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Reactions of Platinum(II) Aqua Complexes. 3. Multinuclear (^{15}N, ^{195}Pt, ^{13}C, and ^{1}H) NMR Study of Reactions of Aqua and Hydroxo Complexes with Glycine and (Methylimino)diacetic Acid[1]

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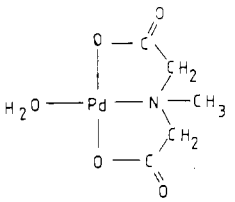
$Pt(H_2O)_4^{2+}$ with glycine (glyH) gives $Pt(H_2O)_3$(glyH-*O*)$^{2+}$ and $Pt(H_2O)_2$(glyH-*O*)$_2^{2+}$ and with (methylimino)diacetic acid (midaH_2) $Pt(H_2O)_3$(midaH_2-*O*)$^{2+}$. The mida complex, when heated, does not give *mer*-Pt(mida)(H_2O) but a complex mixture of species, probably with Pt–N–CH_2CO_2–Pt bridging. *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ with glycine gives *cis*-$Pt(NH_3)_2$(glyH-*O*)$(H_2O)^{2+}$, characterized by ^{15}N, ^{195}Pt, ^{13}C, and ^{1}H NMR, which only slowly converts to the chelate complex $Pt(NH_3)_2$(gly-*N*,*O*)$^+$. Analogous reactions occur with midaH_2. *cis*-$Pt(NH_3)_2(OH)_2$ in alkaline solution reacts slowly with glycinate to give *cis*-$Pt(NH_3)_2$(gly-*N*)$_2$ and *cis*-$Pt(NH_3)_2$(gly-*N*)(OH).

Introduction

We have recently described the complexes formed by reaction of $PtCl_4^{2-}$ with iminodiacetic acid and (methylimino)diacetic acid (midaH_2).[2] In the course of this work, we found that the complexes previously described as meridional platinum(II) compounds (e.g., K[Pt(mida)Cl]·2HCl)[3] were, in fact, platinum(IV) compounds (e.g., *fac*-K[Pt(mida)Cl_3]). While searching for possible routes to a genuine *mer*-platinum(II) complex (eventually *mer*-K[Pt(mida)Cl] was prepared with use of K_2PtCl_4[2]), we noted that *mer*-Pd(mida)(H_2O) had been reported, from reaction of Pd(NO_3)$_2$ in water (essentially $Pd(H_2O)_4^{2+}$) with midaH_2.[4] We repeated this preparation and found that all properties including NMR spectra of the product, Pd(mida)(H_2O), were consistent with its having the *mer* structure I, in agreement with conclusions



I

by other authors.[5] We therefore examined the reaction between $Pt(H_2O)_4^{2+}$ and midaH_2 but obtained no simple compound analogous to the palladium complex, I. Multinuclear NMR (including ^{195}Pt ($I = {}^1/_2$, 34% abundance) and ^{15}N ($I = {}^1/_2$)) has proved to be a very powerful tool in studying the reactions in solution of ligands with $Pt(H_2O)_4^{2+}$ [6,7] and the related aqua ion *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$.[8-11] This technique was therefore applied to the study of reactions of midaH_2 with these cations. When it became apparent that related reactions should also be observed for other amino acids, the study was extended to include reactions of glycine (glyH) with the platinum cations. Since (^{15}N)glycine was readily available, this also allowed additional spectroscopic confirmation of the reactions proposed.

δ_{Pt} in monomeric complexes is sensitive primarily to the set of bound donor atoms and only secondarily to the geometry of the complex and structure of the ligands. δ_{Pt} changes regularly from +31 for $Pt(H_2O)_4^{2+}$ to −2579 for $Pt(NH_3)_4^{2+}$ as coordinated water is replaced by ammonia, and complexes with other N or O donors may be expected to give peaks in the same regions as the corresponding amine–aqua compounds.[8,10] This is extremely useful in assigning peaks to particular complexes.

A preliminary account of some of this work has been published.[12]

Experimental Section

Preparations of starting platinum complexes and instrumental methods were as previously described.[7,11] ^{15}N-substituted glycine (99% Stohler) was supplied by Novachem (Melbourne).

All NMR chemical shifts are positive to lower shielding. ^{15}N, ^{195}Pt, and ^{13}C spectra were run in H_2O and are ^{1}H decoupled.

^{195}Pt (21.4 MHz) shifts are relative to a separate sample of Na_2PtCl_6 in H_2O (0.5 g/mL).

^{15}N (10.1 MHz) shifts are relative to the $^{15}NH_4^+$ signal in a coaxial capillary containing 5 M $^{15}NH_4{}^{15}NO_3$ in 2 M HNO_3. Quoted Pt–N coupling constants are, where possible, those measured from ^{15}N spectra, since line widths in ^{15}N spectra are much narrower than those in ^{195}Pt spectra.

^{13}C (25.05 MHz) shifts are relative to external tetramethylsilane (Me_4Si) with the shift of internal dioxane taken as 67.73 ppm.

^{1}H (100 MHz) shifts are relative to the methyl resonance of 3-(trimethylsilyl)propanesulfonate (TSS) in D_2O.

Preparation of [$Pt(NH_3)_2$(gly-*N*,*O*)]NO_3. A 0.2047-g sample of *cis*-$Pt(NH_3)_2(NO_3)_2$ (0.576 mmol) was dissolved with warming in 5 mL of water, and 0.417 g of glycine (0.556 mmol) in 2 mL of water was added. After 30 min, 1 M NaOH solution was added to increase the pH to 6, and the solution was heated at 60 °C for 15 min. The solution was allowed to cool and then concentrated in a vacuum desiccator over concentrated H_2SO_4 to 1 mL volume, to give the product as colorless crystals, which were filtered off and air-dried. The yield was 0.12 g (57%).

The IR spectrum (Nujol and HCBD mulls) showed $\nu_{C=O}$ at 1630 cm^{-1} as expected for coordinated carboxylate[13] and a broad ionic nitrate peak at 1350 cm^{-1}.

Anal. (J. Kent, this department) calcd for $C_2H_{10}N_4O_5Pt$: C, 6.6; H, 2.7; N, 15.3; Pt, 53.4. Found: C, 6.6; H, 2.8; N, 15.2; Pt, 53.2.

Results

^{195}Pt and ^{15}N NMR data are given in Table I.

$Pt(H_2O)_4^{2+}$ with midaH_2. The reaction, which we thought might give *mer*-Pt(mida)(H_2O), was monitored initially by ^{1}H NMR. A solution of $Pt(D_2O)_4^{2+}$ was prepared by dissolving freshly precipitated $Pt(OH)_2$[7] in dilute D_2SO_4/D_2O solution, and an approximately equimolar quantity of solid midaH_2 was added. The ^{1}H spectrum in the strongly acid solution (pD <1) was identical with that of the free ligand under the same conditions

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

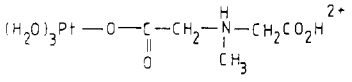
compd[a]	structure	δ_{Pt}[b]	^{15}N(ammine)[c] δ_N	J(Pt-N)	ligand trans to NH_3	^{15}N(gly)[c] δ_N	J(Pt-N)
$Pt(H_2O)_3(O_2CCH_3)^+$ [d]		−20 (s)					
$Pt(H_2O)_3(glyH\text{-}O)^{2+}$	III	−8.1 (s)				+8.95	0
$Pt(H_2O)_2(glyH\text{-}O)_2^{2+}$	IV or V	−35.5 (s)				+8.95	0
	IV or V	−42.3 (s)				+8.95	0
$Pt(H_2O)_3(midaH_2\text{-}O)^{2+}$	II	−2 (s)					
$Pt(NH_3)_2(O_2CCH_3)(H_2O)^+$ [e]		−1585.0 (dd)	−87.19	393.6	H_2O		
			−81.67	348.1	$-O_2C-$		
$Pt(NH_3)_2(glyH\text{-}O)(H_2O)^{2+}$	VIII	−1582.2 (dd)	−87.19	392.1	H_2O	+9.00	0
			−82.64	358.4	O(gly)		
$Pt(NH_3)_2(midaH_2\text{-}O)(H_2O)^{2+}$	XIII	−1579.4 (dd)	−87.28	392.5	H_2O		
			−82.78	362.3	O(mida)		
$Pt(NH_3)_2(O_2CCH_3)_2$ [e]		−1581.5 (t)	−83.12	349.6	$-O_2C-$		
$Pt(NH_3)_2(glyH\text{-}O)_2^{2+}$	IX	−1573.8 (t)	−83.85	359	O(gly)	+9.00	0
$Pt(NH_3)_2(gly\text{-}N,O)^+$	X	−2128.6 (ddd)[f]	−84.91	331.1	O(gly)	−54.43	275.0
			−64.93	301.3	N(gly)		
$Pt(NH_3)_2(midaH\text{-}N,O)^+$	XIV	−2080.4 (br t)	−76.40	355.4	O(mida)		
			−68.90	306.6	N(mida)		
$Pt(NH_3)_2(gly\text{-}N)(OH)$	XII	−2126 (dt)	[g]	287[h]	OH	−47.9	314[h]
			[g]	287[h]	N(gly)		
$Pt(NH_3)_2(gly\text{-}N)_2$	XI	−2661 (tt)	−65.2	280	N(gly)	−49.3	312

[a] All ammine complexes with ^{15}N-substituted ammine, and cis. [b] Shifts to lower shielding from $PtCl_6^{2-}$; s = singlet, d = doublet, t = triplet, br = broad. [c] Shifts to lower shielding from $^{15}NH_4^+$; coupling constants (Hz) from ^{15}N spectrum, except where otherwise noted. [d] From ref 7. [e] From ref 11. [f] For fully ^{15}N-substituted compound. [g] Overlaps with other peaks. [h] From ^{195}Pt spectrum.

(δ_{CH_2} = +4.31, δ_{CH_3} = +3.20, both singlets). NaOD/D_2O solution was added to bring the pD up to 2–3, just below the precipitation point for platinum hydroxide, and still the spectrum showed only two singlets which could be attributed to free ligand, slightly broader than before.

If the solution was heated at this stage, or allowed to stand overnight, the pD decreased, indicating that coordination had occurred. The spectrum then showed a multitude of peaks near 3.2 and near 4.5 ppm.

^{195}Pt NMR was then used to study the reaction. A solution of $Pt(H_2O)_4^{2+}$ in 1 M $HClO_4$ was prepared, as previously described,[7] and an approximately equimolar amount of solid $midaH_2$ was added. The ^{195}Pt spectrum in this strongly acid solution showed only a singlet at +31 ppm assigned to $Pt(H_2O)_4^{2+}$.[6,7] NaOH solution was added to increase the pH to 2.0. A new peak grew over 1 h at −2 ppm, assigned to a mida complex. δ_{Pt} depends primarily on the donor atoms bound to platinum,[14] and this shift corresponds to platinum bound by four O atoms, PtO_4, rather than PtO_3N, which would be expected at much higher shielding.[8] The new compound may then be most reasonably assigned as $Pt(H_2O)_3(midaH_2\text{-}O)^{2+}$ (II) (cf. $Pt(H_2O)_3(O_2CCH_3)^+$, δ_{Pt} = −20[7]).



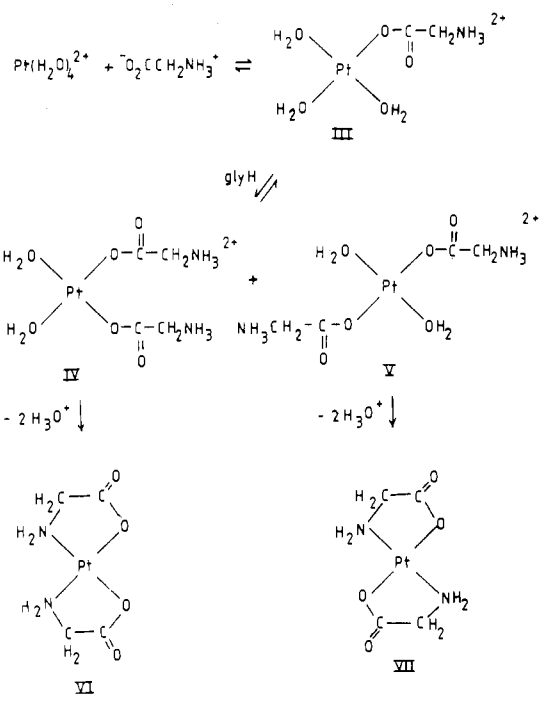
II

This complex must also be formed under similar conditions in the ^1H NMR experiment, but its peaks are coincident with those from free ligand.

When a solution containing II was heated or allowed to stand overnight, all ^{195}Pt peaks disappeared. Taken with the multitude of peaks observed in the parallel ^1H experiment, this suggests that polynuclear complexes containing Pt–N–CH_2–CO_2–Pt bridges were formed, giving a large number of different environments for both platinum and the ligand nuclei. Many platinum atoms would also be coordinated by quadrupolar ^{14}N, which would broaden the platinum signals.

$Pt(H_2O)_4^{2+}$ with glyH (Scheme I). An approximately equimolar amount of glycine (either ^{14}N or ^{15}N) was added to a solution of $Pt(H_2O)_4^{2+}$ in 1 M $HClO_4$, and NaOH solution was added to increase the pH to 3. Three new peaks grew to higher shielding from that from the starting complex, assigned to a

Scheme I. Reactions of $Pt(H_2O)_4^{2+}$ with Glycine



mono(glycine-*O*) (III) and *cis*- and *trans*-bis(glycine-*O*) (IV and V) complexes (there is no obvious basis for assigning a specific peak to each geometrical isomer). Shifts are slightly pH dependent. With standing, the pH fell to 1.5. The spectrum shown in Figure 1 and the shifts in Table I were obtained at this pH.

If (^{15}N)glycine was used, the ^1H-decoupled ^{15}N spectrum at this stage showed two singlets slightly to lower shielding from $^{15}NH_4^+$, at +7.45 ppm due to free glycine (partly protonated)[15] and at +8.95 ppm due to O-bound glycine (peaks from III, IV, and V all coincident). No Pt–N coupling was observed in ^{195}Pt or ^{15}N spectra.

A small amount of brownish precipitate also formed as the pH fell, on standing. From the IR spectrum, it appears to be a mixture of the isomers of $Pt(gly\text{-}N,O)_2$ (VI and VII) contaminated with hydrated platinum oxide, which slowly precipitates from a solution

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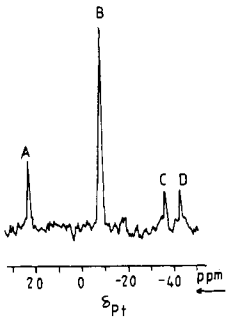
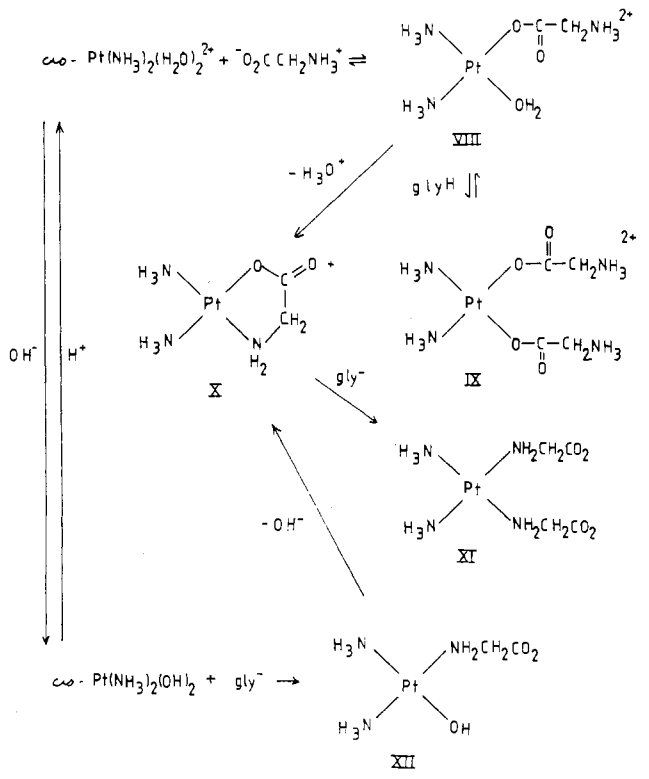


Figure 1. 21.4-MHz ^{195}Pt NMR spectrum of a solution (pH 1.5) obtained by addition of glycine to $Pt(H_2O)_4^{2+}$ in $HClO_4/H_2O$: (A) $Pt(H_2O)_4^{2+}$; (B) $Pt(H_2O)_3(glyH\text{-}O)^{2+}$ (III); (C, D) isomers of $Pt(H_2O)_2(glyH\text{-}O)_2^{2+}$ (IV, V).

Scheme II. Diammineplatinum(II) Compounds with Glycine and Glycinate



of $Pt(H_2O)_4^{2+}$ allowed to stand at pH >2.[16] The acid generated inhibits further reaction, and the solution becomes indefinitely stable. If NaOH solution was added to maintain the pH at 3–4 for several hours, much more of the insoluble precipitate formed, and platinum signals became too weak to be detected. The ^{15}N spectrum of the solution showed much weaker peaks near +8 ppm, and a very weak singlet at −52.9 ppm, probably due to a trace of chelate complex remaining in solution.

***cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ with glyH (Scheme II).** A solution of *cis*-$Pt(^{15}NH_3)_2(NO_3)_2$ in H_2O shows peaks in its ^{195}Pt and ^{15}N NMR spectra due to *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (δ_{Pt} = −1583.7, 1:2:1 triplet; δ_N = −85.83, singlet with satellites, $^1J(^{195}Pt\text{–}^{15}N)$ = 390.6 Hz),[9-11] with very much weaker peaks, ignored in future discussion here, due to *cis*-$Pt(^{15}NH_3)_2(ONO_2)(H_2O)^+$.[11] Addition of an equimolar amount of (^{14}N)glycine caused a new set of peaks to grow in NMR spectra (Table I), assigned to *cis*-$Pt(^{15}NH_3)_2(glyH\text{-}O)(H_2O)^{2+}$ (VIII), analogous to *cis*-$Pt(^{15}NH_3)_2(O_2CCH_3)(H_2O)^+$.[11] The similarity of δ_{Pt} (−1582.2) to that of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ indicates that platinum is still bound by two N atoms and two O atoms. Observation of a doublet of doublets in the ^{195}Pt spectrum and two singlets with satellites in the ^{15}N spectrum indicates that the coordinated ammine ligands are nonequivalent. The Pt–N coupling constants correspond to one ammine being trans to water, and the other trans to a ligand of slightly higher trans influence, carboxylate. The latter coupling (358.4 Hz) is a little larger than in the acetate analogue (348.1 Hz), presumably owing to the effect of the positively charged amine group.

When (^{15}N)glycine was used, an identical ^{195}Pt spectrum was obtained, and the ^{15}N spectrum showed two additional singlets at +9.53 ppm, due to free glycine (at pH 4.0), and at +9.00 ppm, due to VIII. The ^{15}N chemical shift and lack of Pt–N coupling again confirmed that glycine nitrogen was not coordinating.

In a parallel experiment using *cis*-$Pt(^{14}NH_3)_2(NO_3)_2$ and (^{14}N)glycine in D_2O, the ^1H NMR peak due to the methylene protons of VIII was identified, a singlet at 3.74 ppm, with no resolved coupling to ^{195}Pt (cf. free glycine at pD 3.5, 3.60 ppm). The methyl protons of *cis*-$Pt(NH_3)_2(O_2CCH_3)(H_2O)^+$ also showed a singlet, without detectable coupling to platinum.[11]

The methylene C atoms of VIII showed a singlet at 42.15 ppm with satellites (^3J(Pt–O–C–C) = 32 Hz) (cf. ^3J(Pt–O–C–CH_3) in the acetate analogue, 32.3 Hz[11]). The carboxyl C atom of VIII gave a singlet at 175.34 ppm, significantly more shielded than in the acetate complex (183.47 ppm), which is in the range more typical of coordinated carboxylate.[17] ^2J(Pt–O–C), 11.6 Hz, is also much less than in the acetate, 30 Hz. These differences probably arise because of the proximity of the NH_3^+ group in the glycine complex.

Even when equimolar quantities of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ and glycine were used, new NMR peaks, in addition to those from VIII and the diaqua complex, soon appeared in the spectra, which were assigned to *cis*-$Pt(NH_3)_2(glyH\text{-}O)_2^{2+}$ (IX) (^{15}N and ^{195}Pt data, Table I). These peaks became more intense if excess glycine was used (^1H and ^{13}C data: δ_H, singlet, 3.70; C(methylene) coincident with peaks from VIII, 42.15 ppm, ^3J(Pt–O–C–C) = 32 Hz; C(carboxyl) 175.57 ppm, ^2J(Pt–O–C) 12 Hz). This complex is analogous to *cis*-$Pt(NH_3)_2(O_2CCH_3)_2$.[11] When (^{15}N)glycine was used, the glycine ^{15}N peak was coincident with that from VIII, at +8.95 ppm.

There was no change in the ^{195}Pt, ^{15}N, and ^1H spectra of VIII and IX between pH 4.5 and 1.5, which is consistent with the amine group of coordinated glycine remaining protonated over this range.

Some weaker peaks were also observed in the ^{15}N spectra, probably due to dinuclear species, as observed with acetate.[11]

VIII and IX persisted in solution at 25 °C for several hours, but peaks assigned to the chelate complex $Pt(NH_3)_2(gly\text{-}N,O)^+$ (X) slowly grew, while the pH decreased from an initial value near 4.5 to 1.5. Conversion to X was almost complete after 24 h. Heating at 60 °C for 15 min, or adding NaOH solution to increase the pH to 8, caused rapid formation of X. If, on the other hand, $HClO_4$ was added immediately after addition of glycine to the diaqua complex to make the initial pH 1.5, VIII and IX formed within 1 h, but after 3 weeks there was still only a trace of X present, and several more weeks were required before the reaction neared completion.

The chloride salt $[Pt(NH_3)_2(gly\text{-}N,O)]Cl$ has been previously reported,[18] but not NMR data. $[Pt(NH_3)_2(gly\text{-}N,O)]NO_3$ was isolated from the reaction solution, and analytical results and IR spectra (see Experimental Section) are consistent with the configuration assigned on the basis of NMR.

^1H and ^{13}C NMR spectra were run with use of (^{14}N)glycinate compound. The ^1H spectrum in D_2O showed a singlet at 3.61 ppm, with satellites (^3J(Pt–N–CH_2) = 32.0 Hz). The large Pt–N–CH_2 coupling is as expected for a chelate complex.[19] The methylene protons were not exchanged with solvent deuterium even after several hours at pD 10. The ^1H-decoupled ^{13}C spectrum showed two singlets with satellites: δ_C(methylene) = 47.57, J(Pt–C) = 28.3 Hz; δ_C(carboxyl) = 190.04, J(Pt–C) = 39.0 Hz.

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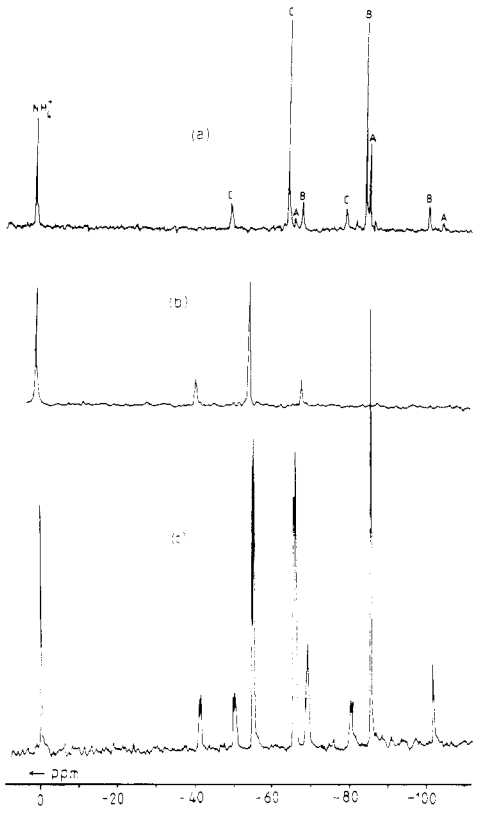


Figure 2. ^{1}H-decoupled 10.1-MHz ^{15}N NMR spectra of solutions in H_2O: (a) $Pt(^{15}NH_3)_2(gly\text{-}^{14}N,O)^+$ ((A) *cis*-$Pt(HH_3)_2(H_2O)_2^{2+}$, (B) NH_3 trans to glycinate O, (C) NH_3 trans to glycinate N); (b) $Pt(^{14}NH_3)_2(gly\text{-}^{15}N,O)^+$; (c) $Pt(^{15}NH_3)_2(gly\text{-}^{15}N,O)^+$.

^{15}N spectra were run on samples with three nitrogen isotopic substitutions, allowing unambiguous assignments of all ^{15}N peaks (Table I): $Pt(^{15}NH_3)_2(gly\text{-}^{14}N,O)^+$ (Figure 2a), $Pt(^{14}NH_3)_2(gly\text{-}^{15}N,O)^+$ (Figure 2b), and $Pt(^{15}NH_3)_2(gly\text{-}^{15}N,O)^+$ (Figure 2c). For the first two isotopomers, each distinct ^{15}N nucleus gave a singlet with satellites, but in the totally ^{15}N-substituted compound, ^{15}N–Pt–^{15}N coupling of 3.9 Hz was observed between the glycinate N atom and the trans ammine N atom (cf. 5.4 Hz in *cis*-$Pt(^{15}NH_3)_2((^{15}N_2)N$-methylimidazole)$_2^{2+}$[9]). ^{1}J(Pt–N) trans to carboxylate, 331.1 Hz, is lower than in VIII or *cis*-$Pt(^{15}NH_3)_2(O_2CCH_3)(H_2O)^+$, suggesting that the trans influence of carboxylate has increased with its incorporation into a chelate ring. The parameters in Table I for $^{15}NH_3$ trans to glycinate N may be compared with those reported for $Pt(^{15}NH_3)_4^{2+}$ (δ_N = −65.5, ^{1}J(Pt–N) = 283 Hz).[10]

Of the three isotopomers, only $Pt(^{15}NH_3)_2(gly\text{-}^{15}N,O)^+$, with no quadrupolar ^{14}N bound, gave a sharp ^{195}Pt spectrum, a doublet of doublets of doublets (Figure 3) from coupling to three nonequivalent ^{15}N nuclei, at −2128.6 ppm. This shift is in the region expected for a PtN_3O complex (cf. −2070 ppm for $Pt(^{15}NH_3)_3(H_2O)^{2+}$ [8,20]).

$Pt(NH_3)_2(gly\text{-}N,O)^+$ (X) with gly^- (Scheme II). Addition of alkali to a solution containing $Pt(^{15}NH_3)_2(gly\text{-}^{15}N,O)^+$ (X) and (^{15}N)glycine caused two new doublets with satellites to appear in the ^{15}N NMR spectrum, assigned to *cis*-$Pt(^{15}NH_3)_2(gly\text{-}^{15}N)_2$ (XI). Assignments in Table I were confirmed by varying the isotopic substitution. The trans ^{15}N(ammine)–Pt–^{15}N(gly) coupling is 3.7 Hz. The ^{195}Pt spectrum showed a triplet of triplets at −2661 ppm, in the region expected for a PtN_4 complex (cf. $Pt(^{15}NH_3)_4^{2+}$, −2579 ppm[10]).

***cis*-$Pt(NH_3)_2(OH)_2$ with gly^- (Scheme II).** If the pH of a solution of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ is increased to 6–8, the hydroxo-bridged oligomers $[Pt(NH_3)_2(\mu\text{-}OH)]_n^{n+}$ (n = 2, 3) predominate, but at higher pH, *cis*-$Pt(NH_3)_2(OH)_2$ is stable (NMR of (^{15}N)ammine complex: δ_{Pt} = −1572, triplet; δ_N = −76.9, ^{1}J(Pt–N) = 293 Hz).[10,11]

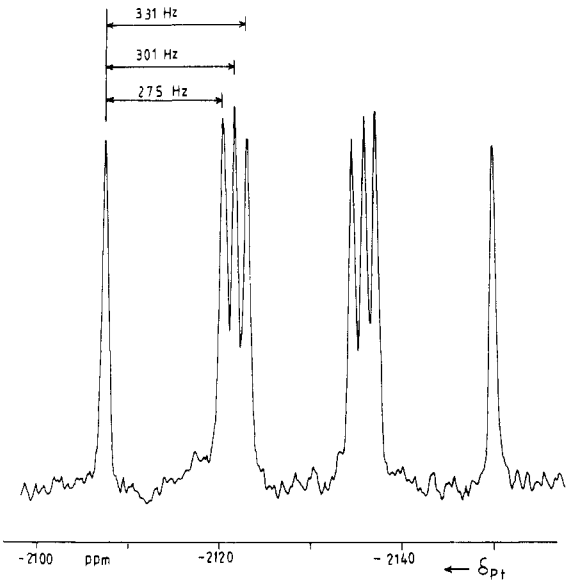


Figure 3. 21.4-MHz ^{1}H-decoupled ^{195}Pt NMR spectrum of $Pt(^{15}NH_3)_2(gly\text{-}^{15}N,O)^+$ (X) in H_2O.

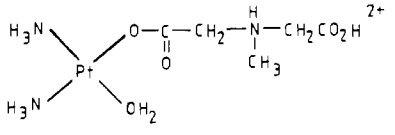
At pH 12.8, there was no detectable reaction over 2 weeks between *cis*-$Pt(NH_3)_2(OH)_2$ and glycine. Reaction was still slow over the pH range 9–11 and probably occurred only because of the presence of a small proportion of *cis*-$Pt(NH_3)_2(OH)(H_2O)^+$.

After several days at pH 9–11, a solution obtained from *cis*-$Pt(^{15}NH_3)_2(OH)_2$ and (^{15}N)glycinate showed, in addition to peaks from the starting material, ^{195}Pt peaks due to *cis*-$Pt(^{15}NH_3)_2(gly\text{-}^{15}N)_2$ (XI) at −2661 ppm and a doublet of triplets assigned to *cis*-$Pt(^{15}NH_3)_2(gly\text{-}^{15}N)(OH)$ (XII) at −2126 ppm. The doublet splitting was 314 Hz, which, by analogy with XI, could be assigned to ^{1}J(Pt–N(gly)). The triplet coupling, 287 Hz, then corresponds to ^{1}J(Pt–N(ammine)) both trans to hydroxide and trans to glycinate N. The "accidental" similarity of the last two couplings causes the ^{195}Pt pattern to be a doublet of triplets, rather than the expected doublet of doublets of doublets. All ^{15}N peaks from XII overlapped with the more intense peaks from XI and *cis*-$Pt(^{15}NH_3)_2(OH)_2$ so that ^{15}N shifts and accurate Pt–N coupling constants could not be obtained. Close examination of the spectra did reveal that δ_N(gly) for XII was −47.9 ppm.

Peaks due to the chelate complex X were also observed in some spectra. The intensity changes with time are consistent with a major reaction sequence as follows: *cis*-$Pt(NH_3)_2(OH)_2$ with gly^- gives *cis*-$Pt(NH_3)_2(gly\text{-}N)(OH)$ (XII), which very slowly closes the chelate ring to form $Pt(NH_3)_2(gly\text{-}N,O)$ (X), which is subsequently attacked by gly^- to form *cis*-$Pt(NH_3)_2(gly\text{-}N)_2$ (XI) (Scheme II), causing the concentration of X to pass through a maximum.

As these reactions proceed, OH^- is released, increasing the pH and inhibiting further reaction (it is difficult to buffer these solutions without introducing potential ligands[11]). If acid was added to reduce the pH to 6, the chelate complex X formed rapidly.

***cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ with $midaH_2$.** The ^{195}Pt and ^{15}N NMR spectra were obtained soon after solutions of *cis*-$[(Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ and $midaH_2$ were mixed and were very similar to those for *cis*-$Pt(^{15}NH_3)_2(glyH\text{-}O)(H_2O)^{2+}$ (VIII) (Table I), allowing confident assignment to *cis*-$Pt(^{15}NH_3)_2(midaH_2\text{-}O)(H_2O)^{2+}$ (XIII). The ^{1}H NMR spectrum of XIII in D_2O

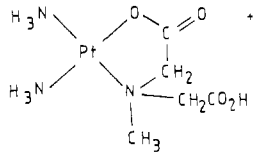


XIII

(20) Appleton, T. G.; Hall, J. R.; Ralph, S. F., to be submitted for publication.

showed three singlets, without any platinum coupling, at 3.01 (*N*-methyl), 4.03, and 4.08 (methylene) ppm (cf. the spectrum of the free ligand at pD 1.5, singlets at 3.16 and 4.04 ppm).

With standing, the solution gradually became more acidic, and a new set of NMR peaks assigned to the chelate compound Pt-($^{15}NH_3$)$_2$(midaH-*N*,*O*)$^+$ (XIV) grew. The ^{15}N spectrum was very



XIV

similar to that for Pt($^{15}NH_3$)$_2$(gly-^{14}*N*,*O*)$^+$ (X) (Table I). The ^{195}Pt spectrum showed a broad triplet (two Pt–^{15}N couplings that are not very different, with broadening from interaction with ^{14}N) at −2080.4 ppm. The ^{13}C spectrum showed carboxyl peaks at 185.63 ppm (coordinated) (J(Pt–C) = 7.8 Hz) and 171.56 ppm (uncoordinated) (J(Pt–C) = 18.5 Hz), methylene peaks at 67.22 ppm (J(Pt–C) = 23.4 Hz) and 63.71 ppm (J(Pt–C) = 12.7 Hz), and the *N*-methyl resonance at 52.06 ppm (J(Pt–C) = 11.7 Hz). Overall, the spectrum was similar to that of Pt(midaH-*N*,*O*)Cl_2^-.[2]

The ^1H NMR spectrum of XIV was dependent on pD. At pD 3.5, where the uncoordinated carboxyl group is mainly deprotonated, the *N*-methyl group showed a singlet at 2.98 ppm with satellites, ^3J(Pt–N–CH_3) = 30.8 Hz, and each methylene group gave an AB pattern. Weaker peaks from platinum coupling were not sufficiently well defined to be analyzed. At pD 13, both AB quartets disappeared as the methylene protons exchanged for solvent deuterium, but the less shielded quartet disappeared much more rapidly and may therefore be assigned as due to the chelated acetate arm. At pD 3.5, the methylene protons of the chelate ring have δ_{H_A} = 3.94, δ_{H_B} = 3.81, and $J(H_AH_B)$ = 17.2 Hz and the methylene protons of the uncoordinated arm δ_{H_A} = 3.62, δ_{H_B} = 3.49, and $J(H_AH_B)$ = 17.5 Hz. At pD 1.5, where the uncoordinated carboxyl is mainly protonated, the methylene protons of the chelate ring gave (at 100 MHz) a singlet at 3.92 ppm (i.e. their chemical shifts had become more similar) and the methylene protons of the uncoordinated arm gave δ_{H_A} = 3.89, δ_{H_B} = 3.80, and $J(H_AH_B)$ = 16.5 Hz. It is clear that the methylene protons on the uncoordinated arm have been most affected by the protonation of the carboxyl group, as would be expected. The *N*-methyl resonance at pD 1.5 occurred at 3.03 ppm with Pt–N–CH_3 unchanged at 30.7 Hz.

Discussion

Although many complexes of platinum(II) and −(IV) with amino acids are known,[21] there have been no previous reports of compounds in which an amino acid binds to platinum only through carboxylate oxygen. This coordination mode is well-known for some other metal ions (e.g., Co(III)),[22] but for Pt(II), generally accepted as "class b" or "soft",[23] bonds to nitrogen will be thermodynamically more stable in general than bonds to oxygen. The initially formed O-bound compounds VIII and XIII are converted to the thermodynamically more stable N,O-chelate compounds X and XIV only slowly under acid conditions because there is no convenient kinetic pathway while the amine group is protonated. Since acid is released in the chelation reaction, it is self-inhibiting.

Analogous compounds would not be expected to be detected when amino acids displace ligands much less labile than H_2O—for example, chloride. The energy input or time required to break Pt–Cl bonds will also suffice to convert an O-bonded ligand to a N,O- or N-bonded ligand. If, on the other hand, the metal–aqua bond is much more labile than in *cis*-Pt$(NH_3)_2(H_2O)_2^{2+}$ (e.g., in Pd(II) complexes, or trans to methyl in methyl–platinum(IV) complexes[24,25]), the Pt–carboxylate bond will also be relatively labile. The O-bound ligand is likely to exchange rapidly with solvent water, making detection of the compound difficult, and rearrangement to a chelate or N-bound compound is also likely to be faster.

When one is considering the details of interactions of platinum compounds with complex molecules with multiple potential binding sites, such as proteins or nucleic acids, or such questions as the transport of platinum complexes to various sites in an organism or a cell, it may be appropriate to consider not only Pt–N and Pt–S bonding, known to be thermodynamically very stable, but also "metastable" complexes formed with carboxylate, phosphate, and other O-donor groups.

Behavior of the type described here is not limited to amino acid complexes. Analogous reactions occur, for example, with amino phosphonate ligands, $^+NH_3(CH_2)_nPO_3H^-$.[26]

The greater kinetic inertness of Pt(II) relative to Pd(II) is probably mainly responsible for the different products obtained when $midaH_2$ reacts with $M(H_2O)_4^{2+}$ (M = Pd, Pt). The meridional compound Pd(mida)(H_2O) (I) formed in the more labile system is presumably the most stable thermodynamically, despite the expected angle strain at nitrogen,[27] as it maximizes coordination of the metal to N and carboxylate groups. The platinum analogue is probably the most stable species thermodynamically in that system also, but once there is significant Pt–NCH_2CO_2–Pt bridging, the Pt–O bonds are too inert to allow reversion to a simple monomeric compound.

The kinetic inertness of the Pt–OH bonds, which prevents any detectable reaction of *cis*-Pt$(NH_3)_2(OH)_2$ with glycinate at high pH and inhibits ring closure in *cis*-Pt$(NH_3)_2$(gly-*N*)(OH) (XII), is also quite remarkable. We have also noted that *cis*-Pt$(NH_3)_2(OH)_2$ and Pt$(NH_3)_3(OH)^+$ do not react with ammonia at high pH.[20] A similar lack of reaction of PtIV–OH groups with glycinate carboxylate groups to form N,O-chelated glycinate has been reported.[28,29]

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Registry No. II, 94570-86-2; III, 94570-87-3; IV, 94570-88-4; V, 94668-01-6; IV, 14281-82-4; VII, 15685-00-4; VIII, 87890-74-2; IX, 87890-75-3; X, 87890-78-6; XI, 94570-89-5; XII, 94570-90-8; XIII, 87890-76-4; XIV, 94570-91-9; [Pt$(NH_3)_2$(gly-*N*,*O*)]NO_3, 94570-85-1; *cis*-Pt$(NH_3)_2(NO_3)_2$, 41575-87-5; Pt$(H_2O)_4^{2+}$, 60911-98-0; *cis*-Pt$(NH_3)_2(H_2O)_2^{2+}$, 20115-64-4; *cis*-Pt$(NH_3)_2(OH)_2$, 63700-88-9.

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