Synthesis, Characterization, and Reactivity of Platinum Cysteinato and Related Thiolato Complexes: Molecular Structure of $Pt_2(\mu$-*N*-acetyl-L-cysteine-*S*$)_2$(bpy)$_2$

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Reaction of $PtCl_2$(2,2′-bipyridine) (**1**) with equimolar amounts of *N*-acetyl-L-cysteine (L-accysH), mercaptopropanoic acid (mpaH), 2-aminoethanethiol (aetH), or cysteine (cysH) in water at pH 7 leads to the isolation of [$Pt_2(\mu$-L-*S*$)_2$(bpy)$_2$] (L = L-accys (**2**), mpa (**3**), aet (**4**), cys (**5**)). The molecular structure of **2** was determined through a single-crystal X-ray diffraction study. Crystallographic data for **2**·4H_2O: monoclinic *C*2, *Z* = 4, *a* = 19.491(4) Å, *b* = 19.266(4) Å, *c* = 11.494(2) Å, β = 102.88(3)°, *V* = 4208(2) Å^3. The ^{1}H and ^{13}C{^{1}H} NMR spectra of **2**−**5** in D_2O solution are consistent with a μ-S dimeric formulation. The spectra of **2** and **5** are more complex than those of **3** and **4** due to the presence of chiral ligands. The η^2-N,S monomeric complexes Pt(η^2-L-*N,S*)(bpy) (L = aet (**7**), cys (**8**)) are produced upon adjusting an aqueous solution of **4** and **5** to pH 11 or directly from the reaction of **1** with aet or cys at pH 11. Complexes **7** and **8** were characterized through ^{1}H and ^{13}C{^{1}H} NMR spectroscopy. The similar chemical shifts observed in ^{195}Pt NMR spectroscopic studies of the μ-S dimer complexes **2** and **4** are markedly different than that observed for the η^2-N,S monomeric complex **7**. Reaction of **1** with penicillamine (pen) and penicillamine methyl ester (penOMe) in aqueous solution at pH 7 gives rise to $Pt_2(\mu$-pen-*S*$)_2$(bpy)$_2$ (**9**) and $Pt_2(\mu$-penOMe-*S*$)_2$(bpy)$_2$ (**11**), respectively. ^{1}H NMR spectroscopic studies of **9** and **11** indicate the complexes to have μ-S dimeric rather than η^2-N,S or η^2-O,S monomeric structures. Heating an aqueous solution of **5** at 70 °C results in its conversion to the η^2-N,S monomeric complex **8**. In contrast, both **4** and **11** are stable at 80 °C suggesting thermal conversion of **5** to **8** proceeds through deprotonation of the amine group via a N−O proton transfer. Reaction of **1** with pen at pH 11 produces Pt(η^2-pen-*N,S*)(bpy) (**10**). The structural similarity of **10** to **7** and **8** is evident through comparison of the aromatic region of ^{1}H NMR spectra of **10**.

Introduction

A limitation of the use of cisplatin as an antitumor drug is its concentration-dependent nephrotoxicity.[1,2] Binding of platinum to sulfur-functionalized protein residues is generally accepted[3] as the molecular basis of this toxicity. A recent study[4] has also indicated that the chemotherapeutic effect of cisplatin may be partially due to inactivation of DNA polymerase-α as a result of Pt−cysteine binding. In order to gain a more detailed understanding of platinum(II) complexes of biological thiols, there have been a number of studies[5−11] of the reaction of sulfur-containing amino acids with *cis*-$PtCl_2(NH_3)_2$ and *cis*-[$Pt(NH_3)_2(H_2O)_2$]$^{2+}$. However, the structures of the reaction products have not been definitively determined.[12] For example, the initial product of the reaction of *cis*-$PtCl_2(NH_3)_2$ with glutathione (GSH) has been assigned several formulations: monomeric bis(η^2-GS-*N,S*);[5] monomeric (η^1-GS-*S*);[10] dimeric bis(μ-GS-*S*).[9] This ambiguity is partly due to the eventual conversion of these products to μ-S polymers upon labilization of the ammine ligands.[6,9,10] Greater stability has been found with analogous complexes containing less labile, chelating diamines. For example, Srivastava and co-workers[13] have isolated a platinum 2,2′-bipyridine (bpy) cysteinato complex. Similarly, we recently isolated[14] the *N*-acetylcysteinato (accys) complex, $Pt_2(\mu$-accys-*S*$)_2$(bpy)$_2$ (**2**). This complex is the bpy analog of [$Pt_2(\mu$-accys-*S*$)_2(NH_3)_4$]$^{2+}$, which Appleton *et al.*[9] previously generated and studied in solution by multinuclear NMR spectroscopy. In a preliminary communication,[14] we reported a single-crystal X-ray structural determination of **2**, which confirmed the formulation proposed by Appleton *et al.* We have prepared and characterized a series of related platinum bpy complexes. We report here the general structural trends revealed by multinuclear NMR spectroscopic studies and the full details of the single-crystal X-ray structural determination of **2**.

Experimental Section

General Details. The following were purchased from Aldrich Chemical Co. and used without further purification: D-cysteine hydrochloride monohydrate, 3-mercaptopropanoic acid, 2-aminoethanethiol hydrochloride, *N*-acetyl-L-cysteine, 2,2′-dipyridyl, D-penicillamine, and D-penicillamine methyl ester hydrochloride.

The ^{1}H, ^{13}C{^{1}H}, ^{31}P, and ^{195}Pt NMR spectra were recorded on a GN Omega 500 spectrometer at 500.1, 126, and 107.2 MHz, respectively. The ^{1}H NMR data are listed downfield from TMS at 0.00 ppm. The ^{13}C NMR chemical shifts were referenced against an external standard of dioxane, while the ^{195}Pt chemical shifts were referenced with respect to chloroplatanic acid. The ^{31}P chemical shift was referenced with an external standard of phosphoric acid. The optical

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(1) Krakoff, I. H. *Cancer Treat. Rep.* **1979**, *63*, 1523−1525.
(2) Dentno, M.; Luft, F. C.; Yum, N. M.; Williams, S. D.; Einhorn, L. H. *Cancer* **1978**, *41*, 1274−1281.
(3) Borch, R. F.; Pleasants, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 6611−6614.
(4) Kelley, T. J.; Moghaddas, S.; Bose, R.; Basu, S. *Cancer Biochem. Biophys.* **1993**, *13*, 135−146.
(5) Odenheimer, B.; Wolf, W. *Inorg. Chim. Acta* **1982**, *66*, L41-L43.
(6) Dedon, P. C.; Borch, R. F. *Biochem. Pharmacol.* **1987**, *36*, 1955−1964.
(7) Corden, B. J. *Inorg. Chim. Acta* **1987**, *137*, 125−130.
(8) Lempers, E. L. M.; Inagaki, K.; Reedijk, J. *Inorg. Chim. Acta* **1988**, *152*, 201−207.
(9) Appleton, T. G.; Connor, J. W.; Hall, J. R.; Prenzler, P. D. *Inorg. Chem.* **1989**, *28*, 2030−2037.
(10) Berners-Price, S. J.; Kuchel, P. W. *J. Inorg. Biochem.* **1990**, *38*, 305−325.
(11) Djuran, M. I.; Lempers E. L. M.; Reedijk, J. *Inorg. Chem.* **1991**, *30*, 2648−2652.
(12) Lempers E. L. M.; Reedijk, J. *Adv. Inorg. Chem.* **1991**, *37*, 175−217.
(13) Kumar, L.; Kandasamy, N. R.; Srivastava, T. S. *Inorg. Chim. Acta* **1982**, *67*, 139−143.
(14) Mitchell, K. A.; Streveler, K. C.; Jensen, C. M. *Inorg. Chem.* **1993**, *32*, 2608−2609.

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rotation of **2** was measured on a Jasco DIP-370 digital polarimeter. Conductivity measurements were performed with an Orian 122 conductivity meter.

Preparation of Pt(bpy)Cl$_2$ (1). A solution of $K_2[PtCl_4]$ (2.00 g, 4.81 mmol) and 2,2′-bipyridine (0.754 g, 4.81 mmol) in water (100 mL) is refluxed for 0.5 h. The resulting orange precipitate was isolated by filtration, washed with diethyl ether (3 × 15 mL), and vacuum dried (1.76 g, 86% yield).

Preparation of Pt$_2$(μ-accys-*S*)$_2$(bpy)$_2$ (2). A solution of *N*-acetyl-L-cysteine hydrochloride (0.076 g, 4.81 mmol) in water (5 mL) is brought to pH 11.0 with 1 M KOH. $PtCl_2$(2,2′-bipyridine) (0.200 g, 4.81 mmol) is added to the solution and the resulting suspension stirred at 25 °C for 5 days. The solution is filtered and treated with acetone (80 mL) followed by diethyl ether (90 mL). Upon 3 days of standing, light yellow crystals arise from the dark brown oil which separated below the clear solution (0.150 g, 62% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 8.75 (br s, 1H), 8.62 (br s, 1H), 8.28 (m, 2H), 8.12 (m, 2H), 7.82 (m, 1H), 7.76 (m, 1H) (8H, aromatic); 4.32 (br m, SCH_2CH); 3.59, 3.20 (br m, SCH_2); 1.62 (s, $NHC(O)CH_3$). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) (δ): 1.75.0 (*C*(O)O); 174.4 (*C*(O)CH_3); 155.9, 148.0, 130.1, 126.0 (aromatic); 56.0 (SCH_2CH); 38.1 (SCH_2); 22.7 ($NHC(O)CH_3$). ^{195}Pt NMR (107.2 MHz, D_2O) (δ): −2909 ppm. $[\alpha]^{25}$: +0.63.

Preparation of Pt$_2$(μ-mpa-*S*)$_2$(bpy)$_2$ (3). A solution of 3-mercaptopropanoic acid (8.40 μL, 2.41 mmol) in water (2 mL) is brought to pH 11.0 with 1 M KOH. $PtCl_2$(2,2′-bipyridine) (0.100 g, 2.41 mmol) is added to the solution and the resulting suspension stirred at 65 °C for 5 h. The yellow solution is filtered and treated with acetone (100 mL). The resulting yellow precipitate is isolated by filtration and washed with acetone (3 × 15 mL) and diethyl ether (5 × 10 mL) (0.011 g, 10% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 8.73 (d, 2H), 8.32 (t, 2H), 8.15 (d, 2H), 7.81 (t, 2H) (8H, aromatic); 3.24 (t, J_{H-H} = 6 Hz, SCH_2); 2.74 (t, J_{H-H} = 6.5 Hz, $CH_2C(O)O$). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) (δ): 175.1 (*C*(O)O); 154.9, 146.7, 142.6, 128.9, 124.8 (aromatic); 34.9 (SCH_2); 31.4 ($CH_2C(O)O$).

Preparation of [Pt$_2$(μ-aet-*S*)$_2$(bpy)$_2$][2Cl] (4). $PtCl_2$(2,2′-bipyridine) (0.200 g, 4.81 mmol) is added to a solution of 2-aminoethanethiol hydrochloride (0.054 g, 4.81 mmol) in water (10 mL). The resulting suspension is stirred at 55 °C for 3.5 h. The yellow solution is filtered and treated with acetone (200 mL). The resulting orange precipitate is isolated by filtration and washed with acetone (5 × 10 mL) and absolute ethanol (5 × 10 mL). Following purification on a Sephadex G-10 column, the product is recrystallized from acetone/water and dried under high vacuum (0.203 g, 46% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 8.71 (d, 2H), 8.27 (t, 2H), 8.14 (d, 2H), 7.81 (t, 2H) (8H, aromatic); 3.53 (m, SCH_2); 3.20 (m, CH_2NH). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) (δ): 156.2, 147.9, 144.2, 130.4, 126.1 (aromatic); 40.8 (SCH_2); 32.6 (CH_2NH_2). ^{195}Pt NMR (107.2 MHz, D_2O) (δ): −2895 ppm. Λ_M = 310 cm^2 Ω^{-1} mol^{-1}.

Preparation of Pt$_2$(μ-cys-*S*)$_2$(bpy)$_2$ (5). Under an atmosphere of nitrogen, $PtCl_2$(2,2′-bipyridine) (0.200 g, 4.81 mmol) is added to a solution of D-cysteine hydrochloride (0.076 g, 4.35 mmol) in water (2 mL). The resulting suspension is stirred at 25 °C for 17 h. The orange solution is filtered and placed on a Sephadex G-10 column. The product is precipitated with acetone (100 mL) and isolated by filtration. Following acetone washings (3 × 15 mL), the product is dried under high vacuum (0.016 g, 73% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 9.06 (d, 2H), 8.68 (br m, 2H), 8.31 (m, 4H), 8.18 (d, 4H), 7.90 (m, 2H), 7.81 (m, 2H), (8H, aromatic); 3.76 (t, J_{H-H} = 5.9 Hz, SCH_2CH); 3.52 (m, SCH_2). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) (δ): 172.0 (*C*(O)O); 156.3, 156.0, 149.1, 147.8, 144.0, 130.2, 126.0 (aromatic); 54.5 (SCH_2CH); 36.8 (SCH_2). Λ_M = 16 cm^2 Ω^{-1} mol^{-1}.

Preparation of Pt$_2$(μ-mpa-*S*)$_2$(P(CH$_3$)$_3$)$_4$ (6). $PtCl_2(P(CH_3)_3)_2$ (0.100 g, 2.41 mmol) is added to a solution of 3-mercaptopropanoic acid (21.0 μL, 2.41 mmol) in water (10 mL). The resulting suspension is stirred at 25 °C for 1.5 h. The light yellow solution is filtered and treated with acetone (50 mL) followed by diethyl ether (50 mL). The light brown oil which separates beneath the clear solution is isolated and dried under high vacuum to an off-white powder (0.095 g, 43% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 3.26 (br m, SCH_2); 3.19 (d, J_{H-H} = 4.2 Hz, $CH_2C(O)O$); 1.65 (d, J_{P-H} = 9.9 Hz, $P(CH_3)_3$. ^{31}P NMR (202.4 MHz, D_2O) (δ): −15.9 ($P(CH_3)_3$, J_{P-Pt} = 1417 Hz).

Preparation of [Pt(η^2-aet-*N,S*)(bpy)][Cl] (7). A solution of 2-aminoethanethiol hydrochloride (0.027 g, 2.41 mmol) in water (10 mL) is brought to pH 11.0 with 1 M KOH. $PtCl_2$(2,2′-bipyridine) (0.100 g, 2.41 mmol) is added to the solution and the resulting suspension stirred at 35 °C for 24 h. The red solution is treated with acetone (100 mL) and filtered. The precipitate is discarded, and the filtrate is treated with additional acetone (50 mL) and allowed to stand at 0 °C for 12 h. The red precipitate is then isolated by filtration and washed with acetone (3 × 15 mL). The crude product is purified on a Sephadex G-10 column, recrystallized from acetone/water, and dried under high vacuum (0.097 g, 88% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 8.58 (d, 1H), 8.52 (d, 1H), 8.19 (t, 1H), 8.05 (m, 2H), 7.97 (d, 1H), 7.66 (t, 1H), 7.41 (t, 1H) (8H, aromatic); 2.96 (t, J_{H-H} = 9.1 Hz, J_{Pt-H} = 60 Hz, SCH_2); 2.32 (t, J_{H-H} = 6.1 Hz, CH_2NH_2). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) (δ): 157.1, 154.7, 152.9, 149.1, 141.9, 141.4, 130.1, 129.5, 125.2, 125.0 (aromatic); 55.3 (SCH_2); 27.6 (CH_2NH_2). ^{195}Pt NMR (107.2 MHz, D_2O) (δ): −3178 ppm. Λ_M = 153 cm^2 Ω^{-1} mol^{-1}.

Preparation of Pt(η^2-cys-*N,S*)(bpy) (8). A solution of **5** (0.050 g, 0.531 mmol) in water (10 mL) is heated at 70 °C for 30 min. The yellow solution is filtered and treated with acetone (100 mL). The resulting yellow precipitate is isolated by filtration and purified on a Sephadex G-10 column. The product is recrystallized from acetone/water and dried under high vacuum (0.018 g, 72% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 8.74 (d, 1H), 8.64 (d, 1H), 8.24 (t, 1H), 8.18 (d, 1H), 8.13 (d, 2H), 7.71 (t, 1H), 7.49 (t, 1H), (8H, aromatic); 3.97 (t, J_{H-H} = 5.9 Hz, J_{Pt-H} = 45 Hz, SCH_2CH); 2.72, 2.64 (dd, $^2J_{H-H}$ = −12.7 Hz, $^3J_{H-H}$ = 4.83 Hz, $^2J_{H-H}$ = −12.5 Hz, $^3J_{H-H}$ = 7.1 Hz, SCH_2). $^{13}C\{^1H\}$ NMR (300 MHz, D_2O) (δ): 173.8 (*C*(O)O); 157.5, 155.1, 152.6, 149.2, 142.1, 141.5, 129.8, 129.4, 125.1, 125.0 (aromatic); 67.1 (SCH_2CH); 29.3 (SCH_2). Λ_M = 18 cm^2 Ω^{-1} mol^{-1}.

Preparation of Pt$_2$(μ-pen-*S*)$_2$(bpy)$_2$ (9). Under an atmosphere of nitrogen, $PtCl_2$(2,2′-bipyridine) (0.100 g, 2.41 mmol) is added to a solution of D-penicillamine (0.035 g, 2.41 mmol) in water (5 mL). The resulting suspension is stirred at 25 °C for 72 h. The orange oil is treated with acetone (100 mL). The resulting yellow precipitate is isolated by filtration and washed with acetone (3 × 15 mL) and dried under high vacuum (0.058 g, 46% yield). ^{1}H NMR (500 MHz, MeOD) (δ): 9.42 (d, 1H), 8.73 (d, 1H), 8.62 (d, 1H), 8.48 (m, 2H), 8.18 (t, 1H), 7.88 (t, 1H), 7.25 (t, 1H) (8H aromatic); 4.82 (s, $SC(CH_3)_2CH$); 1.99, 1.35 (s, $(CH_3)_2$). $^{13}C\{^1H\}$NMR (126 MHz, MeOD) (δ): 171.2 (C(O)O); 158.2, 156.8, 153.9, 150.1, 142.6, 142.5, 129.4, 128.9, 125.5, 125.4 (aromatic); 71.2 ($SC(CH_3)_2$); 52.0 ($CH(NH_2)(C(O)O)$); 29.9, 25.9 ($(CH_3)_2$).

Preparation of Pt(η^2-pen-*N,S*))(bpy) (10). Under a nitrogen atmosphere, a solution of D-penicillamine (0.035 g, 2.41 mmol) in water (2 mL) is brought to pH 11.0 with 1 M KOH. $PtCl_2$(2,2′-bipyridine) (0.100 g, 2.41 mmol) is added to the solution and the resulting suspension stirred at 25 °C for 72 h. The bright red solution is filtered and treated with acetone (100 mL) followed by diethyl ether (100 mL) and allowed to stand for 24 h. The resulting red precipitate is isolated by filtration and washed with cold diethyl ether (5 × 15 mL). The crude product is purified on a Sephadex G-10 column, recrystallized from acetone/diethyl ether/water, and dried under high vacuum (0.086 g, 66% yield). ^{1}H NMR (500 MHz, D_2O) (δ): 8.55 (d, 1H), 8.32 (d, 1H), 8.11 (t, 1H), 8.04 (d, 1H), 7.95 (d, 2H), 7.64 (t, 1H), 7.30 (m, 1H) (8H, aromatic); 3.23 (s, $CH(NH_2)(C(O)O)$); 1.50, 1.25 (s, $SC(CH_3)_2$). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) (δ): 173.7 (*C*(O)O); 156.3, 153.8, 151.1, 147.7, 140.8, 140.3, 128.7, 128.2, 124.0, 123.9 (aromatic); 75.3 ($SC(CH_3)_2$); 45.4 ($CH(NH_2)(C(O)O)$); 28.9, 27.9 ($SC(CH_3)_2$). Λ_M = 60 cm^2 Ω^{-1} mol^{-1}.

Preparation of [Pt$_2$(μ-penOMe-*S*))$_2$(bpy)$_2$]Cl$_2$ (11). Under an atmosphere of nitrogen, $PtCl_2$(2,2′-bipyridine) (0.200 g, 4.81 mmol) is added to a solution of D-penicillamine methyl ester hydrochloride (0.084 g, 4.35 mmol) in water (2 mL). The resulting suspension is stirred at 25 °C for 48 h. The bright orange solution is filtered and treated with acetone (5 mL) followed by diethyl ether (100 mL). The orange oil which separates beneath the clear solution is placed on a Sephadex G-10 column. The product is recrystallized from acetone/diethyl ether/water, and dried under high vacuum. (0.130 g, 56% yield). ^{1}H NMR (500 MHz, MeOD) (δ): 9.35 (d, 1H), 8.90 (d, 1H), 8.73 (d, 1H), 8.63 (m, 1H), 8.50 (m, 2H), 8.17 (t, 1H), 7.90 (m, 1H)) (8H, aromatic); 7.20 (t, 1H), 6.83 (t, 1H) (NH_2); 4.60 (s, $CH(NH_2)(C(O)OCH_3)$); 3.84 (s, $C(O)OCH_3$)); 1.96, 1.34 (s, $SC(CH_3)_2$. $^{13}C\{^1H\}$ NMR (126 MHz, MeOD) (δ): 170.4 ($C(O)OCH_3$); 158.1, 156.7, 153.8, 149.9, 142.7,

Table 1. Summary of Crystal Data for **2**·4 H_2O

formula	$Pt_2C_{30}N_6O_{10}S_2H_{30}$
fw	1072.9
cryst dimens, mm	0.5 × 0.1 × 0.1
cryst system	monoclinic
space group	*C*2 (No. 5)
a, Å	19.491(4)
b, Å	19.266(4)
c, Å	11.494(2)
β, deg	102.88(3)
V, Å^3	4208(2)
Z	4
ϱ_{calc}, g/cm^3	1.719
λ, Å (Mo Kα radiation)	0.710 73
T, K	298
scan type	ω
scan rate, deg/min	2.0−29.3
2θ range, deg	3.0−45.0
μ, mm^{-1}	6.794
max, min transm coeff	0.977, 0.616
extinction corr	N/A
reflcns collcd	2542
indpdt reflcns	2372
unique data with $I > 1\sigma(I)$	2335
R,[a] %	6.68
R_w,[b] %	10.71
goodness of fit[c]	1.24

[a] $R = \sum||F_o| - |F_c||/\sum F_o$. [b] $R_w = [w\sum(|F_o| - |F_c|)^2/\sum w F_o^2)]^{1/2}$. [c] GOF $= [w\sum(|F_o| - |F_c|)^2/N_o - N_v)]^{1/2}$.

142.5, 129.4, 128.9, 125.6, 125.4 (aromatic); 71.5 (*S*C(CH$_3$)$_2$); 53.3 (*C*H(NH$_2$)(C(O)OCH$_3$)); 64.0 (C(O)O*C*H$_3$)); 31.1, 25.6 (SC(*C*H$_3$)$_2$). Λ_M = 244 cm^2 Ω^{-1} mol^{-1}.

Crystallographic Studies. Crystals of **2** suitable for X-ray diffraction were obtained by slow evaporation of an acetone/diethylether/water solution of **2**. The crystal was mounted on glass fiber with epoxy. Centering and data collection were performed on a Nicolet P3 automated diffractometer. The unit cell parameters were obtained by least-squares refinement of the setting angles of 20 reflections. Crystal and instrument instability were monitored with a set of three standard reflections measured every 97 reflections, with no significant deviations. An ellipsoid semiempirical absorption correction was applied. Details of other crystal data and relevant information is listed in Table 1.

The structure was initially solved in the centrosymmetric space group *C*2/*m* using a model in which the chiral β-carbon of the accys ligand was thermally disordered over two positions.[14] An equal number of D and L *N*-acetylcysteinato ligands are contained in this model. However, subsequent optical rotation experiments showed complete retention of the L configuration of *N*-acetyl-L-cysteine upon coordination. The only major violation of the mirror symmetry imposed by the centrosymmetric space group is the position of the relatively light β-carbons. However, in accordance with the established optical activity of the complex, the structure was redetermined in the noncentrosymmetric space group *C*2.[15] The structure was solved by using the direct methods program SHELX PLUS (Nicolet Instrument Corp.) and refinement by full matrix least-squares procedures. The platinum and sulfur atoms were refined with anisotropic temperature coefficients, and the remaining atoms were refined isotropically. During the refinement, four peaks not associated with the platinum complex became apparent in the difference Fourier maps. The peaks were refined anisotropically as the oxygens of water solvates. All hydrogen atoms were introduced at fixed calculated positions, and their coordinates were allowed to vary in the final cycle of full-matrix least-squares refinement.

Results and Discussion

Diplatinum Bis(μ-thiolato) Complexes. Reaction of $PtCl_2$(2,2′-bipyridine) (**1**) with equimolar amounts of L-accysH, mercaptopropanoic acid (mpaH), 2-aminoethanethiol (aetH), or cysteine (cysH) in water at pH 7 leads to the isolation of [Pt_2(μ-L-*S*$)_2$(bpy)$_2$] (L = L-accys (**2**), mpa (**3**), aet (**4**), cys (**5**)) as seen in Scheme 1. Complexes **2** and **3** are obtained in superior yield through reaction at pH 11.

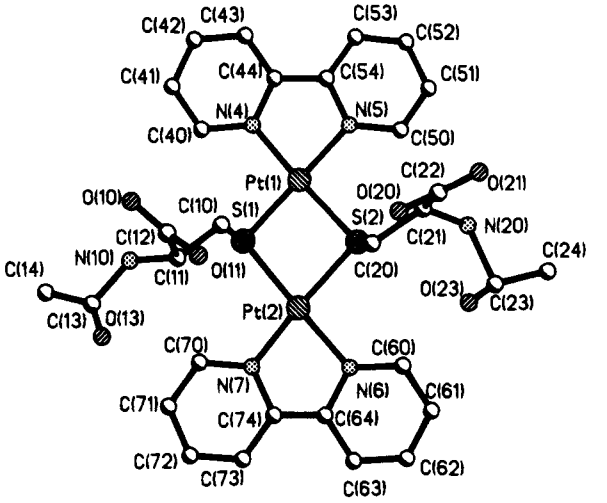

Figure 1. Projection of Pt_2(μ-L-accys-*S*$)_2$(bpy)$_2$ (**2**) with thermal ellipsoids at arbitrary radii. The hydrogen atoms have been omitted for clarity.

Scheme 1

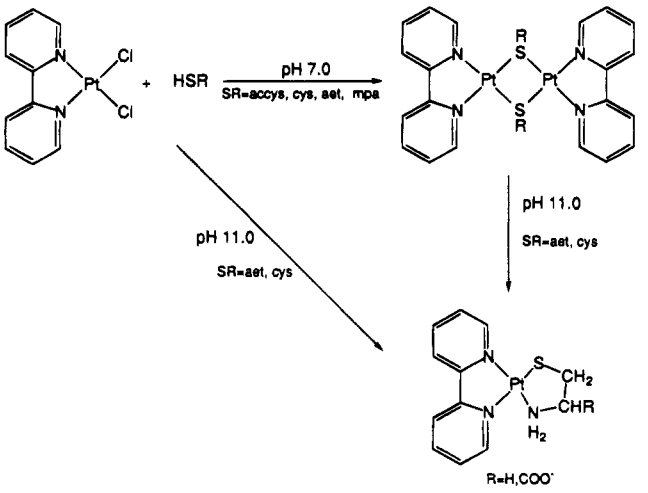

Table 2. Bond lengths (Å) for **2**·4H_2O

Pt(1)−N(4)	2.010 (16)	C(22)−O(20)	1.304 (46)
Pt(1)−N(5)	2.017(30)	C(22)−O(21)	1.135(37)
Pt(1)−S(2)	2.328(10)	N(20)−C(23)	1.668(53)
Pt(1)−S(1)	2.253(14)	O(23)−C(23)	1.097(60)
Pt(2)−N(6)	2.061(25)	S(1)−C(10)	1.856(28)
Pt(2)−N(7)	1.959(21)	C(10)−C(11)	1.495(38)
Pt(2)−S(2)	2.330(10)	C(11)−C(12)	1.622(50)
Pt(2)−S(1)	2.281(14)	C(11)−N(10)	1.393(39)
C(44)−C(54)	1.427(37)	C(12)−O(10)	1.137(43)
C(64)−C(74)	1.338(36)	C(12)−O(11)	1.218(52)
S(2)−C(20)	1.928(39)	N(10)−C(13)	1.432(45)
C(20)−C(21)	1.550(47)	C(13)−O(13)	1.182(50)
C(21)−C(22)	1.538(49)	C(13)−C(14)	1.370(54)
C(21)−N(20)	1.397(45)	C(23)−C(24)	1.661(81)

The molecular structure of **2** was determined through a single-crystal X-ray diffraction study. A diagram of the obtained structure is seen in Figure 1. Selected bond distances and angles are listed in Tables 2 and 3, respectively. The final fractional atomic coordinates are given in Table 4. The heavy atom framework is identical to that which has been proposed by Appleton *et al.* on the basis of multinuclear NMR spectroscopic studies[9] for the species initially formed in the reaction between *cis*-$PtCl_2(NH_3)_2$ and model protein cysteine residue compounds including GSH and accysH. The reaction of [Pt(dien)Cl]$^+$ (dien

(15) The reanalysis of the X-ray data and optical rotation measurement were prompted by a communication received from Professor Ivan Bernal (Department of Chemistry, University of Houston) subsequent to the publication of ref 14.

Table 3. Bond Angles (deg) for **2**·4H_2O

N(4)−Pt(1)−N(5)	81.2(10)	N(4)−Pt(1)−S(2)	177.5(5)
N(5)−Pt(1)−S(2)	96.4(9)	N(4)−Pt(1)−S(1)	99.7(6)
N(5)−Pt(1)−S(1)	176.2(11)	S(2)−Pt(1)−S(1)	82.8(5)
N(6)−Pt(2)−N(7)	79.7(10)	N(6)−Pt(2)−S(2)	96.6(8)
N(7)−Pt(2)−S(2)	176.3(7)	N(6)−Pt(2)−S(1)	178.4(8)
N(7)−Pt(2)−S(1)	101.5(7)	S(2)−Pt(2)−S(1)	82.1(4)
C(43)−C(44)−C(54)	125.9	N(4)−C(44)−C(54)	113.6
Pt(1)−N(4)−C(40)	124.2(5)	Pt(1)−N(4)−C(44)	115.0(5)
C(44)−C(54)−C(53)	122.2	C(44)−C(54)−N(5)	117.0
Pt(1)−N(5)−C(50)	127.1(9)	Pt(1)−N(5)−C(54)	112.8(9)
C(63)−C(64)−C(74)	122.5	N(6)−C(64)−C(74)	117.4
Pt(2)−N(6)−C(60)	128.6(7)	Pt(2)−N(6)−C(64)	111.2(7)
C(64)−C(74)−C(73)	124.7	C(64)−C(74)−N(7)	115.3
Pt(2)−N(7)−C(70)	124.0(6)	Pt(2)−N(7)−C(74)	115.8(6)
Pt(1)−S(2)−Pt(2)	95.1(4)	Pt(1)−S(2)−C(20)	109.0(11)
Pt(2)−S(2)−C(20)	93.4(10)	S(2)−C(20)−C(21)	106.8(24)
C(20)−C(21)−C(22)	114.7(29)	C(20)−C(21)−N(20)	116.3(27)
C(22)−C(21)−N(20)	110.8(28)	C(21)−C(22)−O(20)	109.8(28)
C(21)−C(22)−O(21)	126.1(31)	O(20)−C(22)−O(21)	123.8(33)
C(21)−N(20)−C(23)	116.7(29)	Pt(1)−S(1)−Pt(2)	98.6(7)
Pt(1)−S(1)−C(10)	100.5(9)	Pt(2)−S(1)−C(10)	105.6(9)
S(1)−C(10)−C(11)	120.1(18)	C(10)−C(11)−C(12)	106.7(23)
C(10)−C(11)−N(10)	117.5(27)	C(12)−C(11)−N(10)	110.6(25)
C(11)−C(12)−O(10)	116.8(33)	C(11)−C(12)−O(11)	112.4(30)
O(10)−C(12)−O(11)	130.6(40)	C(11)−N(10)−C(13)	125.0(28)
N(10)−C(13)−O(13)	111.8(34)	N(10)−C(13)−C(14)	113.6(32)
O(13)−C(13)−C(14)	131.2(38)	N(20)−C(23)−O(23)	106.3(39)
N(20)−C(23)−C(24)	91.5(32)	O(23)−C(23)−C(24)	161.1(50)

= diethylenetriamine) and GSH has also been proposed to yield a (μ-thiolato)diplatinum complex.[16] The unusual syn orientation of the accys ligands probably is adopted in order to establish the observed hydrogen bonding interactions with the water solvates. The *N*-acetylcysteinato ligand was found to retain the same L configuration as the free ligand. The optical activity of **2** was verified through the polarimetric observation of an optical rotation ($[\alpha]^{25} = +0.63$).

The aromatic region of the ^{1}H NMR spectra of **3** and **4** in D_2O solution consist of the expected 1:1:1:1 four resonance pattern seen in Figure 2. The aromatic region of the $^{13}C\{^1H\}$ NMR spectra of both complexes contain the expected 5 resonances. The ^{1}H and ^{13}C NMR spectra of **2** and **5** are more complex. As seen in Figure 3, a six resonance patterns with 1:1:2:2:1:1 intensity ratios are observed in the aromatic region of the ^{1}H NMR spectra of **2** and **5**. Similarly, the aromatic region of the $^{13}C\{^1H\}$ NMR spectra of **2** and **5** demonstrates that the two pyridine rings of the bpy ligands are rendered inequivalent by the presence of chiral centers in the ligands.

The similarity of the platinum coordination environments of **2** and **4** is demonstrated by ^{195}Pt NMR spectroscopy. As seen in Table 5, comparable chemical shifts of −2909 and −2895 ppm are observed for the resonances for **2** and **4**, respectively. Unfortunately, low solubility of **3** in D_2O prohibited determination of its ^{195}Pt NMR spectrum for comparison. However, the diplatinum bis(μ-thiolato) formulation of the closely related mpa complex [$Pt_2(\mu$-mpa-*S*$)_2(PMe_3)_4$] (**6**) was established by ^{1}H and ^{31}P NMR spectroscopy. The ^{1}H NMR spectrum of **6** shows one doublet (J_{P-H} = 9.9 Hz) corresponding to the equivalent methyl protons on the trimethylphosphine ligands. The dimeric formulation was confirmed by ^{31}P NMR which shows a single resonance at −15.9 ppm as would be expected in a dimeric complex in which both phosphines are equivalent.

The ^{1}H NMR spectra of **2**−**6** provide a further indication that the thiolate ligands of these complexes have the same mode of coordination. As seen in Table 5, the α hydrogens of the thiolate ligands of all 5 complexes are observed at a similar chemical shift. These resonances as well as those observed for the aromatic protons of the complexes are noticably broadened.

(16) Lempers E. L. M.; Reedijk, J. *Inorg. Chem.* **1990**, *29* 217−222.

Table 4. Atomic Coordinates (×10^4 Å) and Equivalent Isotropic Displacement Coefficients (Å^2) for **2**·4H_2O

	x	*y*	*z*	*U*
Pt(1)	1500(1)	0	6260(1)	47(1)
Pt(2)	416(1)	−21(1)	3457(1)	50(1)
C(40)	1885(10)	−1376(9)	7497(14)	23(7)
C(41)	2286	−1787	8397	36(8)
C(42)	2715	−1476	9394	71(14)
C(43)	2744	−754	9492	60(13)
C(44)	2342	−343	8593	44(11)
N(4)	1913	−654	7595	43(8)
C(50)	1909(18)	1421(17)	7408(26)	113(21)
C(51)	2243	1834	8365	152(30)
C(52)	2649	1526	9388	101(20)
C(53)	2721	806	9456	80(16)
C(54)	2386	393	8499	79(16)
N(5)	1981	701	7476	62(11)
C(60)	−84(15)	1400(14)	2244(21)	55(10)
C(61)	−443	1784	1268	94(17)
C(62)	−826	1444	258	105(20)
C(63)	−850	721	225	101(20)
C(64)	−491	337	1202	91(19)
N(6)	−108	677	2211	68(12)
C(70)	−120(13)	−1380(12)	2409(17)	78(14)
C(71)	−481	−1798	1480	68(12)
C(72)	−856	−1495	427	58(11)
C(73)	−871	−774	303	39(10)
C(74)	−511	−357	1231	38(9)
N(7)	−135	−660	2285	49(9)
S(2)	1047(5)	797(6)	4764(7)	37(4)
C(20)	1726(17)	944(18)	3798(30)	60(9)
C(21)	2157(17)	1597(18)	4299(30)	64(9)
C(22)	2823(15)	1716(15)	3818(26)	41(7)
O(20)	2910(16)	1199(18)	3130(28)	109(10)
O(21)	3162(12)	2201(12)	3947(20)	60(6)
N(20)	1777(14)	2213(14)	4282(25)	64(8)
O(23)	1494(16)	2151(18)	2287(27)	107(10)
O(30)	2093(13)	100(19)	1673(19)	89(11)
O(40)	636(21)	3667(51)	−188(73)	480(76)
O(50)	4512(12)	2287(17)	3945(26)	93(12)
O(60)	4080(13)	1205(23)	2153(32)	132(17)
S(1)	1024(6)	−775(9)	4840(10)	77(7)
C(10)	1814(12)	−1025(12)	4286(20)	19(5)
C(11)	1759(16)	−1569(16)	3341(27)	52(8)
C(12)	2531(18)	−1629(18)	3038(30)	56(8)
O(10)	2887(15)	−2061(16)	3501(24)	83(8)
O(11)	2610(18)	−1219(19)	2272(31)	123(11)
N(10)	1514(13)	−2221(12)	3578(23)	45(6)
C(13)	1176(22)	−2707(20)	2690(36)	69(10)
O(13)	1191(13)	−2520(14)	1716(23)	76(7)
C(14)	1101(21)	−3355(19)	3134(33)	61(9)
C(23)	1409(23)	2537(26)	2942(42)	84(13)
C(24)	1246(36)	3287(32)	3541(51)	145(24)

A possible explantion of this broadening is that, in solution, syn and anti conformers of the complexes are interconverting on the NMR time scale.

Formation of N,S Chelate Complexes. N,S chelate complexes are produced upon adjusting an aqueous solution of the μ-S dimer complexes **4** and **5** to pH 11 or directly from the reaction of **1** with aet or cys at pH 11. The complexes Pt(η^2-L-*N,S*)(bpy) (L = aet (**7**), cys (**8**)) were characterized through NMR spectroscopy in aqueous solution at pH 7. Chelation of the aet ligand in **7** is evident by observation of ^{195}Pt (J_{Pt-H} = 60 Hz) satellites on the ^{1}H NMR resonance of the methylene protons α to the nitrogen. Unlike **7**, ^{195}Pt satellites are not observed for the proton α to the nitrogen at 20 °C in the 500 MHz ^{1}H NMR spectrum of **8**. Broadening of the satellite resonances is expected as a result of enhanced chemical shift anisotropy relaxation at the high magnetic field.[17] Heating the sample to 80 °C alleviates this problem, and the ^{195}Pt satellites (J_{Pt-H} = 50 Hz) are observed. As seen in Figure 4, the aromatic

(17) Lallemand, J.-Y.; Soulie, J.; Chottard, J.-C. *J. Chem. Soc., Chem. Commun.* **1980**, 436.

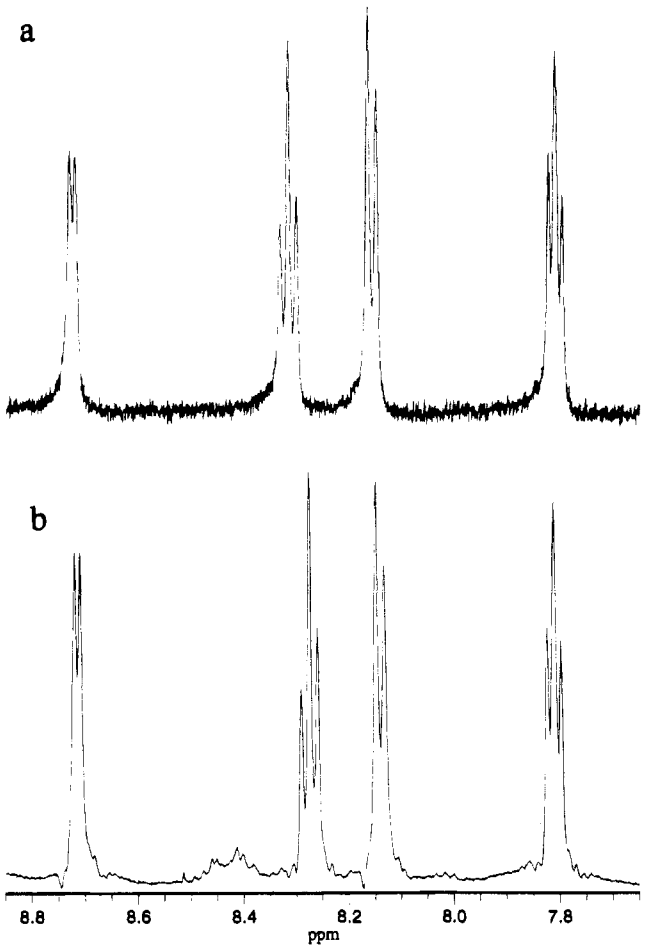

Figure 2. ^{1}H NMR spectra (500 MHz) of the aromatic region of (a) $Pt_2(\mu$-mpa-*S*$)_2$(bpy)$_2$ (**3**) and (b) $Pt_2(\mu$-aet-*S*$)_2$(bpy)$_2$ (**4**) in D_2O solution.

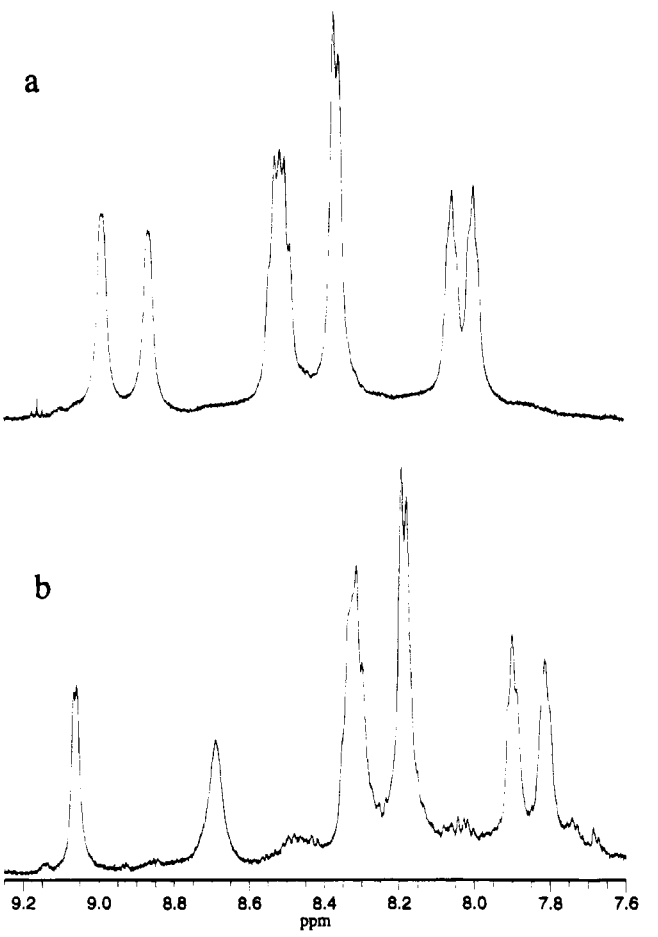

Figure 3. ^{1}H NMR spectra (500 MHz) of the aromatic region of (a) $Pt_2(\mu$-L-accys-*S*$)_2$(bpy)$_2$ (**2**) and (b) $Pt_2(\mu$-cys-*S*$)_2$(bpy)$_2$ (**5**) in D_2O solution.

region of the ^{1}H NMR spectra of **7** and **8** show that the pyridine rings of the bpy ligands are inequivalent due to asymmetry in the immediate coordination sphere of the platinum. This inequivalance is apparent in the $^{13}C\{^1H\}$ NMR of these complexes. Additional verification that complexes of a different structural type are obtained via the coordination of aet and cys at pH 11 is seen in Table 5. The ^{195}Pt NMR of **7** shows a single resonance at −3178 ppm. This chemical shift is quite different from those observed for the dimeric complexes **2** and **4**. The chemical shifts of the thiol α hydrogens observed in the ^{1}H NMR spectra of **7** and **8** are also markedly different from those observed for **2**−**6**.

Chelation of the N,S donor ligands clearly requires deprotonation of the amine group. In contrast to **4**, heating an aqueous solution of **5** at 70 °C for 5 min results in its conversion to the N,S chelate complex **8**. Evidently, this conversion involves the transfer of a proton from nitrogen to oxygen. This mechanism of deprotonation is not available to the μ-S dimer **4** thus accounting for its stability at 70 °C in aqueous solution at pH 7.

Srivastava and co-workers have reported[13] that a chelate complex results from the reaction of cysteine with **1** in methanol. However, they formulate the product as the O-protonated, cationic complex [Pt(η^2-cysH-*N,S*)(bpy)]$^+$. Comparison of the ^{1}H NMR spectra of this product and **8** in D_2O indicate they are the same species. Conductivity experiments in aqueous solution indicate that the complex is the neutral species at pH 7.

Penicillamine. The same reactivity patterns observed for **1** with aet and cysteine are found for penicillamine (pen). Thus reaction in aqueous solution at pH 7 gives rise to $Pt_2(\mu$-pen-*S*$)_2$(bpy)$_2$ (**9**) while Pt(η^2-pen-*N,S*)(bpy) (**10**) is obtained at pH 11. The structural similarity of **10** to **7** and **8** is evident through comparison of the aromatic region of the ^{1}H NMR spectra of **10** as seen in Figure 4. Unlike **7** and **8**, ^{195}Pt satellites were not observed for the ^{1}H NMR resonance of the methine proton of the pen ligand. We were unable to overcome the broadening of these signals due to chemical shift anisotropy relaxation either by heating the sample to 80 °C or by obtaining a spectrum at a lower, 90 MHz, magnetic field.

Table 5. ^{1}H NMR (500 MHz, D_2O) Chemical Shifts (ppm) of Thiol α-Hydrogens and ^{195}Pt NMR (107.2 MHz, D_2O) Chemical Shifts (ppm) for μ-S Dimer and *N,S* Chelate Complexes

complex	$\delta(^1H)$ (ppm) of thiol α hydrogens	$\delta(^{195}Pt)$ (ppm)
[Pt_2(bpy)$_2$(μ-L-accys-*S*)$_2$] (**2**)	3.59, 3.20 (br m)	−2909
[Pt_2(bpy)$_2$(μ-mpa-*S*)$_2$] (**3**)	3.24 (t, J_{H-H} = 6 Hz)	
[Pt_2(bpy)$_2$(μ-aet-*S*)$_2$]$^{+2}$ (**4**)	3.53 (m)	−2895
[Pt_2(bpy)$_2$(μ-cys-*S*)$_2$] (**5**)	3.52 (m)	
[Pt_2($P(CH_3)_3$)$_4$(μ-mpa-*S*)$_2$] (**6**)	3.26 (br m)	
[Pt(bpy)(η^2-aet-*N,S*)]$^+$ (**7**)	2.32 (t, J_{H-H} = 6.1 Hz)	−3178
[Pt(bpy)(η^2-cys-*N,S*)] (**8**)	2.72 (dd, $^2J_{H-H}$ = 12.7 Hz, $^3J_{H-H}$ = 4.83 Hz) 2.64 (dd, $^2J_{H-H}$ = 12.5 Hz, $^3J_{H-H}$ = 7.1 Hz)	

The aromatic region of the ^{1}H NMR spectrum of **9** is shown in Figure 5. This spectrum differs from those observed for **2** and **5** in that there are no accidental resonance overlaps. The greater bulk of the pen ligand may result in an amplification of the spectral effects due to the presence of chiral centers. However, it is important to note that, due to the tendency of **9** to aggregate in aqueous solution, its ^{1}H NMR spectrum was obtained in methanol-d_4 rather than D_2O as was the case for **2** and **5**.

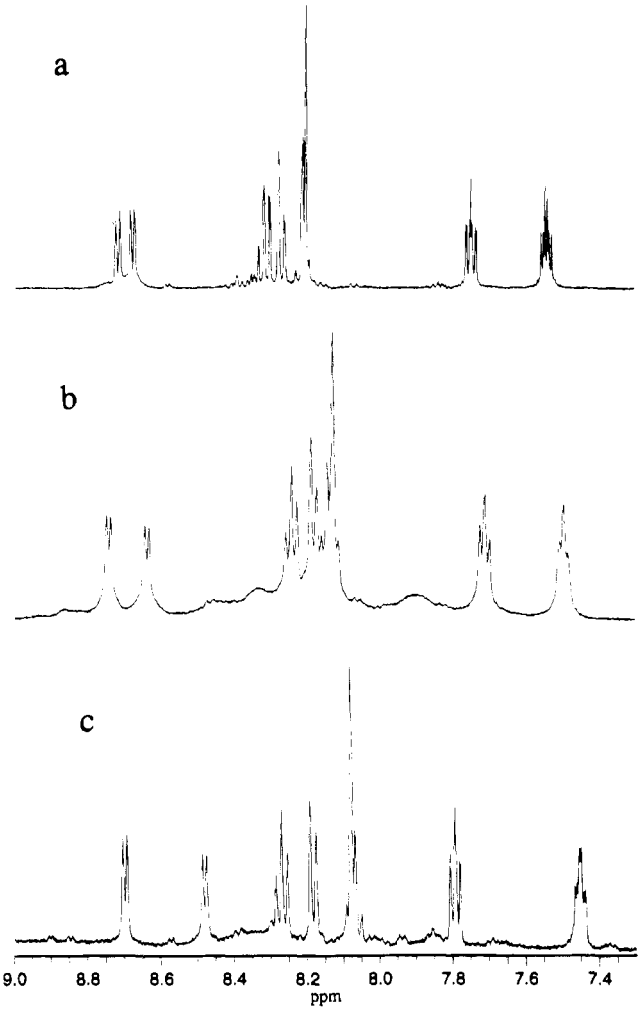

Figure 4. ^{1}H NMR spectra (500 MHz) of the aromatic region of (a) $Pt_2(\eta^2$-aet-*N,S*$)_2(bpy)_2$ (**7**), (b) $Pt_2(\eta^2$-cys-*N,S*$)_2(bpy)_2$ (**8**), and (c) $Pt_2(\eta^2$-pen-*N,S*$)_2(bpy)_2$ (**10**) in D_2O solution.

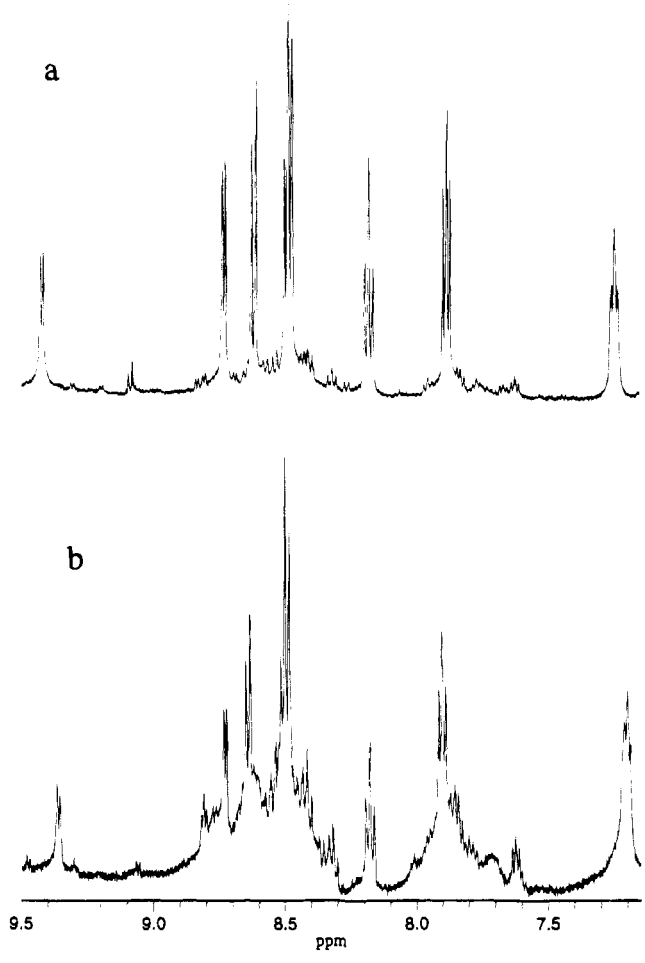

Figure 5. ^{1}H NMR spectra (500 MHz) of the aromatic region of (a) $Pt_2(\mu$-pen-*S*$)_2(bpy)_2$ (**9**) and (b) $Pt_2(\mu$-penOMe-*S*$)_2(bpy)_2$ (**11**) in methanol-d_4 solution.

In view of the spectral differences between **9** and **2**, we considered the possibility that **9** was not a μ-S dimer, but rather a η^2-O,S chelate complex. Appleton *et al.* have proposed[8] that η^2-O,S-coordinated species are among products resulting from the reaction of $[Pt(NH_3)_2(H_2O)_2]^{2+}$ with penicillamine. In order to investigate this possibility, the reaction of **1** with penicillamine methyl ester (penOMe) was explored. As seen in Figure 5, the aromatic region of ^{1}H NMR spectrum of the resulting complex is nearly identical to that observed for **9**. Since O,S chelation is precluded by O-methylation, we conclude that the inequivalance of the bpy pyridine rings in **9** due to the presence of the chiral center in the penicillamine ligand. We therefore assign μ-S dimer structures to both the penicillamine complex **9** and the penicillamine methyl ester complex $Pt_2(\mu$-penOMe-*S*$)_2(bpy)_2$ (**11**).

Complex **11** afforded us an additional opportunity to verify our hypothesis that the thermal conversion of **5** to **8** proceeds through deprotonation of the amine group via proton shift tautomerism. As is the case with **4**, this mechanism of deprotonation is not available to the O-alkylated complex **11**. As expected, no change was observed in the ^{1}H NMR spectrum of a D_2O solution of **11** which was heated to 80 °C for 30 min.

Conclusion

Our results allow for the prediction and identification of the products arising from the reaction of diaminoplatinum complexes with sulfur-containing amino acids. Reaction at pH 7 yields dimeric μ-S products while reaction at pH 11 produces monomeric η^2-*N,S* complexes. Our NMR studies have established that differentiation and assignment of these two structure types can be accomplished on the basis spectroscopic features. We have found that N,S chelation requires deprotonation of the amine group. In addition to pH adjustment, the deprotonation of the nitrogen can be accomplished thermally by the transfer of a proton from nitrogen to oxygen. Finally, while O,S chelate complexes may play intermediate roles in the chemistry of these complexes, such species were not observed in our studies.

Acknowledgment. We gratefully acknowledge the valuable input of Professor Ivan Bernal concerning the crystallographic study of **2** and the assistance of Mr. Wesley Yoshida and Dr. Walt Niemczura with the NMR spectroscopic studies. We thank Johnson Matthey for their generous loan of K_2PtCl_4. This work was supported by the University of Hawaii Research Council.

Supporting Information Available: Tables of anisotropic thermal parameters and H atom coordinates and isotropic displacement coefficients for $Pt_2(\mu$-L-accys-*S*$)_2(bpy)_2$, **2**·4H_2O (2 pages). Ordering information is given on any current masthead page.

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