Noninvasive metal NMR methods, based on the different relaxation properties of the two ion pools, have recently been proposed by us (see accompanying paper) and others[36] for the investigation of Li^+ and K^+ transport in biological systems. The alternative methods, which are based on a modified inversion recovery (MIR) pulse sequence, do not involve the use of shift reagents. However, the MIR method may not be applicable to certain biological systems and other nuclei, such as $^{23}Na^+$ transport, where a clear distinction in T_1 relaxation times for the intra- and extracellular compartments may not be present. Interestingly, the transmembrane Na^+ distribution ratio ($[Na^+]_{RBC}/[Na^+]_{plasma}$) removed by ^{23}Na NMR in the presence of 3 mM $Dy(PPP)_2^{7-}$ was different from that obtained from a NMR approach based on a difference in T_2 relaxation times for intra- and extracellular RBC Na^+ ions.[38] In those cases where no difference exists between T_1 or T_2 values for intra- and extracellular metal ion resonances, the shift reagent method may continue to be the only alternative despite its limitations.

Acknowledgment. We are grateful to Mr. Joseph Schluep for his help with the SEM pictures. Financial support from a Grant-in-Aid from the American Heart Association of Metropolitan Chicago and USPHS Grant MH45926-01 from the National Institute of Mental Health is gratefully acknowledged by D.M.d.F.

Registry No. $Dy(PPP)_2^{7-}$, 81868-53-3; $Tm(PPP)_2^{7-}$, 89031-43-6; $Dy(TTHA)^{3-}$, 91264-39-0; $Dy(PcPcP)_2^{7-}$, 129102-69-8; $Dy(DOTP)^{5-}$, 115701-67-2; Li, 7439-93-2; Na, 7440-23-5.

(36) Seo, Y.; Murakami, M.; Suzuki, E.; Watari, H. *J. Magn. Reson.* **1987**, *75*, 529.
(37) Chu, S. C.-K.; Qiu, H. Z.-H.; Springer, C. S., Jr.; Wishna, A. *J. Magn. Reson.* **1990**, *87*, 287.
(38) Okerlund, L. S.; Gillies, R. J. *Ann. N.Y. Acad. Sci.* **1987**, *508*, 437.

Contribution from the Department of Chemistry, University of Queensland, Brisbane, Australia 4072

Reactions of the *cis*-Diamminediaquaplatinum(II) Cation with 2-Aminomalonic Acid and Its Homologues, Aspartic and Glutamic Acids. Rearrangements of Metastable Complexes with Carboxylate-Bound Ligands to N,O-Chelates and Formation of Di- and Trinuclear Complexes[1]

Trevor G. Appleton,* John R. Hall, Donald W. Neale, and Craig S. M. Thompson

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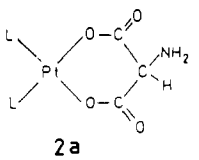
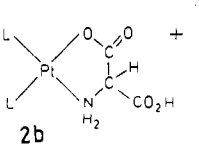
Reactions of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (**1**) with 2-aminomalonic acid ($amalH_2$), aspartic acid ($aspH_2$), and glutamic acid ($gluH_2$) have been studied by multinuclear (^1H, ^{13}C, ^{195}Pt, ^{15}N) NMR spectroscopy. With $aspH_2$ or $gluH_2$, **1** gives initially a complex in which the ligand is bound through only one carboxylate group, *cis*-$Pt(NH_3)_2(LH_2\text{-}O)(H_2O)^{2+}$. At pH <2, the α-carboxyl group is bound predominantly, but at pH 4–5, both carboxylate groups are involved to a similar extent. Over 2–3 days at pH 1.5, a complex with five-membered N,αO-chelate ring is formed, $Pt(NH_3)_2(LH\text{-}N,\alpha O)^+$. Reaction of aminomalonate with **1** gives initially a complex $Pt(NH_3)_2(amalH\text{-}O,O')^+$, with a six-membered chelate ring. Over 2–3 days at pH 1.5, this complex converts to $Pt(NH_3)_2(amalH\text{-}N,O)^+$, with a five-membered ring. In solutions sufficiently acidic to protonate the uncoordinated carboxyl group, decarboxylation then occurs over several days to give the glycinate complex $Pt(NH_3)_2(gly\text{-}N,O)^+$. The carboxylate group that is not part of the five-membered chelate ring in each of the three complexes $Pt(NH_3)_2(L\text{-}N,O)$ is able to coordinate to platinum from excess **1**. With aspartic and glutamic acids, one or two $Pt(NH_3)_2(L)$ moieties can coordinate to one diammineplatinum(II) cation, to give $[\{Pt(NH_3)_2(L)\}\{Pt(NH_3)_2(H_2O)\}]^{2+}$ or $[\{Pt(NH_3)_2(L)\}_2\{Pt(NH_3)_2\}]^{2+}$, respectively. One $Pt(NH_3)_2(amal)$ molecule can react with **1** to give $[\{Pt(NH_3)_2(amal)\}\{Pt(NH_3)_2(H_2O)\}]^{2+}$, which is in equilibrium with $[\{Pt(NH_3)_2\}_2(amal)]^{2+}$, in which the carboxylate group involved in a five-membered N,O-chelate ring with one Pt atom also bridges to the second Pt atom to complete a six-membered O,O′-chelate ring.

Introduction

Gandolfi et al.[2] recently described the preparation of a series of complexes *cis*-$PtA_2(amal)$, where A is an amine ligand and $amalH_2$ is 2-aminomalonic acid, by reaction of *cis*-$[PtA_2(H_2O)_2]SO_4$ with Ba(amal). Significant antitumor activity was claimed for some of the compounds. They considered only the O,O′-chelate structure **2a** for their complexes, with the role of



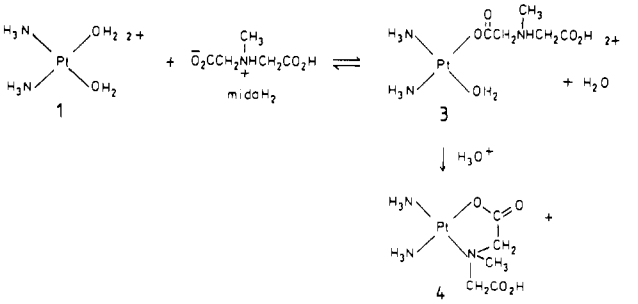
2a



2b

the amine group primarily to provide enhanced solubility for complexes of a substituted malonate ligand. However, N,O-chelation is a well-established coordination mode (e.g., in Co(III) complexes[3]) for 2-aminomalonate and derivatives. We have shown by multinuclear NMR[4] spectroscopy that (methylimino)diacetic acid ($midaH_2$) reacts with *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (**1**) to give

Scheme I



(1) Presented in part at the XXVII International Conference on Coordination Chemistry, Broadbeach, Australia, July 2–7, 1989; Abstract T5.
(2) Gandolfi, O; Apfelbaum, H. C.; Blum, J. *Inorg. Chim. Acta* **1987**, *135*, 27.
(3) Goodwin, T. J.; Mulqi, M. W.; Williams, P. A.; Vagg, R. S. *Inorg. Chim. Acta* **1985**, *98*, 141.
(4) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 673.

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initially a complex **3** in which the ligand is bound through only one oxygen atom, with subsequent chelate ring closure to the thermodynamically stable N,O-chelate complex **4** (Scheme I). Others have subsequently confirmed the presence of N,O-chelate rings in complexes *cis*-PtA_2(ida) and analogues with N-substituted iminodiacetates.[5,6] We have also shown that N,O-chelation is common for other platinum(II) complexes with iminodiacetate-type ligands[7] and with phosphonate analogues.[8] We therefore considered it possible that the 2-aminomalonate complexes described by Gandolfi et al.[2] could be N,O-chelates, with structure **2b**, rather than O,O'-chelates, **2a**. The NMR and IR data presented by these authors do not allow an unequivocal structural assignment. We therefore set out to study the reactions in solution of **1** with 2-aminomalonate, with the use of the multinuclear NMR techniques that we have successfully applied to the study of reactions of **1** with other polydentate amino acids and analogues.[4,8]

L-Aspartic acid ($aspH_2$) and L-glutamic acid ($gluH_2$) are homologues of 2-aminomalonic acid. Previous ^1H NMR studies on the complexes $Pt(asp)_2^{2-}$ and $Pt(glu)_2^{2-}$ have established that five-membered N,αO-chelate rings are present and that the methine proton readily undergoes base-catalyzed exchange with deuterium from solvent D_2O.[9,10] Reactions of these ligands with **1** were also included in this study, for comparison with the 2-aminomalonate and iminodiacetate systems.

Experimental Section

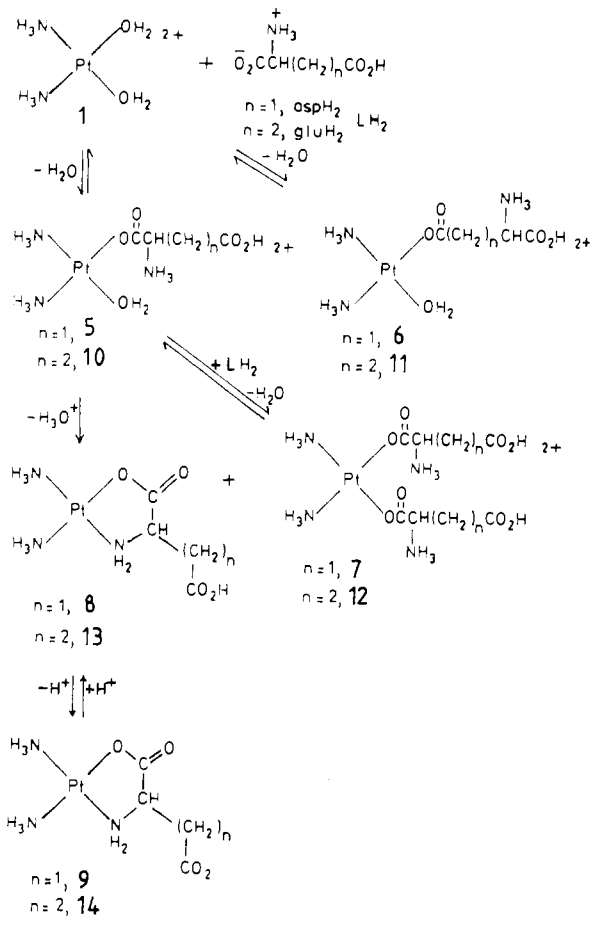
Starting Materials. $(^{15}NH_4)_2SO_4$ (>98% ^{15}N) (Cambridge Isotopes) was supplied by Novachem (Melbourne, Australia). L-Aspartic and L-glutamic acids were used as supplied by Koch-Light. *cis*-$Pt(NH_3)_2(ONO_2)_2$ (with ammine nitrogen either ^{15}N or ^{14}N) was prepared as previously described.[11,12] *cis*-$Pt(ND_3)_2(ONO_2)_2$ was prepared by evaporation of a solution of *cis*-$Pt(NH_3)_2(ONO_2)_2$ in D_2O in a vacuum desiccator over concentrated sulfuric acid.

Hydrolysis of Diethyl 2-Aminomalonate. The following adaptation of the literature procedure[13] was used. Diethyl 2-aminomalonate hydrochloride (Sigma) (5 g, 0.024 mol) was dissolved in 30 mL of water with potassium hydroxide (4.63 g, 0.0825 mol). The solution was refluxed 4 h and then allowed to cool. Concentrated hydrochloric acid was added dropwise until the pH was 4.5. The solution was then allowed to stand overnight in a refrigerator. The colorless crystals that deposited were filtered off, washed with small volumes of cold water and then ethanol, and air-dried (2.83 g). The product was the monopotassium salt of 2-aminomalonic acid, K(amalH), which gave satisfactory analytical results. The filtrate was concentrated to 10 mL and then cooled in ice to give a second crop (0.60 g). The total yield was 92%.

NMR Spectra. Spectra were run under conditions similar to those previously described.[4,7-9] Spectra of nuclei other than ^1H were ^1H-decoupled. Chemical shifts are positive to lower shielding. The following references were used: 10.1-MHz and 40.4-MHz ^{15}N NMR spectroscopy, the $^{15}NH_4^+$ signal from a coaxial capillary containing 5 M $^{15}NH_4{}^{15}NO_3$ in 2 M HNO_3; 21.4-MHz ^{195}Pt NMR spectroscopy, a separate sample containing 0.5 g of Na_2PtCl_6 in 2 mL of H_2O; 100.4-MHz and 25.05-MHz ^{13}C NMR spectroscopy, internal dioxane, taken as 67.73 ppm.

There was a small difference between ^{15}N shifts obtained at the different field strengths, which is not surprising when the reference is in a coaxial capillary, and the configuration of the sample tube with respect to the magnetic field is changed from parallel (superconducting magnet) to perpendicular (electromagnet). The shifts from the high-field measurements were corrected to correspond with those at lower field by adding 0.11 ppm to the values. Where possible, Pt–N coupling constants were measured from ^{15}N, rather than ^{195}Pt spectra, because of the narrower line widths.

Scheme II



Typical NMR Experiment. The following procedure was used to prepare a sample in a 10-mm-diameter NMR tube (^{15}N, ^{195}Pt, ^{13}C spectra). *cis*-$Pt(NH_3)_2(ONO_2)_2$ (0.15 g, 0.42 mmol) was suspended in 3 mL of H_2O. The mixture was heated briefly, with stirring, to dissolve the solid. The solution was filtered through a cotton wool plug into a 10-mm-diameter NMR tube. Solid ligand (0.34 mmol) was added, and the mixture was shaken until it dissolved. Dilute HNO_3 or NaOH solution was added until the pH (usually measured by Merck narrow-range indicator paper) was in the desired range. For ^{15}N or ^{195}Pt spectra, ^{15}N-enriched ammine complex was used. For ^{13}C spectra (unless otherwise noted), D_2O solutions were used.

Preparation of $[\{Pt(NH_3)_2\}_2(amal)](NO_3)_2\cdot H_2O$ (22). *cis*-$Pt(NH_3)_2(ONO_2)_2$ (0.180 g, 0.510 mmol) was dissolved with warming and stirring in 1 mL of water, and the solution was added to solid K(amalH) (0.080 g, 0.555 mmol), which dissolved. The pH of the solution was adjusted to 6.5–7 with 1 M NaOH solution and maintained at this level for 4 h. A solution of a further 0.180 g of *cis*-$Pt(NH_3)_2(ONO_2)_2$ dissolved in 1 mL of water was then added, and the pH of the solution was adjusted to 4.5–5. The solution volume was decreased to 1 mL under vacuum, and the solution was stored in a refrigerator for 36 h, during which time a white solid deposited. The supernatant solution was removed by decantation. The solid was washed quickly with a small volume of cold water and then dried in a vacuum desiccator over silica gel. The yield of $[\{Pt(NH_3)_2\}_2(amal)](NO_3)_2\cdot H_2O$ was 0.247 g (68%). Anal. Calcd for $C_3H_{17}N_7O_{11}Pt_2$: C, 5.0; H, 2.4; N, 13.7. Found: C, 5.0; H, 2.4; N, 13.7.

The IR spectrum of the solid showed peaks characteristic of ν(O–H) at 3520 and 3300 cm^{-1}, as well as a broad strong band centered at 3200 cm^{-1} from ν(N–H). Strong, broad bands characteristic of ν(C=O) occurred at 1575 and 1660 cm^{-1}, but not above 1700 cm^{-1}, where peaks from free –COOH would be expected.

Results

Reactions of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) with Aspartic Acid (Scheme II). Aspartic acid ($aspH_2$) (0.8 mol equiv) was added to a solution of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**), and then dilute HNO_3 was added to adjust the pH to the range 1–2. Two new singlets (with satellites from coupling to ^{195}Pt, $I = {}^1/_2$, 34% abundance)

(5) Hoeschele, J. D.; Farrell, N.; Turner, W. R.; Rithner, C. D. *Inorg. Chem.* **1988**, *27*, 4106.
(6) Khokhar, A. R.; Lumetta, G. J.; Newman, R. A.; Doran, S. L. *Inorg. Chim. Acta* **1988**, *151*, 249.
(7) Appleton, T. G.; Berry, R. D.; Hall, J. R. *Inorg. Chem.* **1985**, *24*, 666.
(8) Appleton, T. G.; Hall, J. R.; McMahon, I. J. *Inorg. Chem.* **1986**, *25*, 726.
(9) Erickson, L. E.; McDonald, J. W.; Howie, J. K.; Clow, R. P. *J. Am. Chem. Soc.* **1968**, *90*, 6371.
(10) Erickson, L. E.; Dappen, A. J.; Uhlenhopp, J. C. *J. Am. Chem. Soc.* **1969**, *91*, 2510.
(11) Boreham, C. J.; Broomhead, J. A.; Fairlie, D. P. *Aust. J. Chem.* **1981**, *34*, 659.
(12) Appleton, T. G.; Berry, R. D.; Davis, C. A.; Hall, J. R.; Kimlin, H. A. *Inorg. Chem.* **1984**, *23*, 3514.
(13) Fitzpatrick, J. H.; Hopgood, D. *Inorg. Chem.* **1974**, *13*, 568.

grew together in the ^{15}N NMR spectrum over several hours, at −82.7 ppm (J(Pt–N) = 359 Hz) and at −87.2 ppm (J(Pt–N) = 392 Hz), as the singlet with satellites from **1**[11,12] decreased in intensity. With this high shielding, these peaks must be due to ammine trans to coordinated oxygen.[4,11,12,14] A Pt–N coupling of 359 Hz is characteristic of ammine trans to carboxylate, and that of 392 Hz characteristic of ammine trans to water. The ^{195}Pt NMR spectrum of this species showed a doublet of doublets at −1577 ppm, close to the 1:2:1 triplet from **1**, clearly corresponding to a PtN_2O_2 complex.[14] These peaks may therefore be assigned to a complex *cis*-$Pt(^{15}NH_3)_2(aspH_2\text{-}O)(H_2O)^{2+}$, in which aspartic acid is coordinated to platinum through one carboxylate group and the remaining coordination site is occupied by H_2O.

There are two isomers possible for *cis*-$Pt(NH_3)_2(aspH_2\text{-}O)(H_2O)^+$: **5**, in which the α-carboxyl group (adjacent to the methine group) coordinates, and **6**, in which the β-carboxyl group (adjacent to the methylene group) coordinates. The values of pK_{a1} and pK_{a2}, corresponding to acid dissociation of the α- and β-carboxyl groups, respectively, are 1.9 and 3.7.[15] In a solution with pH 1–2, the α-carboxyl group would be more likely to be deprotonated and so would be expected to be more available for coordination. Isomer **5** would be expected to be favored under these conditions. The 100.4-MHz ^{13}C NMR spectrum at pD 1.5 in D_2O was consistent with this formulation. The peak due to the α-carboxylate group at 176.6 ppm was shifted 4.3 ppm to lower shielding relative to the free ligand. This is typical of the coordination shifts observed when a $Pt\text{–}O_2C\text{–}CH_2\text{–}N$ bond is formed.[4,16,17] None of the other carbon nuclei was shifted to lower shielding by more than 0.5 ppm.

The NMR spectra of the various nuclei run under these strongly acidic conditions also showed additional minor peaks. Some of these could be made more intense by varying the conditions, which allowed them to be assigned. For example, addition of a larger proportion of aspartic acid to the initial solution of **1**, still maintained near pH 1.5, caused peaks to grow that could be assigned to *cis*-$Pt(NH_3)_2(aspH_2\text{-}\alpha O)_2^{2+}$ (**7**). Only one enantiomer (L) of aspartic acid was used in these experiments, so that the two aspartic acid ligands, and the two ammine groups, in **7** are related by a C_2 axis. The ^{195}Pt NMR spectrum of this species showed a 1:2:1 triplet at −1573 ppm (J(Pt–N) = 363 Hz), and the ^{15}N spectrum one singlet at −83.9 ppm (with satellites two weak to be observed in our spectra).

Another set of peaks of low intensity in ^{15}N and ^{195}Pt spectra run with pH near 1.5 corresponded to the other isomer of *cis*-$Pt(^{15}NH_3)_2(aspH_2\text{-}O)(H_2O)^{2+}$ (**6**), in which the β-carboxyl group, rather than α-carboxyl, coordinates. These peaks became relatively much more intense when the spectra were run with the pH of solution adjusted to 4 immediately after aspartic acid had been added to the solution of **1**. The ^{195}Pt spectrum showed a doublet of doublets at −1582 ppm, with J(Pt–N) = 394 Hz from ammine trans to H_2O and 353 Hz from ammine trans to β-carboxylate, and the ^{15}N spectrum a signal at −87.2 ppm, from ammine trans to H_2O coincident with the corresponding peak from **5**, and at −82.1 ppm, from ammine trans to β-carboxylate. Eventually, the peaks due to **6** became more intense than those due to **5**. At this pH, both of the carboxyl groups of the free ligand will be significantly deprotonated, as opposed to the situation at pH 1.5, where only the α-carboxyl will be deprotonated. Furthermore, in this less strongly acidic solution, **5** is converted more rapidly into **8**, with a five-membered N,αO-chelate ring. No corresponding rearrangement of **6** occurs to form a six-membered ring (see below). Thus, while **5** is consumed by direct reaction to form **8**, the concentration of **6**, once it has formed, is decreased only by dissociation of the β-carboxylate group, followed by coordination of α-carboxyl (possibly from a different aspartic acid molecule) to give **5** and, eventually, **8**. No attempt was made to assign peaks due to **6** in ^{13}C or ^1H spectra.

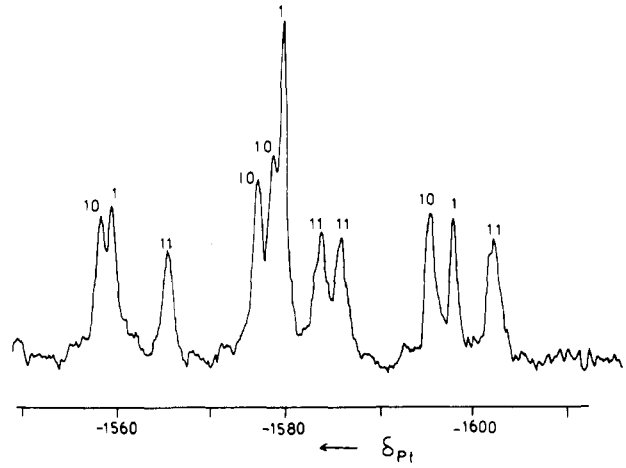


Figure 1. ^{195}Pt NMR spectrum (21.4-MHz) of a solution obtained from cis-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ and glutamic acid in H_2O at pH 4. Numerals on the peaks correspond to species as labeled in Scheme II: *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**); *cis*-$Pt(^{15}NH_3)_2(glutH_2\text{-}\alpha O)(H_2O)^{2+}$ (**10**); *cis*-$Pt(^{15}NH_3)_2(glutH_2\text{-}\gamma O)(H_2O)^{2+}$ (**11**).

A number of other weak peaks were also present in ^{15}N spectra, which were not assigned. Some of these could be due to other isomers of *cis*-$Pt(^{15}NH_3)_2(aspH_2\text{-}O)_2^{2+}$, in which one or both of the aspartic acid ligands coordinate through β-carboxylate.

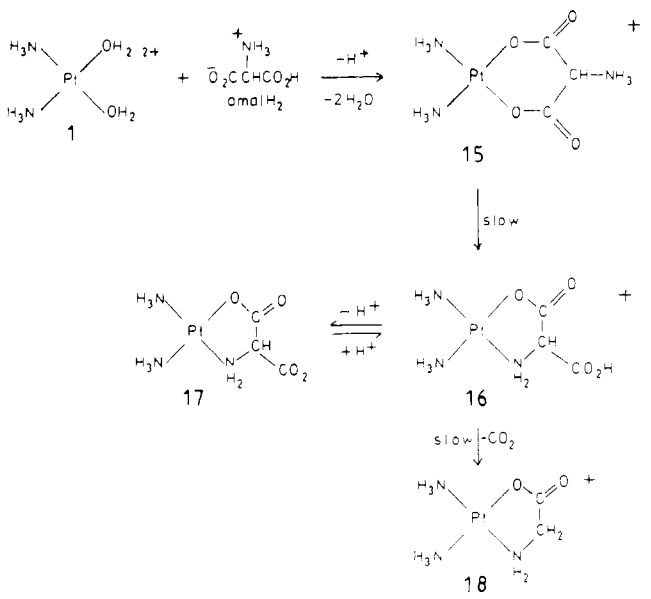
A solution of **5**, **1**, and free aspartic acid, prepared near pH 1.5 as described above, was allowed to stand for several days. Apart from peaks due to excess **1**, the ^{15}N NMR spectrum of the solution then showed two singlets with satellites. One (−64.7 ppm, J(Pt–N) = 304 Hz) clearly corresponded to ammine trans to nitrogen, and the other (−84.6 ppm, J(Pt–N) = 333 Hz) to ammine trans to carboxylate in a chelate ring.[4,16] The ^{195}Pt NMR spectrum showed a broad multiplet, as expected if ^{14}N coordinates,[4,18] at −2160 ppm, corresponding to a PtN_3O complex.[4,14] The complex may therefore be formulated as containing a N,O-chelate ring. There are two isomers possible. The chelate ring may be five-membered, with α-carboxylate coordinated, or six-membered, involving β-carboxylate. The 25.05-MHz ^{13}C spectrum allowed the structure to be assigned as **8**, with a five-membered chelate ring. In the carboxylate region, the spectrum showed a peak (flanked by satellites, J(Pt–C) = 25.4 Hz) at 188.3 ppm. Such a low shielding is characteristic of a carboxylate group that is part of a five-membered chelate ring.[4,17] A carboxylate group that is part of a six-membered chelate ring would be expected at significantly higher shielding (e.g., 181.1 ppm in the β-alaninate complex $Pt(NH_3)_2(\beta ala\text{-}N,O)^+$[16]). The spectrum also showed a second carboxyl peak, without resolved satellites, at 176.0 ppm, shifted only slightly from the β-carboxyl resonance of the free ligand. The methine carbon, 55.4 ppm, was deshielded by 4.7 ppm relative to the free ligand, and the methylene carbon, 37.9 ppm, by 2.8 ppm. It is not surprising that the platinum coupling to the methylene carbon, 40.1 Hz, is larger in magnitude than that to the methine carbon, 23.4 Hz, as contributions to the Pt–C coupling constant from two- and three-bond coupling pathways tend to cancel in a five-membered chelate ring.[19]

When the pH of a solution of **8** was increased to >5, small changes in spectra occurred corresponding to deprotonation of the uncoordinated carboxyl group of **8** to give **9**. In none of our spectra were any peaks observed of significant itensity that could be assigned to a αO,βO-chelate complex.

Reactions of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) with Glutamic Acid (Scheme II). The reactions of **1** with L-glutamic acid were analogous to those observed with L-aspartic acid and are summarized in Scheme II. In ^{195}Pt and ^{15}N NMR spectra chemical shifts and coupling constants were very similar to those from

(14) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 4685.
(15) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 1, p 487.
(16) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Aust. J. Chem.* **1986**, *39*, 1347.
(17) Appleton, T. G.; Hall, J. R.; Prenzler, P. D. *Inorg. Chem.* **1989**, *28*, 815.
(18) Ismail, I. M.; Kerrison, S. J. S.; Sadler, P. J. *Polyhedron* **1982**, *1*, 57.
(19) Sarneski, J. E.; Erickson, L. E.; Reilley, C. N. *J. Magn. Reson.* **1980**, *37*, 155.

Scheme III



aspartic acid analogues. The isomer of $Pt(NH_3)_2(gluH_2\text{-}O)(H_2O)^{2+}$ that predominated at low pH (<2) was again that with the α-carboxylate group coordinated (**10**), with the γ-carboxylate-bound isomer (**11**) formed in significant proportions at higher pH (3–5). Figure 1 shows the ^{195}Pt NMR spectrum of a solution containing both **10** and **11**, as well as **1**. All data were again consistent with the formation of a five-membered N,αO-chelate ring (**13**), with no detectable amount of the other isomer with a seven-membered ring. Each ^{13}C spectrum, compared with the spectrum of the corresponding aspartate complex, showed the expected additional resonance due to the second methylene group.

Reactions of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) with 2-Aminomalonic Acid (Scheme III). When K(amalH) was added to a solution of **1**, and the pH of the solution was adjusted to 1–2, the course of the reaction that followed was quite different from that between **1** and aspartic or glutamic acid. With ^{15}N ammine complex, the ^{15}N NMR spectrum of the solution run soon after mixing showed a strong singlet at −80.7 ppm, with satellites (J(Pt–N) = 373 Hz). These NMR parameters correspond to ammine trans to an oxygen donor, and the Pt–N coupling constant is near the upper end of the observed range for ammine trans to carboxylate.[14,16] Both ammine ligands are equivalent. The only possible complex that satisfies these requirements is $Pt(^{15}NH_3)_2(amalH\text{-}O,O')^+$ (**15**), with a six-membered chelate ring, an example of the type of structure (**2a**) proposed by Gandolfi et al.[2] for their aminomalonate complexes. There were no peaks in the spectrum that could be assigned to a complex analogous to **5**, in which the ligand is bound to the metal through just one carboxyl group. The ^{195}Pt spectrum of this solution showed a 1:2:1 triplet at −1732 ppm. This shift is in the range for a PtN_2O_2 complex but is significantly to higher shielding from that for the nonchelate complexes discussed above. Such a shift is typical for complexes containing a six-membered ring from a substituted malonate ligand (e.g., −1694 ppm, J(Pt–N) = 366 Hz, for the ethylmalonate analogue and −1723 ppm, J(Pt–N) = 360 Hz, for the cyclobutanedicarboxylate complex[20]). The ^{13}C spectrum of the solution in H_2O showed just two signals, at 58.7 and 172.4 ppm, little shifted from the shifts for corresponding carbon atoms in the free ligand, as usually observed for substituted malonate ligands.[20] As the methine proton of the aminomalonate ligand rapidly exchanged with deuterium from solvent D_2O, no ^1H NMR spectra were obtained.

This chelate complex, **15**, was more stable kinetically than complexes such as **5**, with amino acid bound through a single carboxylate, but even at pH 1.5, the peaks due to **15** in the ^{15}N spectrum decreased in intensity over several days, while peaks grew that could be assigned to the N,O-chelate complex $Pt(^{15}NH_3)_2$(amalH-N,O)$^+$ (**16**) (−65.27 ppm, J(Pt–N) = 309 Hz, for ammine trans to N and −84.77 ppm, J(Pt–N) = 337 Hz, for ammine trans to carboxylate). This conversion was much faster at pH 5, requiring only several hours. There were small changes in the ^{15}N NMR spectrum of the N,O-chelate complex as the pH was changed from 1.5 to 5, corresponding to deprotonation of the uncoordinated carboxyl group of **16**, to give **17**.

When a solution of **16** was allowed to stand in solution sufficiently acidic (pH <2) that the carboxyl group was protonated, peaks due to the glycinate complex $Pt(NH_3)_2$(gly-N,O)$^+$ (**18**) (only just resolved from those from **16**) slowly grew in the ^{15}N NMR spectrum, as decarboxylation of **16** occurred. The reaction was complete after 5 days at pH 1.5, 25 °C. This decarboxylation is not surprising, as free aminomalonic acid decarboxylates slowly in acidic solution. At pH 5 the decarboxylation reaction was very much slower and could not be detected at 25 °C at pH 6–8. A 25.05-MHz ^{13}C spectrum of **17** at pH 6 showed a methine peak (63.6 ppm) and two carboxylate peaks (at 186.2 ppm (J(Pt–C) = 26.2 Hz) for carboxyl carbon in the chelate ring and at 171.5 ppm for the other carboxyl carbon). In acidic solutions, where decarboxylation occurred, the ^{13}C spectrum showed peaks corresponding to the glycinate complex, with only one carboxyl peak (190.0 ppm, J(Pt–C) = 39.0 Hz[4]).

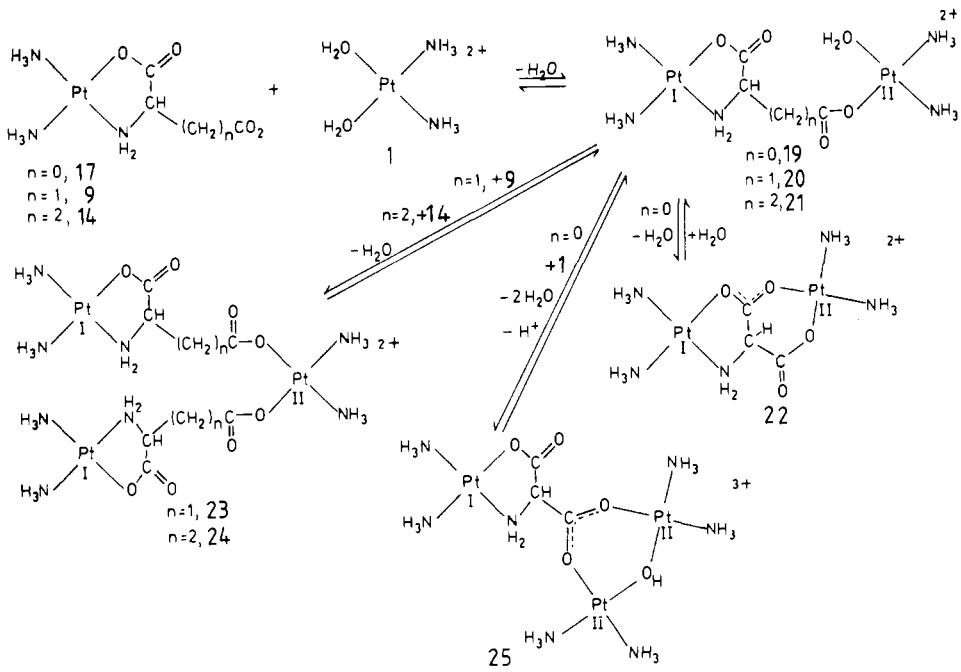
We were now in a position to determine the likely product obtained under Gandolfi's reaction conditions,[2] which involved reaction of *cis*-$[PtA_2(H_2O)_2]SO_4$ with Ba(amal) in aqueous solution overnight at room temperature, followed by filtration and concentration of the solution at reduced pressure below 45 °C. The solid was then precipitated with ethanol. We carried out this procedure with A = $^{15}NH_3$ and obtained the ^{15}N NMR spectrum of the product. As we anticipated from our results reported above, there was no O,O′-chelate complex, **15**. Our product was a mixture of $Pt(^{15}NH_3)_2$(gly-N,O)$^+$ (**18**) (approximately 75%) and $Pt(^{15}NH_3)_2$(amal-N,O) (**17**) (approximately 25%). The relative proportions of glycinate and aminomalonate-N,O complexes would depend on the precise conditions used for concentrating the solution and, possibly, on the particular amine ligand A used, but our results do indicate that this is not a very reliable method for the preparation of pure aminomalonate complexes and certainly does not give an O,O′-chelate complex.

Reactions of the N,O-Chelate Complexes with Excess *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) (Scheme IV). Each of the N,αO-complexes, **9**, **14**, and **17**, has a free carboxylate group, which can coordinate to another platinum atom if an excess of the diaqua complex is present. For example, reaction of the aspartate complex $Pt(^{15}NH_3)_2$(asp-$N,\alpha O$) (**9**) with more *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**), at pH 4–5, caused four new singlets with satellites to grow in the ^{15}N NMR spectrum. Two of these were only slightly shifted from the peaks from **9**, being barely resolved in the 10.1-MHz spectrum. They were more easily resolved in the 40.4-MHz spectrum (−64.54 and −84.51 ppm). The remaining peaks, at −82.1 ppm (J(Pt–N) = 352 Hz) and −87.0 ppm (J(Pt–N) = 393 Hz), were very similar to those observed for *cis*-$Pt(^{15}NH_3)_2(aspH_2\text{-}\beta O)(H_2O)^{2+}$ (**6**). These four peaks were therefore assigned to $[\{Pt(^{15}NH_3)_2\}(asp)\{Pt(^{15}NH_3)_2(H_2O)\}]^{2+}$ (**20**), in which the free β-carboxylate of **9** has coordinated to a platinum atom from a second diaqua cation, **1**. The ^{195}Pt NMR spectrum showed, in addition to the triplet from **1**, and a broad peak at −2160 ppm from overlapping signals from **9** and Pt_I of **20**, a doublet of doublets at −1579 ppm, corresponding to Pt_{II} of **20** (cf., −1582 ppm for **6**) (atom labeling is given on the structures in Scheme IV). The ^{15}N NMR spectrum also showed peaks that could be assigned to a complex in which two diammineplatinum–aspartate moieties coordinate through β-carboxylate to a third diammineplatinum(II) unit, **23**: two peaks slightly shifted from those for **9**, corresponding to ammine ligands bound to Pt_I, and a third peak at −83.4 ppm (J(Pt–N) = 351 Hz), close to that previously observed for *cis*-$Pt(^{15}NH_3)_2(aspH_2\text{-}\alpha O)_2^{2+}$ (**7**), corresponding to two equivalent ammine ligands bound to Pt_{II}, trans to β-carboxylate.

The ^{13}C NMR spectrum of a solution containing **1**, **9**, **20**, and **23** showed three sets of aspartate carbon peaks. For example, as illustrated in Figure 2, there were six carboxyl carbon peaks.

(20) Neidle, S.; Ismail, I. M.; Sadler, P. J. *J. Inorg. Biochem.* **1980**, *13*, 205.

Scheme IV



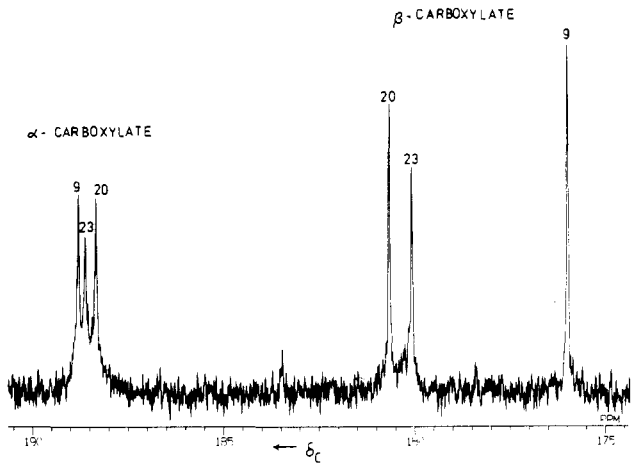


Figure 2. ^{13}C NMR spectrum (100.5-MHz) in the carboxylate region of a solution from *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ and aspartic acid (1.4:1) in H_2O after 5 days at pH 4. Numerals on the peaks correspond to the species present as labeled in Scheme IV: $[\{Pt(NH_3)_2\}(asp)\{Pt(NH_3)_2(H_2O)\}]^{2+}$ (**20**); $[\{Pt(NH_3)_2(asp)\}_2\{Pt(NH_3)_2\}]^{2+}$ (**23**); $Pt(NH_3)_2$(asp-*N*,*αO*) (**9**).

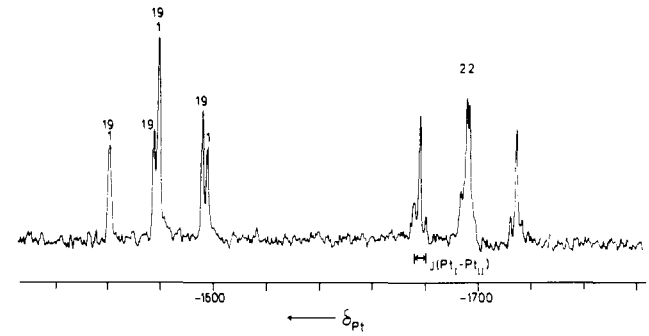


Figure 3. Part of the 21.4-MHz ^{195}Pt NMR spectrum (PtN_2O_2 region) of a solution obtained by dissolving $[\{Pt(^{15}NH_3)_2\}_2(amal)](NO_3)_2 \cdot H_2O$ (**22**) in H_2O. Numerals on peaks correspond to the species present as labeled in Scheme IV: *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (**1**); Pt_{II} of $[\{Pt_I(NH_3)_2\}(amal)\{Pt_{II}(NH_3)_2(H_2O)\}]^{2+}$ (**19**); Pt_{II} of $[\{Pt(NH_3)_2\}_2(amal)]^{2+}$ (**22**).

Peaks had already been assigned to **9**. By consideration of relative peak intensities in spectra from solutions with differing proportions of reactants, it was possible to assign all of the remaining peaks to **20** and **23**.

Analogous complexes, **21** and **24**, were formed in the glutamate system. Under comparable conditions, there tended to be a larger proportion of the triplatinum species (**24**) relative to the diplatinum complex (**21**) than with aspartate.

Addition of dilute HNO_3 to these solutions of aspartate or glutamate complexes to lower the pH of the solution to 2 or less caused these carboxylate coordination reactions to be reversed, to regenerate **1** and **8** or **13**.

When excess *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ was added to the solution of $Pt(NH_3)_2$(amal-*N*,*O*) (**17**), and the solution was allowed to stand, a white solid deposited, which analyzed for $[\{Pt(NH_3)_2\}_2(amal)](NO_3)_2 \cdot H_2O$. When this sparingly soluble solid (with ^{15}N-enriched ammine ligands) was redissolved in water, the ^{195}Pt NMR spectrum of the solution showed broad peaks in the PtN_3O region near −2100 ppm and in the PtN_2O_2 region, the spectrum shown in Figure 3. A triplet at −1580 ppm could be assigned to **1**. Overlapping with it was a doublet of doublets at −1579 ppm, with peak separations corresponding to Pt–N coupling constants 358 and 391 Hz. These peaks were assigned to Pt_{II} in a complex $[\{Pt(NH_3)_2\}(amal)\{Pt(NH_3)_2(H_2O)\}]^{2+}$ (**19**), analogous to the aspartate complex **20** discussed above. The spectrum also showed another doublet of doublets at −1697 ppm, each peak of which was flanked by "satellite" peaks from coupling with a second platinum nucleus (J(Pt–Pt) = 100 Hz). One Pt–N coupling constant, 374 Hz, is at the higher end of the normal range for ammine trans to carboxylate, while the other, 396 Hz, corresponds to ammine trans to a weak oxygen donor. A structure that is consistent with these data is $[\{Pt(NH_3)_2\}_2(amal)]^{2+}$ (**22**), in which coordinated water has been displaced from Pt_{II} in **19** by a carboxyl oxygen atom that is ideally placed to form a six-membered O,O′-chelate ring. The shift for Pt_{II} is close to that observed for $Pt(NH_3)_2$(amalH-*O*,*O*′)$^+$ (**15**) (−1732 ppm; see above).

In our experience, platinum(II) aqua complexes are seldom sparingly soluble, and no solids deposited from solutions of aspartate and glutamate analogues of **19**. We therefore propose that the solid that deposits is the nitrate salt of $[\{Pt(NH_3)_2\}_2(amal)]^{2+}$ (**22**). When this solid is redissolved in water, an equilibrium is set up immediately between **19** and **22**, with subsequent slower partial dissociation of **1** from **19**. With ^{15}N-substituted ammine present, the ^{15}N NMR spectrum would be expected to show four singlets with satellites for each of **19** and **22**, with additional peaks growing from **1** and $Pt(^{15}NH_3)_2$(amal-*N*,*O*)$^+$ (**17**). These peaks were all observed. The Pt–N coupling constant for ammine trans to the Pt_I–O bond (in the N,O-chelate ring) in **19**, 335 Hz, increased to 358 Hz in **22**, indicating a weakening

of the Pt_I–O bond when the carboxylate bridge forms. The carboxylate bridge in **22** is highly asymmetric, with the Pt_{II}–O(bridge) bond much weaker still, with a trans Pt–N coupling constant of 396 Hz, even larger than J(Pt–N) from ammine trans to water in **19**, 391 Hz. Nevertheless, the Pt_I–Pt_{II} coupling pathway in **22** must be Pt–O–C–O–Pt, through the bridging carboxylate, as the coupling is not present in **19**. The Pt_{II}–carboxylate bond in **19** (trans Pt–N coupling 358 Hz) appears to become weaker when this bond is incorporated in the six-membered chelate ring in **22** (trans Pt–N coupling 374 Hz).

Because of the sparing solubility of **22**, and the variety of species formed when it redissolved, we were unable to obtain a satisfactory ^{13}C spectrum from this solution.

When a solution of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ (**1**) was added to a solution of $Pt(^{15}NH_3)_2$(amal-*N*,*O*) (**17**) maintained near pH 5 and the ^{195}Pt and ^{15}N spectra were monitored, peaks due to **19** and **22** were observed. As well, there was an additional doublet of doublets in the ^{195}Pt NMR spectrum at −1824 ppm, with peak separations corresponding to Pt–N coupling constants 369 and 342 Hz. The ^{15}N spectrum showed new peaks at −88.3 ppm (J(Pt–N) = 369 Hz) and −80.1 ppm (J(Pt–N) = 342 Hz) and, slightly shifted from the corresponding peaks in Pt-$(^{15}NH_3)_2$(amal-*N*,*O*) (**17**), peaks at −83.0 and −65.9 ppm. A structure consistent with these data is **25**, in which two $Pt(NH_3)_2$ units are bridged by hyroxide and by the carboxylate group of a $Pt(NH_3)_2$(amal) unit. We have previously reported NMR data for analogous complexes where the bridging carboxylate was from acetate (δ_{Pt} −1548; δ_N for ammine trans to bridging hydroxide −77.4 (J(Pt–N) = 351 Hz); δ_N for ammine trans to bridging acetate −83.6 (J(Pt–N) = 377 Hz)[12]) or from long-chain amino acids.[16] The platinum and nitrogen shifts for **25** differ significantly from those observed for these analogues, probably due to the proximity of the $Pt(NH_3)_2$(amal) moiety to the other platinum centers. There were some weak peaks in some of the spectra of aspartate and glutamate complexes, which may have been due to complexes analogous to **25**, but these were never strong enough to allow assignment with confidence. With the aminomalonate system, no peaks of significant intensity were observed that could be assigned to a complex with $Pt(NH_3)_2$ bound by two carboxylate groups, analogous to the aspartate complex **23** or glutamate complex **24**.

Discussion

The absence of O,O′-chelation for aspartate and glutamate and the formation only of five-membered N,O-chelate rings are further illustrations of the dominating influence of chelate ring size on the chemistry of amino acid complexes of platinum(II), previously noted by ourselves[16] and others.[21] The ability of the carboxylate groups not incorporated into chelate rings to coordinate to another diammineplatinum cation is, in retrospect, not surprising, as there are no significant electronic or steric hindrances to this coordination. The subtle differences between the three ligands in the preferred type of trinuclear complex are, however, probably steric in origin. There is a greater tendency for the glutamate complex $[\{Pt(NH_3)_2(glu)\}_2\{Pt(NH_3)_2\}]^{2+}$ (**24**) to form, relative to mononuclear complexes, than with the corresponding aspartate complexes, and an analogous aminomalonate complex was not observed. Insertion of successive methylene groups between the carboxyl group and the methine carbon of the chelate ring removes the steric bulk of the $Pt(NH_3)_2$(chelate) moiety further from the coordinating carboxylate group, thus decreasing the steric interaction when two carboxylates coordinate cis to each other. In the preferred trinuclear complex with aminomalonate, **25**, the quite different geometry keeps the three $Pt(NH_3)_2$ moieties well separated.

The facile dehydration of $[\{Pt(NH_3)_2\}(amal)\{Pt(NH_3)_2(H_2O)\}]^{2+}$ (**19**) to $[\{Pt(NH_3)_2\}_2(amal)]^{2+}$ (**22**) is an example of the "opportunistic" coordination of platinum by a weak donor atom that is placed in a position favorable to coordination through the constraints imposed by binding of stronger ligands to the metal. This is an indication that, when platinum interacts with complex biomolecules, it is necessary to consider the possible involvement of donor groups that would not normally coordinate, if they are located at similar geometrically favorable sites.

Acknowledgment. We thank the Australian Research Council for financial support.

Supplementary Material Available: Tables S1–S3, listing all ^{195}Pt, ^{15}N, ^{13}C, and ^1H NMR data (4 pages). Ordering information is given on any current masthead page.

(21) Altman, J.; Wilchek, M.; Warshawsky, A. *Inorg. Chim. Acta* **1985**, *107*, 165.