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Crystal and Molecular Structures of Asymmetric *cis*- and *trans*-Platinum(II/IV) Compounds and Their Reactions with DNA Fragments

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The asymmetrically substituted platinum(II) complexes *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 and *trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 have been synthesized and their crystal structures have been determined. Crystals of *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 (**1**) are orthorhombic, space group *P*bca (no. 61) with $a = 10.1994(12)$, $b = 10.494(2)$, $c = 18.826(2)$ Å, $Z = 8$. The structure refinement converged to $R1 = 0.0518$ and $wR2 = 0.1143$. Crystals of *trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 (**2**) are monoclinic, space group $P2_1$/c (no. 14) with $a = 12.141(3)$, $b = 6.0965(9)$, $c = 19.864(3)$ Å, $\beta = 118.71(2)°$, $Z = 4$. The structure refinement converged to $R1 = 0.0711$ and $wR2 = 0.1846$. In addition, the Pt(IV) analogues with axial hydroxide ligands have been synthesized. Also the corresponding bis(carboxylato)platinum(IV) compound of formula *trans,cis,cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2($OOCCH_3$)$_2$ has been obtained by conversion of the hydroxide with acetic anhydride. Reactions of these platinum complexes with 9-methylhypoxanthine and guanosine-5′-monophosphate (5′-GMP) have been studied in significant detail. The course of the reactions was followed by NMR spectroscopy, and ^1H and ^{195}Pt techniques were used to identify the formation of the products. It was found that the Pt(II) compounds easily react with the bases at the N7 position, whereas the Pt(IV) compounds react very slowly (for *trans,cis,cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2($OOCCH_3$)$_2$) or not at all (for *trans,trans,trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2(OH)$_2$). Only in the presence of glutathione does a reaction of the latter with 5′-GMP takes place. In this case a major product was found to be the reduced *trans*-Pt(II) complex with one molecule of 5′-GMP and one molecule of S-bonded glutathione.

Introduction

Cisplatin is a well-established antitumor drug. One of its disadvantages is the need to apply it intravenously. This has resulted in investigations toward orally applicable platinum complexes. A large class of compounds under investigation is a group of platinum(IV) compounds.[1] The kinetics of platinum(IV) are much slower than those of platinum(II). This property is most probably one of the reasons why they can be applied orally and are not degraded too early in the gastrointestinal tract. A group of platinum(IV) compounds with one ammine and one cyclohexylamine ligand has recently been found to be particularly promising in antitumor tests, JM-216 (*cis,cis,trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2($OOCCH_3$)$_2$) being already in clinical trials.[2] The X-ray structure of this compound has been published recently.[3]

Another reason for research toward new compounds originates from the build-up of resistance in cells treated with cisplatin. Most known derivative drugs, e.g. carboplatin, show cross-resistance with cisplatin. Thus new antitumor drugs that do have activity against cells that cannot be treated with cisplatin are highly desired. Other metals, like ruthenium, have also been investigated for their antitumor activity and some show promising *in vitro* activity.[4] More recently, even unconventional platinum complexes, like those with N-donor atoms in trans position, have been investigated.[5] In this respect it is very interesting that a platinum(IV) compound with trans configuration, *trans,trans,trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2(OH)$_2$, abbreviated to JM-335, has been reported to be antitumor active.[6]

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This observation, combined with the fact that Pt(IV) compounds are usually seen as prodrugs for Pt(II) compounds and the generally accepted fact that classical amine complexes have cis geometry, makes these compounds particularly interesting for mechanistic studies and reactions with DNA fragments.[7]

In the present study the binding of mixed ammine−cyclohexylamine platinum compounds to simple derivatives of DNA, i.e. 9-methylhypoxanthine and 5′-GMP is reported. Both Pt(IV) and Pt(II) compounds are investigated. In addition, attention is given to the possible glutathione-assisted reduction of the Pt(IV) compounds to their Pt(II) derivatives.[8] Furthermore, the present paper describes the X-ray structures of both *cis*-Pt$(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2$ (**1**) and *trans*-Pt$(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2$ (**2**).

Experimental Section

Infrared Spectroscopy. Infrared spectra have been recorded as KBr or CsI pellets in the range 4000−250 cm^{-1} on a Perkin-Elmer 580B spectrophotometer. Fourier transform infrared spectra have been recorded as KBr or CsI pellets in the range 4000−400 cm^{-1} and as polyethylene (PE) pellets in the range 600−100 cm^{-1}. A Bruker IFS 113V FT-IR spectrophotometer was used for this purpose.

Elemental Analyses. C, H, and N determinations were performed by the microanalytical laboratory of the University of Dortmund, Dortmund, Germany, using a Carlo Erba Strumentazione element analyzer (Model 1106).

Mass Spectrometry. A Finnigan MAT 900 mass spectrometer was used.

NMR Measurements. ^1H spectra were recorded on a Bruker DPX-300 spectrometer operating at a frequency of 300 MHz. D_2O was used as a solvent with trace amounts of the reference TMA (tetramethylammonium nitrate; $\delta = 3.18$ ppm). ^{13}C spectra were recorded on a Bruker DPX-300 spectrometer operating at a frequency of 75.5 MHz. Chemical shifts were reported relative to the reference TMS (tetramethylsilane). ^{195}Pt spectra were recorded with a Bruker DPX-300 or Bruker AM-200 spectrometer operating at frequencies of 64.5 and 43.0 MHz. Chemical shifts are reported relative to the external reference K_2PtCl_4 ($\delta = -1631$ ppm vs K_2PtCl_6 $\delta = 0$ ppm).[9]

pH Measurements. pH titrations were performed by adding NaOD or DCl ($c = 0.1$ M) to the sample until the required pH was reached. pH values were measured with a radiometer PHM-80 pH meter equipped with an Ingold 6030-02 electrode. All pH measurements were performed at 298 K. The pH meter was calibrated with buffer solutions of pH 4.00, 7.00, and 11.00. Meter readings, reported as pH*, were not corrected for deuterium isotope effects.[10] The pK_a values mentioned in the discussions are valid for H_2O and obtained from literature.[11] Our conclusions will not be affected by this discrepancy because the effect of metal binding is much larger than the deuterium isotope effect.

Starting Materials. *cis*-$Pt(NH_3)_2Cl_2$ was prepared according to Dhara's method.[12] 9-Methyladenine and 9-methylhypoxanthine were prepared according to literature procedures[13,14] as detailed below.

9-Methyladenine. The reaction was carried out in a 250 mL two-necked flask equipped with a reflux condenser and a dropping funnel. A 5 g (0.037 mol) sample of adenine was dissolved in a solution of 1.5 g (0.037 mol) of NaOH in 150 mL of ethanol. After dissolving, the solution was cooled to −5 °C in a salt ice bath. 5.3 g (0.037 mol) of iodomethane was added dropwise, with vigorous stirring. The temperature was kept between 0 and 10 °C during the addition. The solution was heated under reflux for 1 h and stirred for 15 min at room temperature. The solution was cooled to 0 °C. The white precipitate was filtered off and washed with ethanol several times. The crude product was recrystallized from hot water and dried in air. Yield: 3.6 g (65%) colorless needles. ^1H-NMR (D_2O) δ (ppm): 8.07 (H2), 8.03 (H8), 3.78 (N−CH_3). MS (*m/e*): 149.2 (M^+). Anal. Calcd for $C_6H_7N_5$ ($M_w = 149.16$): C, 48.32; N, 46.95; H, 4.73. Found: C, 48.0; N, 47.0; H, 4.8.

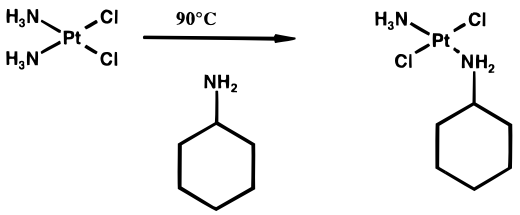

Figure 1. Synthesis of *trans*-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$ (**2**) (JM-334).

9-Methylhypoxanthine. The reaction was carried out in a 250 mL two-necked flask equipped with a reflux condenser. A 2.7 g (0.018 mol) sample of 9-methyladenine was dissolved in 140 mL of 0.8 M HCl. A solution of 1.37 g of $NaNO_2$ in 45 mL of water was added dropwise. The solution was heated for 1 h to 90 °C. After additional stirring for 0.5 h at room temperature, the solution was evaporated to dryness. The yellowish residue was dissolved in 150 mL of hot water and neutralized with solid NaOH. After treatment with charcoal, the solution was filtered off hot. On cooling, colorless needles deposited, which were filtered and dried in air. Yield: 1.01 g (37%). ^1H-NMR (D_2O) (pH* = 5.44) δ (ppm): 8.17 (H2), 8.04 (H8), 3.82 (N−CH_3). Anal. Calcd for $C_6H_6N_4O$ ($M_w = 150.14$): C, 48.00; N, 37.32; H, 4.03. Found: C, 47.8; N, 37.8; H, 4.0.

Syntheses of the Platinum Complexes. ***trans*-Pt$(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2$ (2).** A suspension of 1.0 g (3.33 mmol) of *cis*-$Pt(NH_3)_2Cl_2$ in 20 mL water was treated with a slight excess of cyclohexylamine (677 mg, 6.83 mmol). The mixture was stirred and heated to 90 °C for 3 h and subsequently allowed to cool down to room temperature and filtered. The filtrate was treated with 4.2 mL of concentrated HCl and gently refluxed for 13 h. After the filtrate was cooled in an ice bath, a slightly yellow precipitate deposited, which was filtered off, washed with water, and dried in air. A second fraction was obtained by evaporating half of the filtrate. The product was recrystallized from boiling 0.01 M HCl. Yield: 0.823 g (65%). Crystals suitable for X-ray determination were obtained by crystallization from acetonitrile. Anal. Calcd for $PtC_6Cl_2H_{16}N_2$ ($M_w = 382.19$): C, 18.86; N, 7.33; H, 4.22. Found: C, 19.0; N, 7.3; H, 4.3. IR (KBr) (cm^{-1}): 3291, 3236 s ($(NH_3)_{a+s}$); 3201, 3129 s ($(NH_2)_{a+s}$). FIR(PE) (cm^{-1}): 537, 525 m (Pt−N); 332 vs (Pt−Cl). ^{195}Pt-NMR (DMF-d_7) δ (ppm): −2163. Figure 1 shows a schematic diagram of this reaction.

***cis*-Pt$(c\text{-}C_6H_{11}NH_2)_2I_2$.** K_2PtCl_4 (2.0 g, 4.82 mmol) was dissolved in 100 mL of water and treated with 8.0 g (47 mmol) of KI. The solution was stirred for 10 min at room temperature. Two equivalents of cyclohexylamine (0.958 g, 9.64 mmol) was added dropwise to the resulting K_2PtI_4 solution. The reaction mixture was stirred for 1 h. The yellow precipitate was filtered off and recrystallized from DMF/H_2O. After the precipitate was washed with water, methanol, and diethyl ether, the final product *cis*-$Pt(c\text{-}C_6H_{11}NH_2)_2I_2$ was dried in air. Yield: 2.8 g (90%). Anal. Calcd for $PtC_{12}H_{26}I_2N_2$ ($M_w = 647.24$): C, 22.27; N, 4.33; H, 4.05. Found: C, 22.2; N, 4.3; H, 4.1.

$[Pt(c\text{-}C_6H_{11}NH_2)I_2]_2$. A suspension of *cis*-$Pt(c\text{-}C_6H_{11}NH_2)_2I_2$ (2.8 g, 4.33 mmol) in 22 mL of water and 70 mL of ethanol was treated with 4.4 mL of $HClO_4$ (70%) over a period of 8 days. During reaction the yellow precipitate turned into a red brown precipitate. The suspension was filtered and the precipitate washed with water and dried in air. Yield: 2.21 g (93%). Anal. Calcd for $Pt_2C_{12}H_{26}I_4N_2$ ($M_w = 1096.13$): C, 13.15; N, 2.56; H, 2.39. Found: C, 13.9; N, 2.9; H, 2.4. ^{195}Pt-NMR (DMF-d_7) δ (ppm): −3998 and −4014.

***cis*-Pt$(NH_3)(c\text{-}C_6H_{11}NH_2)I_2$.** A suspension of $[Pt(c\text{-}C_6H_{11}NH_2)I_2]_2$ (2.0 g, 1.82 mmol) in 9 mL of water was mixed with 1.82 mL of 1.5 M NH_4OH (2.73 mmol). The reaction mixture was stirred for 1 day at room temperature. The yellow precipitate was filtered, washed with water, and dried in air. Yield: 1.81 g (88%). Anal. Calcd for $PtC_6H_{16}I_2N_2$ ($M_w = 565.10$): C, 12.75; N, 4.96; H, 2.85. Found: C, 13.9; N, 4.3; H, 2.9. ^{195}Pt-NMR (DMF-d_7) δ (ppm): −3307.

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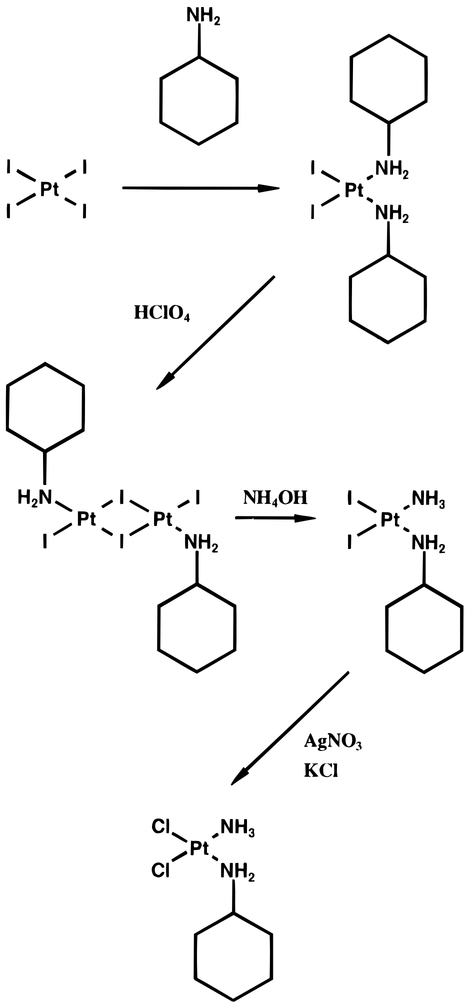

Figure 2. Synthesis of *cis*-[Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2] (**1**).

***cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 (1).** A suspension of *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)I_2 (1.1 g, 1.95 mmol) in 100 mL of water was treated with 1.85 equiv (0.612 g, 3.6 mmol) of $AgNO_3$ for 1 day in the dark. AgI was filtered off and 4 equiv (0.58 g, 54 mmol) of KCl was added to the filtrate. The reaction mixture was stirred for 1 h at 40 °C and allowed to stay 1 day at 4 °C. While the mixture was chilled, a yellow precipitate deposited which was filtered, washed with water, and dried in air. A second fraction was obtained by evaporating half of the solvent. The crude product was recrystallized from 80 °C hot 0.01 M HCl. Yield: 0.357 g (48%). Anal. Calcd for $PtC_6Cl_2H_{16}N_2$ (M_w = 382.19): C, 18.86; N, 7.33; H, 4.22. Found: C, 18.8; N, 7.0; H, 4.0. IR (KBr) (cm^{-1}): 3289, 3237 s ($(NH_3)_{a+s}$); 3201, 3129 s ($(NH_2)_{a+s}$). FIR(PE) (cm^{-1}): 537, 524 m (Pt−N); 327 vs (Pt−Cl). The infrared spectrum of this compound showed one large broad stretching (Pt−Cl) vibration at 327 cm^{-1}, while the trans isomer (**2**) showed one band at a slightly higher wavenumber, i.e. 332 cm^{-1}. Therefore, the configuration of the two isomers of Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 could not be determined using IR-spectroscopy as the only method, and to prove the identity of the compounds, X-ray determinations were carried out (vide infra). ^{195}Pt-NMR (DMF-d_7) δ (ppm): −2165. The reaction scheme for the synthesis of *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 via the iodo-bridged dimer is shown in Figure 2.

Ph_4P[Pt(NH_3)Cl_3]. *cis*-Pt$(NH_3)_2Cl_2$ (0.5 g, 1.67 mmol) and tetraethylammonium chloride (0.33 g, 2.0 mmol) were dissolved in 200 mL of dimethylacetamide and heated to 100 °C for 6 h. During this time, a slow stream of air was bubbled through the reaction mixture. The remaining red viscous solution (60 mL) was allowed to cool down to room temperature. A mixture of ethyl acetate/*n*-hexane (450 mL, 1:1 v/v) was added slowly. An orange precipitate deposited. The reaction mixture was allowed to stand overnight at −20 °C. A clear, colorless solution and a thick orange oil formed. The clear solution was discarded and the oil dissolved in 10 mL of water. The solution was filtered and tetraphenylphosphonium chloride (0.641 g, 1.7 mmol) in 10 mL of water was added. An orange precipitate formed and was filtered off, washed with water, and dried under vacuum. Yield: 0.53 g (48%). IR (KBr) (cm^{-1}): 325 s, b, 340 b (Pt−Cl).

K[Pt(NH_3)Cl_3]. Potassium hexafluorophosphate (142 mg, 0.77 mmol) was dissolved in 10 mL of water. This solution was added to a solution of 0.53 g (0.81 mmol) of Ph_4P[Pt(NH_3)Cl_3] in 20 mL of dichloromethane in a separatory funnel. The resulting mixture was shaken and the water layer lyophilized. Yield: 0.25 g (85%). IR (KBr) (cm^{-1}): 3280, 3220 s ($(NH_3)_{s+a}$); 1610 b, 1310 s ($(NH_3)_{def}$); 315 s, b (Pt−Cl).

An alternative synthesis for *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 was also investigated: 350 mg (0.98 mmol) of K[Pt(NH_3)Cl_3] was dissolved in 15 mL of water. A solution of 6.8 mg (4 mmol) KI in 5 mL of water was added. To this solution 1.2 equiv of cyclohexylamine (9.9 mg) was added dropwise and the solution was stirred for 1 h. During this time a brown precipitate formed which was filtered off, washed with water, and dried in air. Yield: 0.5 g (78%). The brown precipitate was dissolved in 50 mL of water and treated overnight with 1.85 equiv of $AgNO_3$ (0.325 g) in the dark. Then 4 equiv (2.17 mmol, 162 mg) KCl was added to the solution. The reaction mixture was stirred for 1 h at 40 °C and was chilled to 4 °C overnight. During this time a yellow precipitate deposited which was filtered off and recrystallized from 80 °C 0.01 M HCl. Yield: 0.24 g (80%).

The latter synthesis for *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 is very similar to the one published recently by Giandomenico *et al.*[15]

trans,trans,trans-Pt(NH_3)(c-$C_6H_{11}NH_2$)$Cl_2$$(OH)_2$ (JM-335) was obtained as a gift from Johnson Matthey. It was used without further purification.

***trans,cis,cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)$Cl_2$$(OOCCH_3)_2$.** A suspension of *trans,trans,trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)$Cl_2$$(OH)_2$ (200 mg, 0.48 mmol) in acetic anhydride was stirred for 8 days. The suspension was filtered off and washed several times with diethyl ether and dried in air. Yield: 0.16 g (67%). Anal. Calcd for $PtC_{10}Cl_2H_{22}N_2O_4$ (M_w = 500.28): C, 24.01; N, 5.60; H, 4.43. Found: C, 24.2; N, 5.6; H, 4.6.

***cis,cis,trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)$Cl_2$$(OH)_2$.** To a suspension of *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 (200 mg, 0.52 mmol) in 50 mL of water was added hydrogen peroxide (30 % w/v, 286 μL, 2.5 mmol). The reaction mixture was heated under reflux for 2 h and chilled on ice. A yellow precipitate formed which was filtered off, washed with water and small amounts of acetone, and dried in air. Yield: 113 mg (52%). Anal. Calcd for $PtC_6Cl_2H_{18}N_2O_2$ (M_w = 416.21): C, 17.32; N, 6.73; H, 4.36. Found: C, 16.9; N, 6.5; H, 4.5.

Reactions of Platinum Complexes with 9-Methylhypoxanthine and 5′-GMP. Recipes for most of the used reactions are given below.

A suspension of *trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 (**2**) in D_2O was reacted with 2.5 equiv of 9-methylhypoxanthine at pH* = 6, both at room temperature and in the temperature range between 37 and 45 °C. The same reaction was carried out using H8-deuterated 9-methylhypoxanthine to confirm assignments of the H8 and H2 signals. The reaction progress was followed by ^{1}H NMR spectroscopy.

The progress of reaction of *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 (**1**) with 2.5 equiv of 9-methylhypoxanthine at pH* = 6.4 was followed by ^{1}H NMR spectroscopy. The reaction was carried out in D_2O in the temperature range 37−45 °C. Due to the low solubility of **1**, the reaction was started with a suspension. At the end of the reaction, a homogeneous solution had formed.

The reaction of **1** and **2** with 5′-GMP in an 1:2.5 stoichiometric ratio was carried out in NMR tubes in D_2O containing 50 mM phospate buffer (pH* = 6.5). If necessary the pH was adjusted to a value of 6.5 with small amounts of 0.1 M NaOD or DCl solution. The reaction was started with a suspension of the poorly soluble chloride complex. At the end of the reaction period a homogeneous solution had formed. The temperature was kept between 37 and 45 °C. The total concentration of Pt(II) was 5 mM. ^{1}H-NMR spectra of the mixtures were recorded over a period of 9 days.

trans,cis,cis-Pt(NH_3)(c-$C_6H_{11}NH_2$)$Cl_2$$(OOCH_3)_2$ was suspended in a phosphate buffer solution in D_2O (pH* = 6.5, *c*(Pt(IV)) = 5 mM).

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Table 1. Crystallographic Data for **1** (cis) and **2** (*trans*)

	1	**2**
formula	$C_6H_{16}Cl_2N_2Pt$	$C_6H_{16}Cl_2N_2Pt.C_2H_3N$
space group	*Pbca* (No. 61)	$P2_1/c$ (No. 14)
cryst syst	orthorhombic	monoclinic
Z	8	4
a, Å	10.1994(12)	12.141(3)
b, Å	10.494(2)	6.0965(9)
c, Å	18.826(2)	19.864(3)
β, deg		118.71(2)
V, Å^3	2015.0(5)	1289.5(5)
MW	382.19	423.25
D_{calcd}, g cm^{-3}	2.520	2.180
μ_{calcd}, cm^{-1}	144.0	112.7
T, K	150	150
R1^a	0.0518	0.0711
wR2^b	0.1143	0.1773

^{a} $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. ^{b} $wR2 = [\sum[w(F_o{}^2 - F_c{}^2)^2]/\sum[w(F_o2)^2]]^{1/2}$.

Then 2.5 equiv of 9-methylhypoxanthine was added, and the reaction was followed in time by ^{1}H NMR spectroscopy for 14 days. The temperature was kept between 37 and 45 °C.

trans,cis,cis-Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$(OOCCH$_3$)$_2$ was suspended in D$_2$O containing 50 mM phosphate buffer and treated with 2.5 equiv of 5′-GMP (c(Pt(IV)) = 5 mM). The temperature was kept between 37 and 45 °C. During 14 days the course of reaction was followed by ^{1}H NMR spectroscopy.

Both *cis,cis,trans*-Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$(OH)$_2$ and *trans,trans,trans*-Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$(OH)$_2$ were suspended in separate phosphate buffer solutions (pH* = 6.5, c(Pt(IV)) = 5 mM) and treated with 2.5 equiv of 9-methylhypoxanthine or 5′-GMP. The temperature was kept between 37 and 45 °C, and the reaction was followed by ^{1}H NMR spectroscopy. Over 3 weeks, no substantial product formation was observed.

trans,trans,trans-Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$(OH)$_2$ was reacted with 5′-GMP in the presence of glutathione (abbreviated as GSH). Two different ^{1}H NMR experiments were carried out. In the first experiment (A) a suspension of the *trans*-Pt(IV) complex was prepared in phosphate-buffered D$_2$O (c(Pt(IV) = 5 mM, pH* = 6.5) and treated with a D$_2$O solution of 2 equiv of GSH and 5′-GMP. The temperature was kept between 37 and 45 °C, and ^{1}H-NMR spectra were recorded repeatedly over a period of 8 days. In the second experiment (B), a suspension of the *trans,trans,trans*-Pt(IV) complex was reacted for 2 days with 2 equiv of GSH in a phosphate buffered solution at 40 °C. After this period, 2 equiv of 5′-GMP was added and spectra were taken immediately after the addition of 5′-GMP and after 4 days at 40 °C.

A suspension of *trans*-Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$ (5 mM) in phosphate-buffered D$_2$O was treated with 2 equiv of GSH. After 45 h at 40 °C, 2 equiv of 5′-GMP was added to the solution, and the reaction mixture was stored at 40 °C for 4 days.

Crystal Structure Determinations of *cis*- (1) and *trans*-Pt(NH$_3$)-(c-C$_6$H$_{11}$NH$_2$)Cl$_2$ (2). The data on these two crystal-structure determinations are given in the order **1**, **2** unless specified explicitly.

Crystals suitable for X-ray determination, 0.03 × 0.15 × 0.55 mm and 0.15 × 0.50 × 0.50 mm, respectively, were mounted on a Lindemann-glass capillary and transferred into the cold nitrogen stream on an Enraf-Nonius CAD4-T diffractometer with a rotating anode (Mo Kα, 0.710 73 Å, graphite monochromator). Accurate lattice parameters were determined by least-squares treatment, using the setting angles (SET4) of 25 and 23 reflections in the ranges 11.4° < θ < 14.0° and 10.2° < θ < 14.0°.[16] Most reflection profiles are structured. The unit-cell parameters were checked for the presence of higher lattice symmetry.[17] Crystal data and details on data collection and refinement are presented in Table 1. Data were collected in $\omega/2\theta$ mode with scan angle $\Delta\omega = a + 0.35 \tan \theta°$, where $a = 0.86$ and 0.95, respectively. Intensity data of 2651 and 4292 reflections were collected in the range 1.9° < θ < 27.5°, of which 2308 and 2947 are independent. Data were corrected for *Lp* effects and for linear decay of 1 and 2% of the three periodically measured reference reflections $[\bar{2}\bar{1}\bar{4}, 1\bar{2}\bar{3}, 2\bar{3}\bar{2}]$ and $[2\bar{1}5, 322, 402]$, during 6.8 and 13.8 h of X-ray exposure time. An empirical absorption/extinction correction was applied (DIFABS[18] as implemented in PLATON,[19] transmission range 0.196−1.000 and 0.151−1.000). The structure for **2** was solved by automated Patterson methods and subsequent difference Fourier techniques (SHELXS86[20]). The structure for **1** was solved by automated Patterson methods and subsequent difference Fourier techniques (DIRDIF-92[21]). Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL-93[22]); no observance criterion was applied during refinement. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. The hydrogen atoms were refined with a fixed isotropic thermal parameter related to the value of the equivalent isotropic thermal parameter of their carrier atoms by a factor of 1.5 for the methyl/NH$_3$ hydrogen atoms and a factor 1.2 for the other hydrogen atoms. Weights were optimized in the final refinement cycles. For **1** convergence was reached at wR2 = 0.1143 for all 2308 unique reflections, R1 = 0.0518 for 1472 reflections with $F_o > 4\sigma(F_o)$, $w = 1/[\sigma^2(F_o{}^2) + 0.0545P^2]$, where $P = (F_o{}^2 + 2F_c{}^2)/3$, $S = 0.977$, for 101 parameters. For **2** convergence was reached at wR2 = 0.1773 for 2941 reflections, R1 = 0.0711 for 2654 reflections with $F_o > 4\sigma(F_o)$, $w = 1/[\sigma^2(F_o{}^2) + 0.0302P^2 + 113.34P]$, where $P = (F_o{}^2 + 2F_c{}^2)/3$, $S = 1.16$, for 129 parameters. Final difference Fourier maps showed no residual density outside −1.32 and +1.38 e Å^{-3} and −4.26 and +4.66 e Å^{-3} near the heavy atom, probably due to absorption artifacts or unresolved twinning. Positional parameters are listed in Tables 2 and 3. Neutral atom scattering factors and anomalous dispersion corrections were taken from ref 23.

Table 2. Final Atomic Coordinates and Equivalent Isotropic Thermal Parameters for **1** (*cis*) (Esds in Parentheses)

atom	*x*	*y*	*z*	U(eq)^a, Å^2
Pt(1)	0.37197(4)	0.61706(4)	0.02213(3)	0.0179(1)
Cl(1)	0.5450(3)	0.6407(3)	0.0994(2	0.0260(10)
Cl(2)	0.4236(3)	0.8032(3)	-0.0358(2)	0.0261(9)
N(1)	0.3290(9)	0.4457(9)	0.0707(6)	0.020(3)
N(2)	0.2201(10)	0.5961(9)	-0.0454(6)	0.020(3)
C(1)	0.2728(11)	0.4516(10)	0.1425(8)	0.018(4)
C(2)	0.2724(11)	0.3212(12)	0.1761(8)	0.023(4)
C(3)	0.2241(12)	0.3295(13)	0.2522(9)	0.032(5)
C(4)	0.0853(12)	0.3825(13)	0.2539(8)	0.028(4)
C(5)	0.0797(12)	0.5089(12)	0.2153(9)	0.029(4)
C(6)	0.1324(11)	0.5021(11)	0.1391(8)	0.023(4)

^{a} U(eq) = $^1/_3$ of the trace of the orthogonalized U.

Results and Discussion

Structure of *cis*-Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$ (1). Figure 3 shows a labeled diagram of the structure of **1**. Selected bond distances and angles are given in Table 4. A square-planar geometry is found for the platinum atom with angles close to the expected values of 90 and 180°. Compared with an ideal square-planar complex with angles of 90 and 180° of the ligands, the angles between the halide ligand and the ammine/substituted ammine are slightly smaller. The Pt−Cl bond distances [2.300(3) and 2.298(3) Å] are of the expected length. The Pt−N bond lengths [2.064(10) and 2.016(11) Å] are normal and agree well with the published values on other mixed amine/ammine

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Table 3. Final Atomic Coordinates and Equivalent Isotropic Thermal Parameters for **2** (*trans*) (Esds in Parentheses)

atom	*x*	*y*	*z*	*U*(eq)^a, Å^2
Pt(1)	0.24298(5)	0.46701(9)	0.48009(3)	0.0129(2)
Cl(1)	0.1044(3)	0.7298(6)	0.4740(2)	0.0182(12)
Cl(2)	0.3868(4)	0.2092(6)	0.4895(2)	0.0201(12)
N(1)	0.2997(12)	0.673(2)	0.4199(8)	0.017(4)
N(2)	0.1890(13)	0.263(2)	0.5413(7)	0.016(3)
C(1)	0.2124(15)	0.692(3)	0.3379(9)	0.019(4)
C(2)	0.2630(17)	0.856(3)	0.3012(10)	0.023(5)
C(3)	0.171(2)	0.882(3)	0.2154(11)	0.031(6)
C(4)	0.144(2)	0.662(4)	0.1740(11)	0.033(6)
C(5)	0.095(2)	0.501(3)	0.2116(10)	0.030(5)
C(6)	0.1869(16)	0.475(3)	0.2983(9)	0.021(4)
N(3)	0.4034(17)	0.235(3)	0.2079(9)	0.031(5)
C(7)	0.4653(17)	0.232(3)	0.2720(10)	0.024(5)
C(8)	0.544(2)	0.226(4)	0.3552(10)	0.034(6)

^{a} *U*(eq) = $^1/_3$ of the trace of the orthogonalized *U*.

Table 4. Selected Bond Distances (Å), Bond Angles (deg), and Torsion Angles (deg) of **1** (*cis*) and **2** (*trans*)

	1 (*cis*)	**2** (*trans*)
Bond Distances		
Pt−Cl(1)	2.300(3)	2.284(4)
Pt−Cl(2)	2.298(3)	2.289(5)
Pt−N(1)	2.064(10)	2.067(14)
Pt−N(2)	2.016(11)	2.054(14)
N(1)−C(1)	1.470(18)	1.46(2)
Bond Angles		
Cl(1)−Pt−Cl(2)	91.87(12)	178.18(15)
Cl(1)−Pt−N(1)	88.7(3)	89.1(4)
Cl(1)−Pt−N(2)	179.9(5)	91.1(4)
Cl(2)−Pt−N(1)	177.6(3)	90.7(4)
Cl(2)−Pt−N(2)	88.3(3)	89.1(4)
N(1)−Pt−N(2)	91.2(4)	179.2(5)
Pt−N(1)−C(1)	117.0(7)	115.4(11)
Torsion Angles		
Cl(1)−Pt−N(1)−C(1)	71.9(8)	−75.3(11)
N(2)−Pt−N(1)−C(1)	−108.0(8)	
Cl(2)−Pt−N(1)−C(1)		106.5(1)

platinum compounds.[24] The NH_2 moiety of the amine has an equatorial orientation toward the ring. The C−C bond distances of the organic ligand are normal. When this structure is compared with the recently published structure of cyclohexylammonium chloride, the C−N distance [1.470(18) Å] in the present Pt compound is slightly shorter than the value in cyclohexylammonium chloride [1.510(5) Å].[25] In an earlier publication this value was found to be [1.488(8) Å].[26] The closely related Pt(IV) compound JM216 has similar Pt−N distances [2.07 Å] and Pt−Cl distances [2.31 Å], but the N−Pt−N angle in JM216 is larger [94.3(4)°].[3]

Intermolecular hydrogen bonds from NH to Cl play a significant role in the packing of this compound, as follows:

N(1)--H(1A)···Cl(2) [$^1/_2 - x, {}^1/_2 + y, z$]: 3.591(10) Å; $\angle = 171.2(10)°$ (i)

N(2)--H(2A)···Cl(1) [$-^1/_2 + x, 1^1/_2 - y, -z$]: 3.443(10) Å; $\angle = 134(4)°$ (ii)

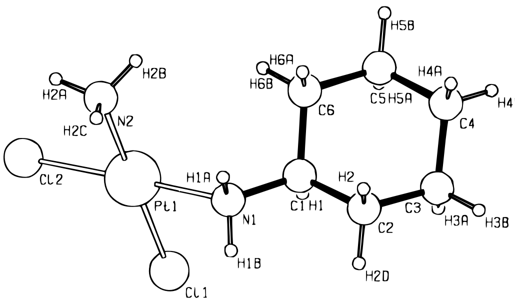

Figure 3. Structure of *cis*-[Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$] (**1**).

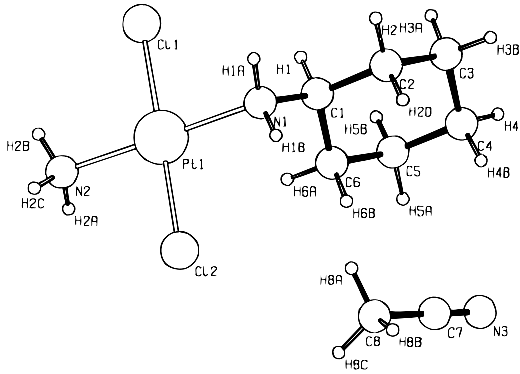

Figure 4. Structure of *trans*-[Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$]·CH$_3$CN (**2**) (JM-334).

N(2)--H(2B)···Cl(2) [$-^1/_2 + x, 1^1/_2 - y, -z$]: 3.549(11) Å; $\angle = 154(7)°$ (iii)

Structure of *trans*-Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$ (2). Figure 4 shows a labeled diagram of the structure of **2**. Selected bond distances and angles are given in Table 4. Like for **1** a square-planar geometry around the platinum atom is found with angles even closer to the expected values of 90° and 180°. Bond distances of Pt−Cl and Pt−N are all within the expected range. The Pt−N distance for the ammine ligand is slightly longer in the trans complex [2.054(14) compared with 2.016(11) Å in the cis compound]. In addition one molecule of acetonitrile is present in the lattice forming a hydrogen bond to an amine NH.

N(2)--H(2C)···N(3) [$^1/_2 - x, -y, {}^1/_2 + z$]: 3.07(2) Å; $\angle = 160(8)°$

Other hydrogen bonding interactions are listed as follows:

N(1)--H(1A)···Cl(2) [$x, y + 1, z$]: 3.509 (13) Å; $\angle = 166.2(17)°$ (ia)

N(1)--H(1B)···Cl(2) [$x + 1, 1^1/_2 - y, 1^1/_2 + z$]: 3.415 (17) Å; $\angle = 130.8(13)°$ (iia)

N(2)--H(2A)···Cl(1) [$x, y - 1, z$]: 3.477 (13) Å; $\angle = 164(5)°$ (iiia)

N(2)--H(2B)···Cl(1) [$x + 1, 1^1/_2 - y, 1^1/_2 + z$]: 3.427 (18) Å; $\angle = 140(6)°$ (iv)

These hydrogen bonding interactions are all intermolecular as expected. No intramolecular hydrogen bonds are observed in this case.

Reactions of *cis*- (1) and *trans*-[Pt(NH$_3$)(c-C$_6$H$_{11}$NH$_2$)Cl$_2$] (2) with 9-Methylhypoxanthine. During the reaction of **2** and 9-methylhypoxanthine the pH was found to remain constant.

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Table 5. Products of Reactions of *cis*- and *trans*-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$ with 9-Methylhypoxanthine and Chemical Shifts of Base Protons

compound	pH*	δ(H2), ppm	δ(H8), ppm
9-mehyp	6	8.05	8.19
trans-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(9\text{-mehyp-}N7)(H_2O)]^{2+}$	6	8.32	8.64
trans-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(9\text{-mehyp-}N7)_2]^{2+}$	6	8.35	8.86
trans-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(9\text{-mehyp-}N7)Cl]^{+}$	6	8.31	8.69
cis-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$with 9-mehyp, species **A**	5.8	8.29	8.53
cis-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$with 9-mehyp, species **B**	5.8	8.27	8.49
cis-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$with 9-mehyp, species **C**	5.8	8.26	8.39
cis-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$with 9-mehyp, species **D**	5.8	8.30	8.59

The subsequent formation of two products was observed. Initially, one molecule of 9-methylhypoxanthine coordinates via N7 which results in the major intermediate product $[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(9\text{-methylhypoxanthine-}N7)(H_2O)]^{2+}$. A second signal appears more downfield with respect to the 1:1 complex after 40 h. This signal has been assigned as the 1:2 complex $[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(9\text{-methylhypoxanthine-}N7)_2]^{2+}$. NMR data are listed in Table 5. When carried out between 37 and 45 °C, this reaction was found to be complete within 8 days, whereas at room temperature it was not found to be complete after 1 month. The main reason for this difference in reactivity is the low solubility of the starting material at room temperature. Signals at $\delta = 8.69$ (H8) and 8.31 (H2) ppm, only observed in the experiment at room temperature, were assigned to $[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(9\text{-methylhypoxanthine-}N7)Cl]^+$. These signals disappeared when small amounts of $AgNO_3$ were added to the solution. A ^{195}Pt NMR recorded at the end of the reaction showed only one signal at $\delta = -2449$ ppm, indicative of a PtN_4 coordination sphere.[27] This chemical shift is in excellent agreement with results obtained for a platinum coordinated to two ammine and two purine(N7) ligands.[28] Measurements of the pH dependence of H8 and H2 signals proves that platinum coordinates to 9-methylhypoxanthine at N7 in both the mono adduct and the bis adduct. The H8 signal of uncoordinated 9-methylhypoxanthine shows a large downfield shift upon lowering the pH* below 2. This is the result of protonation of N7. The shift of H2 is smaller. At pH* = 9.5 a small upfield shift occurs for both H8 and H2 because of deprotonation of N1. In the products there is no shift seen below pH* = 2. This indicates that platinum is coordinating at N7, preventing protonation at this site. Platinum coordination at N7 also results in the well-known lowering of the pK_a of the N1 deprotonation by approximately 1.5 pK units.[29]

The reaction of **1** with 9-methylhypoxanthine would be expected to yield a more complex spectrum of reaction products, due to its lower symmetry. Two different monosubstitution products are expected, depending on whether the incoming 9-methylhypoxanthine ligand will occupy the trans position with respect to either the ammine or the cyclohexylamine ligand. For the disubstituted product, two H2 and two H8 signals are expected, because of the nonequivalence of the 9-methylhypoxanthine ligand trans to the ammine and the cyclohexylamine ligand. Indeed, upon reaction with **1** eight new signals in the H2/H8 region emerged. The ^{1}H NMR results are listed in Table 5. The four products are denoted as **A**, **B**, **C**, and **D**. During these measurements no considerable pH drop was observed, and therefore the possibility of N1 coordination has been ruled out.

Table 6. Products of Reactions of *cis*- and *trans*-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$ with 5′-GMP, Chemical Shift of H8, and Coupling Constant of H1′ to H2′ (pH* = 6)

compound	δ(H8), ppm	^3J(H1′−H2′), Hz
5′-GMP	8.16	6.1
trans-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(GMP\text{-}N7)_2]^{2+}$	8.92	5.7
trans-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(GMP\text{-}N7)Cl]^{+}$	8.82	5.7
trans-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(GMP\text{-}N7)(H_2O)]^{2+}$	8.76	5.7
cis-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(GMP\text{-}N7)_2]^{2+}$	8.56, 8.53	2.6, 2.2
cis-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(GMP\text{-}N7)X]^{+}$	8.53, 8.52	4

The pH dependence of the H2 and H8 signals of the products shows the same behavior as is the case for the products of the trans isomer. Therefore, it was concluded that in the observed products N7 coordination occurs. The assignment of an evolving signal to a particular species formed during the course of reaction was not possible for the majority of signals. The assignment of the H2/H8 signals, however, was possible by carrying out deuteration experiments. Because of their similar behavior in pH-titration experiments, products **B** and **C** have tentatively been identified as the 1:2 complex, whereas product **A** is assigned to the 1:1 aqua adduct. The signals of this product increased first and then decreased during the reaction. Product **D** is always present in trace amounts during the reaction and, therefore, could well be the 1:1 chloro adduct. ^{1}H NMR spectra recorded at 288 K and 333 K indicate that rotation about the Pt−N7 bond is still possible.

Reactions of *cis*- (1) and *trans*-$[Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2]$ (2) with 5′-GMP. ^{1}H NMR was used to monitor the reactions of both **1** and **2** with 5′-GMP. New signals appearing in the H8 and H1′ region of the spectra after 2 h (the reaction was essentially complete after 8 days), besides those of the free nucleotide, indicate that Pt-GMP adducts are formed. Upon reaction with **2**, one signal occurs at 8.82 ppm after 2 h at 37 °C. Upon further reaction a second signal at 8.92 ppm appears. The intensity of that second signal rises during the course of the reaction and was found to be higher than the intensity of the first detected signal after 23 h, strongly suggesting that the first signal is the signal of a monosubstituted complex, whereas the second signal is the signal of a bis(nucleotide) complex formed when the reaction continues. The majority of the observed signals are summarized in Table 6. Tentative assignments are based on results obtained by Marcelis *et al.* with transplatin.[30] A ^{195}Pt NMR recorded at the end of the reaction showed one signal at $\delta = -2474$ ppm, indicating a PtN_4 coordination sphere around the Pt and in agreement with results obtained by Miller and Marzilli.[28] The H1′ doublet of the sugar residue in the 1:2 complex shows a vicinal coupling constant of 5.7 Hz, which is negligibly lower than that of free 5′-GMP (6 Hz). Compared with transplatin this value was found to be 0.7 Hz higher in the 1:2 complex *trans*-$Pt(NH_3)_2(5'\text{-GMP-}N7)_2$ at the same pH.

The reaction of **1** yields mainly two products. After 2 h one small doublet signal is detected in the aromatic region of the ^{1}H NMR. Upon further reaction two new signals form gradually, whereas the former doublet signal disappears. The two new signals maintain identical intensities during the reaction. The reaction of **1** with 5′-GMP was found complete

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Table 7. Products of Reactions of Pt(IV) Complexes with 9-Methylhypoxanthine and 5′-GMP, Chemical Shifts of H2 and H8, and Coupling Constant of H1′ to H2′ (pH* = 6.5)

compound	δ(H2), ppm	δ(H8), ppm	^3J(H1′−H2′), Hz
t,c,c-[$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OOCCH_3)_2$ with 9-mehyp, product A	8.37	8.87	
t,c,c-[$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OOCCH_3)_2$ with 9-mehyp, product B	8.35	8.86	
t,c,c-[$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OOCCH_3)_2$ with 5′-GMP, product **A**		8.89	5.9

after 8 days at 37 °C. Two signals are observed in the ^{1}H NMR spectrum of the final reaction mixture. It appears that these signals originate from the bis(nucleotide) complex *cis*-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)(5'\text{-GMP-N7})_2$ because of the nonequivalence of the H8 signals. Unfortunately, ^{195}Pt NMR measurements failed due to the poor solubility of the products. When the pH was lowered below 6, a white precipitate formed and the intensity of the signals of the bis(nucleotide) complex decreased. In fact, Chu and co-workers observed a similar effect when cisplatin was reacted with 5′-GMP.[31] Spectra recorded at 288 and 330 K showed no remarkable changes, and hence, no evidence for diastereoisomers was found. The results are included in Table 6. Platinum coordination to nucleotides is known to cause a change in the sugar-ring conformation from S-type (C2′-*endo*) to N-type (C3′-*endo*), which results in a change of the H1′−H2′ coupling constant.[32] The H1′ doublet of the sugar residue in the assumed 1:2 complex shows a vicinal coupling constant $^3J(H1'-H2') = 2.6$ and 2.2 Hz, whereas the corresponding value for free 5′-GMP was found to be 6.0 Hz. Compared to the corresponding trans isomer, the decrease observed for the cis isomer is more remarkable. In the 1:2 complex both H8 signals should have the same intensity. In the recorded spectra, this was not the case. This might be due to a possible overlap with signals from 1:1 complexes but can also be caused by a difference in H/D exchange rate.

The pH dependence of the chemical shift of the H8 protons in the reaction mixtures confirms that in the case of the cis, as well as the trans isomer, N7 coordination of 5′-GMP occurs. An increase in chemical shift for H8 around pH* 2, as observed for protonation of N7 in free 5′-GMP (pK_a of N7 = 2.5) is not found in the reaction products because N7 is platinated and no longer accessible to protonation.[33] Moreover, the H8 resonance is shifted to a lower field in the pH region around 6, because of 5′-phospate deprotonation (pK_a = 6.2) and shifted again to higher field around pH 9, where N1 is deprotonated (pK_a = 9.5).

Reaction of *trans,cis,cis*-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OOCH_3)_2$ with 9-Methylhypoxanthine and 5′-GMP. Upon reaction of *trans,cis,cis*-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OOCH_3)_2$ with 2.5 equiv of 9-methylhypoxanthine at 37 °C, pH = 6.5, substantial product formation was observed after 70 h. Two new signals are observed for the H8 protons at δ = 8.87 and 8.86 ppm. The intensity of the latter increases with the reaction time. The reaction was stopped after 14 days, because the gradual deuterium exchange on H8 reduced signal intensity.[34] Table 7 gives a listing of the ^{1}H NMR data.

Interestingly, ^{1}H NMR data of the starting material could not be obtained due to its poor solubility. Upon reaction with 9-methylhypoxanthine, two signals at δ = 2.10 and 2.02 ppm were detected which were assigned to the methyl group of the acetate ligand. Upon reaction, the latter signal increased in intensity, but no characteristic Pt(IV) satellites were observed. The H8 signals of the two products, A and B, exhibit no coupling with platinum either. This strongly suggests that reduction of platinum(IV) to platinum(II) has occurred.[35]

During the reaction of *trans,cis,cis*-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OOCCH_3)_2$ with 5′-GMP, a second signal in the H8 region of 5′-GMP was observed after 141 h, which was shifted downfield with respect to that of free 5′-GMP. The signal increased during the experiment and showed no Pt(IV) satellites, suggesting that reduction to platinum(II) has occurred here as well. Table 7 gives a listing of selected ^{1}H NMR shifts. Similar to the reaction with 9-methylhypoxanthine, two signals were observed for the acetate ligand at δ = 2.10 ppm, and 1.92 ppm indicating that two different kinds of acetate species are present in solution. The H1′ doublet of the sugar residue in platinated product A shows a vicinal coupling of 5.9 Hz, suggesting that the equilibrium between N- and S-type sugar-ring conformation remains almost unchanged upon platination.

So, the platinum(IV) complex *trans,cis,cis*-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OOCCH_3)_2$ reacts with 9-methylhypoxanthine and 5′-GMP to yield mainly one product. It appears that these products contain ligands coordinated to Pt(II) via the N7 positions. The absence of ^{1}H−^{195}Pt(IV) couplings suggests that a reduction of Pt(IV) to Pt(II) has occurred, although no unambiguous assignment of the product is possible.

cis,cis,trans-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OH)_2$ and its all trans analogue do not react under the conditions described above (pH* = 6.5, T = 37−45 °C, t = 14 days), neither with 9-methylhypoxanthine nor with 5′-GMP. Therefore, it was decided to perform this reaction in the presence of a cellular reducing agent.

Reactions of *trans,trans,trans*-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OH)_2$ with 5′-GMP in the Presence of GSH. The reaction of *trans,trans,trans*-$Pt(NH_3)(c\text{-}C_6H_{11}NH_2)Cl_2(OH)_2$ with 2 equiv of GSH and 2 equiv of 5′-GMP was carried out in two different ways. In the first experiment (A) the Pt(IV) solution was treated with a solution containing both the glutathione and the 5′-GMP. In the second experiment (B), the Pt(IV) solution was first treated with glutathione, and after 2 days, 2 equiv of 5′-GMP was added.

During both reactions the cystein-βCH_2 signals change from a multiplet at 2.96 ppm to two multiplets at 2.96 and 3.32 ppm. This is the result of the oxidation of GSH to GSSG by Pt(IV). However, in a solution of equimolar amounts of 5′-GMP and GSH oxidation of GSH was observed as well. Therefore, this experiment was repeated under argon atmosphere: no change in the NMR spectra was seen in a period of over one month. Experiment A was also repeated under argon atmosphere. The spectra were very similar to the ones obtained when dioxygen was not excluded. It is clear that the reduction of Pt(IV) by GSH is not influenced by the presence of dioxygen from the air.

In experiment A two new signals in the H8 region are observed at 8.90 and 8.87 ppm. These increase with respect to the H8 of unreacted 5′-GMP during the reaction. On raising the temperature the two H8 signals merge, indicating that the two peaks belong to rotamers from the same product and that rotation about the Pt−N7 bond is hindered at low temperature.

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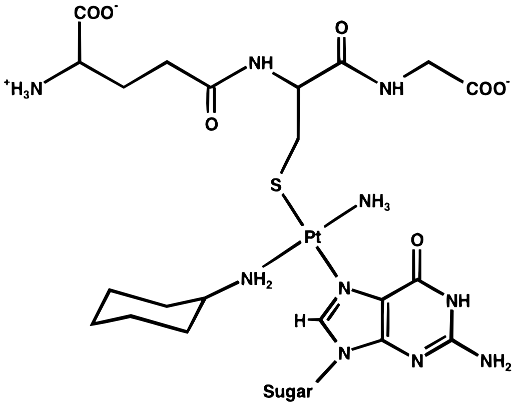

Figure 5. Likely product from the reaction of *trans*-[Pt(NH_3)(c-C_6H_{11}-NH_2)Cl_2] and 5′-GMP in the presence of GSH, experiment A.

In experiment B new signals in the H8 region are observed at 8.81 and 8.69 ppm. This reaction proceeds much slower than in experiment A.

For comparison, *trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 was treated in the same way as the Pt(IV) complex in experiment B described above. In this case, new signals in the H8 region appeared at 8.91 and 8.88 ppm, suggesting that in this experiment the same product is formed as in experiment A described above. The H8 signal of these reaction products, as well as that from experiment A, lies in the range expected for a disubstitution product of *trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 and 5′-GMP, as shown above. However, contrary to experiment A, no hindered rotation was observed, suggesting the formation of a Pt(II) complex with two GMP ligands. As an explanation for the observed NMR data in experiment A a Pt(II) complex with one GMP and one GS^- ligand, as is depicted in Figure 3, is a likely possibility.

Unfortunately the structure of the products in experiment B could not be elucidated from the NMR data. From the downfield shift of the H8 signals, however, it is very likely that GMP is platinated at the N7 position.

Comparing experiment A and B one can conclude that GSH reacts with Pt(IV) compounds in at least two steps. At least one reactive intermediate is present, which after reaction with 5′-GMP yields the complex depicted in Figure 5. When GSH is allowed to complete its reaction with Pt(IV) another, as yet unknown, species is formed, which behaves differently in the reaction with 5′-GMP (experiment B).

It is clear that glutathione facilitates the reaction of the Pt(IV) compound with GMP and that it does so by reducing the platinum center to Pt(II).

Concluding Remarks

The crystal structures of *cis*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 and *trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 show square planar geometry with normal Pt−N and Pt−Cl bond lengths. The reactions of these Pt compounds with 9-methylhypoxanthine and 5′-GMP yield N7 coordinated adducts. The final product is [Pt(NH_3)(c-$C_6H_{11}NH_2$)(nucleobase-*N7*)$_2$]$^{2+}$, as expected. We have also been able to show that the new Pt compounds *trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2 and the Pt(IV) analogues with additional acetate or hydroxy ligands yield quite similar 5′-GMP adducts. However, in the case of *trans,trans,trans*-Pt(NH_3)(c-$C_6H_{11}NH_2$)Cl_2-$(OH)_2$ a coreducing agent, like glutathione, is required. Further experiments are required to elucidate the pathways by which glutathione is facilitating the reaction of these types of Pt(IV) compounds.

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Supporting Information Available: Figures showing the pH dependence of the products of the reactions of **1** and **2** with 9-methylhypoxathine and tables of crystallographic data for the compounds **1** and **2** (9 pages). Ordering information is given on any current masthead page.

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