Modification of Platinum(II) Antitumor Complexes with Sulfur Ligands. 1. Synthesis, Structure, and Spectroscopic Properties of Cationic Complexes of the Types $[PtCl(diamine)(L)]NO_3$ and $[\{PtCl(diamine)\}_2(L\text{-}L)](NO_3)_2$ (L = Monofunctional Thiourea Derivative; L-L = Bifunctional Thiourea Derivative)

Ulrich Bierbach,*,† Trevor W. Hambley,‡ and Nicholas Farrell*,†

Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284-2006, and School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia

Received April 10, 1997

A new class of mono- and dinuclear platinum(II) complexes is described that derives from the cisplatin analogues $[Pt(en)Cl_2]$ and $[Pt(dach)Cl_2]$ (en = 1,2-ethanediamine, dach = racemic *trans*-1,2-cyclohexanediamine). The selective substitution of *one* chloro ligand in these species by 1,1,3,3-tetramethylthiourea (tmtu), which requires abstraction of chloride with silver salt in DMF, gives $[PtCl(en)(tmtu)]NO_3$ (**1**) and $[PtCl(dach)(tmtu)]NO_3$ (**2**). Similarly, reactions employing the novel bifunctional thiourea derivatives $C_2H_4(NMeCSNMe_2)_2$ (**3**) and $C_6H_{12}(NMeCSNMe_2)_2$ (**4**) yield the dinuclear complexes $[\{Pt(en)Cl\}_2(\mu\text{-}\mathbf{3}\text{-}S,S')](NO_3)_2$ (**5**) and $[\{Pt(en)Cl\}_2(\mu\text{-}\mathbf{4}\text{-}S,S')](NO_3)_2\cdot 0.5EtOH$ (**6**), respectively. The compounds were characterized by ^1H, ^{13}C, and ^{195}Pt NMR spectroscopy, elemental analyses, and IR data. ^{195}Pt chemical shifts in the −2895 to −2929 ppm region confirm the mixed-donor $[PtN_2ClS]$ coordination for **1**, **2**, **5**, and **6** and thiourea-*S* coordination in all cases. The single-crystal X-ray structures of **2**−**4** have been determined. **2**: monoclinic, space group $P2_1/n$, $a = 10.804$ Å, $b = 16.221$ Å, $c = 21.789$ Å, $\beta = 102.16(1)°$, $Z = 8$. **3**: monoclinic, space group $P2_1/n$, $a = 12.787(2)$ Å, $b = 6.250(1)$ Å, $c = 17.777(3)$ Å, $\beta = 98.21(1)°$, $Z = 4$. **4**: monoclinic, space group $P2_1/n$, $a = 11.097(3)$ Å, $b = 13.717$ Å, $c = 11.925$ Å, $\beta = 97.61(2)°$, $Z = 4$. The Pt−S distance in **2** (2.285(2) Å, mean) is in accordance with the magnitude of shielding found for the ^{195}Pt core and suggests weak π-acceptor properties of tmtu. The bifunctional thiourea derivatives **3** and **4** adopt highly elongated conformations in the solid state where the sulfur atoms and the $n\text{-}(CH_2)_n$ ($n = 2, 6$) linkers are *Z*-oriented. Force field calculations on **3** and **4** imply that the *Z*-form should be the preferred conformer for the thiourea groups in solution. ^1H NMR spectra indicate a dynamic equilibrium of different rotamers due to low barriers of rotation within the thiourea moieties in free and coordinated **3** and **4**. It is suggested that the steric and electronic effects of the peralkylated thiourea derivatives in **1**, **2**, **5**, and **6** may modulate the affinity of the complexes for biomolecules.

Introduction

Endogenous and exogenous sulfur-containing molecules play a significant role in the metabolism of platinum-based antitumor complexes. Binding of *cis*-diamminedichloroplatinum(II) (cisplatin, *cis*-DDP), the antitumor drug,[1] to intracellular thiol groups is known to be the reason for its renal toxicity and other side effects.[2] Reaction with SH groups of protein side chains (e.g., in metallothionein and glutathione, GSH) is thought to trap and deactivate the drug before it reaches its cellular target DNA to form the 1,2 intrastrand cross-link of guanine bases, the likely cytotoxic adduct.[3] Nucleophiles such as thiosulfate and diethyldithiocarbamate are used to reverse[4,5] the above-mentioned side effects of cisplatin in cancer chemotherapy.

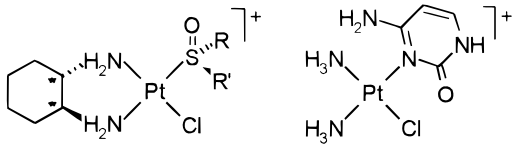
Competitive binding of Pt(II) antitumor complexes to DNA constituents (mainly guanine-*N7* and adenine-*N7*[6]) and protein-bound sulfur (cysteine and methionine residues) is critical to the metabolism and to the stability of the cytotoxic lesions of the drugs. Model studies under physiologically relevant conditions have conclusively shown that the kinetic preference of Pt(II) is for biorelevant *thiols* (cysteine, GSH) rather than (5′-GMP).[7] While a similar *kinetic* effect exists in the system Pt(II)/*thioether*/nucleotide, rearrangement of the Pt(II)−sulfur adduct into the *thermodynamically* favored Pt(II)−(nucleobase) nitrogen adduct is observed. Both intra- and intermolecular sulfur-to-nitrogen migration of the $[Pt(dien)]^{2+}$ fragment (dien = diethylenetriamine) has been established in reactions with *S*-guanosyl-L-homocysteine[8] and *N*-acetyl-L-methionine/5′-GMP,[9] respectively. Recent studies on the interactions of the drug carboplatin with sulfur-containing biomolecules suggest that long-lived Pt(II)−methionine adducts may be important metabolites in vivo.[10]

† Virginia Commonwealth University.
‡ University of Sydney.

(1) Kelland, L. R.; Clarke, S. J.; McKeage, M. J. *Platinum Met. Rev.* **1992**, *36*, 178.
(2) Farrell N. In *Transition Metal Complexes as Drugs and Chemotherapeutic Agents*; Ugo, R., James, B. R., Eds.; Kluwer: Dordrecht, The Netherlands, 1989; Chapter 2 and literature cited therein.
(3) Takahara, P. M.; Frederick, C. A.; Lippard, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 8, 12309.
(4) Treskes, M.; Holwerda, U.; Nijtmans, L. G.; Pinedo, H. M.; van der Vijgh, W. J. *Cancer Chemother. Pharmacol.* **1992**, *29*, 467.
(5) Berry, J. M.; Jacobs, C.; Sikic, B.; Halsey, J.; Borch, R. F. *J. Clin. Oncol.* **1990**, *8*, 1585.
(6) Fichtinger-Schepman, A. M. J.; van der Veer, J. L.; den Hartog, J. H. J.; Lohman, P. H. M.; Reedijk, J. *Biochemistry* **1985**, *24*, 707.
(7) Bose, R. N.; Moghaddas, S.; Weaver, E. L.; Cox, E. H. *Inorg. Chem.* **1995**, *34*, 5878.
(8) Van Boom, S. G. E.; Reedijk, J. *J. Chem. Soc., Chem. Commun.* **1993**, 1397.
(9) Barnham, K. J.; Djuran, M. I.; Murdoch, P. d. S.; Sadler, P. J. *J. Chem. Soc., Chem. Commun.* **1994**, 721.

S0020-1669(97)00420-5 CCC: $15.00
Published on Web 01/31/1998

Chart 1



In a search for new drugs that exhibit biological activity equal or complementary[11] to that of cisplatin, we are currently examining *thiourea* derivatives as a new class of (carrier) ligands. Thiourea (tu) and its *N*-alkylated analogues are known to combine ligand properties of thiolates[12] (π donor) and thioethers[13] (σ donor, π acceptor). The donor properties depend on the particular derivative and on the electronic requirements of the metal center. This has been discussed in detail for Cu(I)[14] and for Fe(II, III) and Ru(II)[15] complexes. The distinct differences between the systems Pt(II)/thiol and Pt(II)/thioether and the possible biological implications stimulated our interest in the effects of thiourea ligands as carrier groups in platinum antitumor complexes.

We recently reported the unusual structure, reactivity, and cytotoxicity data for Pt(IV) complexes of general formula $[PtCl_{4-n}(am(m)ine)_{n+1}L]^{n+}$ (L = 1,1,3,3-tetramethylthiourea, n = 0−2).[16,17] We now extend our studies to novel cationic mononuclear and dinuclear Pt(II) complexes that derive from *cis*-DDP analogues of the type $[PtCl_2(diamine)]$. The resulting mononuclear complexes with one chloro ligand replaced with a thiourea derivative are structurally similar to $[PtCl(SORR')(dach)]NO_3$[18] (dach = *trans*-1,2-cyclohexanediamine) and *cis*-$[Pt(NH_3)_2(cytosine\text{-}N3)Cl]NO_3$[19] (Chart 1). Although violating the classical structure−activity relationships for platinum drugs[20] antitumor activity has been demonstrated for these species.[11] Furthermore, dinuclear complexes are reported where bifunctional thiourea derivatives act as bridging ligands. Compounds that contain more than one platinum center are of interest for alternative long-range interactions with DNA. These are known to determine their biological activity, which is different from that of mononuclear platinum drugs.[21,22]

Experimental Section

Materials and Procedures. The complexes $[PtCl_2(en)]$ and $[PtCl_2(dach)]$ (en = 1,2-ethanediamine, dach = *trans*-1,2-cyclohexanediamine) were prepared by a method described by Dhara[23] using the appropriate diamine. The dach ligand was a racemic mixture of the *R*,*R* and *S*,*S* isomers. Both complexes were characterized by elemental analyses and infrared spectra. All other chemicals and solvents were obtained commercially and used as supplied. All reactions involving silver nitrate as reagent were performed in the dark.

Physical Measurements. ^{1}H (300 MHz) and ^{13}C (75.6 MHz) NMR spectra were recorded on a General Electric QE-300 spectrometer at 20 °C. Chemical shifts (δ, ppm) are referenced to an internal TMS standard. ^{195}Pt NMR spectra were taken at 64.5 MHz with a spectral window of 125 000 Hz and were referenced to external $K_2[PtCl_4]$ (0.1 M in D_2O). Shifts are reported vs $Na_2[PtCl_6]$ standard (δ vs $[PtCl_6]^{2-}$ = δ vs $[PtCl_4]^{2-}$ − 1631).[24] Broad-band proton decoupling was employed in all ^{13}C and ^{195}Pt NMR experiments. Variable-temperature ^{1}H NMR spectra (300 MHz) were recorded on a Varian Gemini-300 instrument. Infrared data were obtained on a Perkin-Elmer 1600 FTIR instrument. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ.

Synthesis of Chloro(1,2-ethanediamine-κ^2N,N')(1,1,3,3-tetramethylthiourea-κS)platinum(II) Nitrate, $[PtCl(en)\{SC(NMe_2)_2\}]NO_3$ (1). A mixture of 3.26 g (10 mmol) of $[PtCl_2(en)]$ and 1.69 g (10 mmol) of $AgNO_3$ in 60 mL of anhydrous DMF was stirred at room temperature for 20 h. Precipitated AgCl was filtered off, and to the filtrate was added 1.32 g (10 mmol) of 1,1,3,3-tetramethylthiourea (tmtu). This solution was stirred for 6 h. DMF was removed under reduced pressure at 30 °C. The solid residue was dissolved in 200 mL of methanol (ca. 2h). The resulting turbid solution was treated with 0.5 g of activated carbon and finally passed through a Celite pad. Concentration of this solution to a final volume of 60 mL and storage at 4 °C for 24 h afforded **1** as a light-yellow microcrystalline solid. Yield: 2.9 g (59%). ^{1}H NMR (DMF-d_7): δ 2.72 (4H, m), 3.28 (12H, s), 5.57 (2H, b, shoulders due to unresolved Pt satellites), 5.84 (2H, b, shoulders due to unresolved Pt satellites). ^{13}C NMR (DMF-d_7): δ 43.7, 47.8, 50.0, 185.3. ^{195}Pt NMR (DMF-d_7): δ −2929. IR (KBr): ν_{as}(CN) 1564 cm^{-1}. Anal. Calcd for $C_7H_{20}N_5ClO_3PtS$: C, 17.34; H, 4.16; N, 14.44; Cl, 7.31; S, 6.61. Found: C, 17.49; H, 4.22; N, 14.35; Cl, 7.15; S, 6.63.

Synthesis of Chloro(*trans*-1,2-cyclohexanediamine-κ^2N,N')(1,1,3,3-tetramethylthiourea-κS)platinum(II) Nitrate, $[PtCl(dach)\{SC(NMe_2)_2\}]NO_3$ (2). A mixture of 3.80 g (10 mmol) of $[PtCl_2(dach)]$ and 1.69 g (10 mmol) of $AgNO_3$ in 50 mL of anhydrous DMF was stirred at room temperature for 24 h. Precipitated AgCl was filtered off, and to the filtrate was added 1.32 g (10 mmol) of 1,1,3,3-tetramethylthiourea (tmtu). This solution was stirred for 8 h. DMF was removed under reduced pressure at 30 °C, and the remaining oil was dissolved in a sufficient amount of ethanol (ca. 150−200 mL). After the solution was treated with activated carbon, it was passed through a Celite pad. Addition of 200 mL of diethyl ether to the filtrate gave an off-white precipitate of crude **2**, which was collected by filtration and recrystallized from hot ethanol. **2** crystallizes as greenish-yellow compact prisms. Yield: 3.4 g (63%). ^{1}H NMR (MeOH-d_4): δ 1.19 (2H, m), 1.34 (2H, m), 1.62 (2H, m), 2.05 (2H, m), 2.40 (2H, m), 3.26 (12H, s), 5.43 (2H, b, slow H,D exchange), 5.83 (2H, b, slow H,D exchange). ^{13}C NMR (MeOH-d_4): δ 25.5, 25.6, 33.7, 33.8, 44.5, 62.9, 65.1. ^{195}Pt NMR (DMF-d_7): δ −2895. IR (KBr): ν_{as}(CN) 1561 cm^{-1}. Anal. Calcd for $C_{11}H_{26}N_5ClO_3PtS$: C, 24.52; H, 4.86; N, 13.00; Cl, 6.58; S, 5.95. Found: C, 24.60; H, 4.96; N, 12.99; Cl, 6.49; S, 6.01.

General Procedure for the Synthesis of the Bifunctional Thiourea Derivatives 3 and 4. To an intensively stirred mixture of 50 mmol of the appropriate *N*,*N*′-dimethyl diamine and 15.33 mL (0.110 mol) of triethylamine in 300 mL of anhydrous tetrahydrofuran (THF) was added dropwise within 30 min a solution of 12.36 g (0.100 mol) of *N*-dimethylthiocarbamoyl dichloride in 50 mL of THF. The strongly exothermic reaction was controlled with an ice bath. Cooling was discontinued when the addition was complete, and the mixture was heated at reflux for another 8 h. After the mixture was stored at room temperature for 12 h, triethylammonium hydrochloride was filtered off, and the solution was concentrated to a volume of 60−80 mL under reduced pressure. Crude **3** and **4** precipitated at 4 °C as slightly yellowish solids, which were recrystallized from THF. The resulting fractions were washed with ice-cold diethyl ether and dried in vacuo at 60 °C.

1,1,3-Trimethyl-3-[2-(1,3,3-trimethylthioureido)ethyl]thiourea, $C_2H_4(NMeCSNMe_2)_2$ (3). Colorless prisms were formed. Yield: 8.5

(10) Barnham, K. J.; Djuran, M. I.; Murdoch, P. d. S.; Ranford, J. D.; Sadler, P. J. *Inorg. Chem.* **1996**, *35*, 1065.
(11) Farrell, N. *Cancer Invest.* **1993**, *11*, 578.
(12) Ashby, M. T. *Comments Inorg. Chem.* **1990**, *10*, 297.
(13) Murray, S. G.; Hartley, F. R. *Chem. Rev.* **1981**, *81*, 365.
(14) Spofford, W. A.; Amma, E. L. *Acta Crystallogr.* **1970**, *B26*, 1474.
(15) Bierbach, U.; Barklage, W.; Saak, W.; Pohl, S. *Z. Naturforsch.* **1992**, *47B*, 1593.
(16) Bierbach, U.; Reedijk, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1632.
(17) Bierbach, U.; Hambley, T. W.; Roberts, J. D.; Farrell, N. *Inorg. Chem.* **1996**, *35*, 5, 4865.
(18) Farrell, N.; Kiley, D. M.; Schmidt, W.; Hacker, M. P. *Inorg. Chem.* **1990**, *29*, 397.
(19) Hollis, L. S.; Amundsen, A. R.; Stern, E. W. *J. Med. Chem.* **1989**, *32*, 128.
(20) Keppler, B. K. *New. J. Chem.* **1990**, *14*, 389.
(21) Zou, Y.; van Houten, B.; Farrell, N. *Biochemistry* **1994**, *33*, 5404.
(22) Farrell, N. *Comments Inorg. Chem.* **1994**, *16*, 373.
(23) Dhara, S. C. *Indian J. Chem.* **1970**, *8*, 193.
(24) Kerrison, S. J. S.; Sadler, P. J. *J. Magn. Reson.* **1978**, *31*, 321.

g (65%). ^{1}H NMR (MeOH-d_4): δ 3.02 (12H, s), 3.08 (6H, s), 4.00 (4H, s). Anal. Calcd for $C_{10}H_{22}N_4S_2$: C, 45.77; H, 8.45; N, 21.35; S, 24.43. Found: C, 45.87; H, 8.55; N, 21.37; S, 24.37.

1,1,3-Trimethyl-3-[6-(1,3,3-trimethylthioureido)hexyl]thiourea, $C_6H_{12}(NMeCSNMe_2)_2$ (4). Colorless needles were formed. Yield: 11.8 g (74%). ^{1}H NMR (MeOH-d_4): δ 1.32 (4H, m), 1.66 (4H, m), 3.02 (6H, s), 3.05 (12H, s), 3.56 (4H, t). Anal. Calcd for $C_{14}H_{30}N_4S_2$: C, 52.80; H, 9.50; N, 17.60; S, 20.12. Found: C, 52.88; H, 9.72; N, 17.80; S, 19.82.

General Procedure for the Synthesis of the Dinuclear Complexes 5 and 6. A mixture of 1.71 g (5.25 mmol, slight excess) of [$PtCl_2$-(en)] and 0.84 g (5 mmol) of $AgNO_3$ in 10 mL of anhydrous DMF was stirred at room temperature for 16 h. Silver chloride was filtered off. The filtrate was cooled to 0 °C, and 2.5 mmol of the appropriate bifunctional thiourea in 5 mL of DMF was added dropwise within 1 h. The solvent was removed in vacuo at room temperature, and the residue was dissolved in 200 mL of methanol. The solution was treated with activated carbon, passed through a Celite pad, and immediately concentrated to a volume of 20 mL. The products were precipitated with 150 mL of diethyl ether, filtered off, and dried in vacuo. Crude **5** and **6** were redissolved in ethanol (ca. 1.5 g/300 mL), and the solutions were concentrated under reduced pressure at room temperature until precipitation started. Both **5** and **6** were obtained as light-yellow microcrystalline solids after storing the solutions at −16 °C for 24 h.

Bis[chloro(1,2-ethanediamine-κ^2N,N')platinum]-μ-[1,1,3-trimethyl-3-{2-(1,3,3-trimethylthioureido)ethyl}thiourea-κ^2S,S'](2+) Dinitrate, [{PtCl(en)}$_2${$C_2H_4(NMeCSNMe_2)_2$}](NO$_3$)$_2$ (5). Yield: 0.82 g (34%). ^{1}H NMR (MeOH-d_4): δ 2.63 (8H, m), 3.18 (6H, s), 3.31 (12H, s), 4.23 (4H, s). ^{195}Pt NMR (DMF-d_7): δ −2921. IR (KBr): ν_{as}(CN) 1558 cm^{-1}. Anal. Calcd for $C_{14}H_{38}N_{10}Cl_2O_6Pt_2S_2$: C, 17.38; H, 3.96; N, 14.47; Cl, 7.33; S, 6.62. Found: C, 17.56; H, 4.07; N, 14.19; Cl, 7.44; S, 6.45.

Bis[chloro(1,2-ethanediamine-κ^2N,N')platinum]-μ-[1,1,3-trimethyl-3-{6-(1,3,3-trimethylthioureido)hexyl}thiourea-κ^2S,S'](2+) Dinitrate Hemiethanol, [{PtCl(en)}$_2${$C_6H_{12}(NMeCSNMe_2)_2$}](NO$_3$)$_2$·0.5EtOH (6). Yield: 1.1 g (42%). ^{1}H NMR (MeOH-d_4): δ 1.16 (t, solv), 1.37 (4H, m), 1.74 (4H, m), 2.60 (8H, m), 3.10 (6H, s), 3.29 (12H, s), 3.58 (q, solv), 3.77 (4H, t). ^{195}Pt NMR (DMF-d_7): δ −2925. IR (KBr): ν_{as}(CN) 1560 cm^{-1}. Anal. Calcd for $C_{19}H_{49}N_{10}Cl_2O_{6.5}Pt_2S_2$: C, 21.80; H, 4.72; N, 13.37; Cl, 6.77; S, 6.12. Found: C, 21.99; H, 4.90; N, 13.09; Cl, 6.72; S, 6.09.

Force Field Calculations. **(a) Energy Minimization and Conformational Search**. The strain energies for 1,1,3,3-tetramethylthiourea (tmtu) and the bifunctional derivatives **3** and **4** were calculated with the MM+ module of HyperChem 3.0 (1993),[25] which uses the 1977 functional form of Allinger's MM2 force field.[26] New atom types and parameters were added to the 1991 parameter list. Point minimizations with the Polak−Ribiere minimizer were used to optimize the structures. A Δ rms gradient of 0.001 kcal/(mol·Å) was chosen as convergence criterion. The conformational search performed on **3** was carried out with the appropriate module in ChemPlus 1.0A (1994).[27] Calculations employed the MMCM method[28] and were based on random variations of all ∠S=C−N−C and ∠N−C−C−N torsions.

(b) Parametrization and Charge Distribution. The parametrization of the MM2 force field that is capable of describing the geometries of peralkylated thioureas was based on experimental data. "Natural" bond lengths and angles that describe the central [SCN_2] unit were deduced from X-ray structures[29] and electron diffraction data[30] of tmtu and tmtu-containing transition metal complexes.[17,31−35] Force constants for bond stretching and angle bending were derived from a normal-coordinate treatment of tmtu[36] and were scaled with the usual factors.[37] Torsional barriers for internal rotation about the C(sp^2)−N bonds were taken from NMR studies.[38] Calculation of electrostatic effects was based on dipole−dipole interactions. Bond dipoles were determined for tmtu from partial charges obtained with the Gasteiger−Hückel method[39] and were scaled to fit the experimental dipole moment of tmtu in benzene.[40] Tables of new atom types, MM2 parameters, bond moments, and a scheme showing fractional charges are available as Supporting Information.

Table 1. Crystal Data for [PtCl(dach)(tmtu)]NO_3 (**2**), $C_2H_4(NMeCSNMe_2)_2$ (**3**), and $C_6H_{12}(NMeCSNMe_2)_2$ (**4**)

	2	**3**	**4**
space group	$P2_1/n$	$P2_1/n$	$P2_1/n$
a, Å	10.804(1)	12.787(2)	11.097(3)
b, Å	16.221(2)	6.250(1)	13.717(2)
c, Å	21.789(3)	17.777(3)	11.925(3)
β, deg	102.16(1)	98.21(1)	97.61(2)
V, Å^3	3732.8(7)	1406.3(4)	1799.2(7)
fw	538.96	262.43	318.54
D_{calcd}, g cm^{-3}	1.918	1.239	1.176
empirical formula	$C_{11}H_{26}ClN_5O_3PtS$	$C_{10}H_{22}N_4S_2$	$C_{14}H_{30}N_4S_2$
Z	8	4	4
abs coeff, cm^{-1}	77.60	3.62	2.94
temp, °C	21	21	21
λ, Å	0.710 69	0.710 69	0.710 69
R^a	0.039	0.033	0.032
$R_w{}^b$	0.030	0.029	0.025

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

X-ray Structural Determination. Suitable crystals of **2** were grown by slow evaporation of an ethanolic solution at room temperature. Single crystals of **3** and **4** were selected from the bulk of recrystallized compound.

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 equipped with a graphite monochromator. The crystallographic data for **2**−**4** are summarized in Table 1. Data were reduced, and Lorentz, polarization, and analytical absorption (for **2**) corrections were carried out using teXsan.[41] The structures were solved by direct methods using SHELXS-86[42] and refined using full-matrix least-squares methods with teXsan.[41] Hydrogen atoms of **3** and **4** were refined with individual isotropic thermal parameters, those of **2** were included at calculated sites with isotropic thermal parameters based on that of the riding atom, and the non-hydrogen atoms were refined anisotropically. Neutral-atom scattering factors were taken from ref 43. Anomalous dispersion effects were included in F_c;[44] the values

(25) *HyperChem*, Release 3.0; Hypercube Inc.: Waterloo, Ontario, Canada, 1993.
(26) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(27) *ChemPlus, Extensions for HyperChem*, Release 1.0a; Hypercube Inc.: Waterloo, Ontario, Canada, 1994.
(28) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.
(29) Vilkov, V.; Akishin, P. A.; Presnyakova, V. M. *J. Struct. Chem. USSR* **1966**, *7*, 1.
(30) Fernholt, L.; Samdal, S.; Seip, R. *J. Mol. Struct.* **1980**, *72*, 217.
(31) Pohl, S.; Bierbach, U.; Saak, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 776.
(32) Bierbach, U.; Saak, W.; Haase, D.; Pohl, S. *Z. Naturforsch.* **1990**, *45B*, 45.
(33) Griffith, E. A. H.; Spofford, W. A.; Amma, E. L. *Inorg. Chem.* **1978**, *17*, 1913.
(34) Griffith, E. A. H.; Charles, N. G.; Rodsiler, P. F.; Amma, E. L. *Acta Crystallogr.* **1982**, *C39*, 331.
(35) Fabretti, A. C.; Giusti, A.; Malavasi, W. *J. Chem. Soc., Dalton Trans.* **1990**, 3091.
(36) Anthoni, U.; Nielsen, P. H.; Borch, G.; Gustavsen, J.; Klaboe, P. *Spectrochim. Acta* **1977**, *33A*, 403.
(37) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982; pp 36−52.
(38) Martin, G. J.; Gouesnard, J. P.; Dorie, J.; Rabiller, C.; Martin, M. L. *J. Am. Chem. Soc.* **1977**, *99*, 1381.
(39) *Sybyl*, Release 6.1; Tripos Inc.: St. Louis, MO, 1994.
(40) Lumbroso, H.; Liégeois, C. *J. Mol. Struct.* **1981**, *77*, 239.
(41) *teXsan, Crystal Structure Analysis Package*; Molecular Structure Corp.: The Woodlands, TX, 1985, 1992.
(42) Sheldrick, G. M. SHELXS-86. In *Crystallographic Computing 3*; Sheldrick, G. M., Krüger, C., Goddard, R., Eds.; Oxford University Press: New York, 1987; pp 175−189.
(43) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, U.K., 1974; Vol. 4.
(44) Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.

Table 2. Positional Parameters for [PtCl(dach)(tmtu)]NO_3 (**2**)

	x	*y*	*z*	B_{eq}, Å^2
Pt(1)	0.10823(3)	0.34295(2)	0.52638(2)	3.469(8)
Pt(2)	0.08701(3)	0.31625(2)	0.74442(2)	4.178(10)
Cl(1)	0.3056(2)	0.3501(2)	0.5911(1)	5.73(7)
Cl(2)	−0.0935(2)	0.3655(2)	0.7711(1)	7.25(9)
S(1)	0.1855(2)	0.2738(2)	0.4514(1)	4.93(7)
S(2)	−0.0221(2)	0.2167(2)	0.6806(1)	5.55(7)
O(1)	0.3491(8)	0.0953(5)	0.7512(4)	8.5(3)
O(2)	0.347(1)	0.0404(6)	0.8377(5)	13.0(4)
O(3)	0.429(2)	0.1418(8)	0.8352(5)	20.3(6)
O(4)	0.789(1)	0.1870(8)	0.4298(7)	14.0(5)
O(5)	0.784(1)	0.144(1)	0.5161(6)	23.3(8)
O(6)	0.706(1)	0.0797(7)	0.4381(6)	12.3(4)
N(1)	0.0240(6)	0.4066(4)	0.5897(3)	3.8(2)
N(2)	−0.0720(6)	0.3412(4)	0.4736(3)	4.1(2)
N(3)	0.3785(7)	0.1708(5)	0.4775(4)	5.7(2)
N(4)	0.2217(8)	0.1451(5)	0.5313(4)	5.5(2)
N(5)	0.1904(6)	0.4080(4)	0.7941(4)	4.8(2)
N(6)	0.2609(6)	0.2810(5)	0.7282(4)	4.8(2)
N(7)	−0.1019(7)	0.1427(5)	0.7752(4)	5.2(2)
N(8)	−0.2507(7)	0.1627(5)	0.6851(4)	5.1(2)
N(9)	0.376(1)	0.0938(7)	0.8077(6)	7.2(3)
N(10)	0.761(1)	0.138(1)	0.4645(10)	10.2(6)
C(1)	−0.1109(9)	0.4170(10)	0.5614(6)	10.5(5)
C(2)	−0.1537(9)	0.3849(10)	0.5070(6)	11.2(5)
C(3)	−0.2898(8)	0.3906(6)	0.4742(5)	5.7(3)
C(4)	−0.371(1)	0.4278(10)	0.5152(7)	11.1(5)
C(5)	−0.324(1)	0.467(1)	0.5675(7)	12.0(6)
C(6)	−0.1880(9)	0.4597(6)	0.5991(5)	5.6(3)
C(7)	0.2677(8)	0.1923(6)	0.4904(5)	4.4(3)
C(8)	0.424(1)	0.0874(7)	0.4793(7)	9.4(4)
C(9)	0.4566(10)	0.2290(7)	0.4520(7)	9.2(4)
C(10)	0.306(1)	0.1153(7)	0.5886(6)	7.7(4)
C(11)	0.0894(10)	0.1351(7)	0.5290(5)	7.2(4)
C(12)	0.325(1)	0.4012(9)	0.7892(9)	12.2(5)
C(13)	0.3585(10)	0.3343(10)	0.7667(6)	9.6(5)
C(14)	0.4898(9)	0.3213(7)	0.7569(5)	6.6(3)
C(15)	0.581(1)	0.377(1)	0.7977(9)	14.7(7)
C(16)	0.549(1)	0.445(1)	0.8198(9)	11.7(6)
C(17)	0.4141(10)	0.4593(7)	0.8279(5)	6.5(3)
C(18)	−0.1325(8)	0.1724(6)	0.7177(4)	4.3(3)
C(19)	−0.194(1)	0.1424(9)	0.8159(5)	9.7(5)
C(20)	0.027(1)	0.1284(8)	0.8076(5)	7.8(4)
C(21)	−0.3274(9)	0.0903(7)	0.6903(6)	7.5(4)
C(22)	−0.3063(9)	0.2184(8)	0.6341(6)	8.3(4)

for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[45] The values for the mass attenuation coefficients were those of Creagh and Hubbell.[46] All other calculations were performed using the teXsan crystallographic software package of Molecular Structure Corp.,[41] and plots were drawn using ORTEP.[47]

Positional atomic coordinates and selected bond lengths and bond angles for **2**−**4** are presented in Tables 2−7. Complete listings of hydrogen coordinates, thermal parameters, and details of least-squares planes calculations have been deposited as Supporting Information.

Results and Discussion

Mononuclear Complexes. (A) Synthetic Aspects. The site-specific functionalization of the *cis*-[$PtCl_2$(am(m)ine)$_2$] geometry with a thiourea ligand through substitution of *one* chloro ligand encounters major synthetic problems. Direct treatment of *cis*-[$PtCl_2(NH_3)_2$], cisplatin, with thiourea (tu) results in an uncontrollable substitution of all four ligands by *S*-donor ligands. The first step was found to be the displacement of an ammine ligand due to the higher trans-effect of the chloro ligands, followed by substitution of labilized chloride trans to sulfur.[48] Considering the above-mentioned reactivities, the use of diamine ligands instead of ammonia appeared favorable. The thermodynamic

Table 3. Positional Parameters for $C_2H_4(NMeCSNMe_2)_2$ (**3**)

	x	*y*	*z*	B_{eq}, Å^2
S(1)	0.25017(5)	0.74684(10)	0.01343(4)	4.24(2)
S(2)	0.49849(5)	0.05551(9)	0.23520(3)	4.00(1)
N(1)	0.2971(1)	0.4962(3)	−0.09809(9)	3.60(4)
N(2)	0.3455(1)	0.3674(3)	0.02309(9)	2.96(4)
N(3)	0.4685(1)	0.2985(3)	0.35310(9)	3.69(4)
N(4)	0.4042(1)	0.4360(3)	0.23568(9)	3.04(4)
C(1)	0.2998(2)	0.5254(3)	−0.0222(1)	2.90(4)
C(2)	0.4551(2)	0.2737(3)	0.2767(1)	2.90(5)
C(3)	0.2729(3)	0.6733(5)	−0.1507(2)	5.07(8)
C(4)	0.2782(3)	0.2849(5)	−0.1332(2)	4.81(7)
C(5)	0.4297(2)	0.2308(4)	0.0026(2)	3.94(6)
C(6)	0.4902(3)	0.5067(5)	0.3887(2)	4.91(7)
C(7)	0.4951(3)	0.1171(5)	0.4035(2)	5.02(7)
C(8)	0.3226(2)	0.5649(4)	0.2634(2)	3.92(6)
C(9)	0.3291(2)	0.3498(4)	0.1024(1)	3.35(5)
C(10)	0.4144(2)	0.4664(4)	0.1558(1)	3.35(5)

Table 4. Positional Parameters for $C_6H_{12}(NMeCSNMe_2)_2$ (**4**)

	x	*y*	*z*	B_{eq}, Å^2
S(1)	0.77842(6)	0.76280(4)	0.23175(5)	4.61(1)
S(2)	0.23864(5)	0.05787(4)	0.31021(5)	3.70(1)
N(1)	0.8515(1)	0.6104(1)	0.1219(1)	3.71(4)
N(2)	0.6843(1)	0.5836(1)	0.2116(1)	3.39(4)
N(3)	0.1943(2)	0.2464(1)	0.3348(1)	3.74(4)
N(4)	0.2878(1)	0.2062(1)	0.1804(1)	3.01(4)
C(1)	0.7710(2)	0.6473(1)	0.1864(2)	3.13(4)
C(2)	0.9358(2)	0.6750(2)	0.0734(3)	5.06(7)
C(3)	0.8858(2)	0.5078(2)	0.1229(2)	4.56(6)
C(4)	0.6229(2)	0.5179(2)	0.1260(2)	4.28(6)
C(5)	0.6145(2)	0.6059(2)	0.3042(2)	3.74(5)
C(6)	0.5792(2)	0.5162(2)	0.3646(2)	3.48(5)
C(7)	0.5283(2)	0.5422(2)	0.4729(2)	3.65(5)
C(8)	0.2406(2)	0.1758(1)	0.2728(2)	2.80(4)
C(9)	0.1206(3)	0.3257(2)	0.2803(3)	4.81(7)
C(10)	0.1701(4)	0.2259(2)	0.4494(2)	5.88(8)
C(11)	0.3417(3)	0.3022(2)	0.1713(3)	4.59(6)
C(12)	0.3065(2)	0.1383(2)	0.0895(2)	3.26(5)
C(13)	0.4317(2)	0.0930(1)	0.0976(2)	3.15(5)
C(14)	0.4398(2)	0.0258(1)	−0.0015(2)	3.14(5)

Table 5. Selected Bond Lengths (Å) and Angles (deg) with Standard Deviations for [PtCl(dach)(tmtu)]NO_3 (**2**)[a]

Bond Lengths			
Pt(1)−Cl(1)	2.298(2)	Pt(1) −S(1)	2.281(2)
Pt(1) −N(1)	2.080(6)	Pt(1)−N(2)	2.042(6)
S(1)−C(7)	1.72(1)	N(3)−C(7)	1.33(1)
N(3)−C(8)	1.44(1)	N(4)−C(7)	1.35(1)
N(3)−C(9)	1.45(1)	N(4)−C(11)	1.43(1)
N(4)−C(10)	1.47(1)		

Bond Angles			
Cl(1)−Pt(1)−S(1)	91.79(9)	Cl(1)−Pt(1)−N(1)	92.7(2)
Cl(1)−Pt(1)−N(2)	176.0(2)	S(1)−Pt(1)−N(1)	175.4(2)
S(2)−Pt(1)−N(2)	92.3(2)	N(1)−Pt(1)−N(2)	83.2(2)
Pt(1)−S(1)−C(7)	104.7(3)	Pt(2)−S(2)−C(18)	109.1(3)
Pt(1)−N(1)−C(1)	108.2(6)	Pt(1)−N(2)−C(2)	108.7(5)
S(1)−C(7)−N(3)	119.4(8)	S(1)−C(7)−N(4)	122.8(7)
C(7)−N(3)−C(8)	123.8(9)	C(7)−N(3)−C(9)	122.1(8)
C(8)−N(3)−C(9)	113.6(8)	C(7)−N(4)−C(10)	120.1(9)
C(7)−N(4)−C(11)	123.2(9)	C(10)−N(4)−C(11)	115.5(9)
N(3)−C(7)−N(4)	117.7(9)		

[a] Molecule 1; see text.

(45) Creagh, D. C.; McAuley, W. J. In *International Tables for X-ray Crystallography*; Wilson, A. J. C., Ed.; Kluwer: Boston, MA, 1992; Vol. C, Table 4.2.6.8, pp 219−222.
(46) Creagh, D. C.; Hubbell, J. H. In *International Tables for X-ray Crystallography*; Wilson, A. J. C., Ed.; Kluwer: Boston, MA, 1992; Vol. C, Table 4.2.4.3, pp 200−206.
(47) Johnson, C. K. *ORTEP: A Thermal Ellipsoid Plotting Program*; Oak Ridge National Laboratory, Oak Ridge, TN, 1965.
(48) Roundhill, D. M. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; Vol. 5, p 480.

Scheme 1

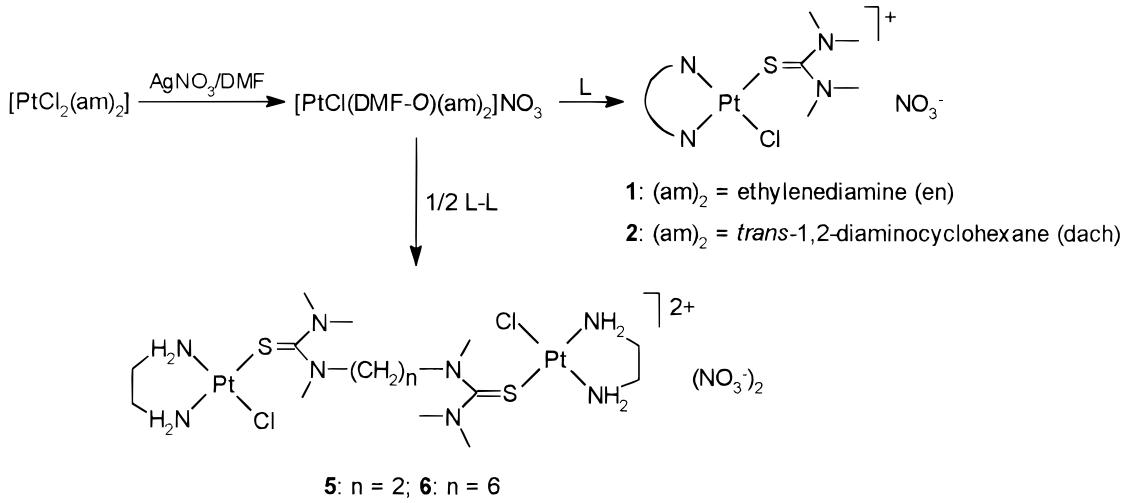


Table 6. Selected Bond Lengths (Å) and Angles (deg) with Standard Deviations for $C_2H_4(NMeCSNMe_2)_2$ (**3**)

Bond Lengths			
S(1)−C(1)	1.682(2)	S(2)−C(2)	1.684(2)
N(1)−C(1)	1.357(2)	N(1)−C(3)	1.453(3)
N(1)−C(4)	1.465(3)	N(2)−C(1)	1.353(2)
N(2)−C(5)	1.460(3)	N(2)−C(9)	1.459(3)
N(3)−C(2)	1.353(2)	N(3)−C(6)	1.457(3)
N(3)−C(7)	1.455(3)	N(4)−C(2)	1.360(2)
N(4)−C(8)	1.459(3)	N(4)−C(10)	1.457(3)
C(9)−C(10)	1.525(3)		
Bond Angles			
C(1)−N(1)−C(3)	120.6(2)	C(1)−N(1)−C(4)	121.6(2)
C(3)−N(1)−C(4)	113.9(2)	C(1)−N(2)−C(5)	123.3(2)
C(1)−N(2)−C(9)	121.4(2)	C(5)−N(2)−C(9)	114.2(2)
C(2)−N(3)−C(6)	121.8(2)	C(2)−N(3)−C(7)	120.9(2)
C(6)−N(3)−C(7)	114.5(2)	C(2)−N(4)−C(8)	122.8(2)
C(2)−N(4)−C(10)	121.2(2)	C(8)−N(4)−C(10)	115.2(2)
S(1)−C(1)−N(1)	121.8(2)	S(1)−C(1)−N(2)	122.0(2)
N(1)−C(1)−N(2)	116.2(2)	S(2)−C(2)−N(3)	122.0(2)
S(2)−C(2)−N(4)	122.2(2)	N(3)−C(2)−N(4)	115.8(2)
N(2)−C(9)−C(10)	112.1(2)	N(4)−C(10) −C(9)	112.9(2)

Table 7. Selected Bond Lengths (Å) and Angles (deg) with Standard Deviations for $C_6H_{12}(NMeCSNMe_2)_2$ (**4**)

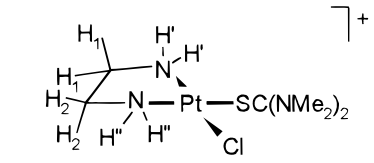
Bond Lengths			
S(1)−C(1)	1.672(2)	N(1)−C(2)	1.461(3)
N(1)−C(1)	1.353(2)	N(2)−C(1)	1.362(2)
N(1)−C(3)	1.459(3)	N(2)−C(5)	1.463(2)
N(2)−C(4)	1.460(3)		
Bond Angles			
C(1)−N(1)−C(2)	120.2(2)	C(1)−N(1)−C(3)	123.2(2)
C(2)−N(1)−C(3)	114.1(2)	C(1)−N(2)−C(4)	121.2(2)
C(1)−N(2)−C(5)	119.5(2)	C(4)−N(2)−C(5)	114.4(2)
S(1)−C(1)−N(1)	122.1(1)	S(1)−C(1)−N(2)	122.8(1)
N(1)−C(1)−N(2)	115.1(2)		

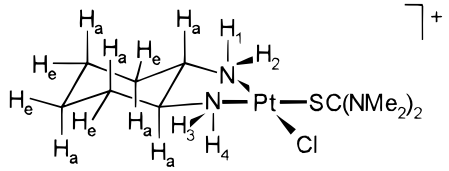
[a] Molecule 1, see text.

stability of the *N*,*N*′-chelates should prevent both *N*-donor displacement as the first step and trans-labilization of the amine by sulfur.

Replacement of one chloro ligand in $[PtCl_2(en)]$ and $[PtCl_2(dach)]$ with 1,1,3,3-tetramethylthiourea (tmtu) gave the cationic complexes $[PtCl(en)\{SC(NMe_2)_2\}]^+$ and $[PtCl(dach)\{SC(NMe_2)_2\}]^+$, which could be isolated as their water-soluble nitrate salts **1** and **2** in approximately 60−70% yields. The reaction via "*monoactivated*" DMF species,[19,49] [PtCl(DMF-*O*)(diamine)]NO_3, proved to be the only practicable method that gave high yields of monosubstituted products (Scheme 1). The

Chart 2





peralkylated thiourea derivative 1,1,3,3-tetramethylthiourea (tmtu) was chosen for various reasons. First, tmtu does not tend to coordination through nitrogen and to desulfurization reactions,[50] unlike partially alkylated and arylated derivatives. Sulfur-bound 1,3-diethylthiourea, $SC(NHEt)_2$, has been shown to easily deprotonate and act as an anionic thioureido ligand which forms a stable *N*,*S*-chelate with Pt^{2+}.[51] Second, the sterically demanding tmtu ligand reduces the undesired substitution of the second chloro ligand. This is in contrast to reactions with 1,3-dimethylthiourea (dmtu) where $[Pt(diamine)\{SC(NHMe)_2\}_2](NO_3)_2$ was the only isolable product (data not shown). Third, besides its overall increased chemical stability, a lipophilic permethylated thiourea could be of importance for the cellular uptake of the complexes by facilitating passive diffusion through the cell membrane. This issue has been discussed in detail elsewhere (e.g., for the axial ligands in Pt(IV) antitumor complexes[17,52,53]).

(B) Solution NMR Studies. ^{1}H NMR spectra of $[PtCl(en)\{SC(NMe_2)_2\}]NO_3$ (**1**) and $[PtCl(dach)\{SC(NMe_2)_2\}]NO_3$ (**2**)

(49) Lippert, B.; Pfab, R.; Neugebauer, D. *Inorg. Chim. Acta* **1979**, *37*, 495.
(50) Brader, M. L.; Ainscough, E. W.; Baker, E. N.; Brodie, A. M. *Polyhedron* **1989**, *8*, 2219.
(51) Okeya, S.; Fujiwara, Y.; Kawashima, S.; Hayashi, Y.; Isobe, K.; Nakamura, Y.; Shimomura, H.; Kushi, Y. *Chem. Lett.* **1992**, 1823.
(52) Giandomenico, C. M.; Abrams, M. J.; Murrer, B. A.; Vollano, J. F.; Rheinheimer, M. I.; Wyer, S. B.; Bossard, G. E.; Higgens, J. D. *Inorg. Chem.* **1995**, *34*, 1015.
(53) McKeage, M. J.; Abel, G.; Kelland, L. R.; Harrap, K. R. *Br. J. Cancer* **1994**, *69*, 1.

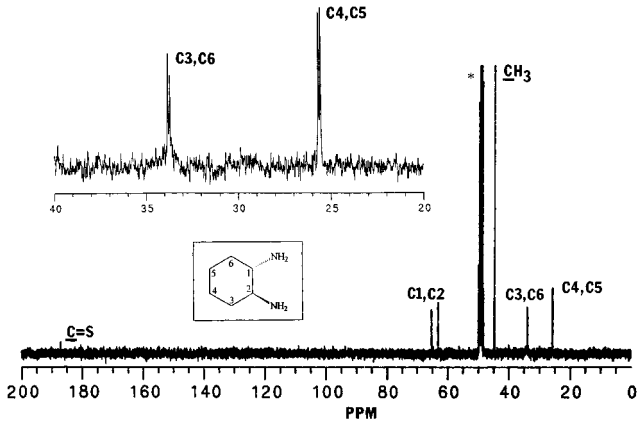


Figure 1. ^{13}C NMR spectrum (75 MHz) of [PtCl(dach)(tmtu)]NO_3 (**2**) in MeOH-d_4 with an expanded view of the 20−40 ppm region and an atom numbering scheme for the cyclohexyl ring. Six distinct resonances for the dach ligand confirm C_1 symmetry for **2** in solution. *C*=S and *C*H$_3$ denote signals of tmtu. The asterisk indicates the solvent peak.

taken in DMF-d_7 and MeOH-d_4, respectively, show integral intensity ratios for the tmtu and diamine protons that indicate the persistence of the monocationic species in solution. Replacement of one chloro ligand in [$PtCl_2$(en)] and [$PtCl_2$(dach)] with tmtu causes a loss of 2-fold symmetry (Chart 2). Thus, the methylene protons of the diamine chelates in **1** and **2** (and methine protons in **2**) become chemically inequivalent under C_s and C_1 symmetries[54] of the complexes, respectively. Accordingly, these should "see" a slightly different magnetic environment. The amine proton signals that are observed in dry deuterated solvents in fact experience the unsymmetrical tmtu−chloro coordination. For **1**, *two* NH resonances were found at 5.57 and 5.84 ppm (for H′ and H″; see Chart 2) in accordance with a fluctuating en ligand. In **2**, all four NH protons are chemically inequivalent (H_1−H_4; see Chart 2) due to the rigid dach ligand and give rise to *four* absorptions at 4.95, 5.08, 5.43, and 5.83 ppm. Heteronuclear ^2J and $^3J(^{195}Pt-^1H)$ couplings are only observed as shoulders for both compounds due to CSA relaxation.[55] Peripheral CH protons, however, are not affected in such a way. For **1**, only a single resonance for the ethylene group is observed at 2.72 ppm that appears slightly broadened due to restricted flexibility of the five-membered chelate ring. Similarly, the five distinct signal groups that were assigned to pairs of axial and equatorial CH protons of the rigid cyclohexane moiety in **2** (see Chart 2) do not confirm the expected complex geometry. The 12 methyl protons of tmtu in **1** and **2** give a sharp singlet absorption at 3.28 and 3.26 ppm, respectively, indicating free rotation about the Pt−S, S−C, and C(sp^2)−N bonds.

^{13}C NMR spectra confirm the symmetry-induced inequivalence of C(1) and C(2) of the en ligand and C(1)−C(6) of the dach ligand in **1** and **2**, respectively (for ^{13}C NMR data, see also the Experimental Section). For **2**, ^{13}C chemical shift differences as small as 0.1 ppm were found for signals assigned to the atom pairs C3/C6 and C4/C5 (Figure 1). A single absorption for the methyl groups of tmtu in **1** and **2** at 43.7 and 44.5 ppm, respectively, is in agreement with ^{1}H NMR results. The ^{13}C chemical shifts for the thiocarbonyl group at 185.3 ppm (for **1**) and 186.5 ppm (for **2**) are indicative of S-bound tmtu. These appear slightly upfield shifted (ca. 5−10 ppm) compared

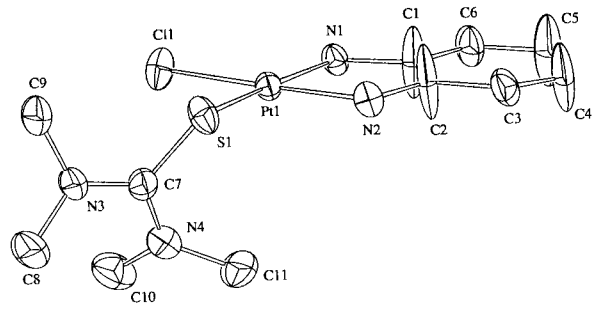


Figure 2. View of one of the independent cations of [PtCl(dach)(tmtu)]NO_3 (**2**) giving atom numbering. Ellipsoids are drawn at the 30% probability level.

to that of the free ligand. This shielding effect, which is much more pronounced for tmtu bound to Pt(IV),[56] is attributed to a lowering of the C=S bond order upon coordination and a N→C-(sp^2) shift of π-electron density.

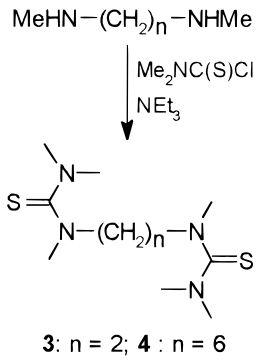
The ^{195}Pt NMR chemical shifts for **1** and **2** at −2929 and −2895 ppm in DMF-d_7 show a substitution shift of ca. 800 ppm to higher field, as expected for the exchange of chloride with a sulfur donor. No $^1J(^{195}Pt-^{14}N)$ couplings are observed due to relaxation effects caused by quadrupolar ^{14}N binding to platinum.[55] Interestingly, ^{195}Pt chemical shifts for the [N_2ClS] environment in analogous complexes with S-bound sulfoxides have been found further upfield in the −3100 to −3300 ppm region.[57,58] This distinct difference between thiourea and sulfoxide sulfurs has been reported before and has been correlated to the degree of covalent bonding involving Pt 5d and ligand-based orbitals (nephelauxetic effect).[59] In the present case, the order of shielding (thiourea-*S* < dmso-*S*) can be best explained in terms of metal-to-ligand π back-bonding and the pronounced π-acceptor properties of S-bound sulfoxides.[60]

(C) X-ray Crystal Structure of [PtCl(dach){SC(NMe$_2$)$_2$}]NO_3 (2). [PtCl(dach){SC(NMe_2)$_2$}]NO_3 (**2**) crystallizes in the monoclinic space group $P2_1/n$ as a racemic mixture due to the presence of both the *R*,*R* and the *S*,*S* form of the *trans*-1,2-cyclohexanediamine (dach) ligand. The structure of **2** consists of two independent molecules packed with weak intermolecular Cl···HN and O···HN hydrogen bonds, one of which is depicted in Figure 2. The two cations have similar geometries and conformations, and both exhibit disorder in the dach ligands. This disorder results in large thermal ellipsoids for four of the carbon atoms with the major axes lying perpendicular to the Pt coordination plane. No separate sites for the contributors to this disorder could be located, and the result is apparently planar cyclohexane rings. Conformational disorder is not feasible for a coordinated dach ligand. We therefore interpret the disorder as a result of both enantiomers occupying a single site. In molecule 1, the dach ring is close to planar, indicating a 1:1 mixture of the two enantiomers. Planarity also results for the five-membered chelate ring as expected for statistical disorder of a δ and a λ conformation. In molecule 2 (not shown), a disordered nonplanar dach ligand is observed, indicating considerable deviation from a 1:1 mixture of enantiomers. The reason for the disorder in both independent molecules lies in the chirality induced in the complex by the disposition of the

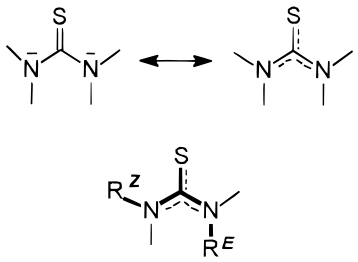
(54) **1** adopts mirror symmetry when interconversion of conformations (δ and λ) of the en chelate is fast on the NMR time scale. This is not feasible for **2** due to the chirality of the dach ligand.

(55) Ismail, I. M.; Kerrison, S. J. S.; Sadler, P. J. *Polyhedron* **1982**, *1*, 57.
(56) Bret, J.-M.; Castan, J.; Commenges, G.; Laurent, J.-P. *Polyhedron* **1983**, *2*, 901.
(57) Sundquist, W. I.; Ahmed, K. J.; Hollis, L. S.; Lippard, S. J. *Inorg. Chem*. **1987**, *26*, 1524.
(58) Landi, J.; Hacker, M. P.; Farrell, N. *Inorg. Chim. Acta* **1992**, *202*, 79.
(59) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem*. **1985**, *24*, 4685.
(60) Davies, J. A. *Adv. Inorg. Chem. Radiochem*. **1981**, *24*, 115.

Scheme 2



Scheme 3



thiourea ligand above or below the coordination plane, which produces two diastereomers. Packing forces in the solid state are evidently not sufficient to produce a discrimination between these diastereomers.

Platinum exhibits a square planar [PtN_2ClS] coordination sphere with tmtu binding through the sulfur atom. The Pt−S bond lengths are marginally shorter than those for Pt−Cl, the reverse of the situation in Pt(IV) complexes with an analogous ligand combination.[17] A comparison of Pt−Cl and Pt−S distances in **2** and *cis*-[$Pt^{IV}Cl_4(NH_3)$(tmtu)][17] proves to be quite instructive. The Pt−Cl bond lengths for **2** (2.296(2) Å, mean) are only slightly shorter than those in the Pt(IV) complex (2.312-(1) Å, mean for bonds cis to sulfur). A similar situation is observed for $[PtCl_4]^{2-}$ (2.310(1) Å)[61] and $[PtCl_6]^{2-}$ (2.314(1) Å).[62] A change in the oxidation state leaves the Pt−Cl distances practically unchanged.[63] In contrast, the Pt−S bond length in **2** (2.284(2) Å, mean) is significantly shorter than that in *cis*-[$Pt^{IV}Cl_4(NH_3)$(tmtu)] (2.354(1) Å). We suggest that this bond shortening may be attributed to π-acceptor properties of tmtu bound to divalent platinum. However, donation of π electrons from the metal to tmtu appears to be much less effective than in analogous sulfoxide complexes (Pt−S 2.204(4) Å in *trans*-[$Pt(NH_3)_2$(dmso-*S*)Cl]$^+$ [57]), which is in agreement with ^{195}Pt NMR data for **1** and **2** (vide supra).

Some of the Pt−N bonds are unusually long, but there is no correlation with the *S*-donor ligand trans to the longer bond, and the apparent bond lengths may be affected by the disorder of the dach ligand. Comparison of the geometry about the thiocarbonyl carbon atom of tmtu in **2** and in free peralkylated thioureas[29] (vide infra) reveals a lengthening of the C−S bond of about 0.05 Å on coordination and a shortening of the C−N bonds by about half of this amount. The bulky thiourea ligands in molecules 1 and 2 are folded back over the Pt atom, giving

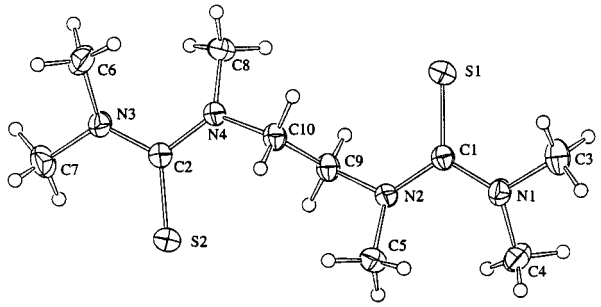


Figure 3. View of $C_2H_4(NMeCSNMe_2)_2$ (**3**) giving atom numbering. Ellipsoids are drawn at the 30% probability level.

close Pt···H contacts (2.67, 2.61 Å). The thiourea ligands deviate from planarity with the $CNMe_2$ groups being twisted by 10−30° out of the plane of the SCN_2 unit.

Dinuclear Complexes. (A) Synthesis and Characterization in Solution of the Didentate Thiourea Ligands $C_2H_4(NMeCSNMe_2)_2$ (3) and $C_6H_{12}(NMeCSNMe_2)_2$ (4). Peralkylated bifunctional thiourea derivatives that act as μ-S,S′ bridging units in our dinuclear platinum complexes (vide infra) were accessible via reaction of an appropriate secondary diamine with *N*-dimethylthiocarbamoyl dichloride in the presence of a tertiary amine. According to this method (Scheme 2) the two novel derivatives $C_2H_4(NMeCSNMe_2)_2$ (**3**) and $C_6H_{12}(NMeCSNMe_2)_2$ (**4**) were obtained in ca. 70% yield. ^{1}H NMR and analytical data (see Experimental Section) are consistent with the expected symmetric bis(thiourea) structures.

In solution *N*-substituted thiourea derivatives exist as an equilibrium mixture of *E*,*Z* conformers (Scheme 3). The pronounced double-bond character of the C(sp^2)−N bonds results in rotational barriers ($\Delta G^{\ddagger}$) of 50−70 kJ/mol for partially alkylated/arylated derivatives as estimated from variable-temperature NMR measurements.[64] In contrast, a barrier as low as 13 kJ/mol has been established for tmtu.[38] Characteristically, ^{1}H NMR spectra of **3** and **4** in DMF-d_7 taken over a +60 to −30 °C temperature range show no splitting or broadening of the signals. This is in contrast to the situation observed for the bifunctional derivative $C_2H_4(NHCSNHMe)_2$ which is structurally related to **3**. For this *N*,*N*′-dialkylated bis(thiourea) an equilibrium mixture of different frozen *E*,*Z* conformers has been detected at temperatures below −10 °C.[65]

(B) X-ray Crystal Structures of $C_2H_4(NMeCSNMe_2)_2$ (3) and $C_6H_{12}(NMeCSNMe_2)_2$ (4). The structures of $C_2H_4(NMeCSNMe_2)_2$ (**3**) and $C_6H_{12}(NMeCSNMe_2)_2$ (**4**) confirm the preparation of the expected bis(thiourea) derivatives. **3** consists of a single molecule (Figure 3), and **4** consists of two independent molecules, both of which are situated on centers of symmetry. The conformations of these two independent molecules differ from each other in the orientation of the thiourea units as indicated by C−N−C−C torsion angles. The torsion angle C1−N2−C5−C6 is −147.4(2)° in molecule 1 (Figure 4) whereas the analogous torsion in molecule 2 (not shown) is −93.6(2)°. The conformation of **3** is similar to that of the second molecule of **4** (C1−N2−C9−C10 −92.5(2)°; C2−N4−C10−C9 91.5(2)°). All conformations are highly elongated and exhibit a *cis*-orientation of the sulfur atoms and the aliphatic

(61) Ohba, S.; Sato, S.; Saito, Y. *Acta Crystallogr.* **1983**, *B39*, 49.
(62) Ohba, S.; Saito, Y. *Acta Crystallogr.* **1984**, *C40*, 1639.
(63) It is assumed that the decrease in radius of the metal center, which usually occurs when its oxidation number increases, is compensated by the increase in radius that accompanies the change in coordination number. See also: Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.
(64) Walter, W.; Ruess, K.-P. *Liebigs Ann. Chem.* **1971**, *746*, 54.
(65) ^{1}H NMR spectra (300 MHz, DMF-d_7) taken at low temperatures show multiple signals for the methyl(ene) protons. The broad singlets assigned to the chemically inequivalent NH protons (a, b) in Me*H*^{a}NC(S)*NH*^{b}−$(CH_2)_2$−*NH*^{b}C(S)*NH*^{a}Me at δ 7.60 and 7.68 are affected in the same way. Additional peaks appear at δ 8.11, 7.93, and 7.63 upon lowering the temperature (Bierbach, U.; Farrell, N. Unpublished results).

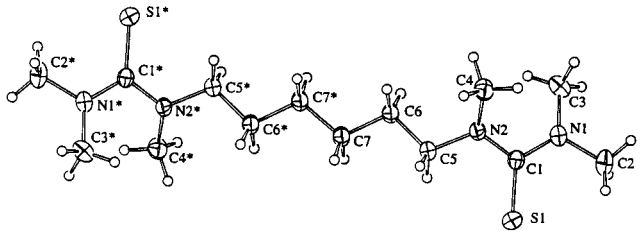


Figure 4. View of one of the independent molecules of C_6H_{12}-$(NMeCSNMe_2)_2$ (**4**) giving atom numbering. Ellipsoids are drawn at the 30% probability level.

C_2 and C_6 linkers and are designated *Z,Z* conformers according to Scheme 3 and conventions introduced in the following section.

(C) Force Field Calculations on the Peralkylated Thiourea Derivatives. The relative stability of different *E,Z* forms of substituted thioureas, i.e., the relative population of conformers in solution, has been shown to affect the biological activity of pharmaceuticals that contain this functional group.[66] 1D and 2D NMR data did not provide information about the solution structures of **3** and **4**. This is due to the absence of characteristic couplings and rapid fluctuation of intramolecular nonbonding distances in these species. For this reason, a MM2-based force field was developed and optimized to reproduce the structure of tmtu with sufficient accuracy and was finally used to model the preferred conformations of the bis(thiourea) derivatives.

Characteristic structural features for energy-minimized tmtu are in agreement with experimental data: (i) the structure exhibits C_2 symmetry with the characteristic "conrotatory twisting" of the dimethylamino groups out of the SCN_2 plane ($\varphi \approx 30°$); (ii) the nitrogen atoms show a planar configuration; (iii) the calculated dipole moment (μ_{MM2}) of 4.77 D is in good agreement with the experimental value of 4.65 D determined in benzene.[40] A table of geometrical parameters is available as Supporting Information.

A conformational search on the bis(thiourea) **3** followed by geometry optimizations yielded at least 30 conformations with a maximum energy difference of 16 kJ/mol. The basic rotamers observed are *Z,Z*, *E,Z*, and *E,E*, which differ in the position of the ethylene bridge in each thiourea moiety (results for **4** are similar and are not reported). Three conformations of **3** are shown in Figure 5, each of these representing the minimum-energy form of the *Z,Z*, *E,Z*, and *E,E* rotamers. The *E,Z* and *E,E* forms of **3** were found to be energetically disfavored compared to the *Z,Z* form by amounts of 5.5 and 8.4 kJ/mol, respectively. These values suggest that for **3** the population of the *Z,Z* form is higher than 80% at room temperature, according to Boltzmann's equation. The orientation of both thiourea fragments with respect to the central ethylene bridge is anti in all cases. The rotamer with the ethylene bridge in the *Z* position of both thiourea groups, *Z,Z*-**3**, proved to be the structure of lowest energy (global minimum). The overall geometry of this model is in good agreement with the solid-state structure of **3** reported in this paper (see Supporting Information). The torsional angles C1−N2−C9−C10 and C2−N4−C10−C9 (±95.8°) and the angles between planes S1−N1−N2−C1/N1−C1−C3−C4 and S2−N3−N4−C2/N3−C2−C6−C7 (36.5°) are reproduced very well. Intramolecular sulfur−sulfur distances in the different rotamers are 6.5 Å (*Z,Z*), 7.1 Å (*E,Z*), and 8.3 Å (*E,E*). The tendency of **3** to adopt the *Z,Z* form in solution

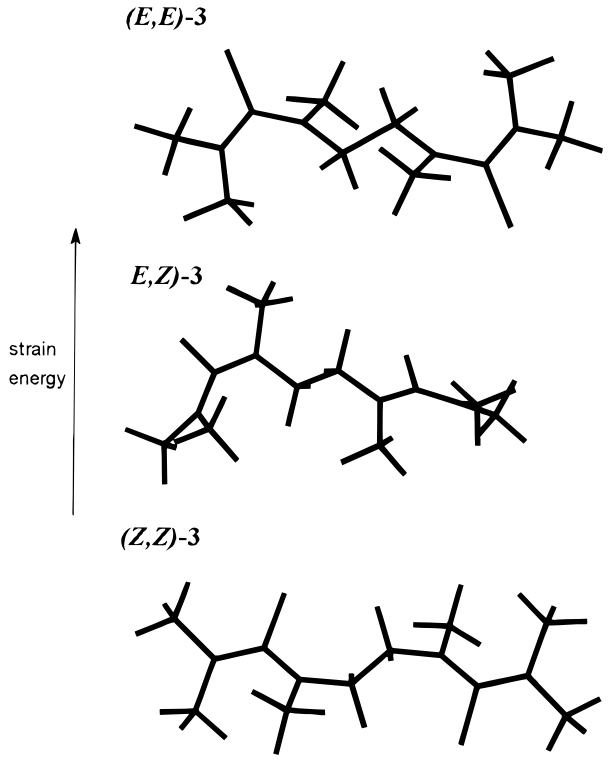


Figure 5. Three representative strain-minimized conformations of **3**. Note the increase in steric strain on going from the *Z,Z* to the *E,E* form.

could have consequences for dinuclear complex formation and undesired competition reactions, e.g. *S,S′* chelation of one Pt center. Furthermore, a similar preferred conformation of **3** as a bridging ligand could be important for the "bite" of the dinuclear platinum complexes and their DNA cross-linking properties.

(D) Synthesis and Characterization of [{PtCl(en)}$_2${C_2H_4-$(NMeCSNMe_2)_2$}]$(NO_3)_2$ (5) and [{PtCl(en)}$_2${C_6H_{12}-$(NMeCSNMe_2)_2$}]$(NO_3)_2$·0.5EtOH (6). Reaction of 1 equiv of "monoactivated" [$PtCl_2$(en)] with $^1/_2$ equiv of the bis(thiourea) compounds, according to Scheme 1, gave the doubly charged cationic complexes [{PtCl(en)}$_2${$C_2H_4(NMeCSNMe_2)_2$}]$^{2+}$ and [{PtCl(en)}$_2${$C_6H_{12}(NMeCSNMe_2)_2$}]$^{2+}$ as their nitrate salts **5** and **6**. Formation of the undesired chelate complexes [Pt(en)-{*S,S′*-bis(thiourea)}$^{2+}$ was reduced by adding the didentate ligand to a concentrated solution of platinum complex. These unavoidable side products show ^{195}Pt NMR shifts in the −3400 to −3500 ppm region, which is indicative of a [PtN_2S_2] environment (a shift of −3400 ppm was reported for the unstable species *cis*-[$Pt(NH_3)_2(tu)_2$]$^{2+}$ in water[59]). Reactions performed at low temperatures, where the rate of undesired substitution of the second chloride should be decreased, gave water-soluble **5** and **6** in ca. 40% yield.

^{1}H NMR spectra of **5** and **6** in MeOH-d_4 confirmed the preparation of symmetric dinuclear complexes with two [PtCl-(en)]$^+$ units bridged by *one* bis(thiourea) derivative. The signals are sharp and show no indication of restricted rotation in the thiourea groups at room temperature. Platinum coordination causes a slight downfield shift for all the resonances of the bifunctional thiourea derivatives compared to the free ligands (see Experimental Section) due to an inductive effect of the metal. Consequently, groups closest to the conjugated SCN_2 system are affected most. ^{195}Pt NMR data are consistent with a [PtN_2ClS] environment (δ −2921 and −2925 for **5** and **6** in DMF-d_7, respectively).

(66) Silverman, R. B. *Medizinische Chemie für Organiker, Biochemiker und pharmazeutische Chemiker*; VCH: Weinheim, Germany, 1995; pp 93−95.

Conclusions

In this paper, we reported the synthesis of thiourea-modified cisplatin analogues and the effects of sulfur coordination on the structure and spectroscopic properties. Mono- and bifunctional peralkylated thiourea derivatives have been introduced as mono- and didentate sulfur ligands in a new class of cationic platinum(II) complexes exhibiting a mixed-donor [N_2ClS] coordination. Two major synthetic problems that complicate the preparation of such complexes proved to be the strong nucleophilicity and the trans-effect of sulfur. The undesired labilization and displacement of the amine ligands required the use of chelating diamines as nonleaving groups.

The Pt−S bond in [PtCl(dach)(tmtu)]NO_3 (**2**) is considerably shorter than in structurally related mixed-donor platinum(IV) species[17] (ca. 0.07 Å) but significantly longer than in analogous cationic platinum(II) sulfoxide complexes (ca. 0.08 Å). These data (and ^{195}Pt NMR shifts) point to weak π-acceptor properties of the thiourea ligand that are less pronounced than those discussed for sulfoxides. The nature of the Pt−S bond may determine the kinetic lability/thermodynamic stability of **1**, **2**, **5**, and **6** in biological systems, which is relevant for their metabolism and their mechanism of action.

Despite an increase in the C(sp^2)−N bond order in tmtu and the bis(thiourea) ligands upon coordination to Pt^{2+} (IR, NMR, X-ray), barriers of rotation are low, and conformational flexibility is observed for all the ligands. Force field calculations on the bis(thiourea) derivatives show that, while rapid interconversion of different *E,Z* forms is observed, these rotamers are unlikely to equally contribute to the equilibrium mixture in solution. The preference for a certain conformer in solution, as observed in the solid state, should determine the effective Pt−Pt distance in dinuclear complexes where such derivatives serve as bridging ligands.

The distinct donor properties and the steric effects (bulkiness, conformation) of the thiourea ligands are critical to the reactivity of the complexes and their affinity for potential biological target molecules. These issues are related to the biological activity of the novel compounds described in this paper and will be addressed in part 2 of this work.[67]

Acknowledgment. This work was supported by a research fellowship (to U.B.) from the Deutsche Forschungsgemeinschaft (DFG, Bonn, Germany) and by the American Cancer Society (Grant No. DHP-2E). We thank W. C. Heraeus GmbH (Hanau, Germany) for a generous loan of $K_2[PtCl_4]$.

Supporting Information Available: Tables of crystallographic data, anisotropic displacement coefficients, H atom coordinates, bond lengths and angles, and least-squares planes for **2**−**4** (Tables S1−S17), MM2 force field parameters, new atom types, bond moments, and calculated fractional charges for tmtu (Table S18, Figure S1), and calculated and experimental geometrical parameters (Tables S19 and S20) for tmtu and **3** (15 pages). Ordering information is given on any current masthead page.

IC970420Y

(67) Bierbach, U.; Roberts, J. D.; Farrell, N. *Inorg. Chem.* **1998**, *37*, 717.