# Articles

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## NMR Study of the Reactions of the *cis*-Diamminediaquaplatinum(II) Cation with Glutathione and Amino Acids Containing a Thiol Group[1]

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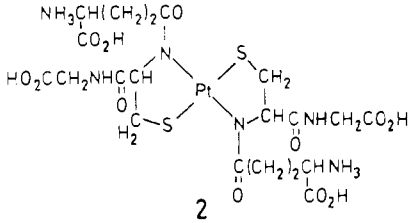
$^{195}Pt$, $^{15}N$, $^{1}H$, and $^{13}C$ NMR spectra have been used to study the reactions between *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (**1**) and amino acids containing a thiol group. *N*-Acetyl-L-cysteine, DL-homocysteine, and glutathione each form a dinuclear complex containing a $Pt_2S_2$ four-membered ring. Ammonia is slowly lost from these complexes. L-Cysteine ($cysH_2$) gives a similar complex, together with smaller quantities of *cis*-$Pt(NH_3)_2(SCH_2CH(NH_3)(CO_2H))_2^{2+}$ and $Pt(NH_3)_2(cysH\text{-}N,S)^+$. Penicillamine ($penH_2$) with **1** in strongly acidic solution gives initially the complex $[\{Pt(NH_3)_2\}_2(penH)]^{3+}$, in which the two Pt atoms are bridged by sulfur and carboxylate. After standing, this complex isomerizes to one in which sulfur still bridges the two Pt atoms, but with one also coordinated by ammine nitrogen and the other by carboxylate oxygen.

### Introduction

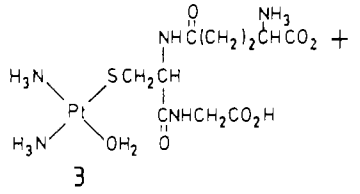
The nephrotoxicity of antitumor platinum drugs has been ascribed to their reactions with thiol groups of proteins.[2] The tripeptide glutathione ($glutH_5$, Figure 1) provides a model compound for study of these interactions. Glutathione is also present in significant concentrations in cytosplasm and may consequently react with platinum compounds before they can reach DNA[3,4] or may react with them after they are bound to DNA.[4-6] These reactions to some extent protect the tumor cells from the action of the platinum drug. As well, many sulfur ligands have been used, including glutathione itself, to provide protection against toxic effects of these drugs, both in laboratory animals and human patients.[7] There has consequently been considerable interest in the reactions of glutathione with *cis*-$Pt(NH_3)_2Cl_2$ and its analogues.

Odenheimer and Wolf[8] reported that reaction of *cis*-$Pt(NH_3)_2Cl_2$ with 2 mol equiv of glutathione in saline solution at 37 °C over 4-5 days gave a yellow solid that was analyzed as $Pt(gluH_4)_2$, which was assigned structure **2**, largely on IR evidence.



**2**

They noted that the ammonia originally present was readily lost once glutathione coordinated. Dedon and Borch[9] also obtained a solid from similar reactions, with empirical formula $Pt(glutH_4)_2 \cdot 3H_2O$, but proposed that it was polymeric. Shanjin et al.[10] obtained a $^{13}C$ NMR spectrum of the product of reaction between *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (**1**) and glutathione. Since peaks due to $C_{10}$ and $C_6$, near the thiol group, appeared to be affected most by coordination, they proposed the structure **3**, in which only



**3**

sulfur is coordinated. Corden[11] has reported preliminary results from a UV study of the reaction of *cis*-$Pt(NH_3)_2Cl_2$ with glutathione in phosphate buffer at pH 7, at 40 or 65 °C. His results suggested that, with excess glutathione present, two glutathione molecules coordinated to each platinum atom, and he proposed that *cis*-$Pt(NH_3)_2(glutH_4\text{-}S)_2$ was formed. He did not discuss the possibility of ammonia loss during the reaction. Roos et al.[12] have also studied by UV spectroscopy the reaction of *cis*-$Pt(NH_3)_2Cl_2$ with glutathione under conditions close to physiological. They found that an initial rapid reaction was followed by a much slower second reaction, but, again, UV spectra did not allow ready identification of the complexes produced. Dedon and Borch[9] used the rate of disappearance of *cis*-$Pt(NH_3)_2Cl_2$ (determined chromatographically) to determine rates of reaction with glutathione, cysteine, and some other sulfur donors.

A common approach to help shed light on the reactions of a relatively complex ligand is to study the reactions of a simpler analogue. In the past, this approach has not been very fruitful with this system. There have, for example, been numerous studies of the reactions of platinum compounds with cysteine, and almost every conceivable coordination mode has been proposed for the ligand, often on the basis of slender evidence. The most realistic description of the product of reaction between *cis*-$Pt(NH_3)_2Cl_2$ and cysteine is due to Odenheimer and Wolf,[8] who obtained a precipitate insoluble in common solvents, which they proposed was "of a polymeric nature" and "of constant elemental composition...although there appears to be no simple molar ratio between the components of the complex". It was evident from the analytical

(1) Presented in part at the Third International Conference on Bioinorganic Chemistry, Noordwijkerhout, The Netherlands, July 1987: Appleton, T. G.; Connor, J. W.; Hall, J. R.; Prenzler, P. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 382.
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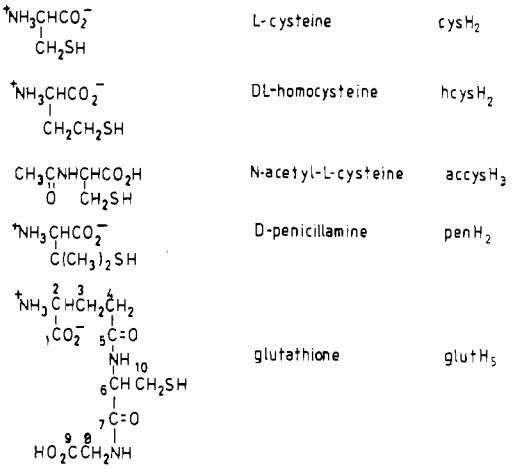
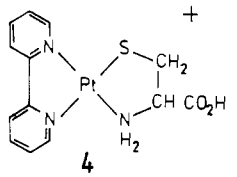



**Figure 1.** Ligands and abbreviations.

data that there had been loss of some, but not all, of the ammonia originally coordinated. With chelating diamine ligands, the probability that this ligand will be lost is much lower, and the 2,2′-bipyridyl complex **4** has been well characterized.[13]



**4**

In view of our successful application of multinuclear NMR ($^{15}N$, $^{195}Pt$, $^{13}C$, $^{1}H$) to the study of reactions between *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (**1**) and a variety of amino acids and derivatives,[14-17] we decided to apply these techniques to the study of reactions of **1** with glutathione and the amino acids and derivatives containing a thiol group that are shown in Figure 1.

In the course of our work, we became aware of results obtained by other workers that are complementary to ours. Reedijk et al.[18] have shown that the diethylenetriamine complex [Pt(dien)Cl]Cl reacts initially with glutathione to form a 1:1 complex with the ligand bound through sulfur, with subsequent reaction to form a complex in which sulfur bridges between two Pt(dien) units. Dedon and Borch[9] and Berners-Price and Kuchel[19] have studied by NMR the reactions of glutathione with *cis*- and *trans*-$Pt(NH_3)_2Cl_2$. The trans isomer gave a well-defined complex in which two glutathione ligands coordinated through sulfur to each platinum atom. The cis isomer, by contrast, apparently gave a mixture of polymeric species, with broad NMR peaks, and facile loss of coordinated ammonia was noted. When *cis*-$Pt(NH_3)_2Cl_2$ was allowed to react with red blood cells, free ammonia was generated, which was attributed to loss of ammonia from glutathione complexes.[19] *cis*-$Pt(NH_3)_2Cl_2$ inhibits activity of a number of enzymes dependent on thiol groups for their function.[9]

## Experimental Section

**Starting Materials.** $(^{15}NH_4)_2SO_4$ (99% $^{15}N$; Cambridge Isotopes) was supplied by Novachem (Melbourne). Amino acids were used as supplied (D-penicillamine, DL-homocysteine, *N*-acetyl-*L*-cysteine from Sigma; L-cysteine from Koch-Light; glutathione from Polysciences). No impurities were detected in $^{1}H$ and $^{13}C$ NMR spectra, except for the presence of some methanol in the *N*-acetylcysteine. Samples of *cis*-$Pt(NH_3)_2(ONO_2)_2$ (with $^{14}N$ or $^{15}N$, $^{1}H$ or $^{2}H$ in the ammine ligands) were prepared as previously described.[16,20,21]

**Table I.** Microanalytical Data for Solids Precipitated from Solutions of *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ and Thiol Amino Acids and Glutathione

| ligand | prep no. | anal., % C | H | N | S |
|---|---|---|---|---|---|
| *N*-acetylcysteine | I | 10.9 | 2.6 | 7.7 | 6.0 |
| | II | 11.0 | 2.3 | 6.1 | 6.6 |
| | III | 11.5 | 2.5 | 6.6 | |
| calcd for "$Pt(NH_3)_2$(accysH)" | | 15.4 | 3.4 | 10.8 | 8.2 |
| cysteine | I | 8.5 | 2.1 | 8.6 | 6.4 |
| | II | 7.2 | 2.3 | 8.8 | 6.8 |
| | III | 8.9 | 2.7 | 9.5 | |
| calcd for "$Pt(NH_3)_2$(cys)" | | 10.3 | 3.2 | 12.1 | 9.2 |
| glutathione | | 15.4 | 2.5 | 6.0 | 4.7 |
| calcd for "$Pt(glutH_4)_2$" | | 33.7 | 4.5 | 11.8 | 9.0 |

**Spectra.** The 10.1-MHz $^{15}N$, 21.4-MHz $^{195}Pt$, 25.05-MHz $^{13}C$, and 100-MHz $^{1}H$ NMR spectra were recorded as previously described[14,15,21] on a JEOL FX-100 instrument with the use of a 10-mm tunable probe (a 5-mm tube was used for $^{1}H$ spectra). An internal lock on deuterium of the solvent $D_2O$ was used for $^{13}C$ and $^{1}H$ spectra. Spectra of other nuclei were run with a $^{7}Li$ external lock. The 400-MHz $^{1}H$ and 100.4-MHz $^{13}C$ spectra were obtained with internal deuterium lock on a JEOL GX-400 instrument, as previously described,[16] the $^{1}H$ spectra with the use of a 5-mm $^{13}C/^{1}H$ probe, and $^{13}C$ spectra with a 10-mm tunable probe. $^{1}H$ spectra (60 MHz) were recorded on a Varian EM-360 spectrometer. Spectra of all nuclei other than $^{1}H$ were $^{1}H$-decoupled. Chemical shifts are positive to lower shielding. Because of the negative nuclear Overhauser enhancement in $^{1}H$-decoupled $^{15}N$ spectra, all NMR peaks are actually emissions, but for convenience, the spectrometer phase was adjusted to represent them in the conventional absorption mode.

$^{15}N$ shifts (±0.1 ppm) are relative to $^{15}NH_4^+$ in a coaxial capillary containing 5 M $^{15}NH_4{}^{15}NO_3$ in 2 M $HNO_3$. $^{195}Pt$–$^{15}N$ coupling constants were measured from $^{15}N$ spectra, which, because of narrower line widths, gave more accurate values (±1 Hz) than $^{195}Pt$ spectra. $^{195}Pt$ shifts (±5 ppm) were measured relative to a separate sample of $Na_2PtCl_6$ in aqueous solution (0.5 g/mL). $^{13}C$ shifts (±0.01 ppm) are reported relative to external tetramethylsilane, with dioxane ($\delta_C$ 67.73) as internal reference. Proton chemical shifts are relative to the methyl signal of 3-(trimethylsilyl)propanesulfonate (TSS).

IR spectra were obtained as Nujol and hexachlorobutadiene mulls with a Perkin-Elmer 283B grating spectrometer, calibrated by using the 1601- and 1028-$cm^{-1}$ bands of polystyrene.

**Typical NMR Experiment: Reaction of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ with *N*-Acetylcysteine.** A solution of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ was prepared by gently heating a suspension of solid *cis*-$Pt(^{15}NH_3)_2(ONO_2)_2$ (0.15 g, 0.42 mmol) in 3 mL of $H_2O$. The pH of this solution was approximately 1.5. The solution was filtered through a cotton wool plug into a 10-mm-diameter NMR tube. The $^{15}N$ NMR spectrum was run to check sample purity and showed the expected singlet with "satellites" (from coupling with $^{195}Pt$, $I = {}^1/_2$, 34% abundance) at −85.8 ppm ($^1J(^{195}Pt–^{15}N)$ = 390 Hz) from *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**).[20,21] Solid *N*-acetylglycine (0.055 g, 0.34 mmol) was added slowly, with shaking to dissolve it. Accumulation of data for a $^{15}N$ or $^{195}Pt$ spectrum commenced within 5 min. A similar procedure was used for $^{13}C$ spectra, except that *cis*-$Pt(^{14}NH_3)_2(ONO_2)_2$ was dissolved in $D_2O$. For $^{1}H$ spectra, the solution was prepared on one-third of the above scale, with *cis*-$Pt(^{14}ND_3)_2(ONO_2)_2$ in $D_2O$.

Similar procedures were used for other thiol amino acids. With penicillamine, 1 M $HNO_3$ was added to the solution of **1** to produce a strongly acidic solution (pH < 0.5) before addition of the ligand.

From the solutions initially containing **1** and *N*-acetylcysteine, a yellow solid deposited after several days. The solid was filtered off, washed with water, and air-dried. Microanalyses were obtained for samples in which [$^{14}$N]ammine was present, from three different experiments (Table I). As mentioned below, analogous solids were obtained with cysteine, homocysteine, and glutathione, and analytical results for some of these materials are also included in Table I.

## Results and Discussion

**Reactions of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ (1) with *N*-Acetyl-L-cysteine (accysH$_3$).** The reactions of *N*-acetylcysteine with **1** were

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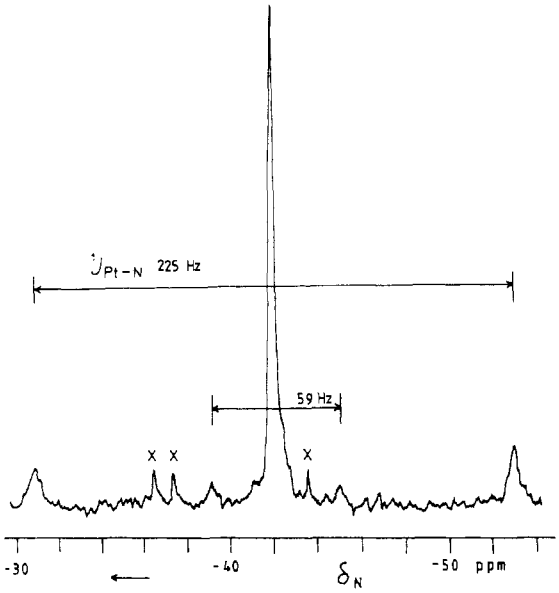
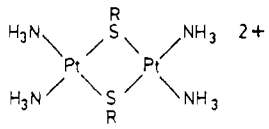



**Figure 2.** $^{15}N$ NMR spectrum (10.1 MHz) of $[\{Pt(^{15}NH_3)_2(accysH_2\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5a**) in $H_2O$. Peaks marked × are due to impurities, possibly including species formed after loss of coordinated ammonia.

studied in greater detail than those of the other thiol ligands. When 0.8 mol equiv of this ligand was added to a solution of *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**), the $^{15}N$ spectrum run soon after mixing showed, in addition to peaks from unreacted **1**, the spectrum shown in Figure 2, a moderately sharp central peak at −42.1 ppm, flanked by "satellite" peaks that were significantly broader. A peak to such low shielding can, in this system, correspond only to ammine trans to sulfur.[22] Since there is no accompanying peak of comparable intensity corresponding to ammine trans to an O or N donor (which would occur to higher shielding[22]), the peak must be assigned to a complex in which there is a sulfur-donor ligand coordinated trans to each of the two ammine ligands. Since the reaction was carried out with a small excess of **1**, and since the peaks due to residual **1** were relatively weak, the observed peaks cannot be assigned to *cis*-$Pt(^{15}NH_3)_2(accysH_2\text{-}S)_2$. The simplest species consistent with the observed spectrum is the sulfur-bridged dimer ($[\{Pt(^{15}NH_3)_2(accysH_2\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5a**). The formation of four-membered $Pt_2S_2$ rings from bridging thiolate ligands is well-known.[23]




**5**

| | |
|---|---|
| **a** | RS = accysH$_2$ |
| **b** | cysH |
| **c** | hcysH |
| **d** | glutH$_4$ |

There are two isomers of **5a**, syn and anti, which are shown in Figure 3 (parts a and b, respectively). From models, the anti isomer appears to be less sterically crowded and so would be expected to predominate. With the asymmetric center of the *N*-acetyl-L-cysteine ligand taken into account, it is evident that, in the syn isomer, the two Pt atoms are related by a $C_2$ axis perpendicular to the $Pt_2S_2$ plane. In the anti isomer, a $C_2$ axis lies in this plane, passing through the two Pt atoms, which are nonequivalent. The syn and anti isomers are interconverted by inversion about the sulfur atoms. If the rate of inversion is fast compared with the difference between resonance frequencies for the different environments, the $^{15}N$ spectrum will show an averaged

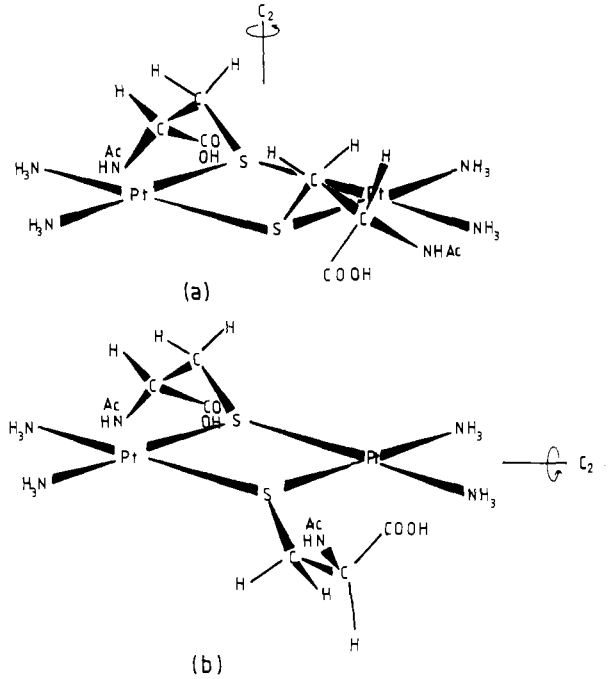



**Figure 3.** Isomers of $[\{Pt(NH_3)_2(accysH_2\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5a**): (a) syn; (b) anti.

spectrum. This appears to be the case.

The isotopomer that contains no $^{195}Pt$ nuclei (four-ninths of the total population) will then give a singlet at the central resonance frequency. For the isotopomer with one $^{195}Pt$ nucleus (four-ninths of the total population) the $^{15}N$ spectrum would be expected to be the A part of a $A_2A'_2X$ spectrum (X = $^{195}Pt$), but if $J_{AA'} = J_{A'X} = 0$, the ammine ligands bound directly to $^{195}Pt$ would give a doublet separated by $^1J(Pt\text{–}N)$ ($J_{AX}$) and the other ammine ligands would add to the central resonance. The spectrum may be interpreted on this basis. The broadening of the "satellite" peaks could be due to the Pt–S–Pt–N coupling ($J_{A'X}$) being nonzero but small, but it is also possible that the differences between the Pt–N coupling constants for the different Pt atoms in the syn and anti isomers are larger than the differences between resonance frequencies, giving less efficient time averaging for the "satellite" signals. Chemical shift anisotropy relaxation of the Pt nuclei could also be relatively fast in this bulky dimeric cation, which may lead to broadening of the satellite peaks, even at a relatively low magnetic field strength. In the isotopomer with two $^{195}Pt$ nuclei (one-ninth of the total population) the $^{15}N$ spectrum would be expected to be the A part of a complex $A_2A'_2XX'$ spectrum. Because of the low population of this isotopomer, and the expected complexity of the spectrum, peaks from this isotopomer would be expected to be weak. The weak peaks at ±24.5 Hz from the central resonance may be part of this pattern. Other weak peaks that were not symmetrical about the central resonance were assigned to minor components of the reaction mixture.

The value of $^1J(Pt\text{–}N)$, 225 Hz, is significantly less than the values obtained previously for ammine ligands trans to other sulfur-donor ligands (e.g., 243, 243, and 264 Hz trans to $Me_2SO$ $S{=}C(NH_2)_2$, and $-SCN-$, respectively, in triammine complexes[22] and 257 Hz trans to the thioether sulfur of *S*-methyl-L-cysteine in $Pt(^{15}NH_3)_2(mecysH\text{-}S,N)^{+}$[16]). This indicates that the thiolate ligand has a higher NMR trans influence, despite the fact that it is bridging rather than terminal.

The presence of free ammonium ion could be readily detected from the $^{15}N$ NMR spectrum of the solution if the reference capillary containing $^{15}NH_4^+$ was removed. A signal due to free ammonium ion was detected after 20 min and continued to grow with time. These spectra were all run in solutions where the pH had not been adjusted after the reactants had mixed (pH approximately 1). However, when NaOH solution was added soon after mixing to increase the pH to approximately 5, there was no significant change in the spectra obtained.

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(23) Jain, V. K. *Inorg. Chim. Acta* **1987**, *133*, 261.

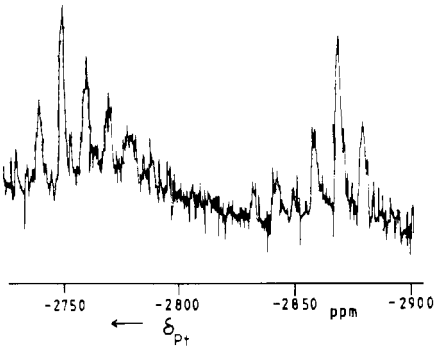



**Figure 4.** $^{195}Pt$ NMR spectrum (21.4 MHz) of $[\{Pt(^{15}NH_3)_2(accysH_2\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5a**) in $H_2O$.

The $^{195}Pt$ NMR spectrum of a solution of **5a** (which was obtained after approximately 2 h of accumulation time) is shown in Figure 4. The major peaks were two broad triplets, at −2750 and −2870 ppm, with the separation within each triplet corresponding to $^1J(Pt\text{–}N)$, 225 Hz. These triplets were assigned to the nonequivalent Pt nuclei of the anti isomer, for isotopomers with only one $^{195}Pt$ nucleus. Since these triplets were approximately 2500 Hz apart, the rate of sulfur inversion would have to be very fast to cause complete averaging of the signals, and it is likely that the inversion at sulfur merely contributes to line broadening. The weaker peaks observed could be due to some or all of the following: (i) the X,Y part of the $A_2B_2XY$ spectrum from the isotopomer of the anti isomer with both platinum nuclei $^{195}Pt$; (ii) peaks from the syn isomer; (iii) peaks from partially deamminated species such as $[(NH_3)_2Pt(accysH_2\text{-}\mu\text{-}S)_2Pt(NH_3)(H_2O)]^{2+}$.

These platinum shifts are to lower shielding than those usually observed for a $PtN_2S_2$ complex (e.g., *cis*-$Pt(NH_3)_2\{SC(NH_2)_2\}_2^{2+}$, −3400 ppm[22]). This is probably due largely to the incorporation of the platinum atoms in a four-membered $Pt_2S_2$ ring and may be compared with the shift from −1572 ppm for *cis*-$Pt(NH_3)_2(OH)_2$ to −1150 ppm for $[\{Pt(NH_3)_2(\mu\text{-}OH)\}_2]^{2+}$.[20]

The 100.4-MHz $^{13}C$ spectrum of **5a** was recorded after an accumulation period of only 2 h, to minimize the effects of ammine loss. It showed no peaks from free *N*-acetylcysteine. The acetyl resonance (23.38 ppm) and two C(O) peaks (175.38 and 174.08 ppm) were quite sharp. Since these carbon atoms are well removed from the sulfur atom, the chemical shift differences between the isomers of **5a** would be expected to be small and would be averaged at intermediate rates of inversion at sulfur. The methine (55 ppm) and methylene (32 ppm) resonances are broader. Since these carbon atoms are closer to sulfur, the chemical shift differences between isomers would be greater, and the signals are not completely averaged.

Because of the relatively long time required to obtain a $^{13}C$ or $^{195}Pt$ NMR spectrum, and the slow decomposition of the complex, it was not practicable to attempt to obtain a series of spectra for these nuclei of the same solution at different temperatures. With the much shorter time required to obtain a $^1H$ spectrum, it was possible to obtain variable-temperature spectra for this nucleus. The 400-MHz spectrum at 276 K showed in the methine region two quartets (intensity ratio approximately 10:1) (Figure 5a), each representing the X part of an ABX pattern. For the reasons given above, the more intense quartet was assigned to the methine protons of the anti isomer of **5a** and the less intense to the syn isomer. The spectrum also showed the AB part of the pattern corresponding to the methylene protons of the major isomer (almost first order), which allowed complete analysis of the spectrum for this isomer ($\delta(H_A)$ 2.86, $\delta(H_B)$ 2.49, $\delta(H_X)$ 5.57, $J_{AX}$ = 3.4 Hz, $J_{BX}$ = 10.1 Hz, $J_{AB}$ = 14.5 Hz). Parts of the AB pattern for the minor isomer were obscured, allowing a partial analysis only ($\delta(H_A)$ = 2.79, $\delta(H_X)$ = 5.40, $J_{AX}$ = 4.0 Hz, $J_{BX}$ = 8.5 Hz, $J_{AB}$ = 14.5 Hz). In the methyl region, the major isomer gave a peak, slightly broadened ($\Delta\nu_{1/2}$ = 4.4 Hz) at 2.26 ppm. The spectrum also showed peaks due to small amounts of free ligand and to other minor components in solution, which partly obscured the methyl region, but the methyl resonance for the minor isomer probably corresponded to a broad peak at 2.24 ppm, just resolved from the methyl resonance of the major isomer.

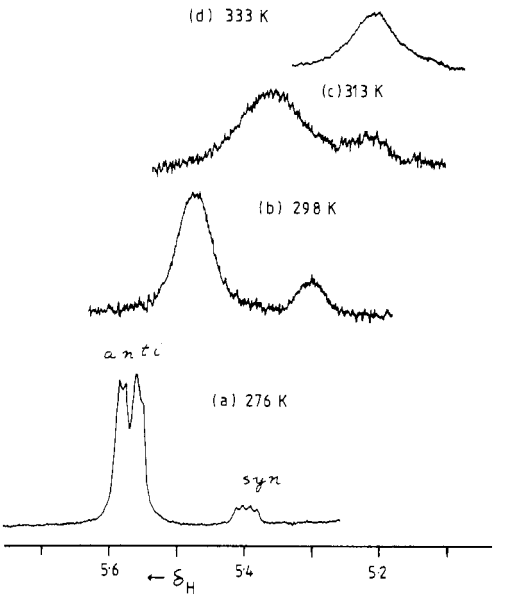



**Figure 5.** Variable-temperature 400-MHz $^1H$ NMR spectra in the methine region from solutions in $D_2O$ containing $[\{Pt(ND_3)_2(accysH_2\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5a**).

At 298 K, the methine region of the spectrum (Figure 5b) showed two broad structureless peaks, as expected if inversion at sulfur was beginning to interconvert the two isomers. It is also evident that the proportion of the minor isomer (syn) relative to the major isomer (anti) had increased compared with that at lower temperatures. The chemical shifts of the methine protons are also quite temperature-dependent, moving to higher shielding at higher temperatures. The methylene region showed two very broad peaks, and the methyl region showed a single peak from **5a**, significantly broadened ($\Delta\nu_{1/2}$ = 10 Hz). At 313 K, the methine signals, while still distinct, were beginning to coalesce (Figure 5c) and the methyl peak was sharper ($\Delta\nu_{1/2}$ = 6 Hz). At 333 K, the highest temperature used, to avoid too rapid decomposition, there was only one broad methine resonance (Figure 5d), and the methyl resonance was still sharper ($\Delta\nu_{1/2}$ = 2.5 Hz). The methylene region still showed two broad peaks (the methylene protons will, of course, always remain nonequivalent). At some hypothetical higher temperature, a sharp ABX pattern would be expected from the methine and methylene protons.

Although *cis*-$(Pt(NH_3)_2(accysH_2\text{-}S)(H_2O)^+$ is probably an intermediate in the formation of **5a**, it was not detected in spectra run within a few minutes of mixing. No peaks were observed corresponding to complexes in which donor atoms other than sulfur coordinate, although there is probably some coordination through these atoms after ammine loss occurs. When solutions of **5a** were allowed to stand for several days, a yellow solid, presumably polymeric, precipitated. The only $^{15}N$ NMR peak observable in the spectrum of the supernatant solution was due to $^{15}NH_4^+$ (i.e., peaks due to **1**, as well as those from **5a**, had disappeared). Analytical results on such samples (Table I) showed some variation and did not fit any simple formulation. The IR spectrum of one sample showed a broad band at 3500–3200 $cm^{-1}$, which could include a number of $\nu$(O–H) and $\nu$(N–H) bands, a band at 1720 $cm^{-1}$, indicating the presence of some uncoordinated protonated carboxyl group,[24] and a band at 1630 $cm^{-1}$, which could be assigned to the acetate group, perhaps overlapping with a band from coordinated carboxylate. Attempts to isolate **5a** by precipitation with a variety of large anions were unsuccessful.

**Reactions of 1 with L-Cysteine ($cysH_2$).** Reactions between **1** and L-cysteine were less readily studied because of the relatively

(24) Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, 3rd ed.; Wiley: New York, 1978; p 308.

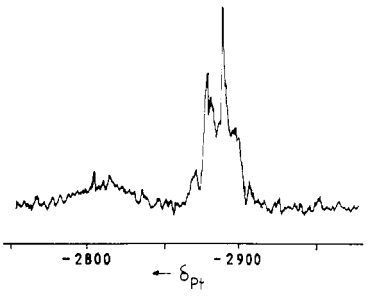
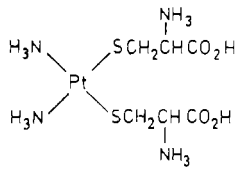



**Figure 6.** $^{195}$Pt NMR spectrum (21.4 MHz) of $[\{Pt(^{15}NH_3)_2(hcysH_2\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5c**) in $H_2O$.

low solubility of cysteine in weakly acidic aqueous solution. Solid cysteine was added to a solution of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$, the mixture was stirred for 30 min, and then the $^{15}$N NMR spectrum of the solution was obtained. Apart from peaks due to unreacted **1**, the spectrum showed a singlet with "satellites" at −42.8 ppm ($J$(Pt–N) = 234 Hz) assigned to $[\{Pt(^{15}NH_3)_2(cysH\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5b**), together with weaker peaks: a singlet at −43.5 ppm (satellites too weak to be observed) probably due to *cis*-$Pt(^{15}NH_3)_2(cysH_2)_2^{2+}$ (**6**) and weak peaks that could be due to the



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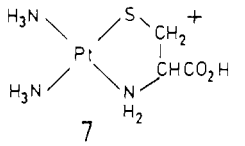


7

chelate complex $Pt(^{15}NH_3)_2(cysH\text{-}N,S)^+$ (**7**) (ammine trans to sulfur −46.1 ppm, ammine trans to cysteine nitrogen −66.7 ppm). If these assignments are correct, the complexes **6** and **7** were present only in relatively low proportions in these solutions, but their analogues were not detected at all in solutions from the other amino acids discussed in this paper.

The spectra also showed that loss of ammonia from the complexes was comparatively rapid in this system. No attempt was made to record a $^{195}$Pt spectrum. A 100.4-MHz $^{13}$C spectrum accumulated over 2 h was quite complex, owing to the presence of a variety of species formed after ammonia loss. A solution allowed to stand deposited a yellow solid, apparently analogous to that formed in the acetylcysteine system. Again, analytical data did not fit any simple formulation, and there was considerable variation in the values from sample to sample (Table I).

**Reaction of 1 with DL-Homocysteine (hcysH$_2$).** The reaction of homocysteine with **1** was analogous to that of *N*-acetylcysteine, with the only peaks present in the $^{15}$N NMR spectrum after addition of the ligand (apart from those due to residual **1**) assignable to the sulfur-bridged dimer $[\{Pt(^{15}NH_3)_2(hcysH\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5c**; −41.8 ppm, $J$(Pt–N) = 222 Hz). In the $^{195}$Pt spectrum of this solution, a complex multiplet was observed at −2890 ppm (with a weaker broad resonance to lower shielding) (Figure 6). Since DL-homocysteine was used, isomers of $[\{Pt(NH_3)_2\}_2(D\text{-}hcysH\text{-}\mu\text{-}S)(L\text{-}hcysH\text{-}\mu\text{-}S)]^{2+}$ would be expected to be present, as well as syn and anti isomers of $[\{Pt(NH_3)_2(D\text{-}hcysH\text{-}\mu\text{-}S)\}_2]^{2+}$ and $[\{Pt(NH_3)_2(L\text{-}hcysH\text{-}\mu\text{-}S)\}_2]^{2+}$. The lack of large chemical shift differences between Pt nuclei in different environments is presumably due in part to the greater distance between the sulfur atom and the asymmetric center in homocysteine compared with cysteine and its derivatives.

From the $^{15}$N NMR spectra, the loss of ammonia from these complexes was much slower than for the cysteine and acetylcysteine complexes. Ismail and Sadler[25] postulated that ammonia would be lost more readily from a *cis*-$Pt(NH_3)_2^{2+}$ moiety bound to a sulfur-containing peptide when that peptide contains other donor atoms that can coordinate to form a chelate ring. When ammonia is lost from the cysteine complex **5b**, the cysteine amine group may coordinate to form a five-membered chelate ring. In the corresponding reaction of the *N*-acetylcysteine complex **5a**, the presence of the *N*-acetyl group might provide some kinetic hindrance to the formation of an analogous five-membered chelate ring, but the ring would be expected to form eventually.[17] The corresponding reaction of the homocysteine complex **5c**, however, would give a less-favored six-membered chelate ring. In similar reactions involving the carboxyl rather than the amine group, **5a** and **5b** would form a six-membered ring but **5c** would give a seven-membered ring. The enhanced kinetic stability of the homocysteine complex **5c** toward ammine dissociation is therefore probably related to the less favorable chelate ring sizes that can be formed in this system. We have previously demonstrated the profound effects of alkyl chain lengths in other reactions of platinum complexes with amino acids[15] and aminoalkyl phosphonates.[26] With standing, all coordinated ammonia was eventually lost, and a polymeric product precipitated.

**Reaction of 1 with Glutathione.** Reaction of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ with glutathione under conditions comparable to those described above for acetylcysteine and homocysteine produced a solution that gave a $^{15}$N NMR spectrum very similar to the spectra obtained with these ligands (singlet at −41.7 ppm, with broad satellites, $J$(Pt–N) = 230 Hz), corresponding to a sulfur-bridged dimeric complex, $[\{Pt(^{15}NH_3)_2(glutH_4\text{-}\mu\text{-}S)\}_2]^{2+}$ (**5d**). The major peaks in the $^{195}$Pt NMR spectrum were two triplets of similar intensity at −2786 and −2856 ppm, assignable to the nonequivalent platinum nuclei of the anti isomer of **5d**.

The $^{15}$N spectra showed that ammonia was lost from the complex at a rate comparable with that for the acetylcysteine analogue **5a**. As with the simpler amino acids, a polymeric yellow solid deposited after solutions had been allowed to stand for several days. The analytical results (Table I) do not correspond to a bis(glutathione) complex. Odenheimer and Wolf[8] and Dedon and Borch[9] obtained compounds with this composition from *cis*-$Pt(NH_3)_2Cl_2$ and excess glutathione, while we used a ratio of glutathione to **1** of approximately 0.8:1.

The 25.05-MHz $^{13}$C spectrum of a solution of **5d** is shown in Figure 7, together with that of free glutathione for comparison. It is evident that the only resonances significantly affected by coordination of the glutathione were those from the methylene ($C_{10}$) and methine ($C_6$) C atoms of the cysteine residue, which were significantly broadened (owing to the intermediate rate of inversion about the sulfur atoms) and shifted to lower shielding. Our spectrum is similar to that described by Shanjin et al.[10] Their postulate that only the sulfur atom of glutathione is involved in coordination to platinum is, from our standpoint, correct, but they are incorrect in formulating the complex present as *cis*-$Pt(NH_3)_2(glutH_4\text{-}S)(H_2O)^+$ (**3**). While structure **3** is compatible with the $^{13}$C spectrum, we rule it out on the basis of our $^{15}$N and $^{195}$Pt data (see arguments used above in discussing the acetylcysteine complex).

As with acetylcysteine, adjusting the pH within the range 1–5 had little effect on the spectra.

**Reactions of 1 with D-Penicillamine (penH$_2$).** Free penicillamine gives a relatively simple $^1$H NMR spectrum in $D_2O$, a singlet corresponding to the methine proton and two singlets from the nonequivalent methyl groups. If this amino acid formed a complex of the type **5**, the $^1$H spectrum would be expected to provide information about the sulfur inversion process more readily than for systems such as the *N*-acetylcysteine one, where even the free ligand gives a relatively complex ABX spectrum for the methylene and methyl protons. We therefore examined the reactions of **1** with penicillamine. It soon became evident, however, that reactions with this ligand are quite different from those for the other thiol ligands discussed above.

When solutions of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$ and penicillamine (0.8 mol equiv) were mixed with pH < 0.5, the $^{15}$N spectrum run immediately showed (in addition to peaks from **1**)

(25) Ismail, I. M.; Sadler, P. J. In *Platinum, Gold, and Other Metal Chemotherapeutic Agents*; Lippard, S. J., Ed.; American Chemical Society: Washington, DC, 1983; p 171.

(26) Appleton, T. G.; Hall, J. R.; McMahon, I. J. *Inorg. Chem.* **1986**, *25*, 720.

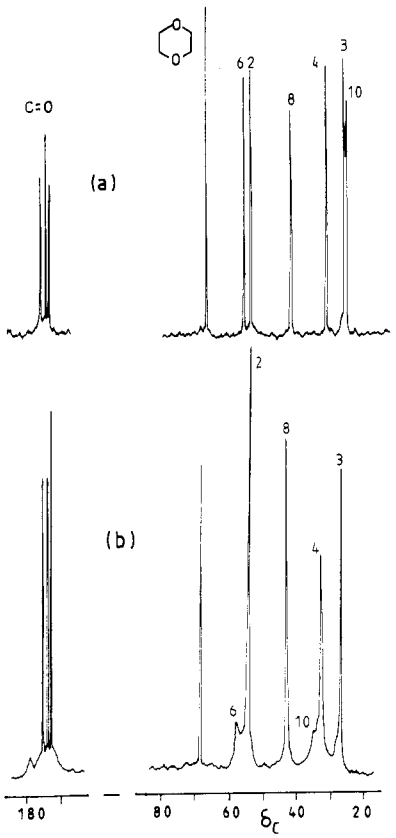



**Figure 7.** $^{13}C$ NMR spectra (25.05 MHz) in $D_2O$: (a) glutathione; (b) glutathione plus *cis*-$Pt(ND_3)_2(D_2O)_2^{2+}$ (**1**). Numbers on peaks represent assignments to carbon atoms numbered as in Figure 1.

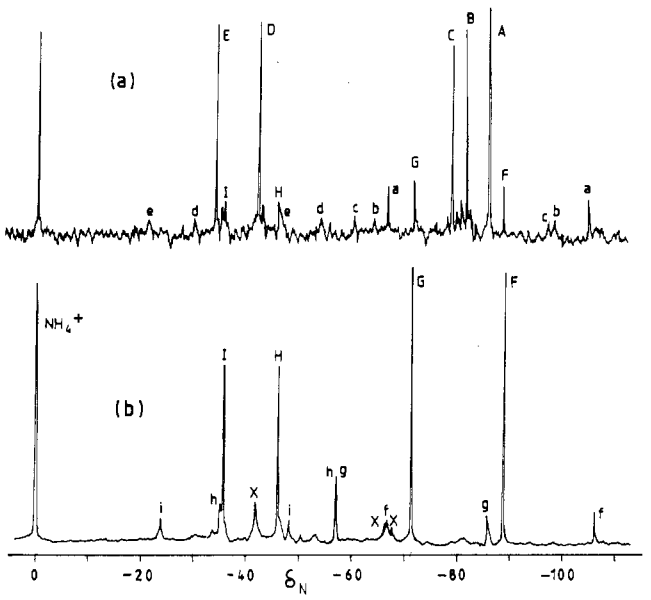



**Figure 8.** $^{15}N$ NMR spectra (10.1 MHz) of a solution prepared by mixing *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**) and penicillamine (0.8 mol equiv) in $H_2O$ at pH approximately 0.5: (a) accumulated 3–30 min after mixing, with a reference capillary containing $^{15}NH_4^+$ being present; (b) accumulated 2–6 h after mixing, with no reference capillary present. Peaks are defined as follows: (A, a) *cis*-$Pt(^{15}NH_3)_2(H_2O)_2^{2+}$ (**1**); (B, b, C, c) **9a** ammine trans to carboxylate; (D, d, E, e) **9a** ammine trans to S; (F, f) **11a** ammine trans to carboxylate; (G, g) **11a** ammine trans to $NH_2$; (H, h, I, i) **11a** ammine trans to S.

four singlets, with satellites, of equal intensity (Figure 8a). Two of these peaks, at −33.8 ppm ($J$(Pt–N) = 254 Hz) and −42.0 ppm ($J$(Pt–N) = 240 Hz), occurred to such low shielding that they must correspond to ammine trans to sulfur and two, at −78.7 ppm ($J$(Pt–N) = 375 Hz) and −81.2 ppm ($J$(Pt–N) = 352 Hz), to ammine trans to oxygen.[22] A coupling constant of 352 Hz is consistent with ammine trans to either carboxylate oxygen or bridging hydroxide,[21,22] but the latter is unlikely at low pH. A coupling constant of 375 Hz could correspond to ammine trans either to water or to carboxylate oxygen.[21,22]

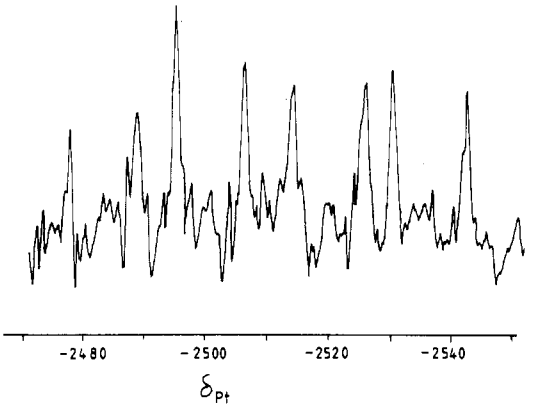
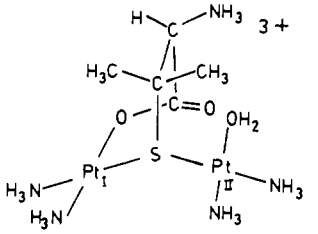



**Figure 9.** $^{195}Pt$ NMR spectrum (21.4 MHz) of $[\{Pt(^{15}NH_3)_2\}_2(penH)]^{3+}$ (**9a**) in $H_2O$.

The $^{195}Pt$ NMR spectrum of this solution showed two doublets of doublets, at −2492 ppm (line separations 240 and 375 Hz) and at −2528 ppm (line separations 254 and 352 Hz) (Figure 9). These shifts are in the region expected for $PtN_2SO$ complexes.[16,22] The sharpness of the lines is also consistent with the absence of any bound $^{14}N$ nuclei. No definite assignments could be made of peaks due to Pt–Pt coupling. Because of the relatively small different in chemical shift for the nonequivalent Pt nuclei, the pattern from these peaks would be expected to be second order.

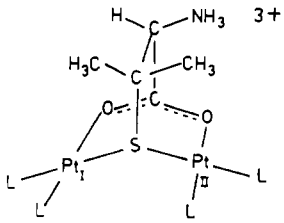
The $^1H$ NMR spectra of this species showed three singlets, two due to the nonequivalent methyl protons (1.47, 1.70 ppm) and the third to the methine proton (4.52 ppm, significantly less shielded than the free ligand in the same solution) (Figure 10). The 400- and 100-MHz spectra were similar, with no additional peaks due to coupling with $^{195}Pt$ observed at the lower field.

When reactions were carried out with varying ratios of penicillamine and **1**, careful study of relative intensities of the peaks in the various spectra, due to unreacted **1**, the free ligand, and this complex, led us to the conclusion that one penicillamine molecule must coordinate to two $Pt(NH_3)_2^{2+}$ moieties. Two structures consistent with the NMR data are **8** and **9a**. A model of **8**, in which the Pt atoms are bridged only by sulfur, suggests




**8**

that this species would be sterically crowded. There appears to be little hindrance to close approach between the carboxyl group and the water molecule coordinated to $Pt_{II}$. The model of **9a**, in




**9**

**a** L = $NH_3$

**b** $L_2$ = en

which the carboxylate group bridges as well as sulfur, shows that the bicyclic system would be rigid, with little steric crowding or

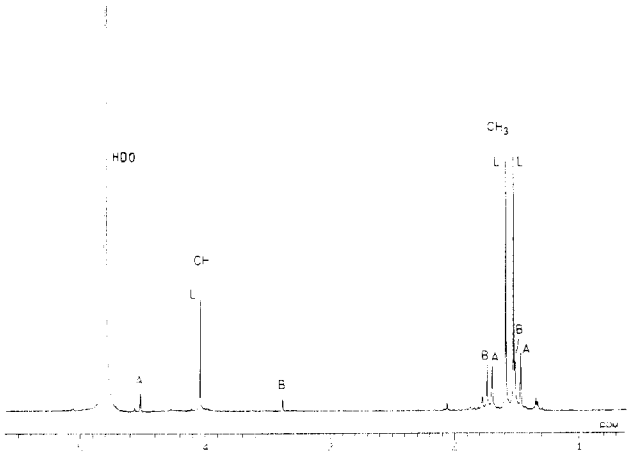
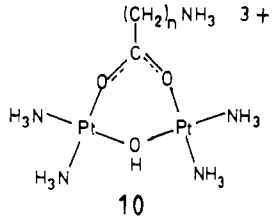



**Figure 10.** $^1$H NMR spectrum (400 MHz) of a solution obtained by addition of excess penicillamine to an acidic solution (pD 0.5) of *cis*-$Pt(ND_3)_2(D_2O)_2^{2+}$ (**1**) in $D_2O$: (L) peaks due to free penicillamine; (A) peaks due to **9a**; (B) peaks due to **11a**.

angle strain. This complex might be expected to have greater thermodynamic and kinetic stability than **8**. The six-membered Pt–O–C–O–Pt–S ring has some similarity to the carboxylate/hydroxo bridges in complexes we have previously reported,[15] such as **10**. In subsequent discussion, we shall refer to the complex

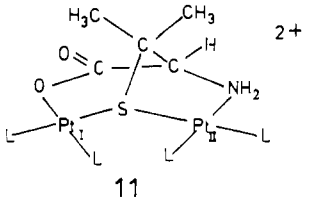



**10**

as **9a**. This structure, with one penicillamine ligand per dinuclear unit, is presumably preferred over structure **5**, because the latter structure would be sterically destabilized because of the presence of the two methyl groups on the carbon atom adjacent to sulfur.

Even in strongly acidic solutions (pH < 0.5), **9a** converts within 2 h to a new complex. The reaction was monitored by $^{15}$N, $^{195}$Pt, and $^1$H NMR. The $^{15}$N NMR spectrum (Figure 8b) showed four singlets with satellites: two assigned to ammine trans to sulfur (−35.9 ppm, $J$(Pt–N) = 244 Hz; −46.1 ppm, $J$(Pt–N) = 221 Hz), one to ammine trans to nitrogen (−71.3 ppm, $J$(Pt–N) = 288 Hz) and one to ammine trans to carboxylate oxygen (−88.8 ppm, $J$(Pt–N) = 354 Hz). The $^{195}$Pt spectrum (Figure 11) showed a broad singlet at −2948 ppm and a sharp doublet of doublets at −2408 ppm (peak separations 244 and 354 Hz) with each peak flanked by satellites from Pt–Pt coupling ($J$(Pt–Pt) = 393 Hz). This observation proves that this is a dinuclear species with nonequivalent Pt nuclei. The broad singlet is in the chemical shift range characteristic of a $PtN_3S$ complex (cf. $Pt(NH_3)_3\{SC(NH_2)_2\}^{2+}$, −2962 ppm[22]), and the broadening is typical of a complex with $^{14}$N bound to platinum.[27] The sharp doublet of doublets is in a similar region to the peaks observed for **9a** and corresponds to a $PtN_2SO$ complex.

The only structure consistent with these data is **11a**. Models indicate that the bicyclic system is less rigid than in **9a**. There




**11**

**a** L = $NH_3$

**b** $L_2$ = en

(27) Ismail, I. M.; Kerrison, S. J. S.; Sadler, P. J. *Polyhedron* **1982**, *1*, 57.

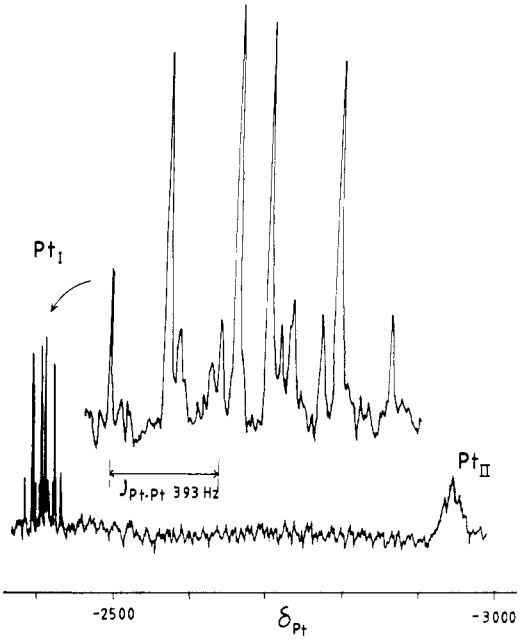



**Figure 11.** $^{195}$Pt NMR spectrum (21.4 MHz) of $[\{Pt(^{15}NH_3)_2\}_2(pen)]^{2+}$ (**11a**) in $H_2O$.

appears to be little angle strain or steric interaction. Since **9a** is converted quantitatively into **11a**, **11a** in thermodynamically more stable than **9a**. Under strongly acidic conditions, the amine group remains protonated, and **9a** forms first. Addition of base to increase the pH to 4–5 causes **9a** to convert rapidly into **11a**. The conversion reaction would commence with the breaking of the bond between carboxylate oxygen and $Pt_{II}$. The aqua complex **8** could form in trace amounts as an intermediate. The amine group then coordinates to $Pt_{II}$, with loss of $H_3O^+$. If penicillamine was simply added to a solution of **1**, coordination and deprotonation of the thiolate group and partial formation of **11a** caused protons to be released into the solution, and a mixture of **9a** and **11a** was formed initially, which converted only slowly into **11a**.

The 400-MHz $^1$H NMR spectrum of **11a** (Figure 10) showed the expected singlets from the methyl groups (1.51, 1.74 ppm) and methine proton (3.38 ppm). There is a shift of 1.14 ppm to higher shielding for the methine proton from **9a** to **11a**. The 100- and 60-MHz spectra showed satellite peaks flanking the methine signal, which would correspond to the $Pt_{II}$–N–C–H coupling (94 Hz). This coupling is quite large for a three-bond Pt–H coupling (cf. 32 Hz for $^3J$(Pt–N–C–H) in $Pt(NH_3)_2$(gly-*N*,*O*)$^+$[14]). The dihedral angle, $\phi$, between the planes defined by Pt–N–C and H–C–N is close to 180°, and $^3J$(Pt–N–C–H) is approximately proportional to $\cos^2\phi$.[28,29] The broadening of satellite peaks to the point that they were no longer observed in spectra run at higher fields is due to enhanced chemical shift anisotropy relaxation.[30]

From the growth with time in the $^{15}$N spectra of a peak due to free ammonium ion, it was evident that ammonia was lost from these complexes over several hours. Because of this, attempts to obtain $^{13}$C spectra of **11a** were unsuccessful. Preliminary study of comparable reactions between penicillamine and the ethylenediamine complex $Pt(en)(H_2O)_2^{2+}$ indicated that, although ethylenediamine was eventually lost from the complexes, the reaction was much slower than the loss of ammonia from corresponding ammine complexes. Reactions were followed by $^1$H NMR. The spectra were almost identical with those for the ammine complexes, except for the presence of a complex multiplet near 2.7 ppm from the four methylene protons (all nonequivalent) of ethylenediamine. In strongly acidic solution, **9b** was formed initially (methyl protons 1.44, 1.69 ppm; methine proton 4.52

(28) Erickson, L. E.; McDonald, J. W.; Howie, J. K.; Clow, R. P. *J. Am. Chem. Soc.* **1968**, *90*, 6371.
(29) Appleton, T. G.; Hall, J. R. *Inorg. Chem.* **1971**, *10*, 1717.
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ppm), but its conversion to **11b** (methyl protons 1.47, 1.73 ppm; methine proton 3.38 ppm) was much faster than for the ammine analogues. This may be related to a slightly smaller steric interaction of the chelating ethylenediamine ligand with the rest of the complex. The isomerization occurred too rapidly to allow a $^{13}C$ spectrum to be obtained for **9b**, but a spectrum was obtained for **11b**. It showed peaks due to the methyl groups at 25.45 and 30.60 ppm, to the methine carbon at 73.19 ppm, and to carboxyl carbon at 175.59 ppm. There were six peaks in the range 45–53 ppm, four from the four distinct ethylenediamine C atoms of **11b**, one from unreacted $Pt(en)(D_2O)_2^{2+}$, and one from the quaternary carbon atom of coordinated penicillamine. All of the penicillamine peaks except those from the methyl groups were shifted significantly to lower shielding compared with those of the free ligand.

**Conclusions.** The conditions of our experiments did not, and were not intended to, mimic those existing in vivo. Our results, however, do show the types of complexes that form between diammineplatinum(II) and thiolate amino acids and derivatives when very labile (aqua) leaving groups bound to platinum provide no kinetic hindrance to coordination of the sulfur donor. When leaving ligands are less labile, as with *cis*-$Pt(NH_3)_2Cl_2$, reactions such as ammine loss may be competitive with chloride displacement. Relatively complex mixtures of oligomeric complexes with Pt–S–Pt bridges may then be formed rather than simple dinuclear species. In a living organism, the concentration of platinum complexes will be much less than in our studies, so that, unless dimers are already present before the complexes are injected, formation of compounds with Pt–S–Pt bridges is unlikely. It is, however, possible that thiolate sulfur may form bridges between platinum and another metal present in higher concentration (e.g., $Cu^{2+}$, $Fe^{n+}$).

In agreement with the results of others cited earlier, we have found that coordination of thiolate sulfur to platinum always labilizes coordinated ammonia (presumably initially ammonia trans to sulfur). We have shown qualitatively that this labilization is very dependent on the structure of the thiolate ligand, apparently being maximized when the ligand contains other potential donor atoms so located that they can form a five- or six-membered chelate ring.

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**Registry No.** **1**$(NO_3)_2$, 78022-63-6; **5a**, 120231-68-7; **5b**, 120231-69-8; **5c**, 120231-73-4; **5d**, 120231-72-3; **6**, 120231-70-1; **7**, 120231-71-2; **8**, 120231-74-5; **9a**, 120231-75-6; **9b**, 120231-77-8; **11a**, 120231-76-7; **11b**, 120231-78-9; *cis*-$Pt(^{15}NH_3)_2(ONO_2)_2$, 117228-93-0; $Pt(en)(H_2O)_2^{2+}$, 50475-23-5; $^{195}Pt$, 14191-88-9.

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# Structurally Diverse Manganese(III) Schiff Base Complexes: Chains, Dimers, and Cages

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Manganese(III) forms a rich variety of complexes with the dianion of the Schiff base ligand *N,N'*-disalicylidene-2-hydroxypropylenediamine (2-OH-SALPN) and its ring-substituted derivatives. Single crystals of $[Mn(2\text{-OH-SALPN})OAc]_n$ (**1**) are isolated when manganese(III) acetate is reacted with 2-OH-SALPN, in DMF. This infinite chain shows an anti–anti configuration for the bridging acetates. When **1** is dissolved in methanol and 1 equiv of NaOH is added, a dinuclear $[Mn^{III}_2(2\text{-OH-SALPN})_2(CH_3OH)]\cdot CH_3OH$ complex, **3**, is isolated. X-ray analysis of crystals of the 5-chloro-2-OH-SALPN derivative **4** show this compound to be a monoalkoxy-bridged species with the longest Mn(III)–Mn(III) separation (3.808 Å) yet observed for a discrete single-atom-bridged dimer. If NaOMe is used as a base rather than NaOH, the first example of a totally encapsulated tetrakis(phenolato)–bis(acetato)-caged sodium cation, **5**, is isolated. Two $Mn^{III}$(2-OH-SALPN) units are linked by this sodium ion, forming a bimetallic, trinuclear cluster. The variable-temperature magnetic behavior of these materials shows that spin exchange between the manganese ions is weak or nonexistent [**1**, $J = -1.72$ cm$^{-1}$ and $g = 1.97$; **4**, $J = -3.55$ cm$^{-1}$ and $g = 1.95$; **5**, follows Curie–Weiss law behavior with no evident spin exchange between Mn(III) ions ($g_\parallel = 2.00$, $g_\perp = 2.05$, $D = -6.13$ cm$^{-1}$)]. X-ray crystallographic parameters: **1**, $C_{19}H_{19}N_2O_5Mn$, mol wt 410.3, orthorhombic crystal system (*Pnma*), $a = 6.528$ (4) Å, $b = 16.827$ (6) Å, $c = 16.754$ (6) Å, $V = 1840$ (1) Å$^3$, $Z = 4$, 2054 data collected with $0° < 2\theta < 50°$, 1180 data with $I > 3\sigma(I)$, $R = 0.057$, $R_w = 0.057$; **4**, $C_{36}H_{34}N_4O_8Mn_2Cl_4$, mol wt 900, monoclinic crystal system ($P2_1/c$), $a = 10.944$ (2) Å, $b = 23.275$ (5) Å, $c = 16.047$ (2) Å, $\beta = 99.29$ (1)°, $V = 4034$ (1) Å$^3$, $Z = 4$, 5315 data collected with $0° < 2\theta < 45°$, 3247 data with $I > 2\sigma(I)$, $R = 0.057$, $R_w = 0.045$; **5**, $C_{44}H_{55}N_4O_{18}Mn_2Na$, mol wt 1060, triclinic crystal system ($P\bar{1}$), $a = 9.434$ (5) Å, $b = 10.436$ (4) Å, $c = 12.758$ (8) Å, $\alpha = 94.42$ (4)°, $\beta = 105.50$ (4)°, $\gamma = 91.50$ (4)°, $V = 1205$ (1) Å$^3$, $Z = 1$, 3174 data collected with $0° < 2\theta < 45°$, 2445 data with $I > 3\sigma(I)$, $R = 0.068$, $R_w = 0.068$.

## Introduction

The coordination chemistry of manganese in the +2, +3, and +4 oxidation states is receiving considerable attention due to the biological importance of these ions. It is now firmly established that at least three enzymes (manganese superoxide dismutase,[5] azide insensitive catalase,[6] and the photosynthetic oxygen-evolving complex[7]) use manganese in redox roles at their catalytic center to facilitate the metabolism of the $O_2^{n-}$ unit. All three enzymes probably contain Mn(III) in at least one of their catalytic forms. Therefore, an important area of investigation of the bioinorganic chemistry of manganese is the study of the structure and reactivity of Mn(III) complexes composed of biologically relevant heteroatom donor ligands.

An attractive system for modeling the structure and reactivity of these manganoenzymes is dinuclear Mn(III) complexes containing polydentate Schiff base ligands. Both photochemical water oxidation to generate dioxygen[8] and acid-promoted hydrogen peroxide production[9] have been reported for such dimers. To

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