Kinetics of the Displacement of Chloroacetate Ion from *cis*-Bis(chloroacetato)-bis(isopropylamine)platinum(II) and the (Chloroacetato)(1,5-diamino-3-aza-pentane)platinum(II) Cation

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The displacement of $ClCH_2CO_2^-$ from *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ and $[Pt(dien)(ClCH_2CO_2)]^+$ (dien = 1,5-diamino-3-azapentane) by solvent, Cl^-, Br^-, and SCN^- has been studied in aqueous solution at 25.0 °C. The reactions are catalysed by acid by way of a pre-equilibrium protonation of the carboxylate ligand. In the absence of added acid the cationic monocarboxylato complex exhibits a normal nucleophilic discrimination power, comparable to that of the corresponding chloro complex and the nucleophile-independent pathway makes only a small contribution to the consumption of the substrate. In the uncatalysed reactions of the bis(carboxylato) complex, the nucleophile-independent pathway dominates the substitution by the weak nucleophile, Cl^-, and a relatively strong nucleophile, such as SCN^-, is required to make the direct substitution pathway important. The unusually large contribution from the nucleophile-independent pathway is discussed.

The accidental discovery of the cytostatic properties of *cis*-$[Pt(NH_3)_2Cl_2]$ by Rosenberg *et al.*[1] in 1969 has led to a successful application of this compound to the treatment of testicular cancer[2] and to the discovery of a number of other platinum(II) complexes that possess anti-tumour activity at non-toxic doses when used against experimental tumour systems. Among this group, two types of complex stand out: (*a*) those represented by *cis*-$[Pt(am)_2Cl_2]$[3] and (*b*) those represented by $[Pt(am)_2\{R(CO_2)_2\}]$ where am is a monodentate amine [occasionally $(am)_2$ represents a chelating diamine] and $R(CO_2)_2^{2-}$ is a chelating dicarboxylate, *e.g.* malonate[4] or cyclobutane-1,1-dicarboxylate, which, when am = NH_3 constitutes 'Carboplatin,' a complex now undergoing advanced clinical trials.[5]

It is generally believed that the mechanism for the transport of *cis*-$[Pt(am)_2Cl_2]$ through the body involves the interconversion of the neutral dichloro and the cationic aquo derivatives in response to the ambient chloride concentrations. The known *in vitro* kinetic and equilibrium properties of this system are not inconsistent with such a mechanism. Our interest in the relationship between the stability, lability, and nucleophilicity of oxygen donors with respect to Pt^{II} and other d^8 reactions centres[6] has led us to study the carboxylate ligand and the extent to which its lability is affected by protonation. In general, the impression gained from preliminary work is that the lability of the carboxylate ligand is low, so that a mechanism for the anti-tumour activity of the chelated dicarboxylato species that depends upon a reversible solvolysis (or indeed a preliminary conversion into a dichloro species) seems unlikely unless there is some facile *in vivo* destruction of the co-ordinated carboxylato ligand. Before addressing ourselves to the problem of the displacement of the chelating dicarboxylate, where reversible ring opening might complicate the kinetics, it seemed important to examine some simple monodentate carboxylato systems. Very few mechanistically related studies have been reported,[7] and for this work we have used *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$, a complex that was synthesised at Johnson Matthey plc., for testing as a potential anti-tumour agent, and kindly loaned to us. For comparison purposes we have also synthesised $[Pt(dien)(ClCH_2CO_2)]ClO_4$ (dien = diethylenetriamine, 1,5-diamino-3-azapentane) and have studied its substitution reactions.

Experimental

Compounds and Reagents.—*cis*-Bis(chloroacetato)bis(isopropylamine)platinum(II) was obtained from Johnson Matthey plc. Its i.r., ^1H and ^{13}C n.m.r. spectra, and elemental analyses are all fully consistent with a pure material of the above formulation.

Chloroacetato(1,5-diamino-3-azapentane)platinum(II) perchlorate was prepared by the method of Baddley and Basolo[8] in which a solution of $[Pt(dien)(H_2O)]^{2+}$, prepared by the addition of 2 mol equivalents of $AgClO_4$ to an aqueous solution of [Pt(dien)Cl]Cl, was filtered and treated with a slight excess of $Na(ClCH_2CO_2)$. The reaction mixture was evaporated to small volume and a concentrated aqueous solution of sodium perchlorate was added with vigorous stirring. The white crystals that separated were filtered off, washed with a little cold water and ethanol, and recrystallised from hot water (Found: C, 14.6; H, 3.10; N, 8.75. $C_6H_{13}Cl_2N_3O_6Pt$ requires C, 14.7; H, 3.10; N, 8.55%).

The complex *cis*-$[Pt(Pr^iNH_2)_2Cl_2]$ was a previously characterised sample[3] obtained by the reaction of $K_2[PtCl_4]$ with 2 mol equivalents of 2-aminopropane in aqueous solution. All other reagents were AR grade when possible or else of the highest available quality. Stock solutions were standardised in the usual ways.

Kinetics.—The reactions 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. The subsequent changes were followed spectrophotometrically using a Varian-Cary 219 spectrophotometer, either by repeatedly scanning the spectrum over the range 220—380 nm or by single-wavelength absorbance *versus* time scans at appropriate wavelengths. The concentration was chosen so that, in any run, the individual steps were first-order processes.

Before any kinetic analysis was carried out the nature of the

Table 1. Rate constants for the displacement of $ClCH_2CO_2^-$ from $[Pt(dien)(ClCH_2CO_2)]ClO_4$ by H_2O, Cl^-, Br^-, and SCN^- in the absence and presence of $HClO_4$[a]

$10^3[H^+]$	$10^3[Cl^-]$	$10^4k_{obs.}$	$10^4k_{calc.}$[b]	From plot of $k_{obs.}$ *vs.* $[X^-]$	
mol dm^{-3}		s^{-1}		10^4 slope/dm^3 mol^{-1} s^{-1}	10^4 intercept/s^{-1}
0	30	1.93[c]	1.94		
	50	2.02	2.00		
	80	2.10	2.10		
	100	2.18	2.16		
	200	2.48	2.48		
	300	2.75	2.80		
	400	3.12	3.12		
	500	3.47	3.45	3.21 ± 0.06	1.84 ± 0.02
100	0	3.96	3.77		
	100	4.75	4.75		
	200	5.78	5.73		
	400	7.69	7.69		
	500	8.73	8.68	10.3 ± 0.5	3.6 ± 0.1
200	0	5.83	5.65		
	100	6.95	7.29		
	200	8.53	8.93		
	400	12.5	12.2		
	500	14.5	13.9	18.7 ± 0.2	5.05 ± 0.1
400	0	9.02	9.41		
	100	11.9	12.4		
	200	16.4	15.3		
	400	21.6	21.3		
	500	23.3	24.2	31 ± 2	8.8 ± 0.7
500	100	14.8	14.9		
	200	17.9	18.5		
	400	26.2	25.8		
	500	29.0	29.4	36 ± 1	10.9 ± 0.3
600	0	13.6	13.2		
800	0	17.0	16.9		
1 000	0	21.3	20.7		
	$10^3[Br^-]$				
0	100	3.75	3.60[d]		
	300	8.65	8.60		
	500	13.0	13.6		
	800	20.9	21.1		
	1 000	26.4	26.1	25.0 ± 0.5	1.1 ± 0.2[e]
	$10^3[SCN^-]$				
0	10	8.10	9.6[f]		
	30	25.0	25.0		
	50	41.2	40.5		
	80	63.1	63.6		
	100	79.4	79.1	772 ± 14	1.9 ± 0.8[g]

[a] In water at 25.0 °C, $I = 1.0$ mol dm^{-3} ($NaClO_4$). [b] Using the expression $k_{calc.} = 1.89 \times 10^{-4} + 3.21 \times 10^{-4}\,[Cl^-] + 1.88 \times 10^{-3}[H^+] + 6.6 \times 10^{-3}[H^+][Cl^-]$ s^{-1}. [c] Errors ranging between ± 1 and ±2%. [d] Using the relationship, $k_{calc.} = 1.1 \times 10^{-4} + 2.5 \times 10^{-3}[Br^-]$ s^{-1}. [e] From a weighted linear least-squares analysis of the $k_{obs.}$ *versus* $[Br^-]$ data. [f] Using the expression $k_{calc.} = 1.9 \times 10^{-4} + 7.72 \times 10^{-2}\,[SCN^-]$ s^{-1}. [g] From a weighted linear least-squares analysis of the $k_{obs.}$ *versus* $[SCN^-]$ data.

chemical change was characterised by studies of the ^1H n.m.r. spectra of the reacting solutions in D_2O using Varian FT 80 and XL 200 spectrometers.

Infrared spectra were measured with a Perkin-Elmer 683 spectrophotometer.

Results

Displacement of Chloroacetate from $[Pt(dien)(ClCH_2CO_2)]^+$ *in Aqueous Solution.*—In dilute perchloric acid solution the chloroacetate complex is converted into the aquo complex in a single stage. If the solution, at the end of this reaction, is treated with an excess of NaCl the spectrum changes to that of $[Pt(dien)Cl]^+$ at a rate that follows the relationship, rate = $(2.61 + 0.13) \times 10^{-1}$[complex]$[Cl^-]$ mol dm^{-3} s^{-1} at 25.0 °C and $I = 1.0$ mol dm^{-3} ($NaClO_4$), which compares well with the literature[9] value of 6.2×10^{-1} dm^3 mol^{-1} s^{-1} for the second-order rate constant measured at 30.0 °C and $I = 0.1$ mol dm^{-3}. This, together with the ^1H n.m.r. evidence (the single peak assigned to co-ordinated $ClCH_2CO_2^-$ decreases in height as a new peak corresponding to free $ClCH_2CO_2^-$ appears and increases in height), confirms that the process being followed is the displacement of the carboxylate ligand.

The rate constants for this solvolysis, determined by a non-linear least-squares fit of the absorbance–time data by the expression $A_t = A_\infty + (A_0 - A_\infty)\exp(-k_{obs.}t)$, with A_0, A_∞, and $k_{obs.}$ as the parameters to be optimised (A_t is the absorbance at time t), depend upon $[H^+]$ and the values of $k_{obs.}$ determined at different acid concentrations are collected in Table 1.

In the presence of chloride, with or without the addition of acid, the product of the reaction is $[\mathrm{Pt(dien)Cl}]^+$ with no evidence for the build-up of significant quantities of the aquo intermediate. The first-order rate constants, derived as before, are also collected in Table 1. With added bromide or thiocyanate the corresponding bromo and thiocyanato complexes are formed and the first-order rate constants are also reported in Table 1.

Reactions of *cis*-$[\mathrm{Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2}]$ *in Dilute Aqueous Perchloric Acid Solution.*—The ^{1}H n.m.r. spectrum of *cis*-$[\mathrm{Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2}]$ in D_2O is characterised by peaks at δ 1.30 [d, 12 H, CH_3, ^3J(H–H) = 6.9 Hz], 2.82 (spt, 2 H, CH), and 4.10 (s, 4 H, CH_2 from chloroacetate). All chemical shifts relate to $\mathrm{Si}Me_3(\mathrm{CH_2CH_2CO_2})^-$ at δ 0.00. In the presence of acid, with or without added chloride, there is an immediate shift downfield of the chloroacetate signal (peak a), the extent of which depends upon the acid concentration. In the absence of halide, this is followed by a slow change characterised by a decrease in the height of peak a and the appearance of a new singlet peak at δ 4.16 (peak b) that is slightly sensitive to the concentration of acid and another (peak c) whose chemical shift is very sensitive to $[\mathrm{H^+}]$ (δ 4.28 when $[\mathrm{H^+}] = 0.075$ mol dm^{-3} and δ 4.05 in the absence of added acid). At first, peaks b and c have the same height but eventually peak c increases at the expense of peak b. At the end of the reaction, peak a is absent and the height of b is small compared to that of c. No other peaks were observed in this area. The signals for the methyl protons of the isopropyl group become more complicated during these processes and resolution was not easy. Addition of an excess of NaCl at the end of the reaction leads to a simple spectrum containing peak c, a simple clearly resolved doublet at δ 1.52 [6 H, ^3J(H–H) = 6.1 Hz], and a septet (1 H). Crystals which separated at this stage were shown to be identical in elemental analysis and i.r. spectrum to an authentic sample of *cis*-$[\mathrm{Pt(Pr^iNH_2)_2Cl_2}]$. It is reasonable to conclude that peaks a, b, and c can be assigned to the protons of the chloroacetate ion in *cis*-$[\mathrm{Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2}]$, *cis*-$[\mathrm{Pt(Pr^iN^HH_2)_2(ClCH_2CO_2)(H_2O)}]^+$, and free chloroacetate/chloroacetic acid respectively. The ^{1}H n.m.r. spectra provide no evidence for significant amounts of any other chlorocarboxylato-containing species.

Spectrophotometric studies of the reaction at [complex] *ca.* 4×10^{-4} mol dm^{-3} (*cf.* 10^{-3} mol dm^{-3} in the n.m.r. experiments) were carried out at $I = 1.0$ mol dm^{-3} ($NaClO_4$). The change in absorbance is consistent with two consecutive first-order processes and was analysed by a five-parameter Gauss–Newton least-squares fitting algorithm [A_0, A_i, A_∞, $k_{\mathrm{obs.(1)}}$, and $k_{\mathrm{obs.(2)}}$ being respectively the absorbances of the starting material at $t = 0$, of the intermediate, and of the product at the concentration of complex used, and the required first-order rate constants for the two steps]. The ^{1}H n.m.r. experiments showed that $k_{\mathrm{obs.(1)}} > k_{\mathrm{obs.(2)}}$ and so there was no danger of finding a false solution.[10] These first-order rate constants are collected in Table 2.

Table 2. Rate constants for the first [$k_{\mathrm{obs.}}(1)$] and second [$k_{\mathrm{obs.}}(2)$] stages of the acid-catalysed solvolysis of *cis*-$[\mathrm{Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2}]$ in water at 25.0 °C and $I = 1.0$ mol dm^{-3} ($NaClO_4$)

$[\mathrm{H^+}]$/mol dm^{-3}	$10^4k_{\mathrm{obs.}}(1)$/s^{-1}	$10^4k_{\mathrm{obs.}}(2)$/s^{-1}
0.00	0.438	
0.10	2.32	0.45
0.20	4.22	0.61
0.40	7.53	0.89
0.60	11.9	1.62
0.80	18.3	2.5
1.00	21.0	2.9

When sodium chloride is added to a reaction mixture that has reached the end of the second stage of the above reaction a rapid spectral change takes place in two stages and finally *cis*-$[\mathrm{Pt(Pr^iNH_2)_2Cl_2}]$ is formed. This is consistent with the results of the ^{1}H n.m.r. study carried out at higher concentration and reported above. The two-stage reaction can be resolved into two successive first-order steps and the rate constants evaluated using the Gauss–Newton algorithm. Plots of these rate constants against $[\mathrm{Cl^-}]$ are linear with second-order rate constants of 5.3×10^{-2} and 3.6×10^{-3} dm^3 mol^{-1} s^{-1} respectively for the first and second stages. An authentic sample of *cis*-$[\mathrm{Pt(Pr^iNH_2)_2(H_2O)_2}]^{2+}$, prepared in solution by the action of 2 mol equivalents of $AgClO_4$ on *cis*-$[\mathrm{Pt(Pr^iNH_2)_2Cl_2}]$ in water, had, after filtration, an identical spectrum to that of the reaction mixture at the end of the acid-catalysed reaction and its reaction with chloride also leads, in two stages, to the formation of *cis*-$[\mathrm{Pt(Pr^iNH_2)_2Cl_2}]$ with second-order rate constants, determined in the usual way, of 5.5×10^{-2} and 3.5×10^{-3} dm^3 mol^{-1} s^{-1}, in close agreement with those reported above.

Reactions of cis-$[\mathrm{Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2}]$ *in the Absence of Acid.*— (*a*) *Solvolysis.* On keeping a solution of the complex in D_2O the peak at δ 4.10 decreases and peaks grow at δ 4.05 and 4.15. The reaction is very slow and, after 4 d at 25 °C, the peak for the starting material has nearly gone and the area under the peak assigned to free carboxylate (at δ 4.05) is about twice that of the sum of the areas under the peaks assigned to the monocarboxylato complex and the remainder of the starting material.

The absorbance change in the region 220—360 nm is not inconsistent with two reaction stages, but the second is slow and reversible (addition of $\mathrm{ClCH_2CO_2}^-$ to a solution of the diaquo complex causes a slow small change in spectrum opposite to that observed in the solvolysis). The first part of the absorbance change at 270 nm was analyzed as a single-stage exponential change using a three-parameter Gauss–Newton algorithm. The value obtained in this way, $k_{\mathrm{obs.}} = (4.38 \pm 0.08) \times 10^{-5}$ s^{-1}, at $I = 1.0$, is likely to be somewhat smaller than the true value as a result of this approximation but the error is unlikely to be greater than 20%.

(*b*) *With chloride.* Under preparative conditions, the dicarboxylato complex yields the dichloro species quantitatively. The ^{1}H n.m.r. spectrum of the dicarboxylato complex in D_2O with a relatively small concentration of added sodium chloride indicates, as the reaction proceeds, four separate peaks assignable to the $\mathrm{ClCH_2CO_2}^-$ protons. Three of these correspond to those already assigned to the bis(carboxylato) complex, the aquo(carboxylato) complex, and the free carboxylato anion, while the fourth, at δ 4.15, must be assigned to the *cis*-$[\mathrm{Pt(Pr^iNH_2)_2(ClCH_2CO_2)Cl}]$ species. The presence of a strong signal for the aquo(carboxylato) complex indicates that it is wrong to assume that the aquo intermediate is rapidly consumed by its reaction with chloride. The kinetics were followed spectrophotometrically with $[\mathrm{Cl^-}] > 0.050$ mol dm^{-3} because at lower chloride concentrations the accumulation of significant amounts of aquo intermediate complicated the kinetic analysis to a point where it was beyond the strength of the primary data. The reactions were analysed as a single-stage process (the replacement of the second carboxylate being too slow to follow conveniently) and the rate constants (suffering from the same flaw as that discussed above for the solvolysis) are collected in Table 3.

(*c*) *With bromide.* The reaction of the bis(carboxylato) complex with sodium bromide forms the dibromo complex in good yield. The reaction occurs in two stages which can readily be separated when sufficient bromide is present to prevent the build up of significant concentrations of the intermediate aquo

Table 3. Rate constants for the displacement of $ClCH_2CO_2^-$ from *cis*-$[Pt(Pt^{i}NH_2)_2(ClCH_2CO_2)_2]$ by Cl^-, Br^-, and SCN^- [a]

$[Cl^-]$/mol dm^{-3}	$10^5k_{obs.}(1)$/s^{-1}	$10^5k_{obs.}(2)$/s^{-1}
0.010	3.2 [b]	
0.050	3.9	
0.10	4.2	
0.50	4.6	
1.00	4.7	
$[Br^-]$/mol dm^{-3}		
0.10	5.3 (5.3) [c]	1.37 (1.33)
0.30	6.0 (6.1)	1.55 (1.52)
0.50	6.9 (6.8)	1.61 (1.70)
0.80	7.9 (7.9)	1.97 (1.98)
1.00	8.6 (8.6)	2.20 (2.16)
$[SCN^-]$/mol dm^{-3}		
0.050	5.8 (6.2) [d]	
0.080	9.4 (9.2)	
0.10	11.1 (11.1)	
0.30	31.0 (30.6)	
0.50	49.7 (50.0)	

[a] In water at 25.0 °C, I = 1.0 mol dm^{-3} ($NaClO_4$). [b] Treated as a single-stage reaction. [c] Treated as two consecutive reactions, calculated values in parentheses. [d] Treated as two consecutive reactions with equal rate constants; calculated values in parentheses.

species. The data were analyzed as two consecutive first-order processes and the rate constants are collected in Table 3.

(*d*) *With thiocyanate*. The reaction of the bis(carboxylato) complex with KSCN is much faster than the other processes followed (at comparable nucleophile concentrations) and is not complicated by the build up of significant concentrations of aquo intermediates over the range of thiocyanate concentrations used. At the wavelength of the study, 270 nm, the first stage appears as a spectrophotometric induction period that is then followed by a considerable increase in absorbance. Preliminary analysis of the absorbance–time curves indicated that the rate constants for the two stages were very similar and that the absorbance of the intermediate was considerably smaller than that of the starting material, while that of the final product was much greater. The absorbance *versus* time data were analysed by a five-parameter curve-fitting program using the Marquardt algorithm and the rate constants for the two consecutive processes, which were equal at all thiocyanate concentrations studied, are collected in Table 3.

Discussion

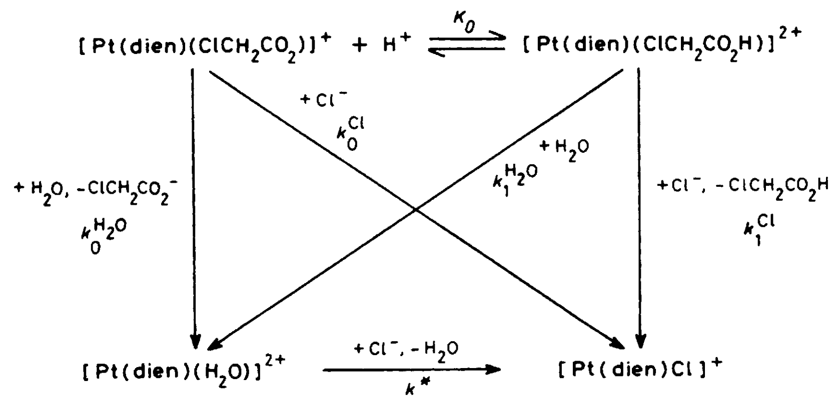
It is convenient, first of all, to consider the reactions of $[Pt(dien)(ClCH_2CO_2)]^+$ in order to establish a simple standard against which to compare the bis(carboxylato) species. In the absence of added NaCl but in the presence of $HClO_4$, the product is $[Pt(dien)(H_2O)]^{2+}$ and the rate constants obey the relationship, $k_{obs.} = k_a + k_b[H^+]$. In the presence of chloride, but without added acid, the product is the chloro complex and the rate constants obey the relationship, $k_{obs.} = k_a + k_c[Cl^-]$. The two treatments, not surprisingly, give the same intercept. In the presence of both acid and chloride, plots of $k_{obs.}$ *vs.* $[Cl^-]$ are linear at constant $[H^+]$ with both the slopes and the intercepts dependent upon $[H^+]$. The overall relationship therefore takes the form (1). The values of the slopes, intercepts, and the derived rate constants are presented in Table 1.

$$k_{obs.} = k_a + k_b[H^+] + k_c[Cl^-] + k_d[H^+][Cl^-] \quad (1)$$

This rate equation is consistent with a mechanism in which there is a pre-equilibrium protonation of the carboxylate ligand and a parallel displacement of the leaving group by a solvolytic (displacement by H_2O) and a direct chloride attack pathway (Scheme 1) which, provided $k^*[Cl^-]$ is large enough to ensure that the concentration of the aquo intermediate is always low compared to that of the reagent and product, leads to the rate law (2) where [substrate] = the sum of the concentration of the unprotonated and the protonated carboxylato complexes. If $K_0[H^+] \ll 1$ over the whole range of acid concentration studied, this will reduce to the observed rate law, with $k_a = k_0^{H_2O}$, $k_b = k_1^{H_2O}K_0$, $k_c = k_0^{Cl}$, and $k_d = k_1^{Cl}K_0$. In the absence of departures from this simple rate law it is not possible to separate the equilibrium constant, K_0, from the rate constants with which it is combined and so comment upon the extent to which protonation increases the lability of the carboxylato group, other than upon the limits of the effect. Because of side effects, the reactions with bromide and thiocyanate could not be studied in the presence of acid.

$$\frac{d[Pt(dien)Cl^+]}{dt} = \frac{k_0^{H_2O} + k_0^{Cl}[Cl^-] + k_1^{H_2O}K_0[H^+] + k_1^{Cl}K_0[H^+][Cl^-]}{1 + K_0[H^+]} \cdot [substrate] \quad (2)$$

The effect of acid on the rates of displacement of carboxylate ligands in associatively activated systems has been examined in



Scheme 1.

Table 4. Second-order rate constants for the displacement of $ClCH_2CO_2^-$ by X[a]

	X: H_2O	Cl^-	Br^-	SCN^-
(*a*) From $[Pt(dien)(ClCH_2CO_2)]^+$				
$10^4\ k_0^X\ (I = 1.0)/dm^3\ mol^{-1}\ s^{-1}$	0.034[b]	3.2	25	770
$\log k_0^X\ (I = 1.0)$	−5.47	−3.50	−2.60	−1.11
$\log k_0^X\ (I = 0.0)$	−5.47	−2.99	−2.09	−0.60
$\log k_2\ (I = 0.0)$[c]	−6.05	−3.53	−2.64	−0.89
(*b*) From *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ (first step)				
$10^4\ k_0^X\ (I = 1.0)/dm^3\ mol^{-1}\ s^{-1}$	0.0090[b]		0.37	9.7
$\log k_0^X$	−6.05		−4.43	−3.01
n_{Pt}^0[d]		3.04	4.18	5.75

[a] In water at 25.0 °C. [b] $k_0^{H_2O}/55.5$ [c] Rate constants for the displacement of Cl^- from $[Pt(en)(NH_3)Cl]^+$ by X^-. Data from ref. 15. For the estimation of the value for X = Cl^- see ref. 16. [d] Data from ref. 17.

the replacement of pyridine-2-carboxylate (N–O) from $[AuCl_2(N–O)]$ by chloride in the presence of acid.[6a] There, the rate-limiting step is the breaking of the Au–O bond but the acid dependence is fully accounted for by the protonation of other, more basic, sites and acid catalysis, as such, is not observed. The breaking of the Au–O bond in the pyridine-2-methanolato complex is acid catalysed and follows a rate law that is similar in many respects to that observed above.[6b] In this case K_0 is large enough for the separation of the $k_1^{Cl}K_0$ terms. More is known about acid catalysis of dissociatively activated substitution of the carboxylato-amine complexes of Co^{III}, Cr^{III}, Rh^{III}, and Ir^{III}, but, in most cases, $k_{obs.} = k_0^{H_2O} + k_1^{H_2O}K_0[H^+]$, and either K_0 is too small, or high enough (but achievable) acid concentrations have not been used to allow the second term to be separated. In the case of *cis*- and *trans*-$[Co(en)_2(CH_3CO_2)_2]^+$ (en = 1,2-diaminoethane) the departure from the first-order dependence on $[H^+]$ has been observed and the rate constant separated from the equilibrium constant.[11] There, K_0 = 1.1 and 6.5 $dm^3\ mol^{-1}$ for the *trans* and *cis* isomers, respectively. In the latter case, the uncatalysed pathway makes a negligible contribution to the reaction and only a rough value is available for $k_0^{H_2O}$ for the *trans* isomer from which the ratio $k_1^{H_2O}/k_0^{H_2O}$ can be estimated to be 3×10^3.

The linearity of the plot of $k_{obs.}$ against $[H^+]$ up to 1.0 mol dm^{-3} indicates that K_0 for $[Pt(dien)(ClCH_2CO_2)]^+$ is less than 0.1 $dm^3\ mol^{-1}$ making $k_1^{H_2O} > 2 \times 10^{-2}\ s^{-1}$ and the ratio $k_1^{H_2O}/k_0^{H_2O} > 10^2$, but it is not possible to say how much greater.

The possibility that the acid-catalysed pathway involves attack at the carbonyl carbon and hence C–O fission, which has been considered in other contexts,[12] can be ruled out because of the $k_d[H^+][Cl^-]$ term. A study of the changing ^1H n.m.r. spectrum of the *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ complex in deuteriomethanol shows that the organic entity displaced in acid solution is the carboxylic acid and the signal from the protons of the methyl ester (which would be expected as part, at least, of the product of C–O fission) does not appear until much later times.

Although it is not possible to separate the individual rate constants for the processes, one can compare the rate constants for the solvolysis and the direct chloride-entry pathway for the unprotonated and the protonated substrates: $k_0^{Cl}/k_0^{H_2O} = k_c/k_a$ = 1.7 $dm^3\ mol^{-1}$ and $k_1^{Cl}/k_1^{H_2O}$ = 3.7 $dm^3\ mol^{-1}$. This is consistent with the idea that, as the positive charge on the substrate increases (or the negative charge decreases), the relative nucleophilicity of an anionic reagent with respect to that of a neutral nucleophile will increase. In this case the effect is very small and the protonation is probably too far away from the reaction centre to be important.

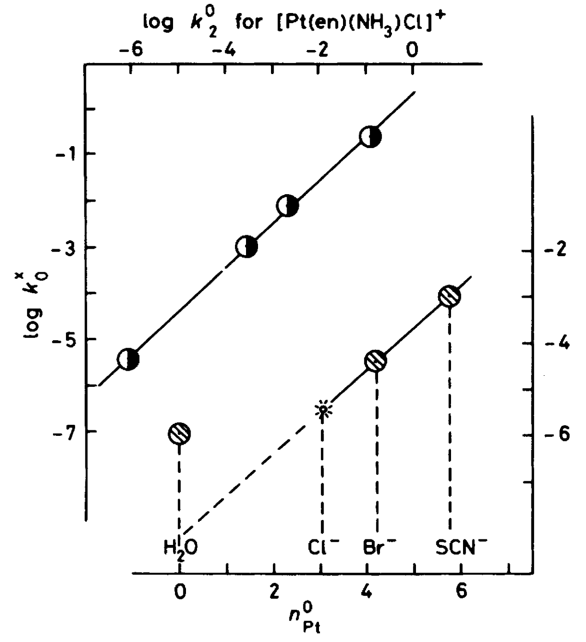


Figure. Plots of $\log k_0^X$ (I = 0.0) for $[Pt(dien)(ClCH_2CO_2)]^+$ (left-hand scale) and *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ (right-hand scale) against the appropriate nucleophilicity scale for the entering nucleophile X (top and bottom scales respectively)

In the absence of added acid the reaction obeys the usual two-term rate law, $k_{obs.} = k_0^{H_2O} + k_0^X[X^-]$, and values for k_0^X are collected in Table 4, together with that for the solvolysis expressed as a second-order rate constant, *i.e.* $k_0^{H_2O}/55.5$. The rate constants for the anionic reagents have been extrapolated to zero ionic strength using the standard relationship for reactions between +1 and −1 charged species, $\log k_0^X$ (at $I = 0$) = $\log k_0^X$ (at $I = I$) + 1.02 $I^{\frac{1}{2}}(1 + I^{\frac{1}{2}})^{-1}$, and since I = 1.0 mol dm^{-3}, $\log k_0^X$ (at $I = 0$) = $\log k_0^X$ + 0.5. These values also appear in Table 4. Using $\log k_2$ (I = 0) for the reactions of the same nucleophiles with $[Pt(en)(NH_3)Cl]^+$ in water at 25.0 °C, *i.e.* the nucleophilicity scale that has been proposed for +1 substrates,[13] a good straight line of slope = 0.95 ± 0.03 is obtained (Figure). The estimation of the value for the nucleophilicity of chloride (in the absence of isotopic exchange data) has been discussed elsewhere.[14] The nucleophilic discrimination factor of $[Pt(dien)(ClCH_2CO_2)]^+$ (0.95) is somewhat smaller than that of the corresponding chloro complex, $[Pt(dien)Cl]^+$ (1.03),[13] but it is now clear that, in complexes of this sort, the nucleophilic discrimination factor does depend to some extent on the nature of the leaving group.[14]

In the absence of added nucleophiles, the displacement of chloroacetate from *cis*-$[Pt(Pr^iNH_2)_2(ClCH_2CO_2)_2]$ takes place in two stages to yield *cis*-$[Pt(Pr^iNH_2)_2(H_2O)_2]^{2+}$. The process is reversible and, in order to drive it to completion, acid must be present at a concentration ⩾ 0.1 mol dm^{-3}. Within the range of concentration, $0.1 \leqslant [H^+] \leqslant 1.0$ mol dm^{-3}, the rate equation takes the form, $k_{obs.} = k_a + k_b[H^+]$. A weighted linear least-squares analysis of the $k_{obs.}$ *versus* $[H^+]$ data gives $k_a(1) = (-2 \pm 4) \times 10^{-4}\ s^{-1}$, $k_a(2) = (5 \pm 12) \times 10^{-7}\ s^{-1}$, $k_b(1) = (2.11 \pm 0.05) \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$, and $k_b(2) = (2.90 \pm 0.15) \times 10^{-4}\ dm^3\ mol^{-1}\ s^{-1}$, for the two stages. The fact that the error in k_a is greater than the magnitude of the intercept reflects the length of the extrapolation and does not mean that there is no acid-independent pathway. In the absence of added acid, the change, treated as a single-stage process, gives $k_{obs.} = 4.4 \times 10^{-5}$ s^{-1}. This is probably a little smaller than the true value of $k_a(1)$ as a result of the approximations introduced in the treatment of the data. No similar estimate can be made of $k_a(2)$.

There is no indication of any tendency for the slope of the plot of $k_{obs.}$ *versus* [H$^+$] to decrease at high [H$^+$] that would indicate an approach to the situation where $K_0[H^+] \not\ll 1$, indeed, any curvature that does exist seems to go in the opposite direction. Therefore, $K_0 < 0.1$ dm^3 mol^{-1} and, assuming that the acid dependence arises from the same cause as that for the monocarboxylato complex, $k_1^{H_2O} > 2 \times 10^{-2}$ s^{-1} and protonation increases the lability by at least three orders of magnitude. The chloroacetato ligand is not basic enough to allow a proper analysis of the acid-dependent processes.

In the absence of acid, the reaction with anionic nucleophiles X$^-$ (X = Cl, Br, or SCN) leads eventually to the formation of *cis*-[Pt(Pr^{i}NH$_2$)$_2$X$_2$]. In the cases where X$^-$ = Br$^-$ or SCN$^-$ the process takes place smoothly in two stages with no significant build up of the aquo intermediate and the rate equations for the two stages take the same form, $k_{obs.} = k_0^{H_2O} + k_0^X[X^-]$. The rate constants, obtained from a weighted least-squares analysis of the $k_{obs.}$ *versus* [X$^-$] data, are collected in Table 4. The kinetics of the reaction with chloride could not be evaluated quantitatively by absorption spectrophotometry. The ^{1}H n.m.r. experiments clearly indicated the two stages of reaction, with *cis*-[Pt(Pr^{i}NH$_2$)$_2$(ClCH$_2$CO$_2$)Cl] as an intermediate, but they also showed the presence of large amounts of aquo intermediates. Thus a kinetic treatment that assumes a rapid consumption of the aquo intermediate is invalid. The absorbance *versus* time data could be made to fit a single exponential expression, but the values of the rate constants obtained in this way were always somewhat smaller than $k_0^{H_2O}$ determined from the reaction with bromide (5.0×10^{-5} s^{-1}) but approached it as [Cl$^-$] increased. Contributions from any [Cl$^-$]-dependent pathway are therefore too small to be observed amid the general background confusion arising from the solvolytic process and it must be concluded that $k_0^{Cl} < 1 \times 10^{-5}$ dm^3 mol^{-1} s^{-1} for the first step.

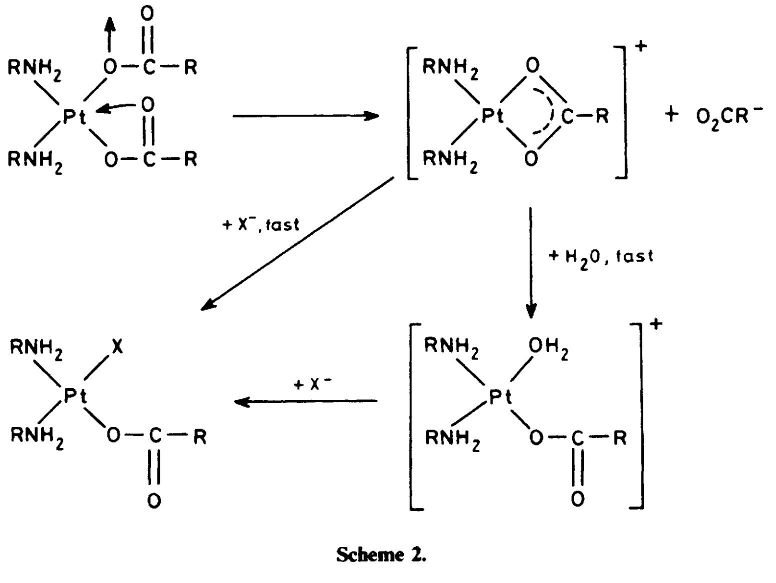
Attempts to examine the reactions of *cis*-[Pt(Pr^{i}NH$_2$)$_2$(ClCH$_2$CO$_2$)$_2$] in the presence of both acid and nucleophile were unsuccessful. In the reaction with chloride, the presence of acid increased the rate at which the aquo complex was formed but had no effect upon its rate of consumption by chloride. Consequently, even larger concentrations of aquo complex built up and a proper kinetic analysis was prevented. It is therefore not possible to say whether or not there is a contribution from the term first order in both acid and chloride corresponding to the $k_1^{Cl}K_0[H^+][Cl^-]$ present in the rate law for the reaction of the [Pt(dien)(ClCH$_2$CO$_2$)]$^+$ complex.

In the presence of acid, the reaction with bromide results in a general decomposition and thiocyanate is sufficiently basic for ligand protonation to complicate the kinetics at the acid concentrations needed.

The reactions of the bis(carboxylato) complex therefore differ in many respects from those of the mono(carboxylato) species. The chloride-dependent pathway does not make a large enough contribution to be detected and direct attack by bromide plays only a very small part. However, the magnitude of the rate constant for the reaction with thiocyanate indicates that this cannot simply be due to the substrate exhibiting an unusually low nucleophilic discrimination factor.

Values of log k_0^X are plotted against n_{Pt}^0[15] for X$^-$ in the Figure. (This scale is appropriate for neutral substrates and the rate constants are unaffected by ionic strength.) Log ($k_0^{H_2O}$/55.5) is also plotted assuming a value of 0.0 for n_{Pt}^0 of H$_2$O. There is clearly no linear relationship of the sort found for the mono(carboxylato) complex. The many differences between the mono and the bis complexes can be accounted for in terms of an unusually large value for $k_0^{H_2O}$, implying that the observed process is not an associative nucleophilic attack by water on the complex. If the values for the Br$^-$ and SCN$^-$ reaction are used to define the nucleophilic discrimination line, the value of k_0^{Cl}, appropriate for the n_{Pt}^0 value assigned to Cl$^-$ (3.04), is 3×10^{-6} dm^3 mol^{-1} s^{-1}, far too small to be observed against the background nucleophile-independent pathway. The slope of this two-point straight line, 0.92, is considerably larger than that claimed (0.65)[16] for the only *cis*-dianionodiamineplatinum(II) complex reported, [Pt(en)Cl$_2$], but it is consistent with the discrimination found for the [Pt(dien)(ClCH$_2$CO$_2$)]$^+$ complex reported above.

While anomalously large nucleophile-independent rate constants have been observed in the reactions of complexes containing very strong *trans*-effect ligands, *e.g.* *trans*-[Pt(PEt$_3$)$_2$(R)Cl] where R is a σ-bonded organic ligand,[17] they are unknown in the reactions of simple dianionodiamine complexes, and the absence of such an anomaly in the reactions of the mono(carboxylato) species where the point for the



Scheme 2.

solvolytic process lies exactly on the line defined by the other three nucleophiles leads us to suggest that the nucleophile-independent pathway involves an internal substitution that gives, transiently, the chelated mono(carboxylato) species (Scheme 2). Chelated acetato species have been identified among the products of the reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with $CH_3CO_2^-$,[7] but they seem to be insufficiently stable to be seen in our system.

It can be concluded that displacement of chloroacetate ions from the diamine complex studied takes place at a rate that is independent of $[Cl^-]$ and under the physiological conditions of temperature and pH would have a half-life of about 3 h for the loss of the first ligand and even longer for displacement of the second. The complexes of pharmacological importance all contain chelated dicarboxylates and, although one might expect that the lability of a co-ordinated carboxylate should depend upon its basicity, and the pK_a of $ClCH_2CO_2H$ (2.85)[18] is close to that of malonate (2.83),[18] one would predict that, under conditions where reversible ring closing was not prevented, the displacement of a bidentate would be very much slower than the displacement of two equivalent monodentate ligands. The internal attack by one carboxylate upon another proposed in this work is greatly impeded if the two carboxylates form part of the same small ring. We are now examining these systems in detail.

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