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Dimerization Processes of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ in Aqueous Solution

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The oligomerization reactions of aqueous solutions of cis-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ *have been investigated by UV spectrophotometry in the pH 4–5 range. In these conditions, the dimer, di-μ-hydroxo-bis[diammineplatinum(II)] cation, is the only detectable reaction product. The dependence of the dimerization kinetics on pH and ionic strength indicates that dimer formation comes principally from* cis-$[Pt(NH_3)_2(H_2O)(OH)]^+$, *with a minor, though not negligible, contribution from* cis-$[Pt(NH_3)_2(H_2O)_2]^{2+}$.

Introduction

Owing to the importance of *cis*-$Pt(NH_3)_2Cl_2$, known to be an effective growth inhibitor of some tumors [1], many efforts have been made in order to understand the real composition of aqueous solutions containing this complex. The hydrolysis processes of *cis*-$Pt(NH_3)_2Cl_2$ have been studied, and both thermodynamic and kinetic parameters relative to the formation of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ complex have been determined [2]. In recent years, oligomeric species such as the dimer, di-μ-hydroxo-bis[diammineplatinum(II)] and the trimer, cyclo-tri-(μ-hydroxo)-tris[*cis*-diammineplatinum(II)] have been isolated from aqueous solutions containing *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ [3, 4], and shown to produce much more toxic effects than *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ [5].

The first investigation on the kinetics and mechanism of the oligomerization of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ was made by ^{195}Pt NMR spectroscopy in the 5–6 pH range [5]. The results showed that the rate of formation of the dimeric species was proportional to the square of the monomer concentration. The *cis*-$[Pt(NH_3)_2(H_2O)(OH)]^+$ species, which is present in equilibrium with the bis-aquo form (pKa_1 = 5.56) [6] in this pH range, was considered as the main monomeric form responsible of the oligomer formation. In a recent investigation on the photochemical behaviour of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and of the oligomeric species [7], the results suggested that the formation of oligomeric species from *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ should also be considered. In the present investigation we have studied the dimerization reaction in the 4–5 pH range, where larger concentrations of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ are present, in order to understand the role of the two monomeric forms in this process.

Experimental

Materials

cis-Dichlorodiammineplatinum(II) was prepared according to reference [8] from K_2PtCl_4 (BDH).

Aqueous solutions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ were obtained from *cis*-$Pt(NH_3)_2Cl_2$ by using stoichiometric amounts of Ag_2SO_4 or $AgClO_4$ as precipitating agents.

Cyclo-tri-(μ-hydroxo)-tris[*cis*-diammineplatinum-(II)] sulphate hexahydrate (trimer sulphate) was prepared according to the methods in reference [3]. In the preparation of this compound some di-μ-hydroxo-bis[diammineplatinum(II)] sulphate tetrahydrate (dimer sulphate) was obtained; it was separated from the more soluble trimer compound by crystallization. The purity of the solid trimer sulphate was checked by IR spectroscopy.

Di-μ-hydroxo-bis[diammineplatinum(II)] perchlorate (dimer perchlorate) was prepared from a solution of $[cis\text{-}Pt(NH_3)_2(H_2O)_2](ClO_4)_2$ following the procedure described in reference [4] for the di-μ-hydroxo-bis[diammineplatinum(II)] nitrate. The IR spectrum of the pale yellow crystals obtained was in good agreement with that previously reported for the dimer nitrate [4], indicating that, contrary to nitrate, formation of trimer perchlorate is negligible.

The dimer sulphate was easily obtained by adding drops of a saturated solution of Na_2SO_4 to a solution of dimer perchlorate. The precipitated crystals were washed with water, ethanol, and then dried for several hours using a rotary pump vacuum. This procedure was found to give much better yield than

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TABLE I. Experimental Conditions and Kinetic Parameters.

pH	$[H_2A^{2+}]_o \times 10^3$ M	k_{obs} M^{-1} sec^{-1}
(a)		
4.1	1.54	0.096
4.18	1.54	0.11
4.36	2.56	0.107
4.43	1.54	0.11
4.47	1.65	0.095
4.62	1.65	0.097
4.7	1.54	0.09
4.86	2.33	0.13
(b)		
4.22	2.8	0.053
4.36	4.9	0.049
4.7	2.8	0.068
4.92	2.8	0.074

[a] Solutions buffered with acetate buffer (μ = 0.1). [b] Solutions buffered with Britton and Robinson buffer (μ = 0.04). All the experiments were carried out at 24 ± 2 °C.

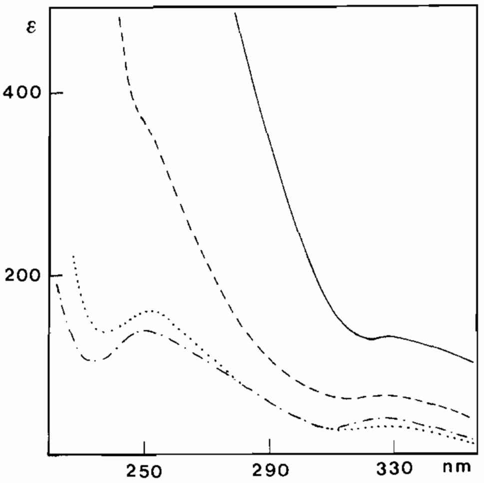

Fig. 1. Absorption spectra of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (pH = 2) (–·–·–), *cis*-$[Pt(NH_3)_2(H_2O)(OH)]^+$ (·······), $[Pt_2(NH_3)_4(OH)_2]^{2+}$ (pH = 6.5) (-------), and $[Pt_3(NH_3)_6(OH)_3]^{3+}$ (pH = 6.5) (———), in aqueous solutions.

a previously reported method [3]. The total platinum concentrations of aqueous solutions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$, trimer and dimer species were checked by the Atomic Absorption Spectrophotometric Technique.

Buffer solutions: Britton and Robinson (B.R.) buffer solutions were prepared by adding 0.2 M NaOH to a 0.04 M acidic solution containing H_3PO_4, CH_3COOH, and H_3BO_3. Acetate buffer solutions were prepared with 1 M NaOH and 1 M CH_3COOH. The ionic strength and the pH values of the buffer solutions are indicated in Table I.

Apparatus and Methods

pH measurements were performed with a Beckman Select Ion 5000 ion analyzer using a standard combination electrode.

UV-Vis spectra were recorded with a Varian Cary 219 Spectrophotometer.

IR spectra were recorded with a Perkin-Elmer mod. 283 Spectrophotometer using KBr pellets.

Atomic Absorption measurements were performed with a Perkin-Elmer mod. 603 Atomic Absorption Spectrophotometer.

The determination of the crystallization water of the dimer sulphate and perchlorate was performed with a Metrohm Karl Fisher Automat E 547 equipment.

Results and Discussion

Figure 1 shows the absorption spectra of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$, of the dimer and trimer species. The spectrum of the monomer was obtained from an aqueous solution of the bisaquo complex kept at lower pH than 2, while for the dimer and trimer complexes the examined solutions were at their natural pH (about 6.5). The spectrum of *cis*-$[Pt(NH_3)_2(H_2O)(OH)]^+$, calculated as described below, is also reported in Fig. 1. It can be noticed that the ϵ values at 330 nm of the dimer and trimer cations are two and three times that of the monomer respectively. On the other hand, the short wavelength d–d band appears as a shoulder in the dimer spectrum and does not appear at all in the case of the trimer. This suggests that while the oligomerization does not affect the local symmetry of each platinum atom, it gives rise to a red shift of the OH → Pt charge transfer band, which hides the short wavelength d–d band. The conversion of monomer to any of the oligomers does not lead therefore to spectral changes in the long wavelength d–d region, but in the short wavelength charge transfer region.

In order to study the kinetics of the oligomer formation, concentrated solutions of $[cis\text{-}Pt(NH_3)_2(H_2O)_2](ClO_4)_2$ or $[cis\text{-}Pt(NH_3)_2(H_2O)_2]SO_4$ (original pH = 2) were diluted ten times in the buffer solutions. Starting from two minutes after mixing, the spectral variations were followed as a function of time. Owing to the acidity of the starting solutions containing the aquo-complex, the pH after mixing was lower by 0.2 units than that of the buffer solutions used. For each experiment, the pH remained constant within ±0.02 units. After very long reaction times, solutions of *cis*-$[Pt(NH_3)_2$-

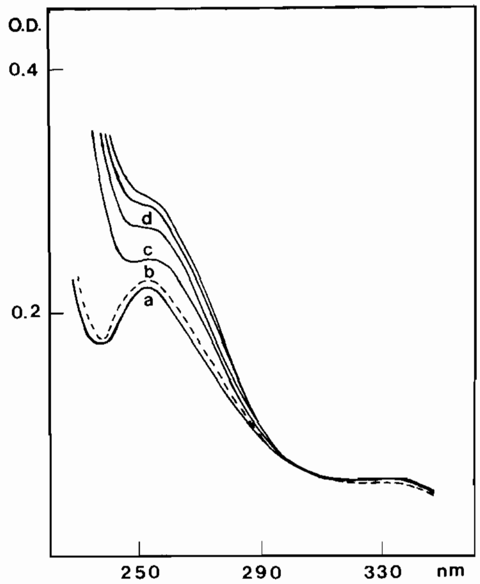

Fig. 2. a) Absorption spectrum of a 1.65 × 10^{-3} *M* solution of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (pH = 2). b, c, d, *etc.*) spectral variations observed as a function of time for the same solution buffered at pH 4.47.

$(H_2O)_2]^{2+}$ buffered with the B.R. buffer gave rise to the formation of a blue unidentified precipitate. No such behaviour was observed with the acetate buffer. The blue product was probably the same that was isolated from solutions containing [*cis*-$Pt(NH_3)_2(H_2O)_2](NO_3)_2$ and KH_2PO_4, and formulated as $H_n[Pt(NH_3)_2PO_4]\cdot\frac{1}{2}H_2O$ [9]. From independent experiments starting with the oligomers and the three components of B.R. buffer, we observed that the formation of the blue compound was due to very slow secondary reactions of the dimeric and trimeric species (as sulphates or perchlorates) with the phosphate buffer in the 4–6.5 pH range.

The spectral variations as a function of time for a monomer solution at pH 4.47 are shown in Fig. 2; for comparison the spectrum of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ is also given. The behaviour was qualitatively the same in the 4–5 pH range. The initial spectrum (curve b), is already different from that of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (curve a). This instantaneous spectral variation is followed by a slower increase in optical density at wavelengths lower than 300 nm (curves c, d, *etc.*). The instantaneous spectral variation (curve b) can be attributed to the well known acid base equilibrium:

$$Pt(NH_3)_2(H_2O)_2^{2+} \xrightleftharpoons{Ka_1} Pt(NH_3)_2(H_2O)(OH)^+ + H^+ \qquad (1)$$

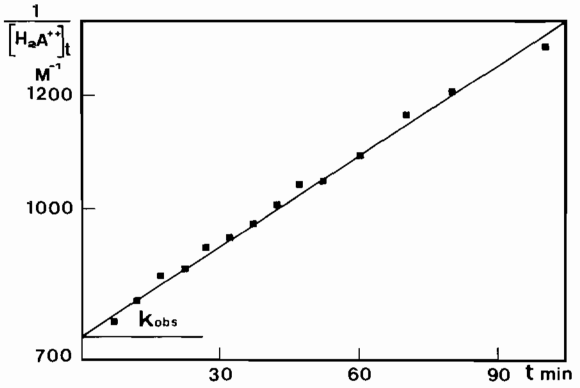

Fig. 3. Second order plot for the disappearance of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ in buffered solution at pH 4.47.

and can be used to calculate the spectrum of $Pt(NH_3)_2(H_2O)(OH)^+$ based on the known value of the equilibrium constant Ka_1 = 2.75 × 10^{-6} [6]. These calculations can be performed at various pH values, giving ϵ values which agree within ±15%. The slower spectral variations are consistent (see Fig. 1) with the formation of oligomers from the monomeric species.

The analysis of the spectral variations (such as those shown in Fig. 2) corresponding to oligomerization at various pH values in the 4–5 pH range can be performed as follows. The knowledge of the spectra of all the species involved (Fig. 1), allows the calculation of the concentrations of the bis-aquo (H_2A^{2+}), dimer (D) and trimer (T) species as a function of the time by resolving a system of three linear independent equations, such as eqn. (2), in which the ϵ's refer to three different wavelengths.

$$O.D. = [H_2A^{2+}](\epsilon_{H_2A^{2+}} + \alpha\epsilon_{HA^+}) + [D]\epsilon_D + [T]\epsilon_T \qquad (2)$$

In eqn. (2) α is the fraction of monomer present as monohydroxospecies (HA^+), *i.e.*, $\alpha = Ka_1/[H^+]$. The calculations show that, in the experimental conditions used, the formation of the trimer product is negligible. This result is in agreement with the temperature dependence of the relative amounts of dimer and trimer found by C. J. Boreham *et al.* [10] by using ^{195}Pt NMR studies. The stability of the dimer product was checked as a function of pH. The absorption spectra of solutions of dimer sulphate buffered in the 4–5 pH range with acetate buffer were identical to that recorded for an equimolar solution of dimer sulphate at natural pH and did not change with time*. Thus, in the experimental conditions used, dimerization is the only oligomerization process, and the dimer product is stable.

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*For footnote, please see overleaf.

Figure 3 shows the second order plot for the disappearance of H_2A^{2+} from which the experimental rate constant k_{obs} is obtained. The k_{obs} values obtained under different experimental conditions are reported in Table I. In the hypothesis that the monohydroxo complex is the only species responsible for the oligomerization processes, eqn. (3) should be used.

$$2H_2A^{2+} \underset{}{\overset{Ka_1}{\rightleftharpoons}} 2HA^+ + 2H^+ \xrightarrow{k_D} D + 2H^+ \qquad (3)$$

From this reaction scheme the following kinetic equation can be drawn:

$$\frac{d[D]}{dt} = k_D[HA^+]^2 = \frac{k_D Ka_1^2 [H_2A^{2+}]^2}{[H^+]^2} = -\frac{1}{2}\frac{d[H_2A^{2+}]}{dt} \qquad (4)$$

which, by integration, gives:

$$1/[H_2A^{2+}]_t = 1/[H_2A^{2+}]_o + \frac{2k_D Ka_1^2}{[H^+]^2}\,t \qquad (5)$$

and

$$k_{obs} = 2k_D Ka_1^2/[H^+]^2 \qquad (6)$$

As to the k_{obs} values reported in Table I, the key observation is that the expected proportionality between k_{obs} and $1/[H^+]^2$ (eqn. 6) is not observed in the pH range investigated; instead, the rate constants are almost pH independent. Moreover, it should be noticed that the k_{obs} values are definitely dependent on the ionic strength of the solutions. The dependence of k_{obs} on the ionic strength is not far from that expected for a reaction between two doubly charged ions (Debye-Huckel expression with a distance of closest approach of 4 Å) but can hardly be fitted using a +1 charge product. These facts suggest that the assumption made (eqn. 3) is not valid, and that in the pH range 4–5 the bis-aquo complex H_2A^{2+} significantly contributes to the dimerization reaction observed.

If a two reactant scheme is to be used (eqn. 7):

$$\begin{tikzcd} 2H_2A^{2+} \arrow[rr, shift left] \arrow[dr, "k_{D1}"', "-2H^+"] & & 2HA^+ + 2H^+ \arrow[ll, shift left] \arrow[dl, "k_{D2}"] \\ & D & \end{tikzcd} \qquad (7)$$

the observed second order rate constant k_{obs} is given by eqn. 8:

$$k_{obs} = 2k_{D1} + 2k_{D2}Ka_1^2/[H^+]^2 \qquad (8)$$

Our results indicate that k_{D1} equals $2.6 \times 10^{-2} \pm 2.9 \times 10^{-3}$ and $4.9 \times 10^{-2} \pm 3.4 \times 10^{-3}$ at $\mu = 0.04$ and 0.1 respectively. Because of the almost pH-independent behaviour, it is difficult to estimate the contribution of k_{D2}. Within the experimental scatter, the data are compatible with k_{D2} values of 0.22 ± 0.1 and 0.25 ± 0.2 at $\mu = 0.04$ and 0.1, respectively.

The results obtained in this work indicate that the reactions of the bis-aquo species, while being probably lower than that of the monohydroxo complex, are not negligible. In particular, in the relatively low pH region investigated, the contribution of the bis-aquo complex becomes the dominant one.

Acknowledgements

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*At pH lower than 3.5 on the contrary, the intensity of the absorption band centered at 254 nm was observed to decrease with the time. The rate of decrease increased as the pH of the solution was lowered. The instability of the dimer at low pH prevents the direct measurement of the rate of dimerization of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$.