Simultaneous Binding of Pt(II) to Three Different Sites (N7, N1, N3) of a Guanine Nucleobase

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Abstract: Reaction of $[(NH_3)_3Pt(H_2O)]^{2+}$ with 9-ethylguanine, GH, gives three products: the mononuclear complex $[(NH_3)_3Pt(GH)]^{2+}$ (**1**), which contains G platinated at N7, the dinuclear complex $[(NH_3)_3Pt(G)Pt(NH_3)_3]^{3+}$ (**2**), which contains the deprotonated 9-ethylguanine ligand platinated at N7 and N1, and the trinuclear complex $\{[(NH_3)_3Pt]_3(G)\}^{5+}$ (**3**), which has a deprotonated guanine ligand platinated at N7, N1, and N3. Formation of **3** occurs on addition of $[(NH_3)_3Pt(H_2O)]^{2+}$ to an aqueous solution of **1** via the intermediate **2** even if no base is added. Its formation is rationalized in terms of an electron-releasing effect of the Pt atom substituting for the proton at N1, similar to the situation in complexes of 1-methyluracil and 1-methylthymine containing a Pt(II) coordinated to N3. The pH dependence of the ^1H NMR chemical shifts of all three complexes has been studied and the relevant acid/base equilibria established. **1** and **3** have been isolated in crystalline form, and the crystal structure of a derivative of **3**, containing half a molecule of $[Pt(NH_3)_4](NO_3)_2$ per trinuclear complex, is reported. $\{[(NH_3)_3Pt]_3(G)\}(NO_3)_5 \cdot 0.5[(NH_3)_4Pt](NO_3)_2 \cdot H_2O$ (**3a**) crystallizes in the space group $P\bar{1}$, with cell dimensions $a = 16.393$ (4) Å, $b = 13.889$ (6) Å, $c = 8.437$ (2) Å, $\alpha = 106.34$ (4)°, $\beta = 94.32$ (3)°, $\gamma = 92.05$ (3)°. The structure was refined to $R = 0.067$ and $R_w = 0.076$ on the basis of 5811 reflections. The geometries of the triammineplatinum(II) moieties and of the tetrammineplatinum(II) cation are normal. As a consequence of threefold Pt coordination, there are significant changes in ring angles of the purine ligand which are associated with the atoms N9, C4, and C5.

The chloro(diethylenetriamine)platinum(II) cation, [Pt-(dien)Cl]$^+$, is frequently used as a model of a heavy-metal electrophile reacting monofunctionally with DNA.[2] Though it binds covalently to DNA of *E. coli* as efficiently as the bifunctional antitumor agent *cis*-$(NH_3)_2PtCl_2$,[3] it induces neither the physicochemical changes (CD, UV, apparent shortening, etc.) nor most of the biological responses of the latter, such as antitumor activity, inhibition of DNA synthesis, induction of DNA repair activity, etc.[2,4] On the other hand, [Pt(dien)Cl]$^+$ shows some distinct biological effects as well: for example, it is weakly mutagenic,[5] it derepresses the viral genome in lysogenic bacteria,[6] and it facilitates the B → Z conformational transition in poly(dG-dC)·poly(dG-dC) through covalent binding to the polymer, presumably N(7) of the guanine residue.[7] Unlike *cis*-$(NH_3)_2PtCl_2$ but similar to *trans*-$(NH_3)_2PtCl_2$, [Pt(dien)Cl]$^+$ thermally stabilizes DNA, possibly through a similar mechanism as suggested for its interaction with hypoxanthine in poly(I), namely by hydrogen bonding of the NH$_2$ groups of the dien ligand to the nucleobases adjacent to the Pt binding site.[8]

The chlorotriammineplatinum(II) analogue, [Pt(NH$_3$)$_3$Cl]$^+$, has been applied less frequently in studies on the interaction of Pt electrophiles with nucleobases,[9] though its reactivity can be expected to be similar to that of the dien complex.

We have been interested in reactions of the aquatriammineplatinum(II) cation, [Pt(NH$_3$)$_3$H$_2$O]$^{2+}$, with the model nucleobase 9-ethylguanine, GH, in order to better understand the behavior of the mixed aqua, guanine complexes *cis*- and *trans*-

$[(NH_3)_2Pt(GH)(H_2O)]^{2+}$ which, in the absence of good donor ligands, lead to complicated products.[10] With N7 being the only crystallographically confirmed Pt binding site of guanine so far,[11,12] we were particularly interested in donor atoms other than N7 and conditions leading to their use (Figure 1). While this work was in progress, the preparation and separation of complexes of dienPt^{II} and *cis*-Pt^{II} with N7, N1, and N1,N7 metal binding to 9-methylhypoxanthine were described.[13] In earlier studies, formation of bridges involving N7,N1,[14] N7,O6,[14,15] and N1,O6[15] in Pt complexes of 6-oxopurines was proposed, and there has been considerable controversy concerning the possibility of a N7,O6 chelate with *cis*-$(NH_3)_2Pt(II)$.[16] The N3 position, however, appears to have been widely ignored as a potential metal binding site in 6-oxopurines, despite the fact that in 6-aminopurines (adenines) this site has been found to accommodate metal binding.[17]

We herewith report the first example of a guanine complex containing three metals, $(NH_3)_3Pt(II)$, simultaneously bound to this nucleobase, through N7, N1, and N3, and discuss conditions leading to its formation.

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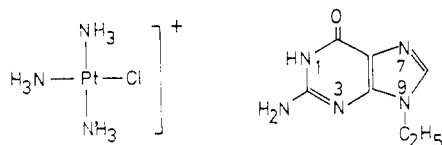
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Figure 1. Composition of the chlorotriammineplatinum(II) cation and of 9-ethylguanine.

Experimental Section

Starting Materials. $[(NH_3)_3PtCl]Cl^{18}$ and $[(NH_3)_3Pt(GH)]Cl_2 \cdot H_2O^{19}$ were prepared as previously described, and 9-ethylguanine, GH, was obtained from Sigma.

Preparation of Compounds. $[(NH_3)_3Pt(GH)](NO_3)_2 \cdot 2H_2O$ (1) was prepared by passing $[(NH_3)_3Pt(GH)]Cl_2 \cdot H_2O$ over an anion exchange column in the NO_3^- form, acidifying the filtrate (pH 6.8, brought to pH 3.6 with 0.4 N HNO_3), evaporating to dryness, and recrystallizing from water: yield 90%, colorless needles. Anal. Calcd for $C_7H_{22}N_{10}O_9Pt$: C, 14.36; H, 3.80; N, 23.93; Pt, 33.32. Found: C, 14.28; H, 3.70; N, 24.55, Pt, 33.6. The perchlorate of 1, $[(NH_3)_3Pt(GH)](ClO_4)_2$ (1a), was obtained by treating $[(NH_3)_3Pt(GH)]Cl_2 \cdot H_2O$ with 2 equiv of $AgClO_4 \cdot H_2O$ in water and crystallization from the acidified ($HClO_4$) solution—slightly yellowish crystals. Anal. Calcd for $C_7H_{18}N_8O_9Cl_2Pt$: C, 13.46; H, 2.96; N, 17.94. Found: C, 13.44; H, 3.10; N, 17.78. If the solution (pH 7) is not acidified, besides 1a a second species 1b (colorless needles) is isolated which analyzes as $[(NH_3)_3Pt(G)] \cdot [(NH_3)_3Pt(GH)](ClO_4)_3 \cdot 3H_2O$, and which probably crystallizes in a similar way as related complexes with three hydrogen bonds between the neutral and the deprotonated guanine ligand.[11f,g] Anal. Calcd for $C_{14}H_{41}N_{16}O_{17}Cl_3Pt$: C, 13.99; H, 3.44; N, 18.65; O, 22.62. Found: C, 14.22; H, 3.39; N, 18.04; O, 22.89. Formation of 1b is reasonable at neutral pH, taking into account that GH in 1 deprotonates with $pK_a \simeq 8.3$ (determined in 0.1 M $NaClO_4$, 20 °C, potentiometrically in the way described earlier[11g]).

$\{[(NH_3)_3Pt]_3(G)\}(NO_3)_5 \cdot 4H_2O$ (3) was prepared as follows: $[(NH_3)_3Pt(GH)]Cl_2 \cdot H_2O$ (1 mmol) and $[(NH_3)_3PtCl]Cl$ (3 mmol) were dissolved in 10 mL of water, 8 mmol of $AgNO_3$ were added, and the mixture was stirred in a stoppered flask (wrapped in Al foil) for 20 h at 50 °C. AgCl was then filtered off, and the clear yellow solution (pH 1.5) was brought to pH 6 by means of 1 N NaOH and then passed over a Sephadex G 10 column. Four products were eluted with water in the following sequence: $[(NH_3)_6Pt_2(G)](NO_3)_3$ (2), 3, 1, and $[(NH_3)_3Pt-(H_2O)](NO_3)_2$. 2 was not obtained analytically pure (contaminated with 3). Collected fractions of 3 were recrystallized from water: yield 450 mg, slightly yellow needles. The main batch of 3 analyzed as $\{[(NH_3)_3Pt]_3(G)\}(NO_3)_5 \cdot 4H_2O$. Anal. Calcd for $C_7H_{43}N_{19}O_{20}Pt_3$: C, 6.47; H, 3.34; N, 20.49; O, 24.64; Pt, 45.06. Found: C, 6.54; H, 3.48; N, 20.70; O, 24.86; Pt, 45.3. The crystals selected for the X-ray work crystallized prior to the main product and though the yellowish color appeared to be more intense than with 3, the IR did not reveal any difference with 3. The crystal structure determination proved that the crystals actually were $\{[(NH_3)_3Pt]_3(G)\}(NO_3)_5 \cdot 0.5[Pt(NH_3)_4](NO_3)_2 \cdot H_2O$ (3a). Anal. Calcd for $C_7H_{43}N_{22}O_{20}Pt_{3.5}$: C, 5.84; H, 3.02; Pt, 47.47. Found: C, 5.65; H, 3.16; Pt, 47.0. The presence of $[(NH_3)_4Pt]^{2+}$ in the preparation of 3 may be rationalized as follows: In the last step of the preparation of $[(NH_3)_3PtCl]Cl$, $[Pt(NH_3)_4]Cl_2$ is used to precipitate $[PtCl_4]^{2-}$ as Magnus Green salt. If a slight excess of $[Pt(NH_3)_4]Cl_2$ is used, it shows up in the end product of the $[(NH_3)_3PtCl]Cl$. The presence of $[Pt(NH_3)_4]^{2+}$ in 3a was qualitatively confirmed by reaction with K_2PtCl_4 which resulted in formation of Magnus Green salt.

Spectra. ^1H NMR spectra were recorded on a JEOL JNM-FX 60 Fourier transform spectrometer (30 °C, D_2O, $N(CH_3)_4BF_4$ as internal standard). Shifts are given in ppm relative to sodium 3-(trimethylsilyl)propanesulfonate (3.1869 ppm upfield from the internal standard). pD variations were made by use of solutions of NaOD and DNO_3. pD values were measured with a glass electrode and obtained by adding 0.4 unit to the meter reading. If pK_a values measured in D_2O are compared with pK_a values obtained in water, 0.4 unit is subtracted from pK_a-(D_2O).[20] $[(ND_3)_3Pt(D_2O)]^{2+}$ solutions were prepared by reaction of $[(NH_3)_3PtCl]Cl$ with 2 equiv of $AgNO_3$ in D_2O.

Crystallography. X-ray data were collected by using a Philips-PW 1100 diffractometer and graphite-monochromated Mo Kα radiation (λ = 0.71069 Å) at room temperature. The 0.7 × 0.5 × 0.4 mm crystal was sealed in a Lindemann glass capillary. Since this rather large crystal was the only good one and we were afraid to destroy it by cutting, it was used

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Table I. Positional Parameters and Temperature Factors ($Å^2$) for the Title Compound

atom	x	y	z	U
Pt1	0.5000 (0)	1.0000 (0)	0.5000 (0)	0.034 (1)
Pt2	0.8326 (1)	0.8577 (1)	-0.0590 (1)	0.032 (1)
Pt3	0.5245 (1)	0.6584 (1)	-0.0083 (1)	0.021 (1)
Pt4	0.7920 (1)	0.4669 (1)	0.3526 (1)	0.032 (1)
N10	0.6119 (8)	1.0696 (11)	0.4813 (16)	0.045 (12)
N11	0.5558 (9)	0.9241 (10)	0.6505 (18)	0.050 (13)
N20	0.8818 (8)	0.9746 (9)	-0.1314 (21)	0.051 (14)
N21	0.8712 (8)	0.7552 (11)	-0.2593 (18)	0.046 (13)
N22	0.7850 (12)	0.9584 (12)	0.1336 (23)	0.071 (18)
N30	0.5299 (7)	0.5310 (8)	-0.1967 (15)	0.029 (10)
N31	0.4006 (7)	0.6591 (10)	-0.0584 (15)	0.036 (11)
N32	0.5215 (7)	0.7846 (9)	0.1856 (16)	0.035 (11)
N40	0.8616 (10)	0.3809 (11)	0.1862 (21)	0.058 (16)
N41	0.7679 (9)	0.3459 (12)	0.4373 (19)	0.055 (15)
N42	0.7159 (8)	0.5534 (11)	0.5186 (16)	0.042 (12)
N1	0.6485 (6)	0.6643 (8)	0.0367 (14)	0.024 (9)
C2	0.6954 (7)	0.7255 (10)	-0.0270 (16)	0.022 (10)
N2'	0.6589 (8)	0.7683 (11)	-0.1374 (18)	0.065 (14)
N3	0.7772 (7)	0.7445 (9)	0.0130 (15)	0.034 (11)
C4	0.8129 (9)	0.6928 (10)	0.1149 (18)	0.033 (13)
C5	0.7653 (9)	0.6268 (10)	0.1727 (16)	0.027 (11)
C6	0.6801 (8)	0.6124 (9)	0.1444 (16)	0.023 (10)
O6'	0.6355 (5)	0.5608 (7)	0.1984 (13)	0.034 (9)
N7	0.8198 (7)	0.5857 (9)	0.2664 (15)	0.030 (10)
C8	0.8936 (9)	0.6255 (12)	0.2637 (20)	0.039 (14)
N9	0.8890 (7)	0.6934 (10)	0.1727 (17)	0.037 (11)
C9'	0.9683 (10)	0.7512 (16)	0.1515 (25)	0.055 (19)
C9''	0.9826 (16)	0.8348 (16)	0.2849 (27)	0.077 (26)
N50	0.7509 (14)	0.1618 (20)	-0.1746 (27)	0.091 (26)
O50	0.7038 (13)	0.2196 (14)	-0.2186 (25)	0.104 (24)
O51	0.7990 (15)	0.1824 (17)	-0.0379 (26)	0.139 (30)
O52	0.7511 (11)	0.0735 (13)	-0.2617 (22)	0.101 (20)
N60	0.9207 (10)	0.1701 (13)	0.2974 (23)	0.059 (17)
O60	0.9594 (10)	0.2552 (12)	0.3465 (25)	0.093 (20)
O61	0.8474 (10)	0.1631 (13)	0.3312 (32)	0.120 (27)
O62	0.9574 (10)	0.0969 (14)	0.2209 (25)	0.100 (22)
N70	0.5415 (8)	0.3330 (10)	0.4836 (17)	0.042 (13)
O70	0.5805 (7)	0.3983 (10)	0.4365 (15)	0.052 (12)
O71	0.4693 (7)	0.3223 (12)	0.4451 (20)	0.076 (16)
O72	0.5733 (9)	0.2872 (9)	0.5687 (16)	0.060 (14)
N80	0.7399 (8)	0.8384 (10)	0.4551 (16)	0.039 (12)
O80	0.7104 (9)	0.7899 (12)	0.5432 (19)	0.076 (17)
O81	0.6945 (8)	0.8710 (10)	0.3651 (17)	0.057 (13)
O82	0.8168 (8)	0.8533 (10)	0.4653 (17)	0.061 (14)
N90	0.6003 (11)	0.0863 (12)	0.0776 (22)	0.059 (17)
O90	0.5901 (17)	0.1595 (14)	0.1913 (25)	0.132 (33)
O91	0.5942 (16)	0.0916 (15)	-0.0611 (22)	0.116 (30)
O92	0.6043 (13)	0.0040 (12)	0.1029 (25)	0.103 (23)
N100	0.0985 (11)	0.4956 (14)	0.2037 (30)	0.084 (23)
O100	0.1567 (10)	0.4468 (12)	0.2052 (22)	0.085 (19)
O101	0.0336 (13)	0.4655 (23)	0.2259 (62)	0.285 (76)
O102	0.1094 (17)	0.5800 (19)	0.1985 (47)	0.204 (54)
O110	0.3029 (9)	0.5635 (11)	0.1901 (19)	0.069 (15)

in its original size. A least-squares calculation with the diffractometer settings for 34 reflections ($24° < 2\theta < 43°$) of the triclinic crystal gave the following cell parameters: a = 16.393 (4) Å, b = 13.889 (6) Å, c = 8.437 (2) Å, α = 106.34 (4)°, β = 94.32 (3)°, γ = 92.05 (3)°, U = 1834.8 $Å^3$. The space group, consistent with the solution and refinement of the structure, is $P\bar{1}$. For $C_7H_{43}N_{22}O_{20}Pt_{3.5}$ with M = 1483.3 g/mol and Z = 1, d_{calcd} = 2.603 g/cm³, d_{obsd} = 2.60 g/cm³.

A total of 6460 unique reflections were measured by using $\theta/2\theta$ scans (θ_{max} = 25°). For the subsequent calculations the set of 5811 reflections with $F_o \geq 2\sigma(F_o)$ was used. Lp and (in a later stage) empirical absorption corrections (μ = 129 cm^{-1})[21] were applied.

The positions of the Pt2, Pt3, and Pt4 atoms were determined from a Patterson map, and the coordinates of the other non-hydrogen atoms were determined in ΔF syntheses. Hydrogen atoms were ignored at all stages. All atoms were refined with anisotropic thermal parameters; R = 0.067, R_w = 0.076, w^{-1} = $\sigma^2(F) + 0.005F^2$. Final atomic coordinates and the U_{eq} values are given in Table I. Thermal anisotropic parameters are included in the supplementary material. The highest peak in the final difference map was 2.8 e $Å^{-3}$ (1.1 Å away from Pt2). Complex scattering

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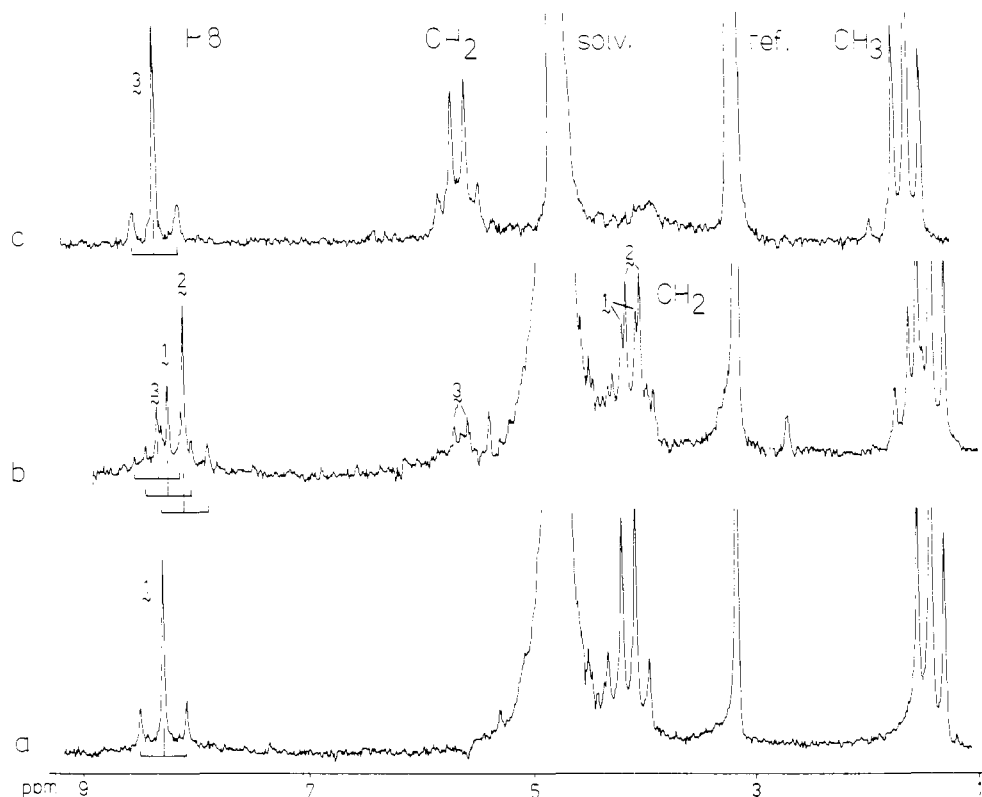
Figure 2. ^{1}H NMR spectra in D_2O: (a) $[(ND_3)_3Pt(GH)](NO_3)_2$ (**1**) (0.1 M, pD 6); (b) $[(ND_3)_3Pt(D_2O)](NO_3)_2$ and **1** (0.1 M each, pD 6.7) after 4 h at 50 °C (pD then readjusted from 1.6 to 7.2) and an additional 16 h at 50 °C (without addition of NaOD the yield of **2** is somewhat lower); (c) $[(ND_3)_9Pt_3(G)](NO_3)_5\cdot4H_2O$ (**3**) (0.1 M G, pD 6). The reference is NMe_4^+.

factors for the neutral atoms were taken from ref 22 and 23. For the calculations the SHELX program package was used.[24]

Results

Solution Studies. Reaction of GH with $[(ND_3)_3Pt(D_2O)]^{2+}$ ($r = 1$, pD 4.6) gives $[(ND_3)_3Pt(GH)]^{2+}$ (**1**) as the exclusive reaction product, containing the GH ligand bound to Pt through N7 as evident from ^{195}Pt coupling with H8 of G ($^3J = 24.4$ Hz). With an excess of $[(ND_3)_3Pt(D_2O)]^{2+}$ over GH, or with $[(ND_3)_3Pt(D_2O)]^{2+}$ added to dissolved $[(NH_3)_3Pt(GH)]^{2+}$ (**1**) ($c_{Pt}:c_{PtGH} = 1, 1.5, 2, 3$), three sets of ^{1}H NMR signals were observed, which were assigned to the mononuclear **1**, the dinuclear complex $[(ND_3)_3Pt(G)Pt(ND_3)_3]^{3+}$ (**2**), and the trinuclear complex $\{[(ND_3)_3Pt]_3(G)\}^{5+}$ (**3**). A typical sequence of spectra is shown in Figure 2, and the pD dependence of the three sets of resonances is shown in Figure 3. All three H8 resonances exhibit ^{195}Pt-^{1}H coupling (24.4 Hz (**1**), (**3**), 24.6 Hz (**2**)), indicating that all three species contain Pt bound through N7. As can be seen, **1** becomes deprotonated with a $pK_a \simeq 8.7$, which is consistent with the potentiometric pK_a determination of $[(NH_3)_3Pt(GH)]Cl_2$ in water (8.3, cf. Experimental Section). In strongly acidic medium, the GH ligand is protonated to give $[(ND_3)_3Pt(GH_2)]^{3+}$ ($0 \lesssim pK_a \lesssim 0.4$). Neither **2** nor **3** are deprotonated below pD 10, suggesting that the 9-ethylguanine ligand in these compounds is already deprotonated and that deprotonation of the NH_2 group at the 2-position has not started yet. **2** is protonated below pD 3 to give $[(ND_3)_3Pt(GH)Pt(ND_3)_3]^{4+}$ ($pK_a \simeq 1.9$). **3** does not exhibit any pH dependence in the range $0 < pD < 10$. As is to be seen from Figure 3, at pD $\simeq 0.4$ the H8 resonances of all three species are identical.

It was the enormous downfield shift of 1.5 ppm of the CH_2 group of the 9-ethylguanine ligand in **3** which indicated a Pt coordination site relatively close to the methylene group and
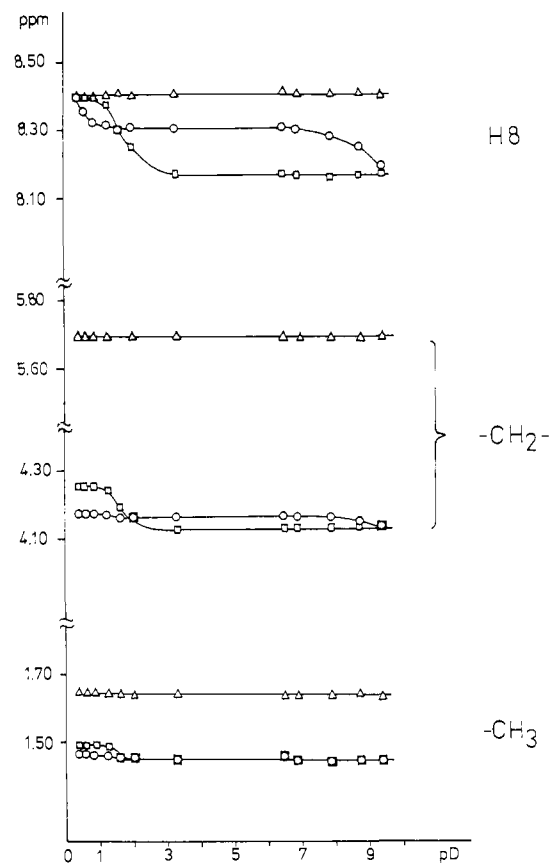
Figure 3. pD dependence of chemical shifts of individual resonances of the mononuclear complex **1**, the dinuclear complex **2**, and the trinuclear complex **3**.
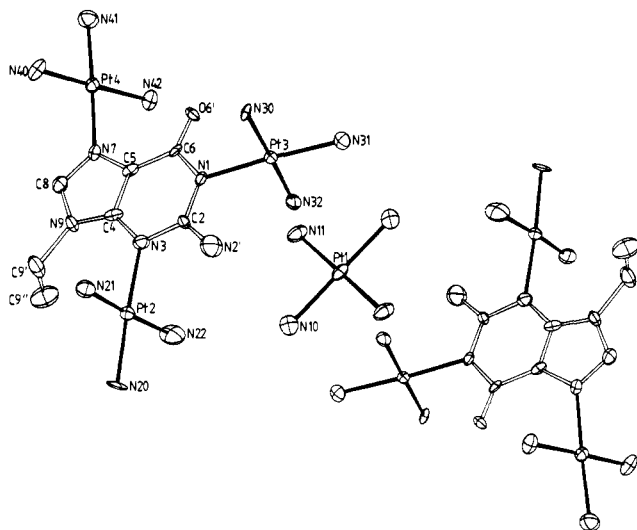
prompted the crystal structure determination of **3**.

Crystal Structure of 3a. A pair of centrosymmetrically arranged cations of $\{[(NH_3)_3Pt]_3(G)\}^{5+}$ is shown in Figure 4. In addition,

(22) Cromer, D. T.; Mann, J. B. *Acta Crystallogr., Sect. A* **1968**, *A24*, 321.

(23) Cromer, D. T.; Libermann, D. *J. Chem. Phys.* **1970**, *53*, 1891.

(24) Sheldrick, G. M.; SHELX program package, University of Göttingen, FRG.

Figure 4. View of **3a**, consisting of a pair of centrosymmetrically arranged $\{[(NH_3)_3Pt]_3(G)\}^{5+}$ cations and a $[Pt(NH_3)_4]^{2+}$ cation in the center of inversion between the two trinuclear species.

there is a $[Pt(NH_3)_4]^{2+}$ cation with Pt on the inversion center, and there are six nitrate anions and six molecules of water of crystallization per pair of **3** which are not shown. Table II lists interatomic distances and angles of the cations. Structural data of the nitrates, possible hydrogen bonding interactions, and dihedral angles are deposited as Supplementary Material. Pt coordination in **3a** is through N7, the deprotonated N1 position, and through N3 of the 9-ethylguanine. The geometries of the three triammineplatinum(II) residues and of the tetrammineplatinum-(II) cation are normal. Due to the relatively large errors, bond lengths of the deprotonated guanine in **3a** cannot be said to differ significantly from values reported for free GH[25] or guanosine,[26] for its hemiprotonated form $H(HG)_2^+$,[27] the fully protonated GH_2^+,[28] and N7 platinated GH,[11g,j] except the N9–C4 bond: it is somewhat shorter in **3a** than in the non-platinated GH structures mentioned above (1.30 (2) Å vs. 1.373 (3) to 1.382 (5) Å). Despite the large errors, there are several significant changes in bond angles as compared to neutral GH or its protonated forms, however. All these differences are associated with atoms N9, C4, and C5. For example, as the Pt coordinates to N3 it pushes away the ethyl group in the 9-position, increasing the C4–N9–C9′ angle ($\sim6°$) and simultaneously decreasing the adjacent C9′–N9–C8 angle ($\sim8°$). At C4, one of the internal ring angles (N3–C4–C5) and the external one (N3–C4–N9) become larger, by $\sim5°$ and $\sim8°$. The internal ring angles at C5 are affected differently, with C4–C5–C6 becoming larger ($\sim5°$) and C4–C5–N7 decreasing to the same extent. There is also an increase in the internal angle at N3 ($\sim4°$ in **3a**) which, though below significance, shows the expected trend for fixation of a substituent.[29] As compared to 9-ethylguanine complexes with N7 platinum binding only,[11g,j] at least the following angles are significantly different in **3a**: C8–N9–C9′ and N3–C4–C5 in **3a** are larger by $\sim8°$.

The G ring in **3a** is slightly nonplanar (cf. Supplementary Material). This refers in particular to the exocyclic groups C9′, O6′, and N2′. All three Pt atoms coordinated to the guanine ring are markedly out of the plane, Pt(4) at N7 most pronounced (−0.39 Å), followed by Pt(2) at N3 (0.29 Å) and Pt(3) at N1 (0.18 Å). While the Pt coordination planes of the $(NH_3)_3Pt$ moieties binding through N1 and N3 are roughly perpendicular to the guanine plane (96.6° and 80.8°), the dihedral angle between the plane of Pt(4), which coordinates through N7, and G is consid-

(25) Destro, R.; Kistenmacher, T. J.; Marsh, R. E. *Acta Crystallogr., Sect. B* **1974**, *B30*, 79.
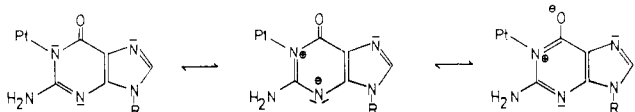
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(29) Singh, C. *Acta Crystallogr.* **1965**, *19*, 861.

Table II. Interatomic Distances (Å) and Angles (deg) of the Cations in $\{[(NH_3)_3Pt]_3(G)\}(NO_3)_5\cdot0.5[(NH_3)_4Pt](NO_3)_2\cdot1H_2O$ (**3a**)

(a) Pt Coordination Spheres			
Pt1–N10	2.08 (1)	N10–Pt1–N11	90.8 (6)
Pt1–N11	2.05 (1)	N20–Pt2–N21	91.5 (6)
Pt2–N20	2.05 (2)	N20–Pt2–N22	89.8 (7)
Pt2–N21	2.04 (1)	N20–Pt2–N3	176.7 (5)
Pt2–N22	2.05 (2)	N21–Pt2–N22	175.7 (6)
Pt2–N3	2.05 (1)	N21–Pt2–N3	90.3 (6)
Pt3–N30	2.03 (1)	N22–Pt2–N3	88.3 (6)
Pt3–N31	2.04 (1)	N30–Pt3–N31	91.4 (4)
Pt3–N32	2.04 (1)	N30–Pt3–N32	178.2 (5)
Pt3–N1	2.03 (1)	N30–Pt3–N1	89.6 (4)
Pt4–N40	2.02 (2)	N31–Pt3–N32	89.9 (5)
Pt4–N41	2.04 (2)	N31–Pt3–N1	176.8 (5)
Pt4–N42	2.09 (1)	N32–Pt3–N1	89.1 (4)
Pt4–N7	2.03 (1)	N40–Pt4–N41	88.9 (7)
		N40–Pt4–N42	177.7 (5)
		N40–Pt4–N7	89.5 (6)
		N41–Pt4–N42	90.7 (6)
		N41–Pt4–N7	178.1 (5)
		N42–Pt4–N7	90.9 (5)
(b) Guanine Ligand			
N1–C2	1.37 (2)	Pt3–N1–C6	117 (1)
C2–N2′	1.35 (2)	Pt3–N1–C2	119 (1)
C2–N3	1.36 (2)	C6–N1–C2	124 (1)
N3–C4	1.38 (2)	N2′–C2–N1	119 (1)
C4–C5	1.40 (2)	N2′–C2–N3	118 (1)
C5–C6	1.40 (2)	N1–C2–N3	123 (1)
C6–O6′	1.20 (2)	Pt2–N3–C2	118 (1)
C6–N1	1.39 (2)	Pt2–N3–C4	126 (2)
C5–N7	1.39 (2)	C2–N3–C4	116 (1)
N7–C8	1.32 (2)	N9–C4–N3	131 (2)
C8–N9	1.37 (2)	N9–C4–C5	109 (1)
N9–C9′	1.55 (2)	N3–C4–C5	120 (1)
C9′–C9″	1.37 (3)	N7–C5–C4	106 (1)
N9–C4	1.30 (2)	N7–C5–C6	130 (1)
		C4–C5–C6	125 (1)
		O6′–C6–C5	128 (1)
		O6′–C6–N1	121 (1)
		C5–C6–N1	112 (1)
		Pt4–N7–C5	125 (1)
		Pt4–N7–C8	127 (1)
		C5–N7–C8	108 (1)
		N7–C8–N9	110 (1)
		C9′–N9–C8	120 (1)
		C9′–N9–C4	132 (2)
		C8–N9–C4	108 (1)
		C9″–C9′–N9	108 (2)

erably smaller (64.8°) and close to the value found in [(dien)-Pt(guanosine)]$^{2+}$ with Pt binding to N7 as well.[11e] Although the intramolecular distance between $NH_3(42)$ and O6′ is reasonably short for an intramolecular H-bonding interaction (2.95 Å), the small angle around N42 (79°) makes such an interaction unlikely. Rather, the orientation of the Pt4 plane appears to be dictated by intermolecular hydrogen bonding between the ammonia groups N42, N41, and N40 with oxygens of the nitrate groups.

The existence of half a molecule of $[Pt(NH_3)_4]^{2+}$ per $Pt_3(G)$ in **3a** was unexpected and presented some problem in understanding its origin. As outlined in the Experimental Section, an impurity of $[Pt(NH_3)_4]Cl_2$ in $[Pt(NH_3)_3Cl]Cl$ can be rationalized on the basis of the preparation of $[Pt(NH_3)_3Cl]Cl$. Originally we also considered the possibility that *trans*-$[(NH_3)_2Pt(H_2O)_2]^{2+}$ might be present since we earlier had shown that $[Pt(NH_3)_3Cl]Cl$ can be converted into *trans*-$(NH_3)_2TpCl_2$ with loss of NH_3.[30] The presence of $[Pt(NH_3)_4]^{2+}$ in **3a** was eventually confirmed by reaction with K_2PtCl_4 which gave Magnus Green salt. Thus, although the bulk product consisted of $[(NH_3)_9Pt_3(G)]$-$(NO_3)_5\cdot4H_2O$ (**3**), the crystal selected for the structure determination was from a small impurity of the $[Pt(NH_3)_4]$ adduct **3a**.
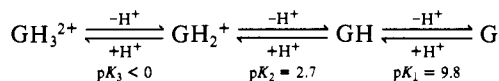
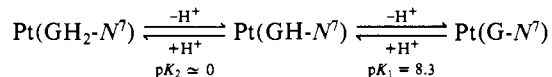(30) Lippert, B.; Lock, C. J. L.; Speranzini, R. A. *Inorg. Chem.* **1981**, *20*, 808.

Figure 5. Schematic description of the effect of Pt binding to the deprotonated N1 position of guanine. Additonal Pt binding through N7, as in **2**, is expected to reduce the electron density at O6 and/or N3. Nevertheless, binding of a third Pt is still possible as can be seen from the formation of **3**.

Discussion

Free 9-ethylguanine, GH, deprotonates (at N1) with a $pK_1 \simeq$ 9.8[31] and becomes protonated (at N7[28]) with a $pK_2 \simeq 2.7$.[31] Under strongly acidic conditions, e.g., in CF_3COOD,[32] G is doubly protonated with the second added proton probably at N3:[32]

$$GH_3^{2+} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} GH_2^+ \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} GH \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} G$$
$$pK_3 < 0 \qquad\quad pK_2 = 2.7 \qquad\quad pK_1 = 9.8$$

Pt binding to N7 as in **1** increases the acidity of the proton at N1 by ca. 1.5 log units, in agreement with findings in similar complexes.[11g,13] It is consistent with the electron-withdrawing effect of the Pt electrophile at N7 that the acidity of the protonated GH_2^+ ligand in the Pt complex ($pK_2 \simeq 0$) is higher as well (by 2.7 log units). The site of protonation which, in free G, is N7 must be different in **1**, and probably it is N3.[33]

$$Pt(GH_2\text{-}N^7) \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Pt(GH\text{-}N^7) \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Pt(G\text{-}N^7)$$
$$pK_2 \simeq 0 \qquad\qquad pK_1 = 8.3$$

With the diplatinated complexes $Pt_2(G -N^1,N^7)$ (**2**) protonation occurs relatively easily, with $pK_1 \simeq 1.5$.[34] This behavior may best be explained by an increase in basicity of the pyrimidine part of the purine ring as a consequence of the substitution of the proton at N1 by Pt(II) and the smaller polarizing effect of Pt relative to H.

$$Pt_2(GH\text{-}N^1,N^7) \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Pt_2(G -N^1,N^7)$$
$$pK_1 = 1.5$$
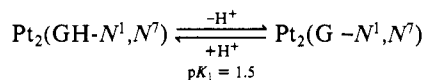
Compared to guanine blocked at N1 and N7 by a proton (GH_2^+), the guanine blocked by Pt at these sites (**2**) is more basic by several orders of magnitude. A rather similar situation is observed with N3 platinated uracil and thymine nucleobases: there, substitution of the proton at N3 by Pt(II) increases the affinity of O4 to accept a proton by 4–5 log units.[35] As a consequence of this increased

basicity, instead of a proton also a metal ion can be bound to this site, leading to a large class of dinuclear and higher nuclear complexes.[36]

The formation of the trinuclear complex **3** can be attributed to a similar effect of the Pt at N1 (Figure 5) and can be expected to be largest in the case of the N1 platinated complex (which has not been prepared in the present work). Despite the partial cancellation of this electron-releasing effect of Pt at N1 by the electron-withdrawing Pt at N7, the remaining basicity in the pyrimidine part of the purine is high enough to accommodate binding of the third Pt at N3. This interpretation is supported by the ^{1}H NMR spectra: **3** is always formed simultaneously with **2** rather than only after all free $[(ND_3)_3Pt(D_2O)]^{2+}$ is used up for formation of **2**, that is after addition of more than 1 equiv of $[(ND_3)_3Pt(D_2O)]^{2+}$ to **1**.

Formation of **2** bears another important aspect: though the pK_a for deprotonation of GH in **1** is 8.3, deprotonation of it is achieved simply by adding excess Pt to a solution of **1**, as is evident from the drop of pH during the formation of **2**.

Conclusion

A compound is described that contains three $(NH_3)_3Pt^{II}$ residues coordinated to 9-ethylguanine. It is the first crystallographically studied example of a complex of a 9-substituted guanine with metal binding sites other than N7. Formation of this compound occurs in steps, with the N7 platinated and the N7,N1 diplatinated complexes being the precursors. Binding of the third Pt to N3 is a consequence of the electron-releasing effect of the Pt substituting the proton at N1. The results suggest that the sequence of nucleophilicity of guanine steps toward Pt(II) is N7 > N1 > N3. There is no convincing argument why, for steric reasons, O6 should not be used in N7 platinated GH as a second, or in N7,N1 diplatinated G as third metal binding site, unless for electronic reasons, viz., that N3 is more basic than O6.

Supplementary Material Available: Tables of atomic and thermal parameters and observed and calculated structure factors and interatomic distances, angles, and deviations of atoms from planes (30 pages). Ordering information is given on any current masthead page.

(31) pK_a values reported for 9-methylguanine only: Frederick, W.; Bernhauer, K. *Z. Physiol. Chem.* **1959**, *317*, 116.
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(34) pK_a converted to water as solvent.
(35) (a) Lippert, B. *Inorg. Chim. Acta* **1981**, *55*, 5. (b) Lippert, B.; Thewalt, U.; Schöllhorn, H.; Goodgame, D. M. L.; Rollins, R. W. *Inorg. Chem.* **1984**, *23*, 2807.

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