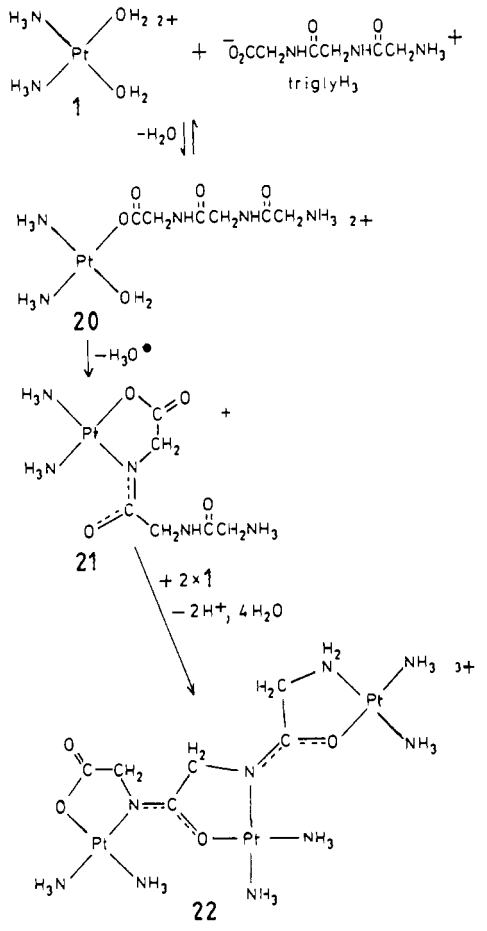
Scheme III



sponding to ammine trans to a N-donor and three to ammine trans to an O-donor (Table III). The 400-MHz ^{1}H NMR spectra of the solids in D_2O each showed the three singlets expected for the methylene protons of **22**, at 4.21, 4.06, and 3.87 ppm. In the digly analogue, **11**, a peak at 3.80 was assigned to $C_{(1)}H_2$, adjacent to the terminal amine group, so the peak at 3.87 ppm in **22** has been assigned to the corresponding methylene group, $C_{(1)}H_2$. In **11**, a peak at 4.03 ppm was assigned to $C_{(3)}H_2$, adjacent to the carboxyl group, so, in **22**, the peak at 4.06 ppm probably is due to $C_{(5)}H_2$. This leaves the peak at 4.21 ppm for $C_{(3)}H_2$, between the two deprotonated peptide groups. The solids were not sufficiently soluble in water to allow a satisfactory ^{13}C spectrum to be obtained.

Sparing solubility of the free ligand made it more difficult to extend our study to tetraglycine (tetraglyH$_4$). The ligand did dissolve slowly in an aqueous solution of **1**, and we were able to observe in the ^{15}N spectrum peaks characteristic of carboxylate-bound peptide complexes, $Pt(NH_3)_2$(tetraglyH$_4$-*O*)$(H_2O)^{2+}$ and $Pt(NH_3)_2$(tetraglyH$_4$-*O*)$_2^{2+}$ (Table III), but we did not investigate this system further.

Conclusions. The most striking aspect of the chemistry of these complexes is the tendency of these oligoglycyl peptides to coordinate multiple diammineplatinum(II) units as in **11** and **22**. The driving force for formation of these complexes appears to be the activation toward platinum binding of each peptide oxygen in succession as the nearby peptide nitrogen coordinates and deprotonates, beginning with the first O(carboxylate),N(peptide)-chelate complex (**17**, **21**). Under conditions that apply biologically, there is unlikely to be sufficient platinum near a particular peptide for more than a single platinum atom to bind to it. However, it is worth noting that the coordination of a platinum atom to a peptide nitrogen can have a profound effect on the chemistry of the oxygen of the same peptide group.

Acknowledgment. We thank the Australian Research Council for financial support. P.D.P. is grateful for the award of an Australian Commonwealth Postgraduate Scholarship. We thank Dr. D. P. Fairlie for useful discussions.

Supplementary Material Available: Tables listing microanalytical data, full crystal data, thermal parameters, bond lengths and bond angles, details of least-squares planes, torsion angles, hydrogen positional and thermal parameters, and close intermolecular contacts (7 pages); a listing of observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

^{195}Pt NMR Spectroscopy of (^{15}N)Peptide Complexes

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The reactions of $PtCl_4^{2-}$ with oligoglycyl peptides in aqueous solution proceed by amine coordination followed by sequential deprotonation and coordination of available peptide nitrogens. Complexes of $PtLCl_3^{2-}$, $Pt(H_{-1}L)X_2^{2-}$, $Pt(H_{-2}L)X^-$, and $Pt(H_{-3}G_4)^{2-}$ (where L = triglycine (G_3), triglycinamide (G_3a), or tetraglycine (G_4), X = Cl^- or OH^-, and H_{-n} designates the number of deprotonated-N(peptide) bonds) are characterized by use of ^{195}Pt NMR spectroscopy. Several bis(peptide) complexes also are identified. Structural assignments are made on the basis of coupling constants with (^{15}N)peptides. The magnitude of the J_{Pt-N} coupling constants are Pt–N$^-$(peptide) > Pt–N(amine) ≈ Pt–NH_3 (N$^-$ denotes the deprotonated peptide nitrogen); the trans influence on Pt–N(amine) or Pt–N$^-$(peptide) is N$^-$(peptide) ≫ OH^-, RNH_2, NH_3 > Cl^-. The chemical shifts for ^{195}Pt are determined primarily by the elements coordinated to platinum(II) and secondarily by their chemical form. Monodentate amine coordination by the oligopeptide or the formation of the first chelate ring with amine and N$^-$(peptide) coordination gives an upfield shift of 110 ppm relative to the signal for the corresponding $Pt(NH_3)X_3^-$ or *cis*-$Pt(NH_3)_2X_2$ complex. Two linked consecutive five-membered rings from peptide chelation cause an offsetting downfield shift of 120 ppm, and three linked consecutive five-membered chelates introduce an additional downfield shift of 250 ppm (relative to the coordination of one or two more NH_3 molecules). Reaction of *cis*-$Pt(NH_3)_2Cl_2$ with (^{15}N)diglycine at pH 11 yields cis complexes of $Pt(NH_3)_2(G_2)OH$, $Pt(NH_3)_2(H_{-1}G_2)$, and $Pt(NH_3)_2(G_2)_2$.

Introduction

Tetrachloroplatinate(II) reacts with oligoglycyl peptides in aqueous solution to form a series of complexes. We are interested in the nature of these complexes and in the ability of platinum to form deprotonated-N(peptide) bonds, where the oligopeptide wraps around the equatorial coordination sites of the metal ion.

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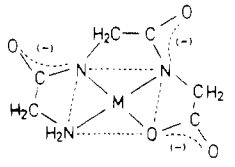
Table I. ^{195}Pt NMR Chemical Shifts for Compounds of the Series $Pt(NH_3)_yX_{4-y}$ (X = Cl^-, OH^-)

complex	δ_{Pt}, ppm	ref	complex	δ_{Pt}, ppm	ref
$PtCl_4^{2-}$	−1650	*a*	$Pt(OH)_4^{2-}$	−165	*d*
cis-$Pt(NH_3)_2Cl_2$	−2097	*b*	*cis*-$Pt(NH_3)_2(OH)_2$	−1572	*b*
$Pt(NH_3)_3Cl^+$	−2354	*c*	$Pt(NH_3)_3OH^+$	−2062	*e*
$Pt(NH_3)_4^{2+}$	−2579	*b*			

[a] Pesek, J.; Mason, W. R. *J. Magn. Reson.* **1977**, *25*, 519–529. [b] Boreham, C. J.; Broomhead, J. A.; Fairlie, D. P. *Aust. J. Chem.* **1981**, *34*, 659–664. [c] Kerrison, S. J. S.; Sadler, P. J. *J. Chem. Soc., Chem. Commun.* **1977**, 861–863. [d] Appleton, T. G.; Hall, J. R.; Ralph, S. F.; Thompson, C. S. *Inorg. Chem.* **1984**, *23*, 3521–3525. [e] Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 4685–4693.

Coordination of this type is known for peptide complexes of Cu(II),[1] Cu(III),[2] Ni(II),[3] Ni(III),[4] Pd(II),[5] Co(III),[6] and Ag(III).[7] (Structure I shows a typical complex with triglycine,



I

$M(H_{-2}G_3)^-$, where H_{-2} indicates two deprotonated-N(peptide) bonds to the metal, M^{2+}.) In the case of Pt(II) the reactions are exceedingly slow to reach equilibrium and UV/vis spectrophotometry does not provide sufficiently distinctive spectral features to identify the species. In an earlier paper from this laboratory[8] we used evidence from Cl^- release, OH^- consumption, and various spectral methods to propose the formation of three complexes: $Pt(H_{-2}G_3)^-$, $Pt(H_{-2}G_3)Cl^{2-}$, and $Pt(H_{-2}G_3)(OH)^{2-}$. However, we have since discovered that the reported ^{195}Pt NMR spectra were erroneous due to instrumental artifacts. Hence, the enormous upfield shift reported for platinum coordination to a deprotonated-N(peptide) group is not correct. In the present work we synthesize (^{15}N)peptides and examine their interaction with $PtCl_4^{2-}$ by ^{195}Pt NMR spectroscopy. Chemical shifts of complexes where ^{15}N (spin $^1/_2$) nuclei are coordinated to the metal are much easier to detect than those for the quadrupolar ^{14}N nuclei that cause line broadening of the ^{195}Pt signal.[9] Additional information

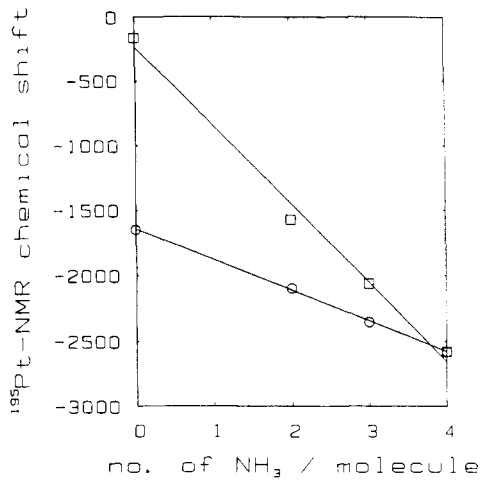


Figure 1. Linear relationships between δ_{Pt} and the number of NH_3 molecules in $Pt(NH_3)_yX_{4-y}$ complexes: (○) X = Cl^-; (□) X = OH^-.

about the number and type of nitrogens coordinated to platinum can be deduced from ^{195}Pt–^{15}N coupling constants. The total chemical shift range for ^{195}Pt NMR spans ca. 15 000 ppm,[10] and the range for the divalent oxidation state of platinum is about 5000 ppm. Change of a single ligand can induce a pronounced platinum chemical shift, and a series of substitutions often show regular changes. Some chemical shifts can be predicted for a given set of ligand atoms in the platinum coordination sphere.[11] Figure 1 shows linear relationships between the chemical shift (δ_{Pt}) and the number of ammonia groups in the series $Pt(NH_3)_yX_{4-y}$ complexes (X = Cl^- or OH^-; Table I). Chemical shifts for complexes with deprotonated-N(peptide) bonds are in the same region expected for ammonia coordination. In addition to the chemical shift information, the coupling patterns and the magnitude of the $^1J_{Pt-N}$ coupling constants in the ^{195}Pt NMR spectra with the (^{15}N)peptides are used for structural assignments. We find evidence for the previously suggested structures[8] and six additional complexes with G_3. Tetraglycine (G_4) and triglycineamide (G_3a) react with $PtCl_4^{2-}$ in a similar manner. A $Pt(H_{-3}G_4)^{2-}$ complex with one amine and three deprotonated-N(peptide) groups is observed with tetraglycine at high pH.

The reactions of *cis*-diamminedichloroplatinum(II) (cisplatin) are of interest because of its use as an antitumor agent. This platinum drug exerts its cytotoxic effects through interactions with DNA.[12] However, reactions of the drug with low and high molecular weight amino acid based nucleophiles are believed to be responsible for toxic side effects.[13] We report the products of the reactions between *cis*-$Pt(^{15}NH_3)_2Cl_2$ and (^{15}N)diglycine, G_2, as studied by ^{195}Pt NMR spectroscopy. At pH values greater than 9, a complex with a deprotonated-N(peptide) bond is formed. No evidence was found for a displacement of the ammine groups.

Experimental Section

Synthesis. Tri- and tetrapeptides were synthesized in our laboratory from (^{15}N)glycine (99%) purchased from MSD Isotopes. (Benzyloxy-

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carbonyl)(^{15}N)glycine (CBZ(^{15}N)gly), (*tert*-butyloxycarbonyl)(^{15}N)-glycine (BOC(^{15}N)gly), and (^{15}N)glycine benzyl ester *p*-toluenesulfonate ((^{15}N)glyOBz·TsOH) were prepared by standard procedures to protect amino acids.[14] All free peptides were prepared from their CBZ and benzyl ester blocked precursors by hydrogenolysis over palladium in a mixture of methanol and water (9/1 v/v). Those precursors were prepared as follows: the dipeptide, CBZ(^{15}N)G(^{15}N)GOBz, was prepared from CBZ(^{15}N)G and (^{15}N)GOBz·TsOH by the mixed carbonic anhydride procedure;[15] tripeptides, including CBZ(^{15}N)GGGOBz, CBZG-(^{15}N)GGOBz, CBZGG(^{15}N)GOBz, and CBZ(^{15}N)G(^{15}N)G(^{15}N)GOBz, were prepared from the corresponding CBZGG and GOBz·TsOH by the same procedure; the tetrapeptide, CBZ(^{15}N)G(^{15}N)G(^{15}N)G(^{15}N)GOBz, was similarly prepared from CBZ(^{15}N)G(^{15}N)G and (^{15}N)G(^{15}N)-GOBz·CF_3COOH. Intermediate dipeptides used in the above coupling reactions were prepared as follows: CBZGG and its corresponding labeled derivatives from the corresponding CBZGGOBz by saponification;[16] (^{15}N)G(^{15}N)GOBz CF_3COOH from *t*-BOC(^{15}N)G(^{15}N)GOBz by treatment with neat trifluoroacetic acid.[14a] Satisfactory elemental analysis were obtained for all free peptides. Anal. Calcd for (^{15}N)G-(^{15}N)G, $C_4H_8{}^{15}N_2O_3$: C, 35.82; H, 6.01; N, 22.38. Found: C, 35.61; H, 6.30; N, 22.19. Calcd for (^{15}N)GGG, $C_6H_{11}N_2{}^{15}NO_4$: C, 37.89; H, 5.83; N, 22.62. Found: C, 37.60; H, 5.88; N, 22.34. Calcd for G-(^{15}N)GG, $C_6H_{11}N_2{}^{15}NO_4$: C, 37.89; H, 5.83; N, 22.62. Found: C, 37.69, H, 5.83; N, 22.44. Calcd for GG(^{15}N)G: $C_6H_{11}N_2{}^{15}NO_4$: C, 37.89; H, 5.83; N, 22.62. Found: C, 37.61; H, 6.03; N, 22.24. Calcd for (^{15}N)G(^{15}N)G(^{15}N)G, $C_6H_{11}{}^{15}N_3O_4$: C, 37.50; H, 5.77; N, 23.43. Found: C, 37.68; H, 5.89; N, 23.18. Calcd for (^{15}N)G(^{15}N)G(^{15}N)G-(^{15}N)G·$^1/_4H_2O$, $C_8H_{14}{}^{15}N_4O_5{}^{\cdot 1}/_4H_2O$: C, 37.71; H, 5.73; N, 23.56. Found: C, 37.78; H, 5.68; N, 23.28.

cis-Pt($^{15}NH_3$)$_2Cl_2$ was prepared from K_2PtCl_4 and $^{15}NH_4OAc$ by use of literature procedures.[17] Anal. Calcd for *cis*-Pt($^{15}NH_3$)$_2Cl_2$, $H_6Cl_2{}^{15}N_2Pt$: H, 2.00; N, 9.94; Pt, 64.58. Found: H, 1.95; N, 10.08; Pt, 64.66.

Reagents. Potassium tetrachloroplatinate(II) (K_2PtCl_4) and *cis*-diamminedichloroplatinum(II) (*cis*-Pt(NH_3)$_2Cl_2$) were obtained from Strem Chemicals. Diglycine, triglycine (Sigma), and tetraglycine (Biosynthetika) were chromatographically homogeneous. The ionic strength of solutions used for equilibrium measurements was adjusted with sodium perchlorate that was prepared from the twice recrystallized salt.

NMR Spectra. ^{195}Pt NMR spectroscopy is used as the primary technique to characterize the species in solution. ^{195}Pt is the only NMR-active isotope of platinum. It has a nuclear spin of $^1/_2$, is 33.7% abundant, and has a relative receptivity of 19.1 times that of ^{13}C in natural abundance. FT-NMR spectra were recorded on a Varian XL-200 spectrometer with a 10-mm broad-band probe at 25 ± 1 °C. The temperature was controlled with an air flow from an Igersoll-Rand Type 31 compressor to a refrigerated air cooler and a heat exchanger.[18] The sample air temperature was measured with a Doric Series 400-A digital thermometer. The total Pt(II) concentrations were 0.1–0.3 M. Typical spectra required 10000–50000 transients (depending on the concentration of the sample), each with 0.1-s acquisition time and 0.1-s delay time. The number of data points were 10000, the pulse width was 30 μs, and the pulse angle was 102°. The signals were proton decoupled by using the Waltz-16 decoupler method in order to minimize thermal gradients in the 10-mm NMR sample tubes.[19] The spectrometer has a spectral width limit of 50000 Hz, which corresponds to roughly 1200 ppm in the ^{195}Pt NMR spectrum. Initially the whole chemical shift range was scanned in a sequence of experiments to locate the resonances. In later experiments only the window of interest was scanned, and runs with changes in the transmitter offset frequency were used to eliminate the possibility of folded peaks. All shifts are reported positive to lower shielding. ^{195}Pt NMR lines are referenced to an external standard of

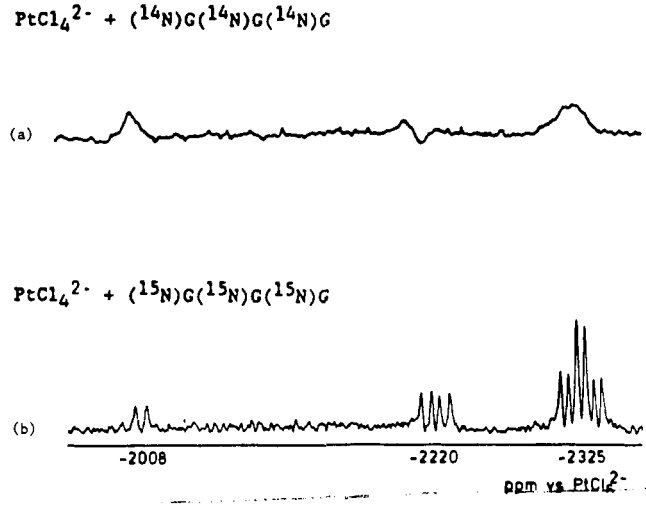

Figure 2. ^{195}Pt NMR spectra of a reaction mixture of $PtCl_4^{2-}$ and triglycine at pH 7 after 1 week: (a) (^{14}N)G_3; (b) (^{15}N)G_3.

Na_2PtCl_6 in 1 M HCl.[11b] Absolute frequencies are used to calculate chemical shifts. The frequencies for the XL-200 instrument are referred to a single master oscillator with an absolute accuracy of better than 5 parts in 10^9 on a long-term basis. $^1J_{Pt-N}$ coupling constants with an estimated error of ±5 Hz are obtained from the ^{195}Pt NMR spectra of complexes with ^{15}N-labeled ligands. Only in very few cases is the coupling to quadrupolar ^{14}N resolvable. Figure 2 shows the difference between a ^{195}Pt NMR spectrum of the complexes formed from $PtCl_4^{2-}$ and unlabeled triglycine 1 week after mixing and a spectrum under the same conditions when ^{15}N-labeled G_3 is used.

Most of the spectra were run in H_2O as the solvent. When mixtures of D_2O and H_2O were used, substantial isotope shifts in the ^{195}Pt NMR spectra could be seen. The resonance of the coordinated doubly deuterated amino group is approximately 100 Hz upfield from that of the singly deuterated species. The presence of two distinguishable resonances indicates that the exchange of protons from the coordinated amine group with H_2O is slow on the NMR time scale; i.e., the residence time of a proton at a particular nitrogen is ≥10 ms. In D_2O solutions corrections for pH meter readings (pD = pH + 0.40)[20] were used.

Methods. UV/vis spectra were recorded on a Perkin-Elmer 320 spectrometer equipped with a Perkin-Elmer 3600 data station. A Corning Model 476051 combination glass electrode and an Orion Model 601 pH meter were used for pH measurements. These were corrected where necessary to the corresponding −log [H^+] values at 25.0 °C and μ = 1.0 M ($NaClO_4$) on the basis of electrode calibration titrations with standard solutions of NaOH and $HClO_4$.

The doubly deprotonated triglycine complexes of platinum(II), Pt-($H_{-2}G_3$)Cl^{2-} and Pt($H_{-2}G_3$)OH^{2-}, were prepared by mixing K_2PtCl_4 with a 3–5% excess of triglycine in H_2O ($[Pt]_T \geq 0.1$ M). The mixture was kept in a pH stat, set to maintain pH values constant between 6 and 7, for 10–14 days. (We constructed the pH stat to compare the output of a digital pH meter to a preset pH value. It switches on a Gelson Minipuls 2 peristaltic pump when the measured pH drops too low. The pump then delivers a small volume of 1.0 M NaOH to the reaction mixture until the preset pH is obtained. The response is sensitive to ±0.1 pH unit.) The color of the reaction mixture changed from red to golden yellow within a day, while base had to be added for several days to maintain a constant pH. After about 10 days of reaction time Pt($H_{-2}G_3$)Cl^{2-} was the major species in solution, but an additional 6 weeks at pH 8 were required to reach completion. An alternative way to prepare Pt($H_{-2}G_3$)Cl^{2-} was to start the reaction of K_2PtCl_4 and G_3 in 1 mM HNO_3. After 4–5 days the ^{195}Pt NMR spectra indicated a mixture of species. Then 1 equiv of base (based on $[Pt]_T$) was added to the reaction mixture and allowed to react for 2 days. This procedure was repeated two more times (a total of 3 equiv of OH^-). The major species after the last reaction (pH 9–10) was Pt($H_{-2}G_3$)Cl^{2-}. Addition of more base to give pH >12 converted all the platinum to one species, Pt($H_{-2}G_3$)OH^{2-}. Addition of acid to give pH <10 caused Pt($H_{-2}G_3$)Cl^{2-} to form again within less than 30 min. The reaction is reversible with pH. To obtain a Cl^--free solution, the reaction mixture at high pH was chromatographed on a Sephadex G-10 column (9-cm long) with H_2O as the mobile phase. Under the conditions used, the platinum complex eluted within the void volume followed by weakly retained Cl^- and more strongly retained OH^-.

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Table II. Observed, Calculated,[a] and Corrected[b] δ_{Pt} Values

complex	peptide, L	δ_{Pt}^{obsd}, ppm	δ_{Pt}^{calcd}, ppm ($\Delta\delta_{Pt}$,[c] ppm)	δ_{Pt}^{corr}, ppm ($\Delta\delta'_{Pt}$,[d] ppm)
$Pt(L)Cl_3^{2-}$ (II)	G_3	−2008	−1878 (−130)	−1988 (−20)
	G_4	−2008	−1878 (−130)	−1988 (−20)
	G_3a	−2007	−1878 (−129)	−1988 (−19)
$Pt(H_{-1}L)Cl_2^{2-}$ (IIIa)	G_3	−2220	−2111 (−109)	−2221 (+1)
	G_4	−2223	−2111 (−112)	−2221 (−2)
	G_3a	−2218	−2111 (−107)	−2221 (+3)
$Pt(H_{-1}L)(OH)_2^{2-}$ (IIIb)	G_3	−1638	−1443 (−195)	−1553 (−85)
$Pt(H_{-2}L)Cl^{2-}$ (Va)	G_3	−2325	−2344 (+19)	−2334 (+9)
	G_4	−2328	−2344 (+6)	−2334 (+6)
	G_3a	−2333	−2344 (+11)	−2334 (+1)
$Pt(H_{-2}L)OH^{2-}$ (Vb)	G_3	−2041	−2048 (+7)	−2038 (−3)
	G_4	−2057	−2048 (−9)	−2038 (−6)
	G_3a	−2038	−2048 (+10)	−2038 (0)
$Pt(L)_2Cl_2^{2-}$ (IV)	G_3	−2315	−2111 (−204)	−2331 (+16)
	G_4	−2318	−2111 (−207)	−2331 (+13)
$Pt(H_{-1}L)_2^{2-}$ (VI)	G_3	−2483	−2579 (+96)	−2487 (+4)
$Pt(H_{-3}L)^{2-}$ (VIII)	G_4	−2315	−2579 (+264)	−2317 (+2)
$Pt(H_{-2}L)L^{2-}$ (VII)	G_3	−2525	−2579 (+54)	−2497 (−28)
	G_3a	−2462	−2579 (+117)	−2497 (+35)
cis-$Pt(NH_3)_2(L)OH$ (IX)	G_2	−2194	−2048 (−146)	−2158 (−36)
cis-$Pt(NH_3)_2(H_{-1}L)$ (X)	G_2	−2594	−2579 (−15)	−2687 (+93)
cis-$Pt(NH_3)_2(L)_2$ (XI)	G_2	−2730	−2579 (−151)	−2797 (+67)

[a] Calculated from additivity of chemical shift values for NH_3, Cl^-, and OH^- according to eq 3 or 4. [b] Values of δ_{Pt} based on δ_{Pt}^{calcd} with corrections for shifts by peptide amine groups (−110 ppm) and linked consecutive chelate rings (+120 ppm for two and +380 ppm for three chelate rings). [c] $\Delta\delta_{Pt} = \delta_{Pt}^{obsd} - \delta_{Pt}^{calcd}$. [d] $\Delta\delta'_{Pt} = \delta_{Pt}^{obsd} - \delta_{Pt}^{corr}$.

Results and Discussion

Relatively high initial concentrations of $PtCl_4^{2-}$ (0.2–0.3 M) are used in order to obtain satisfactory ^{195}Pt NMR signals for the variety of Pt(II)–oligopeptide species that form. As seen in eq 1, the reaction with triglycine to produce the doubly depro-

$$PtCl_4^{2-} + HG_3^{\pm} + 3OH^- \rightarrow Pt(H_{-2}G_3)Cl^{2-} + 3H_2O + 3Cl^- \quad (1)$$

tonated complex (one of the observed species) consumes 3 equiv of base and releases three chloride ions. The added base dilutes the sample, but the Cl^- concentration is still quite high (as large as 0.7 M in some solutions). The initial rate of loss of $PtCl_4^{2-}$ corresponds to its rate of hydrolysis ($k = 3.7 \times 10^{-5}$ s^{-1} at 25.0 °C, $\mu = 0.50$ M) as measured by Elding[21] in acid solutions (eq 2). The half-life of this hydrolysis is 5.2 h, but the overall

$$PtCl_4^{2-} + H_2O \xrightarrow{k} PtCl_3(H_2O)^- + Cl^- \quad (2)$$

substitution and rearrangement reactions become extremely slow (weeks are needed to drive eq 1 to completion) as the chloride concentration increases during the reaction. (The stepwise equilibrium dissociation constants for loss of Cl^- from $PtCl_4^{2-}$ are $K_{d4} = 1.26 \times 10^{-2}$ M, $K_{d3} = 1.4 \times 10^{-3}$ M, $K_{d2} = 1.0 \times 10^{-4}$ M, and $K_{d1} = 1.1 \times 10^{-5}$ M.)[22-24] Nevertheless, the use of $PtCl_4^{2-}$ as a reactant, rather than $Pt(H_2O)_4^{2+}$,[25] is advantageous because chloride complexation prevents the precipitation of platinum hydroxide. Chloride appears to suppress the successive chelation steps of the peptides as well as the initial reaction. Another factor that greatly slows the equilibration of 1:1 mixtures of Pt(II) and the oligopeptides is the initial formation of small amounts of bis(peptide) complexes, which must dissociate to consume all the $PtCl_4^{2-}$ and give the final products.

Although the Pt(II)–peptide solutions were kept for long periods to ensure complete reaction, hydrolysis of the peptides was not observed. Thus, neither glycine nor diglycine were detected in ^{13}C NMR spectra of triglycine reactions.

^{195}Pt NMR Spectra of the Platinum Triglycine Species. The complexes of the fully ^{15}N-substituted triglycine with K_2PtCl_4 show well-resolved ^{195}Pt NMR spectra, where individual coupling constants between nitrogen and platinum can be distinguished. Figure 3a shows the predominant features in a ^{195}Pt NMR spectrum taken 1 day after mixing K_2PtCl_4 and $HG_3^{\pm}$ at pH 7. The largest feature is a singlet at −1685 ppm (i.e. upfield from the $PtCl_6^{2-}$ reference) due to unreacted $PtCl_4^{2-}$. The peak at −2008 is a doublet ($^1J_{Pt-N} = 346$ Hz) due to coordination of ^{15}N to ^{195}Pt, which results in a 1:1 splitting of the resonance.

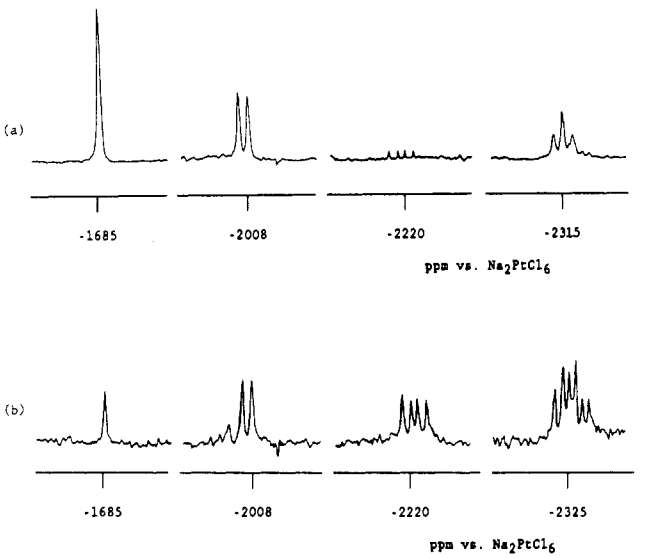


Figure 3. ^{195}Pt NMR spectra of a reaction mixture of $PtCl_4^{2-}$ and $(^{15}N)G_3$: (a) after 1 day at pH 7; (b) after 3 days at pH 7. Assignments are $PtCl_4^{2-}$ (−1685 ppm), $PtG_3Cl_3^{2-}$ (II) (−2008 ppm), $Pt(H_{-1}G_3)Cl_2^{2-}$ (IIIa) (−2220 ppm), *cis*-$Pt(G_3)_2Cl_2^{2-}$ (IV) (−2315 ppm), and $Pt(H_{-2}G_3)Cl^{2-}$ (Va) (−2325 ppm), with some *cis*-$Pt(G_3)_2Cl_2^{2-}$ (IV) still present.

The chemical shifts can be calculated from the linear relationships shown in Figure 1 for $Pt(NH_3)_y(X)_{4-y}$ given in eqs 3 and 4. The δ_{Pt}^{calcd} value is −1878 ppm for a species with one

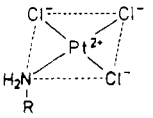
$$X = Cl^- \qquad \delta_{Pt}^{calcd} = -1645 - 233y \quad (3)$$

$$X = OH^- \qquad \delta_{Pt}^{calcd} = -233 - 605y \quad (4)$$

nitrogen and three chloride donors (Table II), whereas $\delta_{Pt}^{calcd} = -838$ ppm for one nitrogen and three oxygen donors. Since $\delta_{Pt}^{obsd} = -2008$ ppm, this pattern is assigned to $Pt(G_3)Cl_3^{2-}$ (II), where

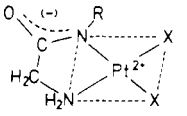
(21) Elding, L. I. *Acta Chem. Scand.* **1966**, *20*, 2559–2567.
(22) Elding, L. I.; Leden, I. *Acta Chem. Scand.* **1966**, *20*, 706–715.
(23) Elding, L. I. *Acta Chem. Scand.* **1970**, *24*, 1331–1340.
(24) Elding, L. I. *Inorg. Chim. Acta* **1978**, *28*, 255–262.
(25) Elding, L. I. *Inorg. Chim. Acta* **1976**, *20*, 65–69.

only the terminal amine group of the triglycine is coordinated.



II

The very small peak at −2220 ppm in Figure 3a is a doublet of doublets, as more clearly seen in Figure 3b. It is correlated with the complex $Pt(H_{-1}G_3)Cl_2^{2-}$ (IIIa). In this structure the

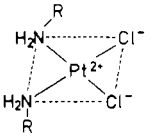


a X = Cl⁻
b X = OH⁻

IIIa,b

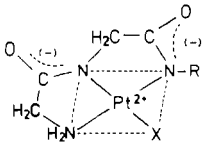
two coordinated nitrogens are chemically and magnetically different, and each nitrogen splits the signal into a doublet with its own characteristic coupling constant. The larger coupling constant $^1J_{Pt-N}$ = 517 Hz is attributed to the platinum–deprotonated peptide nitrogen interaction; the smaller $^1J_{Pt-N}$ = 315 Hz is attributed to the platinum–amine nitrogen (Table III). The magnitude of the coupling constants reflects the strength of the platinum–nitrogen interactions and the degree of s character of the nitrogen bonding orbitals. The bond between the deprotonated nitrogens and platinum is stronger than the bond between the amine nitrogen and metal center, and the peptide nitrogen (sp^2) has more s character than the amine nitrogen (sp^3). The coordination of chloride ions in the third and fourth position is postulated from chemical shift comparisons (δ_{Pt}^{calcd} = −2111 ppm vs δ_{Pt}^{obsd} = −2220 ppm, Table II).

The fourth feature in the early ^{195}Pt NMR spectrum shown in Figure 3a is a triplet at δ_{Pt} = −2315 ppm that corresponds to two equivalent nitrogens coordinated to the platinum nucleus. The coupling constant $^1J_{Pt-N}$ = 345 Hz indicates that the terminal amine group is coordinated rather than the deprotonated peptide group, because the latter would give rise to a much larger coupling constant. Since the trans effect[26] would favor a cis arrangement of the coordinated amine groups, the *cis*-$Pt(G_3)_2Cl_2^{2-}$ complex, IV, is proposed to explain the triplet.



IV

After 3–4 days of reaction time this mixture shows a slightly different pattern (Figure 3b). The magnitude of the singlet signal at −1685 ppm decreases, and the magnitude of the doublet of doublets at −2220 ppm increases. A new multiplet is now found at −2325 ppm, which shows the remains of the triplet at −2315 ppm and a new signal. After several more days of reaction at pH 7 the reaction mixture gives the spectrum shown in Figure 2b. The largest peak in this ^{195}Pt NMR spectrum is a triplet of doublets at −2325 ppm (Figure 4a). This pattern is assigned to $Pt(H_{-2}G_3)Cl^{2-}$, structure Va. Two deprotonated peptide nitrogens



a X = Cl⁻
b X = OH⁻

Va,b

are magnetically equivalent, since they are in approximately the same chemical surroundings. They give rise to the triplet pattern (1:2:1) with a coupling constant $^1J_{Pt-N}$ = 495 Hz. The unique amine nitrogen splits each line of this triplet into a doublet with a coupling constant $^1J_{Pt-N}$ = 240 Hz. The chloride in the fourth position is assigned by comparison (δ_{Pt}^{calcd} = −2344 ppm, δ_{Pt}^{obsd} = −2325 ppm; Table II).

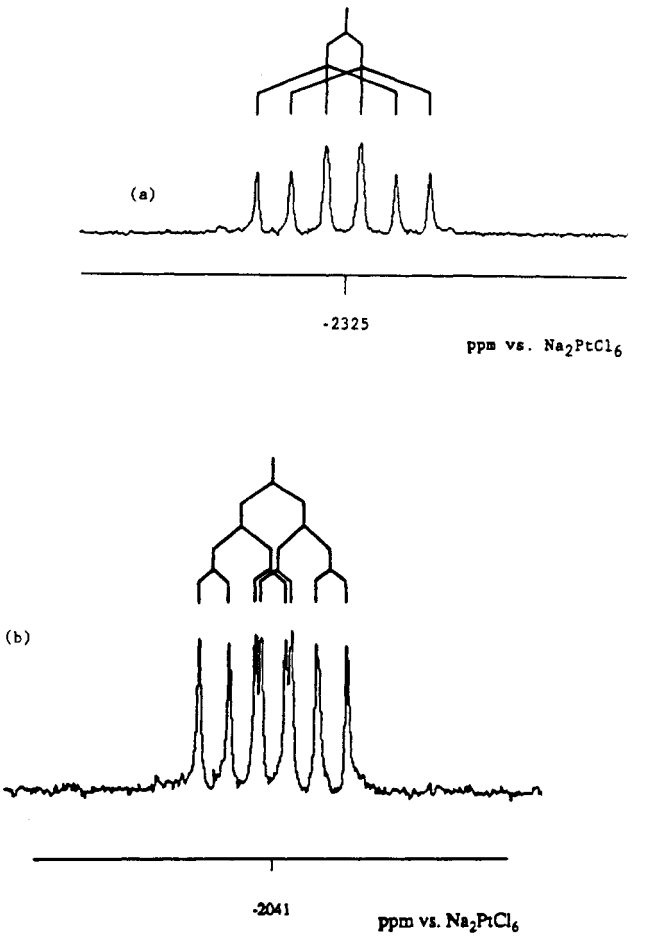


Figure 4. ^{195}Pt NMR spectrum and splitting pattern for (a) $Pt(H_{-2}G_3)Cl^{2-}$ (Va), doublet of triplets with $^1J_{Pt-N}$ = 240 and 495 Hz, respectively, and (b) $Pt(H_{-2}G_3)OH^{2-}$ (Vb), doublet of doublets of doublets with $^1J_{Pt-N}$ = 246, 459, and 508 Hz.

When the pH of a 10–14-day-old reaction mixture of $PtCl_4^{2-}$ and G_3 is increased to pH >12, the only feature detected in the ^{195}Pt NMR spectrum after 6 h is a doublet of doublets of doublets at −2041 ppm ($^1J_{Pt-N}$ = 246, 459, 508 Hz, Figure 4b). The chemical shift corresponds to a downfield shift of 284 ppm from the peak observed at pH 7, which was attributed to $Pt(H_{-2}G_3)Cl^{2-}$. A comparison of ^{195}Pt spectral data for $Pt(NH_3)_2Cl_2$ (−2097 ppm[27]) and $Pt(NH_3)_2(OH)_2$ (−1572 ppm[28]) shows a downfield shift of 263 ppm per Cl^- substituted for OH^-. Therefore, the new spectrum can be assigned to $Pt(H_{-2}G_3)OH^{2-}$, structure Vb. The smallest coupling constant is clearly correlated with the terminal amine group. In accord with the order of trans influence, the next larger coupling constant ($^1J_{Pt-N}$ = 459 Hz) is assigned to the peptide nitrogen trans to OH^-. The terminal amine group has a weaker trans influence, and the bond of the platinum with the deprotonated peptide group trans to it should be stronger than that trans to OH^-. This assigns the largest coupling constant (508 Hz) to the second deprotonated peptide nitrogen. The term trans influence is used to denote the dependence of NMR parameters on the nature of the trans ligand.[29] It serves to distinguish it from

(26) Chernyaev, I. I., *Izv. Inst. Izuch. Platiny Drugikh Blagorodn. Met., Akad. Nauk SSSR* **1927**, *5*, 118–156.

(27) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 4685–4693.

(28) Boreham, C. J.; Broomhead, J. A.; Fairlie, D. P. *Aust. J. Chem.* **1981**, *34*, 659–664.

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Table III. $^1J_{Pt-N}$ Coupling Constants for Platinum(II) Peptide Complexes

complex	peptide	$^1J_{Pt-N}$, Hz: amine[a]	deprotonated N(peptide)[a]		
$Pt(L)Cl_3^{2-}$ (II)	G_3	346 (Cl)			
	G_4	336 (Cl)			
$Pt(H_{-1}L)Cl_2^{2-}$ (IIIa)	G_3	315 (Cl)	517 (Cl)		
	G_4	317 (Cl)	556 (Cl)		
$Pt(H_{-1}L)(OH)_2^{2-}$ (IIIb)	G_3	290 (OH)	512 (OH)		
$Pt(H_{-2}L)Cl^{2-}$ (Va)	G_3	240 (N^-)	495 (Cl)	495 (RNH_2)	
	G_4	248 (N^-)	498 (Cl)	498 (RNH_2)	
$Pt(H_{-2}L)OH^{2-}$ (Vb)	G_3	246 (N^-)	459 (OH)	508 (RNH_2)	
	G_4	254 (N^-)	460 (OH)	491 (RNH_2)	
cis-$Pt(L)_2Cl_2^{2-}$ (IV)	G_3	345 (Cl)			
	G_4	359 (Cl)			
cis-$Pt(H_{-1}L)_2^{2-}$ (VI)	G_3	244 (N^-)		496 (RNH_2)	
$Pt(H_{-3}L)^{2-}$ (VIII)	G_4	243 (N^-)	438 (N^-)	438 (RNH_2)	394 (N^-)
$Pt(H_{-2}L)L^{2-}$ (VII)	G_3	243 (N^-)		513 (RNH_2)	
		209 (N^-)			

[a] The trans ligand is given in parentheses.

the trans effect, which is derived from kinetic ligand substitution behavior.[26]

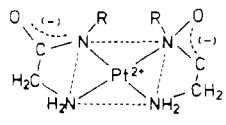
The coordinated OH^- in $Pt(H_{-2}G_3)OH^{2-}$ is replaced within 30 min by Cl^- when the solution is neutralized. The equilibrium constant K_1 in eq 5 is estimated to be 900 from the relative areas

$$Pt(H_{-2}G_3)Cl^{2-} + OH^- \overset{K_1}{\rightleftharpoons} Pt(H_{-2}G_3)OH^{2-} + Cl^- \quad (5)$$

of the corresponding peaks at different pH values. (The relative areas can be used because the T_1 values are similar for these complexes.) If a solution contains appreciable amounts of species IIIa when the pH is increased, a doublet of doublets pattern appears at −1638 ppm with $^1J_{Pt-N}$ coupling constants equal to 512 and 290 Hz, respectively. The chemical shift corresponds to the substitution of two Cl^- by two OH^-, and this new species is assigned structure IIIb.

The NMR spectra for species II–V did not show evidence of peptide bridging between two platinums. The high concentration of chloride ion released from $PtCl_4^{2-}$ tends to prevent the formation of hydroxide complexes at pH 7–8. This in turn reduces the possibility of the formation of hydroxo-bridged dimers or oligomers. The NMR spectra of the hydroxide complexes (IIIb and Vb) were taken about 6 h after the addition of base. This is sufficient time for OH^- to replace Cl^- but is a relatively short time for the formation of oligomers. The UV/vis spectral solutions that were prepared at low concentrations (where oligomers are less likely to form) are similar to the freshly diluted NMR samples. We cannot rule out oligomer formation, but the above evidence suggests this is unlikely under our conditions.

When K_2PtCl_4 and $(^{15}N)G(^{15}N)G(^{15}N)G$ are reacted in a 1:2 ratio at pH 7 for several days, the ^{195}Pt NMR spectrum shows multiplets at −2483 and −2525 ppm. These chemical shift values are within the range reported for complexes with four nitrogen ligands.[28] The pattern at −2483 ppm shows seven equidistant lines of intensity 1:2:3:4:3:2:1. This splitting cannot be due to six equivalent spin-$^1/_2$ nuclei, since then the intensity ratio should be 1:6:15:20:15:6:1. The most likely interpretation is a triplet of triplets where some of the lines coincide (Figure 5a). The pattern fits with the proposed structure of a bis complex *cis*-$Pt(H_{-1}G_3)_2^{2-}$ (VI). The two coordinated amine groups are chemically and



VI

magnetically equivalent, and the two deprotonated peptide groups are also equivalent. Each group of nuclei splits the platinum resonance line into a triplet with a characteristic coupling constant. Since the interaction of the deprotonated peptide group with platinum is stronger than that of the amine group, the larger

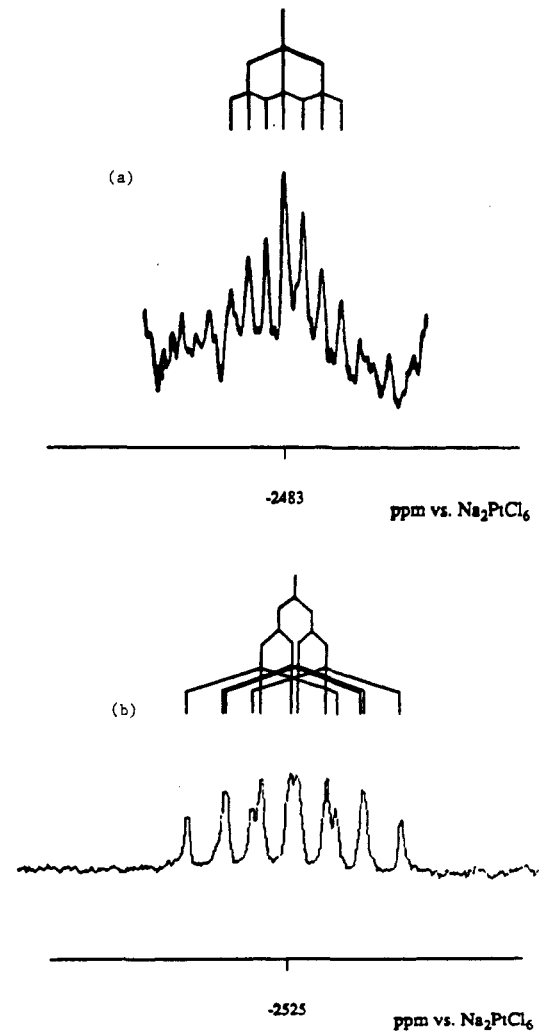


Figure 5. ^{195}Pt NMR spectrum and splitting pattern for (a) $Pt(H_{-1}G_3)_2^{2-}$ (VI), triplet of triplets with partially coinciding lines, $^1J_{Pt-N}$ = 244 and 496 Hz, and (b) $Pt(H_{-2}G_3)G_3^{2-}$ (VII), doublet of doublets of triplets with $^1J_{Pt-N}$ = 210, 243, and 513 Hz, respectively.

coupling constant ($^1J_{Pt-N}$ = 496 Hz) is attributed to the peptide nitrogen as compared to $^1J_{Pt-N}$ = 244 Hz for the amine group. The conformation is assigned cis on the basis of the small coupling constants for the terminal amine group. Also, the kinetic trans effect[26] will favor the formation of *cis*-$Pt(G_3)_2Cl_2^{2-}$, which is expected to lose protons to give $Pt(H_{-1}G_3)_2^{2-}$. If $Pt(H_{-1}G_3)Cl_2^{2-}$ forms first, then the larger trans effect of the deprotonated peptide group as compared to the chloride will also force the incoming G_3 into a cis position.

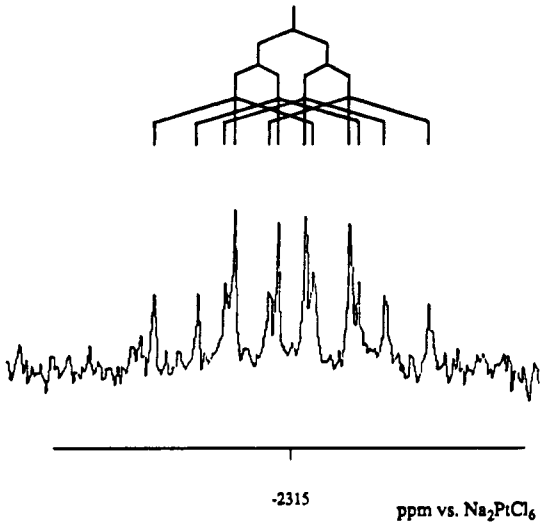
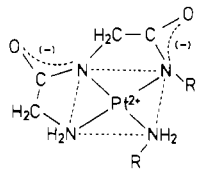


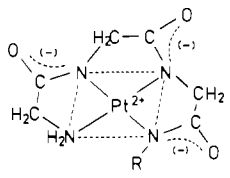
Figure 6. ^{195}Pt NMR spectrum and splitting pattern for $Pt(H_{-3}G_4)^{2-}$ (VIII), doublet of doublets of triplets with $^1J_{Pt-N}$ = 243, 394, and 438 Hz, respectively.

The pattern at −2525 ppm is a doublet of doublets of triplets with $^1J_{Pt-N}$ coupling constants of 210, 243, and 513 Hz, respectively (Table III, Figure 5b). Again, two deprotonated peptide groups are equivalent, and their signal is split by two nonequivalent amine groups (determined by the much smaller coupling constants). The proposed complex is $Pt(H_{-2}G_3)G_3^{2-}$, structure VII, where the second G_3 ligand is coordinated through its terminal amine group in the fourth position.



VII

^{195}Pt NMR Spectra of the Platinum Tetraglycine Species. The reaction of $PtCl_4^{2-}$ with fully ^{15}N-substituted tetraglycine ($[Pt]_T \geq 0.2$ M, 3–5% excess G_4) is analogous to the reaction with G_3. At low pH values (pH ≤3) a mixture of species II, IIIa, and Va forms. The ^{195}Pt NMR chemical shifts and coupling constants for the various species are listed in Tables II and III. While the chemical shifts are only slightly more negative than those of the G_3 species, the coupling constants differ by as much as 35 Hz. Tetraglycine has a potential fourth nitrogen coordination site available, and in high base (pH ≥12) a species with three deprotonated peptide groups, $Pt(H_{-3}G_4)^{2-}$ corresponding to structure VIII, is slowly formed. Because the resonance of this species at



VIII

−2315 ppm overlaps with that of species $Pt(H_{-2}G_4)Cl^{2-}$ (structure Va, δ_{Pt} = −2325 ppm), the $Pt(H_{-3}G_4)^{2-}$ species was only found when ^{15}N-labeled G_4 was used. The splitting pattern for VIII is a doublet of doublets of triplets, as seen from Figure 6. The smallest coupling constant $^1J_{Pt-N}$ = 243 Hz is due to the terminal amine group; the other unique splitting of 394 Hz is due to the deprotonated peptide in the fourth position. Two equivalent sites have a coupling constant of 438 Hz and are attributed to the two central deprotonated peptide nitrogens, rather than the deprotonated peptide nitrogens trans to each other. The explanation for this assignment lies in the steric constraint that the third peptide

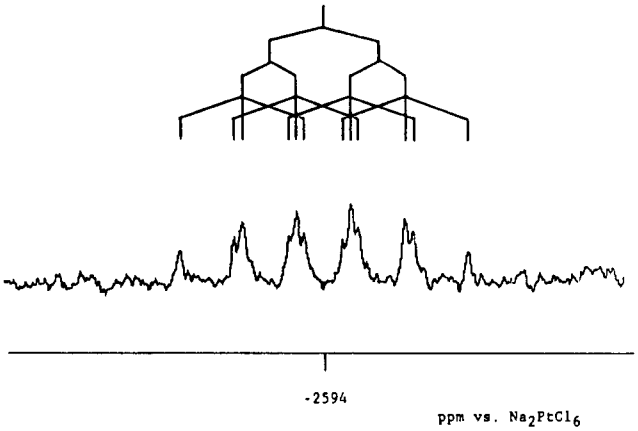


Figure 7. ^{195}Pt NMR spectrum and splitting pattern for $Pt(NH_3)_2(H_{-1}G_2)$ (X), doublet of doublets of triplets with $^1J_{Pt-N}$ = 258, 296, and 513 Hz, respectively.

group will experience in wrapping around the metal center. The bond angles formed between the amine group, the metal ion, and the fourth ligand donor (i.e. the angle on the open side of the complex that does not have a chelate ring) have been measured for a number of peptide complexes that have three linked consecutive five-membered chelate rings.[30] These angles increase from 98.1° for Cu(III), to 104.5° for Ni(II), and to 109° for Cu(II) and parallel increases in the ionic radii of the metal ions. The Pt(II) radius is larger than the Cu(II) radius, and hence, the distortion from a square to a trapezoidal position for the ligand donors in $Pt(H_{-3}G_4)^{2-}$ should be even more pronounced. Even in the case of $Ni^{II}(H_{-3}G_4)^{2-}$ a slight distortion from a square-planar structure is seen in the Ni–N bond distances, which are 1.924, 1.830, 1.820, and 1.875 Å for the sequence from the amine to the third peptide group.[31] Stability constants of copper(II) polyamine complexes with linked consecutive rings also reflect the strain imposed by 5,5,5-membered ring systems.[32]

^{195}Pt NMR Spectra of the Platinum Triglycinamide Species. The reaction of $PtCl_4^{2-}$ with G_3a gives products similar to those with G_3 and G_4 ligands. Resonances are found at −2007 (structure II), −2218 (structure IIIa), −2333 (structure Va), and −2462 ppm. This last resonance is close to the region where platinum complexes with four nitrogen ligands are found and is assigned to structure VIII. In accord with the resonances described for the triply deprotonated species $Pt(H_{-3}G_4)^{2-}$ (VII), the peak for the $Pt(H_{-3}G_3a)^-$ complex would be expected to coincide with that of $Pt(H_{-2}G_3a)Cl^{2-}$ (Va). It was not possible to distinguish between these two species, because the fully ^{15}N-substituted G_3a was not available.

^{195}Pt NMR Spectra of Cisplatin with Diglycine. The reaction of cisplatin with (^{15}N)glycyl(^{15}N)glycine was carried out in a slurry because of low solubility of the platinum complex in water. A 1:1 mixture of platinum/ligand ($[Pt]_T \geq 0.2$ M, 3–5% excess ligand) showed no dissolution of the solid at pH 8–9 over a period of several days. At higher pH values (pH ≥11) a clear, light yellow solution formed within 1 day, and the ^{195}Pt NMR spectra showed peaks at −2130 (trace), −2194, −2594, and −2730 ppm (minor, Table II). The peaks at −2130 and −2194 ppm are quartets with $^1J_{Pt-N}$ coupling constants of 260 and 295 Hz, respectively. The chemical shift range corresponds to the values reported by Appleton et al.[33] for $Pt(NH_3)_2$(gly-*N*,*O*)$^+$ and $Pt(NH_3)_2$(gly-*N*)(OH) of −2130.8 and −2126 ppm, respectively. A proposed structure for the complex at −2194 ppm, which is the major species in solution, is given by $Pt(NH_3)_2(G_2)(OH)$ (IX).

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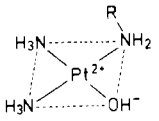
Table IV. $^1J_{Pt-N}$ Coupling Constants for Platinum(II) Diammine Diglycine Complexes

complex	$^1J_{Pt-N}$, Hz: amine[a]	NH_3[a]	deprotonated N(peptide)[a]
cis-$Pt(NH_3)_2(G_2)OH$ (IX)	295 (NH_3)	295 (RNH_2), 295 (OH)	
cis-$Pt(NH_3)_2(H_{-1}G_2)$ (X)	296 (NH_3)	258 (N^-), 296 (RNH_2)	513 (NH_3)
cis-$Pt(NH_3)_2(G_2)_2$ (XI)	293 (NH_3)	293 (RNH_2)	

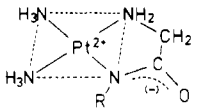
[a] The trans ligand is reported in parentheses.

The signal at −2130 ppm, which is very weak, could result from a small amount of N,O chelation.



IX

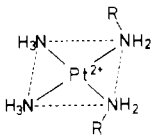
The resonance at −2594 ppm shows a typical splitting pattern due to two nonequivalent and two equivalent nitrogens coordinated to platinum (Figure 7). This species is assigned to $Pt(NH_3)_2(H_{-1}G_2)$, structure X. The terminal amine nitrogen of the G_2



X

and the ammine trans to it are nearly equivalent, and the triplet splitting with $^1J_{Pt-N}$ = 296 Hz is due to their coupling with ^{195}Pt. The largest coupling constant of 513 Hz is assigned to the deprotonated-N(peptide) group, and the ammine trans to it has $^1J_{Pt-N}$ = 258 Hz.

The pattern of the resonance at −2730 ppm is a quintet, and its corresponding complex, $Pt(NH_3)_2(G_2)_2$, is described by structure XI. The ammine ligands and the coordinated terminal



XI

amine groups from the G_2 are magnetically equivalent and give rise to the coupling constant $^1J_{Pt-N}$ = 293 Hz. This assignment is in agreement with Appleton's value of −2661 ppm for $Pt(NH_3)_2$(gly-*N*)$_2$.[33] When excess (^{14}N)glycyl(^{14}N)glycine is added, the bis complex (XI) is the major species in solution (≥80%) and resonates at −2717 ppm.

$^1J_{Pt-N}$ Coupling Constants. One-bond $^{195}Pt-^{15}N$ coupling constants, $^1J_{Pt-N}$, depend on the s character of the Pt orbitals used in bonding to N. The *J* values are expected to be smaller for a nitrogen ligand trans to a ligand that has a large trans influence, since this tends to weaken the trans bond.[34] For *cis*-diammine complexes of platinum(II) the value (Hz) for the $^1J_{Pt-N}$ coupling constants for NH_3 decreases with the trans ligand: H_2O (390), Cl^- (326), OH^- (296), NH_3 (287). The order of trans influence is $H_2O < Cl^- < OH^- < NH_3$. Our studies with the tripeptide complexes of platinum show a similar behavior (Tables III and IV). When all other coordination sites are equal, the trans influence for the coupling of either a terminal amine group or a deprotonated peptide group follows the trend $N^- \gg OH^- \gg NH_3$, $RNH_2 > Cl^-$ (where N^- denotes the deprotonated peptide group). The deprotonated peptide group always has a substantially higher coupling constant than RNH_2 regardless of the trans substituent (e.g. 517 vs 315 Hz in $Pt(H_{-1}G_3)Cl_2^{2-}$. This indicates stronger bond formation, which is also seen from the trans influence.

There also appears to be a substantial cis influence of the deprotonated peptide group, which may be associated with the effect of the chelate rings. The coupling of a terminal amine group trans to Cl^- (which has the smallest trans influence of the ligands studied) is decreased by a N^- in cis position by about 20–30 Hz. On the other hand, terminal amine groups trans to NH_3, NH_2^-, OH^-, or N^- are not affected by a N^- in cis position. The coupling of a deprotonated peptide group is influenced strongly by a neighboring N^-. This effect is ≈25 Hz for G_3 as the ligand and ≈60 Hz for G_4. Some of these effects can be explained by the steric constraints that occur when the peptide ligand is wrapped around the platinum center. When a second deprotonated peptide group is coordinated to the metal, the bonding of the first group will have to be slightly rearranged to accommodate the new bond. These effects are best seen from the spectra of $Pt(H_{-3}G_4)^{2-}$, structure VIII, and $Pt(H_{-2}G_3)G_3^{2-}$, structure VII. In species VIII the coordination of the third deprotonated peptide group can only occur with a distortion of the regular square-planar arrangement, and the trans influence of the first deprotonated peptide group forces $^1J_{Pt-N}$ for the third group to be smaller. The same argument holds for species VII. The first peptide group is more strongly bound than the second one and exhibits a stronger trans influence to make the coupling to the terminal amine group of the second G_3 ligand smaller.

The peptide ligands also influence the $^1J_{Pt-N}$ coupling constants of the terminal amine groups; differences of up to 40 Hz are seen for G_3 and G_4 species with comparable structures.

Table V. ^{195}Pt NMR Chemical Shift Corrections for Peptide Groups vs Ammonia

peptide coord[b]	no. of NH_3 replaced	corr, ppm[a] (add to δ_{Pt}^{calcd})	peptide coord[b]	no. of NH_3 replaced	corr, ppm[a] (add to δ_{Pt}^{calcd})
RNH_2	1	−110	$H_{-3}L$	4	+260
$H_{-1}L$	2	−110	*cis*-$(H_{-1}L)_2$	4	+90
$H_{-2}L$	3	+10	$(H_{-2}L)(L)$	4	+80

[a] $\delta_{Pt}^{corr} = \delta_{Pt}^{calcd}$ + correction, where δ_{Pt}^{calcd} is based on the number of NH_3, Cl^-, and OH^- groups (eqs 3 and 4). [b] L = G_3, G_4, G_3a, and G_2.

^{195}Pt NMR Chemical Shifts. Very large chemical shifts (over a 1100 ppm range) are observed as ammonia, peptides, and OH^- groups replace chlorides in $PtCl_4^{2-}$. Equations 3 and 4 are used to predict the chemical shifts (δ_{Pt}^{calcd}) given in Table II, and these values, together with the $^1J_{Pt-N}$ coupling constants, are used to assign structures for the peptide complexes. Table II shows that δ_{Pt}^{obsd} and δ_{Pt}^{calcd} do not always agree, and the fourth column in the table gives the difference ($\Delta\delta_{Pt}$) between these sets of values (eq 6). There are systematic variations in the δ_{Pt} values when

$$\Delta\delta_{Pt} = \delta_{Pt}^{obsd} - \delta_{Pt}^{calcd} \quad (6)$$

nitrogens from peptides rather than ammonia are coordinated. Table V organizes these variations in the form of chemical shift corrections that can be added to δ_{Pt}^{calcd} to give δ_{Pt}^{corr} values (eq 7). The latter values are in better agreement with δ_{Pt}^{obsd}, as shown

$$\delta_{Pt}^{corr} = \delta_{Pt}^{calcd} + \text{correction} \quad (7)$$

$$\Delta\delta_{Pt}' = \delta_{Pt}^{obsd} - \delta_{Pt}^{corr} \quad (8)$$

by $\Delta\delta_{Pt}'$ (eq 8) in the fifth column of Table II. The δ_{Pt}^{corr} values are useful in order to predict where NMR resonance frequencies can be found for complexes of this type. The corrections also are sufficiently large to merit some consideration of their nature.

Monodentate amine coordination by G_3, G_4, and G_3a in II give δ_{Pt}^{obsd} values that are 130 ppm more negative than the δ_{Pt}^{calcd} value for $Pt(NH_3)Cl_3^-$. Two monodentate amines give δ_{Pt}^{obsd} values that are more negative than δ_{Pt}^{calcd} by 204 and 207 ppm for G_3 and G_4 in IV. Similar differences of 146 and 153 ppm are found for the *cis*-$Pt(NH_3)_2L(OH)$ and *cis*-$Pt(NH_3)_2(L)_2$ complexes (IX and XI). The average correction for all these structures is −110 ± 30 ppm (given for RNH_2 in Table V). A similar effect, but

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smaller in magnitude (≈50 ppm) is seen for the chemical shifts of *cis*-diammine(glycinato)platinum(II) complexes.[33]

The first chelate ring formed by amine and deprotonated-N-(peptide) donors gives δ_{Pt}^{obsd} values that again are about 110 ppm more negative than δ_{Pt}^{calcd} for two coordinated NH_3 molecules. This is seen with structure IIIa for G_3, G_4, and G_3a in Table II. Thus, the combined effect of chelate ring formation and N^--peptide coordination (i.e. $H_{-1}L$ in Table V) gives the same chemical shift expected for monodentate peptide amine (RNH_2) and NH_3 coordination. The formation of a single chelate ring with glycine also has no appreciable effect on the ^{195}Pt NMR shift; δ_{Pt} values for *cis*-$Pt(NH_3)_2$(gly-*N*,*O*)$^+$ and for *cis*-$Pt(NH_3)_2$(gly-*N*)(OH) are −2129 and −2126 ppm, respectively.[33]

Peptide complexes with an amine and two deprotonated-N-(peptide) donors, $Pt(H_{-2}L)X^{2-}$, give δ_{Pt}^{obsd} values close to values expected for $Pt(NH_3)_3X^+$. The average correction (Tables II and V) is only +10 ppm. However, this means that two linked consecutive chelate rings in $H_{-2}L$ have shifted to δ_{Pt} values by +120 ppm relative to what would be calculated for a single chelate ring ($H_{-1}L$) and a coordinated NH_3. A single chelate ring does not seriously distort the RNH_2–Pt–N^- bond angle. Two linked five-membered rings will force deviations from the ideal 90° bond angles between Pt and *cis*-nitrogens to give a distorted square-planar geometry.

The $Pt(H_{-3}G_4)^{2-}$ complex has three linked five-membered rings, and the correction in Table V is +260 ppm. In order for four nitrogens of G_4 to coordinate to give structure VIII, the preferred square-planar sites around platinum must be distorted to a trapezoidal arrangement.[30] This effect is seen in the $^1J_{Pt-N}$ coupling constants as well as in the chemical shift. An additional factor that may contribute to the large chemical shift correction for $Pt(H_{-3}G_4)^{2-}$ is the change of the secondary environment around platinum as the peptide occupies more space and water molecules occupy less space in the vicinity of the metal ion. As platinum becomes surrounded by peptide groups, the chemical shifts are less negative than expected for the corresponding number of coordinated NH_3 molecules. This can be seen in the corrections given in Table V of +90 ppm for structure VI and +80 ppm for structure VII. For the *cis*-$Pt(H_{-1}G_3)_2^{2-}$ complex, where R′ = $CH_2CONHCH_2COO^-$ in VI, the two R′ groups must twist above and below the plane of the complex in order to achieve this coordination. A trans configuration would be much less sterically hindered, but the trans effect of Cl^- causes the cis product to be preferred kinetically. A cis configuration also forms with the bis(triglycine) complex of Cu(II).[35] The steric hindrance of the two R′ groups in VI could distort the geometry around Pt(II) and cause the chemical shift changes. However, the $^1J_{Pt-N}$ values do not change very much and this leads to the suggestion that the secondary environment may also make a contribution to the chemical shift corrections. In structure VII for the bis(triglycine) complex R = $CH_2CONHCH_2CONHCH_2COO^-$ and R″ = CH_2COO^-. Although there would be appreciable steric hindrance between these groups, the steric effects should be less than that for structure VI. Nevertheless, the chemical shift correction is similar. Little is known about effects of multiple chelation or outer-sphere environment on NMR chemical shifts of platinum. We introduce the empirical corrections in Table V, because they represent systematic variations that are helpful in our correlations and because these effects are worthy of additional investigation.

Spectrophotometric Results. The monopeptide species do not show very characteristic UV/vis spectra (Figure 8); the only distinguishable feature is a shoulder at 240 nm with $\epsilon \approx 7200$ M^{-1} cm^{-1} for $Pt(H_{-2}G_3)(OH)^{2-}$. A small absorbance change with −log [H^+] at this wavelength (Figure 9) permits an equilibrium constant to be calculated for eq 9, $K_2 = 10^{9.9}$ M^{-1} for solutions that contains

$$Pt(H_{-2}G_3)OH^{2-} + H^+ \overset{K_2}{\rightleftharpoons} Pt(H_{-2}G_3)^- + H_2O \qquad (9)$$

less than 1×10^{-3} M Cl^-. A chloride-free solution gave the same

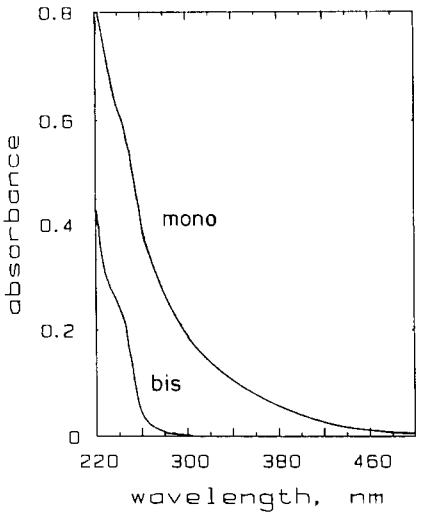

Figure 8. UV/vis spectra for $Pt(H_{-2}G_3)^-$ (I) (mono) and $Pt(H_{-1}G_3)_2^{2-}$ (VI) (bis) complexes ($[Pt]_T = 9.90 \times 10^{-4}$ M, $[Cl^-]_T = 3.96 \times 10^{-3}$ M, $[phosphate]_T = 0.10$ M, $\mu = 1.0$ M ($NaClO_4$), 25.0 °C, −log [H^+] = 7.0, 1-mm cell path).

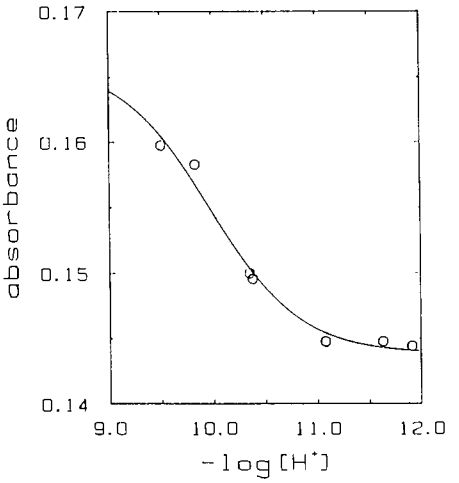

Figure 9. Absorbance dependence on −log [H^+] for equilibrium mixtures of $Pt(H_{-2}G_3)^-$ (I) and $Pt(H_{-2}G_3)(OH)^{2-}$ (Vb) ($[Pt]_T = 2.00 \times 10^{-4}$ M, $[Cl^-]_T = 8.00 \times 10^{-4}$ M, $\mu = 0.1$ M ($NaClO_4$), 25.0 °C, 240 nm, 0.1-cm cell path).

K_2 value within experimental error. The pK_a value of 9.9 (±0.1) for $Pt(H_{-2}G_3)^-$ is lower than that reported for the corresponding Cu(II) complex (11.8 at 25 °C, $\mu = 0.1$ M)[36] and similar to that found for Pd(II) (9.2 at 25 °C, $\mu = 0.1$ M).[37] From K_1 and K_2, an equilibrium constant K_3 ($=1/(K_1K_2K_w) = 14$ M^{-1}) can be estimated for the displacement of the carboxylate group (or H_2O) in the fourth coordination position by chloride (eq 10). The equilibrium constant for $Pt(H_{-2}G_3)Cl^{2-}$ formation (K_3) is similar in magnitude to that for the formation constant of $PtCl_3(H_2O)^-$ + Cl^- to give $PtCl_4^{2-}$ ($1/K_{d4} = 77$ M^{-1}).[22]

$$Pt(H_{-2}G_3)^- + Cl^- \overset{K_3}{\rightleftharpoons} Pt(H_{-2}G_3)Cl^{2-} \qquad (10)$$

The UV/vis spectrum for the bis complex formed with triglycine is given in Figure 9. The molar absorptivities of the bis complex are much less than the values for the mono complex. The spectral differences at 260 nm as a function of excess G_3^- permit the equilibrium constant in eq 11 to be evaluated: $K_4 = 7.5$ (±0.8)

$$Pt(H_{-2}G_3)^- + G_3^- \overset{K_4}{\rightleftharpoons} Pt(H_{-1}G_3)_2^{2-} \qquad (11)$$

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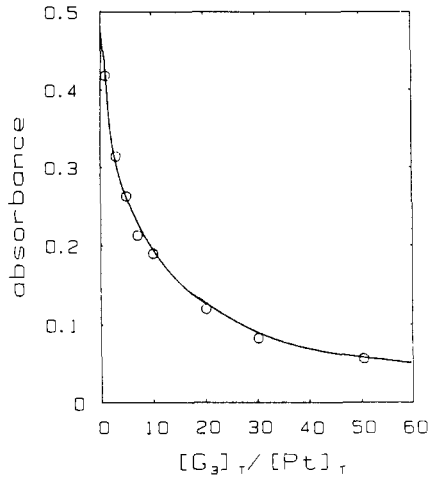

Figure 10. Absorbance dependence on excess $[G_3]$ to give $Pt(H_{-1}G_3)_2^{2-}$ (VI) ($[Pt]_T = 9.90 \times 10^{-4}$ M, $[Cl^-]_T = 3.96 \times 10^{-3}$, [phosphate]$_T$ = 0.10 M, -log $[H^+]$ = 7.0, μ = 1.0 M ($NaClO_4$), 25.0 °C, 260 nm, 1-mm cell path).

$\times 10^3$ M^{-1}. This constant was measured in the presence of 0.1 M phosphate buffer at pH 7.0 with 9.9×10^{-4} M $[Pt]_T$ (Figure 10). The equilibrium constant K_4 is smaller by a factor of 20 than the corresponding constant determined for Pd(II) (1.6×10^5 M^{-1})[37] but is much larger than the value for Cu(II) (1.74×10^2 M^{-1}).[38]

Conclusions

Deprotonated-N(peptide) complexation to Pt(II) occurs even in acidic solutions with high Cl^- concentrations. After 1 week, the reaction of $PtCl_4^{2-}$ with triglycine gives $Pt(H_{-2}G_3)Cl^{2-}$ as the major species (>60%) in 0.65 M Cl^- at pH 3.85. Since the platinum(II) chloride complexes are quite strong (i.e. $[PtCl_4^{2-}]/([PtCl^+][Cl^-]^3) = 10^{9.0}$ M^{-3}), this indicates that Pt-N^-(peptide) bond formation in the absence of Cl^- should occur below pH 1. However, the initial coordination reaction is extremely slow in acid. Our results show that platinum forms much stronger M(II)-N(peptide) bonds than copper,[1] nickel,[3] or palladium.[5] On the other hand, when a third N^-(peptide) group coordinates, as in $M^{II}(H_{-3}G_4)^{2-}$, relatively high pH is needed to give the corresponding platinum complex. This is consistent with a less favorable formation of three linked five-membered chelate rings around the larger Pt(II) ion. The ^{195}Pt-^{15}N NMR coupling constants and the ^{195}Pt chemical shifts also provide evidence for this effect. The use of ^{195}Pt NMR in conjunction with ^{15}N-substituted ligands provides an excellent method to characterize the peptide complexes that are slow to equilibrate in solution.

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Stepwise Hydrolysis Kinetics of Tetrachloroplatinate(II) in Base

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The stepwise hydrolysis of tetrachloroplatinate(II) in basic solution is investigated by ^{195}Pt NMR spectroscopy. Four sequential reactions are observed when 0.05 M $PtCl_4^{2-}$ is reacted with 1.0 M NaOH:

$$PtCl_4^{2-} \xrightarrow[k_1]{OH^-} PtCl_3(OH)^{2-} \xrightarrow[k_2]{OH^-} cis\text{-}PtCl_2(OH)_2^{2-} \xrightarrow[k_3]{OH^-} PtCl(OH)_3^{2-} \xrightarrow[k_4]{OH^-} Pt(OH)_4^{2-}$$

The reactions are not reversible, and the individual pseudo-first-order rate constants (s^{-1}, 25 °C, μ = 1.15 M) are as follows: $k_1 = 6.6 \times 10^{-5}$, $k_2 = 8 \times 10^{-5}$, $k_3 = 3.3 \times 10^{-6}$, $k_4 = 2.2 \times 10^{-6}$. The hydroxide ion concentration dependence for the first reaction, corrected to μ = 0.50 M, gives $k_1^{corr} = k_1^{H_2O} + k_1^{OH}[OH^-]$, where $k_1^{H_2O}$ is 3.6×10^{-5} s^{-1} and k_1^{OH} is 3.7×10^{-5} M^{-1} s^{-1}. The UV-vis spectrum of each Pt(II) species is resolved from repetitive scans on the basis of the NMR-determined rate constants. Dissolved O_2 (1 atm pressure) in 0.8 M OH^- converts $Pt(OH)_4^{2-}$ to $Pt(OH)_6^{2-}$ with a pseudo-first-order rate constant of 3×10^{-5} s^{-1}.

Introduction

Although the stepwise acid hydrolysis of tetrachloroplatinate(II) in aqueous acidic solution has been well studied,[1-12] much less is known about the hydrolysis of this complex in basic solution. Previous papers[2,3] reported only the kinetics of substitution for the first chloride ion. In hydroxide concentrations up to 0.1 M,[2,3] the proposed rate-determining step is the replacement of chloride ion by water (eq 1) followed by a rapid neutralization with hydroxide ion (eq 2).

$$PtCl_4^{2-} + H_2O \rightarrow PtCl_3(H_2O)^- + Cl^- \quad (1)$$

$$PtCl_3(H_2O)^- + OH^- \rightleftharpoons PtCl_3(OH)^{2-} + H_2O \quad (2)$$

Our investigation of the base hydrolysis of $PtCl_4^{2-}$ by ^{195}Pt NMR spectroscopy shows that four sequential reactions take place (eq 3). The rate constants are all larger than predicted from the

$$PtCl_4^{2-} \xrightarrow[k_1]{OH^-} PtCl_3(OH)^{2-} \xrightarrow[k_2]{OH^-} cis\text{-}PtCl_2(OH)_2^{2-} \xrightarrow[k_3]{OH^-} PtCl(OH)_3^{2-} \xrightarrow[k_4]{OH^-} Pt(OH)_4^{2-} \quad (3)$$

acid hydrolysis values,[11] and k_1 shows a hydroxide dependence in high base concentrations (≥0.5 M). The reactions are not

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