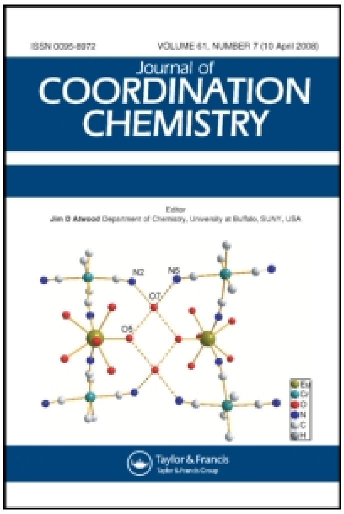

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KINETICS OF THE *CIS*-DICHLORODIAMMINEPLATINUM(II)-OXALATE REACTION IN AQUEOUS SOLUTION

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The substitution of the chloride ligands in *cis*-$Pt(NH_3)_2Cl_2$ by oxalate has been studied in neutral and slightly acidic aqueous solutions. At 50°, the reaction is first-order with respect to complex concentration. The estimated first-order rate constant ($3.9 \times 10^{-4} sec^{-1}$ at 50°) and the activation energy (17 kcals/mole) are similar to the corresponding values reported for the aquation of the complex ion. The reaction rate is only slightly pH dependent in the pH range 3–7 indicating that $C_2O_4^{-2}$ and $HC_2O_4^-$ have similar reactivities. The rate of the reaction is inhibited by the presence of excess free chloride. These data have been interpreted in terms of a mechanism involving the rate-determining aquation of the complex. By comparison with previous studies in which amine molecules were employed as substituting groups oxalate is a very weak nucleophile. It is suggested that the known biological activity of dichloro complexes of platinum(II) involves reaction at nitrogen-containing rather than oxygen-containing sites in the biologically active molecules.

INTRODUCTION

Several kinetic studies have been reported in which poly-basic amines displace labile halide ligands from platinum(II) complexes in aqueous solution. It has been noted that for the direct attack of diethylenetriamine on $PtBr_4^{-2}$ or $PtCl_4^{-2}$ increased protonation of the amine decreases the reaction rate[1,2]. The much slower reaction between *cis*-$Pt(NH_3)_2Cl_2$ and diethylenetriamine proceeds according to a two-term rate law.[3] A comparison with the kinetic data reported by Martin[4] for the acid hydrolysis of the *cis* complex suggested that the amine substitution reaction proceeds partially via a rate-determining aquation of the complex ion. Palocsay and Rund[5] have detected a similar solvent participation for the reaction of 1 : 10 phenanthroline with $PtCl_4^{-2}$. The *cis*-$Pt(NH_3)_2Cl_2$— oxalate system is an interesting extension of the above studies because nucleophilic oxygen rather than nitrogen sites are involved and the attacking groups exist as anionic $C_2O_4^{-2}$ or $HC_2O_4^-$ rather than cations in weakly acidic and basic solutions. Although many studies have been reported in which water is the nucleophile in a platinum(II) substitution reaction,[4] this paper gives the first detailed report of the kinetics of substitution of platinum(II) by a bidentate oxygen-containing ligand.

EXPERIMENTAL SECTION

Cis-$Pt(NH_3)_2Cl_2$ was prepared and analyzed as described in a previous publication.[3] *Anal.* Calcd for *cis*-$Pt(NH_3)_2Cl_2$: Pt 65.2; Cl 23.63. Found: Pt 65.3; Cl 23.8. Aqueous complex solutions exhibited an absorption maximum at 300 nm and a minimum at 247 nm in agreement with the observations of Reishus and Martin.[4] The water for kinetic experiments was redistilled from alkaline permanganate. All other materials were of reagent grade.

For the kinetic experiments summarized in Tables I and II reactions were initiated by the addition of weighed amounts of finely powdered *cis*-$Pt(NH_3)_2Cl_2$ to aqueous solutions of oxalate. Where necessary, the ionic strengths and *p*H values of the resultant solutions were controlled by the inclusion of KNO_3 and HNO_3 in the original oxalate solution. Reactions were followed by a previously reported spectrophotometric procedure[3] utilizing the increases in optical densities at 300 nm as the *cis*-$Pt(NH_3)_2Cl_2$ was consumed. The molar extinction coefficient of the product complex was approximately four times that of the reactant complex. A white crystalline solid was precipitated when completed reaction mixtures were cooled to 10°. Elemental analysis of this material was consistent with that calculated for *cis*-$Pt(NH_3)_2C_2O_4$. *Anal.* Calcd.: Pt 61.5; C 7.57; N 8.83; H 1.91.

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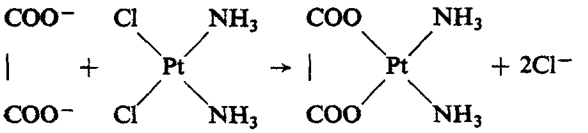
Found: Pt 60.5; C 7.48; N 8.62; H 1.96. These data indicate that oxalate displaced chloride ligands as indicated by equation 1.



. . . (1)

In all experiments oxalate was present in excess concentration compared to the reactant complex. Under these circumstances pseudo-first order kinetics were observed as defined by equation 2.

$$\text{Rate} = k[\text{Pt(NH}_3)_2\text{Cl}_2] \qquad (2)$$

A typical kinetic plot, in which good linearity was observed for two to three half-lives, is given in Figure 1.

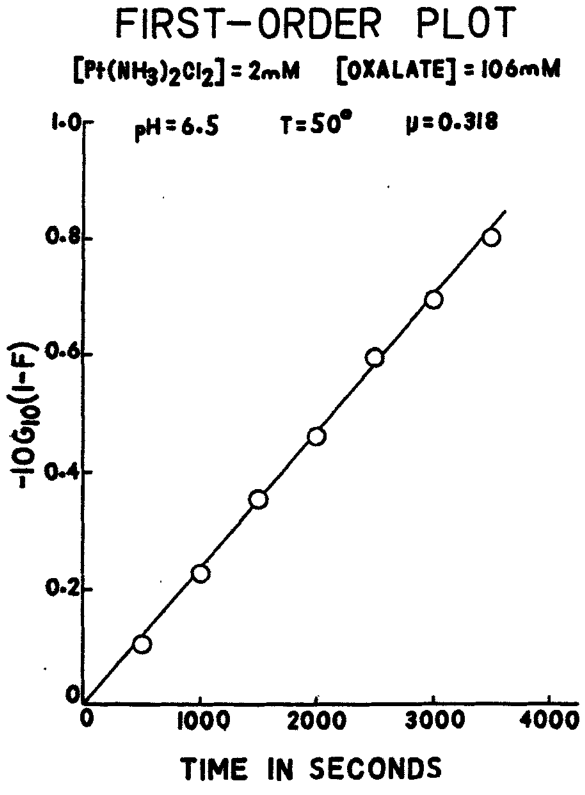


FIGURE 1 Integrated first-order plot.

Because the proposed reaction mechanism involves aquation of the complex, the equilibrium constant for aquation, as defined by equation 3, was estimated at 50°. This method, which has been described by Martin,[4] involved ageing solutions of the chloro complex, and titrating the resultant weakly acidic aquo complex to an end point of *p*H 8.9 with sodium hydroxide solutions. Titrations must be completed within a few minutes to prevent further aquation of the residual $\text{Pt(NH}_3)_2\text{Cl}_2$. Although large experimental errors are involved in this procedure, reasonably consistent values for K_3 were obtained for different chloride concentrations as shown in Table I. These data are of similar magnitude to the K_3 values obtained by Martin[4] at other temperatures ($3.3 \times 10^{-3}M$ at 25° and $3.9 \times 10^{-3}M$ at 35°).

TABLE I

Estimated equilibrium concentrations of species in aqueous solutions of *cis*-$\text{Pt(NH}_3)_2\text{Cl}_2 \cdot T = 50°$ C

$\text{Pt(NH}_3)_2\text{Cl}_2$	$\text{Pt(NH}_3)_2(\text{H}_2\text{O})\text{Cl}^+$	Cl^-	K_3
milli-molar concentrations			molar
0.61	1.39	1.39	3.2×10^{-3}
0.98	1.02	3.02	3.1×10^{-3}
1.15	0.85	4.85	3.6×10^{-3}

Average value of $K_3 = 3.3 \times 10^{-3}$ molar

$$\text{Pt(NH}_3)_2\text{Cl}_2 + \text{H}_2\text{O} \underset{k_B}{\overset{k_A}{\rightleftharpoons}} \text{Pt(NH}_3)_2(\text{H}_2\text{O})\text{Cl}^+ + \text{Cl}^- \quad K_3$$

. . . (3)

RESULTS

In the presence of excess oxalate pseudo-first-order kinetics were always observed. A typical integrated first-order plot, which shows good linearity for more than two half-lives is given in Figure 1.

The dependence of observed first-order rate constants on reactant concentrations in the *p*H range 6.5–7.0 is shown by Table II. The experimental data are consistent with the two-term rate law indicated in equation 4.

$$\text{Rate} = (k_1 + k_2[\text{oxalate}])[\text{Pt(NH}_3)_2\text{Cl}_2] \qquad (4)$$

For the conditions in Table I, k_1 and k_2 were equal to 3.9×10^{-4} sec^{-1} and $1.0 \times 10^{-3}M^{-1}$ sec^{-1}, respectively.

The *p*H dependence of the reaction was studied through the *p*H range 7.0–1.5. The results, which are given in Table III, indicate that the rate constant is independent of the hydrogen ion concentration

TABLE II

Determination of first order rate-constants (pH 6.5–7.0, 50.0°, $\mu = 0.318$[a])

Molar concn. × 10^3		10^4k sec^{-1}	
$Pt(NH_3)_2Cl_2$	Oxalate	Obsd.	Calcd.[b]
0.5	25	4.3	4.2
1.0	25	4.2	4.2
2.0	25	4.0	4.2
0.5	50	4.6	4.4
1.0	50	4.4	4.4
2.0	50	4.5	4.4
0.5	106	4.8	4.9
1.0	106	4.9	4.9
2.0	106	5.2	4.9

[a] By addition of potassium nitrate.

[b] From $k = 3.9 \times 10^{-4}$ sec^{-1} + 1.0 × .0^{-3} M^{-1}sec^{-1} [oxalate].

in the pH range 5–7. This justifies the use of unbuffered aqueous solutions in the kinetic studies reported in this manuscript.

It was found that the presence of free chloride ion inhibited reaction rates. Observed pseudo-first-order rate constants for reaction mixtures in which aqueous complex solutions had been pre-equilibrated with varying chloride ion concentrations are given in Table IV. These reactions were initiated by mixing pre-equilibrated complex solutions with oxalate solutions. Because both components of the reaction mixture contained the same concentration of potassium chloride no significant change in chloride concentration was produced by this operation.

Finally, the temperature dependence of the substitution reaction was studied at a relatively low oxalate concentration. These data, which are plotted in Figure 2, are consistent with an activation energy of approximately 17 kcals/mole.

TABLE III

pH dependence of first-order rate constants ($T = 50.0°$, $\mu = 0.318$, $Pt(NH_3)_2Cl_2$ = 1 mM, oxalate = 50 mM)

Initial pH	10^4k sec^{-1}
6.93	4.4
5.22	4.6
3.43	4.2
2.83	3.1
2.40	2.5
1.55	1.7

DISCUSSION

Two term rate laws, such as equation 4, have been reported many times for substitution reactions of square planar complexes.[6] It has been proposed that the mechanistic path corresponding to k_1 involves an initial slow aquation followed by a relatively rapid reaction between the incoming ligand and the aquo complex. The other term is consistent with direct reaction between the complex and the incoming ligand.[7] For the *cis*-$Pt(NH_3)_2Cl_2$-oxalate reaction, however, the relative values of k_1 and k_2 are such that the oxalate dependent term accounts for only ~20% of the total reaction at the highest oxalate concentration studied. It is possible that this oxalate dependence could be an electrostatic effect caused by the substitution of oxalate for nitrate in order to maintain constant ionic strength. In any event, direct reaction between oxalate and the complex must be slow and the estimated value for k_2 allows the reaction rate at zero oxalate concentration to be obtained by extrapolation.

TABLE IV

Dependence of reaction rate on free chloride concentration ($Pt(NH_3)_2Cl_2$ = 1 mM, T = 50°, $\mu = 0.318$, pH = 6.5–7.0)

10^3 Initial molar concn.		10^4k sec^{-1}	
Cl^-	Oxalate	Obsd.	Calcd.[a]
0	106	4.9	4.9
10	103	3.0	3.3
30	96	1.9	1.9
50	89	1.4	1.3
100	69	0.7	0.6

[a] From $k = \dfrac{4.9 \times 10^{-4}\ \text{sec}^{-1} \times [\text{oxalate}]}{[\text{oxalate}] + 5[Cl^-]}$

Martin[4] has studied the hydrolysis of *cis*-$Pt(NH_3)_2Cl_2$. Using this data (first-order constant = 2.5×10^{-5} sec^{-1} at 25° and activation energy = 19.7 kcals/mole) it is possible to calculate a value of 3.4×10^{-4} sec^{-1} for the rate constant at 50°. This value is quite close to the numerical value of k obtained for the oxalate substitution reaction at 50° (3.9×10^{-4} sec^{-1}). It seems reasonable to propose, therefore, that the first-order term for the substitution reaction corresponds to a mechanism involving rate-determining aquation of the complex. The obtained activation energy for the oxalate substitution reaction is approximately 2 kcals/mole less than the reported value for the aquation reaction.[4] The latter value, however, was based upon measurements over a narrow 10° temperature range and is subject to considerable experimental error.

Reactions reported in Table II were carried out in unbuffered solutions. Measurement of *p*H values for solutions before and after reaction indicated that the *p*H values were always within the range 6.5–7.0. From the data for the *p*H dependence of reactions in Table III it is apparent that reaction rates are not sensitive to changes in hydrogen ion concentration within the narrow pH range employed for the reactions in Table II. This is not surprising because reported equilibrium studies for oxalic acid[8] show that the unprotonated oxalate ion predominates in great excess above *p*H 6. The initial and final absorption spectra obtained for the reaction mixtures in Table II were similar for all reactions indicating that the same product was produced in every instance. Because the reaction rate varies by only 10% between *p*H 3.5 and 7.0 it would appear that $C_2O_4^{-2}$ and $HC_2O_4^-$ react at comparable rates. This is to be expected if the rate determining step of the reaction is aquation of the complex because oxalate species would not be involved in the activated complex. The decrease in reaction rates in the more acidic media could be attributed to the presence of $H_2C_2O_4$ which is not a Lewis base. Because of the known complexity of acidic solutions of oxalato complexes of platinum[9] such an analysis would be questionable.

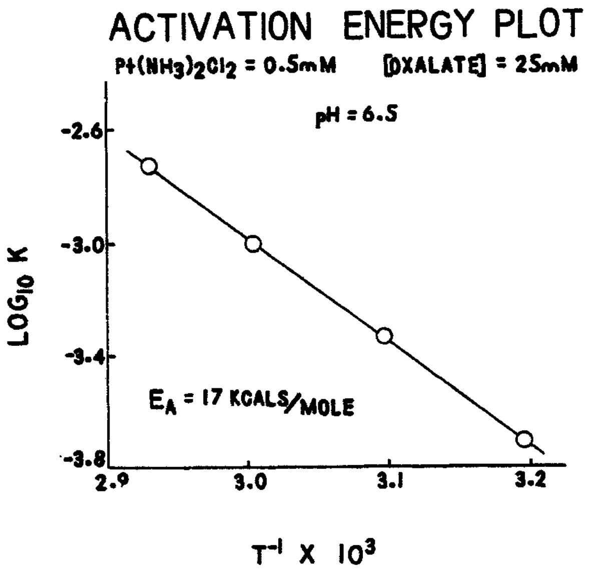


FIGURE 2 Determination of activation energy

An obvious reaction mechanism consistent with the oxalate independent term in equation 3 involves aquation of the complex followed by reaction between the aquo complex and oxalate. This mechanism was tested by studying the effect of added chloride ion on reaction rates. Optical densities for reacted solutions indicated that the reaction did not proceed to completion at chloride ion concentrations above 100 m*M*. Consequently, rate constants were estimated from initial rates for chloride concentrations above 30 m*M*. Because chloride should compete with oxalate for the aquo complex, the rate of formation of $Pt(NH_3)_2C_2O_4$ should be slower in the presence of chloride. The reaction rate under these circumstances, which is predicted in equation 6, can be obtained by a steady-state treatment using equations 3 and 5.

$$Pt(NH_3)_2(H_2O)Cl^+ + C_2O_4^{-2} \xrightarrow{k_c} Pt(NH_3)_2C_2O_4 + Cl^- + H_2O \quad (5)$$

$$k = \frac{k_A k_C \text{ oxalate}}{k_B[Cl^-] + k_c[\text{oxalate}]} \quad (6)$$

If it is assumed that $k_B = 5k_c$ a reasonable agreement is obtained between predicted rate constants and those calculated from experimental data as shown in Table IV. These results imply that chloride ion reacts more rapidly with the aquo complex than comparable concentrations of oxalate ion.

An analysis of the data in this report indicates that the reactivity of the oxalate is so low that the aquation reaction is barely rate-determining at the lowest employed oxalate concentrations. The aquation equilibrium constant is 3.3×10^{-3} molar and the rate constant for the forward aquation reaction is 3.9×10^{-4} sec^{-1}. This results in a calculated rate constant for the reverse reaction of chloride with the aquo complex of $1.2 \times 10^{-1} M^{-1}$ sec^{-1}. From equation 6 the rate constant for the reaction of aquo complex and oxalate must be $2.4 \times 10^{-2} M^{-1}$ sec^{-1}, because $k_B = 5k_c$. The value of k_c [oxalate] from equation 5 would be 6×10^{-4} sec^{-1} for the lowest oxalate concentration employed (25 m*M*). This value is less than twice the magnitude of the aquation rate constant. At higher oxalate concentrations aquation of $Pt(NH_3)_2Cl_2$ would be clearly rate-determining.

All of our data imply that the *cis*-$Pt(NH_3)_2Cl_2$-oxalate reaction proceeds through a predominant aquation path. It would appear that oxalate is a much weaker nucleophile than dibasic or tribasic amines[3] with regard to direct substitution of halide ligands in platinum(II) complexes.

Dihalide complexes of platinum are known to inhibit tumors[10] and deactivate certain enzymes such as leucine aminopeptidase.[11] Detailed mechanisms for the enzyme inhibition reactions have not been proposed but it appears possible that the enzyme becomes bound to the metal at two sites. This could result from the displacement of two chloride ligands by nucleophilic groups on the protein chain. Our studies of substitution of *cis*-$Pt(NH_3)_2Cl_2$ by oxalate and amines suggest that platinum complexes are much more likely to react with a biologically active material at a nitrogen-containing site rather than at an oxygen-containing site.

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