0 and A_L are the optical densities of solutions of $PdCl_4^{2-}$ and $Pd(Cyd)Cl_3^-$, respectively, at the concentration $[Pd]_T$. Formation of $Pd(H_2O)Cl_3^-$ is allowed for by eqns. 10 and 11. The A_L values were calculated from optical densities of $PdCl_4^{2-}$–cytidine mixtures containing excess palladium without added acid. For these solutions the isosbestic point at *ca.* 450 nm is observed and $(A_0 - A)$ values are proportional to the amount of added cytidine. Calculated concentrations of the complexes were occasionally checked with measurements at different wavelengths. The equilibrium concentrations of H^+ and $CydH^+$ were obtained from mass balance equations. The calculated mean value of $K_1' = [Pd(Cyd)Cl_3^-][H^+][Cl^-]/[PdCl_4^{2-}][CydH^+]$ is 2.29 ± 0.05 *M*.

The ratio of the equilibrium constants for substitution of chloride by cytidine in H_2O and D_2O ($K_1'/K_1'(D) = 2.39$) is the ratio of the acidity constants

of cytidine in these solvents. From the reported value of $pK_a = 4.13$ for $CydH^+$ in H_2O [7] the value of $pK_a = 4.51$ is obtained for $CydD^+$ in D_2O. Dividing K_1' by $K_a(CydH^+)$ gives the equilibrium constant of reaction (1) $K_1 = 3.1 \times 10^4$. From the ratio $K_2'(D)/K_1'(D)$ the equilibrium constant of reaction (2) is calculated to be $K_2 = 2.8 \times 10^3$.

The ^1H n.m.r. spectra of alkaline solutions of $PdCl_4^{2-}$ and cytidine show that palladium complexes of the nucleoside deprotonated at $C(4)NH_2$ occur [8]. The analysis of the concentration dependence of the spectra is more conveniently performed with H6 signals, which are more distinct than H5 signals. A solution of 0.18 *M* K_2PdCl_4 and 0.08 *M* cytidine in the presence of 0.04 *M* Na_2CO_3 displays a H6 doublet at $\delta = 7.92$ due to $Pd(Cyd)Cl_3^-$ and two rather broad overlapping doublets centered at $\delta = 7.12$ and 7.08 ($J_{5-6} = 7.5$ Hz) assigned to complexes of deprotonated cytidine. The high field H6 signals are cancelled out by addition of acid. If the cytidine/palladium mol ratio is increased the doublet at 7.08 undergoes an intensity increase compared to the doublet at 7.12. When excess alkali (KOH or Na_2CO_3) is added to equimolar solutions of $PdCl_4^{2-}$ and cytidine only a single very broad resonance at $\delta = 7.1$ is observed.

System Pd(en)Cl_2–Pyridine

Spectra of this system in the range 300–450 nm distinctly show the occurrence of reactions (5) and (6). Spectra of equilibrium mixtures with a given palladium concentration and increasing amounts of pyridine in the presence of added chloride initially display an isosbestic point at 352 nm. Constant absorbance is then not observed at any wavelength until an isosbestic point at 317 nm is formed and a limiting spectrum approached. This spectrum is identical with the spectra of 1:4 or 1:10 Pd(en)Cl_2–pyridine solutions with the same palladium concentration with no added chloride and is assigned to the complex $Pd(en)(Py)_2^{2+}$. The spectrum of the complex $Pd(en)(Py)Cl^+$ was calculated from spectra of Pd(en)Cl_2–pyridine mixtures at the concentrations for which the isosbestic point at 352 nm is apparent. Under these conditions changes of optical densities from the spectrum of Pd(en)Cl_2 are proportional to the amount of added pyridine.

The equilibrium constant, K_1' of reaction (5) was obtained from the equilibrium constant, K_1', of reaction (12), carried out in the

$$Pd(en)Cl_2 + PyH^+ = Pd(en)(Py)Cl^+ + H^+ + Cl^- \qquad (12)$$

presence of added acid, under conditions in which the isosbestic point at 352 nm is kept. The concentration ranges used are: $[Pd(en)Cl_2] = 8.3 \times 10^{-4}$–$8.8 \times 10^{-4}$ *M*, $[Py] = 5 \times 10^{-4}$–6.6×10^{-3} *M*, $[H^+] = 1.5 \times 10^{-3}$–$7.6 \times 10^{-3}$ *M*, $[Cl^-] = 0.10$–0.30 *M*. The degree of hydrolysis of Pd–Cl bonds in the complexes Pd(en)Cl_2 and $Pd(en)(Py)Cl^+$ was assumed to be small at the chloride concentration used by analogy with the corresponding complexes $Pd(NH_3)_2Cl_2$, for which the stepwise hydrolysis constants are log $K = -2.3$ and -3.4, and $Pd(NH_3)_3Cl^+$, log $K = -3.0$ [5]. The spectra of Pd(en)Cl_2 in the presence of 0.1 and 1.0 *M* chloride are identical to within 2–3%. Moreover, reactions involving protonation of ethylenediamine at the conditions used for K_1' measurements can be ruled out since the spectra of Pd(en)Cl_2 in neutral or acidic solution ($[H^+] \leqslant 2.5 \times 10^{-2}$ *M*) are identical and the isosbestic point at 352 nm is apparent from the Pd(en)Cl_2–PyH^+ equilibrium mixtures. Evidence for displacement of the chelating ligand is obtained at higher concentrations of added acid and chloride. In each experiment changes in the absorption at 375 nm were measured upon addition of increasing amounts of pyridine and acid to a solution of Pd(en)Cl_2. Equilibrium concentrations of the complexes were obtained by eqns. 13 and 14, where $[Pd]_T$ is the total

$$[Pd(en)Cl_2] = [Pd]_T(A - A_L)/(A_0 - A_L) \qquad (13)$$

$$[Pd(en)(Py)Cl^+] = [Pd]_T(A_0 - A)/(A_0 - A_L) \qquad (14)$$

palladium concentration, A is the optical density of the equilibrium mixture, A_0 and A_L are the optical densities of solutions of Pd(en)Cl_2 and $Pd(en)(Py)Cl^+$, respectively, at the concentration $[Pd]_T$. Calculated concentrations of the complexes were occasionally checked with measurements at different wavelengths. The hydrogen ion concentrations were obtained by pH measurements on the equilibrium mixtures. The amount of added acid was sufficiently great in any case to give quantitative protonation of uncomplexed pyridine. The concentrations of PyH^+ were obtained by mass balance equations. The calculated mean value of

$$K' = [Pd(en)(Py)Cl^+][H^+][Cl^-]/[Pd(en)Cl_2][PyH^+]$$

is 0.118 ± 0.004 *M*. Agreement of observed K_1' values confirms that reactions other than (12) do not occur to any appreciable extent under the conditions used for measurements. Dividing K_1' by K_a of pyridine ($pK_a = 5.24$ [9]) gives the equilibrium constant of reaction (5), $K_1 = 2.05 \times 10^4$.

The equilibrium constant, K_2, for reaction (6) was measured using solutions of Pd(en)Cl_2 and pyridine with no added acid in the presence of excess chloride. The concentration ranges used are: $[Pd(en)Cl_2] = 8.5 \times 10^{-4}$–$8.8 \times 10^{-4}$ *M*, $[Py] = 1.3 \times 10^{-3}$–$8.3 \times 10^{-3}$ *M*, $[Cl^-] = 0.5$–1.0 *M*. The concentrations of the complexes were calculated with eqns. 15–17, where $[Pd]_T$ is the total concentration of palladium; $\Delta A'$ is the difference in absorption between the equilibrium mixture and a solution of Pd(en)Cl_2 at the concentration $[Pd]_T$, measured at 352 nm (*i.e.* the wavelength of the isosbestic point of Pd(en)Cl_2

and $Pd(en)(Py)Cl^+$); $\Delta A_0'$ is the difference in the absorptions of $Pd(en)(Py)_2^{2+}$ and $Pd(en)Cl_2$ both at the concentration $[Pd]_T$, measured at 352 nm; $\Delta A''$ is the difference in absorption between the equilibrium mixture and a solution of $Pd(en)(Py)_2^{2+}$ at the concentration $[Pd]_T$, measured at 317 nm (*i.e.* the wavelength of the isosbestic point of $Pd(en)(Py)Cl^+$ and $Pd(en)(Py)_2^{2+}$); $\Delta A_0''$ is the difference in the absorptions of $Pd(en)Cl_2$ and $Pd(en)(Py)_2^{2+}$ both at the concentration $[Pd]_T$, measured at 317 nm.

$$[Pd(en)(Py)_2^{2+}] = [Pd]_T \Delta A'/\Delta A_0' \quad (15)$$

$$[Pd(en)Cl_2] = [Pd]_T \Delta A''/\Delta A_0'' \quad (16)$$

$$[Pd(en)(Py)Cl^+] = [Pd]_T - [Pd(en)Cl_2] - [Pd(en)(Py)_2^{2+}] \quad (17)$$

The concentrations of free pyridine were calculated by mass balance equations. Measured pH values of the solutions were much greater than $pK_a(PyH^+)$ in each case. The calculated mean value of $K_2 = [Pd(en)(Py)_2^{2+}][Cl^-]/[Pd(en)(Py)Cl^+][Py]$ is $(1.41 \pm 0.06) \times 10^3$. Agreement of observed K_2 values for reaction (6) confirms that reactions other than chloride substitution do not occur to any appreciable extent under the conditions used for measurements.

System $Pd(en)Cl_2$–Cytidine

Spectra of this system in the range 300–450 nm distinctly show the occurrence of reactions (3) and (4). Changes in spectra of equilibrium mixtures with a given palladium concentration and increasing amounts of cytidine in the presence of added chloride are similar to those observed in the $Pd(en)Cl_2$–pyridine system. The equilibrium constant K_1 of reaction (3) was obtained from the equilibrium constant K_1' of reaction (18), carried out in the presence of added acid.

$$Pd(en)Cl_2 + CydH^+ = Pd(en)(Cyd)Cl^+ + H^+ + Cl^- \quad (18)$$

Measurements of K_1' and K_2 were carried out using methods analogous to those used for the system $Pd(en)Cl_2$–pyridine. However, substitution of the first chloride by cytidine (eqn. 3) is not quantitative even at low ligand/metal mol ratios and with no added acid. Therefore, the spectrum of $Pd(en)(Cyd)Cl^+$ was obtained from iterative calculations. The equilibrium concentrations of the complexes for calculation of K_1' were obtained by equations analogous to (13) and (14) from measurements of the absorption at 375 nm under conditions in which the isosbestic point of $Pd(en)Cl_2$ and $Pd(en)(Cyd)Cl^+$ (at 355 nm) is kept. The concentration ranges used are: $[Pd(en)Cl_2] = 8.5 \times 10^{-4}$–$8.9 \times 10^{-4}$ *M*, $[Cyd] = 4 \times 10^{-4}$–4.5×10^{-3} *M*, $[H^+] = 9.5 \times 10^{-3}$–$1.0 \times 10^{-2}$ *M*, $[Cl^-] = 0.3$ *M*. The calculated mean value of $K_1' = [Pd(en)(Cyd)Cl^+][H^+][Cl^-]/[Pd(en)Cl_2][CydH^+]$ is 0.155 ± 0.004 *M*. Dividing K_1' by K_a of cytidine gives the equilibrium constant of reaction (3), $K_1 = 2.1 \times 10^3$.

The equilibrium concentrations of the complexes for calculation of K_2 were obtained by equations analogous to (15–17). Values of $\Delta A'$ and $\Delta A_0'$ were measured at 355 nm, *i.e.* the wavelength of the isosbestic point of $Pd(en)Cl_2$ and $Pd(en)(Cyd)Cl^+$, values of $\Delta A''$ and $\Delta A_0''$ at 334 nm, *i.e.* the isosbestic point of $Pd(en)(Cyd)Cl^+$ and $Pd(en)(Cyd)_2^{2+}$. The spectrum of $Pd(en)(Cyd)_2^{2+}$ was obtained from solutions of $Pd(en)Cl_2$ containing excess cytidine (*e.g.* 10–20 equivalents) with no added chloride. The concentration ranges used for K_2 measurements are: $[Pd(en)Cl_2] = 8.5 \times 10^{-4}$–$9.3 \times 10^{-4}$ *M*, $[Cyd] = 1.4 \times 10^{-3}$–$1.8 \times 10^{-2}$ *M*, $[Cl^-] = 1.0$ *M*. The calculated mean value of $K_2 = [Pd(en)(Cyd)_2^{2+}][Cl^-]/[Pd(en)(Cyd)Cl^+][Cyd]$ is $(3.6 \pm 0.1) \times 10^2$. Agreement of observed values of equilibrium constants K_2 for reaction (4) confirms that reactions other than chloride substitution do not occur to any appreciable extent under the conditions used for measurements.

Discussion

The estimated equilibrium constants for reactions (1–6) are listed in Table I together with reported data for the system $PdCl_4^{2-}$–NH_3 [5]. The differences in log K_1 values for a given complex reacting with different ligands, L, represent the relative stabilities of the Pd–L bonds formed. The following factors may determine the relative stability of the structurally similar complexes $Pd(en)(Cyd)Cl^+$ and $Pd(en)(Py)Cl^+$: (1) different donor abilities of the heterocyclic ligands toward palladium(II); (2) steric effects of the exocyclic substituents ortho to the binding site of cytidine; (3) hydrogen bonding of cytidine exocyclic groups with either the ethylenediamine NH_2 groups or the metal center. It has been shown that hydrogen bonding and repulsive nonbonded interactions involving exocyclic groups can influence the stability of purine and pyrimidine metal complexes [10]. Intramolecular steric factors have also

TABLE I. Equilibrium Constants for Substitution of Chloride in Palladium(II) Complexes in Water at 25 °C, $I = 1.0$ *M*.

System	log K_1	log K_2
$PdCl_4^{2-}$–cytidine	4.49	3.45
$Pd(en)Cl_2$–cytidine	3.32	2.56
$Pd(en)Cl_2$–pyridine	4.31	3.15
$PdCl_4^{2-}$–NH_3[a]	7.16	5.72

[a]Data from reference [5].

been suggested to be determinative of the molecular conformation of platinum(II) complexes with substituted pyrimidines in the solid state [11]. The occurrence of intramolecular hydrogen bonding between exocyclic carbonyl oxygen of pyrimidine ligands and coordinated ammonia in platinum(II) complexes has been shown by crystallographic studies [12]. A strong intramolecular interaction Pd···HN has been claimed to occur in the complexes Pd(1-methylcytosine)$_2$(SCN)$_2$ and Pd(deoxycytidine)$_2$Cl$_2$ [13]. The n.m.r. signal of the NH_2 cytosine protons in these compounds is shifted to lower field ($\Delta\nu >$ 1.4 ppm) relative to the free ligand and split into two resonances 0.3 to 1.0 ppm apart from each other. The observed nonequivalence is attributed to a selective interaction between the palladium atom and one hydrogen of the amino group. It should be noted, however, that even greater shift and splitting of the NH_2 resonance are observed upon protonation of cytosines (*e.g.* the NH_2 signal occurs at $\delta = 6.91$ for cytosine and at $\delta = 9.85$, 8.75 for protonated cytosine in DMSO [3]). The activation energy for rotation about the C–NH_2 bond in the complexes is calculated to be *ca.* 80 KJ mol^{-1} compared to 25 KJ mol^{-1} for uncomplexed cytosines. The high value found has been related to metal–ligand hydrogen bonding rather than to enhancement of the partial double bond character of the C–NH_2 bond by complexation. Accordingly, the Pd–H–N interaction should be assigned to the class of strong hydrogen bonds [14]. However, this deduction is not consistent with crystallographic results showing only a weak metal–hydrogen interaction in the complex Pd(1-methylcytosine)$_2$Cl$_2$ [3b].

The equilibrium constants for the substitution reactions of the palladium(II) complexes can be relevantly compared with the stability constants of 1:1 adducts of Cu^{2+} with cytidine (log $K = 1.4$, $I =$ 0.16 *M*), pyridine (log $K = 2.5$, $I = 0.1$ *M*) and ammonia (log $K = 4.0$, $I = 0$) [9]. It has been inferred that predominant binding at N3 occurs for the 1:1 adducts of Cu^{2+} with cytosine and cytidine in aqueous solution and that the interaction with O2 is so weak as to contribute negligibly to the stabilities [15]. It must be pointed out that steric requirements and possible hydrogen bonding modes in the copper complexes are different with respect to the palladium complexes. Therefore, it is significant that the Δ log K_1 value for Pd(en)Cl$_2$ reacting with pyridine and cytidine (1.0) is very close to the Δ log K value for the copper complexes with the same ligands (1.1) and also to the ΔpK_a value of the bases (1.1). The Δ log K_1 value for $PdCl_4^{2-}$ reacting with ammonia and cytidine (2.7) is also very close to the Δ log K value for the copper complexes (2.6). In this case both Δ log K values are two units lower than the ΔpK_a of the ligands. The consistent trend in the results of Δ log K(Pd) and Δ log K(Cu) suggests that hydrogen bonding and repulsive nonbonded interactions involving exocyclic groups of the pyrimidine do not contribute significantly to the stability of the palladium complexes studied. In particular, it appears that the relative stability of the complexes Pd(en)(Cyd)Cl$^+$ and Pd(en)(Py)Cl$^+$ is dictated by the difference in basicity of the donor site of the ligands toward palladium(II).

The difference between log K_1 and log K_2 is 0.76 for the system Pd(en)Cl$_2$–cytidine and 1.16 for the system Pd(en)Cl$_2$–pyridine. The somewhat smaller Δ log K value for the palladium–cytidine complexes might be taken as an indication of the presence of interbase N(4)H$_2$···O(2) hydrogen bonds in the *cis*-bis(cytidine) complexes, of the type observed in the complex cation *cis*-diammine-bis(1-methylcytosine)-platinum(II) [11]. However, the same difference between Δ log K values is observed for the systems $PdCl_4^{2-}$–cytidine (Δ log $K = 1.04$) and $PdCl_4^{2-}$–NH_3 (Δ log $K = 1.44$). It is noted that, while the configuration of the complex Pd(NH$_3$)$_2$Cl$_2$ in aqueous solution is not established, a *trans* configuration is most likely dominant for the complex Pd(Cyd)$_2$-Cl$_2$ [2]. It can be inferred from the above results that interligand hydrogen bonding and steric interactions are not determinative of the stabilities of the bis(cytidine) complexes, although the possibility that these factors cancel out to a large extent cannot be excluded.

It has been reported recently that in solutions of Pd(en)(H$_2$O)$_2^{2+}$ and cytidine complexes of the deprotonated nucleoside occur, where metal atoms are bridged by cytosine ring anions through N3 and N4 [1]. The formation of complexes of cytidine deprotonated at C(4)NH_2 in alkaline solutions of $PdCl_4^{2-}$ and the ligand has been described before [8]. The observed dependence of the ^{1}H n.m.r. spectra of this system upon the metal/ligand mole ratio suggests that coordination equilibria among anionic cytidine bridged complexes occur, similarly to the Pd(en)$^{2+}$–cytidine system.

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