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Reactions of the *cis*-Diamminediaquaplatinum(II) Cation with Glycinamide, *N*-Glycylglycine, and *N*-(*N*-Glycylglycyl)glycine. Crystal Structure of a Complex with Two Diammineplatinum(II) Cations Bound to Glycylglycinate[1]

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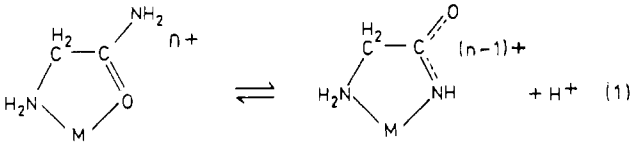
Multinuclear (^{15}N, ^{195}Pt, ^{1}H, ^{13}C) NMR spectroscopy has been used to study the reactions of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ with glycinamide (glyamH), *N*-glycylglycine ($diglyH_2$), and *N*-(*N*-glycylglycyl)glycine ($triglyH_3$). With glycinamide near pH 5 a N,O-chelate complex is formed, $Pt(NH_3)_2(glyamH\text{-}N,O)^{2+}$. Addition of alkali in an attempt to form a N,N'-chelate with deprotonated ligand caused rapid hydrolysis to $Pt(NH_3)_2(gly\text{-}N,O)^+$ and NH_3 (glyH = glycine). With glycylglycine ($diglyH_2$), the initial complex formed was *cis*-$Pt(NH_3)_2(diglyH_2\text{-}O)(H_2O)^{2+}$, in which the ligand is bound only through the carboxyl oxygen. When the solution was allowed to stand near pH 5, a new complex formed, $[\{Pt(NH_3)_2\}_2(digly)]^{2+}$, in which one platinum atom is bound to the ligand through terminal oxygen and peptide nitrogen and the second platinum atom is chelated by the peptide oxygen and terminal nitrogen. The crystal structure of the sulfate salt has been determined and confirms this stoichiometry. Crystals of $[\{Pt(NH_3)_2\}_2(digly)](SO_4)\cdot 1.35H_2O$ are triclinic, space group $P\bar{1}$, with $a = 6.157$ (2) Å, $b = 9.248$ (4) Å, $c = 14.550$ (7) Å, $\alpha = 105.78$ (2)°, $\beta = 91.79$ (2)°, $\gamma = 105.51$ (2)°, and $Z = 2$. With excess glycylglycine near pH 4, NMR peaks due to the complex in which terminal carboxylate and peptide nitrogen chelate to diammineplatinum were observed. In strongly acidic solution (pH <1), this complex converts to the other N,O-chelate complex in which terminal nitrogen and peptide oxygen chelate. The peptide bond in the latter complex slowly hydrolyzes in acid, to give $Pt(NH_3)_2(gly\text{-}N,O)^+$. With $triglyH_3$, there was formation initially of *cis*-$Pt(NH_3)_2(triglyH_3\text{-}O)(H_2O)^{2+}$ and subsequently of $[\{Pt(NH_3)_2\}_3(trigly)]^{3+}$, with three Pt atoms bound through N,O-chelate rings.

Introduction

In our continuing study of the reactions of the diamminediaquaplatinum(II) cation, *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (**1**), with amino acids and their derivatives, we recently described the reaction of **1** with *N*-acetylglycine ($acglyH_2$).[2] This system was of interest to us because the ligand might provide a model for the O-terminal end of a peptide or protein. Our results are summarized in Scheme I. The complexes **3** and **4** were the first complexes reported in which *N*-acetylglycine acts as a N,O-chelating ligand.

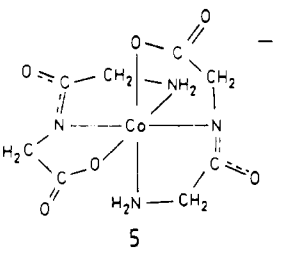
We have now extended this study to include the reactions of **1** with glycinamide, $NH_2CH_2C(O)NH_2$ (glyamH), which might provide a model for the N-terminal end of a peptide or protein, and the simple oligoglycyl peptides *N*-glycylglycine, or diglycine, $^+NH_3CH_2C(O)NHCH_2CO_2^-$ ($diglyH_2$), and *N*-(*N*-glycylglycyl)glycine, or triglycine, $^+NH_3CH_2C(O)NHCH_2C(O)NHCHCO_2^-$ ($triglyH_3$). Atom numbering for all of these ligands was as shown in Figure 1.

The potential donor atoms for glycinamide are the amine nitrogen ($N_{(1)}$), amide oxygen, and amide nitrogen ($N_{(2)}$). With labile metal ions (Ni^{2+}, Cu^{2+}), the equilibrium shown in eq 1 exists.[3] The equilibrium between $N_{(1)},N_{(2)}$- and $N_{(1)},O$-chelate complexes of Ru(III) is catalyzed by Ru(II).[4]



For *N*-glycylglycine, the potential donor atoms are carboxyl oxygen ($O_{(2)}$), peptide nitrogen ($N_{(2)}$) (especially if deprotonated), peptide oxygen ($O_{(1)}$), and terminal amine ($N_{(1)}$). In most of its complexes, the ligand has been able to bind to three meridional coordination sites on a metal ion. It then most characteristically coordinates as a planar tridentate ligand, for example, in the cobalt(III) complex **5**.[5,6] If the ammine groups of **1** remain bound to the metal, such a coordination mode is not possible in our system.

cis-Tetraammineruthenium(III) complexes have been characterized in which glycylglycine is bound through the terminal amine group and either peptide nitrogen or peptide oxygen, with the interconversion between $N_{(1)},N_{(2)}$- and $N_{(1)},O_{(1)}$-chelate complexes catalyzed by ruthenium(II).[4]



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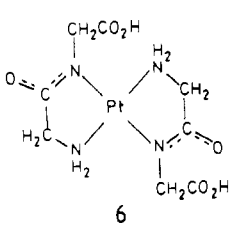
Very few platinum(II) complexes with glycylglycine have been reported. Volshtein and Motyagina[7] have reported the preparation of *trans*-$PtCl_2(diglyH_2\text{-}N_{(1)})_2$. Mogilevkina et al.[8] reported that reaction of this compound with alkali gave $Pt(diglyH)_2$. On the basis of IR spectroscopy, the structure **6** was assigned. Nance and Frye[9] obtained dinuclear complexes **7** from reaction of Zeise's anion, $PtCl_3(C_2H_4)^-$, with dipeptides. This structure was assigned on the basis of IR spectroscopy. It was claimed that the structure was confirmed by an X-ray crystal structure determination on



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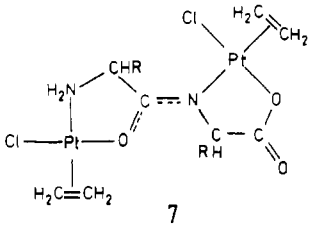

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[‡] The University of Sydney.

(1) Presented in part by: Appleton, T. G.; Hall, J. R.; Prenzler, P. D. 27th International Conference on Coordination Chemistry, Broadbeach, Australia, July 2-7, 1989; Abstract T5.
(2) Appleton, T. G.; Hall, J. R.; Prenzler, P. D. *Inorg. Chem.* **1989**, *28*, 815.
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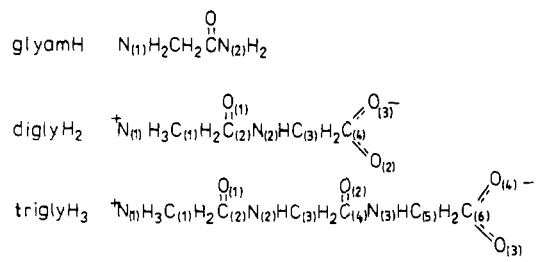
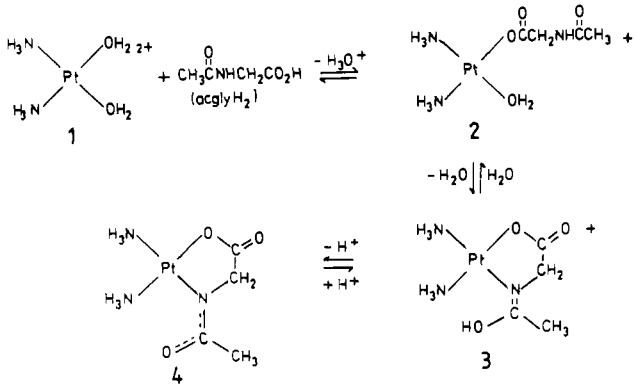


Figure 1. Labeling of atoms in ligands.

Scheme I



one of the compounds, but details of the structure have not, to our knowledge, been published.

Margerum et al.[10] have shown that $PtCl_4^{2-}$ reacts with small oligoglycyl peptides to give complexes in which the deprotonated peptide acts as a planar tri- or tetradentate ligand. Very recently,[11] some of these complexes have been characterized by ^{195}Pt NMR spectroscopy, with the use of ^{15}N-labeled ligands. They also reported briefly that reaction of *cis*-$Pt(NH_3)_2Cl_2$ with glycylglycine at pH 11 gave $Pt(NH_3)_2$(diglyH-$N_{(1)}$)(OH), $Pt(NH_3)_2$(diglyH-$N_{(1)}$)$_2$, and a chelate complex $Pt(NH_3)_2$(digly). These studies complement ours, in that different starting complexes and reaction conditions (strongly alkaline) were used.

Experimental Section

Starting Materials. $(^{15}NH_4)_2SO_4$ and (^{15}N)glycine (99% ^{15}N, Cambridge Isotopes) were supplied by Novachem (Melbourne, Australia). *N*-Glycylglycine labeled at the terminal amine group (50% ^{15}N) was prepared from (^{15}N)glycine by the Protein and Nucleic Acid Synthesis Unit at this University. *N*-Glycylglycine (Fluka) and *N*-(*N*-glycylglycyl)glycine (Sigma) were used without further purification. Glycinamide hydrochloride (Calbiochem) was converted to the nitrate salt by reaction with the stoichiometric quantity of $AgNO_3$ in aqueous solution, followed by filtration to remove AgCl, and evaporation of the filtrate on a steam bath. *cis*-$Pt(NH_3)_2(ONO_2)_2$ (with either ^{14}N- or ^{15}N-containing ammine), $Pt(^{14}ND_3)_2(ONO_2)_2$, and solutions of *cis*-$[Pt(NH_3)_2(H_2O)_2](SO_4)$ were prepared as previously described.[2,12-14] Microanalyses were carried out by the microanalytical service in this Department.

Spectra. Instrumentation and general techniques for obtaining NMR and IR spectra were as previously described.[2,12,13] NMR spectra of all nuclei other than ^1H were ^1H-decoupled. Chemical shifts are positive to lower shielding. ^1H shifts (100 and 400 MHz) are relative to the methyl resonance of sodium 3-(trimethylsilyl)propanesulfonate (TSS). ^{13}C shifts (±0.01 ppm) (25.05 and 100.5 MHz) are relative to internal dioxane taken as 67.73 ppm. ^{15}N shifts (±0.1 ppm) (10.1 MHz) are relative to $^{15}NH_4^+$ from 5 M $^{15}NH_4{}^{15}NO_3$ in 2 M HNO_3 in a coaxial capillary. ^{195}Pt–^{15}N coupling constants (±1 Hz) were measured from ^{15}N rather than ^{195}Pt spectra because of narrower line widths. ^{195}Pt shifts (±5 ppm) were measured relative to a separate sample of Na_2PtCl_6 (0.5 g in 2 mL of H_2O). Because of the negative nuclear Overhauser effect in ^1H-decoupled ^{15}N spectra, all NMR peaks were actually emissions, but for convenience, instrument phase was adjusted to present them in conventional absorption mode.

IR spectra were run on Nujol mulls.

NMR Samples. To prepare a solution for the purpose of following a reaction of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**) with one of the ligands by ^{15}N or ^{195}Pt NMR spectroscopy, approximately 0.15 g of *cis*-$Pt(^{15}NH_3)_2(ONO_2)_2$ was dissolved in 3 mL of water by gently warming the stirred suspension. The solution was filtered into an NMR tube (10-mm diameter), and the ^{15}N NMR spectrum was run, to check that it showed only the expected singlet with satellites from *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**)[12,14] (Table III) (apart from very weak peaks from *cis*-$Pt(^{15}NH_3)_2(ONO_2)(H_2O)^+$[12]). The ligand was then added as a solid, usually an amount slightly less than equimolar with **1**. A 1 M HNO_3 or NaOH solution was added if required to adjust the pH to a desired value (measured with narrow-range indicator strips (Merck or Riedel-de-Haen)). Spectrum accumulation commenced within 5 min of mixing.

For ^{13}C spectra, a similar procedure was used, except that D_2O was the solvent and *cis*-$Pt(^{14}NH_3)_2(ONO_2)_2$ the starting complex. For ^1H spectra, solutions of *cis*-$Pt(^{14}ND_3)_2(ONO_2)_2$ in D_2O were prepared on approximately one-third of the above scale, and spectra were run in 5-mm-diameter tubes.

Preparation of Salts of $[\{Pt(NH_3)_2\}_2$(digly)$]^{2+}$ (11). To prepare the nitrate salt, *cis*-$Pt(NH_3)_2(ONO_2)_2$ (0.2675 g, 0.758 mmol) was dissolved (with warming and stirring) in 2 mL of water. To the filtered solution, solid *N*-glycylglycine (0.499 g, 0.378 mmol) was added slowly, with stirring to dissolve it. The pH of the solution was then 3.5. The solution was allowed to stand for 4 h, by which time the pH had decreased to 1.0. The pH was increased to 5.5 by addition of 2 M NaOH solution. The solution was allowed to stand overnight, after which some solid had appeared and the supernatant solution had again become strongly acidic (pH approximately 0.5). The pH was again increased to 6.0 by addition of 2 M NaOH solution. After a further 4 h, the white solid was filtered off, washed with a small volume of cold water, and air-dried. The yield of crude solid was 0.17 g. This solid was dissolved in the minimum volume of water (8 mL), and the solution was filtered and then concentrated to small volume (0.5 mL) in a vacuum desiccator over *silica gel*. The solid was filtered off and dried as before. The yield of recrystallized product was 0.15 g (56%).

The IR spectrum showed two broad peaks corresponding to ν(N–H) at 3080 and 3160 cm^{-1}, two ν(C=O) bands at 1625 and 1595 cm^{-1}, and a band due to nitrate at 1315 cm^{-1}. There were no peaks that could be assigned to water molecules.

The sulfate salt was obtained by addition of 0.088 g of glycylglycine to a solution of $[Pt(NH_3)_2(H_2O)_2]SO_4$ prepared from 0.25 g of *cis*-$Pt(NH_3)_2Cl_2$ and 0.25 g of Ag_2SO_4 in 10 mL of H_2O. The pH was maintained at 4 by small additions of 1 M NaOH solution. Some solid precipitated within 1 h. The supernatant liquid was decanted off and allowed to stand and slowly evaporate. Further crops of crystals were harvested at 3- and 6-day intervals. One crystal from the third batch was used for the crystal structure determination of $[\{Pt(NH_3)_2\}_2$(digly)$](SO_4)\cdot 1.35H_2O$.

Preparation of Salts of $[\{Pt(NH_3)_2\}_3$(trigly)$]^{3+}$ (22). To prepare the nitrate salt, 0.244 g of *cis*-$Pt(NH_3)_2(ONO_2)_2$ (0.690 mmol) was dissolved with warming in 2 mL of H_2O. TriglyH$_3$ (0.0435 g, 0.230 mmol) in 0.5 mL of H_2O was added. The pH was maintained at 4–5 by small additions of 1 M NaOH solution for 3 days. The white solid that crystallized was filtered off, washed with cold water and then acetone, and air-dried. The yield of $[\{Pt(NH_3)_2\}_3$(trigly)$](NO_3)_3\cdot H_2O$ was 0.031 g. Concentration of the filtrate gave a further 0.0513 g of solid. The total yield was 33%.

The sulfate salt, $[\{Pt(NH_3)_2\}_3$(trigly)$]_2(SO_4)_3\cdot 5H_2O$, was prepared in a similar way from a solution of $[Pt(NH_3)_2(H_2O)_2]SO_4$.

Crystallography. Cell constants were determined by a least-squares fit to the θ values of 25 independent reflections, measured and refined

Table I. Crystallographic Data for $[\{Pt(NH_3)_2\}_2$(digly)$](SO_4)\cdot 1.35H_2O$

emp formula: $C_4H_{20.7}N_6O_{8.35}Pt_2S$	fw 708.77
a = 6.157 (2) Å	space group $P\bar{1}$
b = 9.248 (4) Å	T = 21 °C
c = 14.550 (7) Å	λ = 0.71069 Å
α = 105.78 (2)°	ρ_{calcd} = 3.083 g cm^{-3}
β = 91.79 (2)°	μ = 186.4 cm^{-1}
γ = 105.51 (2)°	trans coeffs = 0.033–0.239
V = 763.4 Å^3	$R(F_o)$ = 0.038
Z = 2	$R_w(F_o)$ = 0.043

(10) Kirvan, G. E.; Margerum, D. W. *Inorg. Chem.* **1985**, *24*, 3017.
(11) Schwederski, B. E.; Lee, H. D.; Margerum, D. W. Presented at the 27th International Conference on Coordination Chemistry, Broadbeach, Australia, July 2–7, 1989; Abstract T4.
(12) Appleton, T. G.; Berry, R. D.; Davis, C. A.; Hall, J. R.; Kimlin, H. A. *Inorg. Chem.* **1984**, *23*, 3514.
(13) Appleton, T. G.; Connor, J. W.; Hall, J. R. *Inorg. Chem.* **1988**, *27*, 130.
(14) Boreham, C. J.; Broomhead, J. A.; Fairlie, D. P. *Aust. J. Chem.* **1981**, *34*, 659.

Table II. Positional Parameters ($\times 10^4$) for $[\{Pt(NH_3)_2\}_2(digly)](SO_4)\cdot 1.35H_2O$

	x	y	z	occ
Pt(1)	−4799 (1)	5655 (1)	8721 (1)	
Pt(2)	12301 (1)	6491 (1)	6786 (1)	
N(1)	−5691 (10)	3438 (7)	7815 (5)	
C(1)	−4303 (12)	3375 (10)	7013 (6)	
C(2)	−2117 (13)	4727 (8)	7259 (6)	
O(1)	−2028 (9)	5856 (7)	8030 (4)	
N(2)	−523 (10)	4734 (7)	6737 (5)	
C(3)	−706 (13)	3378 (8)	5925 (5)	
C(4)	1379 (15)	3562 (10)	5371 (7)	
O(2)	2809 (11)	4915 (8)	5632 (5)	
O(3)	1574 (11)	2447 (8)	4736 (6)	
N(3)	−3544 (11)	7910 (7)	9582 (5)	
N(4)	−7613 (11)	5332 (8)	9404 (6)	
N(5)	1904 (12)	8150 (8)	7957 (6)	
N(6)	5125 (12)	8127 (9)	6631 (6)	
S(1)	−1907 (3)	11369 (2)	8684 (1)	
O(4)	−1610 (12)	9809 (8)	8277 (5)	
O(5)	−1003 (12)	11965 (8)	9712 (5)	
O(6)	−4350 (9)	11248 (7)	8613 (5)	
O(7)	−736 (11)	12402 (9)	8161 (6)	
O(8)	1352 (27)	337 (19)	6538 (12)	0.66 (2)
O(8′)	2298 (35)	114 (26)	5916 (16)	0.34 (2)
O(9)	4526 (4)	591 (64)	4922 (43)	0.35 (2)

on an Enraf-Nonius CAD4-F diffractometer with a graphite monochromator. The crystallographic data are summarized in Table I. Data were reduced and Lorentz, polarization, decomposition, and absorption corrections were applied by using the Enraf-Nonius Structure Determination Package.[15] The structure was solved by Patterson methods and was refined by full-matrix least-squares methods with SHELX-76.[16] All non-hydrogen atoms with the exception of the partially occupied O(water) atoms were refined anisotropically. Hydrogen atoms were included at calculated sites (C–H, N–H = 0.97 Å) with group isotropic thermal parameters. Scattering factors and anomalous dispersion corrections used for Pt were taken from ref 17, and all others were those supplied in SHELX-76.[16] Non-hydrogen atom coordinates are listed in Table II. Listings of H atom coordinates, anisotropic thermal parameters, close intermolecular contacts, torsion angles, details of least-squares planes calculations, and observed and calculated structure factor amplitudes have been deposited as supplementary material. Figure 3 was drawn by using the program ORTEP.[18]

Results and Discussion

Satisfactory analytical results were obtained for the solid compounds isolated. ^{15}N and ^{195}Pt NMR data are given in Table III, ^{13}C data in Table IV, and ^{1}H data in Table V.

The following general principles were used in making structural assignments from NMR spectra:

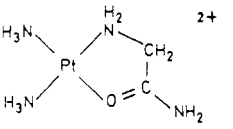
(i) ^{195}Pt chemical shifts depend primarily on the donor atom set. PtN_2O_2 complexes resonate near −1580 ppm, and PtN_3O, near −2100 ppm.[12,14,19,20]

(ii) The ^{195}Pt NMR signal is broadened if one or more ^{14}N atoms binds to Pt, because ^{195}Pt–^{14}N coupling is partially collapsed by rapid quadrupole-induced relaxation of the ^{14}N nucleus.[20,21]

(iii) In ^{15}N NMR spectra with ^{15}N-enriched ammine ligands, δ_N and J(Pt–N) depend primarily on the ligand trans to ammine: δ_N is the range −63 to −66 ppm and J(Pt–N) = 265–310 Hz for an ammine trans to a N-donor ligand; δ_N is in the range −78 to −88.5 ppm and J(Pt–N) = 320–400 Hz for an ammine trans to an O-donor ligand.[12,14,19,20]

(iv) When coordinated carboxylate is part of a five-membered chelate ring, the carbon atom resonates in the vicinity of 190 ppm, very much to lower shielding compared to that of coordinated carboxylate in a nonchelate complex or a six-membered chelate ring.[2]

Reaction of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) with Glycinamide. Significant reaction of **1** with $[NH_3CH_2C(O)NH_2](NO_3)$ ($(glyamH_2)(NO_3)$) did not occur at pH 0.5, but at pH 5, ^{15}N, ^{195}Pt, ^{13}C, and ^{1}H NMR spectra all showed as the only peaks with significant intensity (apart from those due to free ligand) those assigned to $Pt(NH_3)_2(glyamH\text{-}N_{(1)},O)^{2+}$ (**8**) (Tables III–V). The



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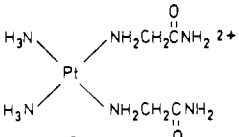
complex was formulated as containing chelated glycinamide rather than as *cis*-$Pt(NH_3)_2(glyamH\text{-}N_{(1)})(H_2O)^{2+}$ because a Pt–N coupling constant of 354 Hz is much lower than would be expected for ammine trans to H_2O (376 Hz in $Pt(^{15}NH_3)_3(H_2O)^{2+}$[19]). Furthermore, such a coordinated water molecule would be expected to have a pK_a value in the range 6–7 (pK_a for $Pt(NH_3)_3(H_2O)^{2+}$ = 6.37[22]). If a coordinated water molecule were deprotonated to give the corresponding hydroxo complex, the NMR parameters for an ammine ligand trans would be affected.[19,22] When the pH of the solution was increased to 10, the ^{15}N NMR spectrum still showed the same peaks, without change in chemical shift or Pt–N coupling constant (although additional peaks were also present—see below). We therefore concluded that amide oxygen rather than H_2O was coordinated. Kerrison and Sadler[23] showed by ^{15}N and ^{195}Pt NMR spectroscopy that acetamide reacts with **1** to give a complex in which amide oxygen is bound.

The overall similarity of the ^{1}H and ^{13}C NMR parameters for **8** compared with those for the glycinate complex, **10**, is also as expected if both complexes contain five-membered N,O-chelate rings. If the shift of an amide carbon atom is affected by incorporation in a five-membered ring in a way similar to that for the shift of a carboxyl carbon (see principle iv above), we would expect it to be very much to low shielding in **8**, as observed (191.34 ppm). ^{13}C data for $(glyamH_2)Cl$[24] are given in Table IV for comparison. The ^{13}C NMR spectrum was run at 100.5 MHz. Since platinum nuclei in planar complexes undergo rapid chemical shift anisotropy-induced relaxation at high fields,[25] we did not expect to observe satellites from coupling to ^{195}Pt in this spectrum.

Reaction of **1** with excess $(glyamH_2)(NO_3)$ at pH 4–5 did not produce any additional compounds, but at pH 7, an additional singlet with satellites was observed in the ^{15}N spectrum, which was assigned to *cis*-$Pt(^{15}NH_3)_2(glyamH\text{-}N_{(1)})_2^{2+}$ (**9**) (Table III—cf., ^{15}N NMR parameters for *cis*-$Pt(^{15}NH_3)_2(gly\text{-}N)_2$[20])



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When a solution of **8** was allowed to stand at pH 2–5, peaks due to the glycinate chelate complex $Pt(^{15}NH_3)_2(gly\text{-}N,O)^{+}$ (**10**) grew slowly, so that, after several days, this complex, formed by hydrolysis of the C–N amide bond, predominated in solution. There was no evidence from any of our spectra for the formation of a $N_{(1)},N_{(2)}$-chelate complex. It was thought that this isomer might be favored at higher pH, where the amide group would be

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Table III. ^{15}N and ^{195}Pt NMR Data

compd[a]	struct no.	δ_{Pt}[b]	δ_N	J(Pt–N), Hz	ligand trans to NH_3
$Pt(NH_3)_2(H_2O)_2^{2+}$[c]	**1**	−1580 (t)	−85.8	390	H_2O
$Pt(NH_3)_2$(gly-*N*,*O*)$^+$[d]	**10**	−2129 (br)	−64.9	301	NH_2
			−84.9	331	O_2C
$Pt(NH_3)_2$(gly-*N*)$_2$[d]		−2661 (br)	−65.2	280	NH_2
$Pt(NH_3)_2$(acglyH-*O*)$(H_2O)^+$[e]	**2**	−1583 (dd)	−85.1	353	O_2C
			−87.3	392	H_2O
$Pt(NH_3)_2$(acgly-*N*,*O*)[e]	**4**	−2022 (br)	−64.1	269	N
			−87.5	319	O_2C
$Pt(NH_3)_2$(glyamH-$N_{(1)}$,*O*)$^{2+}$	**8**	−2108 (br)	−64.8	306	$N_{(1)}H_2$
			−88.3	354	O=C
$Pt(NH_3)_2$(glyamH-$N_{(1)}$)$_2^{2+}$	**9**	*f*	−65.5	288	$N_{(1)}H_2$
$[\{Pt(NH_3)_2\}_2$(digly)$]^{2+}$[g]	**11**	−2023 (br)	−64.3	300 (A)	$N_{(1)}H_2$
			−65.3	294 (B)	$N_{(2)}$
			−84.5	328 (C)	$O_2C_{(4)}$
			−86.1	376 (D)	$OC_{(2)}$
$Pt(NH_3)_2$(diglyH$_2$-$O_{(2)}$)$(H_2O)^{2+}$	**12**	−1584 (dd)	−82.1	354	$O_2C_{(4)}$
			−87.3	392	H_2O
$Pt(NH_3)_2$(diglyH$_2$-$O_{(2)}$)$_2^{2+}$	**13**	−1576 (t)	−83.9	356	$O_2C_{(4)}$
$Pt(NH_3)_2$(diglyH-$N_{(1)}$)$_2$	**14**	*f*	−65.5	289	$N_{(1)}H_2$
$Pt(NH_3)_2$(diglyH$_2$-$O_{(2)}$(diglyH-$N_{(1)}$)	**16**	*f*	−66.0	295	$N_{(1)}H_2$
			−82.6	342	$O_2C_{(4)}$
$Pt(NH_3)_2$(diglyH-$N_{(1)}$,$O_{(1)}$)$^+$	**15**	−2100 (br)	−64.9	308	$N_{(1)}H_2$
			−88.6	360	$O{=}C_{(2)}$
$Pt(NH_3)_2$(diglyH-$N_{(2)}$,$O_{(2)}$)$^+$	**17**	−2143 (br)	−64.5	275	$N_{(2)}$
			−87.3	322	$O_2C_{(4)}$
$Pt(NH_3)_2$(triglyH$_3$-$O_{(3)}$)$(H_2O)^{2+}$	**20**	−1583 (dd)	−82.1	354	$O_2C_{(6)}$
			−87.2	393	H_2O
$Pt(NH_3)_2$(triglyH$_2$-$N_{(3)}$,$O_{(3)}$)$^+$	**21**	−2020 (br)	−64.5	273	$N_{(3)}$
			−87.0	321	$O_2C_{(6)}$
$[\{Pt(NH_3)_2\}_3$(trigly)$]^{3+}$	**22**	−2036 (br)	−64.3	*h*	N
			−64.9		N
			−65.3		N
			−84.5		O
			−84.7		O
			−86.3		O
$Pt(NH_3)_2$(tetraglyH$_4$-*O*)$(H_2O)^{2+}$			−82.1	356	O_2C
			−87.2	393	H_2O
$Pt(NH_3)_2$(tetraglyH$_4$-*O*)$_2^{2+}$			−82.8	350	O_2C

[a] All complexes cis, with ammine groups highly enriched in ^{15}N. [b] t = triplet; dd = doublet of doublets; br = broad. [c] From ref 12. [d] From ref 22. [e] From ref 2. [f] Not measured. [g] ^{15}N peaks labeled as in Figure 2. [h] Satellite peaks from Pt–N coupling too weak to allow coupling constants to be measured.

Table IV. ^{13}C NMR Data

		^{13}C shifts, ppm			
				methylene	
compd[a]	struct no.	carboxyl	amide	adjacent to carboxyl	adjacent to amine
$Pt(NH_3)_2$(gly-N,O)$^+$[b]	**10**	190.04		47.57	47.57
$Pt(NH_3)_2$(acgly-*N*,*O*)[c]	**4**	190.6	180.7	56.2	
(glyamH$_2$)Cl[d]			174.90		50.8
$Pt(NH_3)_2$(glyamH-$N_{(1)}$,*O*)$^{2+}$	**8**		191.34		49.44
diglyH$_2$ (pD 4)		174.40 ($C_{(4)}$)	168.72 ($C_{(2)}$)	42.29 ($C_{(3)}$)	41.58 ($C_{(1)}$)
$[\{Pt(NH_3)_2\}_2$(digly)$]^{2+}$	**11**	188.59[e]	187.52[e]	56.62	48.75
$Pt(NH_3)_2$(diglyH$_2$-$O_{(2)}$)$(H_2O)^{2+}$	**12**	179.14	168.55	43.30	41.58
$Pt(NH_3)_2$(diglyH$_2$-$N_{(1)}$,$O_{(1)}$)$^{2+}$	**15**	172.66	187.57	45.50	51.03
$Pt(NH_3)_2$(diglyH-$N_{(2)}$,$O_{(2)}$)$^+$	**17**	187.70	178.80	53.50	44.20

[a] All compounds cis; H = ^1H or ^2H. [b] From ref 22. [c] From ref 2. [d] From ref 25. [e] These assignments could be reversed.

deprotonated. However, when NaOH solution was added to increase the pH of a solution of **8** to 10, peaks due to **8** (with shifts and coupling constants unchanged, as noted above) rapidly decreased in intensity (they had almost disappeared after 30 min) while those due to the glycinato complex $Pt(NH_3)_2$(gly-*N*,*O*)$^+$ (**10**) grew. Peaks due to **9** were not affected during this time, and free glycinamide hydrolyzes very slowly under these conditions. The facile base-catalyzed hydrolysis of glycinamide and related ligands in Co(III) complexes is well-known.[26]

Formation of $[\{Pt(NH_3)_2\}_2$(digly)$]^{2+}$ from *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) and *N*-Glycylglycine. Reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ with glycylglycine, with periodic additions of 1 M NaOH solution to restore the pH of the solution to the range 4–6, caused slow deposition of a colorless solid, which gave analytical data corresponding to the formulation $[\{Pt(NH_3)_2\}_2$(digly)$](NO_3)_2$. Uncoordinated –COOH groups usually show an IR peak above 1700 cm^{-1}.[27] No such peak was observed. The solid redissolved sparingly in water. When the ammine ligands were highly enriched in ^{15}N, the ^{15}N NMR spectrum of the resultant solution showed four singlets of equal intensity, each with satellites (Figure 2). Two of the peaks (A and B in Figure 2) occurred to lower

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Table V. ^1H NMR Data

compd[a]	struct no.	δ_H (J(Pt-H), Hz)[b] methylene adjacent to carboxyl	methylene adjacent to amine
$Pt(NH_3)_2$(gly-N,O)$^+$ [c]	**10**	3.61 (32.0)	3.61 (32.0)
$Pt(NH_3)_2$(acgly-N,O)[d]	**4**	4.11 (24.2)	
glyamH			3.84
$Pt(NH_3)_2$(glyamH-$N_{(1)},O$)$^{2+}$	**8**		3.97 (29.4)
diglyH$_2$ (pD 5)		3.78 ($C_{(3)}H_2$)	3.83 ($C_{(1)}H_2$)
$[\{Pt(NH_3)_2\}_2$(digly)$]^{2+}$	**11**	4.03 (25.4)	3.80 (32.7)
$Pt(NH_3)_2$(diglyH$_2$-$O_{(2)}$)$(H_2O)^{2+}$ [e]	**12**	3.96	3.88
$[\{Pt(NH_3)_2\}_3$(trigly)$]^{3+}$ [e,f]	**22**	4.06	3.87

[a] All complexes cis; H = ^1H or ^2H (compounds are N- and O-deuterated). [b] Where Pt-H coupling was observed. [c] From ref 22. [d] From ref 2. [e] Spectrum was run only at 400 MHz; coupling to platinum not observed. [f] δ_H = 4.21 for methylene group between two peptide groups.

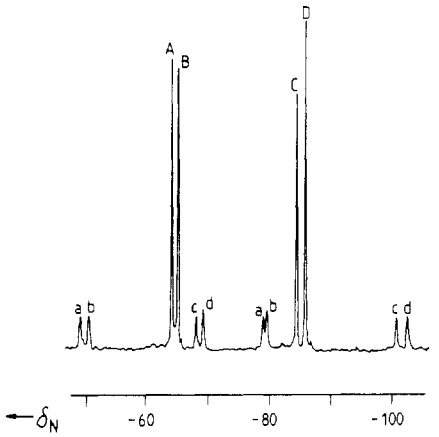


Figure 2. ^1H-decoupled 10.1-MHz ^{15}N NMR spectrum of a solution of $[\{Pt(^{15}NH_3)_2\}_2$(digly)$](NO_3)_2$ in H_2O. Peaks marked with lower case letters are "satellite" peaks of those marked with the corresponding upper case letters.

shielding and must be due to ammine trans to coordinated nitrogen, while two (C and D), to higher shielding, must be due to ammine trans to oxygen. The ^{195}Pt NMR spectrum showed a broad peak at −2023 ppm, in the region corresponding to a PtN_3O complex. The ^{15}N peaks therefore could not arise from a mixture of PtN_2O_2 and PtN_4 complexes. Since there are four nonequivalent ammine ligands, the Pt atoms to which they are bound must also be nonequivalent, but because of the peak broadness (from coordination of ^{14}N to platinum), the peaks from the different Pt atoms were not resolved. The only structure consistent with all these data is **11** (Scheme II), which is analogous to the structure **7** proposed by Nance and Frye[9] for the compounds they obtained from reaction of Zeise's salt with dipeptides.

When *cis*-$[Pt(NH_3)_2(H_2O)_2](SO_4)$ was used as the starting material, rather than the nitrate, an analogous sulfate salt crystallized, $[\{Pt(NH_3)_2\}_2$(digly)$](SO_4)\cdot 1.35H_2O$, which gave NMR spectra similar to those from the nitrate salt. The crystal structure of the sulfate has been determined by X-ray diffraction. The structure consists of a $[\{Pt(NH_3)_2\}_2$(digly)$]^{2+}$ cation, a SO_4^{2-} anion, and approximately 1.35 H_2O molecules disordered over three sites. There are hydrogen bonds involving ammine and amine groups, the carboxylate group, the SO_4^{2-} anion, and the H_2O molecules. Bond lengths and angles are listed in Tables VI and VII. The structural analysis confirms that one Pt is bound to the N(amine) and O(peptide) atoms of digly, and the other, to the N(peptide) and one of the O(carboxylate) atoms. A view of the complex cation is shown in Figure 3. Details of the structure of the cation from the crystal structure are discussed below.

Specific assignments in Table III for the ^{15}N NMR peaks were made by comparisons of the shifts and coupling constants with those of the glycinate, acetylglycinate, and glycinamide N,O-chelate complexes. The assignment of peak A to ammine trans

Table VI. Bond Lengths (Å) for $[\{Pt(NH_3)_2\}_2$(digly)$]$-$(SO_4)\cdot 1.35H_2O$

N(1)-Pt(1)	2.031 (6)	O(1)-Pt(1)	2.000 (5)
N(3)-Pt(1)	2.043 (6)	N(4)-Pt(1)	2.017 (7)
N(2)-Pt(2)	2.022 (6)	O(2)-Pt(2)	1.997 (6)
N(5)-Pt(2)	2.030 (7)	N(6)-Pt(2)	2.042 (7)
C(1)-N(1)	1.465 (10)	C(2)-C(1)	1.526 (10)
O(1)-C(2)	1.295 (9)	N(2)-C(2)	1.260 (10)
C(3)-N(2)	1.446 (9)	C(4)-C(3)	1.533 (12)
O(2)-C(4)	1.272 (10)	O(3)-C(4)	1.219 (11)

Table VII. Bond Angles (deg) for $[\{Pt(NH_3)_2\}_2$(digly)$](SO_4)\cdot$ $1.35H_2O$

O(1)-Pt(1)-N(1)	82.5 (2)	N(3)-Pt(1)-N(1)	173.5 (2)
N(3)-Pt(1)-O(1)	91.1 (2)	N(4)-Pt(1)-N(1)	94.9 (3)
N(4)-Pt(1)-O(1)	177.0 (3)	N(4)-Pt(1)-N(3)	91.5 (3)
O(2)-Pt(2)-N(2)	82.3 (3)	N(5)-Pt(2)-N(2)	99.9 (3)
N(5)-Pt(2)-O(2)	177.8 (3)	N(6)-Pt(2)-N(2)	171.9 (3)
N(6)-Pt(2)-O(2)	90.5 (3)	N(6)-Pt(2)-N(5)	87.3 (3)
C(1)-N(1)-Pt(1)	109.5 (5)	C(2)-C(1)-N(1)	112.0 (7)
O(1)-C(2)-C(1)	115.6 (6)	N(2)-C(2)-C(1)	121.5 (7)
N(2)-C(2)-O(1)	122.8 (7)	C(2)-O(1)-Pt(1)	116.3 (5)
C(2)-N(2)-Pt(2)	129.1 (6)	C(3)-N(2)-Pt(2)	111.6 (5)
C(3)-N(2)-C(2)	119.1 (6)	C(4)-C(3)-N(2)	112.7 (6)
O(2)-C(4)-C(3)	115.2 (8)	O(3)-C(4)-C(3)	119.8 (8)
O(3)-C(4)-O(2)	124.9 (9)	C(4)-O(2)-Pt(2)	117.8 (6)

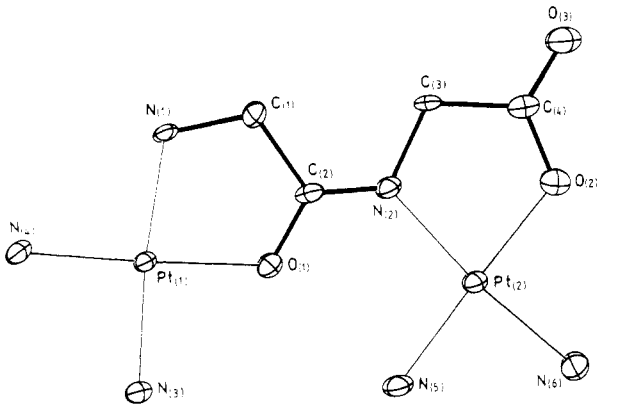


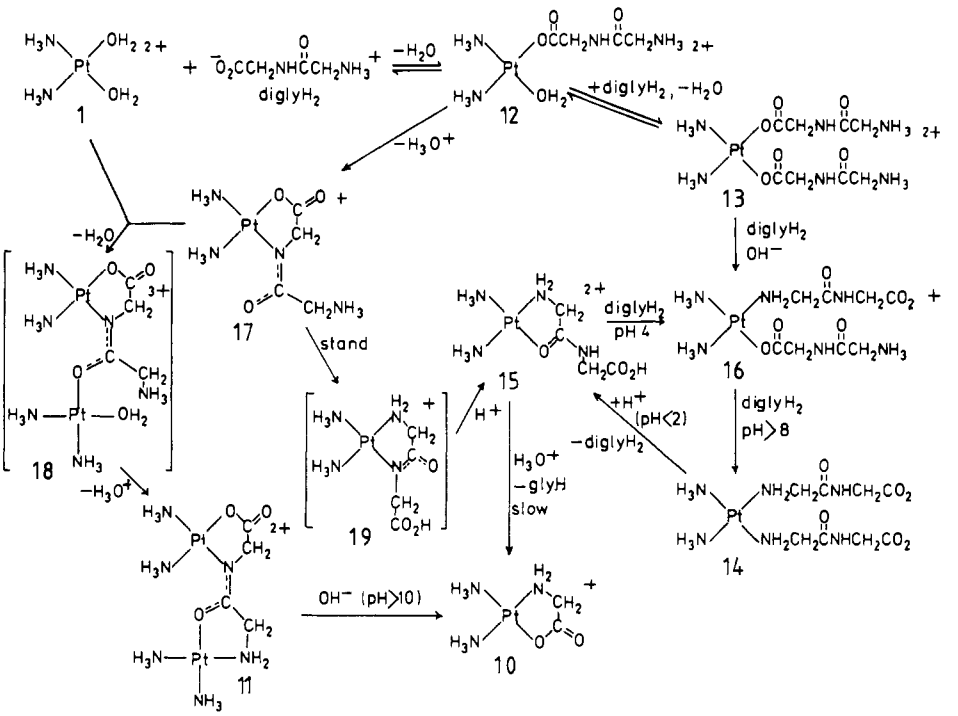
Figure 3. ORTEP plot of the complex cation in $[\{Pt(NH_3)_2\}_2$(digly)$]$-$(SO_4)\cdot 1.35H_2O$, giving the crystallographic numbering. 30% probability ellipsoids are shown.

to the amine nitrogen ($N_{(1)}$) was confirmed by an experiment using glycylglycine 50% labeled at $N_{(1)}$ with ^{15}N. The ^{15}N NMR spectrum showed peaks B–D unchanged from the spectra obtained with ^{14}N-enriched digly. Peak A (−64.3 ppm) appeared as a 1:2:1 triplet, comprising a singlet (from the isotopomer with $^{14}N_{(1)}$-enriched glycylglycine) superimposed on a doublet from ^{15}N–Pt–^{15}N coupling in the isotopomer with $^{15}N_{(1)}$-enriched glycylglycine ($J(^{15}N$–Pt–$^{15}N)$ = 3.9 Hz). Such coupling is observed only for ^{15}N nuclei that are mutually trans.[19,20,28] The ^{15}N signal from coordinated $N_{(1)}$ of the glycylglycine molecule was a doublet from coupling to the trans ammine ligand (3.9 Hz; the ammine ligands were 99% ^{15}N) at −47.5 ppm, with satellite doublets from coupling with ^{195}Pt (291 Hz). The large coordination shift to higher shielding compared with that for free glycylglycine (δ_N +6.1) is expected[29] (cf., δ_N for glycinate nitrogen in $Pt(NH_3)_2$-$(^{15}NH_2CH_2CO_2)^+$ (**10**), −54.4 ppm, J(Pt-N) = 275 Hz[20]).

The ^1H and ^{13}C spectra of a solution of $[\{Pt(NH_3)_2\}_2$(digly)$](NO_3)_2$ in D_2O each showed peaks corresponding to a single coordinated ligand molecule, as expected for structure **11**. The 100-MHz ^1H NMR spectrum showed two singlets, each with satellites from coupling to ^{195}Pt. Assignments in Table V are based on comparisons with acetylglycinate (**4**) and glycinamide (**8**) complexes. The 100.5-MHz ^{13}C spectrum of a solution of **11**

(28) Alei, M.; Vergamini, P. J.; Wageman, W. E. *J. Am. Chem. Soc.* **1979**, *101*, 5415.
(29) Mason, J. *Chem. Rev.* **1981**, *81*, 205.

Scheme II



showed four peaks (satellite peaks were not observed under these conditions). Peaks at 187.52 and 188.59 ppm corresponded to the carboxylate and amide carbon atoms, with the low shieldings compared with those of the free ligand consistent with incorporation of these carbon atoms in five-membered chelate rings. There is no obvious basis for assignment of particular peaks to $C_{(2)}$ or $C_{(4)}$. The methylene resonances were assigned by comparison with those of **4** and **8**.

Structure of the Complex Cation in $[\{Pt(NH_3)_2\}_2(digly)](SO_4)\cdot 1.35H_2O$. The complex cation is close to being planar; the largest deviations from the least-squares plane for the entire molecule are for $C_{(1)}$ and $O_{(2)}$, (+0.201 and −0.160 Å) and result from a skew puckering of the five-membered chelate ring involving $Pt_{(1)}$. The carboxylate groups ($C_{(3)}$, $C_{(4)}$, $O_{(2)}$, $O_{(3)}$) and the linking group of the peptide ($C_{(1)}$, $C_{(2)}$, $O_{(1)}$, $N_{(2)}$) are both planar to within 0.002 Å. The Pt–N(ammine) bond lengths range from 2.017 (7) to 2.043 (6) Å, and the Pt–N(amine) and Pt–N(peptide) bond lengths also fall into this range. The Pt–O(peptide) and Pt–O(carboxylate) bond lengths are indistinguishable, 2.000 (5) and 1.997 (6) Å, respectively. This is the only reported determination of a Pt–O(peptide) bond length. Similar Pt–N(amine) and Pt–O(carboxylate) bond lengths (2.037 (4) and 2.002 (4) Å, respectively) are observed in *trans*-[Pt(gly-*N*,*O*)$_2$].[30] The Pt–N(peptide) bond in the present structure (2.022 (6) Å) is longer than that in [Pt(glycyl-L-methioninate)Cl] of 1.98 Å,[31] which is the only other such bond whose length has been established crystallographically. The shorter bond in that structure may be a consequence of steric constraints resulting from tridentate coordination of the peptide.

Other Reactions of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) with *N*-Glycylglycine (Scheme II). It is obvious that there must be intermediates in the reaction between **1** and glycylglycine, which are formed before the dinuclear complex **11**. By monitoring NMR spectra, it has been possible to identify some of these intermediates, as well as other complexes formed in these reactions under different conditions.

The pH of a solution of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ was adjusted to 4.0 by addition of 1 M NaOH solution, and then solid glycylglycine was added (molar ratio approximately 1:1). The pH immediately after mixing was still close to 4.0 and was maintained at that value by occasional additions of NaOH solution. After several minutes, two new singlets with satellites appeared in the ^{15}N NMR spectrum that were assigned to $Pt(^{15}NH_3)_2(diglyH_2\text{-}O_{(2)})(H_2O)^{2+}$ (**12**), in which glycylglycine is coordinated to platinum through the carboxylate group only (Table III—note the similarity to the parameters for the acetylglycine complex **2**). The ^{195}Pt NMR spectrum of the same solution showed the expected doublet of doublets in the region corresponding to a PtN_2O_2 complex. It is not surprising to us that glycylglycine should coordinate in this way, since we have shown that numerous simple amino acids (i.e., amino acids without strongly coordinating groups in their side chains) coordinate initially to platinum through carboxylate oxygen under mildly acidic conditions.[2,20,32] Nevertheless, this is, to our knowledge, the first time such a coordination mode has been reported for glycylglycine. When a similar reaction was carried out with glycylglycine that had been labeled 50% with ^{15}N at the terminal amine group ($N_{(1)}$), the ^{15}N signals from the ammine ligands were the same as when ^{14}N-containing ligand was used (i.e., no splittings due to ^{15}N–Pt–^{15}N couplings were observed). Peaks from free and coordinated glycylglycine coincided in a singlet at +6.1 ppm. Since a significant shift to higher shielding and satellite peaks from coupling to ^{195}Pt would be expected if the amine group coordinated,[20,28] this provides additional evidence that terminal nitrogen is not coordinated in this complex.

Free glycylglycine gives two singlets in its ^1H NMR spectrum in D_2O corresponding to the two different methylene groups. Over the pD range 4–7, when the zwitterion $^+ND_3CH_2C(O)NDCH_2CO_2^-$ is present, these occur at 3.78 ($C_{(3)}H_2$, adjacent to carboxyl) and 3.83 ppm ($C_{(1)}H_2$, adjacent to the ammine group).[33] In the 400-MHz spectrum of **12** near pD 4, the corresponding peaks were at 3.96 and 3.88 ppm, respectively. Unlike the peaks due to free $diglyH_2$, these shifts were unaffected by pD over the range 0.5–5. As expected, the methylene group adjacent to coordinated carboxyl is affected more by coordination to platinum than the more remote methylene group.

The 100.5-MHz ^{13}C NMR spectrum of glycylglycine zwitterion at pD 4 showed the expected four peaks. Shifts are listed in Table

(30) Freeman, H. C.; Golomb, M. L. *Acta Crystallogr., Sect. B* **1969**, *B25*, 1203.
(31) Freeman, H. C.; Golomb, M. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1523.
(32) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Aust. J. Chem.* **1986**, *39*, 1347.
(33) Kin, M. K.; Martell, A. E. *J. Am. Chem. Soc.* **1969**, *91*, 872.

IV (these values differ slightly from those calculated from the data of Christl and Roberts,[34] who reported shifts relative to CS_2, with $N(CH_3)_4^+$ as internal reference). There were small shifts relative to the free ligand for the C atoms of **12**, especially for the carboxyl carbon ($C_{(4)}$) and adjacent methylene carbon ($C_{(3)}$) (Table II). Assignment of peaks to **12** was aided by the fact that these shifts were not affected by change in pH over the range 0.5–6, as were the shifts for the free ligand.

If a reaction between *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**) and glycylglycine was carried out under similar conditions, except that glycylglycine was in large (4-fold) excess, the ^{15}N NMR spectrum shortly after mixing showed an additional singlet with satellites, and the ^{195}Pt spectrum a triplet, assigned to *cis*-$Pt(^{15}NH_3)_2$(diglyH$_2$-$O_{(2)}$)$_2^{2+}$ (**13**) (Table III).

If NaOH solution was added to a solution containing **12**, **13**, and excess glycylglycine, to increase the pH of the solution to 8.5, the peaks due to **12** and **13** were quickly replaced by a singlet with satellites at −65.5 ppm (J(Pt–N) = 289 Hz), which was assigned to *cis*-$Pt(NH_3)_2$(diglyH-$N_{(1)}$)$_2$ (**14**) (which Margerum[11] has reported from reaction of *cis*-$Pt(NH_3)_2Cl_2$ and diglyH$^-$ at high pH). The direct reaction of *cis*-$Pt(NH_3)_2(OH)_2$ with glycylglycinate is slow, because of the inertness of the Pt–OH bond (cf., reactions of glycinate[20]).

When dilute HNO_3 was added to the solution containing **14**, to make it strongly acidic (pH <0.5), there was no immediate change in the ^{15}N spectrum, but when the solution was allowed to stand for several hours, the peaks from **14** slowly disappeared, to be replaced (in ^{15}N, ^{195}Pt, and ^{13}C spectra (Tables III and IV)) by peaks assigned to **15**, in which platinum is chelated by amine nitrogen ($N_{(1)}$) and peptide oxygen ($O_{(1)}$). The ^{15}N and ^{195}Pt NMR parameters are very similar to those for the glycinamide complex **8**. Especially notable was the presence of a ^{15}N peak to relatively high shielding (−88.6 ppm) assigned to ammine trans to peptide oxygen ($O_{(1)}$). The presence of a five-membered chelate ring was confirmed by the observation of one peak at very low shielding in the ^{13}C spectrum (187.57 ppm, assigned to the amide carbon, $C_{(2)}$). The displacement of one *N*-glycylglycine molecule from *cis*-$Pt(NH_3)_2$(diglyH$_2$-$N_{(1)}$)$_2$ by acid to form **15** contrasts with the inertness of the Pt–N bonds of *cis*-$Pt(NH_3)_2$(glyH-N)$_2$ under similar conditions.[20]

Over a period of several days, peaks due to the glycinate complex **10** slowly grew in the ^{15}N spectrum from the acidic solution of **15**. The peptide bond in **15** appears to be more easily hydrolyzed than in free glycylglycine, which was unaffected under comparable conditions. There were no peaks from the dinuclear complex **11** in the spectra under these conditions.

When alkali was added to a solution containing **15** and excess glycylglycine, to increase the pH to 4, peaks from **15** decreased in intensity in the ^{15}N NMR spectrum, to be replaced by two new singlets with satellites, which were assigned to *cis*-$Pt(NH_3)_2$(diglyH-$N_{(1)}$)(diglyH$_2$-$O_{(2)}$)$^+$ (**16**), which would be formed by attack of the carboxylate group of free glycylglycine on the Pt–$O_{(1)}$ bond in the chelate ring of **15**.

When a solution prepared from **1** and glycylglycine in mole ratios ranging from 2:1 to 1:1 was allowed to stand near pH 4 for several hours, peaks due to *cis*-$Pt(NH_3)_2$(diglyH$_2$-$O_{(2)}$)$(H_2O)^{2+}$ (**12**) initially grew in ^{15}N NMR spectra, as those due to **1** decreased. Peaks due to the dinuclear complex **11** then slowly grew, until eventually they became the dominant peaks in the spectrum, and the solid salt deposited. Only weak, transient peaks were observed in addition to these.

Even when glycylglycine was present in large excess (e.g., initial **1**:diglyH$_2$ mole ratio = 1:4), significant quantities of the dinuclear complex **11** were still formed, but additional peaks were also present due to other species. After 24 h, the ^{15}N spectrum showed two sets of peaks, in addition to those from **11**. One set, which continued to grow with time, corresponded to *cis*-$Pt(NH_3)_2$(diglyH-$N_{(1)}$)(diglyH$_2$-$O_{(2)}$)$^+$ (**16**). The other set consisted of two singlets with satellites of equal intensities, very similar to those for $Pt(^{15}NH_3)_2$(acgly-*N*,*O*) (**4**) (Table III), which were assigned to the complex **17**, in which glycylglycinate is coordinated through carboxyl $O_{(2)}$ and peptide $N_{(2)}$. The presence of one resonance at very low shielding (187.7 ppm) in the 100.5-MHz ^{13}C spectrum (Table IV) is expected if a five-membered chelate ring is present. Complex **17** would be easily formed by ring closure from **12**, with deprotonation of the peptide nitrogen, $N_{(2)}$. This deprotonation might to some extent activate the peptide oxygen, $O_{(1)}$, toward reaction with a second diaqua cation (**1**) to form an intermediate **18**, which would be expected to undergo facile ring closure to form the dinuclear complex **11** (Scheme II). In the presence of a large excess of glycylglycine, there is not sufficient free diaqua complex **1** present to react with all of the complex **17** that is formed, allowing the concentration of **17** to increase.

In an attempt to determine the conditions under which the peptide bond of **17** protonates, dilute HNO_3 was added to the solution containing **17**, but there was no significant shift in the ^{15}N peaks down to pH <0.5. Protonated **17** must therefore be a strong acid. This contrasts with the behavior of $Pt(NH_3)_2$(acgly-*N*,*O*) (**4**), whose protonation to **3** was readily observed by ^{15}N NMR spectroscopy with pK_a estimated as 2.6.[2] When the acidic solution of **17** was allowed to stand, the peaks due to **17** slowly decreased in intensity, while those due to the $N_{(1)}$,$O_{(1)}$-chelate, **15**, grew. The conversion of **17** into **15** is probably initiated by the cleavage of the platinum–carboxylate bond of **17**, followed by coordination of the amine group to give $Pt(NH_3)_2$(diglyH-$N_{(1)}$,$N_{(2)}$)$^+$ (**19**), which then isomerizes to $Pt(NH_3)_2$(diglyH$_2$-$N_{(1)}$,$O_{(1)}$) (**15**). Conversion of **17** to **15** will also occur at pH 5, but under these conditions, **15** reacts with excess diglyH$_2$ to form $Pt(NH_3)_2$(diglyH-$N_{(1)}$)(diglyH$_2$-$O_{(2)}$)$^+$ (**16**) (see above).

Direct reaction of **1** with glycylglycine in strongly acidic solution (pH <1) gave $Pt(NH_3)_2$(diglyH$_2$-$O_{(2)}$)$(H_2O)^{2+}$ (**12**) initially (more slowly than at pH 4). Peaks due to the dinuclear complex **11** slowly increased in intensity but never became dominant. Peaks from $Pt(NH_3)_2$(diglyH-$O_{(2)}$,$N_{(2)}$)$^+$ (**17**) were observed, but never became very strong, as peaks due to the other isomer Pt$(NH_3)_2$(diglyH$_2$-$N_{(1)}$,$O_{(1)}$)$^{2+}$ (**15**) grew. In a more acidic solution, the coordination of the amine group is inhibited, but there will probably also be more facile cleavage of the platinum–carboxylate bond in **17**, so that the overall conversion of **17** to **15** is faster. Slow hydrolysis occurred to produce $Pt(NH_3)_2$(gly-*N*,*O*)$^+$ (**10**).

The dinuclear complex [{$Pt(NH_3)_2$}$_2$(digly)]$^{2+}$ (**11**), once formed, is quite robust. A solution at pH 4–5 remained unchanged for weeks. Excess glycylglycine at this pH had no effect. In strongly acid solution (pH <1), there was very slow hydrolysis of the peptide bond to give $Pt(NH_3)_2$(gly-*N*,*O*)$^+$ (**10**) (incomplete after several weeks). In strongly alkaline solution (pH >10) hydrolysis to **10** and glycine occurred much more rapidly, over several hours.

Reactions of 1 with *N*-(*N*-Glycylglycyl)glycine (Scheme III). Reactions of **1** with triglyH$_3$ were not followed in as much detail as those with diglyH$_2$. We wished mainly to determine whether the tendency to form polyplatinated species extended to this oligoglycyl peptide. Reaction at pH 4 initially gave $Pt(NH_3)_2$(triglyH$_3$-$O_{(3)}$)$(H_2O)^{2+}$ (**20**), identified by its characteristic ^{15}N spectrum, very similar to that from the digly analogue, **12** (Table I). When the solution was allowed to stand for several hours, two new peaks grew, which could be assigned to $Pt(NH_3)_2$(triglyH$_2$-$N_{(3)}$,$O_{(3)}$)$^+$ (**21**) (analogous to **17**) (Table III). With further standing, a colorless solid crystallized (with nitrate or sulfate as the counterion). Microanalyses were consistent with the formulations [{$Pt(NH_3)_2$}$_3$(trigly)]$(NO_3)_3$·H_2O and [{$Pt(NH_3)_2$}$_3$(trigly)]$_2(SO_4)_3$·$5H_2O$, respectively. IR spectra showed peaks due to the respective counteranions and lattice water but none that could be assigned to uncoordinated –COOH (above 1700 cm^{-1}). It therefore appeared likely that these solids contained the cation **22**, with a triplatinated trigly^{3-} ligand, and this was confirmed by NMR spectra of the solution obtained when the sparingly soluble solids were redissolved in water. The ^{15}N spectra, which were run at 40.4 as well as 10.1 MHz, to provide additional dispersion, showed six peaks (satellite peaks were too weak to allow Pt–N coupling constants to be measured reliably), three corre-

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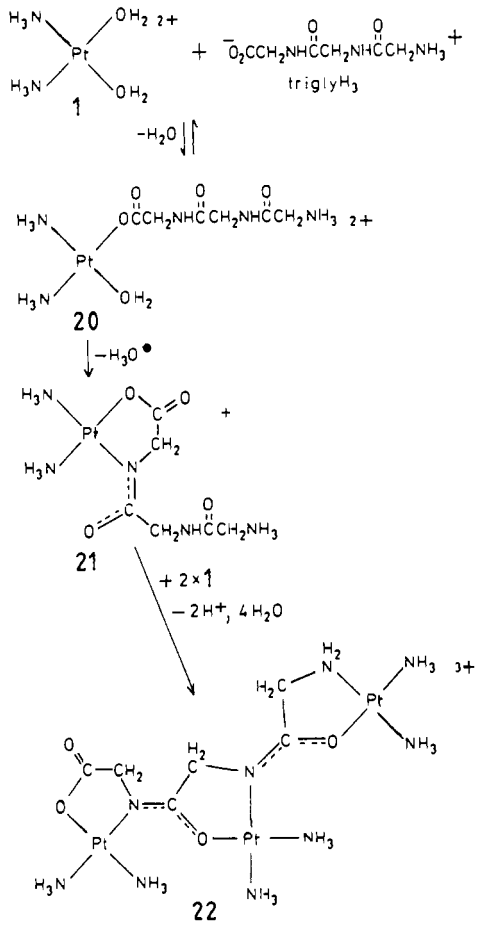
Scheme III



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.

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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.

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^{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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