(on N) and 10 H (on C). Since the residual valence on NH is 0.2, the residual valence on the remaining H atoms is 0.74, or 0.074 valence unit per H atom.

As suggested earlier,[11] in order to form aquo complexes of platinum, certain hydrogen-bonding requirements must be fulfilled. The coordinated water molecule must form two strong bonds, where it would donate the protons. This was observed in the structures described in the Introduction.[1,14,17] In our compound, the aquo ligand also forms two strong bonds, the first with one oxygen atom of the intramolecular sulfate ligand (O(5)---O(4) = 2.627 (8) Å) (Table IV) and the second with a molecule of lattice water (O(5)---O(6) = 2.629 (8) Å). Therefore, the lattice molecule of water O(6) plays a very important role in the stabilization of the crystalline structure. On the basis of the valence sums in Figure 2, O(3), O(4), and O(6) are underbonded (1.80, 1.81, and 1.84). Therefore, these atoms must be hydrogen bonded to the CH groups. The application of Brown's theory to the crystal structure of $[Pt(NH(CH_3)C_2H_4NH(CH_3))(SO_4)(H_2O)]\cdot H_2O$ seems very interesting, and a more detailed theoretical study, including van der Waals interactions, should improve the results.

Sulfate ions are usually believed to be bidentate ligands toward Pt(II) in the solid state. In aqueous solution, ^{195}Pt NMR has shown the presence of $[PtL_2(SO_4)(H_2O)]$ species.[25,26] In crystalline $[Pt(NH(CH_3)C_2H_4NH(CH_3))(H_2O)(SO_4)]\cdot H_2O$, the hydrogen-bonding system is probably much more efficient when the sulfate ligand is monodentate and a water molecule occupies the fourth coordination site of the platinum(II) atom. The four oxygen atoms of the sulfate ligand are involved in the hydrogen-bonding system, where they accept protons from the water molecules or from the -NH groups (Table IV).

The packing of the molecues in the crystal is shown in Figure 3. It consists of layers of molecules parallel to the *bc* plane held together in the *a* direction by hydrogen bonds between the amine groups and the sulfate ligands. The N(1)---O(1) and N(2)---O(2) distances are 2.845 (8) and 2.851 (8) Å, respectively, and the angles are very favorable for hydrogen bonds (Table IV). Besides the two hydrogen bonds already mentioned, where the coordinated water molecule O(5) donates protons to a sulfate oxygen O(4) and to the lattice molecule of water O(6), there are two other hydrogen bonds where O(6) donates protons to two sulfate oxygen atoms O(2) and O(3). The angle O(2)---O(6)---O(3) is 119.7 (3)°. Therefore, one oxygen atom in the sulfate ligand O(2) seems to accept two protons, one from N(1) and one from the lattice molecule of water O(6).

Acknowledgment. The authors are grateful to the Natural Sciences and Engineering Research Council of Canada and to the Ministère de l'Education (FCAR) for financial support and also to Dr. Brown for the calculations of bond valences.

Supplementary Material Available: Tables S1-S4, listing anisotropic thermal parameters, torsion angles, weighted least-squares planes, and calculated hydrogen coordinates (4 pages); Table S5, listing of calculated and observed structure factors (12 pages). Ordering information is given on any current masthead page.

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Equilibrium and Kinetic Studies of Monoaquo Complexes of Platinum(II). 1. Formation from Corresponding Chloro Species by Hydrolysis

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Rate (k_1) and equilibrium constants (K_h) for the hydrolysis of *cis*(*N*,*S*)-Pt(amino acid)(dimethyl sulfoxide)Cl complexes (denoted Pt-Cl) have been determined for amino acids glycine, sarcosine, and *N*,*N*-dimethylglycine at 35 °C. K_h and k_2, the rate constant for the reverse reaction, were determined by potentiometric titration (with a chloride-sensitive electrode) of the aquo species derived from the chloro species by reaction with $AgNO_3$. Rate constants for the base hydrolysis of Pt-Cl at high pH, determined by both NMR and potentiometric techniques, correspond closely to those obtained from the low-pH titrations, indicating that the hydrolysis occurs by reaction with water solvent over a substantial pH range. For both glycine and sarcosine complexes of Pt-Cl, addition of NaOH leads to rapid establishment of an equilibrium mixture of Pt-Cl and the N-coordinated, OH-substituted species that results from opening of the chelate ring. This mixture slowly reverts to Pt-OH as the Pt-Cl is hydrolyzed by solvent water. Second-order rate constants, k_{Ag}, are also reported for the silver-assisted hydrolysis of the chloride complexes, making possible an assessment of the relative importance of the two mechanisms of hydrolysis. Variation among the three species is less than 1 order of magnitude for all four constants: $k_1 \cong 10^{-4}$ s^{-1}, $k_2 \cong 10$ M^{-1} s^{-1}, $K_h \cong 10^{-5}$ M, $k_{Ag} \cong 10^{-2}$ M^{-1} s^{-1}.

Extensive investigations of the mechanism of the interaction of the anticancer drug *cis*-diamminedichloroplatinum(II) (DDP) with DNA and with simpler nucleotides and nucleosides have emphasized the importance of aquo species derived from the chloro species by hydrolysis in a low-[chloride] medium.[1,2] The acidic aquo species is readily deprotonated by bases to yield the corresponding mono- and dihydroxo species.[3,4] At pH values near the pK_a, μ-OH-bridged dimer and trimer species are readily formed from the partially neutralized aquo species.[5,6]

We have earlier reported NMR evidence for isomer assignments[7,8] and a detailed study of the mechanism of Cl^--catalyzed and Me_2SO-catalyzed isomerization of cis and trans (N,S) isomers of mixed amino acid-dimethyl sulfoxide complexes of platinum(II).[9] The equilibration studies included a comparison of rates

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of isomerization with rates of chloride ion and dimethyl sulfoxide exchange, but they did not take into account the effects of hydrolysis of chloro species. Like Pt(dien)Cl^+, which has been used extensively to investigate trends in substitution reactions,[10] and to probe reactions with nucleotides,[11,12] these species have only a single chloride. We therefore undertook an investigation of the rates of chloride hydrolysis and the acid–base and dimerization properties of the resultant aquo species of these monochloro complexes.

The hydrolysis of the chloro species, denoted Pt–Cl, can be represented by

$$\text{Pt–Cl} + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} PtOH_2^+ + Cl^- \qquad (1)$$

for which the equilibrium constant, K_h, is given by $K_h = (PtOH_2^+)(Cl^-)/(PtCl)$. We have employed potentiometric methods to determine both K_h and k_2, the second-order rate constant for displacement of H_2O by Cl^-, by monitoring the displacement of coordinated water of the aquo species by chloride ion with a chloride-specific electrode. The first-order rate constant for hydrolysis, k_1, was then determined from the condition that $K_h = k_1/k_2$.

In the course of preparing the aquo species from the corresponding choro species by reaction 2, we noted a significant effect

$$\text{Pt–Cl} + H_2O + Ag^+ \xrightarrow{k_{Ag}} PtOH_2^+ + AgCl(s) \qquad (2)$$

of the silver ion concentration on the rate of hydrolysis. This silver-assisted hydrolysis, characterized by a second-order rate constant k_{Ag}, has been investigated both by NMR spectroscopy and by potentiometric methods using a silver electrode to monitor the silver ion concentration.

In this paper we report the hydrolysis data for three cis(N,-Me_2SO) amino acid complexes of general formula Pt(Me_2SO)(amino acid)Cl (amino acids: glycine = gly, sarcosine = sar, and N,N-dimethylglycine = dmg). For glycine and sarcosine, these are the thermodynamically favored isomers.[9] Acid–base and dimerization properties of Pt(dien)OH_2^{2+} [13] and of the aquo species described here are reported in separate papers.[23]

We have also investigated the hydrolysis of these chloro species by OH^-. The rate of reaction of OH^- with Pt(dien)Cl^+ is independent of hydroxide concentration.[10] The observed first-order rate constant appears to be a measure of the rate of reaction of Pt–Cl with H_2O. We therefore expected to be able to use the reaction with KOH as an alternative independent method to determine k_1. For the dmg complex, this expectation was realized. However, for the other two amino acids, this method was complicated by a facile ring-opening reaction that has confused earlier work on these mixed amino acid–Me_2SO complexes.[14] The details of this ring-opening reaction and the competing displacement of chloride ion have been clarified by NMR methods.

Experimental Section

Starting Materials. The platinum complexes used in this research were prepared from K_2PtCl_4, Me_2SO, and the corresponding amino acids as described earlier.[9]

NMR Spectra. Proton NMR spectra were recorded at 60 MHz with a Perkin-Elmer R-600 Fourier transform spectrometer. Ten to one hundred scans were averaged to improve signal/noise for the relatively dilute solutions used in the experiments. All spectra were recorded at magnet temperature, 35 °C. One set of 300-MHz proton spectra were obtained at 22 °C by using an IBM NF/300 proton spectrometer.

Potentiometric Measurements of Ion Concentrations. Potentiometric measurements of Ag^+ and Cl^- concentrations and pH employed appropriate electrode combinations and meters as follows: Silver measurements used a Beckmann silver billet-type electrode and a Cu/$CuSO_4$ reference electrode in combination with a Corning Model 10 pH meter. The electrode was standardized against 0.0100 M $AgNO_3$, and the response was satisfactorily Nerstian over three decades in silver concentration. Chloride measurements used an Orion Model 9417B chloride-specific electrode and a Cu/$CuSO_4$ reference electrode in combination with the Corning Model 10 meter. The meter was calibrated with standard KCl solutions at total ionic strength 0.05, maintained with KNO_3. Measurements of pH were made with a combination electrode and the Corning Model 10 pH meter standardized with pH 4.00 and 7.00 buffers.

The output of the meters was either recorded manually, fed to a Houston Omniscribe strip chart recorder, or input to an adac system 1200 laboratory computer with convenient analog input for layer processing either with the computer or after transfer to a DEC VAX 8600 computer. Statistical analysis and curve fitting employed RS/1 routines resident in the VAX computer.

Kinetics of Silver-Assisted Hydrolysis. The kinetics of the silver-assisted hydrolysis of the chloro complexes was followed by both NMR and potentiometric methods. Figure 1 shows the proton spectral changes for a solution of 0.05 M Pt(dmg)(Me_2SO)Cl and 0.05 M $AgNO_3$ in D_2O at 35 °C. The conversion of the chloro species, denoted Pt–Cl, to the corresponding aquo species, denoted Pt–OH_2^+, is readily apparent in both S-methyl and N-methyl regions of the spectrum. Precipitation of AgCl in the course of the reaction did not seriously disturb the quality of the spectra. The concentrations of Pt–Cl and Pt–OH_2^+ were calculated from the relative peak heights of central Me_2SO peaks. Second-order plots of 1/(Pt–Cl) vs. time or of ln (Pt–Cl)/(Ag^+) (for unequal initial concentrations of reagents) were satisfactorily linear, while first-order plots of ln (Pt–Cl) vs. time showed substantial curvature.

After the second-order behavior in the silver-assisted hydrolysis was noted, kinetic runs were monitored potentiometrically with the silver electrode. For these experiments, the initial concentrations of Ag^+ and Pt–Cl were kept equal (0.050 M) and second-order plots of 1/(Ag^+) vs. time were employed to obtain the rate constants. In some cases, the curvature in the plots was significant after 2 half-lives as the contribution of the simple unassisted hydrolysis became more significant.

Titration of Aquo Species with KCl(aq). The 0.05 M solution of aquo species and AgCl precipitate, contained in the thermostated well-stirred cell, was then titrated with standardized KCl (0.5–1.0 M), and the displacement of the coordinated water by Cl^- was monitored with the

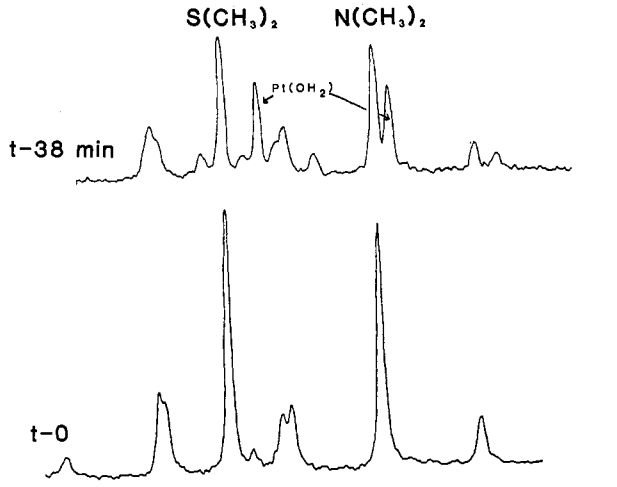

Figure 1. Proton NMR spectra of a solution of 0.05 M *cis*(N,S)-Pt(dmg)(Me_2SO)Cl and 0.05 M $AgNO_3$ in D_2O at 35 °C.

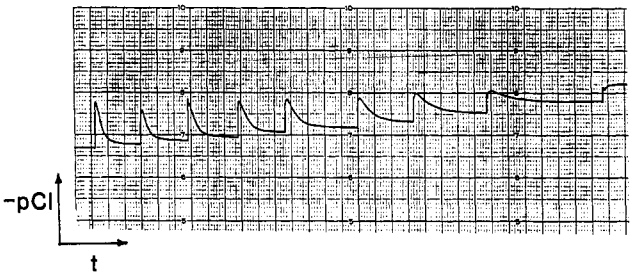

Figure 2. Chloride ion depletion curves for the stepwise titration of 0.050 M *cis*(N,S,)-Pt(dmg)(Me_2SO)OH_2^+ with 1.00 M KCl at 35 °C.

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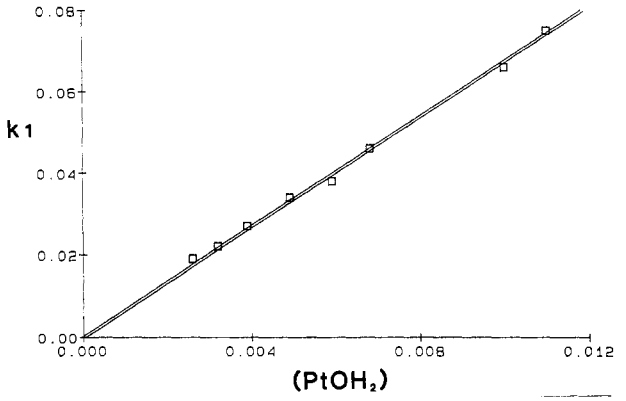


Figure 3. Graphical determination of k_2 for *cis*(*N*,*S*,)-Pt(gly)-$(Me_2SO)OH_2^+$ at 35 °C from the concentration dependence of the chloride ion depletion rate constant, k_1.

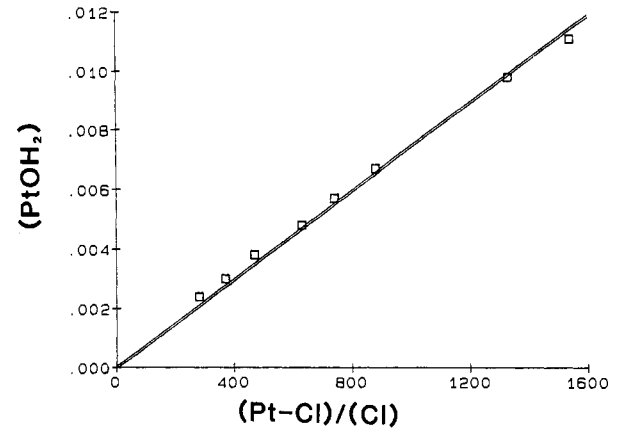


Figure 4. Graphical determination of K_h for *cis*(*N*,*S*)-Pt(gly)$(Me_2SO)Cl$ from KCl titration of aquo species at 35 °C.

chloride-sensitive electrode. The KCl was added in small (0.050-mL) increments, and the chloride electrode response was recorded as a function of time after each addition. Typical chloride depletion curves are illustrated in Figure 2. The rate of chloride reaction decreases as the concentration of unreacted Pt–OH_2^+ decreases.

Analysis of Chloride Depletion Curves. After a preliminary experiment in which the decay of chloride was shown to follow second-order kinetics when stoichiometric KCl and Pt–OH_2^+ were mixed, the following approach was employed to obtain both rate and equilibrium data for the hydrolysis reaction from the chloride reaction curves obtained in the complete KCl titration of Pt–OH_2^+:

Since the Pt–OH_2^+ was present in substantial excess during most of the titration, the chloride reaction was treated as a pseudo-first-order process with a pseudo-first-order rate constant, k, given by

$$(Cl)_t = (Cl)_\infty + [(Cl)_0 - (Cl)_\infty]e^{-kt} \quad (3)$$

where $(Cl)_t$ etc. are chloride concentrations at time t etc. The advantage of this approach is that it yields $(Cl)_\infty$, the equilibrium concentration of chloride, which for most of the titration is below the concentration of Nernstian response of the chloride electrode. Reliable chloride concentrations can be determined for 3–4 half-lives after addition of an initial burst of KCl, which raises the chloride concentration to about 0.002 M.

A plot of k vs. the concentration of unreacted aquo species, (Pt–OH_2^+), calculated from the moles of KCl added and the moles of aquo species initially present, was then employed to obtain k_2 as the slope. Such a plot is shown in Figure 3 for *cis*(*N*,*S*)-Pt(gly)$(Me_2SO)OH_2^+$.

K_h Determination from Titration Curve. The rate of chloride reaction after KCl addition was used to determine k_2 in eq 1. In like manner, the calculated equilibrium concentrations of chloride ion after each addition of KCl were employed to determine K_h. It can be shown that the midpoint pCl in a titration of aquo species with KCl is numerically equal to pK_h, and such titration curves can be used to determine K_h. However, since the high pCl values near the beginning of the titration are based on extrapolated pCl values that lie beyond the range of reliability of the chloride electrode, K_h values were determined from the data for the latter third of the chloride titration as follows: The initial concentration of aquo species was determined from the end point indicated by the titration curve itself. An average value of K_h for the last five to ten points of the titration was then determined graphically as the slope of a plot of (Pt–OH_2^+) vs. $(Pt–Cl)/(Cl)_\infty$, where the concentrations of aquo and chloro species were calculated from the volumes and concentrations of reagents added at each point and the equilibrium $(Cl)_\infty$ values were determined from the graphical analysis of the chloride reaction curves. A plot for the glycine complex is shown in Figure 4.

Table I. Second-Order Rate Constants for the Silver-Assisted Hydrolysis of Chloro Complexes of General Formula Pt(amino acid)$(Me_2SO)Cl$ at 35 °C

amino acid	method	$(Pt–Cl)_0$, M	$(Ag^+)_0$, M	k_{Ag}, M^{-1} s^{-1}
gly	NMR	0.050	0.050	0.022
	NMR	0.100	0.100	0.022
	Pot.	0.050	0.050	0.024
	Av			0.023
sar	NMR	0.029	0.029	0.0067
	NMR	0.024	0.071	0.0049
	Pot.	0.050	0.050	0.0086
	Av			0.0067
dmg	NMR	0.028	0.028	0.0086
	NMR	0.028	0.084	0.0103
	Pot.	0.050	0.050	0.0075
	Av			0.0088

Table II. Rate and Equilibrium Constants for Hydrolysis of Monochloro Complexes of Platinum(II)

complex	T, °C	10^5K_h	10^5k_1, s^{-1}	k_2, M^{-1} s^{-1}
Pt(gly)$(Me_2SO)Cl$	35	0.78	5.2	6.80
Pt(sar)$(Me_2SO)Cl$	35	0.51	3.6	7.10
Pt(dmg)$(Me_2SO)Cl$	35	1.17	13.3	11.3
Pt(dien)Cl^+	25	30[a]	25[a]	0.99[a]
Pt$(Me_2SO)(H_2O)Cl_2$	25	25	80[b]	20.5[b]
Pt$(en)Cl_2$	25	276[c]	?	?

[a] Reference 19. [b] Reference 20. [c] Reference 21.

Kinetics of Hydrolysis of OH^-. The rate of hydrolysis by hydroxide ion was monitored by both NMR and potentiometric methods. The proton spectral changes for the reaction of KOH with *cis*-Pt(dmg)-$(Me_2SO)Cl$ (0.05 M in each reagent) are parallel to those observed in the silver-assisted hydrolysis (Figure 1), with the product having chemical shifts characteristic of the Pt–OH species rather than the Pt–OH_2^+ species. Relative concentrations of Pt–Cl and Pt–OH were determined from peak heights of corresponding Me_2SO peaks. A first-order plot of ln (Pt–Cl) vs. time was linear over 4 half-lives, while the second-order plot of 1/(Pt–Cl) vs. time showed substantial curvature.

For the same dmg complex, the reaction was also followed by monitoring the pH after adding small increments of KOH (about 0.05 mequiv/mmol of Pt–Cl). A plot of (OH^-), calculated from the pH vs. time plot, was linear over 1 order of magnitude change in (OH^-) after each addition. The slopes of these (OH^-) vs. time plots decreased as the concentration of unreacted Pt–Cl decreased. The data are consistent with the rate law

$$\text{rate} = -d(Pt–Cl)/dt = -d(OH^-)/dt = k_1(Pt–Cl) \quad (4)$$

where the rate is given by the slope of the (OH^-) vs. time plot and k_1 can be calculated from a plot of rate vs. (Pt–Cl).

In contrast to the case of the dmg complex, for the gly and sar complexes, after each addition of KOH, the pH dropped rapidly by 1–2 units, indicating a rapid consumption of most of the OH^- ion. The subsequent slow equilibration of pH and Cl^- concentrations was monitored potentiometrically. A more thorough analysis of the reaction was afforded by a proton NMR spectroscopy study at 300 MHz.

Results

Kinetics of Silver-Assisted Hydrolysis. Second-order rate constants for the silver-assisted hydrolysis of chloro complexes at 35 °C are summarized in Table I. Data are included for both NMR and potentiometric experiments. Standard deviations in rate constants for individual experiments were generally less than 10% of the values themselves. Agreement between the two methods is satisfactory. We judge the average value reported for K_{Ag} for each complex to be reliable to ±20%.

Hydrolysis Data. Rate and equilibrium constants for the hydrolysis of chloro complexes at 35 °C are presented in Table II. In each case, the value given is based on the graphical analysis of data from several decay curves as described in the Experimental

Table III. Rate and Equilibrium Constants at 35 °C Based on Pt–Cl + OH^- Reactions

complex	method	$10^5 k_{OH}$, s^{-1}	$10^{-4}K_h'$	$10^{-4}K_h/K_wK_a$[a]
sar	pot. (Cl^-)	6.1 ± 0.7	2.3 ± 0.6	2.1 ± 0.5
	pot. (pH)	~11		
gly	pot. (pH)	6.8 ± 0.6	1.5 ± 0.2	2.0 ± 0.5
dmg	pot. (pH)	9.2 ± 0.3	6 ± 2	7.7 ± 0.5
	NMR	12.5 + 0.2		
	NMR	18.3 + 0.4		

[a] Calculated by using k_a values from ref 23 and $K_w = 2.9 \times 10^{-14}$.

Section. The values given for k_1 are calculated from the independent determinations of k_2 and K_h, since $K_h = k_1/k_2$. Literature data for other similar chloro complexes are included for convenient comparison.

Hydroxide Reactions. Rate constants and equilibrium constants for the hydrolysis of these chloro complexes by hydroxide are given in Table III. The first-order rate constants obtained by NMR and potentiometric methods agree reasonably well for the dmg complex. The first-order rate constants for the reaction of the dmg complex with hydroxide ion also agree quite well with values of k_1 calculated from k_2 and K_h. This observation is consistent with the slow step in the hydrolysis being the displacement of Cl^- by water molecules over the entire pH range of these experiments.

The rate constants for the gly and sar complexes were obtained from the rate of increase of chloride ion concentration after addition of small increments of KOH. Like the rate of hydroxide consumption by the dmg complex, the rate of release of Cl^- by the gly and sar complexes decreases as the concentration of untitrated Pt–Cl decreases. The value reported in each case is the slope of a plot of the rate of chloride ion production vs. concentration of untitrated Pt–Cl.

Table III also includes an estimate of the equilibrium constant for the base hydrolysis reaction

$$\text{Pt–Cl} + OH^- \rightleftarrows \text{Pt–OH} + Cl^- \quad (5)$$

based on the equilibrium pH value. This value can be compared for each complex with the equilibrium constant calculated from K_h and K_a, the acid dissociation constant of the corresponding aquo complex, since

$$K_h' = K_h/K_wK_a \quad (6)$$

This comparison, included in Table III, gives some indication of the internal consistency of the closely related experiments.

NMR Evidence for the Mechanism of Hydrolysis at High pH. A careful 300-MHz proton NMR study of the reaction of the sarcosine chloro complex has illuminated additional details of the base hydrolysis reaction while confirming the principal conclusion: the hydrolysis at high pH, like the hydrolysis at low pH, occurs primarily by reaction with solvent water. The time dependence of the 300-MHz proton NMR spectrum of 0.050 M Pt(sar)-(Me_2SO)Cl in 0.035 M NaOD/D_2O is shown in Figure 5. The changes in concentration of four distinct species (identified on the 28-h trace) are most evident in the *N*-methyl region of the spectrum, but corresponding changes are also evident in the Me_2SO portion of the spectrum. The addition of the NaOD very rapidly converts a corresponding amount of chloro species (I) to a second species (II). Over the next few hours, as the concentration of II decreases, the concentration of a third species (III) increases to a maximum and then declines as the concentration of the hydroxo substitution product (IV) predominates. The approximate time variation of the relative concentrations of the four species, determined from *N*-CH_3 peak heights, is shown in Figure 6.

Proton NMR parameters for all observable protons of the four species seen in Figure 5 are summarized in Table IV. The *N*-CH_3 peaks are well defined singlets, flanked by ^{195}Pt satellites. Because of the chirality at the coordinated nitrogen of sarcosine, the two methyl groups of coordinated Me_2SO are not equivalent and an observable chemical shift difference is expected. This potential difference is not observed for II in any of the traces, but it is evident for both III and IV in all traces where their concentrations are

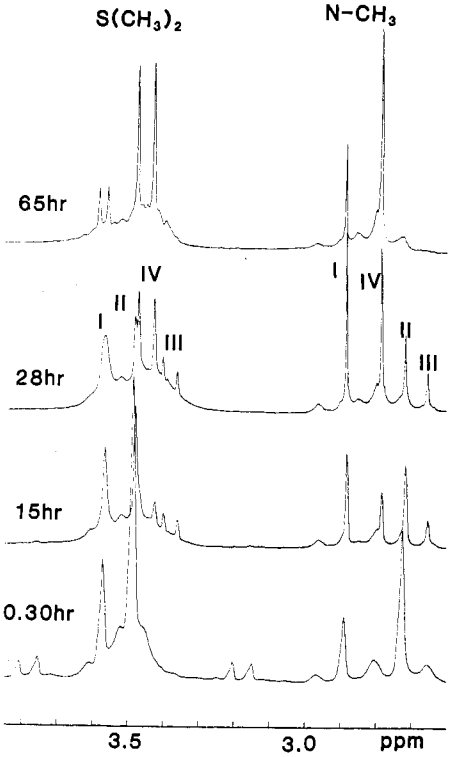


Figure 5. Proton NMR spectral changes for the reaction of 0.035 M NaOD with 0.050 M *cis*(*N*,*S*)-Pt(sar)(Me_2SO)Cl in D_2O at 22 °C.

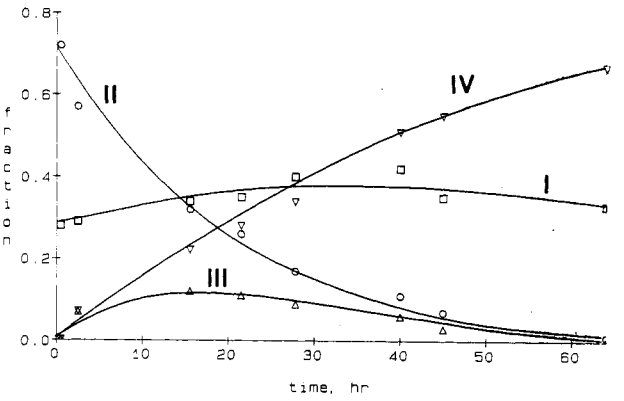


Figure 6. Time variation in the concentration of the species involved in the reaction of 0.035 M NaOD with 0.050 M *cis*(*N*,*S*)-Pt(sar)-(Me_2SO)Cl at 22 °C.

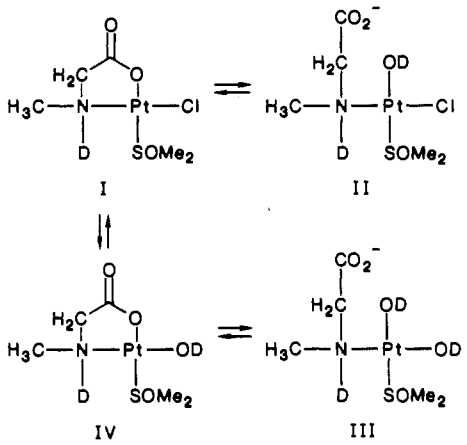
Table IV. Proton Chemical Shifts with Three-Bond ^1H–^{195}Pt Coupling Constants in Parentheses for *cis*(*N*,*S*)-(Sarcosine)(dimethyl sulfoxide)platinum(II) Species[a]

species	CH_2		*S*-CH_3		*N*-CH_3
I: Pt(N–O)SCl	4.123	3.419	3.567		2.887
	(<10)	(73)	(24)		(47)
II: PtNS(OD)Cl^-	3.780	3.176	3.481		2.722
	(29)	(55)	(22)		(43)
III: PtNS$(OD)_2^-$			3.403	3.363	2.658
			(2.4)	(24)	(30)
IV: Pt(N–O)S(OD)			3.474	3.428	2.788
			(27)	(27)	(39.6)

[a] (N–O) = chelated sarcosine; N = N-coordinated sarcosine; S = S-coordinated Me_2SO. Chemical shifts are in ppm relative to internal DSS; $^3J_{Pt-H}$ values are in Hz.

sufficient to see the peaks. For the initial chloro species (I), the single methyl peak observed initially splits into two peaks as the reaction progresses and the pH slowly drops to its equilibrium value. The pH at coalescence for I is about 10, comparable to the coalescence pH we determined for the CH_2 AB pattern of Pt(sar)Cl_2^- from NMR measurements on H_2O solutions.[15] The

Scheme I



relatively high initial pH also leads to exchange of CH_2 protons, so that the AB doublets of II, which are evident in the initial trace, rapidly disappear as the reaction proceeds.

The spectral changes shown in Figure 5 are consistent with the reaction sequence presented in Scheme I. The rapid formation of II on addition of NaOD to I accounts for the rapid disappearance of a corresponding quantity of Pt–Cl (I) in the NMR spectrum and for the unexpectedly low pH of the solution (relative to 0.035 M NaOD). Ultimately, the simple substitution product (IV) predominates. Competing equilibria between I and II and between I and IV could account for the eventual conversion of I to IV, but the presence of III suggests that hydrolysis could also occur by I → II → III → IV. The NMR parameters of IV are identical with those of the product formed by addition of 1 mol of OD^-/mol of $Pt–OD_2^+$, while the parameters of III are identical with the product formed by addition of 2 mol of NaOD/mol of $Pt–OD_2^+$. Furthermore, the pattern of changes in NMR spectral parameters in going from I to IV is closely parallel to the pattern in going from II to III. In both cases, both *N*-CH_3 and *S*-CH_3 shifts move upfield while three-bond coupling between ^{195}Pt and either methyl decreases somewhat. According to the assignments given in Table IV, both changes correspond to replacement of the Cl^- trans to coordinated sarcosine nitrogen by OD^-.

Though III could be involved as an intermediate in the hydrolysis of I, the observed rate of hydrolysis argues for the pathway shown in Scheme I. The overall rate of conversion of II to IV is very close to the rate of hydrolysis of I at low pH. The disappearance of II at 22 °C fits a first-order ln (II) vs. time plot with $k_1 = 1.5 \times 10^{-5}$ s^{-1} (±5%). This suggests strongly that the slow step in the conversion is the hydrolysis of I by solvent water to $Pt–OD_2^+$, for which k_1 at 35 °C is 3.6×10^{-5} s^{-1} (±20%). In the high-pH medium, the $Pt–OD_2^+$ species would be rapidly deprotonated to IV, of course.

Further evidence for the predominance of the water pathway comes from other NMR and pH measurements. The NMR spectra of solutions of I or IV with NaOD freshly added have confirmed that equilibrium between chelate species and corresponding ring-opened OH^--substituted species (I to II and IV to III) is established within a few seconds. III and IV initially appear at about the same rate (Figure 6), but this may reflect how much OD^- is available early in the reaction rather than the relative rates of hydrolysis of I and II. The pH measurements on similar solutions reveal that (OD^-) decreases by another order magnitude as II is converted to IV. Species IV is strongly favored thermodynamically, but a significant concentration of III can exist until the excess OD^- is further depleted. On the basis of the pH values obtained over the course of the reaction, equilibrium constants for both ring-opening reactions, I + OD^- → II and IV + OD^- → III, are about 10^3 M^{-1}. Such values account for the shift in IV/III ratio observed in the later stages of the reaction. The ring-opened species, II and III, provide a convenient way for the system to store OD^-, but neither of these species is thermodynamically significant relative to the hydrolysis product, IV, when less than 1 mol of NaOD/mol of Pt is equilibrated with Pt–Cl.

Discussion

Relative Importance of Simple and Silver-Assisted Hydrolyses. The independent determinations of the rates of simple and silver-assisted hydrolyses permit an assessment of the relative importance of the two pathways for the different complexes under specified experimental conditions. Although silver salts are widely employed to convert halo species to corresponding aquo species, surprisingly little attention has been devoted to the process. It is probably assumed that the Ag^+ ions are simply available to precipitate the halide ions formed by hydrolysis by solvent water. For low concentrations of silver ion and halo complex, this may be the case. However, for the complexes reported in this paper, the silver-assisted pathway is the predominant pathway for conversion to aquo species at high silver ion concentration.

The relative importance of the two pathways depends, of course, on the silver concentration, since the silver-assisted pathway is a second-order pathway. A quantity that shows the relative importance of the two pathways is $k_1/[k_1 + k_{Ag}(Ag^+)]$, the fraction of the hydrolysis that involves only solvent water. Whereas less than 10% of the hydrolysis involves silver ion when (Ag^+) < 0.001 M, more than 50% of the hydrolysis involves silver ion when (Ag^+) > 0.10 M. Thus, the contribution of the silver-assisted pathway would not be evident in experiments done at low silver ion concentrations.

The mechanism by which Ag^+ increases the rate of hydrolysis of the chloride species can be envisioned as involving a chloride-bridged intermediate that loses AgCl on displacement by water in a slow step, eq 7 and 8. A steady-state treatment then

$$Pt–Cl + Ag^+ \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} Pt–Cl–Ag^+ \quad (7)$$

$$Pt–Cl–Ag^+ + H_2O \xrightarrow{k_8} Pt–OH_2^+ + AgCl(s) \quad (8)$$

leads to the conclusion that $k_{Ag} = k_7k_8(k_{-7} + k_8)$. An extensive recent review of metal ion catalyzed aquation of transition-metal complexes is devoted almost entirely to CN = 6 complexes mainly of Co(III) and Cr(III),[16] with only one series of papers on the aquation of Pt(II) complexes. These papers report spectral evidence for a halide-bridged species containing the Pt–X–Hg moiety, analogous to the chloride-bridged Pt–Cl–Ag moiety suggested here, in the Hg^{2+}-catalyzed hydrolysis of *trans*-Pt(gly)NH_3Cl^+ and *trans*-Pt(gly)NH_3Br^+.[17] Similar halide-bridged species have been suggested as intermediates in silver-assisted reactions of organic halides.[18]

Trends in Rate and Equilibrium Constants. The variation in rate and equilibrium constants among this series of compounds is not great and does not follow a consistent pattern with methyl substitution. First of all, though the glycine complex is the most sensitive to silver-assisted hydrolysis, the dimethylglycine complex has the largest k_1 value for simple hydrolysis. The aquo complex of dimethylglycine is also the most reactive to chloride ion.

The hydrolysis constants for these species are all smaller by 1 order of magnitude than that of Pt(dien)Cl^+.[19] The difference appears to involve both a smaller k_1 and a larger k_2 for these species. The hydrolysis rate and equilibrium constants of these species are also smaller than those of *trans*-Pt(Me_2SO)(H_2O)Cl_2,[20] which differs from these amino acid complexes mainly in having another chloride, rather than a nitrogen, trans to the chloride that

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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]

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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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