The hydrolysis products of *cis*-diamminedichloroplatinum(II) 5. The anation kinetics of *cis*-$Pt(X)(NH_3)_2(OH_2)^+$ (X = Cl, OH) with glycine, monohydrogen malonate and chloride

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Abstract

The spectrophotometrically determined rate constants, k_{obs} (s^{-1}), for the anation of *cis*-$PtCl(NH_3)_2(OH_2)^+$ with glycine (Nu = gly at pH = 7.4), or sodium hydrogen malonate (Nu = $Hmal^-$ at pH = 4.3) can be represented by the equation $k_{obs} = k_o + k_{Nu}[Nu]$, where k_o is an hydrolysis rate constant independent of the nucleophile concentration but dependent on pH, and k_{Nu} is a nucleophile dependent path. With Nu = $Hmal^-$, $k_o \sim 0$ and the first step is monodentate coordination, followed by a second (k_{cy}), nucleophile independent path, due to ring closure. With Nu = gly, the ring closure reaction is sufficiently fast as to appear synchronous with coordination and k_o is the base hydrolysis rate constant for *cis*-$PtCl(OH)(NH_3)_2$ at pH = 7.4. Kinetic parameters associated with the anation are k_{Hmal} (25.0 °C, pH = 4.3, I = 1.0 M) = 9.90×10^{-4} M^{-1} s^{-1}, $\Delta H^{\ddagger} = 74.8$ kJ mol^{-1}, $\Delta S^{\ddagger} = -52$ J K^{-1} mol^{-1}; k_{gly} (25.0 °C, pH = 7.4, I = 1.0 M) = 2.75×10^{-4} M^{-1} s^{-1}, $\Delta H^{\ddagger} = 62.7$ kJ mol^{-1}, $\Delta S^{\ddagger} = -103$ J K^{-1} mol^{-1}; k_{cy} (25.0 °C, pH = 4.3, I = 1.0 M) = 1.03×10^{-5} s^{-1}, $\Delta H^{\ddagger} = 88.9$ kJ mol^{-1}, $\Delta S^{\ddagger} = -42$ J K^{-1} mol^{-1}. The rate (k_3, s^{-1}) of the chloride release from *cis*-$PtCl(OH)(NH_3)_2$ to give *cis*-$Pt(OH)NH_3)_2(OH_2)^+$ and rate of chloride uptake (k_{-3}, M^{-1} s^{-1}) have been measured at pH = 7.4. Kinetic parameters are $k_3 = 2.39 \times 10^{-5}$ s^{-1} (25.0 °C, pH = 7.4, I = 1.0 M) $\Delta H^{\ddagger} = 82.4$ kJ mol^{-1}, $\Delta S^{\ddagger} = -57$ J K^{-1} mol^{-1} and $k_{-3} = 9.37 \times 10^{-4}$ M^{-1} s^{-1} (25.0 °C, pH = 7.4, I = 1.0 M), $\Delta H^{\ddagger} = 61.7$ kJ mol^{-1}, $\Delta S^{\ddagger} = -96$ J K^{-1} mol^{-1}. From these rate constants, $K_3 = (k_3[k_{-3}]^{-1})$ is calculated to be 2.55×10^{-2} at 25.0 °C. These data have been used to comment on the nucleophilicity of *cis*-$PtCl(NH_3)_2(OH_2)^+$.

Introduction

The 1980s have seen a considerable resurgence in interest in Pt(II) chemistry as a result of the discovery of Rosenberg *et al.* [1] that *cis*-$PtCl_2(NH_3)_2$ can be used in anti-tumor cancer therapy. We are currently studying the kinetics of hydrolysis and anation of this compound and its hydrolysis products under acid, base, and physiological pH conditions [2–4]. These studies highlight the importance of *cis*-$PtX(NH_3)_2(OH_2)^+$ (X = OH, Cl) as the most likely Pt(II) containing species available to bind to replicating DNA at pH = 7.4 [4, 5]. Consequently, it is of interest to establish reactivity patterns for these (aniono)(aqua) products, and this is the basis for the present publication.

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Experimental

cis-$PtCl_2(NH_3)_2$ was purchased from Strem Chemical Company and used as supplied. All other reagents were AR quality or the best reagent grade available. A Radiometer pH-stat (TTT1c) coupled to a Radiometer titrigraph (SER2) with the appropriate glass (G202c) and calomel (TS-1) electrodes was used for all pH measurements. The instrument was calibrated with 0.01 M borax buffer (pH = 9.038 at 45.0 °C). A Varian DMS100 recording spectrophotometer was used to record the UV (345–220 nm) spectra of the reacting solutions.

Hydrolysis of cis-$PtCl(OH)(NH_3)_2$ and the chloride ion anation of cis-$Pt(OH)(NH_3)_2(OH_2)^+$ at pH = 7.4

A stock solution of *cis*-$PtCl(NH_3)_2(OH_2)^+$ (2.38×10^{-3} M) was prepared by allowing *cis*-$PtCl_2(NH_3)_2$ (0.1786 g) to hydrolyse in 1.0 M $NaClO_4$ (245 ml) plus 0.1 M $HClO_4$ (5 ml) at 50 °C for 3–4 h and then overnight at room temperature.

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TABLE 1. Spectrophotometrically determined rate constants for the forward and reverse reactions associated with eqn. (2) at pH = 7.4 (I = 1.0 M)

T (°C)	[K]	$10^4 \times k_3$ (s^{-1})	$10^4 \times k_3$ (calc.)[a] (s^{-1})	$10^4 \times k_{obs}$ (s^{-1})	$10^3 \times k_{-3}$[b] (M^{-1} s^{-1})	$10^3 \times k_{-3}$ (calc.)[c] (M^{-1} s^{-1})
25.0	[298.2]		0.239			0.937
35.2	[308.4]	0.749 ± 0.042 0.730 ± 0.170	0.741	4.39 ± 0.86	2.20	2.21
40.2	[313.4]	1.23 ± 0.20 1.29 ± 0.34 1.25 ± 0.29	1.26	6.67 ± 0.67	3.39	3.29
45.2	[318.4]	2.14 ± 0.32 2.07 ± 0.38 2.12 ± 0.81	2.10	9.25 ± 0.67	4.63	4.84
49.7	[322.9]	3.24 ± 0.32 3.27 ± 0.58	3.28	13.9 ± 0.64	6.94	6.79

[a]Calculated from the activation parameters: k_3 (25 °C) = 2.39×10^{-5} s^{-1}, $\Delta H^{\ddagger} = 82.4 \pm 0.8$ kJ mol^{-1}, $\Delta S^{\ddagger} = -57 \pm 2$ J K^{-1} mol^{-1}. [b][Cl^-] = 0.2 M, $k_{-3} = 5\ k_{obs}$ (M^{-1} s^{-1}). [c]Calculated from the activation parameters k_{-3} (25 °C) = 9.37×10^{-4} M^{-1} s^{-1}, $\Delta H^{\ddagger} = 61.7 \pm 3.2$ kJ mol^{-1}, $\Delta S^{\ddagger} = -96 \pm 6$ J K^{-1} mol^{-1}.

TABLE 2. Forward (k_3) and reverse (k_{-3}) rate constants, and equilibrium constants, for the hydrolysis of *cis*-$PtCl(OH)(NH_3)_2$ (eqn. (2)) at pH = 7.4 (I = 1.0 M)

T (°C)	[K]	$10^5 \times k_3$[a] (s^{-1})	$10^4 \times k_{-3}$[b] (M^{-1} s^{-1})	$10^3 \times K_3$[c,d]
10.0	[283.2]	0.392	2.39	16.4
15.0	[288.2]	0.732	3.84	19.1
20.0	[293.2]	1.34	6.05	22.2
25.0	[298.2]	2.40	9.41	25.5
30.0	[303.2]	4.22	14.4	29.3
35.0	[308.2]	7.28	21.8	33.4
40.0	[313.2]	12.4	32.5	38.1
45.0	[318.2]	20.6	47.9	43.0
50.0	[323.2]	33.9	69.6	48.7

[a]Calculated from the expression: $k_3 = 1.75 \times 10^{10}$ exp(−84.85/RT). [b]Calculated from the expression: $k_{-3} = 1.63 \times 10^8$ exp(−64.15/RT). [c]Calculated from the expression: $K_3 = [k_{-3}]^{-1} = 107.4$ exp(−20.68/RT). [d]The variation of K_3 with temperature indicates that the forward reaction is endothermic with $\Delta H^{\circ} = 20.7$ kJ mol^{-1}. Other thermodynamic parameters associated with the forward reaction are ΔG° (298.2) = +9.10 kJ mol^{-1} and ΔS° (298.2) = +39 J K^{-1} mol^{-1}. The corresponding data for K_1 (eqn. (3)) are $\Delta H^{\circ} = +7.52$, $\Delta G^{\circ} = +11.4$ and $\Delta S^{\circ} = -13$.

This solution (70 ml) was placed in the temperature controlled reaction vessel of the Radiometer pH-stat and peristaltically pumped (100 ml/min) through a 2.00 cm flow-through cell in the Varian spectrophotometer. Glass and calomel electrodes were placed in the solution and the pH was maintained at 7.4 by manual addition of 0.1 M NaOH (in 1.0 M $NaClO_4$) as the reaction proceeded. Absorbance versus time data were collected at 300, 282 and 255 nm. At the end of the reaction (6–8 $t_{1/2}$), the solution was made 0.2 M in Cl^-, by the addition of solid NaCl, and the rate of chloride uptake (k_{obs}, s^{-1}) was monitored spectrophotometrically, with the pH maintained at 7.4 by manual addition of 0.1 M $HClO_4$ (in 1.0 M $NaClO_4$).

First-order rate constants for the forward reaction (eqn. (2); k_3, s^{-1}; Table 1) were calculated from the absorbance versus time data and values for k_{-3}, M^{-1} s^{-1} (Table 1, eqn. (2), pH = 7.4) were calculated from the expression $k_{-3} = 5\ k_{obs}$. Values of K_3 (eqn. (2)) were obtained from $K_3 = k_3[k_{-3}]^{-1}$ (Table 2).

Chloride ion anation of cis-$Pt(OH)(NH_3)_2(OH_2)^+$ at pH = 7.8

Spectrophotometric scans of *cis*-$Pt(OH)_2(NH_3)_2$ [3, 4] solutions (75 ml, 1.67×10^{-3} M) titrated with $HClO_4$ to fixed pH in the range pH = 2–10 showed that the maximum *cis*-$Pt(OH)(NH_3)_2(OH_2)^+$ concentration formed at pH = 7.8, in agreement with the measured pK_a of 7.87 [6].

Consequently, solutions (75 ml) of *cis*-$Pt(OH)_2(NH_3)_2$ (2.22×10^{-3} M) in NaOH (0.01 M) plus NaCl (0.05–0.4 M) were adjusted to pH = 7.8 with $HClO_4$ in the pH-stat and pumped through a 2.00 cm spectrophotometer cell.

Spectrophotometric changes at 300, 285 and 255 nm were found to be chloride ion and temperature dependent, and constant pH was maintained by manual addition of 0.1 M $HClO_4$. Values of k_{-3} (eqn. (2), Table 3) were calculated from the expression $k_{-3} = k_{obs}[Cl^-]^{-1}$.

Reaction of cis-$PtCl(NH_3)_2(OH_2)^+$ with glycine

Experimental conditions were similar to those described for the hydrolysis of *cis*-$PtCl(OH)(NH_3)_2$,

TABLE 3. Spectrophotometrically determined rate constants for the chloride anation of *cis*-$Pt(OH)(NH_3)_2(OH_2)^+$ at pH = 7.8 (I = 1.0 M)

T (°C)	[K]	$[Cl^-]$ (M)	$10^4 \times k_{obs}$ (s^{-1})	$10^3 \times k_{-3}$[a] (M^{-1} s^{-1})	$10^3 \times k_{-3}$ (calc.)[b] (M^{-1} s^{-1})
20.3	[293.5]	0.60	6.05 ± 0.69	1.01 ± 0.11	0.968
25.0	[298.2]				1.27
25.4	[298.6]	0.20	2.62 ± 0.31	1.31 ± 0.15	1.30
		0.30	3.80 ± 0.71	1.27 ± 0.24	
		0.40	5.22 ± 0.68	1.31 ± 0.17	
		0.50	6.29 ± 0.78	1.26 ± 0.16	
		0.80	9.80 ± 0.67	1.23 ± 0.08	
30.3	[303.5]	0.40	7.04 ± 0.45	1.76 ± 0.11	1.72
		0.60	10.5 ± 1.3	1.74 ± 0.21	

[a] $k_{-3} = k_{obs}[Cl^-]^{-1}$. [b] Calculated from the activation parameters: k_{-3} (25.0 °C) = 12.7×10^{-4} M^{-1} s^{-1}, $\Delta H^{\ddagger} = 39.5 \pm 3.1$ kJ mol^{-1}, $\Delta S^{\ddagger} = -168 \pm 6$ J K^{-1} mol^{-1}.

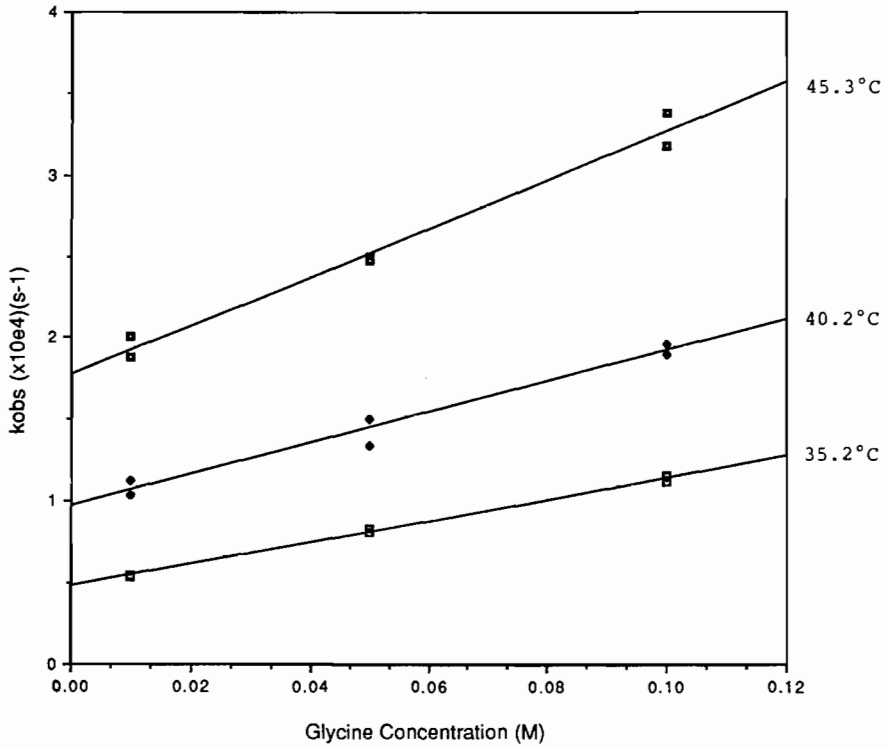


Fig. 1. Plots of k'_{obs} vs. [glycine] for the anation of *cis*-$PtCl(NH_3)_2(OH_2)^+$ to give $Pt(gly)(NH_3)_2$, at pH = 7.4.

except that solid glycine (sufficient to give concentrations of 0.01, 0.05 or 0.1 M) was added prior to the immersion of the glass and calomel electrodes. The pH was adjusted to 7.4 by addition of 0.1 M NaOH (in 1.0 M $NaClO_4$) but very little further pH adjustment was required during the course of the reaction due to the self-buffering nature of glycine. Spectral changes were monitored between 360 and 235 nm, with absorbance versus time data collected at 304 and 245 nm. Second order rate constants $k_{Nu} = k_{gly}$, M^{-1} s^{-1} (Table 4) were obtained from plots of the pseudo-first-order data (k'_{obs}, s^{-1}) versus [glycine] (Fig. 1, Table 4) and values for $k_o = k_{2,OH}$ (s^{-1}) (eqn. (1), Table 4) were obtained from the intercepts (Fig. 1).

$$k'_{obs} = k_o + k_{Nu}[Nu] \quad (1)$$

Reaction of cis-$PtCl(NH_3)_2(OH_2)^+$ with hydrogen malonate ion

A stock solution of *cis*-$PtCl(NH_3)_2(OH_2)^+$ (2.38×10^{-3} M) was prepared by allowing *cis*-

TABLE 4. Spectrophotometrically determined rate constants for the reaction of *cis*-$PtCl(NH_3)_2(OH_2)^+$ with glycine (pH = 7.4; I = 1.0 M $NaClO_4$)

T (°C)	[K]	[glycine] (M)	$10^4 \times k'_{obs}$ (s^{-1})	$10^4 \times k_{gly}$[a] ($M^{-1}\ s^{-1}$)	$10^4 \times k_{gly}$ (calc.)[b] ($M^{-1}\ s^{-1}$)	$10^5 \times k_{2,OH}$[c] (s^{-1})	$10^5 \times k_{2,OH}$[d] (s^{-1})
25.0	[298.2]				2.75		
35.2	[308.4]	0.1	1.12 ± 0.21	6.69	6.57	4.71	4.37
			1.15 ± 0.31				
		0.05	0.827 ± 0.07				
			0.804 ± 0.13				
		0.01	0.528 ± 0.03				
			0.536 ± 0.04				
40.2	[313.4]	0.1	1.96 ± 0.46	9.48	9.85	9.71	7.54
			1.90 ± 0.33				
		0.05	1.50 ± 0.32				
			1.34 ± 0.43				
		0.01	1.04 ± 0.29				
			1.12 ± 0.20				
45.3	[318.5]	0.1	3.39 ± 0.55	15.0	14.7	17.7	12.1
			3.18 ± 0.55				
		0.05	2.50 ± 0.54				
			2.48 ± 0.39				
		0.01	2.00 ± 0.37				
			1.88 ± 0.49				

[a]Estimated from the slope of the k'_{obs} vs. [glycine] plots (Fig. 1). [b]Calculated from the activation parameters: $\Delta H^{\ddagger} = 62.7 \pm 5$ kJ mol^{-1}, $\Delta S^{\ddagger} = -103 \pm 10$ J K^{-1} mol^{-1}. [c]Estimated from the intercept of the k'_{obs} vs. [glycine] plots (Fig. 1). [d]Extrapolated from the $k_{2,OH}$ data obtained independently and more reliably from the hydrolysis of *cis*-$PtCl(OH)(NH_3)_2$ in 0.1 M NaOH [3].

$PtCl_2(NH_3)_2$ (25 mg) to hydrolyse in 1.0 M $NaClO_4$ (24.8 ml) plus 0.1 M $HClO_4$ (10.2 ml) at 50 °C for 3–4 h, and left overnight at room temperature. A 0.1 M NaHmal solution (I = 1.0 M) was prepared from equal volumes of 0.2 M malonic acid and 0.2 M of NaOH, both in 0.9 M $NaClO_4$. Solutions of 0.05 M and 0.01 M NaHmal (I = 1.0 M) were similarly prepared. A 2.0 ml sample of the *cis*-$PtCl(NH_3)_2(OH_2)^+$ solution was placed in one of the separate test tubes attached to the arms of a glass Y-shaped rapid mixing device and a 1.0 ml sample of the NaHmal solution was placed in the other. The arms of the mixing device were then immersed in a temperature controlled water bath and a dry 1.00 cm spectrophotometer cell was mounted in the vertical position. On inversion, the solutions were rapidly mixed, the cell was placed in the temperature controlled cell compartment of the spectrophotometer, the glass Y was removed, and the repeat fixed-wavelength mode of the spectrophotometer was activated.

The two consecutive reactions were monitored separately. The first reaction (k_{obs}, s^{-1}, Table 5) was followed at 245 nm for (10–20) × 5 min cycles (depending on the temperature) and the second reaction was followed at 290 nm. Only the second reaction (k_{cy}, independent of [$Hmal^-$], Table 5) developed an isosbestic point (at 267 nm).

Results and discussion

Figure 2 shows a complete hydrolysis reaction profile for *cis*-$PtCl_2(NH_3)_2$ under a variety of pH conditions. Rate and equilibrium constants have been established [2–4, 6] for all these interconversions apart from eqn. (2)

$$cis\text{-}PtCl(OH)(NH_3)_2 + H_2O \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} cis\text{-}Pt(OH)(NH_3)_2(OH_2)^+ + Cl^- \quad (2)$$

with $K_3 = k_3[k_{-3}]^{-1}$, which is similar to eqn. (3)

$$cis\text{-}PtCl_2(NH_3)_2 + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} cis\text{-}PtCl(NH_3)_2(OH_2)^+ + Cl^- \quad (3)$$

with $K_1 = k_1[k_{-1}]^{-1}$ [2], except that Cl^- has been substituted for OH^-.

Hydrolysis of cis-PtCl(OH)(NH$_3$)$_2$

The kinetics of both the forward and the reverse reaction (k_3 and k_{-3}, respectively) corresponding to eqn. (2), have been measured at pH = 7.4, using *cis*-$PtCl(NH_3)_2(OH_2)^+$ [2, 3] as a source of the starting material. At pH = 7.4 both *cis*-$PtCl(NH_3)_2(OH_2)^+$ and *cis*-$PtCl(OH)(NH_3)_2$ are available for hydrolysis (pK_{a3} = 6.85 [6]) but only *cis*-$PtCl(OH)(NH_3)_2$ reacts

TABLE 5. Spectrophotometrically determined rate constants for the reaction of *cis*-$PtCl(NH_3)_2(OH_2)^+$ with sodium hydrogen malonate (pH = 4.3, I = 1.0 M $NaClO_4$)

T (°C)	[K]	[NaHmal][a] (mM)	$10^4 \times k_{obs}$ (s^{-1})	$10^3 \times k_{Hmal}$[b] (M^{-1} s^{-1})	$10^3 \times k_{Hmal}$ (calc.)[c] (M^{-1} s^{-1})	$10^4 \times k_{cy}$ (s^{-1})	$10^4 \times k_{cy}$ (calc.)[d] (s^{-1})
37.3	[310.5]	33	1.54 ± 0.20	3.19	3.37	0.408 ± 0.058	0.444
		17	0.544 ± 0.017			0.482 ± 0.065	
		3.3	0.222 ± 0.02			0.441 ± 0.053	
40.2	[313.4]	33	1.69 ± 0.11	4.82	4.49	0.620 ± 0.11	0.616
		17	1.05 ± 0.09			0.603 ± 0.096	
		3.3	0.409 ± 0.029			0.604 ± 0.10	
45.2	[318.4]	33	2.50 ± 0.10	7.19	7.16	1.17 ± 0.11	1.07
						1.01 ± 0.11	
						0.955 ± 0.055	
		17	1.48 ± 0.03			1.01 ± 0.08	
		3.3	0.504 ± 0.052			1.10 ± 0.31	
50.0	[323.2]	33	3.84 ± 0.18	10.82	11.04	2.09 ± 0.45	1.79
						1.71 ± 0.34	
		17	2.10 ± 0.06			1.85 ± 0.5	
		3.3	0.599 ± 0.023			1.61 ± 0.065	

[a]Calculated from the weight of Na_2mal used. [b]Calculated from the slope of the k_{obs} vs. [$Hmal^-$] plots (Fig. 3). [c]Calculated from the activation parameters: k_{Hmal} (25 °C) = 9.9×10^{-4} M^{-1} s^{-1}, $\Delta H^{\ddagger} = 74.8 \pm 6$ kJ mol^{-1}, $\Delta S^{\ddagger} = -52 \pm 12$ J K^{-1} mol^{-1}. [d]Calculated from the activation parameters: k_{cy} (25.0 °C) = 1.03×10^{-5} s^{-1}, $\Delta H^{\ddagger} = 88.9 \pm 4$ kJ mol^{-1}, $\Delta S^{\ddagger} = -42 \pm 8$ J K^{-1} mol^{-1}.

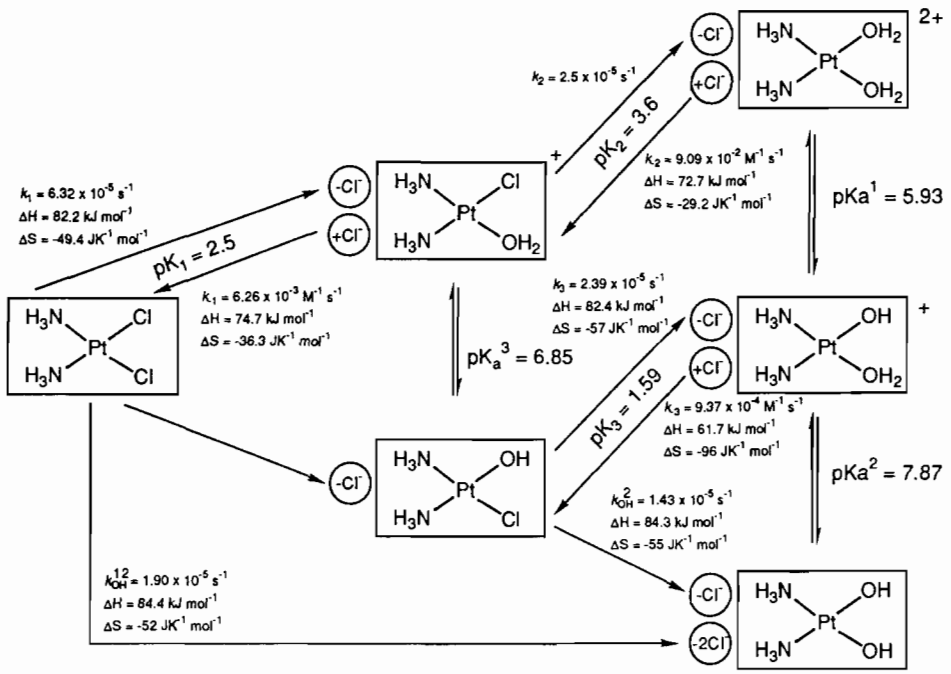


Fig. 2. A general hydrolysis scheme for *cis*-$PtCl_2(NH_3)_2$ at 25.0 °C.

to any extent [2–4]. As reaction (2) proceeds, the equilibrium shifts to provide more *cis*-$PtCl(OH)(NH_3)_2$ and eventually *cis*-$Pt(OH)(NH_3)_2(OH_2)^+$ is the major product. Constant pH is maintained by the manual addition of NaOH solution. Some *cis*-$Pt(OH)_2(NH_3)_2$ will also form ($pK_{a2} = 7.87$) but *cis*-$Pt(NH_3)_2(OH_2)_2^{2+}$ is most unlikely ($pK_{a1} = 5.93$). This forward reaction is characterised by spectrophotometric isosbestic points at 271 and 323 nm and first-order rate constants (k_3) were calculated from absorbance versus time data collected at 300, 282 and 255 nm (Table 1). At the end of the reaction, the solution was made 0.2 M in chloride ion, by the addition of solid NaCl, and,

as the reverse reaction proceeded, constant pH was maintained by the manual addition of $HClO_4$ solution.

Initially, an isosbestic point at 271 nm was observed, but this shifted to 282 nm at later stages of the reaction indicating that the reverse of eqn. (3) was taking place via the *cis*-$PtCl(NH_3)_2(OH_2)^+$ present at pH = 7.4. Consequently, absorbance versus time data were monitored at 282 nm and these were used to calculate pseudo-first-order rate constants (k_{obs}) which, in turn, gave values for $k_{-3} = 5\ k_{obs}$ ($M^{-1}\ s^{-1}$) (Table 1).

A knowledge of k_3 and k_{-3} now permits the calculation of K_3 ($= k_3/k_{-3}$) over a range of temperatures (Table 2) giving K_3 (25 °C) $= 2.55 \times 10^{-2}$ for eqn. (2) (X = OH^-) compared with K_1 (25°) $= 1.01 \times 10^{-2}$ for eqn. (3) (X = Cl^-).

The major kinetic difference between the reactions shown in eqns. (2) and (3) appears in the pre-exponential function of the Arrhenius expression for the reverse (anation) reaction.

The rate of chloride anation of *cis*-$Pt(OH)NH_3)_2(OH_2)^+$ was also measured spectrophotometrically by addition of chloride ion to *cis*-$Pt(OH)_2(NH_3)_2$ solutions adjusted with $HClO_4$ to pH = 7.8. Under these conditions, coordinated H_2O is replaced by chloride ion and the final product at high [Cl^-] is a dihydroxo, dichloro mixture. As the reaction proceeds an isosbestic point at 271 nm develops which shifts to 282 nm, and constant pH was maintained by manual addition of $HClO_4$ solution. Pseudo-first-order rate constants (k_{obs}, Table 3) were calculated from absorbance versus time data collected at 282 nm and values of k_{-3} ($M^{-1}\ s^{-1}$) were calculated from the expression, $k_{-3} = k_{obs}[Cl^-]^{-1}$.

Close agreement between k_{-3} (pH = 7.4) and k_{-3} (pH = 7.8) is not to be expected ($9.4 \times 10^{-4}\ M^{-1}\ s^{-1}$ versus $12.7 \times 10^{-4}\ M^{-1}\ s^{-1}$ at 25 °C) considering that the *cis*-$Pt(OH)(NH_3)_2(OH_2)^+$ concentration is pH dependent and the product distribution will be difficult, but the discrepancy between the activation parameters (Table 6) is not readily explicable.

Anation of cis-$PtCl(NH_3)_2(OH_2)^+$ by hydrogen malonate

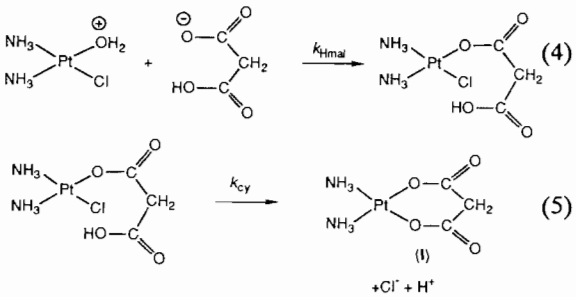
Mixing solutions of NaHmal and *cis*-$PtCl(NH_3)_2(OH_2)^+$ at pH = 4.3 (the 'natural' buffered pH of NaHmal) results in a time dependent spectrophotometric change (absorbance increase) in the 235–260 nm region. No distinct isosbestic points were observed, and the absorbance in the 270–330 nm region was hardly changed. This initial reaction was [$Hmal^-$] dependent and was monitored at 245 nm to give pseudo-first-order rate constants (k_{obs}, s^{-1}).

Plots of k_{obs} versus [$Hmal^-$] were linear (Fig. 3) but there was no systematic temperature dependent trend for the intercept. We would expect that k_o in eqn. (1) for this reaction (corresponding to k_2 in eqn. (3a)), would be ~0 as the background chloride release (eqn. (3a)) has an unfavourable equilibrium

$$cis\text{-}PtCl(NH_3)_2(OH_2)^+ \underset{k_{-2}}{\overset{k}{\rightleftharpoons}} cis\text{-}Pt(NH_3)_2(OH_2)_2^{2+} + Cl^- \quad (3a)$$

constant (Fig. 2) [3]. There will however, be a small contribution to the overall reaction from this path but the data are not sufficiently accurate to produce sensible temperature dependent intercepts. The more accurately determined slopes represent $k_{Nu} = k_{Hmal}$ ($M^{-1}\ s^{-1}$) in eqn. (1) and these data are presented in Table 5.

As the reaction proceeds, a second, [$Hmal^-$] independent phase develops, with a sharp isosbestic point at 267 nm and a decrease in absorbance of the '(chloro)(aqua)' chromophore in the 270–320 nm region. These consecutive reactions are best described by eqns. (4) and (5),



and k_{cy} data (Table 5) were obtained at 290 nm. Previous investigations [11] have shown that **I** can be synthesised in good yield from *cis*-$PtCl_2(NH_3)_2$ in aqueous DMF containing NaHmal.

Recent multinuclear NMR studies [12, 13] using *cis*-$Pt(NH_3)_2(OH_2)_2^{2+}$ and aminomalonate show that the complex analogous to **I** is rapidly formed, but subsequently isomerises to the N,O chelate. There was no evidence for a non-cyclised product in these studies [12, 13] indicating the importance of the coordinated chloro ligand in stabilizing such a species.

Reaction of cis-$PtCl(NH_3)_2(OH_2)^+$ with glycine

The pH of a solution containing *cis*-$PtCl(NH_3)_2(OH_2)^+$ and glycine was adjusted to 7.4 using 0.1 M NaOH. Very little subsequent pH adjustment was required as the reaction proceeded, and the spectrophotometric changes showed a well defined isosbestic point at 275 nm, to give a final, featureless UV spectrum with the absorbance increasing uniformly and continuously from 360 nm. The rate of change of the reaction was monitored

TABLE 6. Kinetic parameters for the reactions of some square planar Pt(II) complexes at 25.0 °C

Complex	Solvent	Chloride release			Reference
		$10^5 \times k$ (s^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})	
$PtCl_4^{2-}$	H_2O	3.9			10
$PtCl_3(NH_3)^-$	H_2O	5.6			10
cis-$PtCl_2(NH_3)_2$	1.0 M $HClO_4$	6.32	82.2	−49	2
	H_2O	2.5	82.3	−59	7
	0.1 M NaOH[a]	1.90	84.4	−52	3
trans-$PtCl_2(NH_3)_2$	0.01 M HNO_3	6.62	75.2	−84	8
	H_2O	9.8			10
cis-$PtCl(OH)(NH_3)_2$	pH = 7.4	2.39	82.4 ± 0.8	−57 ± 2	this work
$PtCl_2$(en)	0.01 M HNO_3	5.2	92	−18	8
	H_2O	3.4			9
$PtCl_2$(RRchxn)	0.1 M $HClO_4$	7.25	67.8	−97	5
	0.1 M NaOH[a]	3.81	76.2	−74	5
cis-$PtCl(NH_3)_2(OH_2)^+$	1.0 M $HClO_4$	2.5			3
$PtCl(en)(OH_2)^+$	H_2O	4.4			9

	Nucleophile	Ionic strength (M)	Anation pH	$10^4 \times k_{Nu}$ (M^{-1} s^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})	
cis-$PtCl(NH_3)_2(OH_2)^+$	Cl^-	1.0	<1	62.6	77.2	−36	2
	$Hmal^-$	1.0	4.3	9.90	74.8	−52	this work
	gly	1.0	7.4	2.75	62.7	−103	this work
cis-$Pt(OH)(NH_3)_2(OH_2)^+$	Cl^-	1.0	7.4	9.37	61.7 ± 3.2	−96 ± 6	this work
		var.	7.8	12.7	39.5 ± 3.1	−168 ± 6	this work
$PtCl(RR\text{-}chxn)(OH_2)^+$	Cl^-	0.3	<1	130	74.8	−30	5
$PtCl(en)(OH_2)^+$	Cl^-	0.318	≥1	154	73.1	−33	10
trans-$PtCl(NH_3)_2(OH_2)^+$	Cl^-	<0.1	2	4630	70.2	−25	8

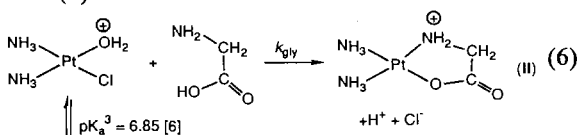
[a]Both chloro ligands lost.

at 304 (absorbance decrease) and 245 (absorbance increase) nm to give pseudo-first-order, k'_{obs} (s^{-1}) rate constants (Table 4). Plots of k'_{obs} versus [glycine] (pH = 7.4) were linear at the three temperatures used, and well separated, temperature dependent intercepts were obtained on the k'_{obs} axis (Fig. 2).

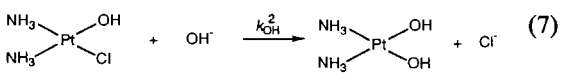
Thus

$$k'_{obs} = k_{2,OH} + k_{gly}[gly] \quad (1a)$$

corresponding to the two competing reactions (6) and (7)



(6)



(7)

The gradients of the k_{obs} versus [glycine] plots yield values for k_{gly} and the intercepts values for $k_{2,OH}$. A more precise determination of these latter rate constants has been obtained previously [3], and the agreement between the two sets of measurements is reasonably satisfactory (Table 4).

The reaction between *cis*-$PtCl_2(NH_3)_2$ and glycine at pH = 7.3 in aqueous solution has been investigated by Saudek and co-workers [14]. Using NMR spectroscopy as a probe, the products of the reaction were determined to be mainly **II**, with a trace of *cis*-$[Pt(NH_3)_2(NH_2CH_2CO_2H)_2]^{2+}$. The crystal structure of **II** has recently been reported [15].

Conclusions

We are now in a position to speculate on the possible fate of hydrolysis products from *cis*-$PtCl_2(NH_3)_2$ under physiological conditions as biological fluids contain ligands with both NH_2- (as amino acids) and carboxylate sites as potential donor groups. After hydrolysis of the *cis*-$PtCl_2(NH_3)_2$ in the cell plasma ($[Cl^-] \sim 4$ mM) at pH = 7.4, there is sufficient *cis*-$PtCl(NH_3)_2(OH_2)^+$ present at equi-

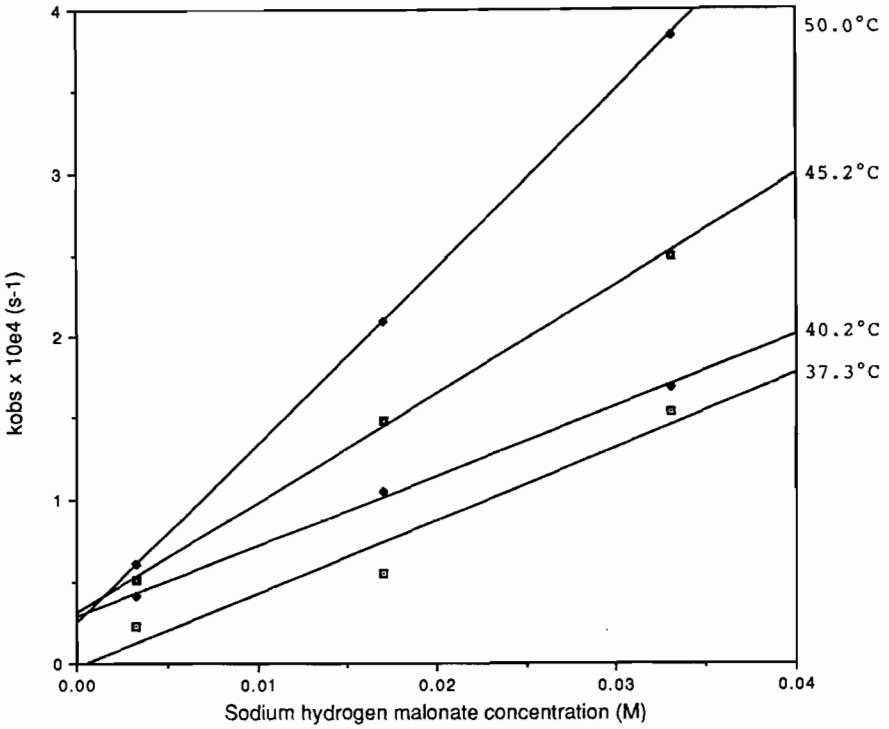


Fig. 3. Plots of k_{obs} vs. [hydrogen malonate] for the anation of *cis*-$PtCl(NH_3)_2(OH_2)^+$ at pH = 4.3 according to eqn. (4).

librium (~30%) [16] to provide a reasonable concentration of 'labile platinum', in contrast to the *cis*-$PtCl(OH)(NH_3)_2$, which must be classed as 'inert platinum', with respect to anation. Nevertheless, this 'inert platinum' can provide a mobile, but unreactive source of 'labile platinum' for, as the aqua ion is removed by anation, the hydroxo will shift to the aqua form to maintain the equilibrium concentration as determined by pK_{a3} (=6.85).

Of the anating ligands so far investigated, the anionic systems such as Cl^- or $Hmal^-$ are more effective nucleophiles than the zwitterionic glycine, with a relative order of reactivity (Table 6) of 23(Cl^-):4($Hmal^-$):1(gly), respectively. (Activation parameters are similar, so rate constant comparisons are valid.) This is perhaps fortunate, otherwise protein material would compete unfavourably with the 'labile platinum' for the binding sites in replicating DNA.

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