be strictly metal in character. This appears in the diagram in Figure 6 as a coupling interaction between the bipyridine π-level and one of the metal orbitals (3b). Strong counter-ligand π-bonding effects may serve to decrease the 3b-2b separation. This appears for the Fe(bpy)(DBSQ)(DBCat) and Fe(en)(DBSQ)-(DBCat) complexes as a shift of 100 nm in the lowest energy transition, with this transition appearing at higher energies for the ethylenediamine complex. The only other well-characterized monomeric anionic complex of this series, $Fe(acac)(RCat)_2^-$ (R = $CONHCH_2CO_2Et$),[11] also shows evidence of this effect relative to $Fe(bpy)(Cl_4Cat)_2^-$. Ligand substituent effects contribute to this comparison, but the transition that appears to correspond to the 595-nm band of the bipyridine complex appears at 537 nm for $Fe(acac)(RCat)_2^-$. Fenske's calculations on the $Cr(bpy)(Q)_2$ series show in a dramatic way how metal and quinone orbital energies depend upon the overall charge of the complex. Oxidation of $Cr(bpy)(Cat)_2^-$ to the $Cr(bpy)(SQ)_2^+$ cation results in stabilization of the metal d orbitals with a slight increase in the energy of the quinone π-levels. The effect of this is that increased mixing between metal and quinone levels occurs and, upon oxidation, levels that are largely localized metal and ligand orbitals become separated by only tenths of electronvolts in energy. How this carries over to the related iron series is unclear, but it may be anticipated that the members of the redox series with the closest metal and quinone orbital energy separation will be cationic in charge.

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Registry No. $Fe(bpy)(Cl_4SQ)(Cl_4Cat)$, 138666-82-7; $Fe(Cl_4SQ)_3$, 68846-32-2; $(PPh_4)[Fe(bpy)(Cl_4Cat)_2]$, 138666-84-9; $(CoCp_2)[Fe(bpy)(Cl_4Cat)_2]$, 138666-85-0; $(PPh_4)[Fe(bpy)(Cl_4Cat)_2]\cdot CH_2Cl_2$, 138666-86-1; $Fe(OPPh_3)(Cl_4CatH)(Cl_4Cat)\cdot C_3H_7OH$, 138666-88-3; $Fe(bpy)(Cl_4SQ)_2^+$, 138666-89-4.

Supplementary Material Available: Tables of magnetic susceptibility data for $Fe(bpy)(Cl_4SQ)(Cl_4Cat)$ and $(PPh_4)[Fe(bpy)(Cl_4Cat)_2]$ and, for $(PPh_4)[Fe(bpy)(Cl_4Cat)_2]$ and $Fe(OPPh_3)_3(Cl_4CatH)(Cl_4Cat)$, tables giving crystal data and details of the structure determinations, anisotropic thermal parameters, hydrogen atom locations, and bond lengths and angles and diagrams showing intermolecular packing interactions (32 pages); tables of structure factors (21 pages). Ordering information is given on any current masthead page.

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Studies of Platinum(II) Methionine Complexes: Metabolites of Cisplatin[1]

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Reactions of L-methionine (L-MetH) with $[PtX_4]^{2-}$ (X = Cl, Br, I) in 1:1 and 2:1 mole ratios have been studied in aqueous solutions at pHs from 1.9 to 8.7 using ^1H, ^{13}C, ^{15}N, and ^{195}Pt NMR spectroscopy. Some related reactions of L-ethionine, and D-methionine methyl ester were also studied. For $[Pt(L\text{-}MetH\text{-}S,N)Cl_2]$, two diastereomers were characterized, one present in ca. 10% excess, the major form having an approximate envelope ring conformation and the minor form being a flattened boat, whereas in the crystalline state both isomers have the same ring conformation. The carboxylate group of the diastereomers (pK_a 2.57) does not coordinate under these conditions. The value of $\Delta G^{\ddagger}$ (74.6 kJ mol^{-1}, 337 K) for S inversion is higher than that for nonchelated analogues. At low pH (ca. 2), the predominant form of the 2:1 complex is the partially-ring-opened species *cis*-$[Pt(L\text{-}MetH\text{-}S,N)(L\text{-}MetH_2\text{-}S)Cl]^{2+}$. This transforms reversibly into ring-closed forms at neutral pH, and of these *cis*-$[Pt(L\text{-}Met\text{-}S,N)_2]$ predominates by about 10:1 over *trans*-$[Pt(L\text{-}Met\text{-}S,N)_2]$. For both of these ring-closed species, the three possible diastereomers (*R,R*: *R,S*/*S,R*; *S,S*) are resolved in ^{195}Pt NMR spectra. The 2:1 complexes are thought to be metabolites of the anticancer drug cisplatin. Reactions of cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, and *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with L-methionine in 1:1 and 1:2 mole ratios, at pH 2-7, were also studied. The assignments of ^{15}N and ^{195}Pt resonances were greatly aided by the use of various combinations of natural abundance ^{14}N and ^{15}N enrichment in both ammonia and methionine. For 1:1 reactions with cisplatin, the major products are $[Pt(L\text{-}Met\text{-}S,N)(NH_3)_2]^+$, *cis*- and *trans*-$[Pt(L\text{-}Met\text{-}S,N)(NH_3)Cl]$, and the three diastereomers of *cis*-$[Pt(L\text{-}Met\text{-}S,N)_2]$, and for the 1:2 reactions the products are the diastereomers *R,R*-, *R,S*/*S,R*-, *S,S*-*cis*-$[Pt(L\text{-}Met\text{-}S,N)_2]$, together with minor amounts of *R,R*-, *R,S*/*S,R*-, *S,S*-*trans*-$[Pt(L\text{-}Met\text{-}S,N)_2]$.

Introduction

The amino acid methionine[3] (L-MetH) may play an important role in the metabolism of platinum anticancer drugs both in vivo and in cell culture media. Methionine-containing Pt(II) metabolites have been identified in the urine of patients receiving *cis*-$[PtCl_2(NH_3)_2]$ therapy.[4] As well, Pt(II)-methionine complexes form rapidly in plasma after injection of cisplatin into rats,[5] and methionine appears to enhance the nephrotoxicity of cisplatin.[6] Various attempts have been made to characterize Pt(II)-methionine complexes by HPLC methods.[5,7] Ammonia release

(1) Portions of this work were presented at the following. The 1989 International Chemical Congress of Pacific Basin Societies, Honolulu, HI, 1989; BIOS 88. (b) SAMBAS III, Bosen, Germany, 1990; Abstr. 019, p 73.

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(3) Abbreviations used: L-MetH, L-methionine; D-Met-Me, D-methionine methyl ester; L-EthH, L-ethionine; en, 1,2-diaminoethane; pH*, pH meter reading in D_2O solution; TSP sodium 3-(trimethylsilyl)-2,2,3,3-tetradeuteriopropanoate. Where there is ambiguity, the terms cis and trans refer to like coordinated atoms (e.g. N's of L-MetH and NH_3). A primed complex (e.g. **1A'**) differs from an unprimed complex (**1A**) by removal of protons from (uncoordinated) carboxyl groups of methionine.

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can be detected for reactions of cisplatin with L-methionine (L-MetH) in cell culture media, blood plasma, and aqueous solution.[8-11]

Surprisingly little NMR data on Pt(II)–methionine complexes are available in the literature.[11,12] Erickson et al.[12] have reported the chemical shifts of the S–CH_3 groups in $[Pt(MetH)Cl_2]$, *cis*-$[Pt(Met)(NH_3)Cl]$ (cis N's), and $[Pt(Met)(NH_3)_2]^+$, but their spectra obtained at 60 MHz were complex and difficult to analyze. Appleton et al.[11] have recently presented NMR data consistent with either S, N, or S, O coordination in $[Pt(L\text{-}Met)(NH_3)_2]$ but again did not analyze their ^1H NMR spectra in detail.

Various other workers[4,13] have assigned structures to isolated Pt(II)–methionine complexes on the basis of chemical reactivity, infrared data, and other measurements, but the only X-ray crystal structures reported appear to be those of $[Pt(L\text{-}MetH\text{-}S,N)Cl_2]$ and $[Pt(DL\text{-}MetH\text{-}S,N)Cl_2]$.[14]

Although it is possible to observe sulfur inversion of Pt(II)-coordinated thioethers by ^{195}Pt NMR spectroscopy,[15-18] only studies on amido derivatives of methionine, such as *N*-acetyl-L-methionine have been reported so far, and no studies of inversion in complexes of methionine itself have been reported. This is probably a consequence, in part, of the low solubility of $[Pt(L\text{-}MetH\text{-}S,N)Cl_2]$ which precludes the use of ^{195}Pt NMR (natural abundance 33.8%, receptivity 19.9 relative to ^{13}C). Also, with ^{195}Pt–^{14}N (natural abundance of ^{14}N 99.6%) bonds present, ^{195}Pt resonances are likely to be broadened by quadrupolar effects, and ^{15}N NMR is not feasible at low concentrations with natural-abundance ^{15}N (natural abundance 0.4%).

In this paper, we have used a combination of ^1H, ^{13}C, ^{15}N, and ^{195}Pt NMR spectroscopy to investigate reactions of L-MetH, D-Met-Me and L-EthH with $K_2[PtX_4]$ (X = Cl, Br, I) in 1:1 and 2:1 mol ratios in aqueous solution. The use of high-frequency ^1H NMR spectroscopy (500 MHz) has made possible the complete assignment of the spectra for some of the Pt(II)–methionine complexes, and the use of ^{15}N-enriched L-MetH has allowed the observation of both ^{195}Pt and ^{15}N NMR peaks. This has provided new insights into the chemistry of Pt(II)–methionine complexes including the populations of diastereomers related by S inversion, the dependence of S inversion rates on the other coordinated groups, and the factors which influence ring closure. We have also studied reactions of cisplatin and its diaqua analogue with L-methionine in aqueous media. The assignment of resonances of the products was aided greatly by comparisons of ^{15}N and ^{195}Pt NMR spectra of products derived from [^{14}N]- or [^{15}N]-cisplatin and [^{14}N]- or [^{15}N]-methionine in various combinations. The stereochemistry of the major Pt(II)–methionine product is different from that previously assumed for the isolated in vivo metabolite.

Experimental Section

Materials. L-Methionine and D-methionine methyl ester HCl were purchased from Sigma, [^{15}N]-L-methionine (99 atom% ^{15}N) from MSD Isotopes, $K_2[PtCl_4]$ and *cis*-$[PtCl_2(NH_3)_2]$ from Johnson Matthey, and all other chemicals from Aldrich. Deuteriated phosphate buffer (0.1 M) pH* 7 was prepared by freeze-drying solutions in H_2O and redissolving in D_2O, with pH* readjustment as necessary. ^{15}N-enriched cisplatin was synthesized as previously described[19] and was recrystallized from aqueous potassium chloride. The diaqua complex $[Pt(NH_3)_2(H_2O)_2]^{2+}$ (deuteriated when prepared in D_2O) was prepared in situ by addition of slightly less than 2 mol equiv of $AgNO_3$ to an aqueous solution of cisplatin followed by removal of the AgCl precipitate.

NMR Spectroscopy. NMR spectra were obtained at 297 K unless otherwise stated on the following instruments: JEOL FX200 (^1H 200 MHz), JEOL GSX270 (^{15}N 27.38 MHz, ^{195}Pt 57.87 MHz, ^{31}P 109.3 MHz), JEOL GSX500 (^1H 500 MHz, ^{15}N 50.70 MHz, ^{195}Pt 108.0 MHz), Bruker AM400 (^{15}N 40.55 Hz, ^{195}Pt 85.6 MHz), and Bruker AM500 (^1H 500 MHz, ^{13}C 125.75 MHz) using 5-mm NMR tubes except for ^{195}Pt spectra on the AM400 for which 10-mm tubes were used. The chemical shift references were as follows (all external except ^1H and ^{13}C): ^1H and ^{13}C, TSP; ^{15}N, 1.5 M $^{15}NH_4Cl$ in 1 M HCl containing 10% D_2O; ^{195}Pt, 1 M $Na_2[PtCl_6]$ in D_2O or 1 M $K_2[PtCl_4]$ containing 1 M NaCl in D_2O at −1614 ppm (referenced to $[PtCl_6]^{2-}$); ^{31}P, 85% H_3PO_4.

For ^1H NMR, typical acquisition conditions for 1D spectra were as follows: 45–60° pulses; 16–32K data points; 2–3-s relaxation delay; collection of 64–256 transients; final digital resolution of 0.17 Hz/pt. When necessary, the residual HOD resonance was suppressed by continual or gated secondary irradiation. Exponential and Gaussian functions were applied to the free induction decays prior to transformation as required. No ^{195}Pt–^1H couplings were clearly resolved in ^1H spectra at 500 MHz; ^{195}Pt satellites are likely to be broadened at this frequency by relaxation via ^{195}Pt chemical shift anisotropy.[20] Standard programs were used to acquire phase-sensitive 2D COSY and NOESY spectra. For the latter, a mixing time of 250 ms was used. Spectra were simulated using the Bruker PANIC program.[21]

$^{15}N\{^1H\}$ NMR single-pulse spectra (gated ^1H decoupling, without NOE's) and INEPT and DEPT spectra were acquired using standard programs. Typical pulsing conditions were as follows: 30–40° pulses; 32 K data points; 2-s relaxation delay; 10 000–20 000 transients; digital resolution of 0.5 Hz/pt. In INEPT and DEPT pulse sequences, delays of $1/4J$ and $1/2J$ were used with a $^1J(^{15}N\text{–}^1H)$ value of 73 Hz.

$^{13}C\{^1H\}$ NMR spectra were typically the result of 2700 transients collected into 32K data points using 50° pulses and relaxation delays of 3 s.

$^{31}P\{^1H\}$ NMR spectra were typically the result of 60–70° pulses, 16K data points, 1.5-s relaxation delay, 1500 transients, and digital resolution of 1 Hz/pt.

For $^{195}Pt\{^1H\}$ NMR spectra, composite pulse or bilevel decoupling was used to avoid sample heating. Typical acquisition conditions were as follows: 50–90° pulses; 32K data points, 1-s relaxation delay; 10 000–50 000 transients; digital resolution of 3 Hz/pt. Large frequency widths were used (ca. 1700 ppm), but it was not feasible to scan all regions of the ^{195}Pt shift range for each sample, each of which required an overnight run.

Sample Preparation. All samples for NMR were made up in D_2O solutions, except for ^{15}N INEPT and DEPT studies for which 90% H_2O/10% D_2O was used, and were shielded from the light by Al foil. In the formulas assigned to the complexes, the deuteriation of exchangeable protons (–NH_2, –NH_3, –CO_2H, and H_2O) is ignored. The procedures described below refer to both natural abundance and ^{15}N-enriched L-MetH and Pt(II)–ammine complexes which were used in all four combinations of $^{14/15}NH_3$ and [$^{14/15}N$]-L-MetH. In general, spectra were rerecorded after the samples had stood for long periods (days or weeks) to check that they were at equilibrium. Typical preparations were as follows.

$[PtCl_4]^{2-}$ + L-MetH (1:1). A solution containing $K_2[PtCl_4]$ (10.5 mg, 25.3 μmol), [^{15}N]-L-MetH (3.50 mg, 23.3 μmol), and NaCl (4.5 mg, 77 μmol) in D_2O (0.6 mL) was heated at 353 K for 10 min in the dark giving a clear yellow solution of pH* 1.9.

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Table I. ^{1}H NMR Data for 1:1 Pt(II)–L-Methionine Complexes

	δ						^3J(H–H), Hz							
complex	α-CH	β_a-CH_2	β_b-CH_2	γ_a-CH_2	γ_b-CH_2	S-CH_3	α–β_a	α–β_b	β_a–β_b	β_a–γ_a	β_a–γ_b	β_b–γ_a	β_b–γ_b	γ_a–γ_b
Pt(L-MetH-*S*,*N*)Cl_2														
isomer A (major)	3.615	2.258	2.595	3.036	2.884	2.570	10.2	2.2	16.0	11.5	2.4	2.4	5.9	14.6
isomer B (minor)	3.745	2.320	2.565	2.993	2.825	2.552	7.6	3.5	16.0	9.7	2.4	2.4	8.5	13.9
[Pt(L-Met-*S*,*N*)Cl_2]$^-$ [a]														
isomer A (major)	3.291	2.146	2.524	2.837	2.835	2.560	10.4	2.5	15.9	11.8	2.2	2.4	5.8	14.3
isomer B (minor)	3.423	2.160	2.498	2.949	2.760	2.534	7.8	3.5	15.9	9.2	2.2	2.2	9.1	13.7
Pt(L-MetH-*S*,*N*)Br_2														
isomer A (major)	3.555	2.242	*b*	2.995	2.872	2.598	10.3	2.2	16.0	11.8	2.4	2.6	5.7	14.5
isomer B (minor)	3.739	2.396	*b*	2.939	2.762	2.616	6.8	3.7	13.6	10.4	2.2	2.6	7.7	14.1

[a] Two sets of ^{13}C peaks were observed (δ): α-CH 56.56, 57.80; β-CH_2 30.27, 30.97; γ-CH_2 33.64, 34.20; S-CH_3 23.41, 23.87 (CO_2^- not detected). [b] Overlapped.

$[PtBr_4]^{2-}$ + L-MetH (1:1). Using the same procedure, a clear yellow solution was obtained from $K_2[PtBr_4]$ (2.96 mg, 4.99 μmol), [^{15}N]-L-MetH (0.76 mg, 5.03 μmol), and NaBr (6.0 mg, 58.3 μmol), with pH* 1.9.

$[PtI_4]^{2-}$ + L-MetH (1:1). The iodide complex was generated in situ by mixing $K_2[PtCl_4]$ (1.54 mg, 3.71 μmol) with excess KI (4.60 mg, 27.7 μmol), and [^{15}N]-L-MetH (0.56 mg, 3.70 μmol) in D_2O (0.6 mL) and heating for 1 h at 70 °C to give a brown solution of pH* 2.2.

In general the solubilities of the 1:1 products decreased markedly in the order Cl > Br > I. The S/N ratio was therefore low for the ^{195}Pt spectrum of the iodo complex, and no attempt was made to obtain its ^{15}N NMR spectrum.

$[PtCl_4]^{2-}$ + L-MetH (1:2). A solution containing $K_2[PtCl_4]$ (27.0 mg, 65.1 μmol), [^{15}N]-L-MetH (20.0 mg, 133 μmol), and NaCl (6.0 mg, 103 μmol) in D_2O (0.6 mL) was heated at 343 K for 2 min, giving a pale yellow solution, pH* 2.4. When the pH* was raised to 7.0 (NaOD), the solution became colorless.

$[PtBr_4]^{2-}$ + L-MetH (1:2). The above procedure was repeated using $K_2[PtBr_4]$ (39.3 mg, 66.2 μmol) and NaBr (8.60 mg, 83.6 μmol), giving a pale yellow solution, pH* 2.4.

The 1:2 adducts have much higher solubilities than the 1:1 species.

***cis*-$[PtCl_2(NH_3)_2]$ + L-MetH (1:1).** For time-dependent ^{1}H NMR studies, *cis*-$[PtCl_2(NH_3)_2]$ (30.1 mg, 0.10 mmol) was dissolved in 0.1 M phosphate buffer (6 mL) pH* 7 by stirring for 30 min at 310 K. To this was added 1 mL of a solution of L-MetH (15 mg, 0.10 mmol) in the same buffer, giving a solution containing 14 mM L-MetH and Pt(II). This mixture was incubated at 310 K and aliquots were removed at 1, 2, 4, 8, 24, and 72 h, quenched by cooling to 277 K, and then warmed to 297 K immediately prior to the acquisition of NMR spectra. ^{1}H NMR spectra of mixtures at apparent equilibrium were also recorded for similar reactions at Pt(II) concentrations of 7 and 150 mM. In the latter case, the concentration exceeds the solubility of cisplatin, and solid *cis*-$[PtCl_2(NH_3)_2]$ and L-MetH were added directly to phosphate buffer or D_2O (0.6 mL) in the NMR tube. This was ultrasonicated for ca. 5 min and heated at 343 K overnight to drive the reaction to completion.

***cis*-$[PtCl_2(NH_3)_2]$ + L-MetH (1:2).** *cis*-$[PtCl_2(NH_3)_2]$ (10.3 mg, 34 μmol) and L-MetH (10.4 mg, 69 μmol) in D_2O (0.6 mL) were heated at 353 K for 30 min and allowed to cool before recording NMR spectra. The rapid solubilization of cisplatin at this mole ratio in comparison with the 1:1 reaction (above) was notable.

***cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ + L-MetH (1:1 and 1:2).** L-MetH (7.6 mg, 50 μmol in 0.2 mL of D_2O) was added to a solution of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ in D_2O (0.1 M, 0.5 mL). Spectra were recorded after the solution had stood for 1 h at 290 K. A similar procedure was also used for the 1:2 mixture, and spectra were recorded without heating and also after heating at 343 K for 1 h. The pH*s of the above solutions at the time of NMR measurement were 4.2–4.8. The pH* values of some solutions were then adjusted to 7.0 to allow comparison of ^{1}H spectra obtained from cisplatin reactions.

Adjustments of pH were made using solutions of NaOD or HNO_3, and pH measurements were made using a Corning 145 pH meter equipped with a combination electrode. To determine the pK_a of the carboxylate group in [Pt(MetH-*S*,*N*)Cl_2], a 1:1 solution of $[PtCl_4]^{2-}$ and L-MetH was prepared in a D_2O solution containing 0.1 M NaCl and titrated over the range pH* 0.95–5.16. The chemical shifts of the α-CH protons of the two enantiomers were fitted to the Henderson–Hasselbach equation using a computer program supplied by Dr. A. Lane (NIMR, Mill Hill).

Results

$[PtX_4]^{2-}$ + L-MetH (1:1) (X = Cl, Br, I). A typical 500-MHz ^{1}H NMR spectrum obtained from a solution containing $[PtCl_4]^{2-}$ (38 mM) and 1 mol equiv of L-MetH in 0.13 M NaCl solution, pH* 1.9, is shown in Figure 1a. There are two distinct singlets at 2.570 and 2.552 ppm assignable to S–CH_3 protons, and two sets of resonances at 3.615 ppm and 3.745 ppm assignable to α-CH protons. This suggests the formation of two distinct Pt(II)–L-MetH products in slow exchange on the NMR time scale.

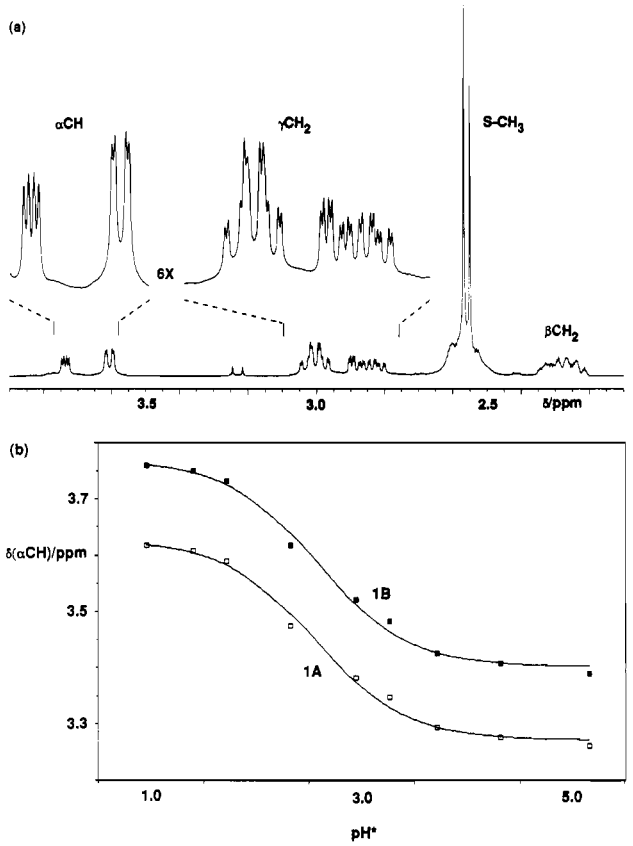

Figure 1. (a) 500-MHz ^{1}H NMR spectrum of a 1:1 solution of $[PtCl_4]^{2-}$ and L-MetH in 0.13 M NaCl solution in D_2O, pH* 1.9, showing the two sets of resonances for the diastereomers **1A** and **1B** of [Pt(MetH-*S*,*N*)Cl_2] related by inversion at S. (b) Plots of the chemical shifts of the α-CH protons of isomers **1A** and **1B** versus pH*.

A similar 1:1 mixture (5 mM) was titrated over the pH* range 0.95–5.16. Plots of the shifts of the two sets of α-CH protons versus pH*, Figure 1b, gave pK_a values of 2.57 and 2.58 for the low- and high-frequency α-CH peaks, respectively.

A crystalline sample of the known complex [Pt(L-MetH-*S*,*N*)Cl_2][14] was prepared and this gave a spectrum identical to that of the above 1:1 mixture when dissolved in D_2O (with difficulty—ultrasonication and heating) at pH* 1.9. The spectrum described above was fully assigned to two isomers **1A** and **1B** (Figure 2) with the aid of spectral simulation and by analysis of phase-sensitive 2D COSY spectra. The chemical shifts and coupling constants are listed in Table I. At both low and high pH values, there are marked decreases in the values of $^3J(H_\alpha–H_{\beta a})$ and $^3J(H_{\beta a}–H_{\gamma a})$ for isomer **1B** compared to **1A**, and an increase in $^3J(H_{\beta b}–H_{\gamma b})$. No ^{195}Pt–^{1}H couplings were resolvable at 500

Table II. ^{15}N NMR Data for 1:1 and 1:2 Pt(II)–[^{15}N]-L-Methionine Complexes

complex	δ			$^1J(^{195}Pt-^{15}N)$, Hz	trans to ^{15}N	comment
Pt(L-MetH-*S*,*N*)Cl_2	−41.85			325	Cl	isomer A
	−41.76			325	Cl	isomer B
$[PtCl_4]^{2-}$ + 2L-MetH	18.50					*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Cl]$^{2+}$
pH* 2.4	−22.56	−22.62	−23.30	ca. 265	S	*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Cl]$^{2+}$ and
	−23.58	−23.96	−24.23	ca. 265	S	*cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$
	−40.23	−40.94	−41.09	ca. 292	N	*trans*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ [a]
pH* 8.7	−20.09	−20.33	−21.12	ca. 272	S	*cis*-[Pt(L-Met-*S*,*N*)$_2$]
	−38.25	−38.56	−38.91	*b*	N	*trans*-[Pt(L-Met-*S*,*N*)$_2$]

[a] This group of three peaks constitutes about 6% of the total intensity of the observed (single pulse) ^{15}N resonances. [b] Ca. 280 Hz but weak and broad.

Table III. ^{195}Pt NMR Data for 1:1 and 1:2 Pt(II)–[^{15}N]-L-Methionine and Pt(II)–[^{14}N]-D-Methionine Methyl Ester Complexes

system	δ[a]	$^1J(^{195}Pt-^{15}N)$, Hz	trans to ^{15}N	assignment[b]
$[PtCl_4]^{2-}$ + L-MetH	−2946 d	327	Cl	*R*-[Pt(L-MetH-*S*,*N*)Cl_2] (**1A**) (major)
pH* 1.9	−2955 d	329	Cl	*S*-[Pt(L-MetH-*S*,*N*)Cl_2] (**1B**) (minor)
$[PtCl_4]^{2-}$ + L-MetH	−2951 d	326	Cl	*R*-[Pt(L-Met-*S*,*N*)Cl_2]$^-$ (**1A′**) (major)
pH* 6.0	−2967 d	331	Cl	*S*-[Pt(L-Met-*S*,*N*)Cl_2]$^-$ (**1B′**) (minor)
$[PtBr_4]^{2-}$ + L-MetH	−3319 d	305	Br	*R*-Pt(L-MetH-*S*,*N*)Br_2] (**2A**) (major)
pH* 1.9	−3321 d	308	Br	*S*-[Pt(L-MetH-*S*,*N*)Br_2] (**2B**) (minor)
	−3360 s			[Pt(L-MetH-*S*)Br_3]$^-$ (**3**)
$[PtI_4]^{2-}$ + L-MetH	−4098 d	262	I	*R*/*S*-[Pt(L-MetH-*S*,*N*)I_2] (**4**)
$[PtCl_4]^{2-}$ + 2L-MetH	−3584 d	258	S	*R*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Cl]$^{2+}$ (**5A**)
pH* 2.4	−3586 d	258	S	*R*,*S*-*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Cl]$^{2+}$ (**5B**)
	−3604 d	260	S	*S*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Cl]$^{2+}$ (**5C**)
	−3605 d	260	S	*S*,*S*-*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Cl]$^{2+}$ (**5D**)
	−3634 t	272	S	*R*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ (**6A**)
	−3640 t	268	S	*R*,*S*/*S*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ (**6B**)
	−3676 t	272	S	*S*,*S*-*cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ (**6C**)
pH* 7.2	−3636 t	277	S	*R*,*R*-*cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6A′**)
	−3637 t	278	S	*R*,*S*/*S*,*R*-*cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6B′**)
	−3690 t	272	S	*S*,*S*-*cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6C′**)
	−3444 t	292	N	*R*,*R*-*trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7A′**)
	−3462 t	290	N	*R*,*S*/*S*,*R*-*trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7B′**)
	−3498 t	292	N	*S*,*S*-*trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7C′**)
$[PtBr_4]^{2-}$ + 2L-MetH	−3708 d	275	S	*R*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Br]$^{2+}$ (**8A**)
pH* 2.4	−3712 d	275	S	*R*,*S*/*S*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Br]$^{2+}$ (**8B**)
	−3725 d	250	S	*S*,*S*-*cis*-[Pt(L-MetH-*S*,*N*)(L-MetH_2-*S*)Br]$^{2+}$ (**8C,D**)
	−3626 t	273	S	*R*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ (**6A**)
	−3638 t	273	S	*R*,*S*/*S*,*R*-*cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ (**6B**)
	−3663 t	266	S	*S*,*S*-*cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ (**6C**)
	−3889 s			*R*-*cis*-[Pt(L-MetH-*S*)$_2Br_2$] (**9A**)
	−3899 s			*S*-*cis*-[Pt(L-MetH-*S*)$_2Br_2$] (**9B**)
$[PtCl_4]^{2-}$ + D-Met-Me	−2963			*R*-[Pt(L-Met-Me-*S*,*N*)Cl_2] (**10A**)
	−2974			*S*-[Pt(L-Met-Me-*S*,*N*)Cl_2] (**10B**)
	−2816			Pt(L-Met-Me-*S*)Cl_3]$^-$ (**11A**)
	−2820			[Pt(L-Met-Me-*S*)Cl_3]$^-$ (**11B**)
	−2058 br			?

[a] Key: s, singlet; d, doublet; t, triplet; br, broad. All data obtained at 297 K. [b] Chiral assignments have been included for labeling purposes only and are not absolute. To be consistent with the labeling of the 1:1 complex, we have assumed that *R* centers give the highest frequency ^{195}Pt shifts.

MHz, but at 200 MHz broad satellites were observed and a $^3J(^{195}Pt-^1H)$ value of 56 Hz was measured for the Pt–S–CH_3 peaks.

The ^{13}C NMR spectrum is also consistent with the presence of two isomers **1A** and **1B** in solution (Table I) as is the 27.4-MHz $^{15}N\{^1H\}$ INEPT spectrum, which shows two singlets, separated by 2.5 Hz at 297 K each with broadened ^{195}Pt satellites (Table II). Two doublets are seen in the 57.9-MHz ^{195}Pt spectrum at −2946 and −2955 ppm, i.e., separated by 521 Hz at 297 K, with $^1J(^{195}Pt-^{15}N)$ values of 328 Hz (Table III). At the higher frequency of 107.2 MHz these two doublets were broadened but still well-resolved. Integration of ^1H and ^{195}Pt spectra both suggested a slight predominance of one isomer, **1A** (in 10% excess over isomer **1B**).

To investigate dynamic exchange reactions further, 2D ^1H phase-sensitive NOESY[22] and variable-temperature ^1H, ^{15}N, and ^{195}Pt NMR spectra were investigated. In the ^1H NOESY spectrum, negative cross-peaks were seen connecting the two sets of α-CH proton resonances for **1A** and **1B**, similarly connecting β-CH_2 and γ-CH_2 peaks of **1A** and **1B**. When the temperature of the sample was raised, the two S–CH_3 ^1H NMR singlets coalesced at 337 K (pH* 1.9), giving an inversion rate of 19 s^{-1} and ΔG^* of 74.6 kJ mol^{-1} at this temperature.[23] In the ^{15}N INEPT NMR spectrum, the two singlets coalesced at 318 K and separated further on cooling (8 Hz at 268 K). The separation between the two doublets in the ^{195}Pt spectrum decreased from 521 Hz at 297 K to 470 Hz at 343 K.

[Pt(L-MetH-*S*,*N*)X_2] (X = Br, I). Complexes were generated in solutions containing Pt(II), L-MetH, and Br^- or I^-. The ^1H NMR spectrum of the bromide complex (**2A,B**) is very similar to that of the chloride complex (**1A,B**) including the pattern of changes in $^3J(H-H)$ values between the isomers. From an in-

(22) Derome, A. E. *Modern NMR Techniques for Chemistry Research*, Pergamon: Oxford, England 1987; p 239.

(23) $k = \pi\delta\nu/\sqrt{2}$; $\Delta G^* = (1.914 \times 10^{-2})\ T[10.319 + \log(T/k)]$. See: Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982. Strictly this formula applies only when there are equal populations of the two states. Also, in the case of Pt NMR spectra, differential temperature dependencies of peaks could contribute to changes in peak separations. Both of these effects are assumed to be minor in the present case.

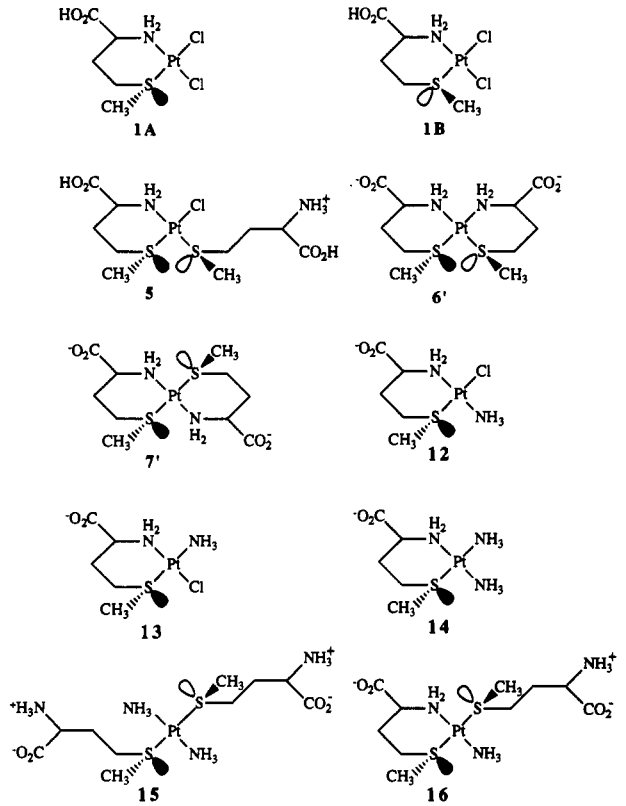

Figure 2. Structures of Pt(II)–methionine complexes, showing the two diastereomers of [Pt(L-MetH-*S*,*N*)Cl_2], **1A** (major, *R* configuration at *S*, envelope ring conformation) and **1B** (minor, *S* configuration at S, flattened boat ring conformation), the ring-opened ("dangling-arm") complex [Pt(L-MetH-*S*,*N*)(L-$MetH_2$-*S*)Cl]$^{2+}$ (**5**) where there are four isomers of this complex, dependent on the chirality at S, *cis*- and *trans*-[Pt(L-Met-*S*,*N*)$_2$] (**6'**) and (**7'**) where there are three diastereomeric forms being dependent on the chirality at S, with the *R*,*S* and *S*,*R* forms superimposable, and **13**–**16**. The overall charges on the complexes are not shown.

vestigation of the temperature dependence, the exchange rate for sulfur inversion and ΔG^* at the coalescence temperature (335 K) were determined to be 20 s^{-1} and 71.8 kJ mol^{-1}, respectively.

The ^{195}Pt NMR spectrum of the bromide complex consists of two doublets ($^1J(^{195}Pt-^{15}N)$ 305 and 308 Hz) at −3319 and −3321 ppm, i.e., separated by 116 Hz at 297 K. Another minor peak was observed from the reaction solution at −3360 ppm.

The reaction solution for the iodide complex (**4**) gave a ^{1}H NMR spectrum with relatively broad peaks, but only one major doublet ($^1J(^{195}Pt-^{15}N)$ = 262 Hz) was seen in the ^{195}Pt NMR spectrum at −4098 ppm and 297 K.

$[PtCl_4]^{2-}$ + D-Met-Me or L-EthH (1:1). The product from the reaction of D-Met-Me gave a ^{1}H NMR spectrum very similar to that from the reaction involving L-MetH above, with additional resonances for CH_3 ester peaks (Table IV). Similarly, the 500-MHz ^{1}H NMR spectrum of the L-EthH complex resembled that for L-MetH, only now the two sets of S–CH_2 resonances overlapped and the two CH_3 peaks appeared as triplets at 1.408 and 1.419 ppm.

$[PtCl_4]^{2-}$ + L-MetH (1:2). ^{1}H NMR spectra of this reaction mixture at 297 K are very complicated, even at 500 MHz. At pH* 2.4, the α-CH region of the 1D spectrum, 3.70–4.25 ppm, and the phase-sensitive COSY spectrum suggest that there are 10 species present (Table IV). Eight singlets assignable to S–CH_3 groups are resolvable in the range 2.55–2.70 ppm. A phase-sensitive NOESY spectrum (297 K, pH* 2.4) showed five exchange cross-peaks in the α-CH region.

When the temperature of the sample was raised progressively from 297 to 343 K, the eight resolved S–CH_3 peaks collapsed at different temperatures to give three S–CH_3 peaks, including the singlet at 2.691 ppm, which appeared to remain unchanged in this temperature range.

Table IV. ^{1}H NMR Data for 1:1 Pt(II) Complexes of L-Ethionine and D-Methionine Methyl Ester and 1:2 Pt(II)–L-Methionine Complexes

	δ				
	α-CH	β-CH_2	γ-CH_2	S–CH_3	other
Pt(L-EthH-*S*,*N*)Cl_2	3.572	2.1–2.7	2.8–3.2	1.408[a]	2.8–3.2[b]
	3.672			1.419[a]	
Pt(D-Met-Me-*S*,*N*)Cl_2	3.68	2.2–2.6	2.8–3.0	2.55	3.81[c]
	3.86			2.54	3.82[c]
$[PtCl_4]^{2-}$ + 2L-MetH[d]	3.704, 3.925	2.4–2.7	2.9–3.2	2.691	
pH* 2.4	3.871, 3.925			2.660	
	3.909, 3.920			2.649	
	4.081, 4.158			2.615	
	4.179, 4.242			2.602	
				2.582	
				2.568	
				2.558	
pH* 7	3.60–3.65	2.2–2.7	2.9–3.2	2.602	
	3.74–3.78	2.2–2.7	2.9–3.2	2.648	

[a] S–CH_2CH_3. [b] S–CH_2CH_3. [c] O–CH_3. [d] The order of listing the α-CH and S–CH_3 shifts is arbitrary—those on the same line are not necessarily from the same species; the pairing of α-CH values is based on exchange observed in phase-sensitive NOESY experiments.

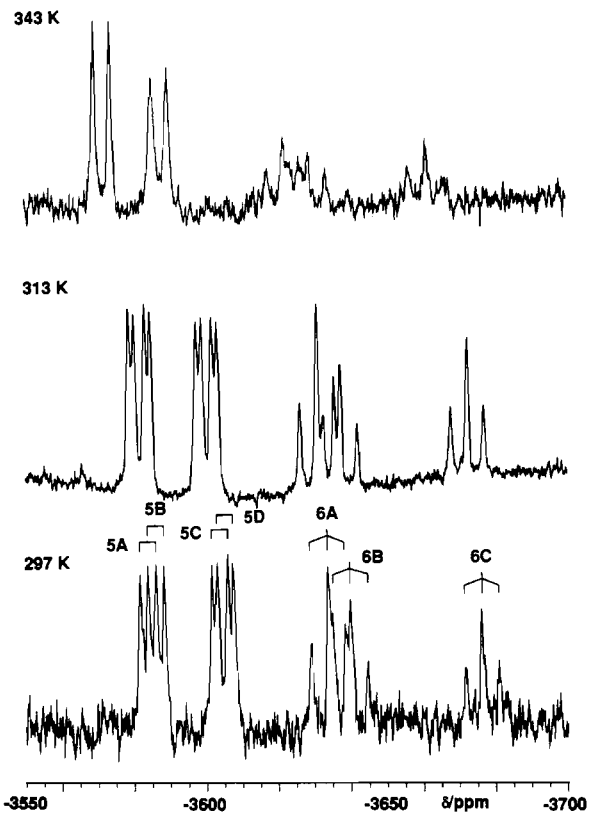

Figure 3. ^{195}Pt NMR spectra of a 1:2 mixture of $[PtCl_4]^{2-}$ (0.1 M) and [^{15}N]-L-MetH in D_2O containing 0.17 M NaCl at pH* 2.4 and (a) 297, (b) 313, and (c) 343 K showing the peaks for *cis*-[Pt(L-MetH-*S*,*N*)$_2$]$^{2+}$ and [Pt(L-MetH-*S*,*N*)(L-$MetH_2$-*S*)Cl]$^{2+}$ and the rapid inversion of S of the dangling-arm L-MetH in the latter complex at high temperature.

The pH* of the sample was raised from 2.4 to 7.2. Only two S–CH_3 peaks were then resolvable and there was a general broadening of the spectrum. The broadening appeared to be independent of the Pt concentration (5–110 mM), but some sharpening was observed on cooling the sample to 268 K.

The 57.87-MHz ^{195}Pt NMR spectra of this reaction solution were easier to interpret. At pH* 2.4 and 297 K with [^{14}N]-L-MetH, four broad signals spanning 95 ppm were observed. Use of [^{15}N]-L-MetH led to a dramatic resolution of fine structure on these peaks which now appeared as two sets of 1:1:1:1 quartets at high frequency together with two overlapping triplets and a

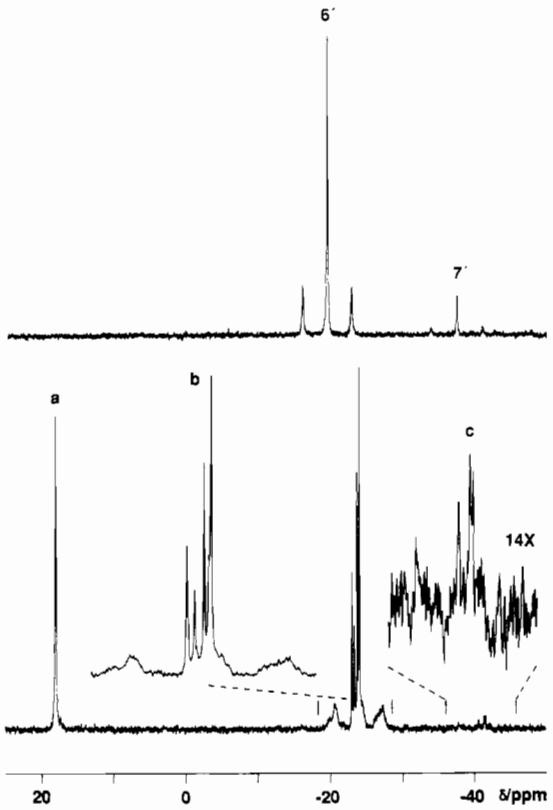

Figure 4. 50.7-MHz $^{15}N\{^1H\}$ INEPT spectrum of a 1:2 mixture of $[PtCl_4]^{2-}$ and [^{15}N]-L-MetH in 0.17 M NaCl, 10% of D_2O, and (bottom) pH 2.4 at 298 K or (top) pH 8.7 at 346 K. Assignments are as follows: (a) noncoordinated $-NH_3^+$ of **5**; (b) coordinated N trans to S, for **5** and **6** with broadened ^{195}Pt satellites; (c) coordinated N trans to N for **7′**.

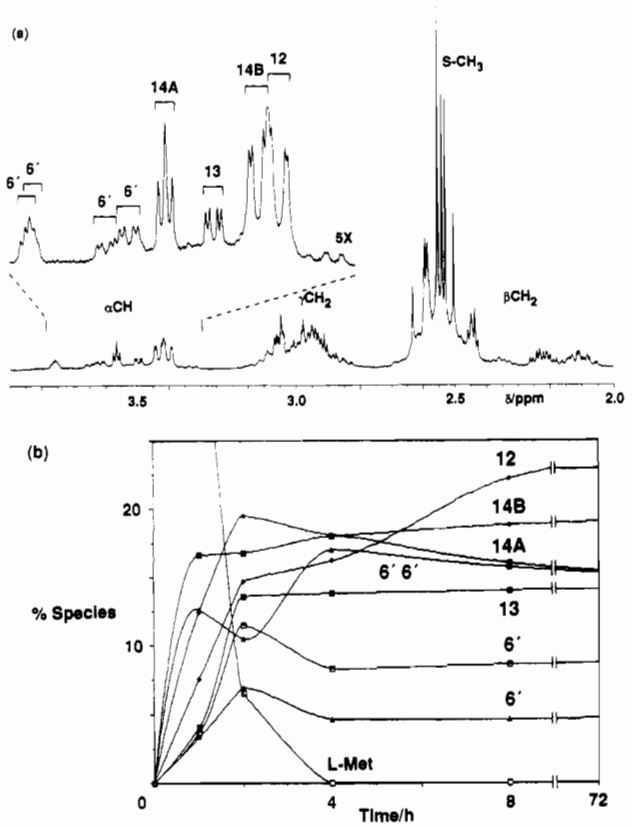

Figure 5. (a) 500-MHz ^{1}H NMR spectrum of a mixture of *cis*-$[PtCl_2(NH_3)_2]$ and L-MetH (1:1) (14 mM), which had reacted at 310 K in deuteriated phosphate buffer, pH* 7, for 72 h (at equilibrium). (b) Plot of the variation with time of the intensities of the α-CH resonances in the ^{1}H NMR spectra of the above reaction. As can be seen from part a, the accuracy is limited by peak overlap. Each set of peaks (except that for L-Met) was assumed to have Pt satellites even though they could not be integrated.

further triplet at low frequency (Figure 3; Table III). In addition, three broad unresolved peaks of low intensity were present at ca. −3440, −3480, and −4010 ppm.

When the solution was heated, it was apparent that each ^{195}Pt quartet consisted of two overlapping doublets. The two doublets at highest frequency (**5A,B** separation 121 Hz at 297 K) coalesced at ca. 323 K, with an associated $^1J(^{195}Pt-^{15}N)$ of 258 Hz. The remaining two doublets (**5C,D** separation 85 Hz at 297 K) coalesced at ca. 327 K and had a similar associated $^1J(^{195}Pt-^{15}N)$ of 260 Hz (Figure 3). There was little change in the three triplets at higher temperature except that the two at ca. −3637 ppm moved further apart.

When the pH* of this solution was raised from 2.4 to 7.2, all four ^{195}Pt doublets disappeared, and two groups of three triplets were seen in the ranges −3444 to −3498 ppm (**7′A–C**) and −3636 to −3690 ppm (**6′A–C**) (Table III). The former set of triplets was ca. 10% of the intensity of the latter. When this solution was heated, the two triplets originally seen at −3636 and −3637 ppm merged, such that only two triplets were seen in this region at 343 K. The less intense high-frequency triplets could not be detected at this temperature. This pH-induced structural change was reversible on lowering the pH* from 7.2 to 2.4; i.e., the original spectrum containing four doublets and three triplets was regenerated. We also showed that ^{195}Pt NMR spectra obtained from mixtures of $[PtCl_4]^{2-}$ and 2 mol equiv of L-MetH at pH* 7.2 and from $[Pt(L\text{-MetH})Cl_2]$ (**1**) and 1 mol equiv of L-MetH at pH* 7.5 are almost identical; i.e., they contain triplets for **6′A–C** and **7′A–C** in similar proportions.

The ^{15}N INEPT and DEPT spectra obtained from the 1:2 mixture at pH* 2.4 and 297 K showed a singlet at 18.5 ppm, a group of at least six peaks at ca. −23.5 ppm with broadened ^{195}Pt satellites and a less intense set of peaks at ca. −41 ppm also with ^{195}Pt satellites (Table II; Figure 4). When the temperature of the sample was raised to 346 K, the group of peaks at ca. −23.5 ppm collapsed to two peaks and that at ca. 18 ppm remained unchanged. When the pH was raised to 8.7, the latter singlet disappeared (reversible on lowering the pH), and the other two groups of peaks shifted to higher frequency by about 3 ppm. When the temperature of this sample was raised to 346 K, only two singlets, both with satellites, were seen (Figure 4): −19.5 ppm, $^1J(^{195}Pt-^{15}N)$ = 273 Hz, and −37.6 ppm, $^1J(^{195}Pt-^{15}N)$ = 293 Hz.

$[PtBr_4]^{2-}$ + L-MetH (1:2). The ^{1}H NMR spectra for this system are very similar to those obtained from reactions of $[PtCl_4]^{2-}$ with L-MetH at both pH* 2.4 and 6.5. In the ^{195}Pt NMR spectrum, triplets similar to those seen for the chloride system are observed (shifts within 15 ppm) but the four doublets seen at high frequency, at pH* 2.4, are replaced by three doublets (**8**) at low frequency of the triplets (−3708 to −3725 ppm) (Table III). Also, two small singlets are seen at −3889 (**9A**) and −3899 (**9B**) ppm. When the sample was heated to 343 K, the two high-frequency doublets coalesced to give one doublet, $^1J(^{195}Pt-^{15}N)$ = 275 Hz.

***cis*-$[Pt(NH_3)_2Cl_2]$ or *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ + L-MetH. 1:1 Reactions.** We studied the time course of reactions of cisplatin with L-MetH at a 1:1 mole ratio (7 and 14 mM) in 0.1 M phosphate buffer, pH* 7.0 at 310 K. A typical ^{1}H NMR spectrum from such a reaction at apparent equilibrium is shown in Figure 5a. It is complicated even at 500 MHz. Eight major sets of peaks assignable to α-CH protons are present in the region 3.4–3.8 ppm, and eight singlets for S–CH_3 protons are observed from 2.50 to 2.64 ppm. The β-CH_2 and γ-CH_2 proton resonances are highly overlapped but many sets are resolved in phase-sensitive 2D COSY spectra (Table V). The time courses for intensity changes of the α-CH and S–CH_3 peaks, Figure 5b, enabled us to correlate those sets of resonances which belonged to the same species. Negative cross-peaks in phase-sensitive 2D NOESY spectra showed that magnetization transfer was occurring between certain sets of resonances, attributable to S inversion; see Table V. The observation of coalescence of certain S–CH_3 ^{1}H NMR peaks at elevated temperature also confirmed S-inversion. Where possible,

Table V. ^{1}H NMR Data for Products of the Reaction of Cisplatin with L-Methionine (1:1, 14 mM) in 0.1 M Phosphate Buffer, pH* 7

	δ^a							
proton[b]	**12**	**14A**	**14B**	**13**	**6'A–C**			
α-CH	3.402	3.565	3.431	3.495	3.617	3.751	3.650	3.764
β_a-CH_2	2.106	2.449	2.231	2.140	2.350	2.582	2.365	2.463
β_b-CH_2	2.605	2.449	2.578	2.514	2.577	*c*	2.558	*c*
γ_a-CH_2	2.98	2.89	3.06	2.84	3.08	*c*	3.11	*c*
γ_b-CH_2	2.92	2.97	3.04	2.97	3.0	*c*	*c*	*c*
S-CH_3	2.531	2.541	2.556	2.504	2.584	2.587	2.633	2.595
	J(H–H),[a,d] Hz							
	12	**14A**	**14B**	**13**	**6'A–C**			
α–β_a	11.1	5.0	10.5	8.3	9.4	8	8.6	8
α–β_b	2.0	5.0	2.8	3.2	3.4	*c*	3.7	*c*
β_a–β_b	16	16	16	0	15	16	16	15
β_a–γ_a	11	5.6	10	9	10	*c*	10	*c*
β_a–γ_b	3.2	5.0	4	4.2	5	*c*	5	*c*
γ_a–γ_b	16	15	16	16	15	*c*	15	*c*

[a] The accuracy with which some values could be measured was limited by peak overlap. Assignments: see Figure 2 and Table VI. [b] Pairing of α-CH resonances is based on exchange observed in phase-sensitive experiments; the pairing of α–CH and S–CH_3 values is based on their time-dependent behavior. Many assignments should therefore be regarded as tentative (see text). [c] Overlapped. [d] β_b–γ_a and β_b–γ_b values not listed due to extensive overlap.

^3J values were measured from 1D spectra (Table V). The assignments proposed in Table V are based on species identified in ^{195}Pt NMR spectra of similar solutions (e.g. **14** and **6'** are the only species seen in 1:1 reactions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with L-MetH). As can be seen from Figure 5b, >90% of the L-MetH reacts within 2 h and all has reacted by 4 h. At this time ca. 35% of the L-Met is present in complex **14** with no loss of NH_3 from Pt, ca. 30% in **12** and **13** with displacement of one NH_3 ligand, and ca. 25% in **6'** with loss of both coordinated NH_3 moieties. After this time only minor changes in the product distribution are seen with slight further loss of NH_3 and apparent conversion of **14** into **12**. However, higher concentrations of reactants were necessary to obtain spectra with reasonable S/N ratios for ^{195}Pt NMR spectra. With 150 mM Pt, the pH* of the 0.1 M phosphate buffer solution (initially 7) dropped to 5.8 by the time equilibrium was reached. When reactions were carried out in the absence of phosphate buffer, the equilibrium pH* was 4.2. ^{195}Pt spectra at pH* 4.2, 5.8, and 7.0 in the presence or absence of phosphate were very similar.

Although in the time course experiments phosphate buffer was necessary to control the pH*, we observed the same species as products at equilibrium (at the same pH*) even when no buffer was used. To detect possible phosphato species, we recorded ^{31}P NMR spectra of equilibrium mixtures (14 mM). Four small ^{31}P NMR peaks at 6.35, 6.50, 6.86, and 7.46 ppm were detected, in addition to that for phosphate (0.78 ppm). Integration of these (relative to phosphate) suggested that about 3 mM bound phosphate was present, with the peak at 6.86 ppm accounting for ca. 75% of this. No ^{195}Pt satellites were detected.

Peaks in ^{195}Pt NMR spectra for these solutions were more readily assigned. Most of the multiplets can be assigned with the aid of the chemical shifts, $^1J(^{195}Pt–^{15}N)$ couplings, multiplicities, ^{15}N "decoupling" via the use of combinations of $^{14/15}NH_3$/[$^{14/15}$N]-L-MetH (Figure 6), and temperature and frequency (58 and 108 MHz) dependences.

The most prominent ^{195}Pt peaks in a solution containing cisplatin and L-MetH at a 1:1 mole ratio at equilibrium are overlapping multiplets at ca. −3154 ppm, which at other temperatures and at higher frequency are clearly seen to consist of two quartets (−3147 ppm and −3161 ppm at 297 K, the latter being ca. 30% more intense) with ^1J values of 277 and 271 Hz respectively. These peaks are assignable to R/S-[Pt(L-Met-S,N)$(NH_3)_2]^+$ (**14**). The multiplet at −3064 ppm appears as a triplet at higher temperature (supplementary material) and a broadened quartet at higher frequency (108 MHz). These resonances broaden when ^{14}N is

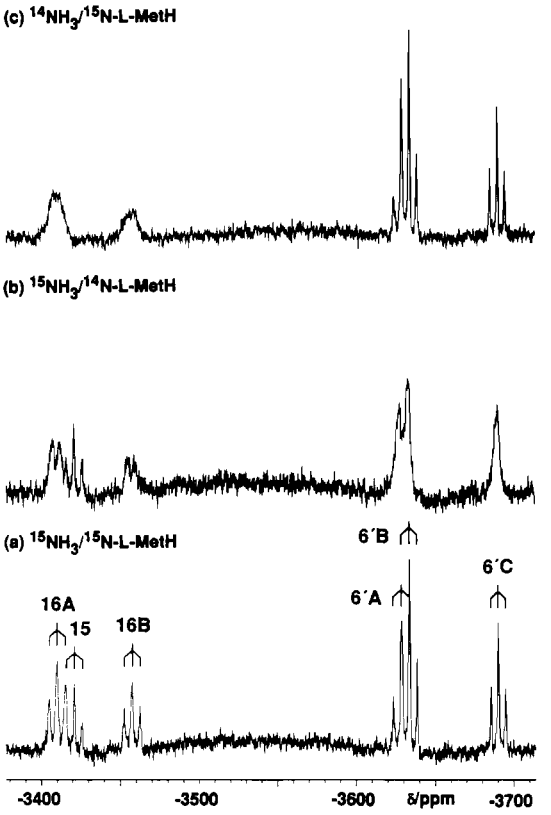

Figure 6. ^{195}Pt NMR spectra of a reaction mixture of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and L-MetH (1:2, pH* 4.2) after reaction at 297 K for ca. 8 h: (a) $^{15}NH_3$/[^{15}N]-L-MetH; (b) $^{15}NH_3$/[^{14}N]-L-MetH; (c) $^{14}NH_3$/[^{15}N]-L-MetH. Assignments are as follows: **16A**, *R,R/S-trans*-[Pt(L-Met-S,N)(L-MetH-S)$NH_3]^+$; **16B**, *S,R/S-trans*-[Pt(L-Met-S,N)(L-MetH-S)$NH_3]^+$ (slow inversion of sulfur-chelated L-Met, fast inversion of monodentate S-bound L-Met); **15**, *R,R*; *R,S/S,R*; and *S,S-trans*-$[Pt(L\text{-MetH-}S)_2(NH_3)_2]^{2+}$ (fast inversion at both sulfurs); **6'A**, *R,R-cis*-[Pt(L-Met-S,N)$_2$], **6'B**, *R,S/S,R-cis*-[Pt(L-Met-S,N)$_2$], and **6'C**, *S,S-cis*-[Pt(L-Met-S,N)$_2$] (slow inversion at S). Only ^{15}N bound to ^{195}Pt gives rise to multiplet splittings. In part b, ^{15}N couplings are still resolvable for **16A** and **16B** even in the presence of ^{14}N broadening.

present in either NH_3 or L-MetH (compare with Figure 6), indicating that both must be present in the complex. This multiplet was analyzed as two overlapping doublets of doublets of similar intensity arising from ^{195}Pt–^{15}N couplings (^1J values of 240 and 347 Hz) together with splittings due to S inversion (rapid at high temperature) and is assigned to R/S-*cis*-[Pt(L-Met-S,N)(NH_3)Cl] (**13**). From the coalescence at 343 K, values for k of 753 s^{-1} and ΔG^* of 65.5 kJ mol^{-1} were calculated. The triplet at −3044 ppm resolves into two overlapping triplets (^1J values of 275 Hz) of unequal intensity (ca. 1:0.6) at higher temperature and again arises from a species containing both NH_3 and L-MetH ligands. This is assigned to *trans*-[Pt(L-Met-S,N)(NH_3)Cl] (**12**) (Table VI).

The two broad multiplets at ca. −3010 and −2970 ppm are unassigned. They broadened beyond detection at 323 K, and weak doublets of doublets, one of which (ca. −2950 ppm) is assignable to R/S-[Pt(L-Met-S,N)Cl_2] (**1**) were then visible in this region. To lower frequency of these peaks are seen three triplets (ca. half the intensity of the peaks for *trans*-[Pt(L-Met-S,N)(NH_3)Cl] (**12**)) arising from the three diastereomers of *cis*-[Pt(L-Met-S,N)$_2$] (Table VI). From the integrations of ^{195}Pt peaks, approximate proportions of products from this 1:1 reaction are as follows: **14** 35%; **12**, 19%; **6'**, 15%; **13**, 11%. The broad peaks at −3010 and −2970 ppm accounting for a further ca. 10% each. When the initial reaction was carried out at a higher temperature (>363 K), the proportion of **14** decreased and amounts of **12** and **13** increased.

A similar reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with L-MetH was studied to aid the identification of species containing coordinated Cl^- ligands in the above reaction. In this case, no ^{195}Pt peaks were seen in the region −2950 to −3100 ppm. The major

Table VI. ^{195}Pt NMR Data for Reactions of Pt(II)–Ammine Complexes with [^{15}N]-L-Methionine

system	δ^a	$^1J(^{195}Pt-^{15}N)$, Hz	trans to ^{15}N	assignment^b
cis-$[PtCl_2(NH_3)_2]$ + L-MetH, pH* 5.8	−3044 t	275	N	*R/S-trans*-[Pt(L-Met-*S*,*N*)(NH_3)Cl] (**12A,B**)
	−3061 d	347	Cl	*R-cis*-[Pt(L-Met-*S*,*N*)(NH_3)Cl] (**13A**)
	−3067 d	240	S	*S-cis*-[Pt(L-Met-*S*,*N*)(NH_3)Cl] (**13B**)
	−3147 q	277	N, S	*R*-[Pt(L-Met-*S*,*N*)$(NH_3)_2]^+$ (**14A**)
	−3161 q	271	N, S	*S*-[Pt(L-Met-*S*,*N*)$(NH_3)_2]^+$ (**14B**)
	−3631 t	270	S	*R,R-cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′A**)
	−3635 t	269	S	*R,S/S,R-cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′B**)
	−3691 t	272	S	*S,S-cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′C**)
cis-$[PtCl_2(NH_3)_2]$ + 2L-MetH, pH* 5.1	−2982 t	280	N	*R-trans*-[Pt(L-MetH-*S*)$(NH_3)_2Cl]^+$ (minor) (**5A**)
	−2984 t	278	N	*S-trans*-[Pt(L-MetH-*S*)$(NH_3)_2Cl]^+$ (minor) (**5B**)
	−3044 t	280	N	*R-trans*-[Pt(L-Met-*S*,*N*)(NH_3)Cl] (minor) (**12A**)
	−3045 t	280	N	*S-trans*-[Pt(L-Met-*S*,*N*)(NH_3)Cl] (minor) (**12B**)
	−3444 t	295	N	*R,R-trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7′A**)
	−3466 t	293	N	*R,S/S,R-trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7′B**)
	−3506 t	290	N	*S,S-trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7′C**)
	−3628 t	280	S	*R,R-cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′A**)
	−3634 t	273	S	*R,S/S,R-cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′B**)
	−3692 t	277	S	*S,S-cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′C**)
cis-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ + L-MetH, pH* 4.8^c	−3147 q	275	N, S	*R*-[Pt(L-Met-*S*,*N*)$(NH_3)_2]^+$ (**14A**)
	−3161 q	275	N, S	*S*-[Pt(L-Met-*S*,*N*)$(NH_3)_2]^+$ (**14B**)
cis-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ + 2L-MetH, pH* 4.2^{c,d}	−3423 t	302	N	*R,R-*, *R,S/S,R-*, and *S,S-trans*-[Pt(L-MetH-*S*)$_2(NH_3)_2]^{2+}$ (**15**)
	−3412 t	296	N	*R,R/S-trans*-[Pt(L-Met-*S*,*N*)(L-MetH-*S*)$NH_3]^+$ (**16A**)
	−3460 t	287	N	*S,R/S-trans*-[Pt(L-Met-*S*,*N*)(L-MetH-*S*)$NH_3]^+$ (**16B**)

^{a} Key: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. ^{b} Tentative assignment of chirality. ^{c} *cis*-[Pt(L-Met-*S*,*N*)$_2$] also seen. ^{d} Sample not heated.

species (66%) detected were the two diastereomers of [Pt(L-Met-*S*,*N*)$(NH_3)_2]^+$ (**14**) together with smaller amounts (14%) of *cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′**) (Table VI) along with a broad featureless resonance at ca. −2900 ppm (20%). The ^{1}H NMR spectrum of this reaction mixture contained intense peaks assignable to [Pt(L-Met-*S*,*N*)$(NH_3)_2]^+$ (**14A,B**) (Table V) and other peaks assignable to *cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′A–C**) (Table V).

1:2 Reactions. ^{195}Pt NMR spectra of reactions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with L-MetH at a 1:2 mole ratio gave rise to spectra such as those shown in Figure 6 soon after mixing, but without heating. The use of $^{14/15}NH_3$/[$^{14/15}$N]-L-MetH substitutions in assignment is illustrated. In Figure 6b the triplet at −3423 ppm is unchanged, cf. Figure 6a, but is very broad in Figure 6c, indicating there are two equivalent $^{15}NH_3$ moieties bound to the Pt and no L-Met nitrogens. The $^1J(^{195}Pt-^{15}N)$ coupling of 302 Hz and the chemical shift are consistent with *trans*-[Pt(L-MetH-*S*)$_2(NH_3)_2]$ (**15**). Diastereomers of this complex are not resolved, presumably due to the high trans influence of the sulfur on the monodentate S–CH_3 causing fast flipping on the NMR time scale. The other two triplets at −3412 and −3460 ppm must have a very similar Pt coordination sphere, e.g. N_2S_2, but unlike the previous species, contain both coordinated ammine and amino N's (Figure 6b,c). This product, *trans*-[Pt(L-Met-*S*,*N*)(L-MetH-*S*)$NH_3]^+$ (**16**) has two diastereomers resolved due to the slow inversion rate of the chelated L-Met, and like *trans*-[Pt(L-Met-*S*)$_2(NH_3)_2]$, does not resolve the faster inversion of the monodentate S-bound L-Met with trans sulfur. It is interesting to note that in Figure 6b the $^{15}NH_3$ coupling for *trans*-[Pt(L-Met-*S*,*N*)(L-Met-*S*)$NH_3]^+$ is resolved even with the [^{14}N]-L-MetH coordinated. The reverse case in Figure 6c does not have this resolution. The three low frequency triplets contain ca. 60% of the total intensity. They have only L-Met bound as can be seen in Figure 6c and are assignable to the three diastereomers of *cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′**). The approximate relative proportions of products are as follows: **6′**, 60%; **16**, 28%; **15**, 12%. When this reaction was driven to apparent equilibrium by heating (30 min at 343 K), resonances for **6′** dominated the spectrum, the high-frequency peaks having disappeared as shown in Figure 7. In addition, three weak triplets are now visible in the range −3444 to −3506 ppm assignable to the three diastereomers of *trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7′**). The cis/trans ratio is ca. 10:1, and the relative diastereomer ratios *R,R*:*R,S*/*S,R*:*S,S* are 1:1.4:1 for the cis isomer, and 2.3:1:1.7 for the trans isomer, respectively. By integration, the relative proportions of species are as follows: **6′**, 89%; **7′**, 11%.

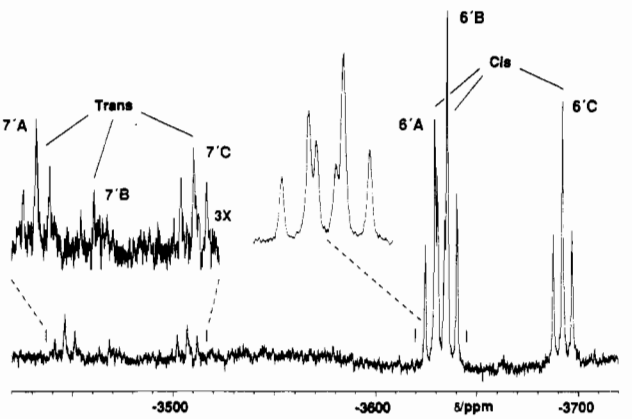

Figure 7. ^{195}Pt NMR spectrum of a 1:2 mixture of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2]^{2+}$ and [^{15}N]-L-MetH in D_2O, pH* 5.8, after reaction at 353 K for 30 min (at equilibrium) showing multiplets for *R,R-*, *R,S/S,R-*, and *S,S-cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′A–C**) and the trans analogues **7′A–C** present in ratios of ca. 10:1. Almost identical spectra were obtained from reactions of $[PtCl_4]^{2-}$ or *cis*-$[PtCl_2(^{15}NH_3)_2]$ with 2 mol equiv of [^{15}N]-L-MetH. The insets show expansions of peaks for three diastereomers of each geometrical isomer. The assignment of diastereomers is arbitrary at this stage, but the populations are clearly not statistical.

^{15}N NMR spectra of equilibrium mixtures containing ^{15}N-enriched L-MetH and cisplatin were investigated using INEPT methods. These spectra were very complicated due to the large number of magnetically distinct ^{15}N's present in many solutions together with the occurrence of ^{15}N–^{15}N couplings and further splittings due to sulfur inversion. Further work is being carried out to analyze these spectra and will be reported elsewhere. In summary, the spectra for the 1:1 reaction contained many peaks spanning the range ca. −20 to −75 ppm, together with an additional prominent peak for NH_4^+ at ca. 0.7 ppm. The spectra from 1:2 reaction mixtures were dominated by resonances at ca. −20 ppm assignable to *cis*-[Pt(L-Met-*S*,*N*)$_2$] (**6′**) with additional peaks at ca. 18 ppm from S-only bound L-Met in *trans*-[Pt(L-MetH-*S*)$(NH_3)_2Cl]^+$ (**5**), ca. −40 ppm due to *trans*-[Pt(L-Met-*S*,*N*)$_2$] (**7′**), and peaks in the range −60 to −70 ppm for NH_3 coordinated to Pt(II).[11]

Discussion

We have studied reactions between $[PtX_4]^{2-}$ (X = Cl, Br, I) and L-methionine and its derivatives under conditions of apparent

equilibrium; i.e., no further reaction appeared to take place with further standing at the same temperature. No attempt has been made here to follow the kinetics of the reactions.

1:1 Pt(II)–L-MetH Complexes. The ^1H, ^{13}C, ^{15}N, and ^{195}Pt NMR spectra from the reaction between $[PtCl_4]^{2-}$ and L-MetH are consistent with the formation of $[Pt(L\text{-MetH-}S,N)Cl_2]$ at pH* 1.9. This complex exists in two diastereomeric forms, **1A** and **1B**, dependent on the chirality of the coordinated thioether S. The observed ^{195}Pt shifts (2946 and −2955 ppm) and $^1J(^{195}Pt–^{15}N)$ coupling constant of 328 Hz are within the range expected for $PtNSCl_2$ coordination with ^{15}N trans to Cl. For example, *trans*-$[PtCl_2(Me_2SO\text{-}S)(Gly\text{-}N)]$ has a shift of −3110 ppm,[19] and a variety of trans chloro–ammine–Pt(II) complexes have $^1J(^{195}Pt–^{15}N)$ values of 326–347 Hz.[10,24–26]

Dynamic inversion at S (i.e. interconversion of complexes **1A** and **1B**) was confirmed by temperature-dependent ^1H and ^{15}N NMR studies. At 337 K (the coalescence temperature for S–CH_3 ^1H NMR peaks at 500 MHz) the ΔG^* value of 74.6 kJ mol^{-1} is greater than that determined previously for related monodentate thioethers such *N*-acetyl-L-methionine[15,16] (63.7 kJ mol^{-1} at 335 K) and therefore indicates that chelation increases markedly the energy barrier for sulfur inversion. In part, this may be related to changes in chelate ring conformation which accompany inversion.

There are significant differences in certain $^3J(^1H–^1H)$ values between isomers **1A** and **1B** (Table I), notably decreases in $^3J(H_\alpha–H_{\beta a})$ and $^3J(H_{\beta a}–H_{\gamma a})$ and increases in $^3J(H_{\beta b}–H_{\gamma b})$. Approximate ring conformations can be derived on the assumption that the magnitudes of ^3J values are similar to those reported previously for six-membered chelate rings, i.e., axial–axial of 9.2–12.5 Hz, axial–equatorial of 2–3.5 Hz, and equatorial–equatorial of 3–6.3 Hz for Pt(II)–propylenediamines.[27] This suggests that the chelate ring in isomer **1A** has an approximate envelope conformation (*R*, (+) configuration at sulfur) whereas isomer **1B** has a flattened boat conformation (*S*, (−) configuration at sulfur) (Figure 2). Both ^1H and ^{195}Pt NMR spectra suggest that isomer **1A** is present in slight excess (10%) over **1B** in solution. Increasing the pH* from 1.9 to 4.6 (ionization of the carboxyl group) has little effect on the ring conformations. Also, blocking the carboxylate by esterification had no effect on the course of the reaction: methionine methyl ester formed an S,N-chelated complex similar to that of L-MetH.

These data obtained for **1A** and **1B** in solution can be contrasted with those determined for the same complex in the solid state by X-ray crystallography[14] in which equal populations of the two diastereomers of $[Pt(L\text{-MetH-}S,N)Cl_2]$ were found with both chair conformations for the six-membered chelate ring and quasi-equatorial carboxyl groups and quasi-axial methyls. The conformations observed in the solid state may be influenced by the presence of intramolecular H-bonding involving the carboxyl groups, and by other crystal-packing effects. Similarly, the carboxyl groups in $[Pd(DL\text{-MetH})Cl_2]$ are involved in intermolecular H-bonding, but for this complex the determination of ring conformations appeared to be hampered by radiation damage to the crystal.[28]

The absence of carboxylate coordination to Pt(II) in solution, under the conditions studied here, is confirmed by the pK_as determined for the carboxylates of isomers **1A** (2.57) and **1B** (2.58), which are the same within experimental error, and similar to that of free L-MetH (2.20).[29] Ionization of the carboxyl group has little effect on the ring conformations of **1A** and **1B** in solution (cf. ^3J values, Table I).

When the halide in $[Pt(L\text{-MetH-}S,N)X_2]$ is changed from Cl to Br to I, the ^{195}Pt NMR shifts follow the expected trend moving to lower frequency, and the value of $^1J(^{195}Pt–^{15}N)$ decreases from 328 to 306 Hz for Br and to 262 Hz for I, in accordance with the increasing trans influence of the halide.[25,26,30] The shift difference for ^{195}Pt NMR peaks of isomers **A** and **B** decreases markedly in the order Cl (530 Hz) > Br (140 Hz) > I (0 Hz) at 279 K, 57.9 MHz, such that only one doublet is observed for the iodide complex at this temperature, presumably due to rapid S inversion on the NMR time-scale. The activation free energy for sulfur inversion was slightly greater with Cl^- (74.6 kJ mol^{-1}, 337 K) as a trans ligand compared to Br^- (71.8 kJ mol^{-1}, 335 K). This is the expected order based on the relative trans influences of halide ions $Cl^- < Br^- < I^-$.[31] The $^3J(H–H)$ values (Table I) suggest that the ring conformations in complexes **2A** and **2B** are similar to those of **1A** and **1B**.

It was notable that in 1:1 reactions involving $[PtBr_4]^{2-}$ an additional small singlet assignable to $[Pt(L\text{-MetH-}S)Br_3]^-$ (**3**) was seen in the ^{195}Pt NMR spectrum, suggesting that Br^- competes more strongly than Cl^- for ring closure. An analogous species may also be present in iodide mixtures but the solubilities of the iodide complexes were too low (poor S/N ratios) to allow investigation of this.

1:2 Pt(II)–L-MetH Complexes. The species formed in 1:2 mixtures of $[PtCl_4]^{2-}$ and L-MetH are most readily identified in ^{195}Pt NMR spectra using ^{15}N-enriched L-MetH. The two high-frequency 1:1:1:1 quartets (297 K) are assignable as two sets of two doublets to the four diastereomers of *cis*-$[Pt(L\text{-MetH-}S,N)(L\text{-MetH}_2\text{-}S)Cl]^{2+}$ (**5**) (Figure 3), present in approximately equal proportions. At high temperature, these coalesce to two doublets, each with splittings of 258 Hz, a value within the range expected for $^1J(^{195}Pt–^{15}N)$ couplings with ^{15}N trans to S.[25,26] These resonances are assigned to diastereomers which differ in the chirality of chelated L-MetH. The slow inversion rate of thioether S in such a chelate ring was also seen for $[Pt(L\text{-MetH-}S,N)Cl_2]$ as described above. At low temperature, the observation of four species can be ascribed to the freezing out of S inversion for the monodentate L-$MetH_2$. For the isomers **5A** and **5B**, the inversion rate of S in the monodentate L-$MetH_2$ was calculated to be 269 s^{-1} at the coalescence temperature (323 K), giving an associated ΔG^* of 64.3 kJ mol^{-1}. For the other two isomers **5C** and **5D**, *k* and ΔG^* values were 193 s^{-1} and 66.0 kJ mol^{-1}, respectively, at 327 K. At this stage the assignment of chirality is arbitrary, but to be consistent with the labeling of the 1:1 complex, we have assumed that *R* centers give the highest frequency ^{195}Pt shifts. These values of *k* and ΔG^* are similar to those observed previously for nonchelated monodentate methionine derivatives in complexes such as $[Pt(L\text{-NAc-Met})Cl_3]^-$.[16]

On the basis of a consideration of both the ^{195}Pt and ^{15}N NMR data, ^{195}Pt triplets at −3634, −3640, and −3676 ppm can be assigned to *cis*-$[Pt(L\text{-MetH-}S,N)_2]^{2+}$ complexes. These species have two equivalent bound nitrogens and $^1J(^{195}Pt–^{15}N)$ values of ca. 270 Hz, which are within the range expected for N trans to S. Their chemical shifts are consistent with N_2S_2 coordination for Pt(II).[25] The three sets of triplets are therefore assigned to the three possible diastereomers (i.e. **6A–C** with *R,R*, *R,S*/*S,R*, and *S,S* chirality at sulfur, respectively). They have nonstatistical populations and slow inversion at sulfur on the NMR time scale due to the presence of chelate rings (no collapse of multiplets up to 343 K).

At higher pH, resonances for ring-opened species are not seen and only the bischelated complexes are observed. At pH* 7.2, three intense triplets are clearly resolved, assignable to the three diastereomers of *cis*-$[Pt(L\text{-Met-}S,N)_2]$. Ring-opening and closure is reversible by reversal of pH*, but only one chelate ring appears to open at low pH*. Triplet resonances of low intensity at −3444, −3462, and −3498 ppm (^1J = 290–292 Hz, Table III) are assigned to the diastereomers of *trans*-$[Pt(L\text{-MetH-}S,N)_2]$, consistent with

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the usual cis/trans shift changes for isomers.[25,26] These account for about $^1/_{10}$th of the 1:2 complexes. The relative populations of *R,R R,S/S,R*, and *S,S* diastereomers for *cis*-[Pt(L-Met-*S,N*)$_2$] are 1.3:1:1 and for *trans*-[Pt(L-Met-*S,N*)$_2$] are 2:1:1.5 respectively. Carturan and Rizzardi[13] assumed that the reaction of L-MetH with **1** gives the trans isomer of **5** followed by ring closure to form the trans isomer **7** and determined the rate of ring closure to be 25 ± 0.9 s^{-1} (308 K) by UV spectroscopy. Although the trans isomer may be the kinetically favored product, it seems likely that isomerization occurs to give thermodynamically more stable cis isomers which predominate under our conditions.

Although difficult to analyze because of the large number of overlapping multiplets, the ^{1}H NMR spectrum of the 1:2 mixture of [PtCl$_4$]$^{2-}$ and L-MetH shows that there are at least five pairs of species involved in exchange processes at low pH*. The coalescence behavior of the S–CH$_3$ singlets with increasing temperature suggests that different types of coordinated sulfur are present, both nonchelated and chelated. The singlet at 2.691 ppm, which did not show any coalescence behavior, is likely to arise from monodentate (S-bound) L-MetH$_2$, whereas the behavior of the remaining S–CH$_3$ peaks is consistent with the presence of at least two other types of (S,N)-chelated L-MetH. Attempts to analyze ^{1}H spectra at neutral pH* where the predominant species is *cis*-[Pt(L-Met-*S,N*)$_2$] (**6′**) were complicated by broadening. This may arise from chemical exchange processes such as changes in ring conformations since some sharpening of the peaks was observed on cooling the sample to 268 K.

The ^{15}N NMR peak at 18.50 ppm in the spectrum of the 1:2 mixture of [PtCl$_4$]$^{2-}$ and L-MetH at pH* 1.9 (Figure 4) is close to that of free L-MetH (20.3 ppm) and can be assigned to the uncoordinated amino group (dangling arm) of monodentate L-MetH$_2$ in *cis*-[Pt(L-MetH-*S,N*)(L-MetH$_2$-*S*)Cl]$^{2+}$ (**5**). This peak disappears (reversibly) with increase in pH to 8.7, i.e., with ring closure. Ring opening of chelated diamine–Pt(II) complexes has been reported previously but was observed only in strongly acidic solutions.[32] The remaining two groups of ^{15}N peaks at ca. −23.5 ppm and −41 ppm are assignable to *cis*-[Pt(L-MetH-*S,N*)$_2$]$^{2+}$ (together with the chelated L-MetH of the dangling arm complex) and to the trans analogue, **7′**, respectively. The latter species was present in only minor quantities and was not detectable in the ^{195}Pt NMR spectrum at low pH. The ^{15}N chemical shift difference (ca. 17 ppm) between the cis and trans isomers of [Pt(L-MetH-*S,N*)$_2$]$^{2+}$ is similar to values reported previously[11] for complexes in which the ligand trans to ^{15}N changes from S to N. At pH 8.7 and 343 K only two ^{15}N resonances with associated ^{195}Pt satellites are seen, Figure 4, corresponding to *cis*- and *trans*-[Pt(L-Met-*S,N*)$_2$] showing that the inversion of S in chelated L-Met is now fast on the ^{15}N NMR time scale. From the coalescence temperatures, $\Delta G^{\ddagger}$ values of ca. 67.1 and 65.5 kJ mol^{-1} were calculated for the cis and trans isomers respectively. No attempt was made to distinguish between the possible interchange pathways for the various diastereomers. Peaks for **6′** and **7′** are readily detected in reactions of cisplatin with L-MetH (1:2). The observed ^1J(^{195}Pt–^{15}N) values of 277 and 292 Hz for the cis and trans isomers, respectively, reflect the change in trans ligand from S to N.

The factors which lead to the stabilization of the cis complexes **6′** and **5** relative to the trans isomers **7′** require further investigation. They are likely to involve both steric and electronic effects; however, we note that cis-coordinated –NH$_2$ groups provide a potential site for strong H-bonding, e.g., involving a water molecule. Attempts to crystallize 1:2 Pt(II)–Met complexes have so far not succeeded and the complexes are currently being purified by chromatographic techniques. Perhaps further analysis, especially of ^{1}H NMR spectra, will then be possible.

The identity of the dangling-arm chloro complex *cis*-[Pt(L-MetH-*S,N*)(L-MetH$_2$-*S*)Cl]$^{2+}$ (**5**) was confirmed by generating the corresponding bromo complex (**8**) by reaction of [PtBr$_4$]$^{2-}$ with 2 mol equiv of L-MetH. The three ^{195}Pt triplets assigned to *cis*-[Pt(L-MetH-*S,N*)$_2$]$^{2+}$ (**6**) were again observed, slightly shifted to higher frequency, presumably due to second-coordination-sphere effects, together with a doublet and two overlapping doublets with shifts consistent[25,26] with the replacement of Cl$^-$ by Br$^-$ (shift change of ca. −117 ppm) in a position trans to the S of chelated L-MetH. In reactions involving Br$^-$, singlets were also seen in ^{195}Pt NMR spectra and on the basis of shifts are tentatively assigned to **9**.

The isolation of [Pt(L-Met-*S,N*)$_2$] from the urine of patients treated with cisplatin has been reported,[4] and it has been assumed that it is the trans isomer, as might be expected on kinetic grounds in view of the high trans effect of S.[31] In our experiments, products observed are likely to be the most thermodynamically stable ones and the cis form was always predominant. Only the cis form of the dangling arm complex **5** was seen at low pH, and hence ring closure would be expected to produce the cis ring-closed complex.

Reactions of Cisplatin and *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ with Methionine. There are only a few previous studies of reactions between cisplatin or *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ and methionine. In an early study, Volshtein et al.[13] proposed the formation of [Pt(MetH)(NH$_3$)$_2$]$^{2+}$, [Pt(MetH)$_2$(NH$_3$)$_2$]$^{2+}$, and [Pt(MetH-*S,N*)(MetH-*S*)(NH$_3$)]$^{2+}$ from reactions of cisplatin (Peyrone's chloride) with MetH. Appleton et al.[11] characterized [Pt(MetH-*S,N*)(NH$_3$)$_2$]$^{2+}$ by multinuclear NMR as a product from the reaction of L-MetH with *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ near pH 5 and in acidic solutions (pH < 0.5) detected the presence of [Pt(L-MetH$_2$-*S*)$_2$(NH$_3$)$_2$]$^{4+}$ and [Pt(L-MetH-*S,O*)(NH$_3$)$_2$]$^{2+}$. They also noted that the complexes readily lost coordinated ammonia. Release of complexed ammonia has also been detected by NMR (^{14}N) in reactions of cisplatin with methionine in blood plasma.[8] There has been considerable interest in both the potential cytoxicity and therapeutic activity of products from reactions of cisplatin with methionine, but it is often assumed that mixing stoichiometric amounts (typically 1:1 and 1:2) produces corresponding 1:1 and 1:2 Pt–Met products. HPLC analyses of the products of such reactions have shown that several species can be formed, but there has been little attempt to identify them.[4,7,33,34] An exception is the characterization by mass spectrometry of [Pt(Met)$_2$], isolated from the urine of patients treated with cisplatin.[4] This was formulated as the trans isomer.

The major products from the 1:1 reaction (14 mM cisplatin) at pH* 7 in phosphate buffer at 310 K are formed within 2 h. The time course of the reaction is most easily followed by ^{1}H NMR spectroscopy, but assignments of peaks can be made only with the aid of ^{195}Pt NMR spectra of similar solutions containing ^{15}N-enriched reactants. It is evident from the ^{31}P NMR spectrum that phosphate coordination plays a minor role in these reactions. Similar high-frequency-shifted ^{31}P NMR peaks have been observed in solutions of *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ containing phosphate[35,36] and nucleotide phosphates.[37] We did not attempt to identify the phosphate-containing complexes because the major species seen in 1:1 reactions of L-MetH with cisplatin were also detected in the absence of phosphate (at the same pH*). One of the major products is [Pt(L-Met-*S,N*)(NH$_3$)$_2$]$^+$ (**14**) for which Appleton et al.[11] have reported ^{1}H, ^{15}N (^{15}NH$_3$), and ^{195}Pt NMR data ([^{14}N]-L-Met complex). The ^1J(^{195}Pt–^{15}N) values for all three N's in this complex are similar (271–277 Hz), even though one NH$_3$ is trans to NH$_2$ and the other is trans to S. The diastereomer with the lowest frequency ^{195}Pt shift (arbitrarily assigned *S* chirality, **14B**) is more abundant (**14A**:**14B** is ca. 1:1.5).

The slow sulfur exchange observed for the ^{195}Pt NMR peaks of **14A** and **14B** even at 343 K is consistent with the relatively high activation barrier expected for chelated L-Met. The markedly different ^3J(^{1}H–^{1}H) values, as reported previously,[11] Table V,

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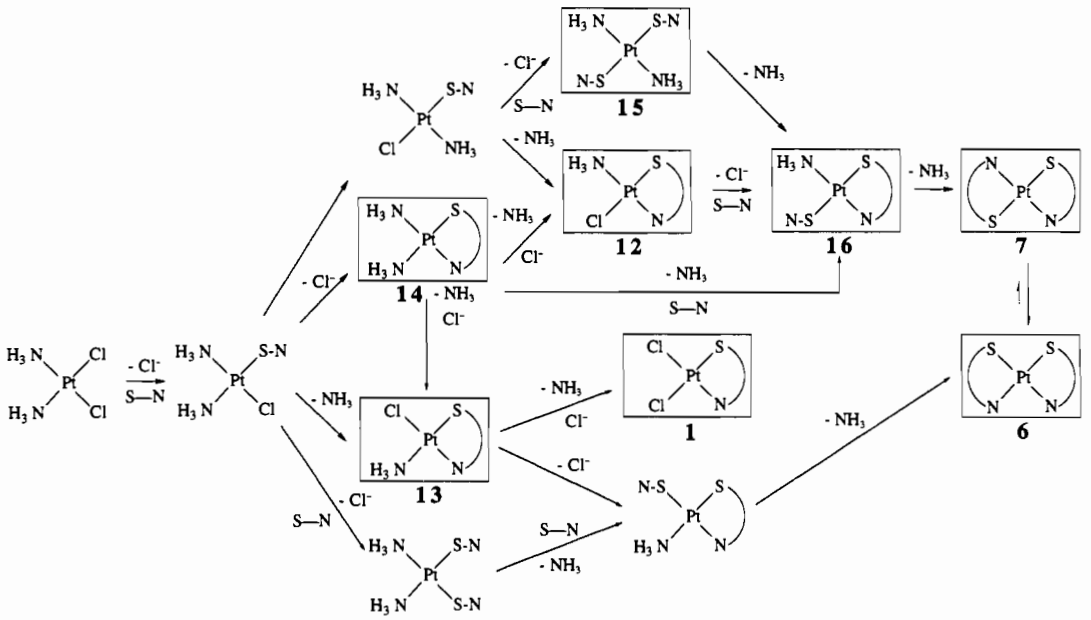
Scheme I. Possible Reaction Pathways for the Formation of *cis*- and *trans*-Pt(Met)$_2$ from Cisplatin and L-MetH[a]



[a] No charges are shown on complexes; L-Met is represented as S–N. Species detected by NMR are boxed. A trace of **1** was detected, as seen previously in reactions of $[PtCl_4]^{2-}$ with L-MetH. Species **15** and **16** are included, but were detected only during the initial stages of reactions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with 2 L-MetH. For the latter, no complexes containing H_2O (or OH^-) were detected. Reactions of cisplatin and its diaqua complex with excess methionine gave **4** as the predominant product (>80%).

suggest that these diastereomers have different ring conformations. From a consideration of models, it would appear that pseudo-equatorial S–CH_3 and CO_2^- groups are maintained on inversion of sulfur, with accompanying changes in the ring conformations from envelope-like (major form) to boat-like (minor form). A similar trend is observed for isomers of [Pt(L-MetH-*S*,*N*)X_2] (X = Cl, Br).

Other prominant products from the 1:1 reaction are *trans*- and *cis*-[Pt(L-Met-*S*,*N*)(NH_3)Cl], **12** and **13**, respectively. The ^{195}Pt NMR resonances for (^{15}N-labeled) **12** and **13** have curious features. The simple triplet for **12** resolves into two triplets at higher temperature with intensity ratios of 1.5:1, assumed to represent the populations of *R*(**12A**):*S*(**12B**) diastereomers. The resolution presumably results from their different temperature dependences (0.3–0.4 ppm/K) whereas the increased S inversion rate at higher temperature might have been expected to lead to their coalescence, as is observed for **13** at 343 K. For **13**, the observed *R*:*S* populations are ca. 1:1. It would appear therefore that the differences in diastereomer populations are greater for complexes with NH_3 cis to S compared to Cl cis to S. The formation of **12** and **13** involves loss of NH_3 from cisplatin with nearly twice as much **12** formed compared to **13**. The detection of 1:2 complexes (**6′**) in 1:1 reactions implies the presence of either non-methionine-bound Pt(II) or oligomers of the type $Pt_x(Met)_y$ ($x/y > 1$) in solution. It is possible that unassigned, broad ^{195}Pt peaks in the range −2900 to −3010 ppm are assignable to the latter type of species, but additional ^{195}Pt NMR peaks may also be present in regions of the spectrum other than that scanned (total scan range for 1:1 reaction mixture was −1540 to −4100 ppm). Complex **6′** is more easily characterized in 1:2 reactions as it is always the major product.

Definitive identification of the equilibrium products formed from the reaction of *cis*-$[PtCl_2(NH_3)_2]$ with 2 mol equiv of L-MetH was possible only using ^{195}Pt NMR and $^{14/15}NH_3$/[$^{14/15}$N]-L-MetH labeled starting materials (e.g. see Figure 6). The major products were the three diastereomers of *cis*-[Pt(L-Met-*S*,*N*)$_2$] (^1J = 277 Hz, Table VI). The ^1J values for the trans diastereomers are slightly higher (ca. 290 Hz) and the ^{15}N shifts for the latter complexes (ca. −40 ppm) are low-frequency-shifted relative to those of cis complex (ca. −20 ppm). Thus it appears likely that the Pt(Met)$_2$ metabolite present in the urine of patients treated with cisplatin is also predominantly the cis isomer, although there could be certain solution conditions which favor stabilization of one isomer over the other. The nature of the initial ligands on platinum appears to play little part in determining the cis/trans ratio, which is similar starting from $[PtCl_4]^{2-}$, *cis*-$[PtCl_2(NH_3)_2]$ or *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$. There is however some variation in the ratio of the *R*,*R*, *R*,*S*/*S*,*R*, *S*,*S* diastereomers of both the cis and trans isomers. Further work is required to determine how this depends on ionic strength, temperature, and solvent and other factors relevant to biofluids. Hydrogen-bonding interactions involving cis-coordinated NH_2 groups and e.g. H_2O or urea could play a role in stabilizing cis configurations.

Although ^{15}N spectra are very complicated, peaks in the expected range for S-only bound L-Met and NH_4^+ are seen for reaction mixtures of L-MetH with cisplatin or the diaqua complex. Full analysis of ^{15}N data requires further 2D and decoupling experiments.

An attempt to relate the observed products from the reactions of cisplatin with L-MetH to plausible pathways is shown in Scheme I. A similar scheme may apply to the diaqua complex, but no species containing coordinated H_2O (or OH^-) were detected. It must be borne in mind that, for the samples used for ^{15}N or ^{195}Pt NMR, much of the cisplatin began in suspension; i.e., initially there was a greater than 1:1 or 1:2 Pt:L-MetH ratio in solution. Some of the products may therefore form by reverse reactions involving Cl^- or NH_3 coordination. However, for the 1:1 reaction in which a comparison was made from ^{1}H NMR spectra between low (homogeneous solution) and high (suspension) concentrations of reactants, the products appeared to be qualitatively similar. Methionine ring closure (S,N) appears to be a very favorable reaction at neutral pH. Ring-opening (S-only-bound L-Met) is observed only during the early stages of reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ or at low pH.[11] The pathways appear to be dominated by the high trans effect of S as expected. Complex **12**, which was a major product in 1:1 reactions, may arise from **14** by NH_3 displacement and Cl^- reattack. This is consistent with the observed temperature dependence of speciation, which results in successively less **14** and more **12** with increasing temperature. Products **15** and **16** were detected in reactions of the diaqua complex with 2 L-MetH (without heating) and may be reactive intermediates in reactions of cisplatin, but were not detected in any equilibrium mixtures. They may form the aqua (or hydroxo) analogue of *trans*-[Pt(L-MetH-*S*)$(NH_3)_2$Cl]$^+$, *trans*-[Pt(L-MetH-*S*)$(NH_3)_2(OH_2)]^{2+}$, for which substitution of coordinated H_2O by a second L-MetH is likely to occur rapidly, to give **15**,

which via ring closure gives **16**.

Conclusions

We have shown here that considerable insight into the structures and dynamics of both 1:1 and 1:2 Pt(II)-L-methionine complexes in solution can be obtained via the use of high-field ^{1}H NMR spectroscopy, combined with ^{195}Pt and ^{15}N NMR spectroscopy, especially with the use of ^{15}N enrichment of L-MetH and polarization-transfer methods for observing ^{15}N resonances. The major thermodynamic products from reactions of 2 mol equiv of L-MetH with $[PtCl_4]^{2-}$ at pH* 7 are the three diastereomers of *cis*-[Pt(L-Met-*S*,*N*)$_2$] with only minor (10%) amounts of the analogous trans complexes. The cis complex undergoes reversible ring-opening at low pH to give four diastereomers of [Pt(L-MetH-*S*,*N*)(L-MetH$_2$-*S*)Cl]$^{2+}$.

The activation barriers for sulfur inversion are higher in the ring-closed compared to the ring-opened forms. We have shown for the 1:1 complex [Pt(L-MetH-*S*,*N*)Cl$_2$] that sulfur inversion in solution is accompanied by a change in the conformation of the six-membered chelate ring, whereas such a difference has not been observed in crystal structures of this and related complexes. Such conformational changes may be important for recognition processes involved in the transport and excretion of Pt(II)-methionine complexes.

Reactions of the anticancer drug cisplatin with the amino acid L-methionine are important because it has been suggested that certain products resulting from the reaction are nephrotoxic.[5] Renal ATPases appear to be more sensitive to inhibition by these products than by cisplatin alone.[38] A complex formulated as the trans isomer of [Pt(Met)$_2$] has been isolated from the urine of patients treated with the drug.[4] For reactions of $[PtCl_4]^{2-}$ with 2 mol equiv of L-MetH in aqueous solution near neutral pH the most stable form of the 1:2 complex is *cis*-[Pt(L-Met-*S*,*N*)$_2$], which exists as three diastereoisomers in equilibrium with minor amounts of the analogous diastereomers of the trans geometrical isomer. These same products, **6'A-C** and **7'A-C**, arise from similar reactions of cisplatin or *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with methionine. The use of combined ^{1}H, ^{15}N, and ^{195}Pt NMR spectroscopy on ^{15}N-enriched materials enabled a number of additional products to be identified, including monoammine complexes containing chelated or monodentate L-Met **12**, **13**, and **16**. Clearly each of these products may have significantly different biological activities and this may affect the interpretation of reported nephrotoxicity and anticancer data obtained from tests on reaction mixtures of cisplatin and methionine.[5] The products from these reactions now need to be separated and tested individually. The bischelated complexes **6'** and **7'** may be inactive and nontoxic; e.g., Melvik and Pettersen[39] found that the presence of excess methionine in culture media greatly reduced the toxicity of cisplatin toward cells. However, as we have shown, facile ring-opening reactions of the bischelated species can occur at low pH, and since some parts of biological cells (lysosomes) can be quite acidic, even bischelated species may become reactive.

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Supplementary Material Available: A figure showing ^{195}Pt NMR spectra at 297, 323, and 343 K of a 1:1 mixture of *cis*-$[PtCl_2(^{15}NH_3)_2]$ (110 mM) and [^{15}N]-L-MetH in 0.1 M deuteriated phosphate buffer, pH* 5.8 (1 page). Ordering information is given on any current masthead page.

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Oxidative Decarbonylation of Transition Metal Carbonyls by Arsenic Selenide Anions: Preparation and Structures of $[M(CO)_2(As_3Se_3)_2]^{2-}$ and $[M(AsSe_5)_2]^{2-}$ (M = Mo, W)

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The reactions of arsenic selenide anionic clusters with $M(CO)_6$ (M = Mo, W) were investigated and the products characterized by IR and ^{77}Se NMR spectroscopy and single-crystal X-ray diffraction of bis (n-Bu)$_4$N$^+$ salts in each case. The reaction of $As_4Se_6^{2-}$ with $M(CO)_6$ generates $[M(CO)_2(As_3Se_3)_2]^{2-}$ (I) in reasonable yield. Compound I contains two As_3Se_3 birdcage fragments bound to the metal center with the metal acting as a basal vertex, completing the birdcage structure of each fragment. The metal is also coordinated by two CO ligands, generating a bicapped trigonal prismatic ligand framework. The reaction of $As_2Se_6^{2-}$ with $M(CO)_6$ generates $[M(AsSe_5)_2]^{2-}$ (II). The metal center is in an irregular coordination environment with three terminal selenides from two $AsSe_5^{3-}$ ligands coordinated to the metal center. Molecule I can be converted to II by addition of red selenium. Reaction mechanisms for the formation of each product are proposed. Crystal data for $[(n\text{-Bu})_4N]_2[[W(CO)_2(As_3Se_3)_2]$: space group $P\bar{1}$, a = 11.575 (3) Å, b = 23.324 (5) Å, c = 30.663 (6) Å, α = 95.63 (2)°, β = 100.01 (2)°, γ = 96.73 (2)°, V = 8036 (3) Å^3, Z = 6, R = 0.0753. Crystal data for $[(n\text{-Bu})_4N]_2[W(AsSe_5)_2]$: space group $C2/c$, a = 18.240 (6) Å, b = 15.434 (5) Å, c = 18.003 (5) Å, β = 103.71 (2), V = 4923 (2) Å^3, Z = 4, R = 0.0716.

Introduction

The coordination chemistry of transition metal sulfides is rich and varied,[1] and their importance in biological[2] and industrial catalytic processes[3] is a driving force for their continued study. Recent investigation of metal selenides and tellurides suggests that the heavier elements will lead to even more unusual chemistry.[4]

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