undergoes hydrolysis. Both the somewhat greater trans effect of chloride (vs. ammonia) and the 2/1 statistical factor favor hydrolysis for this complex compared to the amino acid complexes. Finally, the extent of hydrolysis of these amino acid complexes (as measured by K_h) is substantially less than that of $Pt(en)Cl_2$.[21] This can be attributed to a substantial negative cis influence of the dimethyl sulfoxide, augmented by the 2/1 statistical factor for $Pt(en)Cl_2$.

Mechanism of Hydrolysis by OH^-. The contrasting behavior of the three amino acid complexes in their reaction with hydroxide ion can be accounted for on the basis of their structural differences. Both glycine and sarcosine complexes contain an NH proton. The pK_a of such protons has been estimated to be about 15. Thus, addition of OH^- sufficient to produce a pH of 10–12 would produce a significant concentration of the conjugate base of these complexes by loss of the NH proton. The importance of this conjugate base mechanism for substitution reactions has long been recognized,[22] but it is not clear why the chelate ring and not the chloride of the conjugate base is so readily attacked by OH^-. The large trans effect of Me_2SO is probably an important factor. Loss of the NH proton should greatly strengthen the Pt–N bond in the same way that loss of a proton from coordinated water strengthens the Pt–O bond. This might be expected to lead to loss of the Cl^- trans to N, but the ring-opening reaction is also facilitated: the ring-opening reaction prevails. For the *N,N*-dimethylglycine complex, by contrast, the ring-opening reaction does not occur to a significant extent in competition with the hydrolysis reaction.

This unexpected ring-opening reaction by OH^- is comparable to the unexpected cis(N,N) addition of a second mole of amino acid to the aquo species derived from the preferred isomer of $Pt(alanine)(Me_2SO)Cl$, which Kukushkin and Garganova first reported.[14] This reaction led them to the wrong conclusion about the stereochemistry of the compound, which they incorrectly identified as the trans(N,S) isomer. At high pH values, other ligands will readily displace the O of the coordinated carboxyl group. For the reaction with OH^-, the effect is strictly a kinetic effect. Given enough time, the predominant species is the ring-closed, chloride-substituted species that would result from simple displacement.

An understanding of the chemistry of the formation of aquo (and hydroxo) species from chloro species has enabled us to prepare aquo species readily and to analyze the acid–base and dimerization properties of these aquo species and of $Pt(dien)OH_2^{2+}$.[13] The report of such investigations of these amino acid–Me_2SO complexes will include analysis of the relative importance of chloro, aquo, hydroxo, and dimer species as a function of pH and pCl.[23]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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Equilibrium and Kinetic Studies of Monoaquo Complexes of Platinum(II). 2. Dimerization of $Pt(dien)(H_2O)^{2+}$

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The dimerization of $Pt(dien)(OH_2)^{2+}$ by reaction with the conjugate base $Pt(dien)(OH)^+$ to form the μ-OH-bridged species has been investigated by pH methods. Rate constants at 35 °C for both dimerization ($k_d = 3.3 \times 10^{-3}$ M^{-1} s^{-1}) and dissociation ($k_d = 3.0 \times 10^{-5}$ s^{-1}) and the equilibrium constant ($K_d = 108$ M^{-1}) for the reaction were obtained by monitoring the pH after partial titration with NaOH. The significance of these data is illustrated with species distribution curves of dimer as a function of pH and total platinum concentration.

The aqueous solution chemistry of platinum complexes has attracted considerable interest in the last few years, owing in part to its pertinence to use of *cis*-platinum and related compounds in cancer chemotherapy.[1] Among the most studied platinum chelates are the diethylenetriamine complexes, which have the advantage of relatively simple chemistry for substitution reactions. The chloro complex [Pt(dien)Cl]Cl has been used extensively to probe the details of the reaction of DNA nucleotides and nucleosides with a labile platinum species.[2] Martin and co-workers have employed the analogous palladium species, which had parallel chemistry but which reacts more rapidly.[3]

In spite of the fact that $Pt(dien)Cl^+$ has been studied extensively for many years, confusion about the mechanism of its substitution reactions is still evident. Beattie[4] has recently provided an alternative interpretation of kinetic data for anation of $Pt(dien)(OH_2)^+$,[5] which had been cited as evidence for a 3-coordinate intermediate in the reaction.[6] His interpretation provides values for the rate constants for the hydrolysis reaction

$$Pt(dien)Cl^+ + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Pt(dien)(OH_2)^{2+} + Cl^- \quad (1)$$

and for the corresponding equilibrium constant $K_h = k_1/k_2$.

In their study of the aqueous solution chemistry of $Pd(dien)(OH_2)^{2+}$, Martin and Lim obtained evidence for the formation of a μ-OH bridged dimer of the aquo species.[7] The reaction can be formulated

$$Pd(dien)(OH_2)^{2+} + Pd(diene)(OH)^+ \rightarrow (dien)Pt\text{–}OH\text{–}Pt(dien)^{3+} + H_2O \quad (2)$$

For reaction 2 at 25 °C and 0.5 M KNO_3, Scheller and Martin obtained an equilibrium constant, K_d, of 132 M^{-1}.[8] However, as Martin has pointed out in reviewing the hydrolytic equilibria

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[1] Lippard, S. J. *Science (Washington, D.C.)* **1982**, *218*, 1075.

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[6] Mureinik, R. J. *Coord. Chem. Rev.* **1978**, *25*, 1.

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in these systems, the corresponding "dimerization reaction in $Pt(dien)(OH_2)^{2+}$ awaits study."[3]

As part of a broader study of the aqueous solution chemistry of monoaquo platinum species, we have recently obtained both rate and equilibrium data for the dimerization of these platinum species, i.e., for the process that we will abbreviate

$$Pt\text{-}OH_2^{2+} + Pt\text{-}OH^+ \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} Pt\text{-}OH\text{-}Pt^{3+} + H_2O \qquad (3)$$

The data are of interest in themselves, and the pH relaxation method employed to follow the reactions is probably generally applicable to similar systems. For any partially neutralized solution of the acidic aquo species, the effect of the dimerization is to change the ratio of acid to conjugate base, and hence to change the pH. If less than half of the acid is neutralized, the pH will drop as dimerization occurs; if more than half, it will increase. For a half-neutralized solution, the pH will remain constant as dimerization occurs. In practice, about 10% or 90% neutralization yields maximum changes in the pH associated with the subsequent dimerization. Both rate and equilibrium constants for the dimerization process can be obtained from analysis of the pH decay curves.

Experimental Section

[Pt(dien)I]I. This compound, used to prepare the corresponding aquo species, was prepared from $PtI_2 \cdot H_2O$, which in turn was prepared from K_2PtCl_4 by treatment with KI as reported by Watt and Cude.[9]

$[Pt(dien)(OH_2)](NO_3)_2$. A stock solution of the aquo complex in water was prepared by heating 2 mmol of the iodide complex with 4 mmol of $AgNO_3$ in about 25 mL of water at 50° for 3 h. The reaction mixture was then centrifuged to remove the AgI precipitate, and the solid was washed three times with small portions of water. The washings were added to the decantate. This solution was then rotary evaporated to dryness and carefully diluted to 10.0 mL in a volumetric flask.

Titration and pH Recording Procedures. Titrations and kinetic runs were carried out in a thermostated 10-mL cell, which was fitted with appropriate electrodes and a buret. Titrations and kinetic runs were carried out under an atmosphere of nitrogen. The pH was determined with a Corning Model 10 pH meter with an expanded scale. The output of the meter was connected to a Houston Instruments Omniscribe strip chart recorder. The temporal stability of the system was tested to insure essentially zero drift over several hours before any kinetic runs were made. In the kinetic runs, the pH was monitored for at least 12 h, with the recorder set up to give full scale deflection with a change of 1.00 pH unit.

Results

pK_a Determination. The concentration of stock solution and the pK_a of $Pt(dien)(OH_2)^{2+}$ were both determined by titrations of 1.00-mL portions of the stock solution (about 0.2 M) diluted with 2.00 mL of water with 0.1000 N NaOH in a thermostated titration cell. The titration was carried out rapidly to minimize complications from dimerization. The pK_a (5.87 ± 0.02) was taken as the pH at half neutralization.

Analysis of the Rate Data. The basis of the rate determinations is the shift in the titration curve of $Pt(dien)(OH_2)^+$, which results from the dimerization process as formulated in eq 3. We have written computer procedures using RS/1 software resident in a VAX-8600 computer to generate simulated titration curves based on the full equilibrium model, including the dimerization process. After determining the pK_a in a separate titration, we ran simulated titration curves to estimate the pH changes to be expected from the slow dimerization following rapid partial neutralization. This change is shown in Figure 1 as the difference in pH at a given extent of neutralization between the curve for $K_d = 0$ and the curve for a given K_d value. The dimer curve in Figure 1 corresponds approximately to the experimental conditions employed in kinetic runs and to $K_d = 108\ M^{-1}$, the value determined subsequently on the basis of the equilibrium composition of the solutions employed in the kinetic runs. On the basis of Figure 1, we estimated that the pH would change by more than half a pH unit after 10–20% titration for K_d values near 100 and 0.05 M initial concentration of complex.

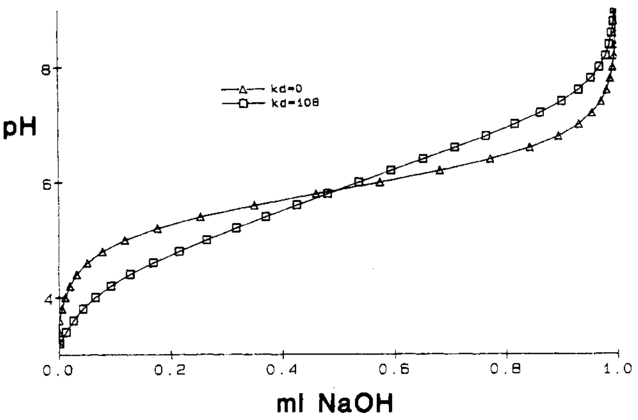

Figure 1. Effect of dimerization on the titration curve of 0.05 M monoaquo platinum complex titrated with 0.100 M NaOH for $pK_a = 5.87$ and $K_d = 108$.

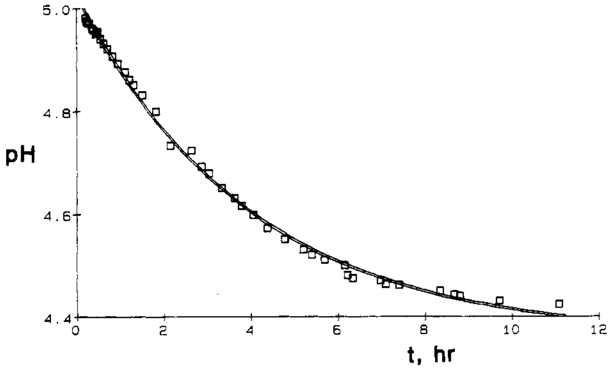

Figure 2. Decay curve reflecting the dimerization reaction of $Pt(dien)(OH_2)^{2+}$ with $Pt(dien)(OH)^+$ at 35 °C: $A_0 = 0.0399$ M; $B_0 = 0.00609$ M.

The experimentally determined pH decay curve for one of the kinetic runs is shown in Figure 2. Over the 12 h of the experiment, the pH changes by about 0.6 unit, in accord with the expectations of the equilibrium model shown in Figure 1 with a K_d value of about 108 and 12% neutralization.

The pH vs. time curves for partially neutralized solutions, diluted to about 0.05 M in Pt, were then used to determine the concentrations of $Pt\text{-}OH_2^{2+} = A$, $Pt\text{-}OH^+ = B$, and dimer $= D$ as a function of time as follows: For each pH value, the ratio B/A was calculated from

$$pH = pK_a + \log (B/A) \qquad (4)$$

Since B_0 and A_0, the initial concentrations of base and acid forms before any dimer formed, were known from the stoichiometry, the concentrations of dimer and of base and acid forms at any time were then calculated from

$$B/A = (B_0 - D)/(A_0 - D) \qquad (5)$$

The concentration of $Pt(dien)(OH)^+ = (B_0 - D)$, calculated from (4) and (5), is shown as a function of time for one of the kinetic runs in Figure 3. Figure 3 also includes the curve calculated by a least-squares linear regression fit of the data, assuming first-order kinetics, i.e.

$$B = B_\infty + (B_0 - B_\infty)e^{-kt} \qquad (6)$$

where B_∞ is the equilibrium concentration of $Pt(dien)(OH)^+$ and k is the first-order rate constant for the approach to equilibrium.

The experimentally determined first-order rate constant, k, can be used to calculate the rate constants k_d and k_{-d} on the basis of an assumed rate law. If we assume second-order dimerization and a first-order reverse reaction, the rate law can be formulated

$$\text{rate} = dB/dt = k_dAB - k_{-d}D \qquad (7)$$

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[9] Watt, G. W.; Cude, W. A. *Inorg. Chem.* **1968**, *7*, 335.

[10] Alcock, R. M.; Hartley, F. R.; Rogers, D. E. *J. Chem. Soc., Dalton* **1973**, 1070.

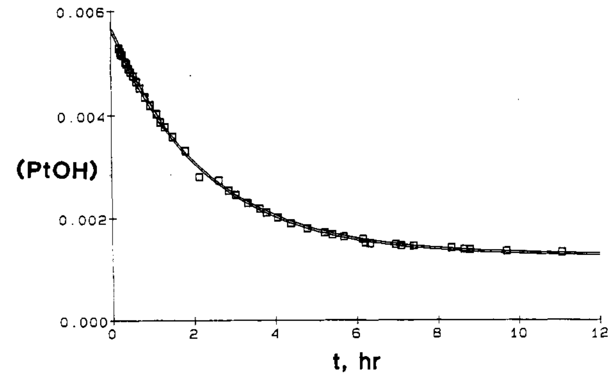

Figure 3. Decay curve of Pt(dien)(OH)$^+$ calculated from the pK_a of Pt(dien)$(OH_2)^{2+}$ = 5.87 and the data in Figure 2. The corresponding least-squares regression equation is [Pt(dien)(OH)$^+$] = 0.00119 + 0.00490 exp(-1.18×10^{-4} t).

Table I. Rate and Equilibrium Data for the Dimerization of Pt(dien)$(OH_2)^{2+}$ at 35 °C

run no.	A_0	B_0	$D_\infty = (B_0 - B_\infty)$	K_d/M^{-1}
1	0.0399	0.006 09	0.004 90	118
2	0.0406	0.005 64	0.004 39	97
mean				108 ± 10

run no.	$10^4k/s^{-1}$	$10^4k_d/M^{-1}\ s^{-1}$	$10^4k_d/M^{-1}$
1	1.18 ± 0.04	33.4	0.28
2	1.19 ± 0.02	32.5	0.33
mean		33 ± 1	0.30 ± 0.03

Under the conditions employed, only a small fraction of the acid form will react, so that the reaction can be treated as a pseudo-first-order reversible reaction with $d_{d'} = k_dA$. The observed first-order rate constant, k, can be identified with $k_{d'} + k_{-d}$. Furthermore, $k_d = k_{d'}/A_\infty$ and $K_d = k_d/k_{-d} = D_\infty/A_\infty B_\infty$, so all three constants can be calculated from the data. Results for two separate kinetic runs at 35 °C are collected in Table I.

Discussion

The dimerization constant for Pt(dien)$(OH_2)^{2+}$, 108 ± 10 M^{-1}, reported here is close to the 132 M^{-1} reported for the corresponding Pd complex at 25 °C.[3,8] For a 0.10 M solution at pH = pK_a, more than half of the complex is in the form of the dimer. Of course, as the pH moves away from the pK_a and for more dilute solutions the extent of dimerization rapidly becomes negligible. The effect of pH and of total concentration of platinum on the fractional populations of the dimer is shown in Figure 4. The fractional populations were calculated from the equilibrium model, which takes into account both dimerization and the acid/base equilibrium. For solutions more dilute than about 0.003 M in Pt, the fractional population of dimer never exceeds 10%, even at pH = pK_a where its concentration is a maximum.

It is not surprising that the dimerization of Pt(dien)$(H_2O)^{2+}$ has not been noticed in connection with any of the kinetic studies that have been done on the compound. Much of that work involved spectrophotometric analysis that required relatively dilute solutions. In addition, much of that work was done at relatively low pH, where the aquo species prevails, or at high pH, where the hydroxo form prevails. The comparative sluggishness of the dimerization reaction relative to competing reactions probably also contributed to its neglect. Though the population distribution shown in Figure 3 and the sluggishness of the dimerization reduce the chances that the process will have any significant effect on reactions of the aquo complex, there may be conditions where dimerization is an important complication. The addition of basic ligands whose conjugate acids have pK_a values comparable to the pK_a of the dien species, about 6, will yield solutions buffered near the pK_a, where the equilibrium fraction of dimer is a maximum. If concentrated solutions of such mixtures are allowed to equilibrate, the concentration of dimer may be significant.

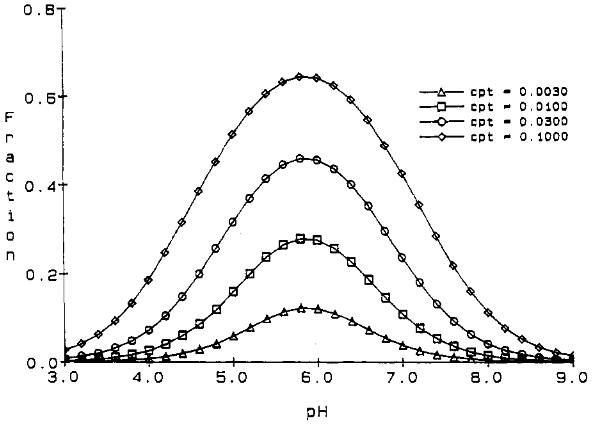

Figure 4. Effect of pH and total platinum concentration on the fractional population of dimers.

The close similarities in the pK_a and K_d for the parallel platinum and palladium dimers add support to Martin's efforts to employ palladium analogues to model the detailed solution chemistry of the more sluggish platinum complexes.[3] The palladium complex is somewhat less acidic (pK_a = 7.74 in 0.5 M KNO_3 at 21 °C vs. 5.87 at 35 °C or 6.13 at 25 °C[10] for the platinum analogue). However, the dimerization constants are both close to 100, so the significance of the dimer species in the two cases is comparable.

The pH relaxation approach, guided by computer modeling as employed in this study, is currently being applied to the somewhat faster dimerization processes of mixed amino acid–Me_2SO–aquo complexes of platinum.[11] The same approach could very likely be used to determine the much faster dimerization rate of the parallel Pd(dien)$(OH_2)^{2+}$ species. The success is fitting the titration data for the palladium complex to an equilibrium model suggests that the rate of dimerization for the palladium species is at least 100–1000 times faster than that of the platinum species, for which an ordinary titration curve shows no perceptible deviation from ideal behavior.

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Registry No. Pt(dien)(OH_2), 48102-16-5; Pt(dien)(OH)$^+$, 48102-15-4.

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(11) Erickson, L. E.; Burgeson, I. E.; Eidsmoe, E.; Larsen, R. G., manuscript in preparation.