with ice and NaH_2PO_4 (1 g), and the products were chromatographed as above.

Solutions of $[(NH_3)_5CoNHCONHC_6H_5](ClO_4)_2 \cdot H_2O$ (0.1–10 mmol) in dimethyl sulfoxide containing CF_3SO_3H (10 mmol) were reacted for 30–40 min (16 °C). The reactions were then quenched with ice (in latter experiments the acid was first neutralized), and the products were chromatographed.

$[(NH_3)_5CoOC(NH_2)NHC_6H_5]_2(S_2O_6)_3 \cdot 3H_2O$ (10 mmol) was stirred in 0.1 M $HClO_4$, 0.1 M NaMES, or 0.1 M NaPhos ($\mu = 1.0$ M ($NaClO_4$)) for 10 half-lives (25 °C) or in 0.1 M NaOH ($\mu = 1.0$ M ($NaClO_4$)) for 30 s (25 °C). Product mixtures were chromatographed, eluted, and quantitated as described above. Some (incomplete) reactions were performed at lower temperatures, and product analyses are corrected to 100% reaction by using the figure determined for recovered reactant.

Kinetic studies utilized routine methods described elsewhere.[11] Rate constants for the parallel first-order reactions of the O- and N-bonded isomers were determined by the usual nonlinear least-squres analysis using absorbance–time traces (at 520 nm) recorded on a Cary 210 spectrophotometer fitted with a thermostated (25.0 ± 0.1 °C) cell block.

Crystallography. The data crystal was defined by four pairs of faces (110), (110), (100), and (111) with distances between them of 0.08, 0.073, 0.072, and 0.175 mm, respectively. Data were collected on a Philips PW1100/20 four-circle diffractometer using graphite-monochromated Cu Kα radiation. Unit cell dimensions and their estimated standard deviations were determined from the setting angles of 25 carefully centered reflections. Data within the range $3 < 2\theta(\text{Cu K}\alpha) < 100°$ spanning one unique quadrant of reciprocal space were collected, corrected for absorption effects, and reduced in the usual way.

Acknowledgment. This work was supported by a grant from the Australian Research Grants Scheme.

Registry No. $[(NH_3)_5CoNH_2CONHC_6H_5]^{3+}$, 119946-90-6; $[(NH_3)_5CoOC(NH_2)NHC_6H_5]^{3+}$, 107440-52-8; $[(NH_3)_5CoNHCONHC_6H_5](ClO_4)_2 \cdot H_2O$, 119946-93-9.

Supplementary Material Available: Table VI, giving thermal parameters (1 page). Ordering information is given on any current masthead page.

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NMR Study of Acid–Base Equilibria and Other Reactions of Ammineplatinum Complexes with Aqua and Hydroxo Ligands[1]

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^{15}N and ^{195}Pt NMR spectra have shown that $[Pt(^{15}NH_3)_3]_2(\mu\text{-}OH)^{3+}$ slowly forms when a solution containing $Pt(^{15}NH_3)_3(H_2O)^{2+}$ and $Pt(^{15}NH_3)_3(OH)^+$ is allowed to stand. By measurement of the change in δ_N or $J(\text{Pt–N})$ as the pH of a solution of $Pt(^{15}NH_3)_3(H_2O)^{2+}$ was changed, the pK_a for this complex was determined (6.37 ± 0.10). Reaction of a solution of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2{}^{2+}$ with chloride gave a solution containing *cis*-$Pt(^{15}NH_3)_2Cl(H_2O)^+$ and *cis*-$Pt(^{15}NH_3)_2Cl_2$. When the pH was increased to approximately 7, a new species, assigned as $[Pt(^{15}NH_3)_2]_2(\mu\text{-}Cl)(\mu\text{-}OH)^{2+}$, was formed. The variation of δ_N trans to water/hydroxide with pH for *cis*-$Pt(^{15}NH_3)_2Cl(H_2O)^+$ allowed the pK_a for this species to be determined (6.85 ± 0.10). Bromide behaved in an analogous way, but *cis*-$Pt(NH_3)(H_2O)_2{}^{2+}$ reacted with 1 mol of iodide to give $[\{Pt(NH_3)_2(\mu\text{-}I)\}_2]^{2+}$. The NMR peaks from this complex were previously wrongly assigned to *cis*-$Pt(NH_3)_2I_2$. Changes in δ_N of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2{}^{2+}$ with pH allowed the values of pK_{a1} and pK_{a2} to be determined, at 5 °C, to reduce the rate of formation of hydroxo-bridged species (5.93 ± 0.10 and 7.87 ± 0.10, respectively).

Introduction

Despite the interest in the chemistry of the antitumor compound *cis*-$Pt(NH_3)_2Cl_2$ and its derivatives in recent years, many aspects of the solution chemistry of these complexes remain relatively unexplored. For example, there are, to our knowledge, no values in the literature from reliable experimental determinations for the acid dissociation constants of the simple species *cis*-$Pt(NH_3)_2(H_2O)_2{}^{2+}$ (**1**) and *cis*-$Pt(NH_3)_2Cl(H_2O)^+$ (**2**). This is despite the frequent mention of such hydrolysis products in discussions of the biochemistry of *cis*-$Pt(NH_3)_2Cl_2$.[2] Grinberg and Ryabchikov[3] reported that although *trans*-$Pt(NH_3)_2(H_2O)_2{}^{2+}$ with NaOH gave a simple titration curve with two distinct "breaks" corresponding to the two deprotonation steps, the cis isomer, **1**, gave a much more complex titration curve, from which they claimed that they could obtain only an average of the two acid dissociation constants. If the data given by Jensen[4] are plotted, it is clear that he, too, obtained a complex titration curve from the titration of **1** with NaOH. He nevertheless analyzed these data to give values (at 20 °C) of pK_{a1} 5.56 and pK_{a2} 7.32. Perumareddi and Adamson[5] reported values of 5.63 and 9.25, respectively, but gave no details of their procedure. We now know[6–10] that, for solutions containing moderate concentrations of *cis*-$Pt(NH_3)_2(OH)(H_2O)^+$, there is rapid formation of hydroxo-bridged oligomers, $[Pt(NH_3)_2(\mu\text{-}OH)]_n{}^{n+}$ ($n = 2, 3$). Attempts to determine the acid dissociation constants of **1** that do not take this oligomerization into account cannot be expected to produce reliable results, especially for pK_{a2} (if the constants are determined, as is usually the case, by titration of **1** with NaOH). Potentiometric determinations have been carried out on analogous complexes with other amines (e.g., *trans*-1,2-diaminocyclohexane,[11] 1,2-diaminoethane (pK_{a1} 5.8, pK_{a2} 7.6)[12]) that may be more valid because of different rates of oligomerization.

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The situation is potentially more complex still for *cis*-$Pt(NH_3)_2Cl(H_2O)^+$ (**2**), since this complex in solution is always present together with *cis*-$Pt(NH_3)_2Cl_2$ and **1**.[7,13]

If ^{15}N-substituted ligands are used, NMR spectroscopy is a powerful tool for characterizing platinum ammine complexes in solution, since both the ^{15}N chemical shift and the ^{195}Pt–^{15}N coupling constant are sensitive primarily to the ligand trans to ammine, and the platinum chemical shift depends primarily on the set of donor atoms[6–9,13–16] (^{195}Pt, $I = {}^1/_2$, 34% abundance; ^{15}N, $I = {}^1/_2$). In this work, NMR spectroscopy is used to (i) study reactions of *cis*-$Pt(NH_3)_2(H_2O)_2{}^{2+}$ (**1**) with halide ions, (ii) study reactions of *cis*-$Pt(NH_3)_2Z(H_2O)^{n+}$ ($Z = Cl^-$, Br^- ($n = 1$); $Z = NH_3$ ($n = 2$)), and (iii) determine acid dissociation constants for *cis*-$Pt(NH_3)_2(H_2O)_2{}^{2+}$ (**1**), *cis*-$Pt(NH_3)_2Cl(H_2O)^+$ (**2**), and $Pt(NH_3)_3(H_2O)^{2+}$ (**3**).

We have recently described the use of ^{15}N NMR to determine the acid dissociation constant of *N*-acetylglycine chelated to the $Pt(^{15}NH_3)_2{}^{2+}$ moiety,[17] and Hollis and Stern[16] have used the ^{195}Pt chemical shift to study the protonation of an ascorbic acid complex.

Experimental Section

Starting Materials. Literature methods were used to prepare the following complexes (containing either ^{14}N or ^{15}N): *cis*-$Pt(NH_3)_2Cl_2$;[7] *cis*-$Pt(NH_3)_2(ONO_2)_2$;[7,9] $[Pt(NH_3)_3(ONO_2)]NO_3$.[13]

NMR Measurements. Instrumentation and basic procedures have been previously described.[9,13] All spectra were run in H_2O and were ^1H decoupled. Shifts to lower shielding are positive. The 21.4-MHz ^{195}Pt NMR spectra are referenced relative to a separate sample of 0.5 g of Na_2PtCl_6 in 2 mL of water and 10.1 MHz ^{15}N spectra to the ammonium ion signal from a 5 M solution of $^{15}NH_4{}^{15}NO_3$ in 2 M HNO_3 in a coaxial capillary.

pH Measurements. A TPS digital pH meter was used with a combination glass/reference electrode calibrated against phthalate (pH 4.01, 25 °C), phosphate (pH 6.87), and borate (pH 9.18) buffer solutions. Solutions were maintained at the desired temperature in glass vessels whose outer walls were jackets through which water from a constant-temperature bath (Colora or Thermomix) was passed. For the measurement of NMR parameters at a particular pH, the NMR probe was maintained at the same temperature as the constant temperature bath in which the sample was immersed. A volume of 5 mL was used for the measurements. pH was adjusted with HNO_3 or NaOH solution, and a 2-mL aliquot was removed and placed in an NMR tube (10 mm diameter), which was then placed in the instrument. The glass electrode remained covered by the solution remaining in the sample vessel. After the measurement, the aliquot was recombined with the bulk sample, and more HNO_3 or NaOH was added to change the pH to a new value. Concentrations of the platinum complexes were near 0.1 M. No electrolytes were added to control ionic strength.

Preparation of $[\{Pt(NH_3)_2(\mu\text{-}I)\}_2](NO_3)_2$ (16). *cis*-$Pt(NH_3)_2(ONO_2)_2$ (0.20 g, 0.563 mmol) was dissolved in 2 mL of H_2O, and a solution of NaI (0.084 g, 0.563 mmol) in 1 mL of H_2O was added dropwise with stirring. After the solution had been allowed to stand at ambient temperature for 20 min, the light brown solid which deposited was collected on a sintered glass funnel, washed successively with small volumes of cold water, ethanol, and ether, and then air-dried. Yield was 0.14 g (59%). Most batches of solid probably contained small quantities of *cis*-$Pt(NH_3)_2I_2$, which caused some variation in analytical results.

The IR spectrum (Nujol and hexachlorobutadiene mulls) showed bands due to ν(N–H) at 3300 and 3180 cm^{-1}, other bands due to coordinated ammonia at 1600 and 830 cm^{-1}, nitrate bands at 1380 and 1325 cm^{-1}, and ν(Pt–N) at 505 cm^{-1}.

Anal. Calcd for $H_{12}I_2N_6O_6Pt_2$: H, 1.4; I, 30.4; N, 10.1; O, 11.5; Pt, 46.7. Found (two separate samples, except for O analysis): H, 1.4, 1.3; I, 28.8, 32.6; N, 9.8, 9.9; O, 11.4; Pt, 45.7, 46.0.

Results and Discussion

Acid Dissociation of $Pt(NH_3)_3(H_2O)^{2+}$. We have previously described[13] the ^{15}N NMR spectrum of $Pt(^{15}NH_3)_3(H_2O)^{2+}$ (**3**): two singlets, with satellites from coupling to ^{195}Pt, in intensity ratio 2:1, corresponding respectively to the mutually trans ammine ligands (−63.8 ppm, J(Pt–N) = 299 Hz) and to ammine trans to water (−88.6 ppm, J(Pt–N) = 376 Hz). When the pH was increased to 10.3, the complex deprotonated to $Pt(^{15}NH_3)_3(OH)^+$ (**4**), and corresponding changes occurred in the ^{15}N spectrum (ammine trans to ammine, −64.3 ppm, J(Pt–N) = 294 Hz; ammine trans to hydroxide −80.4 ppm, J(Pt–N) = 286 Hz).[13] It was noted that the NMR parameters for the ammine ligand trans to water/hydroxide were affected by this deprotonation much more than the parameters for the mutually trans ammine ligands. At intermediate values of pH, **3** and **4** will both be present in equilibrium, in proportions determined by the value of the acid dissociation constant for **3**. Since the protonation/deprotonation reactions are fast on the NMR timescale, only one set of peaks (i.e., two singlets with satellites) is observed, with chemical shifts and coupling constants that are the concentration-weighted averages of the values for **3** and **4**.

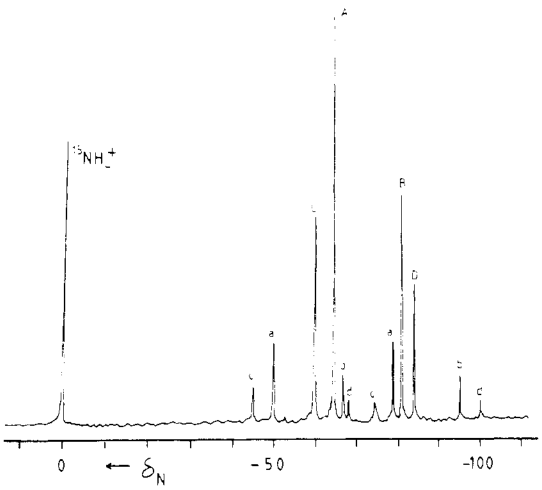
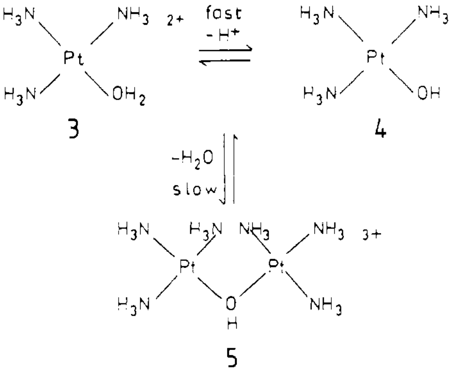


Figure 1. ^1H-decoupled 10.04-MHz ^{15}N NMR spectrum of a solution obtained by adjusting the pH of a solution of $[Pt(^{15}NH_3)_3(H_2O)](NO_3)_2$ to 6.7 and then allowing the solution to stand for 2 weeks. During this time, the pH decreased to 6.5. Peaks are labeled as follows (lower case letters indicate satellites from coupling to ^{195}Pt): for mononuclear complex $Pt(NH_3)_3(H_2O)^{2+}/Pt(NH_3)_3(OH)^+$, (Aa) mutually trans ammine ligands, (Bb) ammine trans to H_2O/OH^-; for dinuclear complex $[\{Pt(NH_3)_3\}_2(\mu\text{-}OH)]^{3+}$ (**5**), (Cc) mutually trans ammine ligands, (Dd) ammine trans to bridging hydroxide.

Scheme I



When such a solution, with pH initially 6.7, was allowed to stand overnight, a new set of peaks (two singlets with satellites) grew in the ^{15}N spectrum. The more intense (−59.8 ppm, J(Pt–N) = 298 Hz) clearly corresponded to mutually trans ammine ligands. The NMR parameters for the weaker singlet (−84.2 ppm, J(Pt–N) = 326 Hz) may be compared with those for ammine trans to bridging hydroxide in $[\{Pt(^{15}NH_3)_2(H_2O)\}_2(\mu\text{-}OH)]^{3+}$ (−81.8 ppm, J(Pt–N) = 339 Hz).[9] The ^{195}Pt NMR spectrum showed a new doublet of triplets with the same Pt–N coupling constants at −2049 ppm. This shift corresponds to a platinum atom bound by three N donors and one O donor.[13,14] The new peaks were therefore assigned to $[\{Pt(^{15}NH_3)_3\}_2(\mu\text{-}OH)]^{3+}$ (**5**) (Scheme I). These peaks

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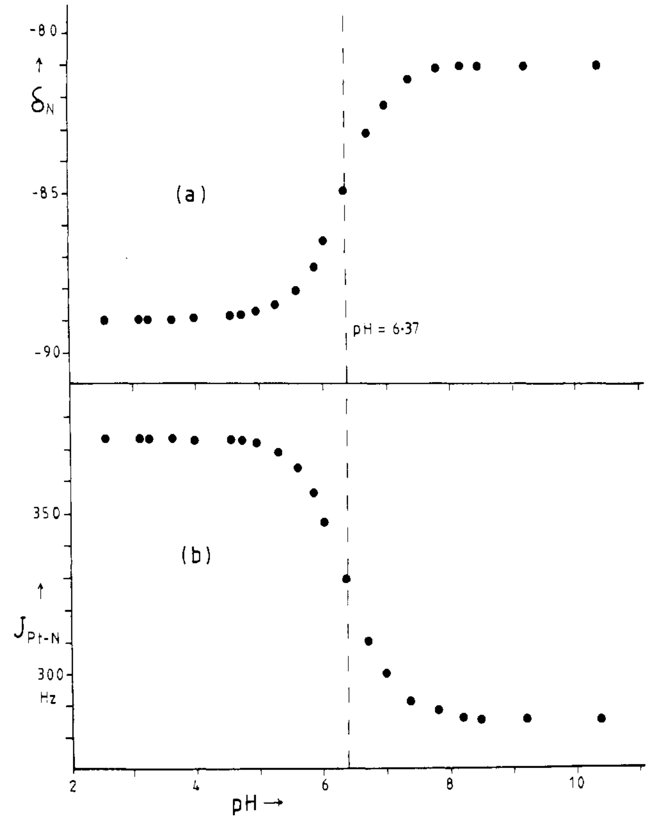


Figure 2. Plots of (a) δ_N and (b) J(Pt-N) trans to H_2O/OH^- against pH at 25 °C for a solution initially composed of $[Pt(^{15}NH_3)_3(H_2O)](NO_3)_2$ (**3**) in H_2O (0.131 M). Solutions of NaOH (0.993 M or 0.055 M) or HNO_3 (1.25 M) were added to change the pH.

continued to grow until equilibrium was reached (approximately 1 week) (Figure 1). With the use of the value of pK_a for **3** determined as described below (6.37), the equilibrium constant

$$K = \frac{[\{Pt(NH_3)_3\}_2(\mu\text{-}OH)^{3+}]}{[Pt(NH_3)_3(H_2O)^{2+}][Pt(NH_3)_3(OH)^{+}]} \qquad (1)$$

was evaluated at 15.0 ± 2.0 mol^{-1} L at 25 °C.

When dilute nitric acid was added to a solution containing **5**, to decrease the pH to 2.0, no changes were observed in the relative proportions of mono- and dinuclear species over 1.5 H. Once formed, the hydroxide bridge is therefore relatively kinetically stable. When this solution was heated, however (25 min, at 80 °C), there was almost total conversion to the aqua complex (**3**). Similar behavior has previously been observed for $[\{Pt(NH_3)_2(H_2O)\}_2(\mu\text{-}OH)]^{3+}$.[9]

^{15}N NMR spectra were obtained on a series of solutions with different pH values, obtained by addition of increasing amounts of sodium hydroxide solution to a solution of **3**. Significant amounts of the dinuclear complex (**5**) did not form in the time required for the experiment. Figure 2 shows plots against pH of δ_N (Figure 2a) and J(Pt-N) (Figure 2b) for the ammine ligand trans to water/hydroxide. Provided the ^{15}N chemical shifts for the protonated and deprotonated forms of the complex, δ_A and δ_B respectively, do not change during the experiment, the acid dissociation constant may be obtained from the measured pH and chemical shift δ with eq 2,[18] derived from the Henderson-Hasselbach equation.

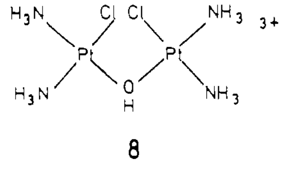
$$pK_a = pH + \log[(\delta - \delta_B)/(\delta_A - \delta)] \qquad (2)$$

The value of pK_a that gives the best (least-squares) fit of eq 2 to the experimental data between pH 5.28 and 7.38 was calculated as 6.35 ± 0.10. An equation analogous to (2) may be written for J(Pt-N). The value of pK_a determined from these measurements was 6.38 ± 0.10, in good agreement with the value obtained from chemical shift measurements. These results may be compared with those recently reported from a potentiometric study[19] of $Pt(dien)(H_2O)^{2+}$: pK_a = 5.87 ± 0.02, and the equilibrium constant for formation of a dinuclear complex was 108 ± 10 mol^{-1} L. In the diethylenetriamine complex, the amine groups are incorporated into five-membered chelate rings, which may cause the groups cis to hydroxide to be "pulled away" to some extent from the hydroxide ligand, decreasing steric interactions in the dinuclear complex.

In practice, it is more convenient to use chemical shift rather than coupling constant measurements for such determinations. The chemical shift measurement requires only the observation of the central resonance. Measurement of the coupling constants requires observation of the weaker satellite peaks, necessitating much longer accumulation times. Apart from higher demand on instrument time, dimerization reactions may occur to a greater extent during the measurement, with resultant changes in solution pH. Plots analogous to those in Figure 2 could be drawn for the ammine ligands cis to water/hydroxide, and similar values of pK_a could be obtained from these measurements, although with lower precision as the variation in the parameters with pH was much less for these ammine ligands.

Complexes with Chloride and Bromide. As previously reported,[7,13] reaction of a solution of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**) with 1 mol equiv of chloride gives a mixture of *cis*-$Pt(^{15}NH_3)_2Cl_2$ (most of which precipitates), *cis*-$Pt(^{15}NH_3)_2Cl(H_2O)^+$ (**2**), and some unreacted **1**. A similar solution may be obtained by reaction of an aqueous suspension of *cis*-$Pt(^{15}NH_3)_2Cl_2$ with an equimolar quantity of silver nitrate. The ^{15}N spectrum of **2** showed two singlets with satellites of equal intensity, at -65.8 ppm (J(Pt-N) = 343 Hz) from ammine trans to chloride, and at -88.8 ppm (J(Pt-N) = 369 Hz) from ammine trans to water. The ^{195}Pt spectrum showed a doublet of doublets at -1841 ppm.[13] The discrepancy between our values (at pH 2.8) for ammine trans to water and those quoted by Boreham et al.[7] (-83.7 ppm, J(Pt-N) = 361 Hz) may be accounted for, as they ran their spectra at pH 6.8, where there would be significant deprotonation of **2**. Their values were comparable to ours at this pH (see below). When a sodium hydroxide solution was added to increase the pH of the solution to 10.3, changes were observed in the NMR spectra, corresponding to deprotonation of **2** to *cis*-$Pt(^{15}NH_3)_2Cl(OH)$ (**6**): ammine trans to chloride, -66.5 ppm (J(Pt-N) = 347 Hz); ammine trans to hydroxide, -78.5 ppm (J(Pt-N) = 288 Hz); ^{195}Pt spectrum doublet of doublets at -1826 ppm.[13]

The pH of a solution of **1**, **2**, and *cis*-$Pt(^{15}NH_3)_2Cl_2$ prepared as described above, with a platinum concentration near 0.1 M, was 2.75. A sodium hydroxide solution was added to increase the pH to 6.7. The ^{15}N spectrum run within 15 min after mixing showed that the mononuclear species (a rapidly interconverting equilibrium mixture of **2** and **6**) was still predominant, but two new singlets with satellites of equal intensity had also appeared. Within 30 min, these had become the major peaks in the spectrum. One singlet with satellites (-84.3 ppm, J(Pt-N) = 321 Hz) may be confidently assigned to an ammine ligand trans to bridging hydroxide. The other set of signals, at -62.2 ppm (J(Pt-N) = 352 Hz) must be due to ammine trans to chloride. The ^{195}Pt NMR spectrum showed a doublet of doublets at -1722 ppm. The new species was formulated as $[\{Pt(^{15}NH_3)_2\}_2(\mu\text{-}Cl)(\mu\text{-}OH)]^{2+}$ (**7**) (Scheme II), in which there is a four-membered ring. This was preferred over the alternative possibility, **8** in which the chloride ligands are terminal rather than bridging, on the following grounds:



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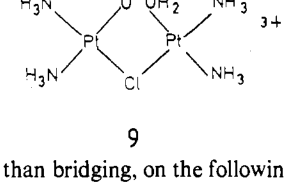

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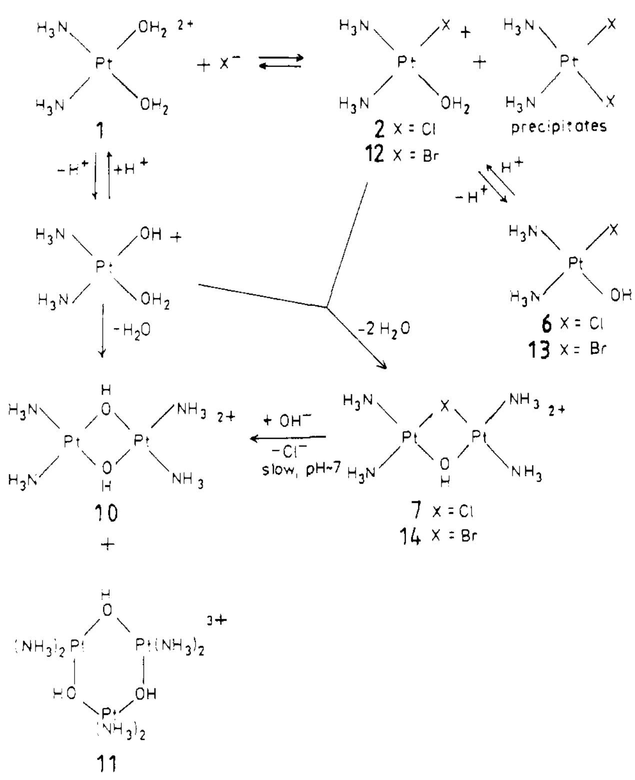
Scheme II



(i) The rapid formation of the new species and the almost complete conversion of mononuclear species to the dinuclear complex are closer to the behavior observed for $[\{Pt(^{15}NH_3)_2(\mu\text{-}OH)\}_2]^{2+}$ (**10**) with a four-membered ring[6-9] than to the behavior of nonring dinuclear complexes such as **5**.

(ii) Although the ^{195}Pt shift to lower shielding compared with that of *cis*-$Pt(^{15}NH_3)_2Cl(OH)$ (**6**) ($\Delta\delta$ 104) is less than the shift difference of $[\{Pt(^{15}NH_3)_2(\mu\text{-}OH)\}_2]^{2+}$ (**10**) compared with *cis*-$Pt(^{15}NH_3)_2(OH)_2$ ($\Delta\delta$ 410),[7] it is still significant. The shift for the hydroxo-bridged dimer is usually ascribed to a "ring strain effect".[7] Angles about platinum would be expected to be different in a $Pt_2Cl(OH)$ ring from a $Pt_2(OH)_2$ ring, which might give a lower shift.

(iii) The Pt–N coupling constant trans to chloride, 352 Hz, is slightly greater than in related complexes with terminal chloride (343 Hz for **2**, 347 Hz for **6**). This difference is too small to be convincing in itself but is in the direction expected if chloride is bridging rather than terminal.

In an attempt to provide additional evidence for the structure of the complex, a sample was acidified with dilute perchloric acid to decrease the pH (initially 6.5) to 2.0. While acidification of either **7** or **8** would ultimately give **2** (with **1** also formed from reaction of **7**), **7** would initially be expected to give $[\{Pt(^{15}NH_3)_2(H_2O)\}_2(\mu\text{-}Cl)]^{3+}$ (**9**), which might be detectable by NMR. However, no peaks assignable to **9** were observed in the ^{15}N spectrum. Peaks due to **2** grew rapidly. If the complex present was initially **7**, it must form **2** and **1** rapidly on the time scale of the experiment (several minutes). The dinuclear complex that is present in solution cannot therefore be formulated as **7** with complete confidence, but shall be labeled so in future discussion.

When the solution was allowed to stand overnight near pH 7, the peaks due to **7** decreased greatly in intensity while those due to the hydroxo-bridged dimer **10** and trimer **11** increased, to become the dominant peaks in the spectrum.

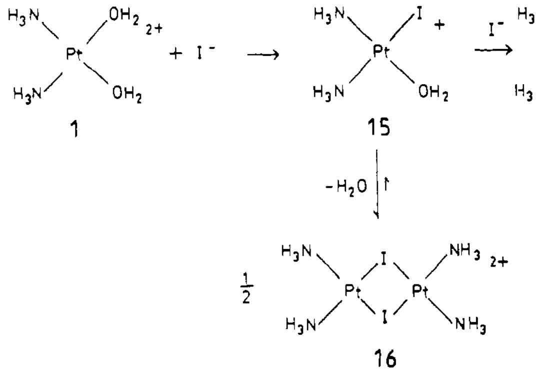
As we mentioned in the Introduction, it would be difficult to determine the acid dissociation constant for coordinated water in *cis*-$Pt(NH_3)_2Cl(H_2O)^+$ (**2**), because of the variety of other complexes that is also usually present with it in solution. With the ammine ligands highly enriched in ^{15}N, ^{15}N NMR spectroscopy provides a means for determining this constant. The proton transfer between *cis*-$Pt(NH_3)_2Cl(H_2O)^+$ and *cis*-$Pt(NH_3)_2Cl(OH)$ (**6**) is rapid on the NMR time scale, so that one singlet with satellites is expected for ammine trans to aqua/hydroxo and one for ammine trans to chloride in these mononuclear complexes. From the shifts reported above for **2** and **6**, it is clear that δ_N trans to aqua/hydroxo is more sensitive to the deprotonation reaction ($\Delta\delta$ 10.3) than δ_N trans to chloride ($\Delta\delta$ 0.7), so the former peak was chosen for measurement. Even if numerous species were present in a given solution at a measured pH, it was only necessary that the ^{15}N signal corresponding to ammine trans to aqua/hydroxo be detected and identified and the shift measured to allow calculation of pK_a for **2**. There was usually no difficulty with this measurement at 25 °C, provided that the spectra were run as quickly as possible. The main limitation of the method is that the measurement of the ^{15}N spectrum requires a finite time (typically 10–20 min) and the pH can change significantly in that time (usually by less than 0.1 pH units, but occasionally up to 0.3 units) as dimerization and other reactions occur. Buffers were not used, as components of common buffers are potential ligands.[9] Values of pH at the beginning and end of a spectrum accumulation period were averaged. The variation of δ_N with pH was qualitatively similar to that shown in Figure 2a for **3**. By a procedure similar to that discussed above for **3**, the pK_a for *cis*-$Pt(NH_3)_2Cl(H_2O)^+$ (**2**) was determined as 6.85 ± 0.10 at 25 °C. This may be compared with the value 6.3 predicted by Martin[2] by comparison with values for other complexes.

Solutions containing *cis*-$Pt(^{15}NH_3)_2Br(H_2O)^+$ (**12**) with smaller amounts of **1** and *cis*-$Pt(^{15}NH_3)_2Br_2$ were prepared by procedures analogous to those used for preparation of solutions containing predominantly *cis*-$Pt(^{15}NH_3)_2Cl(H_2O)^+$ (**2**). We have previously reported[13] NMR parameters for *cis*-$Pt(^{15}NH_3)_2Br_2$, **12**, and the deprotonated complex *cis*-$Pt(^{15}NH_3)_2Br(OH)$ (**13**) (pH >10). Near pH 7, changes occurred in NMR spectra that were analogous to those observed for the chloride system. Thus, peaks due to a dinuclear complex, formulated as $[\{Pt(^{15}NH_3)_2\}_2(\mu\text{-}Br)(\mu\text{-}OH)]^{2+}$ (**14**) quickly became dominant (δ_N trans to bromide −54.4, J(Pt–N) = 342 Hz; δ_N trans to hydroxide −86.6, J(Pt–N) = 315 Hz; δ_{Pt} (doublet of doublets) −1825), and, more slowly, peaks due to $[\{Pt(^{15}NH_3)_2(\mu\text{-}OH)\}_n]^{n+}$ (n = 2,3) grew.

Complexes with Iodide. The addition of 1 mol equiv of sodium iodide to a solution of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**) produced quite different results from those obtained with chloride or bromide. ^{15}N and ^{195}Pt NMR spectra showed only weak peaks assignable to *cis*-$Pt(^{15}NH_3)_2I(H_2O)^+$ (**15**) (δ_N trans to I^- −45.8, J(Pt–N) = 300 Hz; δ_H trans to H_2O −95.3, J(Pt–N) = 350 Hz; δ_{Pt} (doublet of doublets) −2224). The major peaks in the ^{15}N spectrum were a singlet with satellites (−57.0 ppm, J(Pt–N) = 311 Hz), and in the ^{195}Pt spectrum a 1:2:1 triplet (−3198 ppm). We have previously assigned these peaks to *cis*-$Pt(^{15}NH_3)_2I_2$,[13] noting that J(Pt–N) was larger than expected for this complex. It is now clear that this assignment is inconsistent with the stoichiometry of the present reaction, since insufficient iodide was added to convert most of the complex **1** initially present into the diiodo complex. No peaks of significant intensity from **1** remained in the spectrum. Furthermore, the high intensity of the peaks was inconsistent with the low solubility of *cis*-$Pt(^{15}NH_3)_2I_2$, as a saturated aqueous solution of *cis*-$Pt(^{15}NH_3)_2I_2$ at 25 °C did not give a detectable signal. In hot water (80–90 °C) ^{15}N peaks were observed (−50.6 ppm, J(Pt–N) = 270 Hz). With prolonged heating (>1 h) a new singlet with satellites grew (−66.7 ppm, J(Pt–N) = 288 Hz), which was probably due to *trans*-$Pt(^{15}NH_3)_2I_2$. *cis*-$Pt(^{15}NH_3)_2I_2$ was also quite soluble in *N,N*-dimethylformamide. A solution in this solvent gave a singlet with satellites in the ^{15}N spectrum (−52.3 ppm, J(Pt–N) = 264 Hz) and a 1:2:1 triplet in the ^{195}Pt spectrum at −3268 ppm. With the trans and cis influence parameters estimated previously,[13] calculated ^{15}N parameters for *cis*-$Pt(^{15}NH_3)_2I_2$ are δ_N −55.6 and J(Pt–N) = 271 Hz.

The NMR peaks observed when equimolar quantities of **1** and NaI were mixed were therefore assigned to the dinuclear complex $[\{Pt(^{15}NH_3)_2(\mu\text{-}I)\}_2]^{2+}$ (**16**) (Scheme III). The relatively large Pt–N coupling constant, 311 Hz, then corresponds to ammine trans to bridging rather than terminal iodide, and the Pt nucleus res-

Scheme III



onates 70 ppm to lower shielding than for *cis*-Pt($^{15}NH_3)_2I_2$, a small shift, but in the direction expected when the Pt nucleus is incorporated in a four-membered ring (see discussion above). A yellow-brown solid deposited from concentrated aqueous solutions containing **16**. It was difficult to prevent some contamination of this material with *cis*-Pt($NH_3)_2I_2$, but analytical results (see Experimental Section) supported its formulation as [{Pt($NH_3)_2(\mu$-I)}$_2$]($NO_3)_2$. While our work was in progress, O'Halloran et al.[20] published an account of the preparation and crystal structure of the ethylenediamine analogue, [{Pt(en)(μ-I)}$_2$]($NO_3)_2$. They observed a ^{195}Pt NMR peak at −3453 ppm, slightly to lower shielding from the signal from Pt(en)I_2 in dimethylformamide (−3461 ppm). They noted the tendency for the ion [{Pt(en)(μ-I)}$_2$]$^{2+}$ to disproportionate in solution to Pt(en)($H_2O)_2{}^{2+}$ and Pt(en)I_2, which then precipitates.

A sample of [{Pt($^{15}NH_3)_2(\mu$-I)}$_2$]($NO_3)_2$ dissolved in water gave initially in its ^{15}N spectrum only the singlet at −57.0 ppm, with satellites, described above. When the solution was allowed to stand, *cis*-Pt($^{15}NH_3)_2I_2$ slowly deposited, and peaks due to *cis*-Pt($^{15}NH_3)_2I(H_2O)^+$ and [{Pt($^{15}NH_3)_2(\mu$-OH)}$_n$]$^{n+}$ (n = 2, 3) appeared.

In alkaline solution (pH 8–10), *cis*-Pt($^{15}NH_3)_2(OH)_2$ reacted slowly with 1 mol equiv of NaI to give solutions showing NMR peaks assignable to *cis*-Pt($^{15}NH_3)_2I(OH)$ (δ_N trans to I$^-$, −46.2 ppm (J(Pt–N) = 307 Hz); δ_N trans to OH$^-$, −85.8 (J(Pt–N) = 275 Hz); δ_{Pt} −2199 (doublet of doublets)).

Acid Dissociation of *cis*-Pt($NH_3)_2(H_2O)_2{}^{2+}$ (1). The two acid dissociation reactions from **1** are

$$\underset{\text{“AA”}}{cis\text{-Pt}(NH_3)_2(H_2O)_2{}^{2+}} \overset{K_{a1}}{\rightleftharpoons} \underset{\text{“AB”}}{cis\text{-Pt}(NH_3)_2(OH)(H_2O)^+} + H^+ \tag{3}$$

$$\underset{\text{“AB”}}{cis\text{-Pt}(NH_3)_2(OH)(H_2O)^+} \overset{K_{a2}}{\rightleftharpoons} \underset{\text{“BB”}}{cis\text{-Pt}(NH_3)_2(OH)_2} + H^+ \tag{4}$$

These reactions are fast on the NMR time scale, so that only one singlet with satellites is observed in the ^{15}N NMR spectrum from these mononuclear complexes under all pH conditions. *cis*-Pt($NH_3)_2(OH)(H_2O)^+$ rapidly forms oligomers at 25 °C, but if the solution is cooled to 5 °C, the oligomerization reactions are slowed sufficiently to allow measurement of ^{15}N NMR spectra for the mononuclear species. The NMR parameters were constant over the pH range 0–4, where *cis*-Pt($^{15}NH_3)_2(H_2O)_2{}^{2+}$ was present (δ_{AA} −85.69), and over the range pH 10–14, where *cis*-Pt($^{15}NH_3)_2(OH)_2$ was present (δ_{BB} −78.39). The parameters were very sensitive to pH over the range pH 4–10. To minimize spectrum accumulation times, only chemical shifts and not coupling constants were monitored. If δ_{AA}, δ_{BB}, and δ_{AB} correspond to the ^{15}N chemical shifts of the three mononuclear species labeled as in eq 3 and 4 and δ is the measured chemical shift, then

$$\delta = ([AB]\delta_{AB} + [AA]\delta_{AA} + [BB]\delta_{BB})/([AB] + [AA] + [BB]) \tag{5}$$

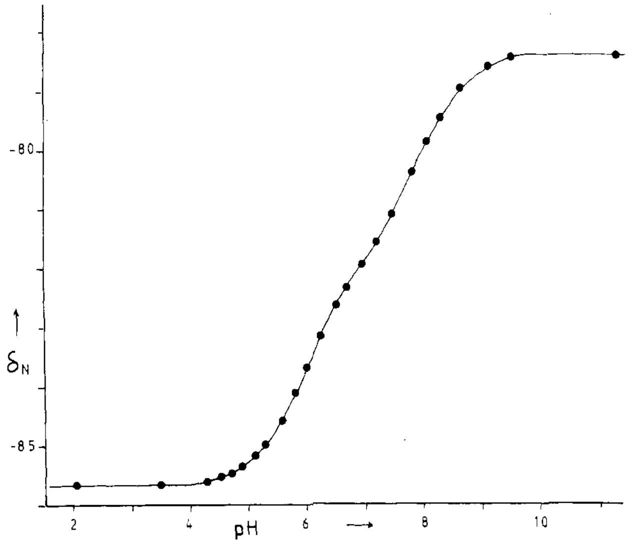


Figure 3. Plot of δ_N against pH at 5 °C for the mononuclear species in solutions obtained from addition of NaOH or HNO_3 to a solution initially containing *cis*-[Pt($^{15}NH_3)_2(H_2O)_2$]($NO_3)_2$ in H_2O. The solid line is the theoretical curve calculated by using pK_{a1} = 5.93, pK_{a2} = 7.87, and δ_{AB} = −82.02.

From the definitions of the dissociation constants, [AA] = [AB][H$^+$]/K_{a1} and [BB] = K_{a2}[AB]/[H$^+$]. Substituting for [AA] and [BB] in eq 5 and canceling [AB] from numerator and denominator, we have

$$\delta = (\delta_{AB} + \delta_{AA}[H^+]/K_{a1} + \delta_{BB}K_{a2}/[H^+])/(1 + [H^+]/K_{a1} + K_{a2}/[H^+]) \tag{6}$$

A similar equation has been previously applied to measurement of absorbance in electronic spectra.[21] With the use of an iterative computer program,[22] the parameters K_{a1}, K_{a2}, and δ_{AB} were varied to give the best least-squares fit to the experimental data over the pH range 4.3–9.1. The values obtained were pK_{a1} = 5.93 ± 0.10, pK_{a2} = 7.87 ± 0.10, and δ_{AB} = −82.02 ± 0.05. The experimental values are shown in Figure 3, together with the theoretical curve plotted by using these values. The value for δ_{AB} may be compared with that predicted from the trans influence parameters for H_2O and OH$^-$ previously determined empirically,[13] −81.65.

This represents the first determination of the acid dissociation constants for **1** that does not suffer from uncertainties associated with the formation of hydroxo-bridged oligomers. Although the low temperature used in our measurements prevents the use of our values in any precise calculations under conditions applying in vivo, they are likely to give a better qualitative insight into equilibria there than some of the previous estimates mentioned in the Introduction.

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Registry No. 1 (unlabeled), 20115-64-4; 2 (unlabeled), 53861-42-0; 3 (unlabeled), 17524-19-5; 4 (unlabeled), 97732-33-7; 5 (unlabeled), 119998-86-6; 6 (unlabeled), 94118-73-7; 7 (unlabeled), 119998-87-7; 10 (unlabeled), 62048-57-1; 11 (unlabeled), 61951-01-7; 12 (unlabeled), 91589-84-3; 13 (unlabeled), 119998-88-8; 14 (unlabeled), 119998-89-9; 15 (unlabeled), 119998-90-2; 16($NO_3)_2$ (unlabeled), 119998-92-4; *cis*-Pt($NH_3)_2Cl_2$, 15663-27-1; *cis*-Pt($NH_3)_2(ONO_2)_2$, 41575-87-5; *cis*-Pt($NH_3)_2Br_2$, 15978-91-3; *cis*-Pt($NH_3)_2I_2$, 15978-93-5; ^{195}Pt, 14191-88-9.

Supplementary Material Available: Tables I–III, showing the variation of NMR parameters with pH (3 pages). Ordering information is given on any current masthead page.

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