Oxidative Addition of the Dithiobis(formamidinium) Cation to Platinum(II) Chloro Am(m)ine Compounds: Studies on Structure, Spectroscopic Properties, Reactivity, and Cytotoxicity of a New Class of Platinum(IV) Complexes Exhibiting *S*-Thiourea Coordination

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Received March 22, 1996[⊗]

The oxidative addition of the salt $[\{SC(NMe_2)_2\}_2]Cl_2\cdot 2H_2O$ (**1**), the disulfide-like dimerized form of 1,1,3,3-tetramethylthiourea (tmtu), to Pt(II) chloro am(m)ine compounds is described. Oxidation of the $[PtCl_3(NH_3)]^-$ anion with **1** in methanol yields *cis*-$[PtCl_4(NH_3)L]$ (**2**; L = tmtu) as the result of the *trans* addition of one tmtu and one chloro ligand. The same mode of oxidation is found in reactions of **1** with $[PtCl(dien)]^+$ (dien = diethylenetriamine) and *trans*-$[PtCl_2(NH_3)_2]$. In these cases, however, the oxidation is followed by (light-independent) *cis,trans* isomerizations, giving *trans,mer*-$[PtCl_2(dien)L]Cl_2$ (**4**) and *fac*-$[PtCl_3(NH_3)_2L]Cl\cdot 0.5MeOH$ (**6**), respectively. The single-crystal X-ray structures of **2** and *trans,mer*-$[PtCl_2(dien)L](BF_4)_2$ (**4a**) have been determined. **2**: monoclinic, space group $P2_1/n$, $a = 6.280(1)$ Å, $b = 13.221(3)$ Å, $c = 16.575(2)$ Å, $\beta = 96.45(1)°$, $Z = 4$. **4a**: monoclinic, space group $C2/m$, $a = 21.093(5)$ Å, $b = 8.9411(9)$ Å, $c = 14.208(2)$ Å, $\beta = 124.65(2)°$, $Z = 4$. The tmtu ligands are S-bound. In **2** a pronounced *trans* influence of the S-donor ligand on the Pt−Cl bond (2.370(1) Å) trans to sulfur is observed. The unusual acidity of the Pt(IV) complexes exhibiting tmtu coordination trans to chloride is attributed to hydrolysis of the labilized $Pt-Cl_{trans}$ bond, which is supported by ion sensitive electrode measurements. An upfield shift of the ^{195}Pt resonances is found on changing the ligand combination from NCl_4S (**2**) to N_3Cl_2S (**4**). This order correlates with the *trans* influences of the ligands: tmtu > am(m)ine > chloride. The cytotoxicity of **2** and **6** in L1210 cell lines is reported and discussed in terms of a possible mechanism of action of the compounds *in vivo*. It is suggested that tmtu may act as a lipophilic carrier ligand and therefore enhance the cellular uptake of the new potential Pt(IV) drugs.

Introduction

Cisplatin, *cis*-diamminedichloroplatinum(II) (*cis*-DDP), the most widely used platinum-based antitumor drug, has been in clinical use for about two decades. In spite of its impressive therapeutic success in the treatment of urogenital cancers, drug resistance and severe toxic side effects remain the major limitations.[1] Thus, the development of novel Pt antitumor drugs with an overall broader spectrum of activity and reduced toxicity is still a synthetic goal in this area of bioinorganic chemistry.

Since the early studies of Rosenberg and co-workers[2] it has been known that antitumor activity is not restricted to complexes containing divalent platinum but is also observed for analogous hexacoordinated Pt(IV) complexes with additional chloro or hydroxo ligands in the axial positions. Pt(IV) complexes in general are coordinatively saturated, kinetically inert 18-electron compounds which, unlike Pt(II) species, do not undergo associative substitution reactions.[3] For that reason it is generally assumed that the mechanism of action of Pt(IV) antitumor complexes involves prior reduction to the analogous Pt(II) form by intracellular bioreductants such as glutathione.[4] Furthermore, it has been concluded from DNA unwinding experiments that Pt(IV) complexes do not form bifunctional adducts with DNA[5] (the putative cytotoxic lesion of *cis*-DDP) unless they are reduced to divalent species after addition of glutathione.[6]

Until recently, axial coordination in Pt(IV) antitumor complexes was restricted to chloro and hydroxo ligands which are normally introduced through oxidation of suitable Pt(II) precursors with chlorine or hydrogen peroxide, respectively.[7] Tetraplatin, tetrachloro(*d,l-trans*-1,2-diaminocyclohexane)platinum(IV), was found to exert promising activity *in vivo* and to be non-cross-resistant to *cis*-DDP.[8] Unfortunately, this drug proved to be too neurotoxic to be a candidate for further clinical trials.[9]

The recent development of acid-stable, lipophilic Pt(IV) *trans*-dicarboxylato complexes stimulated interest in the effects of novel axial ligands on the biological properties of Pt(IV)-based antitumor compounds. (*OC*-6-43)-bis(acetato-*O*)amminedichloro(cyclohexanamine)platinum(IV) (JM-216) is the most likely derivative to become the first orally administered Pt-containing anticancer drug and is currently undergoing worldwide clinical trials.[10] Interestingly, these compounds show enhanced cytotoxicity with increasing lipophilicity of the carboxylato ligands.[11] It has been demonstrated that the variation of axial ligands

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⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1996.

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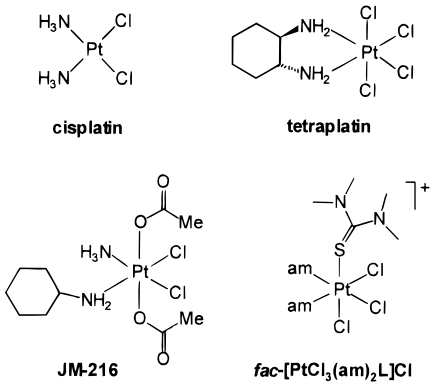
S0020-1669(96)00314-X CCC: $12.00

Chart 1



significantly changes the redox properties[6] of such compounds, which might exert an influence on the reduction kinetics and, consequently, on the biological activity of the Pt(IV) (pro)drugs.

We recently reported on a new class of water-soluble cationic Pt(IV) complexes of general formula *fac*-$[PtCl_3(am)_2L]Cl$ (Chart 1; am = NH_3, $(am)_2$ = diamine, L = 1,1,3,3-tetramethylthiourea (tmtu)).[12] Compounds of this type were accessible via an unusual oxidative addition of the dithiobis(formamidinium) dichloride salt,[13] the disulfide-like oxidized form of tmtu, to cisplatin and analogous compounds. The parent compound (derived from *cis*-DDP) was tested for its antitumor activity in mice bearing P388 leukemia and showed a significant activity comparable with *cis*-DDP at equitoxic dosages.[14] As a continuation of our synthetic studies we were now interested in analogous Pt(IV) compounds derived from Pt(II) precursors exhibiting either no or only minor cytostatic activity.[15] We therefore extended our novel oxidative addition to the ionic species $[PtCl_3(NH_3)]^-$ and $[PtCl(dien)]^+$ (dien = diethylenetriamine) and to *trans*-$[PtCl_2(NH_3)_2]$, transplatin. This paper reports on synthetic aspects as well as on effects of the S-donor ligand on structure and reactivity of the novel Pt(IV) complexes. Their cytostatic activity will be discussed and related to their molecular structures.

Experimental Section

Materials and Procedures. The starting complexes $K[PtCl_3(NH_3)]$ and [PtCl(dien)]Cl were synthesized by the published methods of Abrams[16] and Roat.[17] The salt *fac*-$[PtCl_3(NH_3)_2\{SC(NMe_2)_2\}]$-Cl·0.5MeOH (**6**) was synthesized by the published procedure.[12] All other reagents and solvents were obtained commercially and used as supplied**.** All syntheses and physical measurements in solution reported below were performed in the dark to exclude the influence of light on product formation and reactivity of the new compounds.

Physical Measurements. ^{1}H NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz. All chemical shifts are referenced to TMS, except for spectra taken in D_2O, where DSS (4,4-dimethyl-4-silapentanesulfonic acid) served as internal standard. ^{195}Pt NMR spectra were taken at 64 MHz at 295 K with a solution of $Na_2[PtCl_6]$ in D_2O as external standard. IR spectra were obtained as KBr pellets on a Perkin-Elmer 1600 FTIR instrument. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ. Changes in pH and chloride concentrations of aqueous solutions of **2**−**4** and **6** were followed in time with a Beckman combination electrode and a chloride-sensitive electrode (Fisher Scientific solid-state ISE) equipped with an Ag/AgCl reference electrode, respectively. All compounds were dissolved in 20 μL of DMF and were injected into 50 mL of gently stirred demineralized water of pH 6.8−7.2, making the resulting solutions either 10^{-4} or 10^{-3} M in platinum compound. Hydrolysis was then followed during the first 30 min after injection with an Accumet 925 pH/mV meter equipped with a suitable electrode.

Synthesis of Dithiobis(1,1,3,3-tetramethylformamidinium) Dichloride Dihydrate (1). The compound was synthesized according to a procedure published earlier[13] but was isolated as the dihydrate salt. Removal of the crystal water is possible by prolonged heating at 60−70 °C in vacuo but was found to result in partial decomposition of the compound. ^{1}H NMR (D_2O): δ 3.39 (24 H, s). IR: ν_{as}(CN) 1606 cm^{-1}. Anal. Calcd for $C_{10}H_{28}N_4Cl_2O_2S_2$: C, 32.34; H, 7.59; N, 15.08. Found: C, 32.41; H, 7.57; N, 15.19.

Synthesis of (*OC*-6-32)-Amminetetrachloro(1,1,3,3-tetramethylthiourea-*S*)platinum(IV) (2). A mixture of 1.79 g (5 mmol) of $K[PtCl_3(NH_3)]$ and 1.95 g (5.25 mmol, slight exess) of **1** in 150 mL of anhydrous MeOH was stirred in the dark. The formation of a clear orange-red solution indicated completion of the reaction (ca. 1.5−2 h). The solution was then concentrated to a volume of 50 mL at room temperature under reduced pressure. Precipitation of **2** occurred after storing the mixture at 4 °C for 24 h. Fine orange needles of **2** were collected by filtration and were subsequently washed with small portions of water, EtOH, and diethyl ether and dried: yield 1.67 g, 69%. ^{1}H NMR (DMF-d_7): δ 3.37 (12 H, s), 5.95 (3 H, sept, $^1J(^{14}N-^1H) = 53$ Hz, $^2J(^{195}Pt-^1H) \approx 50$ Hz). IR: ν(NH) 3252, 3148, 3078 cm^{-1}; ν_{as}-(CN) 1579 cm^{-1}. Anal. Calcd for $C_5H_{15}N_3Cl_4PtS$: C, 12.49; H, 3.14; N, 8.55; Cl, 29.17; S, 6.59. Found: C, 12.35; H, 3.11; N, 8.64; Cl, 29.37; S, 6.51.

Synthesis of (*OC*-6-33)-(*N*-(2-Aminoethyl)-1,2-ethanediamine-κ^3*N*,*N*′,*N*′′)dichloro(1,1,3,3-tetramethylthiourea-*S*)platinum(IV) Dichloride−Hemi(methanol) (3). To a solution of 0.4 g (1.1 mmol) of **1** in 15 mL of anhydrous MeOH was added 0.369 g (1 mmol) of crystalline [PtCl(dien)]Cl. After it was stirred in the dark at room temperature for ca. 15 min, the solution had turned yellow and became turbid, indicating the start of precipitation of poorly soluble **3**. The mixture was allowed to react for another 1 h and was then placed in an ice bath for 1 h to complete precipitation. The reaction afforded **3** as a microcrystalline orange-yellow solid, which was filtered off, washed with small portions of hot MeOH, and finally dried in vacuo: yield 0.480 g, 81%. IR: ν(OH) 3391 cm^{-1}; ν(NH) 3179, 2991 cm^{-1}; ν_{as}(CN) 1586 cm^{-1}. Anal. Calcd for $C_{9.5}H_{27}N_5Cl_4O_{0.5}PtS$: C, 19.39; H, 4.63; N, 11.90; Cl, 24.10; S, 5.45. Found: C, 19.35; H, 4.70; N, 11.68; Cl, 24.24; S, 5.57.

Synthesis of (*OC*-6-13)-(*N*-(2-Aminoethyl)-1,2-ethanediamine-κ^3*N*,*N*′,*N*′′)dichloro(1,1,3,3-tetramethylthiourea-*S*)platinum(IV) Dichloride (4). The reaction was set up as described for **3**; however, instead of isolation of the insoluble isomer the suspension was stirred for an additional 30 h in the dark. To the resulting yellow solution was added 20 mL of diethyl ether, affording a light yellow microcrystalline powder which was collected by filtration. The crude **4** thus obtained was recrystallized from MeOH/diethyl ether and dried in vacuo: yield 0.500 g, 87%. ^{1}H NMR (MeOH-d_4): δ 2.85 (2H, m), 3.29 (12H, s), 3.30−3.70 (6H, m), 7.44 (2H, b), 7.65 (2H, b). IR: ν(NH) 2943, 2839 cm^{-1}; ν(CN) 1583 cm^{-1}. Anal. Calcd for $C_9H_{25}N_5Cl_4PtS$: C, 18.89; H, 4.40; N, 12.24; Cl, 24.78; S, 5.60. Found: C, 18.82; H, 4.58; N, 12.19; Cl, 25.25; S, 5.47.

Synthesis of (*OC*-6-13)-(*N*-(2-Aminoethyl)-1,2-ethanediamine-κ^3*N*,*N*′,*N*′′)dichloro(1,1,3,3-tetramethylthiourea-*S*)platinum(IV) Bis(tetrafluoroborate) (4a). Solutions of 0.426 g (0.74 mmol) of **4** and 0.290 g of $AgBF_4$ (1.49 mmol) in 75 and 25 mL of anhydrous MeOH, respectively, were combined and stirred thoroughly. The mixture was allowed to stand in the dark for 2 h. Precipitated AgCl was filtered off over a Celite pad, and the solution was concentrated to a volume of 15 mL under reduced pressure. **4a** crystallized, after the mixture was kept at 4 °C for 12 h, as bright yellow prisms which were filtered

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Table 1. $^{195}Pt\{^{1}H\}$ NMR Data for **2**, **4**, **6**, and Chemically Related Pt(IV) Complexes

compd, solvent	δ_{Pt} (ppm)	$^{1}J(^{195}Pt-^{14}N)$ (Hz)	mult, ratio
cis-$[PtCl_4(NH_3)L]$ (**2**),[a] DMF-d_7	−492	192	triplet, 1:1:1
fac-$[PtCl_3(NH_3)_2L]Cl\cdot 0.5MeOH$ (**6**),[b] MeOH-d_4	−721	173	quintet, 1:2:3:2:1
trans,mer-$[PtCl_2(dien)L]Cl_2$ (**4**),[a] MeOH-d_4	−1110	not resolved	
cis-$[PtCl_4(NH_3)_2]$, H_2O[c]	−145	176[d]	
mer-$[PtCl_3(dien)]Cl$, D_2O[e]	−747		

[a] This work. [b] Reference 12. [c] Reference 31. [d] Calculated from $^{1}J(^{195}Pt-^{15}N) = 247$ Hz by applying the relation of gyromagnetic ratios: $^{15}N/^{14}N = 1.4$. [e] Reference 17.

Table 2. Crystal Data for *cis*-$[PtCl_4(NH_3)L]$ (**2**) and *trans,mer*-$[PtCl_2(dien)L](BF_4)_2$ (**4a**)

	2	4a
space group	$P2_1/n$	$C2/m$
a, Å	6.280(1)	21.093(5)
b, Å	13.221(3)	8.9411(9)
c, Å	16.575(2)	14.208(2)
β, deg	96.45(1)	124.65(2)
V, Å^3	1367.5(3)	2206.1(8)
fw	486.16	674.98
D_{calcd}, g cm^{-3}	2.361	2.028
empirical formula	$C_5H_{15}Cl_4N_3PtS$	$C_9H_{25}B_2Cl_2F_8N_5PtS$
Z	4	4
abs coeff, cm^{-1}	111.23	67.43
temp, °C	21	21
λ, Å	0.710 69	0.710 69
$R(F_o)$[a]	0.016	0.041
R_w[b]	0.016	0.042

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

off and washed with diethyl ether: yield 0.319 g, 64%. ^{1}H NMR (MeOH-d_4): identical with spectrum of **4**. IR: ν(NH) 3272, 3225, 3189, 3142, 3025 cm^{-1}; ν_{as}(CN) 1590 cm^{-1}; $\nu(BF_4)$ 1073 cm^{-1}. Anal. Calcd for $C_9H_{25}N_5B_2Cl_2F_8PtS$: C, 16.01; H, 3.73; N, 10.37; Cl, 10.50; S, 4.75. Found: C, 16.07; H, 3.75; N, 10.35; Cl, 10.92; S, 5.01.

Cytotoxicity Assays. These were performed as described previously.[18] **2** was dissolved in DMF and diluted by serial dilution in saline solution to a final concentration of 0.5% in DMF. All other compounds were dissolved in saline solution.

X-ray Structural Determination. Suitable single crystals of **2** were grown by slow liquid−liquid diffusion of THF into a concentrated (50 mg/mL) solution of the compound in DMF. Crystals of **4a** were grown by evaporation of a methanolic solution at room temperature.

Cell constants were determined by least-squares fits to the θ values of 25 independent reflections, measured and refined on an Enraf-Nonius CAD4-F diffractometer with a graphite monochromator. The crystallographic data for **2** and **4a** are summarized in Table 2. Data were reduced, and Lorentz, polarization, and absorption corrections were applied using the Enraf-Nonius Structure Determination Package. The structures were solved by heavy-atom methods using SHELXS-86,[19] and the solutions were extended by difference Fourier methods. Hydrogen atoms were refined with group isotropic thermal parameters, and all other atoms were refined anisotropically. Full-matrix least squares was used to refine an overall scale factor and positional and thermal parameters. Neutral atom scattering factors were taken from Cromer and Waber.[20] Anomalous dispersion effects were included in F_c;[21] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[22] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[23] All calculations were performed using the teXsan[24] crystallographic software package of Molecular Structure Corp., and plots were drawn using ORTEP.[25]

Table 3. Positional Parameters for *cis*-$[PtCl_4(NH_3)L]$ (**2**)

	x	y	z	B_{eq}
Pt(1)	0.09050(2)	0.68036(1)	0.421224(9)	2.088(4)
Cl(1)	0.4025(2)	0.75440(9)	0.38878(7)	3.12(2)
Cl(2)	0.2070(2)	0.52578(8)	0.37728(7)	3.12(2)
Cl(3)	0.2526(2)	0.64457(9)	0.55421(7)	3.61(3)
Cl(4)	−0.0261(2)	0.83483(8)	0.46494(6)	3.27(2)
S(1)	−0.0784(2)	0.73115(8)	0.29372(6)	2.46(2)
N(1)	−0.1819(7)	0.6140(3)	0.4547(3)	2.96(9)
N(2)	−0.1532(5)	0.5476(3)	0.2248(2)	2.82(8)
N(3)	0.0709(5)	0.6532(3)	0.1633(2)	2.96(8)
C(1)	−0.0478(6)	0.6345(3)	0.2226(2)	2.30(8)
C(2)	−0.3499(9)	0.5340(5)	0.2628(4)	4.0(1)
C(3)	−0.0655(10)	0.4530(4)	0.1979(4)	4.2(1)
C(4)	0.023(1)	0.6076(5)	0.0824(3)	4.5(1)
C(5)	0.2356(9)	0.7323(5)	0.1675(3)	4.0(1)

Table 4. Positional Parameters for *trans,mer*-$[PtCl_2(dien)L](BF_4)$ (**4a**)

	x	y	z	B_{eq}
Pt(1)	0.42176(3)	0.0000	0.66495(4)	2.61(1)
Cl(1)	0.3036(2)	0.0000	0.6397(3)	4.24(8)
Cl(2)	0.5401(2)	0.0000	0.6928(3)	4.13(8)
S(1)	0.4734(2)	0.0000	0.8604(3)	5.8(1)
N(1)	0.4193(4)	−0.2286(7)	0.6459(6)	4.1(2)
N(2)	0.3645(5)	0.0000	0.4893(8)	2.9(2)
N(3)	0.6108(6)	0.128(1)	0.9748(9)	7.1(3)
C(1)	0.3704(6)	−0.2643(10)	0.5202(8)	4.3(2)
C(2)	0.3781(5)	−0.144(1)	0.4566(7)	4.0(2)
C(3)	0.5730(8)	0.0000	0.941(1)	3.9(3)
C(4)	0.576(1)	0.273(2)	0.950(1)	10.2(5)
C(5)	0.691(1)	0.109(3)	1.104(2)	7.8(7)
C(5′)	0.678(2)	−0.151(4)	0.976(2)	12(1)

Table 5. Selected Bond Lengths (Å) and Angles (deg) with Standard Deviations for *cis*-$[PtCl_4(NH_3)L]$ (**2**)

Bond Lengths			
Pt(1)−Cl(1)	2.307(1)	Pt(1)−Cl(2)	2.316(1)
Pt(1)−Cl(3)	2.370(1)	Pt(1)−Cl(4)	2.313(1)
Pt(1)−S(1)	2.354(1)	Pt(1)−N(1)	2.053(4)
S(1)−C(1)	1.764(4)	N(2)−C(1)	1.327(5)
N(3)−C(1)	1.322(5)		

Bond Angles			
Cl(1)−Pt(1)−Cl(2)	89.67(4)	Cl(1)−Pt(1)−Cl(3)	90.82(4)
Cl(1)−Pt(1)−Cl(4)	90.33(4)	Cl(1)−Pt(1)−S(1)	88.76(4)
Cl(1)−Pt(1)−N(1)	177.8(1)	Cl(2)−Pt(1)−Cl(3)	89.89(4)
Cl(2)−Pt(1)−Cl(4)	179.92(4)	Cl(2)−Pt(1)−S(1)	95.51(4)
Cl(2)−Pt(1)−N(1)	90.6(1)	Cl(3)−Pt(1)−Cl(4)	90.19(4)
Cl(3)−Pt(1)−S(1)	174.58(4)	Cl(3)−Pt(1)−N(1)	87.0(1)
Cl(4)−Pt(1)−S(1)	84.41(4)	Cl(4)−Pt(1)−N(1)	89.4(1)
S(1) −Pt(1)−N(1)	93.4(1)	Pt(1)−S(1) −C(1)	108.8(1)

Positional parameters and selected bond lengths and angles are given in Tables 3−6. Listings of atom coordinates, thermal parameters, and details of least-squares planes calculations have been deposited as Supporting Information.

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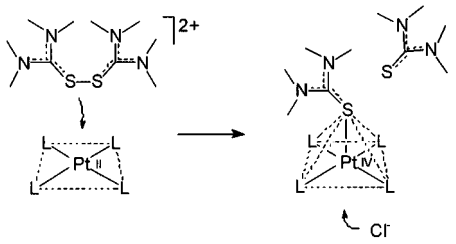
Table 6. Selected Bond Lengths (Å) and Angles (deg) with Standard Deviations for *trans,mer*-$[PtCl_2(dien)L](BF_4)_2$ (**4a**)

Bond Lengths			
Pt(1)−Cl(1)	2.309(3)	Pt(1)−Cl(2)	2.295(3)
Pt(1)−S(1)	2.338(4)	Pt(1)−N(1)	2.058(7)
Pt(1)−N(2)	2.065(9)	S(1)−C(3)	1.73(1)
N(3)−C(3)	1.32(1)		

Bond Angles			
Cl(1)−Pt(1)−Cl(2)	179.2(1)	Cl(1)−Pt(1)−S(1)	85.3(1)
Cl(1)−Pt(1)−N(1)	92.1(2)	Cl(2)−Pt(1)−S(1)	93.9(1)
Cl(1)−Pt(1)−N(2)	88.5(3)	S(1)−Pt(1)−N(1)	96.8(2)
Cl(2)−Pt(1)−N(1)	88.0(2)	S(1)−Pt(1)−N(2)	173.8(3)
Cl(2)−Pt(1)−N(2)	92.4(3)	N(1)−Pt(1)−N(2)	83.4(2)
N(1)−Pt(1)−N(1)[a]	166.3(4)	Pt(1)−S(1)−C(3)	111.0(4)

[a] Symmetry operator: $x, -y, z$.

Scheme 1. Proposed Mechanism of the Oxidative Addition of **1** to Square-Planar Pt(II)



Results and Discussion

Synthetic Studies. The overall reaction of the dithio-(formamidinium) dichloride salt of tmtu (**1**) with Pt(II) chloro am(m)ine complexes, as observed first for *cis*-DDP and related compounds,[12] was found to be an oxidation to Pt(IV) complexes exhibiting a mixed axial chloro/tmtu-*S* coordination. The proposed mechanism of this oxidation (Scheme 1), performed at room temperature in weakly coordinating methanol, requires free chloride, introduced as the anions in **1**.[12] A similar pathway for an oxidative addition was reported for the system $[Pt^{II}(oxalate)_2]^{2-}/H_2O_2/H_2O$.[26] It could be demonstrated by isotope labeling experiments that one axial OH^- ligand in the Pt(IV) product originates from the oxidant $H_2{}^{16}O_2$, whereas the trans OH^- ligand originates from the solvent $H_2{}^{18}O$. A similar mechanism has been established for the oxidation of Pt(II) aqua complexes with chlorine gas in ^{18}O-enriched water.[27] The chloride dependence of the oxidation performed with the cation of **1** might point to a mechanism where the incoming anionic nucleophile facilitates the reaction by reducing unfavorable positive charge on a putative five-coordinate intermediate. Characteristically, no oxidation was observed with the analogous tetrafluoroborate salt of **1** in nonaqueous solvents.

The products of the oxidations of $K[PtCl_3(NH_3)]$, *cis*- and *trans*-$[PtCl_2(NH_3)_2]$, and [PtCl(dien)]Cl with **1** ($[L\text{-}L]Cl_2{\cdot}2H_2O$) and observed isomerizations are presented in Figure 1. In all cases addition of one chloro and one neutral tmtu ligand (L) results in the formation of octahedrally coordinated Pt(IV) complexes which consequently carry an extra positive charge compared to the Pt(II) precursors. Oxidation of the $[PtCl_3(NH_3)]^-$ anion with **1** gives the poorly soluble neutral complex *cis*-$[PtCl_4(NH_3)L]$ (**2**). A *cis* orientation of the ammine and the S-bound thiourea ligand has been established crystallographically (*vide infra*). Similarly, oxidation of the $[PtCl(dien)]^+$ cation leads to *cis,mer*-$[PtCl_2(dien)L]Cl_2{\cdot}0.5MeOH$ (**3**). In **3** retention of the meridional coordination of the dien ligand is observed, as will be discussed on the basis of spectroscopic data. However, *cis* → *trans* isomerization is observed after prolonged stirring of a suspension of **3** in methanol, resulting in *trans,mer*-$[PtCl_2(dien)L]Cl_2$ (**4**), where the chloro ligands occupy the axial positions and tmtu coordinates *trans* to the central nitrogen of the *mer* dien ligand. This reaction occurs in the absence of light. Exchange of the counterions in **4** with tetrafluoroborate gives *trans,mer*-$[PtCl_2(dien)L](BF_4)_2$ (**4a**). A crystal structure determination on **4a** confirms the assumed isomerization, deduced from spectroscopic data and reactivity features in aqueous solution (*vide infra*). Oxidation of *trans*-$[PtCl_2(NH_3)_2]$ with **1** gives mixtures of *mer,trans*-$[PtCl_3(NH_3)_2L]Cl$ (**5**) and the *fac* isomer **6**. Unlike **3** in the Pt(IV)/dien system, which could be isolated due to its poor solubility, **5** is rapidly transformed into **6** before completion of the reaction. Attempts to separate the isomers were not successful. The *trans* → *cis* isomerization proves to be complete after 12 h, as could be followed by means of ^1H NMR spectroscopy. Rapid isomerization of Pt(IV) complexes during recrystallization is not unusual and has been observed before for compounds of the type $[Pt^{IV}Cl_2(OH)_2(NH_3)_2]$.[28]

Infrared Studies. Spectra were recorded for **2**, **3**, **4**, **4a**, and **6** in order to assign the asymmetric CN (C = thiocarbonyl carbon) stretching vibration of the tmtu ligands. Vibration frequencies of 1579 cm^{-1} up to 1590 cm^{-1} (see Experimental Section) are indicative of S-bound tmtu[13] in Pt(IV) complexes.[12]

^1H and ^{195}Pt NMR Studies. The ^1H NMR spectrum of *cis*-$[PtCl_4(NH_3)L]$ (**2**) in DMF-d_7 was found to be similar to that recorded of the structurally related cationic complex *fac*-$[PtCl_3(NH_3)_2L]Cl{\cdot}0.5MeOH$ (**6**) in MeOH-d_4.[12] In addition to a sharp singlet for the methyl protons of tmtu at 3.37 ppm the ammine protons in **2** are observed as a seven-line pattern (1:4:2:4:2:4:1) centered at 5.95 ppm due to heteronuclear couplings ($^1J(^{14}N-^1H) \approx {}^2J(^{195}Pt-^1H) \approx 50$ Hz), characteristic for ammine complexes of Pt(IV).[29]

The ethylene groups of the dien ligand in **4** give rise to complicated multiplets centered at 2.85 ppm and between 3.30 and 3.70 ppm (Figure 2). The observed separation of the high-field part of this ABCD system (2H, $^3J(^{195}Pt-^1H) = 24$ Hz) from the low-field part (6H) by ca. 0.5 ppm has been reported to be indicative of a meridional dien coordination.[30] The ^1H NMR spectrum of the *cis* isomer **3** had to be recorded in D_2O due to its poor solubility in all other solvents. Irrespective of hydrolysis of the complex (*vide infra*), a *mer* orientation of the dien ligand has also been established for **3**.

The ^1H NMR spectrum of the product isolated from the oxidation of *trans*-$[PtCl_2(NH_3)_2]$ with **1** in MeOH-d_4 exhibits two overlapping seven-line N−H patterns centered at 5.82 and 6.01 ppm and two singlets for the methyl protons of the tmtu ligands at 3.35 and 3.30 ppm. In spectra taken of this solution after 12 h the signals at 6.01 and 3.30 ppm had vanished and the signals at 5.82 and 3.35 ppm, attributable to *fac*-$[PtCl_3(NH_3)_2L]Cl$ (**6**),[12] had increased in intensity. These observations imply a *trans* → *cis* isomerization, as depicted in Figure 1.

Proton-decoupled ^{195}Pt NMR spectra were recorded for the new complexes *cis*-$[PtCl_4(NH_3)L]$ (**2**) and *trans,mer*-$[PtCl_2(dien)L]Cl_2$ (**4**). The data are compared to **6** and structurally related Pt(IV) species (Table 1). These compounds represent a series of mixed-ligand Pt(IV) complexes which was regarded as a useful case for studying the influences of variations in the

(26) Dunham, S. O.; Larsen, R. D.; Abbott, E. H. *Inorg. Chem.* **1993**, *32*, 2049.
(27) Gröning, Ö.; Elding, L. I. *Inorg. Chem.* **1989**, *28*, 3366.
(28) Kuroda, R.; Neidle, S.; Ismail, I. M.; Sadler, P. J. *Inorg. Chem.* **1983**, *22*, 3620.
(29) Müller, G.; Riede, J.; Beyerle-Pfnür, R.; Lippert, B. *J. Am. Chem. Soc.* **1984**, *106*, 7999.
(30) Frommer, G.; Preut, H.; Lippert, B. *Inorg. Chim. Acta* **1992**, *193*, 111.

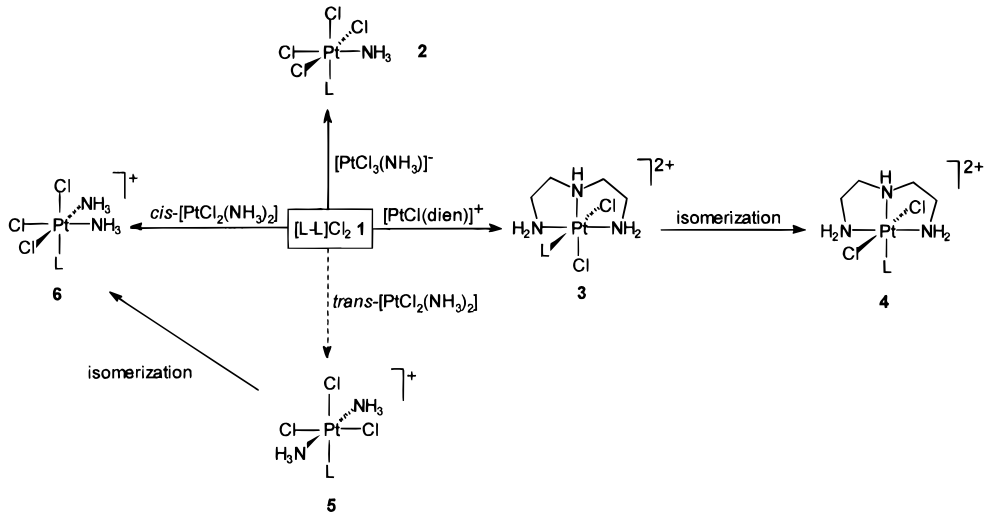


Figure 1. Oxidative addition and isomerization reactions on square-planar Pt(II) complexes (L = $SC(NMe_2)_2$; $[L\text{-}L]^{2+} = [(NMe_2)_2CS{-}SC(NMe_2)_2]^{2+}$). Counterions and crystal solvents have been omitted for clarity.

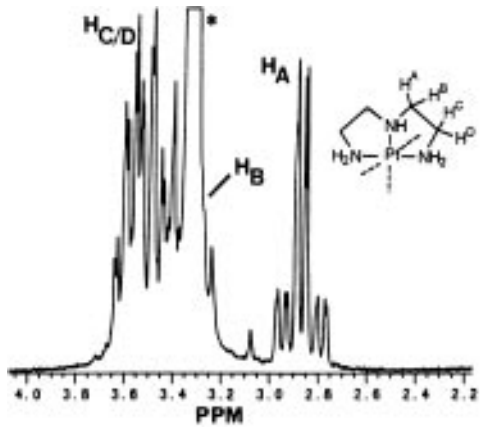


Figure 2. Proton resonances of the ethylene groups of the dien ligand in *trans,mer*-$[PtCl_2(dien)L]Cl_2$ (**4**), showing the characteristic ABCD pattern. The asterisk indicates a truncated peak, assigned to methyl protons of tmtu. H_A shows Pt satellites; H_B overlaps with methyl protons of tmtu.

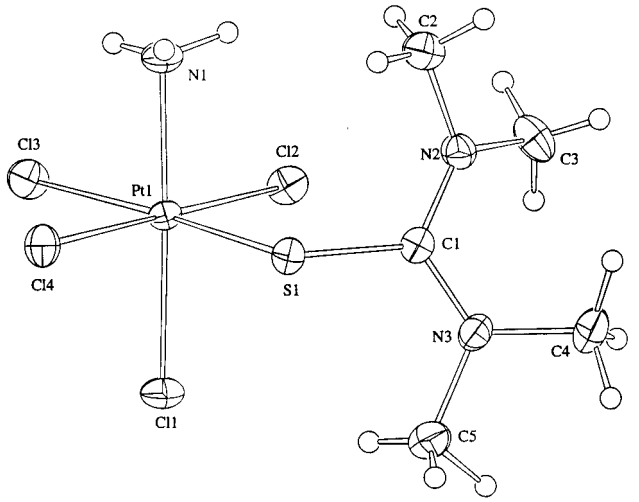


Figure 3. View of one of the molecules of *cis*-$[PtCl_4(NH_3)L]$ (**2**) giving atom numbering. Ellipsoids are drawn at the 30% probability level.

ligand combination on ^{195}Pt chemical shifts and one-bond heteronuclear $^{195}Pt{-}^{14}N$ couplings. As can be clearly seen from the δ_{Pt} shifts, stepwise replacement of a chloro ligand with an amino or ammine ligand on going from **2** to **4** results in a shielding of the Pt core and, consequently, in an upfield shift of the ^{195}Pt resonance. However, a plot of the variation in ^{195}Pt chemical shifts with the number of N-donors does not show the linear substitution pattern usually observed for systems such as $[Pt^{II}(NH_3)_x(H_2O)_{4-x}]^{2+}$ ($x = 1{-}4$)[31] and does not allow for the definition of shift increments ($\Delta\delta$). The difference in δ_{Pt} between **2** and **6** (−229 ppm) was determined to be smaller than that between **6** and **4** (−389 ppm). These findings are probably due to the fact that **4** exhibits tmtu coordination trans to the amine ligand, whereas in **2** and **6** tmtu and the ammine ligand(s) show a *cis* orientation. ^{195}Pt chemical shifts of different *cis/trans* and *mer/fac* isomers of Pt(IV) complexes are usually well-separated.[31] The accumulation of positive charge may also contribute to the strong shielding of the Pt core in **4**. Formal substitution of the chloro ligand trans to dien in *mer*-$[PtCl_3(dien)]Cl$ by tmtu (L) gives *trans,mer*-$[PtCl_2(dien)L]Cl_2$ (**4**). This ligand exchange causes an upfield substitution shift of −363 ppm. Considering all the data stated in Table 1, the order of shielding is thiourea > am(m)ine > chloride, which has been previously observed for other mixed-ligand systems and was found to correlate with the *trans* influence of the ligands.[32]

Pt−N couplings are mainly influenced by the nature of the ligands trans to the am(m)ine ligand, and coupling constants usually decrease with increasing labilizing influence of the *trans* donor atom. However, small effects by *cis*-oriented ligands (including axial ligands in Pt(IV) complexes) have also been discussed.[32] Comparison of $^1J(^{195}Pt{-}^{14}N)$ coupling constants of both **2** and **6** with that of the structurally related *cis*-$[PtCl_4(NH_3)_2]$ (Table 1) implies the following order of *cis* influences: thiourea ≈ chloride < NH_3.

X-ray Crystal Structures of *cis*-$[PtCl_4(NH_3)L]$ (2) and *trans,mer*-$[PtCl_2(dien)L](BF_4)_2$ (4a). The X-ray structure of *cis*-$[PtCl_4(NH_3)L]$ (**2**) is depicted in Figure 3. **2** consists of neutral complex molecules with an octahedral coordination geometry of Pt(IV) which appears slightly distorted due to the bulky peralkylated thiourea derivative. The ammine ligand and the S-bound tmtu show a *cis* orientation. The most striking structural feature of **2** is the difference in Pt−Cl bond lengths between chloro ligands bound cis and trans to sulfur. The Pt−

(31) Ismail, I. M.; Sadler, P. J. In *Platinum, Gold and Other Metal Chemotherapeutic Agents*. ACS Symposium Series 209; American Chemical Society: Washington, DC, 1983; p 171, and literature cited therein.

(32) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 4685.

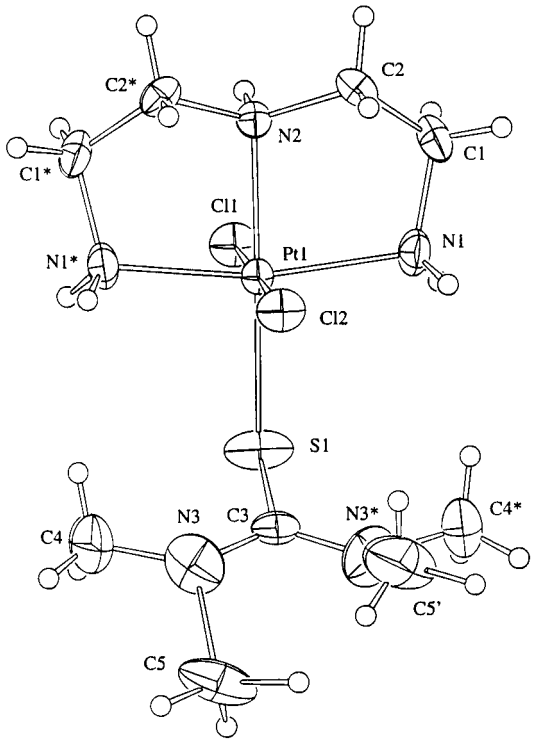


Figure 4. View of one of the complex cations of *trans,mer*-[$PtCl_2$(dien)L](BF_4)$_2$ (**4a**) giving atom numbering. Ellipsoids are drawn at the 30% probability level.

Cl_{trans} bond (2.370(1) Å) is considerably longer than the Pt−Cl_{cis} distances (2.312 Å, mean), which points to a pronounced *trans* influence of the sulfur donor. To our knowledge, this is an unprecedented finding of structural impact caused by a sulfur donor ligand in Pt(IV) complexes. Interestingly, thioether ligands do not exert a comparable lengthening of the Pt^{IV}−Cl_{trans} bond.[33] For ligands with third-period donor atoms an effect of similar magnitude has been observed in phosphine complexes of Pt(IV) such as [$PtCl_5(PEt_3)$]$^-$.[34]

Figure 4 shows one view of the cation of *trans,mer*-[$PtCl_2$(dien)L](BF_4)$_2$ (**4a**) in the solid state. **4a** consists of the complex cation situated on a mirror plane and two tetrafluoroborate anions also located on a mirror plane. The tmtu ligand cannot conform to mirror symmetry due to the conrotatory twisting of the dimethylamino groups (free tmtu adopts C_2 symmetry in the gas phase[35] and in the solid state[36]). The ligand is therefore disordered over two equally occupied sites. The disorder takes the form of two sites for one of the methyl groups (C5 and C5′). The other methyl group (C4) is an average of two nearly coincident sites. Pt(IV) exhibits a mixed Cl_2N_3S coordination sphere with a *mer* dien ligand and axial chloro ligation. The dien ligand adopts a "sting ray" conformation,[37] in accordance with crystallographically imposed mirror symmetry. Deviations from ideal octahedral geometry are mainly caused by the chelating width ("bite") of the dien ligand. Interatomic distances are in the same range as observed for **2** (see Tables 5 and 6). The *trans* influence of the sulfur ligand on the Pt−N bond is not as pronounced as that on the Pt−Cl bond in **2**.

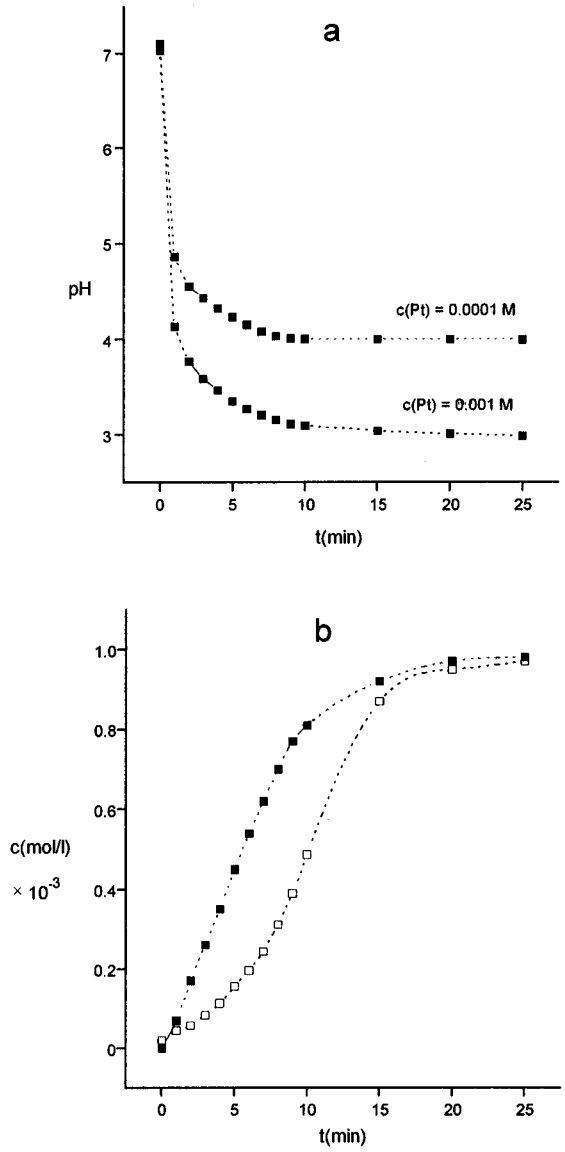


Figure 5. Hydrolysis of **2** monitored by (a) changes in pH of aqueous solutions with time at two different total concentrations in Pt(IV) compound and (b) changes in proton (■) and chloride ion (□) concentrations with time of a 10^{-3} M aqueous solution of **2**. Differences in the profiles of the curves are due to different electrode response times.

Reactivity Studies in Aqueous Solution. The knowledge of the hydrolytic behavior of new Pt antitumor complexes is one important requirement for the design of such drugs. It is known that the activation of Pt(II)-based drugs in reactions with their biological target (DNA) and other biomolecules is accociated with hydrolytic replacement of chloro ligands.[38] Analogous Pt(IV) complexes usually show insignificant hydrolysis due to their kinetic inertness. An unusual reactivity feature is observed for the complexes *cis*-[$PtCl_4(NH_3)$L] (**2**), *cis,mer*-[$PtCl_2$(dien)L]Cl_2·0.5MeOH (**3**), and *fac*-[$PtCl_3(NH_3)_2$L]Cl·0.5MeOH (**6**). These compounds act as **strong monoprotic acids**: aqueous solutions of **2**, **3**, and **6** show a pH drop within 25 min, as depicted for **2** in Figure 5a. Hydrolysis of the Pt−$S_{thiourea}$ bond can be excluded in all cases, since ^{1}H NMR spectra of **2**, **3**, and **6** in D_2O did not show the presence of free tmtu ($\delta_{methyl-H}$ 3.00). In contrast, it has been established by means of ion sensitive electrode measurements that the increase in

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(34) Albinati, A.; Kaufmann, W.; Venanzi, L. M. *Inorg. Chim. Acta* **1991**, *188*, 145.
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(37) Britten, J. F.; Lock, C. J. L.; Pratt, W. M. C. *Acta Crystallogr.* **1982**, *B38*, 2148.
(38) Holler, E. In *Metal Complexes in Cancer Chemotherapy*; Keppler, B. K., Ed.; VCH: Weinheim, Germany, 1993; pp 37−71.

Scheme 2. Proposed Mechanism of Hydrolysis for **2**

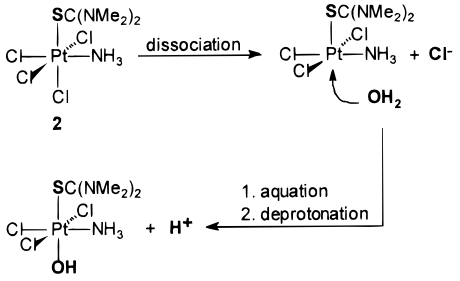


Table 7. Cytotoxicity of **2**, **4**, and **6** in L1210 Leukemia Cells[a]

	ID_{50}, μM	
complex	L1210/0	L1210/DDP
cis-$[PtCl_4(NH_3)L]$ (**2**)	0.19	12.15 (64)[b]
fac-$[PtCl_3(NH_3)_2L]Cl$ (**6**)	0.11	18.91 (172)
trans,mer-$[PtCl_2(dien)L]Cl_2$ (**4**)	>50	>50
cis-$[PtCl_2(NH_3)_2]$ (cisplatin)	0.19	11.63 (61)

[a] All complexes in saline solution except for **2**, which was in 0.5% DMF. [b] Resistance factor, defined as ID_{50}(resistant)/ID_{50}(sensitive), is given in parentheses.

proton concentration is accompanied by the formation of an equimolar amount of chloride ions (Figure 5b). It is noteworthy that hydrolysis of **2**, **3**, and **6** proved to be irreversible and that neither extra chloride (10 times exess) nor catalytic traces of Pt(II) complex nor light have an effect on the rate of hydrolysis. If we take into account all these observations and the labilization of the Pt−Cl bond trans to sulfur, the mechanism given in Scheme 2 seems to be most likely.

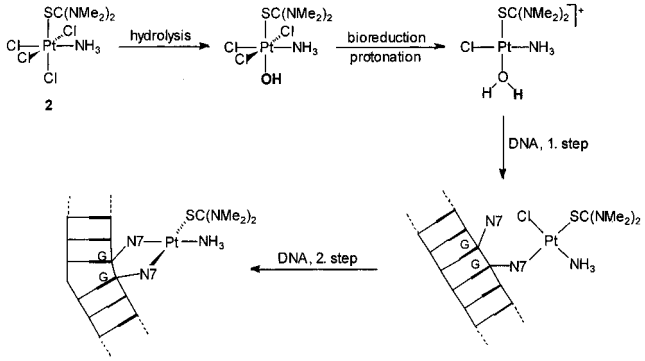
It may be proposed that aquation of the Pt(IV) complexes involves a (thermal) dissociative step (I_d) rather than a Pt(II)-catalyzed mechanism via $Pt^{II}-Cl-Pt^{IV}$ bridges,[39] as usually observed for ligands that are low in the *trans*-influence series. Finally, it should be mentioned that *trans,mer*-$[PtCl_2(dien)L]Cl_2$ (**4**) with the S-donor ligand trans to the chelating amine does not show this pH drop, which strongly supports the proposed mechanism.

Cytotoxicity Studies. The cytotoxicity of complexes **2**, **4**, and **6** was studied in murine L1210 leukemia cells both sensitive and resistant to cisplatin. Preliminary results are presented in Table 7. ID_{50} values for **2** and **6** in cisplatin-sensitive cells (L1210/0) indicate a remarkable activity equivalent to *cis*-DDP, whereas **4** did not show drug response at drug concentrations <50 mM and thus was considered inactive. In the cisplatin-resistant cell line (L1210/DDP), however, ID_{50} values for **2** and **6** reveal a marked decrease in cell growth inhibition and in fact show resistance factors comparable with those for cisplatin. **4** was found to be inactive in the resistant line as well.

It is tempting to correlate these findings with the molecular structures of the Pt(IV) complexes and to speculate on a possible mechanism of action *in vivo*. The following discussion is based on the assumption that compounds **2**, **4**, and **6** act as prodrugs and are reduced to Pt(II) species before exerting biological activity. Bioreduction of *trans,mer*-$[PtCl_2(dien)L]Cl_2$ (**4**) will probably result in loss of the (redox labile) $Cl-Pt^{IV}-Cl$ axis and generate the $[Pt^{II}(dien)L]^{2+}$ cation. This species should have no affinity to guanine-N7 of DNA due to the absence of suitable leaving groups, which would explain the observed inactivity. *fac*-$[PtCl_3(NH_3)_2L]Cl$ (**6**) may be considered a typical water-soluble prodrug which, after loss of axial ligands, generates cisplatin.

(39) Elding, L. I.; Gustafson, L. *Inorg. Chim. Acta* **1977**, *24*, 239.

Scheme 3. One Possible Mechanism of Action of **2**



The most interesting case was found to be the neutral complex *cis*-$[PtCl_4(NH_3)L]$ (**2**), which shows enhanced activity compared to its anionic precursor, $K[Pt^{II}Cl_3(NH_3)]$.[15] The structure of **2** exhibits only **one** ammine ligand and a *cis*-oriented neutral tmtu ligand, which proves to be an unprecedented structural feature in Pt(IV) antitumor complexes. One explanation for the observed cross resistance of **2** to *cis*-DDP could be that, regardless of structural differences, both compounds show the same mode of DNA binding. In the case of a *cis*-DDP-like lesion, altered rates of enzymatic DNA repair in cisplatin-resistant cells would possibly also affect recognition of the structural impact caused by **2**, which would explain the cross resistance.[40] Bifunctional DNA binding with carrier groups other than NH_3 produces conformational changes similar to those of *cis*-DDP, with some differences depending on the nature of the carrier ligand.[41−44] **2** exhibits two potential redox-labile axes (Cl−Pt−S and Cl−Pt−Cl). Considering the *in vitro* activity of **2**, it seems appealing to suggest a mechanism of action (Scheme 3) which involves the formation of a bifunctional adduct with DNA with tmtu as a classical nonleaving group in the place of the second am(m)ine.

Conclusions

The oxidative addition of $[L-L]Cl_2 \cdot 2H_2O$ (L = 1,1,3,3-tetramethylthiourea, tmtu) to Pt(II) chloro am(m)ine compounds has been utilized to introduce an S-donor ligand into Pt(IV) complexes. Besides a pronounced "static" *trans* influence of S-bound tmtu in the solid state, tmtu coordination was found to affect electronic properties such as heteronuclear NMR couplings as well as the reactivity (hydrolysis) of the compounds. *cis*−*trans* isomerizations in this system may also be related to labilizing effects of the S-donor ligand.

Promising *in vitro* activities observed for *cis*-$[PtCl_4(NH_3)L]$ (**2**) and *fac*-$[PtCl_3(NH_3)_2L]Cl$ (**6**) imply that the peralkylated thiourea derivative might be a useful alternative lipophilic carrier ligand in Pt(IV) prodrugs that could, for instance, facilitate passive diffusion of the drug through the cell membrane. Furthermore, it would seem to be worthwhile to test the neutral complex **2** *in vivo* for its resorption and cytostatic activity as a

(40) Cross resistance to cisplatin is not only affected by altered rates of DNA repair but may also be caused by factors such as altered uptake and altered reactivity toward endogenous thiols. Nevertheless, the fact that cisplatin and **2** exhibit identical resistance factors encourages us to speculate that the reason for resistance lies at the DNA level. See also: Van Beusichem, M.; Farrell, N. *Inorg. Chem.* **1992**, *31*, 634. Farrell, N. *Cancer Invest.* **1993**, *11*, 578 and references cited therein.
(41) Hartwig, J. F.; Lippard, S. J. *J. Am. Chem. Soc*. **1992**, *114*, 5646.
(42) Skov, K. A.; Adomat, H.; Doedee, M. J.; Farrell, N. *Anti-Cancer Drug Des.* **1994**, *9*, 103.
(43) Page, J. D.; Husain, I.; Sancar, A.; Chaney, S. G. *Biochemistry* **1990**, *29*, 1016.
(44) Inagaki, K.; Nakahra, H.; Alink, M.; Kidani, Y. *Inorg. Chem.* **1990**, *29*, 4496.

potential orally administrable drug. The observed acid stability of the Pt−S bond in **2** and **6** suggests that the compounds may survive the gastric environment without displacement of the thiourea ligand. The structure of **2** is of interest for the absence of the "classical" *cis*-diam(m)ine coordination in Pt antitumor complexes as well as its use of a new lipophilic group (tmtu) instead of an alicyclic amine (cyclohexylamine) as in the prototype JM-216.

Acknowledgment. This work was supported by a research fellowship (U.B.) of the Deutsche Forschungsgemeinschaft (DFG, Bonn, Germany) and the American Cancer Society (Grant No. DHP-2E). We thank J. Peroutka for his technical assistance in obtaining cytotoxicity data. Thanks are also due to Johnson-Matthey, Ltd. (Reading, England), and W. C. Heraeus GmbH (Hanau, Germany) for their generous loan of K_2PtCl_4.

Supporting Information Available: Tables of crystallographic data, final positional parameters, anisotropic displacement coefficients, H-atom coordinates, and bond lengths and angles for **2** and **4a**, least-squares planes for **2**, and torsional angles for **4a** (12 pages). Ordering information is given on any current masthead page.

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