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The Hydrolysis Products of *cis*-Dichlorodiammineplatinum(II)
2. The Kinetics of Formation and Anation of the *cis*-Diamminedi(aqua)platinum(II) Cation

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Abstract

In basic solution ($[OH^-] \geqslant 0.01$ M), *cis*-$PtCl_2(NH_3)_2$ undergoes hydrolysis of both chloro ligands to give *cis*-$Pt(OH)_2(NH_3)_2$ as the stable end product. The rate of this reaction has been studied spectrophotometrically in aqueous NaOH solution (0.01–1.0 M) containing $NaClO_4$ (μ = 0.01–1.0 M) or NaCl (0.1–1.0 M) over a 35 °C temperature range. The reaction rate is almost independent of $[OH^-]$, ionic strength and added chloride ion and at 25 °C (μ = 0.1 M, $NaClO_4$), $k^{12}_{OH} = 1.90 \times 10^{-5}$ s^{-1}, $\Delta H^{\ddagger}$ = 84.4 kJ mol^{-1} and $\Delta S^{\ddagger} = -52$ J K^{-1} mol^{-1}. The rate of loss of the chloro ligand from *cis*-$PtCl(OH)(NH_3)_2$- (k^2_{OH}, s^{-1}) generated by basification of *cis*-$PtCl(NH_3)_2(OH_2)^+$ is similar to k^{12}_{OH}, with $k^2_{OH} = 1.43 \times 10^{-5}$ s^{-1}, $\Delta H^{\ddagger}$ = 84.3 and $\Delta S^{\ddagger} = -55$ at 25 °C (μ = 0.1 M). Acidification of *cis*-$Pt(OH)_2(NH_3)_2$ (generated from *cis*-$PtCl_2(NH_3)_2$ in 0.01 M NaOH) rapidly forms *cis*-$Pt(NH_3)_2(OH_2)^{2+}$ and this, in turn is slowly anated by the background chloride ion to give an equilibrium *cis*-$PtCl(NH_3)_2(OH_2)^+$, *cis*-$Pt(NH_3)_2(OH_2)_2{}^{2+}$ and Cl^- mixture. The equilibrium constant (K_2) has been measured spectrophotometrically to give at 25 °C (μ = 0.1 M, $NaClO_4$) $K_2 = 2.7 \times 10^{-4}$. Addition of controlled amounts of Cl^- to the *in situ* generated *cis*-$Pt(NH_3)_2(OH_2)_2{}^{2+}$ allows the spectrophotometric measurement of the rate of the anation reaction (k_2).

$$cis\text{-}Pt(NH_3)_2(OH_2)_2{}^{2+} + Cl^- \underset{k_2}{\overset{k_{-2}}{\rightleftharpoons}} cis\text{-}PtCl(NH_3)_2(OH_2)^+$$

At 25 °C, $k_{-2} = 9.09 \times 10^{-2}$ M^{-1} s^{-1}, $\Delta H^{\ddagger}$ = 72.7 kJ mol^{-1}, $\Delta S^{\ddagger} = -29.2$ J K^{-1} mol^{-1}. A knowledge of K_2 and k_{-2} allows the calculation of k_2 ($K_2 = k_2/k_{-2}$) and at 25 °C $k_2 = 2.5 \times 10^{-5}$ s^{-1}. It is difficult to measure k_2 directly by spectrophotometry as, at reasonable *cis*-$PtCl(NH_3)_2(OH_2)^+$ concentrations (>1 mM), the forward reaction proceeds only to the extent of <40% before equilibrium is established.

Introduction

We are currently studying the nature and rate of formation of the hydrolysis products of *cis*-$PtCl_2(NH_3)_2$ under a variety of pH conditions [1]. These hydrolysis products are particularly important as they are believed to be the reactive species responsible for the anti-tumor activity of the parent complex [2].

In acid media, the hydrolysis system can be described by eqns. (1) and (2) with corresponding rate and equilibrium constants $K_1 = k_1/k_{-1}$ and $K_2 = k_2/k_{-2}$.

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

$$cis\text{-}PtCl(NH_3)_2(OH_2)^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} cis\text{-}Pt(NH_3)_2(OH_2)_2{}^{2+} + Cl^- \quad (2)$$

However, as the pH is raised, each coordinated water molecule can participate in an aqua–hydroxo equilibrium and the introduction of an hydroxo ligand into the platinum(II) coordination sphere (by simple deprotonation) may greatly distort the lability patterns of the remaining ligands (chloro or aqua).

Thus kinetic or equilibrium studies in water are subject to some uncertainty as the nature of the oxo ligand (aqua or hydroxo) is uncertain.

In this paper we describe quantitative numerical data for the rate and equilibrium constants associated with eqn. (2). However, to gain entry into this region, we have also had to measure the *cis*-$PtCl_2(NH_3)_2$ hydrolysis regime in basic ($[OH^-] > 0.01$ M) solution.

Experimental

cis-$PtCl_2(NH_3)_2$ was purchased from Aldrich, Sigma or Strem and used without further purification. All other reagents were AR quality or the best Reagent Grade available.

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Base Hydrolysis Kinetics (k^{12}_{OH})

Standard NaOH solutions (0.1 M) were prepared from VOLUCON ampoules. More concentrated solutions were prepared from weighed amounts of NaOH. All solutions were adjusted to the appropriate ionic strength using weighed amounts of $NaClO_4 \cdot H_2O$. Sodium hydroxide solutions (3 ml) were allowed to reach thermal equilibrium in a 1.00 cm cell, placed in the temperature controlled (±0.1 °C) cell compartment of a Varian DMS 100 recording spectrophotometer. Small samples of *cis*-$PtCl_2(NH_3)_2$ were added and, after dissolution (usually within 1 min), repeat scan or repeat fixed wavelength (304, 260 and 236 nm) data collection modes were started. The reaction was monitored until no further change in absorbance with time was observed (6–8 X $t_{1/2}$) and first-order rate constants (Tables 1–3) were calculated from the absorbance versus time data using the normal equations [1].

Determination of k^{2}_{OH}

Samples of *cis*-$PtCl_2(NH_3)_2$ (50 mg) were allowed to hydrolyse in 0.01 M NaOH (45 ml) for 8 X $t_{1/2}$ (48 h at room temperature). Five ml of 0.2 M $HClO_4$ was added and the now acid solution ($[H^+]$ = 0.011 M) was allowed to anate at room temperature (48 h) to give approximately 98% *cis*-$PtCl(NH_3)_2(OH_2)^+$ and 2% *cis*-$Pt(NH_3)_2(OH_2)_2{}^{2+}$. Samples of this solution (2.0 ml) were made alkaline with 1.0 ml NaOH solution (0.3 M), both at the appropriate temperature. This generated *cis*-$PtCl(OH)(NH_3)_2$ (λ_{max} = 267 nm) in 0.1 M NaOH and the subsequent chloride release kinetics were monitored spectrophotometrically at 304, 255 and 250 nm. The resulting absorbance versus time data were used to obtain the k^{2}_{OH} data reported in Table 4.

cis-$Pt(NH_3)_2(OH_2)_2{}^{2+}$ plus Cl^- Kinetics (k_{-2})

Stock solutions of *cis*-$Pt(OH)_2(NH_3)_2$ (3.33 X 10^{-3} M) were prepared by allowing *cis*-$PtCl_2(NH_3)_2$ (50 mg) to hydrolyse for two days at room temperature in 0.01 M NaOH (50 ml). One ml samples of *cis*-$Pt(OH)_2(NH_3)_2$ and $NaCl/HClO_4$ (μ = 2.0 M) solutions were placed in separate test-tubes attached to the arms of a glass Y-shaped rapid mixing device

TABLE 1. Rate constants ($10^4 \times k^{12}_{OH}$, s^{-1})[a] for the hydrolysis of *cis*-$PtCl_2(NH_3)_2$ in NaOH solution

T		$[OH^-]$ variation, μ = 1.0 M ($NaClO_4$)					
°C	K	$[OH^-]$ = 0.01 M		$[OH^-]$ = 0.1 M		$[OH^-]$ = 1.0 M	
		obs.	calc.[b]	obs.	calc.[b]	obs.	calc.[b]
25.0	298.2		0.233		0.155		0.337
35.3	308.5	0.691	0.720	0.554	0.535	0.991	0.995
45.1	318.3	2.18	1.93	1.64	1.69	2.63	2.61
55.2	328.4	4.97	5.13	5.02	4.84	6.74	6.77
$\Delta H^{\ddagger}$ (kJ mol^{-1})		80.7 ± 7.3		90.3 ± 7.0		78.6 ± 0.6	
$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})		−63.1 ± 14		−34.3 ± 14		−66.9 ± 1.2	
		$[OH^-]$ variation, μ = 0.1 M ($NaClO_4$)				$[OH^-]$ variation, μ = 0.01 M	
		$[OH^-]$ = 0.01 M		$[OH^-]$ = 0.1 M		$[OH^-]$ = 0.01 M	
		obs.	calc.[b]	obs.	calc.[b]	obs.	calc.[b]
25.0	298.2		0.164		0.329		0.146
35.4	308.6	0.578	0.578	0.908	0.884	0.560	0.560
37.3	310.5	0.792	0.713	1.14	1.03	0.848	0.719
40.1	313.3	0.959	1.00	1.25	1.38	0.846	0.941
43.0	316.2	1.38	1.39	1.79	1.70	1.44	1.42
45.3	318.5	1.95	1.77	2.60	2.10	1.66	1.84
50.0	323.2	2.74	3.04	3.50	3.16	3.56	3.06
55.3	328.5	4.47	5.08	5.79	4.87	6.26	5.74
60.0	333.2	9.94	8.28	5.99	6.90	9.90	9.68
$\Delta H^{\ddagger}$ (kJ mol^{-1})		90.0 ± 4.1		69.5 ± 8.8		96.5 ± 4.8	
$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})		−34.6 ± 8.2		−97.5 ± 18		−13.8 ± 10	

[a] k^{12}_{OH} obs. data ±10%. [b] Calculated from the cited activation parameters.

TABLE 2. Rate constants ($10^4 \times k^{12}_{\mathrm{OH}}$, s^{-1})[a] for the hydrolysis of *cis*-$PtCl_2(NH_3)_2$ in NaOH solution

T		Ionic strength variation ($NaClO_4$), $[OH^-] = 0.01$ M					
°C	K	$\mu = 0.01$ M		$\mu = 0.1$ M		$\mu = 1.0$ M	
		obs.	calc.[b]	obs.	calc.	obs.	calc.
25.0	298.2		0.145		0.164		0.233
35.3	308.5	0.560	0.560	0.578(0.557)[c]	0.578	0.691(0.631)[c]	0.720
45.2	318.4	1.66	1.84	1.95(1.49)[c]	1.77	2.18(1.64)[c]	1.93
55.1	328.3	6.26	5.74	4.47(4.80)[c]	5.08	4.97(4.88)[c]	5.13
$\Delta H^{\ddagger}$ (kJ mol^{-1})		96.5 ± 4.8		90.0 ± 4.1		80.7 ± 7.3	
$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})		−13.8 ± 10		−34.6 ± 8.2		−63.1 ± 14	

		Ionic strength variation ($NaClO_4$), $[OH^-] = 0.1$ M			
		$\mu = 0.1$ M		$\mu = 1.0$ M	
		obs.	calc.[b]	obs.	calc.
25.0	298.2		0.329		0.155
35.4	308.6	0.908	0.884	0.554	0.535
45.2	318.4	2.60	2.10	1.64	1.69
55.3	328.5	5.79	4.87	5.02	4.84
$\Delta H^{\ddagger}$ (kJ mol^{-1})		69.5 ± 8.8		90.3 ± 7.0	
$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})		−97.5 ± 18		−34.3 ± 14	

[a] k^{12}_{OH} obs. data ±10%. [b] Calculated from the cited activation parameters. [c] NaCl used to control the ionic strength.

TABLE 3. Activation parameters for the base hydrolysis of *cis*-$PtCl_2(NH_3)_2$ at 298.2 K[a]

μ (M)	$10^4 N k^{12}_{\mathrm{OH}}$ (calc.) (s^{-1})	E_a (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
0.01	0.145	99.4 ± 4.8	97.0 ± 4.8	−12 ± 10
0.10[b]	0.190	86.8 ± 3.8	84.4 ± 3.8	−52 ± 8
1.0[c]	0.216	86.0 ± 5.1	83.5 ± 5.1	−54 ± 10
0.10[d]	0.143	86.8 ± 5.2	84.3 ± 5.2	−55 ± 10

[a] k^{12}_{OH} independent of $[OH^-]$ and $[Cl^-]$ in the range 0.01–1.0 M. [b] All data at $\mu = 0.1$ M ($NaClO_4$) combined. [c] All data at $\mu = 1.0$ M ($NaClO_4$) combined. [d] k^{2}_{OH} data (Table 4).

[3] and the arms were immersed in a temperature controlled water bath. 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 repeat fixed wavelength data were recorded. The wavelengths chosen to monitor the reaction (240 and 280 nm) correspond to the isosbestic points measured for k_{-1} [1]. Rate constants from reactions with half-lives as short as 42 s could be determined using this procedure. The $[Cl^-]_i$ chosen were always $\geqslant \times 10[Pt(NH_3)_2(OH_2)_2{}^{2+}]$ and pseudo-first-order rate constants (k_{obs}, s^{-1}) (Table 5) were calculated from the absorbance versus time data.

The second-order anation rate constants (k_{-2}, M^{-1} s^{-1} eqn. (2), Table 5) were calculated from the expression, $k_{-2} = k_{\mathrm{obs}}[Cl^-]_i^{-1}$ (see Fig. 3).

Determination of K_2 [eqn. (2)]

Stock solutions of *cis*-$Pt(OH)_2(NH_3)_2$ (3.2, 1.3 and 0.53 mM) were prepared by hydrolysis of the appropriate amount of *cis*-$PtCl_2(NH_3)_2$ in 0.01 M NaOH. Samples (2.0 ml) were acidified with $HClO_4$ (1.0 ml, 1.5 M) and the mixture allowed to anate at room temperature for 48 h and then at 25 °C for 3 h before recording the UV absorption spectrum.

A knowledge of the molar absorptivity coefficients of the diaqua and chloroaqua ions (see Table 7) at any wavelength (see Fig. 2) allowed the calculation of K_2:

TABLE 4. Spectrophotometrically determined rate constants (k^2_{OH}) for the reaction cis-Pt(Cl)(OH)$(NH_3)_2$ + OH^- → cis-$Pt(OH)_2(NH_3)_2$ + Cl^- (μ = 0.1 M)[a]

T (°C)	$10^5 \times k^2_{OH}$ (s^{-1})	calc.
	obs.	calc.
25.0		1.43
35.2	4.27 ± 0.01	4.37
39.8	7.54 ± 0.12	7.06
45.1	11.3 ± 0.02	12.1
50.1	20.7 ± 0.81	19.7
54.9	30.3 ± 0.08	31.0
60.2	52.0 ± 0.06	50.6

[a] See 'Experimental' for the method of generating cis-PtCl(OH)$(NH_3)_2$. [b] Calculated from the activation parameters: E_a = 86.8 ± 5.2 kJ mol^{-1}, log PZ = 10.3595, $\Delta S^{\ddagger} = -55 \pm 10$ J K^{-1} mol^{-1}.

Results and Discussion

Base Hydrolysis and the Lability of cis-PtCl(OH)(NH₃)₂

Previous workers [4–7] have shown that cis-$PtCl_2(NH_3)_2$ hydrolyses in basic conditions give cis-$Pt(OH)_2(NH_3)_2$ and two chloride ions. There has been considerable speculation as to how this reaction proceeds. Grinberg and Korableva [6] favour a two step process [eqns. (3) and (4)] with reaction (3) being rate determining.

$$\text{cis-PtCl}_2(\text{NH}_3)_2 + \text{OH}^- \xrightarrow{k^1_{OH}} \text{cis-PtCl(OH)(NH}_3)_2 + \text{Cl}^- \quad (3)$$

$$\text{cis-PtCl(OH)(NH}_3)_2 + \text{OH} \xrightarrow{k^2_{OH}} \text{cis-Pt(OH)}_2(\text{NH}_3)_2 + \text{Cl}^- \quad (4)$$

Prior to this investigation the currently available rate constants for the overall process, k^{12}_{OH} (25 °C) of 2.35 X 10^{-5} s^{-1} [7] or 1.3 X 10^{-5} s^{-1} [6] compared with a value for k^2_{OH} (25 °C) of 2.2 X 10^{-5} s^{-1} [4] suggest that the two steps have similar rates.

The rate of the second step is of considerable importance as, if this were rapid, as suggested by Grinberg and Korableva [6], there would be an efficient chloride release path for the second chloride ion in the pH regime where cis-PtCl(OH)$(NH_3)_2$ could be generated, e.g. in blood plasma (pH = 7.4) (Scheme 1).

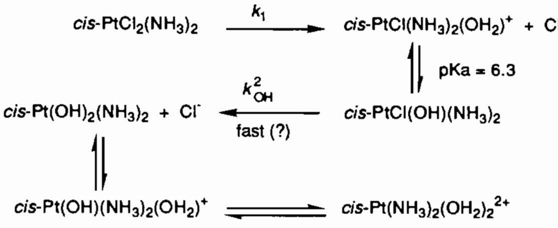
When cis-$PtCl_2(NH_3)_2$ is dissolved in aqueous NaOH solutions there is a smooth spectrophotometric change with an isosbestic point at 276 nm (Fig. 1).

Close inspection shows that this point drifts slightly as the hydrolysis proceeds, supporting the proposal that the reaction is biphasic [eqns. (3) and (4)] but

TABLE 5. Spectrophotometrically measured[a] chloride anation rate constants (k_{-2}) for reaction (2) at μ = 1.0 M ($HClO_4$)[b, c]

$[Cl^-]_i$[d] (M)	10.5 °C (283.7 K)		14.9 °C (288.1 K)		19.7 °C (293.0 K)		25.0 °C (298.2 K)		30.0 °C (303.2 K)	
	$10^3 \times k_{obs}$ (s^{-1})	$10^2 \times k_{-2}$[e] (M^{-1} s^{-1})	$10^3 \times k_{obs}$ (s^{-1})	$10^2 \times k_{-2}$[e] (M^{-1} s^{-1})	$10^3 \times k_{obs}$ (s^{-1})	$10^2 \times k_{-2}$[e] (M^{-1} s^{-1})	$10^3 \times k_{obs}$ (s^{-1})	$10^2 \times k_{-2}$[e] (M^{-1} s^{-1})	$10^3 \times k_{obs}$ (s^{-1})	$10^3 \times k_{-2}$[e] (M^{-1} s^{-1})
0.04	0.871 ± 0.13	2.18 ± 0.32	1.37 ± 0.13	3.43 ± 0.33	2.28 ± 0.29	5.70 ± 0.72	3.57 ± 0.45	8.93 ± 1.15	6.14 ± 0.46	15.4 ± 1.15
0.05	1.07 ± 0.08	2.14 ± 0.16	1.45 ± 0.31	2.90 ± 0.62	2.78 ± 0.22	5.56 ± 0.44	4.50 ± 0.30	9.00 ± 0.60	7.17 ± 1.02	14.3 ± 2.04
0.06	1.11 ± 0.16	1.85 ± 0.23	1.82 ± 0.21	3.03 ± 0.35	3.28 ± 0.56	5.47 ± 0.94	6.34 ± 0.22	10.6 ± 0.37	8.46 ± 1.19	14.1 ± 1.99
0.08	1.43 ± 0.16	1.79 ± 0.20	2.50 ± 0.64	3.13 ± 0.80	4.73 ± 0.91	5.91 ± 1.14	7.33 ± 0.91	9.16 ± 1.14	12.1 ± 1.78	15.1 ± 2.22
0.10	2.08 ± 0.34	2.08 ± 0.34	3.13 ± 0.72	3.13 ± 0.72	6.19 ± 0.89	6.19 ± 0.89	9.34 ± 1.32	9.34 ± 1.32	13.9 ± 0.89	13.9 ± 0.89
0.12	2.35 ± 0.24	1.96 ± 0.20	4.17 ± 0.64	3.48 ± 0.54	7.29 ± 0.88	6.08 ± 0.74	10.4 ± 1.38	8.68 ± 1.15	16.6 ± 0.59	13.9 ± 0.50
	Mean	2.00 ± 0.16	Mean	3.18 ± 0.23	Mean	5.82 ± 0.29	Mean	9.28 ± 0.70	Mean	14.4 ± 0.60
	Calc.[f]	2.03	Calc.[f]	3.25	Calc.[f]	5.40	Calc.[f]	9.09	Calc.[f]	14.3

[a] Reaction monitored at 240 and 280 nm as these are isosbestic points for k_{-1}. [b] $[Pt(NH_3)_2(OH_2)_2{}^{2+}]$ ~ 1.6 × 10^{-3} M. [c] Ionic strength adjusted to 1.0 M using NaCl and $HClO_4$. [d] $[Cl^-]$ initial ⩾ 10[Pt] initial. [e] $k_{-2} = k_{obs}$ $[Cl^-]^{-1}$. [f] Calc. from the activation parameters: E_a = 72.7₅ ± 1.2 kJ mol^{-1}, $\Delta S^{\ddagger} = -29.2 \pm 2.4$ J K^{-1} mol^{-1} and log PZ = 11.7034, i.e. $k_{-2} = 5.051 \times 10^{11} \exp(-72.75/RT)$.



Scheme 1.

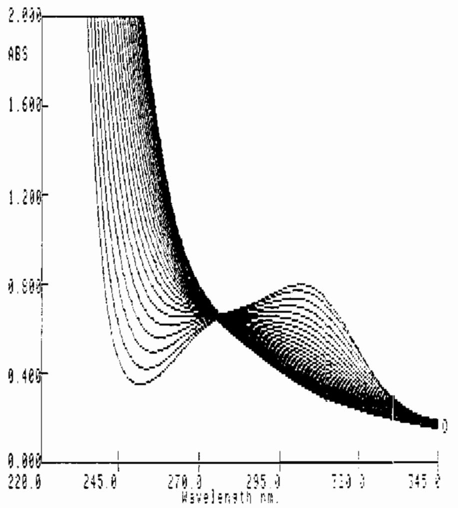
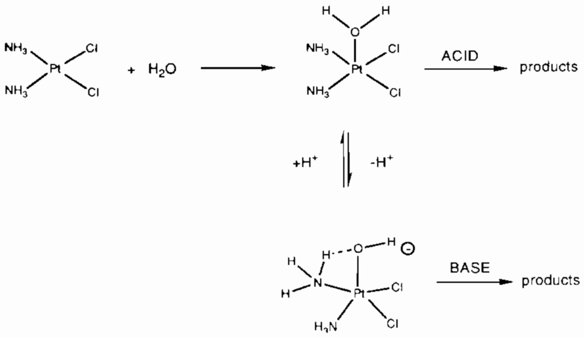


Fig. 1. Spectrophotometric scans for the hydrolysis of *cis*-PtCl$_2$(NH$_3$)$_2$ in base (0.01 M NaOH) at 60.0 °C (2 min intervals). The absorbance at 300 nm decreases with time and the rather broad cross-over area is centered at 276 nm.

with similar rate constants. (If this is the case, then reactions (3) and (4) will have similar isosbestic points.) Analysis of the absorbance versus time data at three different wavelengths gives the same first-order rate constant (k^{12}_{OH}) with no evidence for consecutive reactions and this is in agreement with the results from the chloride release titration data of Grinberg and Korableva [6]. The overall hydrolysis rate constant (k^{12}_{OH}) is almost independent of [OH$^-$], ionic strength and background chloride ion concentration in the range 0.01–1.0 M NaOH (Tables 1–3). We have also been able to measure k^2_{OH} directly using *cis*-PtCl(OH)(NH$_3$)$_2$ generated from the chloroaqua. The reaction proceeds with a sharp isosbestic point (274 nm), close to, but not identical with, the isosbestic point generated in the hydrolysis of the dichloro. The values of k^2_{OH} (Table 4) are slightly smaller than those for k^{12}_{OH} but the activation parameters are very similar (Table 3). Although k^{12}_{OH} and k^2_{OH} are comparable in magnitude (Table 6), the reaction pathway depicted in Scheme 1 is still a potential hydrolysis route in regions of high pH as k^{12}_{OH} (and, by inference, k^2_{OH}) are not inhibited by background chloride ion.

The fact that the rate of base hydrolysis is independent of the hydroxide ion concentration and rather similar to the rate of acid hydrolysis is quite normal for Pt(II) complexes [8]. Indeed, the close agreement between the activation parameters for acid [1] and base hydrolysis (see Scheme 3) suggests that water is the attacking nucleophile in both situations. The observation that base hydrolysis is about three times slower than acid hydrolysis at all temperatures could be due to stabilisation of the transition state according to Scheme 2.



Scheme 2.

Certainly, in this series of complexes, a coordinated OH$^-$ group does not induce any marked labilisation into the Pt(II) coordination sphere. It should also be noted that neither the rate nor the extent of the hydrolysis in basic solution is suppressed by added chloride ions (Table 2).

TABLE 6. Relative chloride release labilities for *cis*-PtCl$_2$(NH$_3$)$_2$ and its hydrolysis products[a]

Complex	Chloride release rate constant (25 °C)	Rate ratio relative to *cis*-PtCl$_2$(NH$_3$)$_2$ in base
cis-PtCl$_2$(NH$_3$)$_2$	$k^{12}_{OH} = 2.41 \times 10^{-5}$ s^{-1}	1.0
cis-PtCl$_2$(NH$_3$)$_2$	$k_1 = 6.32 \times 10^{-5}$ s^{-1}	2.6
cis-PtCl(NH$_3$)$_2$(OH$_2$)$^+$	$k_2 = 2.5 \times 10^{-5}$ s^{-1}[b]	1.03
cis-PtCl(OH)(NH$_3$)$_2$	$k^2_{OH} = 1.43 \times 10^{-5}$ s^{-1}	0.6

[a] Such a comparison should be treated with caution as these rate ratios will only be valid if the activation parameters associated with the chloride release rate constants are similar. If they are not, the relative order of reactivity could easily change with temperature. [b] The extent to which this complex will aquate is highly chloride ion dependent (see Table 9).

Chloride Ion Anation of cis-$Pt(NH_3)_2OH_2)_2^{2+}$

The most important feature of the base hydrolysis of *cis*-$PtCl_2(NH_3)_2$ is its irreversibility to give *cis*-$Pt(OH)_2(NH_3)_2$ and two free chloride ions. We have utilised this observation to gain entry into the reaction chemistry of the *cis*-$Pt(NH_3)_2(OH_2)_2^{2+}$ ion, as the diaqua is rapidly generated upon acidification of *cis*-$Pt(OH)_2(NH_3)_2$. There is then a subsequent slow (complete in hours at room temperature) anation of the diaqua by the background chloride ion to give an equilibrium chloraqua plus diaqua plus chloride ion mixture, the composition of which can be determined spectrophotometrically to give K_2 [eqn. (2)]. The UV absorption spectra of *cis*-$PtCl_2(NH_3)_2$, *cis*-$PtCl(NH_3)_2(OH_2)^+$ and *cis*-$Pt(NH_3)_2(OH_2)_2^{2+}$ in 1 M $HClO_4$ are shown in Fig. 2.

The molar absorptivity coefficients have been determined from (i) weighed samples of the dichloro (ii) using chromatographic techniques to isolate *cis*-$PtCl(NH_3)_2(OH_2)^+$ [1] and (iii) base hydrolysis followed by acidification to generate *cis*-$Pt(NH_3)_2(OH_2)_2^{2+}$. There are also internal constraints on the system by the position and intensity of the isosbestic points generated in the hydrolysis or anation reactions. The data represented by Fig. 2 are given in Table 7.

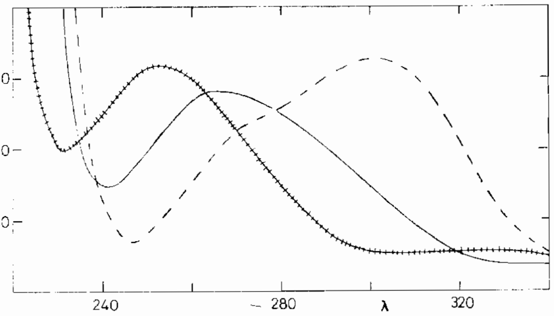


Fig. 2. UV absorption spectra (340–220 nm) of *cis*-$PtCl_2(NH_3)_2$ (– – –), *cis*-$PtCl(NH_3)_2OH_2)^+$ (——) and *cis*-$Pt(NH_3)_2(OH)_2)_2^{2+}$ (++++) in $HClO_4$ solution.

In the spectrophotometric analysis of the chloro-aqua/diaqua/chloride ion equilibrium mixture generated above

$$A_e\lambda = \epsilon_{DA}\lambda C_{DA} + \epsilon_{CA}\lambda C_{CA} \tag{5}$$

where $A_e\lambda$ is the absorbance of the equilibrium mixture at any wavelength (λ); $\epsilon_{DA}\lambda$ and $\epsilon_{CA}\lambda$ are the extinction coefficients of the diaqua and chloro-aqua at that wavelength and C_{DA} and C_{CA} are the equilibrium concentrations of the diaqua and chloro-aqua, respectively. Equation (5) coupled with eqns. (6) and (7)

$$[Pt]_t = C_{DA} + C_{CA} \tag{6}$$

$$[Cl^-]_e = 2[Pt]_t - C_{CA} \tag{7}$$

are sufficient to calculate K_2 at any wavelength

$$K_2 = \frac{C_{DA} \times [Cl^-]_e}{C_{CA}} \tag{8}$$

as $A_e\lambda$, $\epsilon_{DA}\lambda$, $\epsilon_{CA}\lambda$ and $[Pt]_t$ are known. This method becomes quite unreliable in regions where $\epsilon_{DA}\lambda \sim \epsilon_{CA}\lambda$, i.e. close to isosbestic points.

It is also possible to calculate K_2 from pairs of $A_e\lambda$ data where $\epsilon_{CA}\lambda 1 = \epsilon_{CA}\lambda 2$ (Fig. 2). Under these conditions, the simultaneous equations resulting from (5) give

$$C_{DA} = \frac{A_e\lambda 1 - A_e\lambda 2}{\epsilon_{DA}\lambda 1 - \epsilon_{DA}\lambda 2} \tag{9}$$

and this procedure is less reliant on the instrument zero. Both methods have been used to give average values for C_{DA} at equilibrium and K_2 then follows from eqns. (6)–(8).

Previous estimates [11, 12] of K_2 in water are quite similar to our data reported in Table 8.

A value of 2.7×10^{-4} ($\mu = 1.0$ M) for the equilibrium constant associated with reaction (2) puts considerable constraint on the extent to which this reaction will proceed. The data in Table 9 show

TABLE 7. Molar absorptivity coefficients for *cis*-$PtCl_2(NH_3)_2$ and its hydrolysis products in aqueous solution at room temperature[a]

Complex	Solvent	λ_{max} (ϵ, $M^{-1} cm^{-1}$)	λ_{min} (ϵ, $M^{-1} cm^{-1}$)
cis-$PtCl_2(NH_3)_2$[b, c]	0.9% NaCl	301(131)	246(27)
cis-$PtCl(NH_3)_2(OH_2)^+$	1 M $HClO_4$	263(113)	242(59)
cis-$Pt(NH_3)_2(OH_2)_2^{2+}$	1 M $HClO_4$	253(128)	231(79)
	pH = 2[d]	~255(~145)	
cis-$PtCl(OH)(NH_3)_2$	0.1 M NaOH	267(150)	257(146)
cis-$Pt(OH)_2(NH_3)_2$	0.1 M NaOH[e]	320(27), 304(34), 295(45), 270(100), 245(490)	

[a] Isosbestic points associated with eqn. (1) are 279(100) and 240(60) nm and those associated with eqn. (2) are 267(111) and 235(84) nm at μ = 1.0 M (NaCl, $HClO_4$). [b] Ref. 9. [c] There is a marked shoulder at about 280 nm in the UV spectrum of this complex (see Fig. 2). [d] Extrapolated from Fig. 1 of ref. 10. [e] This complex has only a continuous absorbance, increasing with wavelength, in the 350–230 nm region (see Fig. 1).

TABLE 8. Estimates of k_2, k_{-2} and K_2 the rate and equilibrium constants associated with the second step in the acid hydrolysis of *cis*-$PtCl_2(OH_2)_2$ [eqn. (2)] at 25.0 °C

Solvent	k_{-2} ($M^{-1}s^{-1}$)	k_2 (s^{-1})	K_2	Reference
H_2O		3.3×10^{-5}	4×10^{-5}	7
H_2O			1.11×10^{-4}	8
H_2O		2.5×10^{-5}		13
1.0 M $HClO_4$	9.1×10^{-2}	2.5×10^{-5}	2.7×10^{-4}	this research
?	8.9×10^{-2}			14

TABLE 9. Equilibrium concentrations (mmol l^{-1}) of *cis*-$PtCl(NH_3)_2(OH_2)^+$, *cis*-$Pt(NH_3)_2(OH_2)_2{}^{2+}$ and Cl^- in aqueous $HClO_4$ at 25.0 °C using $K_2 = 2.7 \times 10^{-4}$

Initial concentration (mM)	Equilibrium concentrations (mM)		
cis-$PtCl(NH_3)_2(OH_2)^+$	*cis*-$PtCl(NH_3)_2(OH_2)^+$		*cis*-$Pt(NH_3)_2(OH_2)_2{}^{2+}$ = Cl^-
100	95	(95)[a]	5
10	8.5	(85)	1.5
1	0.6	(60)	0.4
0.1	0.022	(22)	0.078
0.01	0.0003	(3)	0.0097

[a] Numbers in parentheses are the % *cis*-$PtCl(NH_3)_2(OH_2)^+$ 'undissociated' at equilibrium.

that a 1×10^{-3} M *cis*-$PtCl(NH_3)_2(OH_2)^+$ solution will aquate to the extent of about 40% completion before equilibrium is reached. In the presence of additional chloride ion the extent of reaction will be even smaller. We have been unable to make accurate spectrophotometric measurements of k_2, despite having chloride ion free solutions of *cis*-$PtCl(NH_3)_2(OH_2)^+$ available [1], because of the small spectrophotometric changes associated with the incomplete chloride release.

In principle, the spectrophotometric changes with time, or the free chloride ion concentration with time data for acidified *cis*-$Pt(OH)_2(NH_3)_2 + 2Cl^-$ solutions could be analysed using second-order reaction equations for the $A + B \rightarrow C$ system with $B_0 = 2A_0$ [15], to give the anation rate constant (k_{-2}). We have preferred to determine k_{-2} under pseudo-first-order conditions, by deliberate addition of additional chloride ion ($>10 \times [Pt]_i$) on acidification of *cis*-$Pt(OH)_2(NH_3)_2$. Under such circumstances, the anation reaction proceeds in two steps and *cis*-$PtCl_2(NH_3)_2$ is the final product at high chloride ion concentration. (The reverse of eqns. (2) and (1)). The rate of the first step [k_{-2} in eqn. (2)] has been determined spectrophotometrically by monitoring the reaction at the isosbestic points for the second step (240 and 280 nm) [1]. Values for k_{obs} (s^{-1}) (Table 5) were calculated from the absorbance versus time data at these wavelengths and plots of k_{obs} versus $[Cl^-]$ were linear (Fig. 3). Table 5 also presents values of k_{-2} ($M^{-1}s^{-1}$) calculated from the expression $k_{-2} = k_{obs}[Cl^-]^{-1}$.

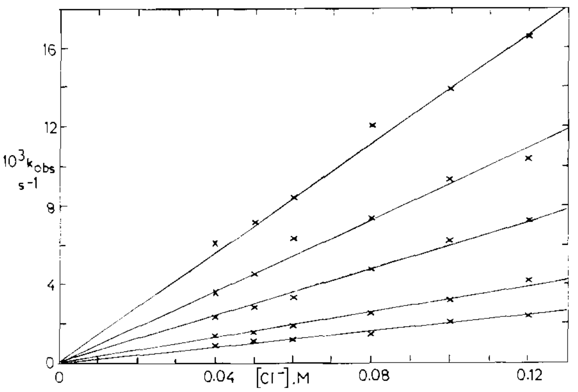


Fig. 3. Plots of k_{obs} vs. $[Cl^-]$ for the anation reaction *cis*-$Pt(NH_3)_2(OH_2)_2{}^{2+} + Cl^- \xrightarrow{k_{-2}}$ *cis*-$PtCl(NH_3)_2(OH_2)^+$. Reading upwards at 10.5, 14.9, 19.7, 25.0 and 30.0 °C.

Recently, values of $k_{-2} = 8.9 \times 10^{-2}$ $M^{-1}s^{-1}$ and $k_{-1} = 6.7 \times 10^{-3}$ $M^{-1}s^{-1}$ have been reported at 25 °C but with unspecified ionic strength [14]. The agreement with our data, $k_{-2} = 9.1 \times 10^{-2}$ $M^{-1}s^{-1}$, $k_{-1} = 6.3 \times 10^{-3}$ $M^{-1}s^{-1}$ [1] at $\mu = 1.0$ M and 25 °C is most satisfactory.

A knowledge of K_2 and k_{-2} at the same temperature and ionic strength conditions allows an estimate of k_2, the rate constant associated with the forward reaction for eqn. (2). Substitution in the expression $K_2 = k_2/k_{-2}$ gives a value of $k_2 = 2.5 \times 10^{-5}$ s^{-1} at 25 °C (μ = 1.0 M). This value is of the same order as previous estimates in water (Table 8) and is not much different from the value of k_1 (= 6.3×10^{-5} s^{-1}, 25.0 °C), the rate constant associated with the forward reaction for eqn. (1) [1].

While for Co(III) and Cr(III) complexes, the variation of acid hydrolysis rate with charge is quite marked, this is not the case for Pt(II) complexes (Table 10). This lack of variation between rate constant and charge is used as evidence for an associative mechanism operating in the aquation of Pt(II) systems [18], (Scheme 2).

TABLE 10. Rate data for the loss of the first chloro ligand in the acid hydrolysis of some chloroammineplatinum(II) complexes at 25 °C

Complex	Solvent	$10^5 \times k$ (s^{-1})	Reference
$PtCl_4^{2-}$	H_2O	3.9	16
$PtCl_3(NH_3)^{-}$ [a]	H_2O	5.6	16
cis-$PtCl_2(NH_3)_2$	H_2O	2.5	16
	1 M $HClO_4$	6.3	1
trans-$PtCl_2(NH_3)_2$	H_2O	9.8	16
$PtCl(NH_3)_3^+$	H_2O	2.6	16
cis-$PtCl(NH_3)_2(OH_2)^+$	1 M $HClO_4$	2.5	this research
$PtCl_2(en)$	H_2O	3.4	17
$PtCl(en)(OH_2)^+$	H_2O	4.4	17

[a] Replacement of *cis* chloro ligand.

Conclusions

The rate and equilibrium data for the *cis*-$PtCl_2(NH_3)_2$ system and its hydrolysis products are summarised in Scheme 3.

Perhaps the most important feature to note is that although k_1 and k_2 have similar values, the acid hydrolysis of *cis*-$PtCl_2(NH_3)_2$ is unlikely to proceed beyond *cis*-$PtCl(NH_3)_2(OH_2)^+$. The small value of K_2 and the background released chloride ion means that appreciable concentrations of *cis*-$Pt(NH_3)_2(OH_2)_2^{2+}$ cannot be formed. Even in the absence of any background chloride ion, the hydrolysis of 1×10^{-3} M *cis*-$PtCl(NH_3)_2(OH_2)^+$ will only proceed to about 40% completion (Table 9).

In base, the situation is quite different due to the absence of any competing equilibrium, complete chloride release occurs even in the presence of excess chloride ion, and *cis*-$Pt(OH)_2(NH_3)_2$ is the stable end product.

Unfortunately we are still not in a position to pinpoint the exact hydrolysis product responsible for the anti-tumor activity of *cis*-$PtCl_2(NH_3)_2$ in the biological regime. The situation is complicated by the fact that the most abundant hydrolysis product may not be the most reactive, and 'substrate milking' of the equilibrium systems shown in Scheme 3 could drive the reaction to completion via an hydrolysis product present in very small concentrations.

Blood plasma has a pH of about 7.4 [19] and under these conditions base hydrolysis (via k_{OH}^{12}) becomes a real possibility. The equilibrium end product composition would then be about 50% *cis*-$Pt(OH)_2(NH_3)_2$ and 50% *cis*-$PtCl(OH)(NH_3)_2$. Indeed, currently accepted mechanisms postulating high chloride ion concentration in the external cell environment preventing hydrolysis of *cis*-$PtCl_2(NH_3)_2$ may be invalid if the pH is high enough for base hydrolysis to occur.

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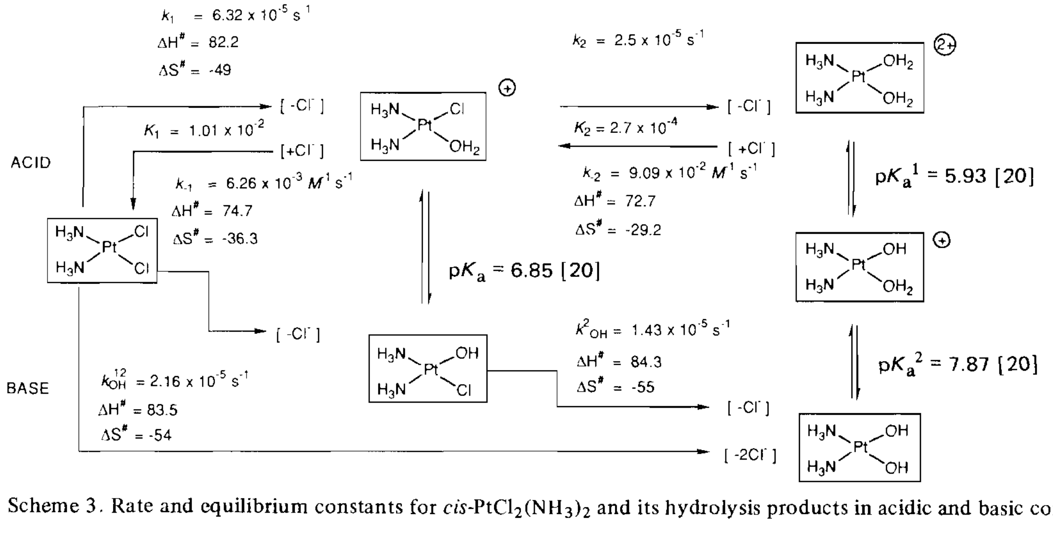

Scheme 3. Rate and equilibrium constants for *cis*-$PtCl_2(NH_3)_2$ and its hydrolysis products in acidic and basic conditions (25 °C).

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