Kinetics of the Displacement of Cyclobutane-1,1-dicarboxylate from Diammine(cyclobutane-1,1-dicarboxylato)platinum(II) in Aqueous Solution

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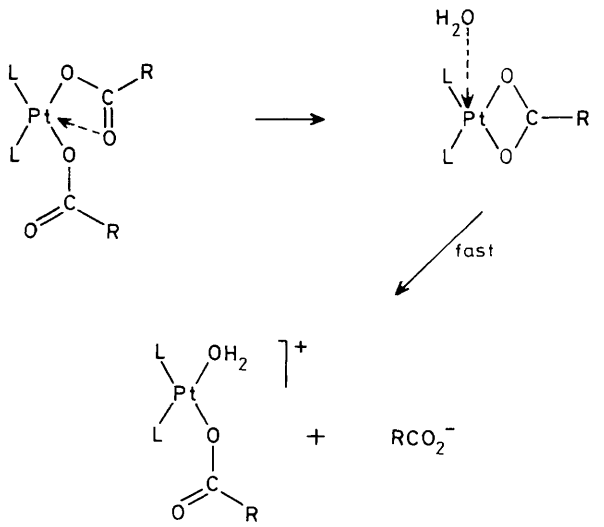
The displacement of 1,1-cyclobutanedicarboxylate ($cbdca^{2-}$) from $[Pt(NH_3)_2(cbdca)]$ has been studied in aqueous solution. In the presence of acid the process resembles the successive displacement of two monodentate carboxylates. The first (ring-opening) stage follows the rate law $k_{obs.} = (k_0 + k_1K_0[H^+])(1 + K_0[H^+])^{-1}$, $k_0 = 8 \times 10^{-5}$ s^{-1}, $K_0 = 0.6$ dm^3 mol^{-1}, $k_1 = 8.0 \times 10^{-4}$ s^{-1} at 25 °C, while the second follows the simple relationship $k_{obs.} = k[H^+]$, $k = 1.61 \times 10^{-4}$ dm^3 mol^{-1} s^{-1} at 25 °C. In the absence of acid and other nucleophiles the complex is inert and in the presence of chloride the displacement of ligand follows a first-order dependence on $[Cl^-]$, $k_{obs.} = k_{Cl}[Cl^-]$. At 80 °C, $k_{Cl} = 1.32 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}. The chelate differs from the bis-monodentate carboxylate species in the great importance of the reverse, ring-closing process, which can be prevented in the presence of acid.

The complex $[Pt(NH_3)_2(cbdca)]$ (cbdca = cyclobutane-1,1-dicarboxylate) is now being used under the name 'Carboplatin' as an effective second-generation platinum-based anti-tumour drug.[1] It is a member of a series of active species of general form $[Pt(am)_2\{R(CO_2)_2\}]$, where am is ammonia or a primary amine [occasionally $(am)_2$ is a chelating diamine] and $R(CO_2)_2^{2-}$ is a chelating dicarboxylate.[2] As part of our interest in the mechanism of the displacement of oxygen donor ligands from four-co-ordinate planar d^8 metal complexes[3,4] we have studied the displacement of monodentate carboxylates from platinum(II) and gold(III). In a recent paper we showed that the absence of a detectable chloride-dependent pathway in the displacement of the first chloroacetate from *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ in aqueous solution was not due to a low nucleophilic discrimination on the part of the substrate but rather to an unusually large contribution from the nucleophile-independent pathway.[5] This effect was not found in the displacement of carboxylates from $[Pt(dien)(RCO_2)]^+$ (dien = 1,5-diamino-3-azapentane) where the value of the nucleophile-independent rate constant, k_1, agrees with that predicted from the known nucleophilicity of water.[5,6] It was suggested that the second carboxylate had a remarkable *cis* labilising effect that facilitated displacement of the first by an internal substitution of the sort that has been used to explain the high *cis* labilising effects of the carboxylate and other oxy-anion ligands in the reactions of chromium(III) complexes[7] (see Scheme 1).

A test of this suggested mechanism would be to make the two carboxylate donors part of a bidentate ligand. An examination of Dreiding models reveals that the trigonal-bipyramidal transition state with three oxygens attached is not feasible geometrically when the two carboxylates form part of a chelate. In particular, the carboxylate oxygen that is to displace the other carboxylate points away from the site that it must occupy in the trigonal plane (Figure 1). When the two carboxylates are not linked there is no constraint. If internal displacement of one carboxylate by the other was indeed the cause of the phenomenon, the ring opening of the chelate would not show this anomalously high solvent-independent pathway.

A study of the displacement of the cyclobutane-1,1-dicarboxylate anion ($cbdca^{2-}$) from $[Pt(NH_3)_2(cbdca)]$ offers an opportunity to make this test with a substance whose reactions both *in vitro* and *in vivo* are of interest in a wide range of contexts. In addition, the cyclobutane group offers a satisfactory compromise between minimum complication and maximum information in the use of ^1H n.m.r. to investigate the course of the reactions.



Scheme 1.

In this paper we report the kinetics of ring opening and ligand displacement in the presence of acid and/or other nucleophiles, especially chloride.

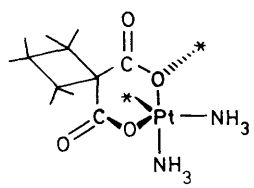


Figure 1. The inability of the third oxygen (acting as entering group) to take up the required position in the trigonal-bipyramidal transition state (indicated by asterisks)

Experimental

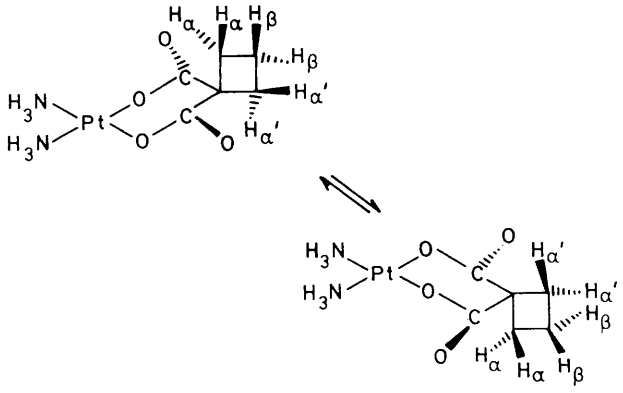
Compounds and Reagents.—Diammine(cyclobutane-1,1-dicarboxylato)platinum(II) was obtained from Johnson Matthey plc. All other reagents were AnalaR grade or of comparable quality.

Kinetics.—Before any kinetic analysis was carried out the nature of the chemical change was established using the ^1H n.m.r. spectra of similar solutions (but with higher concentrations of complex) in D_2O. The reactions for the kinetic studies were initiated by mixing a solution of all the reagents, except the complex, previously brought to the reaction temperature, with an equal volume of a freshly prepared solution of the complex in water that had also been brought to the reaction temperature. Preliminary studies of the reaction with Cl^- in the absence of acid were carried out by placing equal volumes of the same solution of the complex in the sample and reference cell and initiating the reaction by adding a weighed amount of solid NaCl to the solution only. Spectra were then scanned. The reactions were carried out in the thermostatted cell compartment of a Perkin-Elmer Lambda 5 u.v.–visible spectrophotometer and followed either by scanning the spectra over the range 220—380 nm or else, once the conditions had been established, by plotting the change of absorbance with time at a single wavelength.

Infrared spectra were measured with a Perkin-Elmer 683 spectrometer and ^1H n.m.r. spectra were measured using a Varian XL 200 spectrometer.

Results

General Features of the Reactions in the Presence of Acid.—The ^1H n.m.r. spectrum of a freshly prepared solution of $[Pt(NH_3)_2(cbdca)]$ in D_2O at 25 °C contains two signals at δ 2.81 (triplet, 4 H, $^3J_{H-H}$ = 8 Hz) and δ 1.81 (quintet, 2 H, $^3J_{H-H}$ = 8 Hz) assigned to the α and β protons respectively. The ammine protons exchange with solvent before the first measurements can be made. It is probable that the simplicity of the spectrum arises from a rapid inversion at oxygen (see Scheme 2).



Scheme 2.

The spectrum of this solution is completely unchanged even after 60 d at 25 °C. When the solution of the complex (10^{-3} mol dm^{-3}) is acidified with $HClO_4$ or DCl (0.2 mol dm^{-3}), there is an immediate upfield shift of the signal for the α and, to a lesser extent, the β protons, that is followed by a slow change characterised by a decrease in the signals at δ 2.88 ($^3J_{H-H}$ = 8 Hz), growth and subsequent disappearance of a triplet at δ 2.46 ($^3J_{H-H}$ = 8 Hz), and growth of a triplet at δ 2.56 ($^3J_{H-H}$ = 8 Hz). The multiplets due to the β protons are superimposed but can be resolved. The quintet centred on δ 1.88 and assigned to the substrate decreases, while that assigned to the intermediate, δ 1.95, is finally replaced by that of the free acid at δ 2.0. In spite of the fact that the symmetry of the ligand is reduced in the open-ring intermediate, there is no evidence in the n.m.r. spectrum to reflect this, the α protons still appearing as a triplet of sharp peaks (4 H) and the β protons as a quintet (2 H). Although it is probable that this is only a consequence of the similarity of the chemical shifts of the protons on either side of the C_4 ring, we have not been able to rule out a facile exchange between the free and co-ordinated oxygens of the carboxylate group.

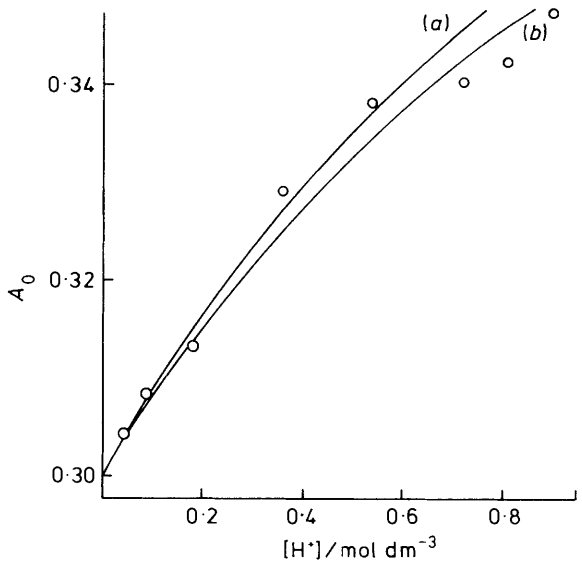


Figure 2. Effect of perchloric acid on the absorbance at 248 nm, A_0, of a solution of $[Pt(NH_3)_2(cbdca)]$. Curves are calculated for (*a*) K_0 = 0.6 dm^3 mol^{-1}, ε_0 = 628 cm^2 $mmol^{-1}$, ε_H = 942 cm^2 $mmol^{-1}$ and (*b*) K_0 = 1.2 dm^3 mol^{-1}, ε_0 = 628 cm^2 $mmol^{-1}$, ε_H = 813 cm^2 $mmol^{-1}$. [Complex] = 4.777 × 10^{-4} mol dm^{-3}, path length 1 cm

Although the final product depends upon the acid used {in the presence of sufficient chloride, yellow crystals of *cis*-$[Pt(NH_3)_2Cl_2]$ separate before the end of the reaction, while in $HClO_4$ solution, *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ is shown to be the final product}, the ^1H n.m.r. changes remain the same and the similarity of the spectra assigned to the intermediates suggests either that the protons in *cis*-$[Pt(NH_3)_2(H_2O)(Hcbdca)]^+$ and *cis*-$[Pt(NH_3)_2Cl(Hcbdca)]$ have similar chemical shifts or that the entry of chloride into the initially formed aqua complex is unimportant.

From the rates at which the signals change in dilute perchloric acid it appears that the rate constants for the two steps of the reaction do not differ by a factor of much more than three, with the ring-opening stage being the faster of the two.

Kinetics of the Reactions in Dilute Perchloric Acid.—The u.v. spectrum of a solution of $[Pt(NH_3)_2(cbdca)]$ in water (*ca.* 5 × 10^{-4} mol dm^{-3}) remains constant for many weeks at 25 °C. If a solution is acidified there is an immediate change in absorbance followed by a slow decrease over the whole range of wavelength scanned. The initial absorbance values, A_0, obtained by extrapolating the measured value back to the time of mixing are plotted against $[H^+]$ in Figure 2. The subsequent changes lead eventually to a spectrum that is identical to that of a freshly prepared solution of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ obtained by the reaction of *cis*-$[Pt(NH_3)_2Cl_2]$ with two molar equivalents of $AgClO_4$ and the removal of AgCl by ultrafiltration. Furthermore the rate constants for the reaction of the

Table 1. Observed first-order rate constants for the displacement of cyclobutane-1,1-dicarboxylate from $[Pt(NH_3)_2(cbdca)]$ in aqueous perchloric acid at 25.0 °C

$[H^+]$/mol dm^{-3}	$10^4k_{obs.}(1)$/s^{-1}	$10^5k_{obs.}(2)$/s^{-1}
0.045	0.97 ± 0.03	0.503 ± 0.003
0.091	1.32 ± 0.05	1.09 ± 0.01
0.100	1.12 + 0.02	1.27 ± 0.01
0.100	1.23 ± 0.05	1.26 ± 0.02
0.182	1.39 ± 0.05	2.45 ± 0.05
0.300	1.66 ± 0.05	4.2 ± 0.1
0.300	2.00 ± 0.04	4.24 ± 0.05
0.364	2.00 ± 0.05	5.2 ± 0.1
0.500	2.39 ± 0.09	7.7 ± 0.02
0.500	2.38 ± 0.07	7.3 ± 0.2
0.500	2.60 ± 0.06	7.5 ± 0.1
0.546	2.52 ± 0.07	8.1 ± 0.2
0.650	2.65 ± 0.07	9.7 ± 0.2
0.700	2.80 ± 0.02	9.8 ± 0.5
0.700	2.76 ± 0.09	9.6 ± 0.4
0.727	3.07 ± 0.09	11.5 ± 0.4
0.800	3.2 ± 0.1	12.2 ± 0.4
0.800	3.0 ± 0.1	12.1 ± 0.4
0.818	3.22 ± 0.09	12.0 ± 0.3
0.818	3.20 ± 0.2	12.8 ± 0.9
0.900	3.5 ± 0.1	14.1 ± 0.4
0.900	3.2 ± 0.1	14.6 ± 0.5
0.900	3.15 ± 0.1	14.8 ± 0.6
1.000	3.8 ± 0.0	15.6 ± 0.6
1.000	3.4 ± 0.2	16 ± 1

solution at the end of the acid-catalysed solvolysis with excess chloride to give *cis*-$[Pt(NH_3)_2Cl_2]$ in two stages, (8.9 ± 0.4) × 10^{-2} dm^3 mol^{-1} s^{-1} and (6.7 ± 0.2) × 10^{-3} dm^3 mol^{-1} s^{-1} at 25 °C, are identical to those of the analogous reactions of an authentic sample of the *cis*-diaqua complex.

The spectral changes associated with the displacement of the dicarboxylate ligand lack crossing points to facilitate the analysis of the biphasic reaction and so the kinetics were followed at 248 nm where the absorbance change is reasonably large. The change of absorbance with time was consistent with two consecutive first-order reactions and was analysed by a five-parameter Gauss–Newton algorithm to obtain the best fit to the expression (1), where A_t is the absorbance at time t, and A_0, A_i, A_∞, $k_{obs.}(1)$, and $k_{obs.}(2)$ the absorbances of the starting materials, the intermediate and the product, respectively, and the two required rate constants, are the five optimised parameters. These rate constants are collected in Table 1.

$$A_t = A_\infty + (A_0 - A_\infty)\exp[-k_{obs.}(1)t] + k_{obs.}(1)(A_i - A_\infty)\{\exp[-k_{obs.}(2)t] - \exp[-k_{obs.}(1)t]\}[k_{obs.}(1) - k_{obs.}(2)]^{-1} \quad (1)$$

Reaction with Chloride and other Nucleophiles in the Absence of Added Acid.—The 200 MHz ^{1}H n.m.r. spectrum of a solution of $[Pt(NH_3)_2(cbdca)]$ in D_2O containing NaCl is identical to that measured in the absence of chloride and changes only slowly. After several days at 25 °C a second triplet appears at δ 2.28 and slowly grows with time at the expense of the one at δ 2.81. The quintet at δ 1.81 does not appear to change significantly and no other signal appears. The triplet appears at the same chemical shift as the carboxylate (H_2cbdca + $NaHCO_3$ in D_2O). In the presence of NaI and NaNCS similar changes take place, but more rapidly.

The u.v. absorption spectrum of a solution of $[Pt(NH_3)_2$-(cbdca)] (10^{-3} mol dm^{-3}) in 2.0 mol dm^{-3} NaCl in water at 80 °C changes smoothly, and with an isosbestic point at 275 nm, to one that is identical to that of a solution of *cis*-$[Pt(NH_3)_2Cl_2]$ of the same concentration. The absorbance change follows a first-order rate law and, in this region of the spectrum, there is no indication of any significant formation of intermediate species. The shorter wavelength part of the spectrum (190—250 nm) also changes markedly and, in order to assist the search for a faster initial stage, equal volumes of a fresh aqueous solution of $[Pt(NH_3)_2(cbdca)]$ were placed in both the reference and sample cells, which were a matched pair. The difference spectrum, measured directly afterwards was a line with $A = 0$. Addition of solid NaCl to make a solution of *ca.* 0.15 mol dm^{-3} in Cl^- led fairly rapidly (at 70 °C) to noticeable spectral changes in the range 190—300 nm characterised by small increases peaking at 214 and 240 nm. These changes were much too small to allow any reliable analyses and soon afterwards a 'negative' peak develops around 232.5 nm. (The product absorbs less than the reagent in this region.) After a short induction period this change developed into a first-order process. This corresponds to the changes observed at longer wavelength and in the ^{1}H n.m.r. spectrum. It was convenient to examine the kinetics of the major change at this wavelength, using water in the reference cell. The decrease in absorbance at 232.5 nm followed a first-order rate law and was analysed in the usual way. The rate constants are collected in Table 2.

Table 2. Rate constants for the displacement of cyclobutane-1,1-dicarboxylate from $[Pt(NH_3)_2(cbdca)]$ (3.2×10^{-4} mol dm^{-3}) in aqueous chloride solution at 80.0 °C*

$[Cl^-]$/mol dm^{-3}	0.200	0.400	0.600	0.800	1.000
$10^5k_{obs.}$/s^{-1}	2.89	5.31	8.19	10.5	13.5

* $k_{obs.} = (1.32 \times 10^{-4})[Cl^-]$/s^{-1}.

Table 3. Observed rate constants for the two steps [(1) and (2)] of the displacement of cyclobutane-1,1-dicarboxylic acid from $[Pt(NH_3)_2$-(cbdca)], in the presence of acid and chloride at 25.0 °C in aqueous solution

	$[Cl^-]$	$10^4k_{obs.}(1)$/s^{-1}	$10^4k_{obs.}(2)$/s^{-1}
$[H^+] = 0.0909$	0	1.2	0.11
	0.227	0.995	0.39
	0.455	0.932	0.49
$[H^+] = 0.227$	0	1.6	0.34
	0.091	1.83	0.81
	0.227	1.82	1.05
$[H^+] = 0.455$	0	2.3	0.70
	0.091	2.92	1.62
	0.227	3.22	1.89

Attempts to follow the reactions with other nucleophiles (Br^-, I^-, NCS^-, thiourea) were unsuccessful because it was not possible to associate the spectrophotometric changes with any specific reaction. The spectra at the end of the reactions were different from those of authentic samples of *cis*-$[Pt(NH_3)_2X_2]$, prepared by adding 2 equivalents of NaX to freshly prepared solutions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and the multiple-scan spectra were not even consistent with *cis*-$[Pt(NH_3)_2X_2]$ being formed as an intermediate species which is then subsequently consumed. It is possible that NH_3 is displaced before $cbdca^{2-}$ is released but the preliminary n.m.r. experiments do not confirm this. The rate of change of absorbance does seem to depend upon the concentration and the nature of X^-.

Reactions with Chloride in the Presence of Acid.—The spectroscopic changes indicate that the presence of chloride affects the products of the reaction. Analysis of the spectrophotometric data is complicated by the distribution of the

intermediates and products between species that do and do not contain chlorine and, as the acid concentration is increased, the rate at which carboxylate is displaced becomes comparable to that of the displacement of water by chloride. The simple spectrophotometric techniques do not allow a proper analysis of such systems. However, spectrophotometric analysis at 300 nm, where the absorbance change is dominated by the formation of chloro species, indicates two consecutive first-order processes, the rate constants of which, obtained in the way described above, are collected in Table 3.

Discussion

In aqueous solution, in the absence of added nucleophile or acid, the lability of $[Pt(NH_3)_2(cbdca)]$ is very low indeed. After 60 d at 25 °C there is no detectable change in the ^1H n.m.r. spectrum and, assuming that 5% reaction would be detected through the appearance of a new triplet due to the α-protons of the cbdca in any intermediate or product, a rate constant, $k_{obs.} < 1 \times 10^{-8}$ s^{-1} is indicated. Roberts and co-workers,[8] measuring the rate of appearance of $cbdca^{2-}$ in phosphate buffer at 37 °C by h.p.l.c., report a rate constant of 7.2×10^{-7} s^{-1}. The difference in the two rate constants is much too great to be accounted for by the difference of temperature and it is possible that the phosphate buffer offers some assistance to the displacement of $cbdca^{2-}$. They also report that Carboplatin can bind to DNA retaining the dicarboxylate (labelled with ^{14}C), presumably bound as a monodentate ligand, and that the subsequent displacement of $cbdca^{2-}$ ($k_{obs.} = 1.3 \times 10^{-5}$ s^{-1} at 37 °C) corresponds to chelation (cross linking) by the DNA.

In any study of the displacement of a bidentate ligand, especially when comparison is to be made with an analogous bis-monodentate system, account must be taken of the reversibility of the ring opening process. By studying the solvolysis in the presence of a non-co-ordinating acid, the analysis can be simplified because protonation of the free end of the carboxylate will reduce, or even prevent, the reverse ring-closing reaction and the ligand displacement then becomes a two-stage consecutive process of the type studied in the solvolysis of the bis-carboxylato complex, *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$.[5] At the same time the acid-catalysed displacement of the carboxylate also becomes important.

The two stages of the acid-catalysed displacement of H_2cbdca can be treated as two consecutive first-order processes because the concentration of acid is always much larger than that of the complex and so remains constant throughout the reaction. At low acid concentrations the rate constant for the first step, $k_{obs.}(1)$, is some 10 times greater than that for the second, $k_{obs.}(2)$, but at higher concentrations the ratio becomes smaller (2—3). The assignment of the larger rate constant to the ring opening and the smaller to the loss of the ligand is confirmed by the study of the changing ^1H n.m.r. spectrum. A plot of $k_{obs.}(1)$ against $[H^+]$ has a very significant intercept at $[H^+] = 0$ (Figure 3). The scatter of the data prevents a precise analysis of the dependence on $[H^+]$ and a linear relationship of the type found for the *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ complex,[5] $k_{obs.}(1) = k_0(1) + k_1(1)[H^+]$, cannot be ruled out. However, there appears to be a tendency towards curvature.

A reaction scheme of the type shown in Scheme 3 would lead to the relationship (2), provided that $[H^+]$ is large enough for $K_0[H^+] \gg 1$ and the ring-closing process, k_{-0}, is not important.

$$k_{obs.}(1) = (k_0 + k_1K_0[H^+])(1 + K_0[H^+])^{-1} \quad (2)$$

The observation that the initial absorbance of a solution of $[Pt(NH_3)_2(cbcda)]$ is dependent upon the acid concentration is consistent with a pre-equilibrium protonation of this sort. The absorption at the time of mixing, A_0, will change with $[H^+]$ according to the relationship (3), where ε_0 and ε_H are the molar absorption coefficients of the unprotonated and protonated forms of the substrate and c is the total concentration of the

$$A_0 = (\varepsilon_0 c + \varepsilon_H c K_0[H^+])(1 + K_0[H^+])^{-1} \quad (3)$$

complex. The best fit of the experimental data in Figure 2 requires $K_0 = 1.2 \pm 0.3$ dm^3 mol^{-1}, $\varepsilon_0 = 628 \pm 25$ cm^2 mmol^{-1} and $\varepsilon_H = 813 \pm 28$ cm^2 mmol^{-1}. However, if this value for K_0 is fed into equation (2) with optimised values for k_0 and k_1 the curvature is too great, Figure 3. Although it might be possible to account for this by distributing the protonated species between a reactive and an unreactive species we believe that this simply reflects experimental error. By giving less weight to the A_0 *vs.* $[H^+]$ data at the highest acid concentrations, where the subsequent reaction causes most interference, a curve with $K_0 = 0.6$ dm^3 mol^{-1} is not unsatisfactory. Both curves are shown in Figures 2 and 3.

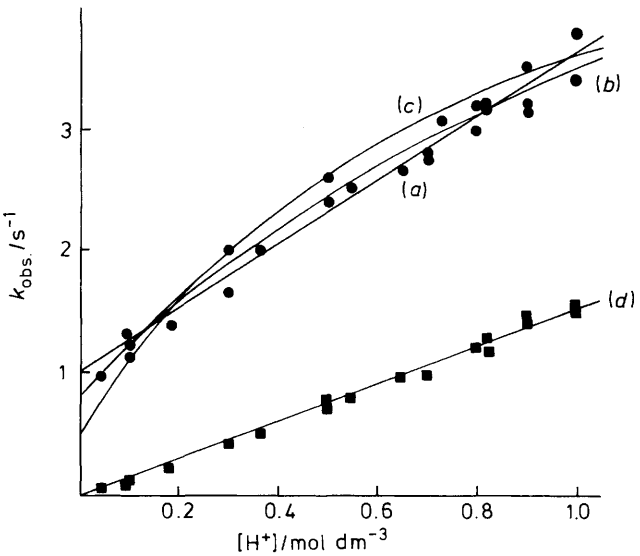
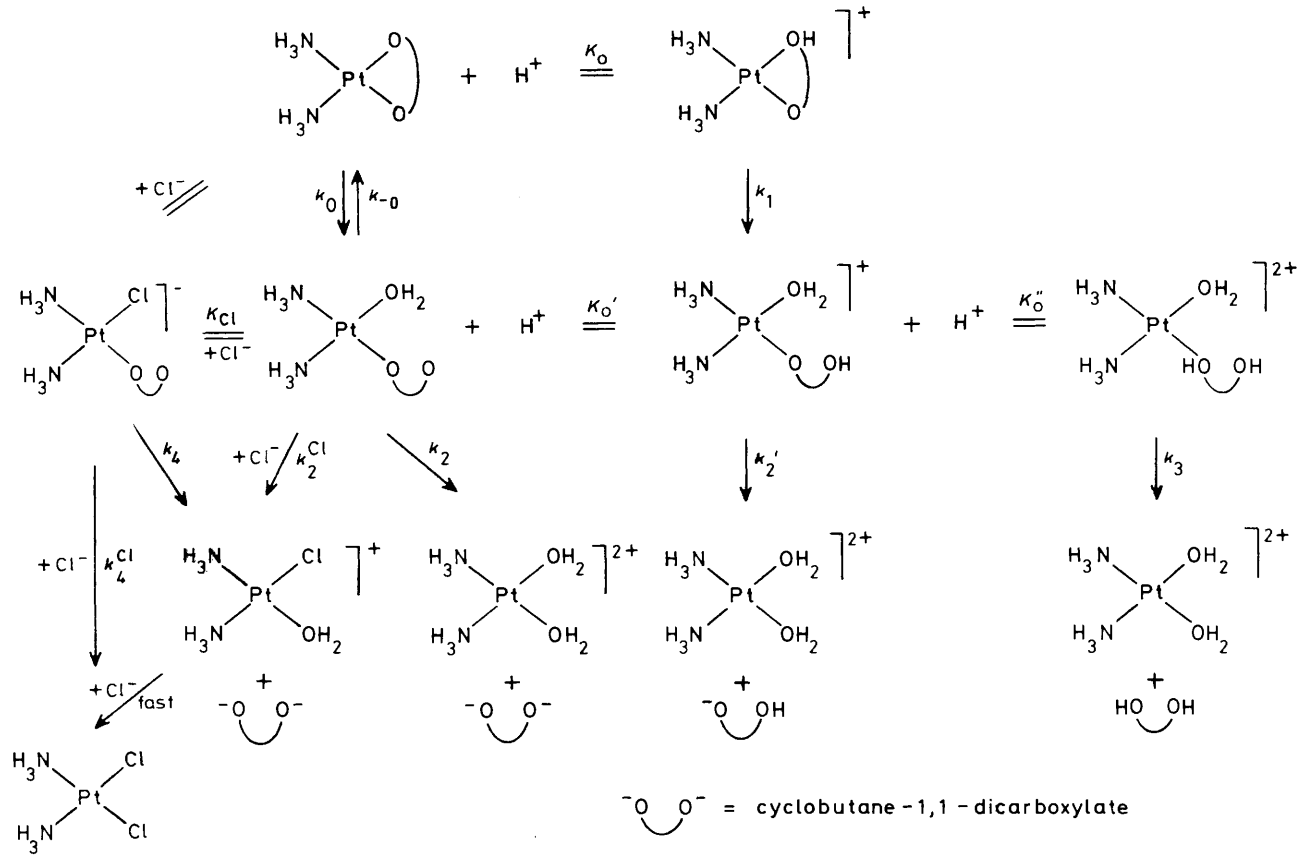


Figure 3. First-order rate constant for the first, $k_{obs.}(1)$ (●), and second, $k_{obs.}(2)$ (■), stages of the displacement of H_2cbdca from $[Pt(NH_3)_2(cbdca)]$ in perchloric acid solution: curves calculated for (*a*) $k_{obs.}(1) = 1.0 \times 10^{-4} + (2.62 \times 10^{-4})[H^+]$, (*b*) $k_{obs.}(1) = \dfrac{0.80 \times 10^{-4} + (8.00 \times 10^{-4})0.6[H^+]}{1 + 0.6[H^+]}$, (*c*) $k_{obs.}(1) = \dfrac{0.47 \times 10^{-4} + (6.2 \times 10^{-4})1.2[H^+]}{1 + 1.2[H^+]}$, (*d*) $k_{obs.}(2) = (1.59 \times 10^{-4})[H^+]$

The rate constant for ring opening in the absence of added acid, k_0, is not greatly sensitive to the uncertainty in the value assigned to K_0, varying from 1.0×10^{-4} s^{-1} when $K_0 \ll 1$ (*i.e.*, the intercept of the best straight line through the data), through 0.80×10^{-4} s^{-1} when $K_0 = 0.6$ dm^3 mol^{-1}, to 0.47×10^{-4} s^{-1} when $K_0 = 1.2$ dm^3 mol^{-1}.

The plot of $k_{obs.}(2)$ against $[H^+]$ is linear and passes through the origin, Figure 3. The slope, $k_3K_0'' = (1.61 \pm 0.03) \times 10^{-4}$ dm^3 mol^{-1} s^{-1}. The negligible intercept $(-6 \pm 2) \times 10^{-6}$ s^{-1} indicates that the acid-independent pathway makes no significant contribution to the process, even at the lowest acid concentration. It has not been possible to determine this value, nor indeed to assign a value to a rate constant (k_2) to the uncatalysed displacement of $cbdca^{2-}$ from $[Pt(NH_3)_2(cbdca)(H_2O)]$ {which may be partly or even totally in the zwitterionic form $[Pt(NH_3)_2(OH)(Hcbdca)]$}.



Scheme 3. = Denotes pre-equilibrium

The absence of any evidence in the ^1H n.m.r. spectrum measured after 60 d in water at 25 °C for the presence of species other than the starting material ($t_{\frac{1}{2}}$ for ring opening is 2—3 h) indicates that ring closing (as represented by the k_{-0} path) is very important in the absence of added acid. Under these circumstances $k_{obs.} = k_0k_2/(k_{-0} + k_2)$. Since $k_{obs.}$ ($< 10^{-8}$ s^{-1}) is much less than k_0 (8×10^{-5} s^{-1}), $k_{-0} \gg k_2$ and the process corresponds to a pre-equilibrium ring-opening followed by a very slow displacement of the dicarboxylate with $k_{obs.} = k_0k_2/k_{-0}$. The absence of any significant n.m.r. signal for a ring-opened intermediate indicates, in addition, that $k_{-0} \gg k_0$. A very small value for k_2 is also indicated. Extrapolation of the rate constant for the second-stage displacement of the dicarboxylate in acid solution to zero acid gives a maximum value of the rate constant for the displacement of Hcbdca$^-$, k_2', to be $< 2 \times 10^{-6}$ s^{-1} and the unprotonated leaving group is likely to be a poorer leaving group (*i.e.*, $k_2 \ll 2 \times 10^{-6}$ s^{-1}).

The reaction in the presence of chloride can be studied at high temperature. The induction period is short and the disturbance to the subsequent first-order displacement of the ligand is too small to be examined quantitatively. At 80 °C, the displacement is first-order in [Cl$^-$] and a plot of $k_{obs.}$ *vs.* [Cl$^-$] has no significant intercept ($< 10^{-6}$ s^{-1}). No data are available to allow an extrapolation to 25 °C but a reasonable $\Delta H^{\ddagger}$ of 60 kJ mol^{-1} would reduce the rate constant by a factor of 10^2.

The involvement of chloride in the displacement of the ligand can occur at the ring-opening and at the loss of the monodentate ligand. In the absence of acid the process can be represented by the left-hand side of Scheme 3. At 80 °C the ring-opening processes can be treated as equilibria, with the displacement of monodentate ligand as the rate-determining step. Sufficient chloride is present for the replacement of H_2O by Cl to be fast and (in the absence of cbdca at least) irreversible.

The rate law, under pseudo-first-order conditions becomes equation (4). Since the experimental results indicate no signi-

$$k_{obs.} = \frac{k_2k_0}{k_{-0}} + \left(\frac{k_2^{Cl}k_0}{k_{-0}} + k_4K_{Cl}\right)[Cl^-] + k_4^{Cl}K_{Cl}[Cl^-]^2 \quad (4)$$

ficant intercept and no departure from a first-order dependence on [Cl$^-$], only the second term on the right-hand side is important. It is not possible, from this alone, to distinguish between the solvolysis of *cis*-[Pt(NH$_3$)$_2$Cl(cbdca)]$^-$ (k_4K_{Cl}) and attack on *cis*-[Pt(NH$_3$)$_2$(H$_2$O)(cbdca)] by Cl$^-$ to displace the dicarboxylate ($k_2^{Cl}k_0/k_{-0}$), indeed both pathways may contribute. However, in view of the much greater importance of direct attack by Cl$^-$ over the unassisted solvolysis in the reactions of [Pt(Pr^{i}NH$_2$)$_2$(H$_2$O)(ClCH$_2$CO$_2$)]$^+$ [5] and [Pt(dien)(RCO$_2$)]$^+$ [5,6] we are very much in favour of the latter pathway.

The reaction with stronger nucleophiles has yet to be examined in detail and, until the nature of the reaction corresponding to the spectrophotometric changes has been identified, a discussion of the kinetics will be premature.

In the presence of both acid and chloride, a proper analysis lies beyond the precision of the data. The consumption of the aqua intermediates by chloride is not always fast compared to their rate of formation and the analysis of a complicated system in terms of two consecutive first-order processes is rather crude. Furthermore the two rate constants are of similar size and the curve-fitting program is not suitable for such a situation. Nevertheless, it would appear that the ring-opening process is

not greatly influenced by the presence of chloride, whereas the displacement of the monodentate ligand is accelerated in the presence of chloride. The data do not bear a more detailed analysis but there is a great similarity to the chloride plus acid dependence of the displacement of $ClCH_2CO_2H$ from $[Pt(dien)(ClCH_2CO_2)]^+$.[5]

This displacement of $cbdca^{2-}$ from $[Pt(NH_3)_2(cbdca)]$ differs in many respects from the displacement of monodentate carboxylates from analogous, but non-chelated, systems. The cbdca-containing substrate is more basic ($K_0 \geqslant 0.6$ dm^3 mol^{-1}) than *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ ($K_0 < 0.1$ dm^3 mol^{-1})[5] and it is much more likely that this is due to the greater basicity of $cbdca^{2-}$, the successive pK_a values of the acid, 3.01 and 5.55 at 25 °C[9] representing the basicity of $Hcbdca^-$ and $cbdca^{2-}$ respectively. This is to be compared with 2.85 for $ClCH_2COOH$.[10]

The problem of relating the individual basicities of a dibasic chelate to basicity-related properties such as leaving-group effects, ring-opening labilities, and *cis* effects have already been discussed in connection with amine ligands[11] and need not be repeated here. It is likely that the effective basicity of the chelate lies between the first and second pK_a values reported above. It has been shown that the basicity of complexes of the type $[Pt(dien)(RCO_2)]^+$ is very sensitive to the basicity of RCO_2^-[6] and there is no reason to believe that the neutral substrates will behave differently. The rate constant for the uncatalysed ring opening (8.0×10^{-5} s^{-1}) is, nevertheless, a little larger than that for the displacement of $ClCH_2CO_2^-$ from *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ (4.38×10^{-5} s^{-1}),[5] whereas the greater basicity would have led us to predict a lower reactivity. There is no evidence for chloride acceleration of ring opening in the presence of acid and it has already been argued above that the chloride dependence of the displacement of $cbdca^{2-}$ in neutral solution resides in the second step. Unfortunately it was not possible to examine the effect of stronger nucleophiles and so it cannot be stated with certainty that the lack of a direct chloride dependent path is due to it being swamped by an unusually large solvolytic contribution. Nevertheless it can be stated that the linking of the two carboxylates in a chelate has not led to a marked diminution of the nucleophile-independent pathway and that the chloride-dependent ring-opening pathway still remains hidden. The concept of a mutual labilization by *cis* carboxylates through some sort of internal displacement involving the non-leaving carboxylate acting as a chelate in the transition state appears to be wrong in the light of these results.

The second stage in the displacement of the dicarboxylate, when $cbdca^{2-}$ or $Hcbdca^-$ is leaving as a monodentate ligand, has many features in common with the displacement of RCO_2^- from *cis*-$[Pt(Pr^iNH_2)_2(H_2O)(ClCH_2CO_2)]^+$ or even $[Pt(dien)(RCO_2)]^+$. The nucleophile- and acid-independent pathway makes no contribution to the reaction, the acid catalysis leads to a linear dependence on $[H^+]$ (*i.e.*, the basicity is too low for $K_0''[H^+]$ even to be significant compared to 1). The value of $K_0''k_3 = 1.61 \times 10^{-4}$ dm^3 mol^{-1} s^{-1} compares with 2.90×10^{-4} dm^3 mol^{-1} s^{-1} for the analogous reaction of *cis*-$[Pt(Pr^iNH_2)_2(H_2O)(ClCH_2CO_2)]^+$[5] and 1.88×10^{-3} dm^3 mol^{-1} s^{-1} for $[Pt(dien)(ClCH_2CO_2)]^+$.[5]

In the absence of acid the difference in the behaviour of the chelate and bis-monodentate complexes is enormous and mainly attributed to the overwhelming importance of the ring-closing reaction, which, in this system at least, is the dominant contribution to a very large kinetic chelate effect.

In terms of the reactivity with chloride *in vivo* it seems very unlikely that Carboplatin is converted to a dichloro species *in vivo* by simple ligand-substitution processes. Enzymatic degradation of the co-ordinated bidentate may be required or else a fixing of the ring-opened intermediate by a species that is a much stronger ligand than chloride.

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