Metal-Modified Base Pairs Involving Different Donor Sites of Purine Nucleobases: *trans*-[a$_2$Pt(7,9-DimeG-*N1*)(9-EtGH-*N7*)]$^{2+}$ and *trans*-[a$_2$Pt(7,9-DimeG-*N1*)(9-EtG-*N7*)]$^+$ (a = NH_3 or CH_3NH_2; 9-EtGH = 9-Ethylguanine; 7,9-DimeG = 7,9-Dimethylguanine). Possible Relevance to Metalated DNA Triplex Structures

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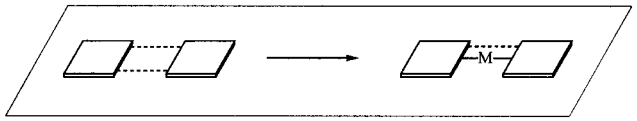
The X-ray crystal structures of four mixed-nucleobase complexes **1a**, **1b**, **2**, and **4** of *trans*-a$_2$Pt^{II} (a = NH_3 or CH_3NH_2) with N1-bonded 7,9-dimethylguanine (7,9-DimeG) and N7-bonded 9-ethylguanine (9-EtGH) are reported. The compounds are discussed in terms of their possible model character for platinated nucleobase triplets of the pu × pu·pym (pu = purine, pym = pyrimidine) type and are compared with known guanine·guanine pairs. Structural differences resulting from a "metal modification" have been studied, as have been stacking and H bonding motifs. **1a** and **1b** are two modifications of the same compound, *trans*-[$(NH_3)_2$Pt(7,9-DimeG)(9-EtGH)]$(ClO_4)_2$·H_2O. X-ray data for **1a**: orthorhombic, $Pca2_1$, a = 13.833(3) Å, b = 14.357(3) Å, c = 13.293(3) Å, Z = 4, R = 0.027. **1b**: monoclinic, $P2_1/n$, a = 13.987(3) Å, b = 12.582(3) Å, c = 15.613(3) Å, β = 104.61(3)°, Z = 4, R = 0.034. *trans*-[$(CH_3NH_2)_2$Pt(7,9-DimeG)(9-EtGH)]$(ClO_4)_2$ (**2**): orthorhombic, $Pca2_1$, a = 13.886(1) Å, b = 14.698(1) Å, c = 13.008(3) Å, Z = 4, R = 0.034. *trans*-[a$_2$Pt(7,9-DimeG)(9-EtG)](ClO_4)·$n H_2O$ (**3**, a = NH_3, n = 2; **4**, a = CH_3NH_2, n = 3). X-ray data for **4**: monoclinic, $C2/c$, a = 23.296(5) Å, b = 10.566(2) Å, c = 22.327(4) Å, β = 93.73(3)°, Z = 8, R = 0.047. The metalated base triplet **2**·(1-MeC) (1-MeC = 1-methylcytosine) has been detected in DMSO-d_6 solution through ^{1}H NMR spectroscopy, and an ab initio optimized structure of an analogous platinated base triplet has been obtained.

Introduction

The idea (Scheme 1) to partially or fully replace protons involved in H bonds between nucleobases by metal entities of suitable geometry, usually linear or trans-square-planar ("metal-modified base pairs"),[1,2] leads to compounds potentially relevant to biology (metal−DNA cross-linking adducts,[3] metal-stabilized mispairs[4]) and medicine (control of gene expression by antisense and antigene strategies[1,5]), as well as to compounds of interest for inorganic chemistry (metal−metal interactions[6]) and supramolecular chemistry (molecular squares[7] and hexagons[8]). The coordination chemistry and H-bonding features of these complexes are determined by (i) the essential coplanarity of the bases (with some rare exceptions[9]) due to a combination of interbase H bonding and the presence of auxiliary ligands (e.g., of trans-oriented am(m)ine groups at the metal), (ii) multifunctionality of the nucleobases, viz., the ability to bind more than a single metal ion, and (iii) the ability of the metalated bases for further association via H bond formation.

Scheme 1



Apart from metal complexes that can be considered analogues of hemiprotonated or fully protonated nucleobase pairs (e.g., of cytosine, guanine, 7-methylguanine, adenine)[10] and, hence, have two identical bases and identical metal binding sites, and complexes to be considered metalated analogues of pairs between complementary bases either in the Watson−Crick or

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Hoogsteen fashion,[1,10] there is also a class of compounds corresponding to metalated forms of mismatches[11] or unusual base pairs and triples.[12] As additional examples of this latter group we report here compounds containing two guanine model nucleobases, 9-ethylguanine (9-EtGH) and its deprotonated form (9-EtG), respectively, and 7,9-dimethylguanine (7,9-DimeG), which are bound via *different* donor sites, N7 and N1, to the metal entity *trans*-a_2Pt^{II} (a = NH_3 or CH_3NH_2). Except for a mixed 9-EtGH, *N6*′,*N6*′,*N9*-trimethyladenine complex of Pt^{II},[13] which displays metal binding to N7 of one base and N3 of the second one, the compounds here presented appear to be the first X-ray structurally characterized examples of this kind. The compounds bear some relevance to metalated analogues of base triplets of the G × G·C type (G = guanine, C = cytosine; first G representing base of third strand).[14]

Experimental Section

Preparation of Starting Compounds. *trans*-a_2PtCl_2 (a = NH_3,[15] CH_3NH_2[16]) was prepared as described. The model nucleobases 9-EtGH and 7,9-DimeG were purchased from Chemogen, Konstanz (Germany).

Preparation of *trans*-[a_2Pt(7,9-DimeG-*N1*)(9-EtGH-*N7*)](ClO$_4$)$_2$·*n*H$_2$O (1, 2). **1** (a = NH_3, n = 1) and **2** (a = CH_3NH_2, n = 0) were prepared as follows: *trans*-a_2PtCl_2 (330 mg, 1.1 mmol) was stirred together with 7,9-DimeG (180 mg, 1 mmol) and KCl (149 mg, 2 mmol) in 200 mL of water at 50 °C in the dark for 4 days. After removal of small amounts of metallic platinum, the slightly yellow solution was concentrated at room temperature under a steady flux of N_2 to 10 mL and then cooled at 4 °C overnight. Excess *trans*-a_2PtCl_2 was filtered off and the filtrate evaporated to dryness, giving a 4:1 mixture of *trans*-[a_2Pt(7,9-DimeG)Cl]Cl, *trans*-[a_2Pt(7,9-DimeG)$_2$]Cl$_2$, and KCl. Without further purification, this mixture was dissolved again in 35 mL of water. After the addition of 9-EtGH (1 mmol), the reaction was performed at 40 °C in the dark for 3 days. After removal of some elemental platinum, the filtrate was concentrated at room temperature under a steady flux of N_2 to 8 mL. Excess 9-EtGH was removed by filtration, and 600 μL of 10 M $NaClO_4$ in water was added. After 2 h at 4 °C, the microcrystalline substance was filtered off, washed with small amounts of water and cold ethanol, and dried.

Two recrystallization steps from water gave 0.21 mmol of pure *trans*-[$(NH_3)_2$Pt(7,9-DimeG)(9-EtGH)](ClO$_4$)$_2$·H$_2$O (**1a** and **1b**) in 21% yield. Anal. Calcd for $C_{14}H_{26}N_{12}O_{11}Cl_2Pt$: C, 20.90; H, 3.26; N 20.90. Found: C, 20.7; H, 3.2; N, 21.0.

Crystals suitable for X-ray crystallography were obtained upon recrystallization from water. Two different modifications were isolated: **1a** at room temperature and **1b** at 4 °C.

2 was obtained in an analogous way. Without further purification 0.798 mmol of **2** could be isolated in 79.8% yield. Anal. Calcd for $C_{16}H_{28}N_{12}O_{10}Cl_2Pt$: C, 23.59; H, 3.47; N, 20.64. Found: C, 23.5; H, 3.6; N, 20.6. Crystals suitable for X-ray crystallography were obtained by recrystallization from water.

1a, **1b.** ^{1}H NMR (200 MHz, D_2O): 8.700 (s, HC(8′)), 8.379 (s, HC(8)), 4.195 (q, $H_2C(91)$), 4.086 (s, $H_3C(7')$), 3.775 (s, $H_3C(9')$), 1.468 (t, $H_3C(92)$). ^{1}H NMR (200 MHz, DMSO-d_6): 11.289 (s, HN(1)), 8.940 (s, HC(8′)), 8.390 (s, HC(8)), 7.602 ($H_2N(2')$), 6.904 ($H_2N(2)$), 4.08 (s, $H_3N(10)$, $H_3N(10')$), 4.103 (q, $H_2C(91)$), 4.032 (s, $H_3C(7')$), 3.695 (s, $H_3C(9')$), 1.401 (t, $H_3C(92)$). ^{195}Pt NMR (42.998 MHz, DMSO-d_6): −2500. FT-IR (KBr): 3689, 3310, 3185, 3133, 3107, 2959, 1674, 1640, 1614, 1587, 1523, 1488, 1448, 1343, 1323, 1209, 1183, 1095, 780, 715, 688, 624, 429.

2. ^{1}H NMR (200 MHz, D_2O): 8.689 (s, HC(8′)), 8.483 (s, HC(8)), 4.235 (q, $H_2C(91)$), 4.104 (s, $H_3C(7')$), 3.789 (s, $H_3C(9')$), 2.109 (t, $H_3C(10)$, $H_3C(10')$), 1.492 (t, $H_3C(92)$). ^{1}H NMR (200 MHz, DMSO-d_6): 11.323 (s, HN(1)), 8.975 (s, HC(8′)), 8.488 (s, HC(8)), 7.981 ($H_2N(2')$), 6.978 ($H_2N(2)$), 4.689 (m, $H_2N(10)$, $H_2N(10')$), 4.127 (q, $H_2C(91)$), 4.046 (s, $H_3C(7')$), 3.702 (s, $H_3C(9')$), 1.957 (t, $H_3C(10)$, $H_3(C10')$), 1.415 (t, $H_3C(92)$). ^{195}Pt NMR (42.998 MHz, DMSO-d_6): −2570. FT-IR (KBr): 3423, 3298, 3253, 3176, 3127, 3090, 2949, 1682, 1641, 1614, 1584, 1521, 1487, 1341, 1208, 1182, 1097, 780, 715, 687, 623, 426.

Preparation of *trans*-[a_2Pt(7,9-DimeG-*N1*)(9-EtG-*N7*)](ClO$_4$)·*n*H$_2$O (3, 4). **3** (a = NH_3, n = 2) was prepared by dissolving **1a** or **1b** (40 mg, 50 μmol) in water (5 mL) by moderate heating. After addition of 50 μL of 1 M NaOH the solution was concentrated at room temperature under a steady flux of N_2 to give a white precipitate, which was filtered off, washed with small amounts of cold water and methanol, and dried. **3** could be isolated in 90% yield. Anal. Calcd for $C_{14}H_{27}N_{12}O_8ClPt$: C 23.29, H 3.77, N 23.28; Found: C 23.1, H 4.0, N 23.3.

3. ^{1}H NMR (200 MHz, D_2O): HC(8′) not detectable due to H/D exchange, 8.206 (s, HC(8)), 4.161 (q, $H_2C(91)$), 4.079 (s, $H_3C(7')$), 3.769 (s, $H_3C(9')$), 1.461 (t, $H_3C(92)$). ^{1}H NMR (200 MHz, DMSO-d_6): 8.939 (s, HC(8′)), 8.105 (s, HC(8)), 7.510 ($H_2N(2')$), 5.413 ($H_2N(2)$), 4.381 (s, $H_2N(10)$, $H_2N(10')$), 4.027 (s, $H_3C(7')$), 4.006 (q, $H_2C(91)$), 3.691 (s, $H_3C(9')$), 1.372 (t, $H_3C(92)$). ^{195}Pt NMR (42.998 MHz, DMSO-d_6): −2572. FT-IR (KBr): 3329, 1617, 1560, 1523, 1476, 1447, 1410, 1330, 1206, 1092, 798, 778, 625.

4 (a = CH_3NH_2, n = 3) was prepared as follows: **2** (151 mg, 185 μmol) was suspended in 5 mL of water at 60 °C. The solution became clear after the addition of 185 μL of 1 M NaOH and was cooled at 4 °C. Crystals suitable for X-ray crystallography could be obtained after 1 week. Elemental analysis of the bulk material revealed the presence of small impurities of $NaClO_4$.

4. ^{1}H NMR (200 MHz, D_2O): HC(8′) not detectable due to H/D exchange, 8.282 (s, HC(8)), 4.185 (q, $H_2C(91)$), 4.100 (s, $H_3C(7')$), 3.788 (s, $H_3C(9')$), 2.069 (s, $H_3C(10)$, $H_3C(10')$), 1.478 (t, $H_3C(92)$). ^{1}H NMR (200 MHz, DMSO-d_6): 8.978 (s, HC(8′)), 8.164 (s, HC(8)), 8.164 ($H_2N(2')$), 5.795 ($H_2N(2)$), 5.000 (m, $H_2N(10)$, $H_2N(10')$), 4.056 (q, $H_2C(91)$), 4.051 (s, $H_3C(7')$), 3.695 (s, $H_3C(9')$), 1.927 (t, $H_3C(10)$, $H_3(C10')$), 1.396 (t, $H_3C(92)$). ^{195}Pt NMR (42.998 MHz, DMSO-d_6): −2579. FT-IR (KBr): 3418, 3336, 3229, 3191, 3135, 2987, 2942, 1617, 1530, 1488, 1449, 1408, 1333, 1200, 1082, 798, 781, 625.

Instrumentation. ^{1}H NMR spectra were recorded at 20 °C on a Bruker AC 200 FT NMR spectrometer using DMSO-d_6 or D_2O as solvents. In D_2O, spectra were measured with presaturation of the solvent resonance. $Si(CH_3)_4$ (in DMSO-d_6) and $N(CH_3)_4^+$ (in D_2O, δ = 3.18 ppm against sodium 3-(trimethylsilyl)propane-1-sulfonate) were used as internal references. DMSO-d_6 was dried over 4 Å molecular sieves prior to use.

IR spectra were recorded on a Bruker IFS 28 FT-IR spectrometer (32 scans in the region between 250 and 4000 cm^{-1}, KBr) and evaluated with the program Opus, version 2.0 (Bruker).

X-ray Structure Determination of 1a, 1b, 2, and 4. Intensity data for **1a**, **1b**, and **4** were collected on an Enraf-Nonius KappaCCD[17] (Mo Kα, λ = 0.710 69 Å, graphite monochromator) with sample-to-detector distances of 26.8, 26.8, and 35.6 mm. They covered the whole sphere of reciprocal space by measurement of 360 frames rotating about ω in steps of 1° with 45, 30, and 60 s scan time per frame. Preliminary orientation matrices and unit cell parameters were obtained from the

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Table 1. Crystallographic Data for Compounds **1a, 1b**, **2**, and **4**

	1a	**1b**	**2**	**4**
empirical formula	$C_{14}H_{26}N_{12}O_{11}PtCl_2$	$C_{14}H_{26}N_{12}O_{11}PtCl_2$	$C_{16}H_{28}N_{12}O_{10}Cl_2Pt$	$C_{16}H_{33}N_{12}O_9PtCl$
fw (g mol^{-1})	804.46	804.46	814.47	768.08
cryst size (mm)	0.50 × 0.15 × 0.15	0.53 × 0.50 × 0.50	0.28 × 0.08 × 0.10	0.13 × 0.13 × 0.03
temp (K)	293	293	103	293
cryst syst	orthorhombic	monoclinic	orthorhombic	monoclinic
space group	*Pca*2$_1$	*P*2$_1$/*n*	*Pca*2$_1$	*C*2/*c*
a (Å)	13.833(3)	13.987(3)	13.886(1)	23.296(5)
b (Å)	14.357(3)	12.582(3)	14.698(1)	10.566(2)
c (Å)	13.293(3)	15.613(3)	13.008(3)	22.327(4)
β (deg)		104.61(3)		93.73(3)
V (Å^3)	2640.0(10)	2658.8(10)	2654.9(5)	5484.0(19)
Z	4	4	4	8
D_{calc} (g cm^{-3})	2.024	2.010	2.038	1.861
μ (Mo Kα) (mm^{-1})	5.595	5.555	5.541	5.282
F(000)	1576	1576	1600	3040
2θ range (deg)	9.3−51.3	9.3−51.4	8.0−50.0	3.5−43.1
reflns collected	71 222	76 650	19 262	35 116
reflns obs	1964 ($I \geq 2\sigma(I)$)	3786 ($I \geq 2\sigma(I)$)	1355 ($I \geq 3\sigma(I)$)	1499 ($I \geq 2\sigma(I)$)
params refined	278	351	231	215
R_{int}	0.061	0.034	0.065	0.091
*R*1 (obs data)[a]	0.027	0.034	0.034	0.047
*wR*2 (obs data)[b]	0.061	0.084	0.044	0.056
goodness-of-fit, *S*	1.04	1.05	1.53	1.03
residual ρ_{max}, ρ_{min} (e Å^{-3})	0.61, −0.67	0.897, −1.264	0.97, −0.59	0.969, −0.767

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] For **1a**, **1b**, **4**: $wR2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$. For **2**: $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

peaks of the first 10 frames, respectively, and refined using the whole data set. Frames were integrated and corrected for Lorentz and polarization effects using DENZO.[18] The scaling as well as the global refinement of crystal parameters was performed by SCALEPACK.[18] Reflections, which were partly measured on previous and following frames, are used to scale the frames on each other. This procedure in part eliminates absorption effects and also considers a crystal decay if present.

The structures were solved by standard Patterson methods[19] and refined with full-matrix least-squares based on F^2 using the SHELXTL-PLUS[20] and SHELXL-93 programs.[21] The scattering factors for the atoms were those given in the SHELXTL-PLUS program. Transmission factors were calculated with SHELXL-97.[22] Most hydrogen atoms were placed at calculated positions and refined with a common isotropic temperature factor. No refinement of hydrogen parameters was applied for the ammine hydrogens and the hydrogens of the water molecule in **1a**, H1 and the methyl hydrogens of 7,9-DimeG in **1b**, and H8 and H8′ in **4**. Only two oxygen atoms of the perchlorate anion and the water molecule in **1b** show disorder.

The X-ray measurements for **2** were carried out on a Quantum CCD detector (Molecular Structure Corp.) at −170 °C using Mo Kα radiation (λ = 0.710 69 Å). Calculations were performed by using the teXsan 1.7 crystallographic software package.[23] Three standard reflections were monitored during the data collection showing no significant variance. The intensities were corrected for absorption by applying Ψ scans of several reflections with the transmission factors ranging from 0.81 to 1.00. The structure was solved by direct methods (SIR 92).[24] Full-matrix least-squares refinement with anisotropic thermal displacement parameters for the Pt, Cl, and O atoms yielded an *R* factor of 0.034 (R_w = 0.044). The final difference Fourier map showed a peak of 0.97 e Å^{-3} located near the Pt atom.

Crystal data and data collection parameters of **1a**, **1b**, **2**, and **4** are summarized in Table 1.

Solution Studies. Acidity constants in D_2O (pK_{a/D_2O}) of **1** and **2** were obtained by evaluating the change of the chemical shift of HC(8) and $H_2C(91)$ of the 9-EtGH residue in dependence on the adjusted pD values (DNO_3/NaOD). All experiments were performed at 5 mM concentration of complex **1** or **2**, respectively (20 °C, I = 0.1 M ($NaNO_3$)). The changes in the chemical shifts were evaluated by a Newton−Gauss nonlinear least-squares curve-fitting procedure. The relationship between the observed chemical shift and the varying pD values is described by eq 1, which has been derived in analogy to reference.[25] In eq 1 δ_{GH} and δ_G represent the chemical shifts of the

$$\delta_{obs} = \frac{\delta_G + \delta_{GH} \times 10^{pK_{a/D_2O} - pD}}{1 + 10^{pK_{a/D_2O} - pD}} \quad (1)$$

9-ethylguanine ligand, which can be protonated (GH) or deprotonated (G) at N1. p$K_{a/D2O}$ corresponds to the negative logarithm of the acidity constant. This acidity constant, which describes the situation in D_2O can be transformed to aqueous solution (H_2O) by application of eq 2.[26] The dilution experiment has been performed by adding successively

$$pK_{D_2O} = (1.015\ pK_{H_2O}) + 0.45 \quad (2)$$

more solvent to an equimolar mixture of **2** and 1-MeC in DMSO-d_6. The concentration range was from 77.72 to 4.97 mM.

Computations. Geometry optimization was performed using the Gaussian94 program.[27] All calculations were carried out at the Hartree−Fock SCF level of theory employing the LANL2DZ basis set. This

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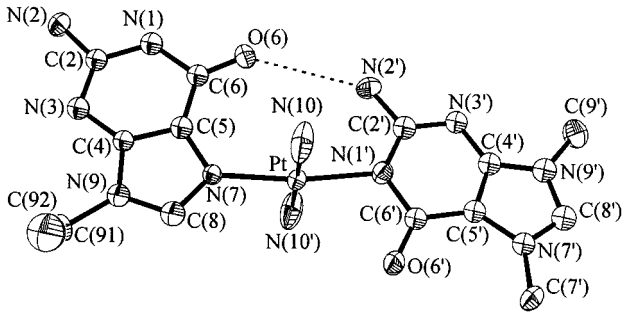
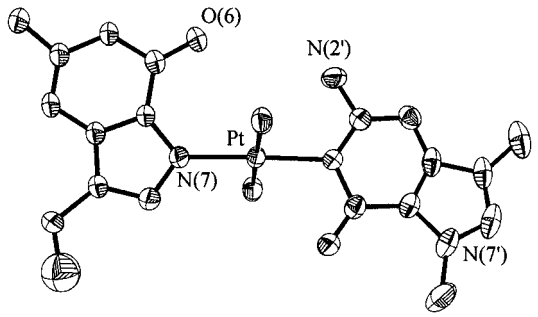
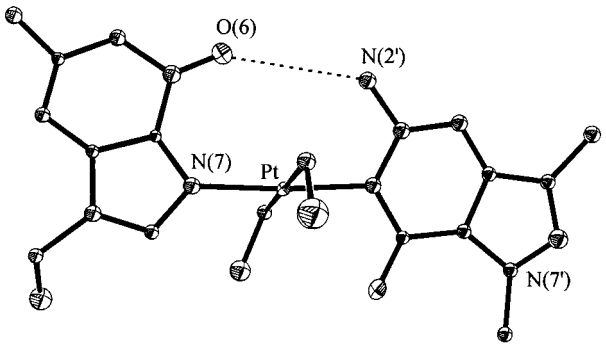


1a



1b



2

Figure 1. Cations of *trans*-[a_2Pt(7,9-DimeG)(9-EtGH)]$(ClO_4)_2 \cdot n H_2O$ (**1a**, **1b**, and **2**) are shown with the atom-numbering schemes. The anions and the water molecule are omitted for clarity. The ellipsoids are drawn at 50% probability.

basis uses the Dunning−Huzinaga double-ζ descriptor[28] for all first-row elements and replaces the core electrons of platinum with the effective core potentials of Hay and Wadt.[29]

Results and Discussion

X-ray Crystal Structure of 1a, 1b, and 2. Metal binding patterns and relative orientations of the guanine nucleobases in compounds **1a**, **1b**, and **2** are identical. The *trans*-a_2Pt^{II} entity (a = NH_3 in **1a** and **1b**; a = CH_3NH_2 in **2**) in each complex is coordinated to N7 of the 9-EtGH ligand and to N1′ of 7,9-DimeG, with the two bases orientated in such a way that O6 of the 9-EtGH and N2′ of 7,9-DimeG are facing each other (Figure 1). There are, however, quite substantial differences in detail (Table 2). These refer essentially to angles, viz., the N7−Pt−N1′ angle, external ring angles of 9-EtGH at the N7 binding site, and angles between 9-EtGH and the Pt coordination planes. The only significant difference in distances is that of the interbase separation O6···N2′. The shortest distance between these sites, 3.11(1) Å in **1a**, correlates with the largest deviation from collinearity of Pt−N7 and Pt−N1′ vectors (171.5(3)°). In fact, this angle is the smallest one in any of the bis(nucleobase) complexes of *trans*-a_2Pt^{II} reported so far.[30] It is certainly consistent with formation of a weak intracomplex hydrogen bond between these two sites. The same applies to **2**, although the H bond is still weaker (3.27(2) Å). It is surprising that this H bond is absent in **1b** (3.88(1) Å). Actually **1b** is the first complex of *trans*-a_2Pt^{II} with the bases in Hoogsteen orientation that is devoid of this H bond.[1,12,31] Although the N7−Pt−N1′ angle in **1b** is closest to 180° (177.3(2)°) and the propeller twist of the two bases is largest in this compound (17.1(2)°), additional features responsible for this long separation are the external angles at N7:[13b] These angles differ in **1a** and **1b** by 4−5° in such a way that Pt−N7−C5 in **1b** is largest (129.1(4)°). This high flexibility at N7 is in contrast to the much smaller variation in external ring angles at N1′ of 7,9-DimeG.[10]

Table 2. Selected Distances (Å) and Angles (deg) in **1a, 1b**, **2**, and **4**

	1a	1b	2	4
Pt−N7	1.985(7)	2.013(4)	2.02(1)	2.028(10)
Pt−N1′	2.043(7)	2.024(4)	2.02(1)	2.009(10)
Pt−N10	2.043(9)	2.044(5)	2.06(1)	1.992(10)
Pt−N10	1.995(10)	2.029(4)	2.06(1)	2.037(10)
N7−Pt−N1′	171.5(3)	177.3(2)	176.1(4)	178.8(4)
C8-N7−Pt	129.8(6)	125.4(4)	129.6(9)	121.7(9)
C5-N7−Pt	124.9(5)	129.1(4)	125.4(8)	131.8(9)
C6′−N1′−Pt	115.8(5)	114.6(4)	117.8(9)	118.1(8)
C2′−N1′−Pt	121.4(6)	123.1(4)	120.1(9)	122.3(9)
9-EtGH/Pt	85.8(3)	65.9(1)	86.4(3)	88.9(2)
7,9-DimeG/Pt	85.3(3)	82.1(1)	71.8(3)	88.8(2)
9-EtGH/7,9-DimeG	10.1(3)	17.1(2)	14.6(3)	2.4(5)
O6···N2′	3.11(1)	3.88(1)	3.27(2)	
O6···O6′				3.94(1)
dev Pt from 9-EtGH	+0.10(1)	+0.06(1)	−0.14(1)	+0.07(1)
dev Pt from 7,9-DimeG	+0.16(1)	+0.05(1)	+0.21(1)	−0.06(1)

Deviations of Pt from the nucleobase planes (Table 2) are generally moderate (0.05−0.16 Å), but in the case of **2**, Pt is significantly out of the plane of the 7,9-DimeG plane by 0.21 Å.

In Figure 2 the H bonding patterns of the two modifications **1a** and **1b** are compared. As can be seen, in addition to intramolecular H bonding in **1a**, there is also interbase H bonding, namely, a bifurcated hydrogen bond between O6′ of 7,9-DimeG and $N2H_2$ (2.81(1) Å) as well as N1H (3.13(1) Å) of 9-EtGH (symmetry operation $^3/_2 - x, y, ^1/_2 + z$). The water molecule and the ClO_4^- anions are situated between layers of cations and make hydrogen bonds to the amine groups at the platinum atom (all H bonds between 3.01(2) and 3.27(1) Å). In **1b**, the only H bond between two cations can be found from N10′ to O6 of a nearby complex (3.01(1) Å). N10′ and the other hydrogen donor and acceptor sites are all occupied by water and perchlorate anions. O12 of a ClO_4^- makes a corresponding bifurcated H bond (like O6′ of 7,9-DimeG in **1a**) to N1H (2.92(1) Å) and $N2H_2$ (3.10(1) Å) of 9-EtGH.

The bifurcated intermolecular H bond in **1a** between O6′ of 7,9-DimeG and NH_2 (2.79(1) Å) and N1H (3.03(1) Å) of 9-EtGH is also seen in compound **2**. There are numerous H bonds or short contacts between oxygen atoms of the ClO_4^- anions and H donors of the cation, including such with aromatic protons, but none of these are unusual (≥2.93(2) Å).

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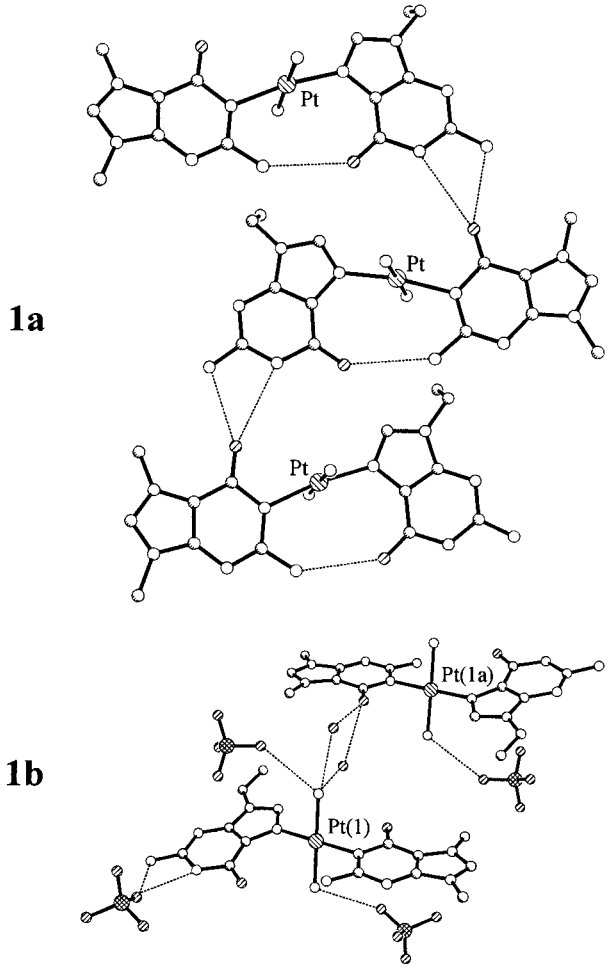

Figure 2. Sections of solid state structures of the two modifications **1a** and **1b** demonstrating different H-bonding interactions.

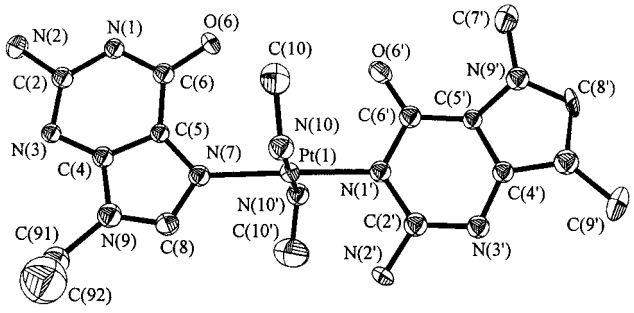

Figure 3. Cation of *trans*-$[(CH_3NH_2)_2Pt(7,9\text{-DimeG})(9\text{-EtG})](ClO_4)\cdot 3H_2O$ (**4**) with the atom-numbering scheme. The anions and the water molecules are omitted for clarity. The ellipsoids are drawn at 50% probability.

X-ray Crystal Structure of 4. Deprotonation of the 9-ethylguanine ligand in **1** or **2** leads to the corresponding 9-ethylguaninato complexes **3** and **4**. Figure 3 gives a view of the cation of *trans*-$[(CH_3NH_2)_2Pt(7,9\text{-DimeG})(9\text{-EtG})]ClO_4\cdot 3H_2O$ (**4**). Unlike in **1a**, **1b**, and **2** the two purine bases are now in an orientation in which the exocyclic O6 oxygens of both bases are facing each other. The O6···O6′ distance is 3.94(1) Å and both bases are nearly coplanar (dihedral angle 2.4(5)°). The two outside angles at the N7 position of 9-EtGH (Table 2) differ by 10.1° (7.8 σ) in such a way as to maximize the O6···O6′ distance. The N7−Pt−N1′ angle is close to 180° (178.8(4)°).

The packing pattern of **4** displays two motifs (Figures 4 and 5): First, pairs of cations are formed in which two cations,

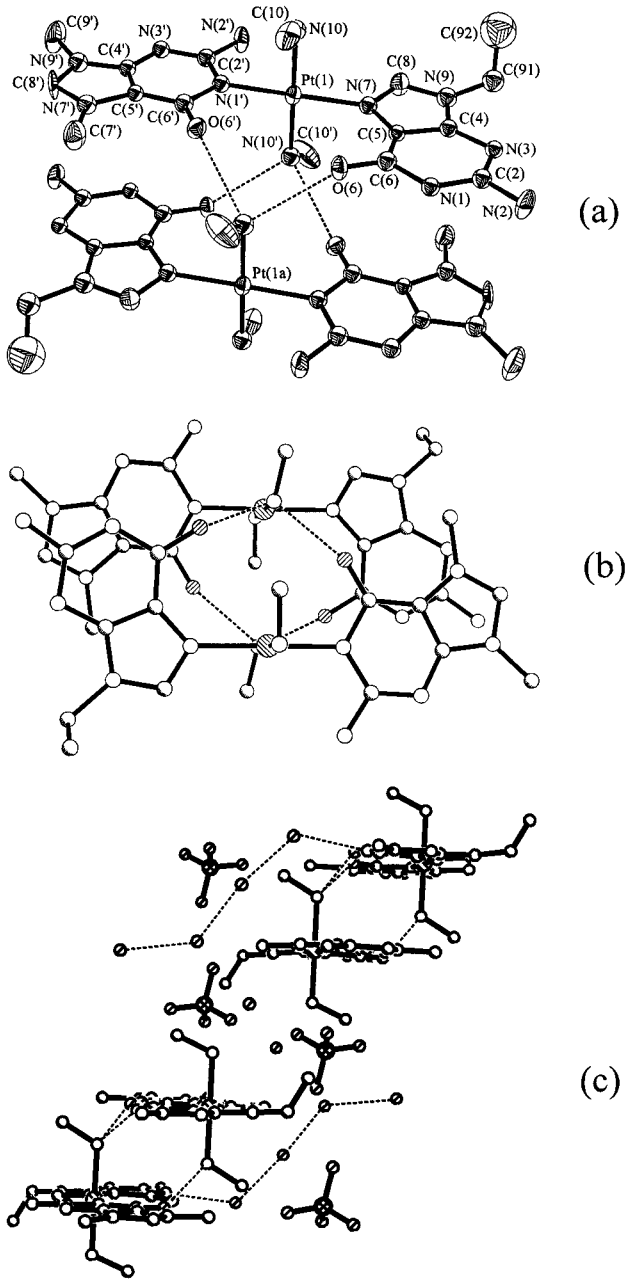

Figure 4. Stacking between pairs of cations of **4** and H-bonding interactions involving CH_3NH_2 ligands and O6 and O6′ of the guanine nucleobases: perspective view (a), top view perpendicular to base planes (b), and view from the side (c).

arranged *head*−*tail* with respect to each other, stack in a step fashion with O6 and O6′ of one cation interacting with a single CH_3NH_2 group of the adjacent cation, resulting in four intermolecular H bonds from which two each have the same length of 2.82(1), 2.83(1) Å (Figure 4). This situation is reminiscent of the packing seen in *trans*-$[(NH_3)_2Pt(1\text{-MeUH-}N3)_2]^{2+}$,[32] *trans*-$[(NH_3)_2Pt(1\text{-MeC})(7,9\text{-DimeG})]^{2+}$,[10] and *trans*-$[(NH_3)_2Pt(9\text{-EtG})(1\text{-MeC})](CF_3SO_3)$.[33] In all these cases, exocyclic oxygen acceptor groups are pointing in the same direction (*head*−*head*) and are involved in intermolecular H bonding with the NH protons of the am(m)ine ligands (Figure 5). At the same time pairs of cations are essentially parallel and at a stacking distance of 3.4−3.5 Å. The extent of base stacking correlates inversely with the angle between the Pt−am(m)ine vectors and the mean plane of the cross-linked bases: If base stacking is substantial, such as in *trans*-$[(NH_3)_2Pt(1\text{-MeUH-}N3)_2]^{2+}$,[32] for

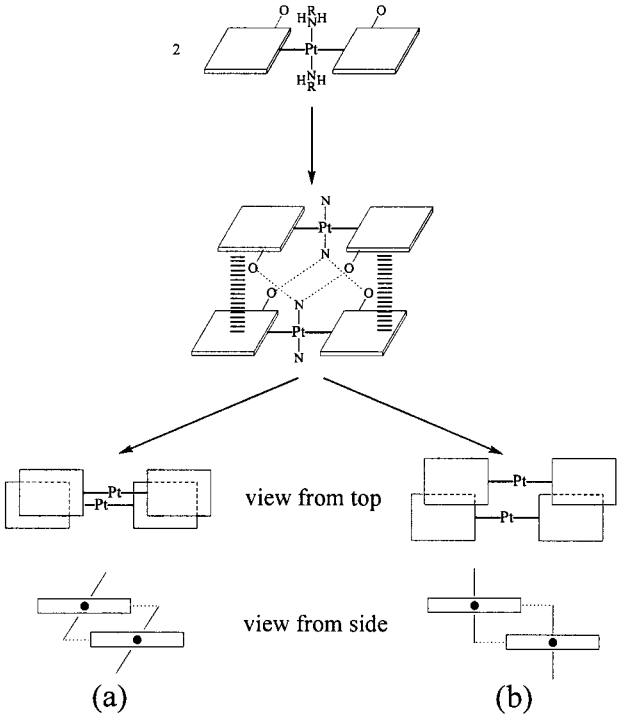

Figure 5. Correlation of the extent of base stacking with the angle between the Pt−am(m)ine vectors and the mean plane of the cross-linked bases in the solid state structures of *trans*-a_2Pt^{II} complexes, when the exocyclic groups of the nucleobase ligands are pointing in the same direction (*head*−*head*).

example, the Pt−am(m)ine vectors are strongly tilted, forming angles of 50−60° (Figure 5a). If, on the other hand, base pair overlap is reduced (Figure 5b), nucleobases and the PtN_4 plane form much larger angles, e.g., 83−85° in *trans*-[$(NH_3)_2$Pt(9-EtG)(1-MeC)](CF_3SO_3)[33] or *trans*-[$(NH_3)_2$Pt(7,9-DimeG)(1-MeC)]$^{2+}$ [10] and 89° in the case of **4**. Second, 9-EtGH ligands make intermolecular contacts between each other via O6 and N2 sites (Figure 6). H bonding between deprotonated guanines thus is not pairwise between N1 and $N2H_2$ sites, as previously observed for deprotonated guanine.[34] A water molecule, which forms a H bond to N1 (N1···O1w, 2.80(1) Å), appears to account for this difference.

Guanine−Guanine Pairing and Metal Modification. Guanine self-pairing occurs in many different ways (Figure 7), depending on the protonation state (neutral, protonated, deprotonated) and other modifications (methylation; metal complexation). For the four homopairs **I**−**IV**[35] enthalpies of formation in the gas phase have been calculated.[36] The symmetric pair **I** with H bonds between pairs of O6 and N1 sites, although in the gas phase almost as stable as the Watson−Crick GC pair,[36] has rarely been observed experimentally. Pair **II**, which is formed between N1′ and N2′ sites of one guanine (G′) and O6 and N7 of the other (G), has been implicated in domain joining to produce the catalytic core of the *Tetrahymena* ribozyme.[37]

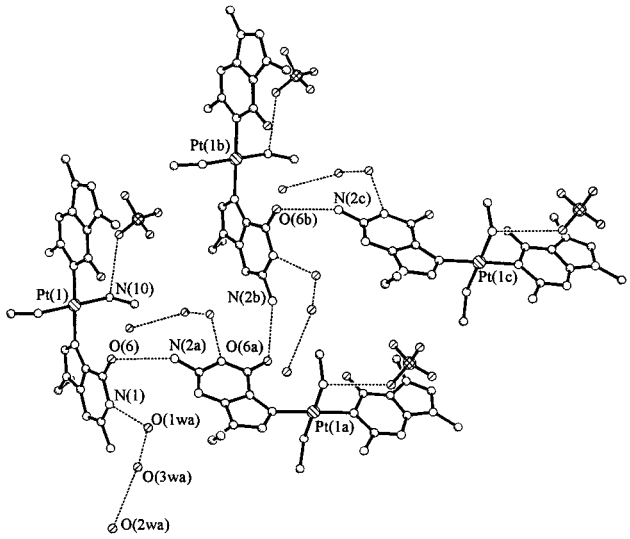

Figure 6. Additional H-bonding motif formed in **4**. The symmetry operations, starting from left, are as follows: x, y, z; $^1/_2 - x, y - ^1/_2, ^3/_2 - z$; $x, y-1, z$; $^1/_2 - x, y - ^3/_2, ^3/_2 - z$.

This pair has been observed experimentally in two slight variations also in a DNA dodecamer containing a GG mismatch.[38] It represents half of the guanine quartets seen in tetrastranded telomere structures.[39,40] Recently, this pattern has been confirmed in high-resolution X-ray studies of DNA duplexes containing guanine overhangs which interact to produce G′ × G•C triplets.[41,42] This triplet is reinforced by an additional H bond between O6′ of (the third) G′ and N4 of C. Pair **III** is realized in the solid state structure of guanines[43] and also in another G′ × G•C triplet,[44] in which the G′ is part of a third strand that runs antiparallel with respect to G. Again, the G within the duplex acts exclusively as H acceptor, while G′ (in the third strand) is exclusively the H donor, albeit N1′ and N2′ have switched sites as compared to **II**. Pair **IV** is seen in parallel-stranded DNA containing a homoguanine pair,[45] and in N7-protonated[46] or N7-platinated[13b,47] guanine.

If protonated or deprotonated guanine bases are considered, additional patterns are possible. For example, in hemiprotonated guanine, the acidic proton is between two N7 sites,[48] and in fully protonated guanine, pairs of H bonds between N7H and O6 are possible,[49] in addition to **IV** mentioned already. Finally,

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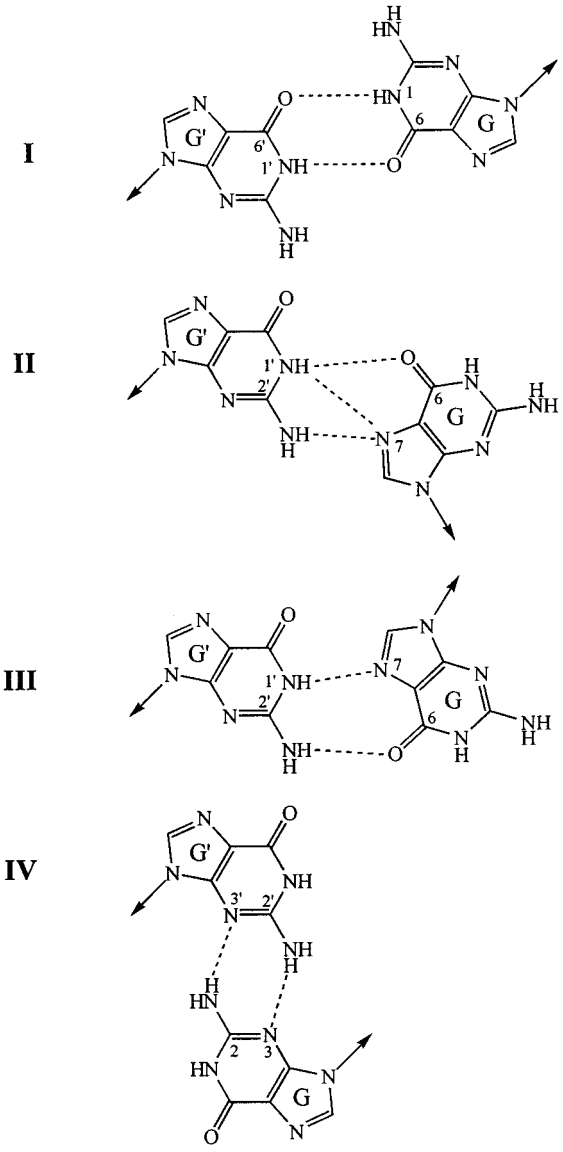

Figure 7. Different possibilities (**I**−**IV**) of self-pairing between two neutral guanine moieties.

deprotonation of a guanine at N1 leads either to a guanine pair with three H bonds (hemideprotonation)[13b,34,50] involving N1, $N2H_2$, and O6 or to a guanine pair with two H bonds between N1 and $N2H_2$.[34]

As far as metal modification of the homoguanine pairs **I**−**IV** is concerned, **1a**, **1b**, and **2** are to be considered such forms of **III**, with G′ representing the 7,9-DimeG and G the 9-EtGH model bases. In the metalated base pair the N1′H···N7 hydrogen bond is replaced by two considerably stronger Pt−N bonds, viz., N1′−Pt−N7. As a consequence, not only is the N1′···N7 separation, estimated around 2.84 Å in the base pair **III**,[36] increased to ca. 4 Å in **1a**, **1b**, and **2** but also the N2′···O6 distance increases, from ca. 3.06 Å in the unmetalated pair[36] to 3.11 Å in **1a** and 3.27(2) Å in **2**. In **1b** (3.88(1) Å) this hydrogen bond is lost.

Compound **4** is a metalated analogue of **II** with one of the two bifurcated H bonds, extending from N1′H to N7, replaced by the N1′−Pt−N7 bonds. Again G′ corresponds to 7,9-DimeG and G to the deprotonated 9-EtG.

Relevance of Model Compounds to Metalated DNA Triplexes. As part of ongoing work in our laboratory to apply metal cross-linking of nucleic acid strands to antigene and antisense strategies[5a,51,52] and to obtain models of relevant adducts,[1,12] we have previously concentrated primarily on metalated triplexes of the type pym × pu·pym (first pym of third strand added to Watson−Crick pu·pym duplex).[5a,51]

The two established G′ × G·C triplets (Figure 8a,b) contain the G′ × G pairs **III** and **II**, respectively, of Figure 7. The orientation of the third strand containing G′ is dictated by the sugar conformation of this base (anti or syn). If the third-strand base adopts the normal anti conformation, Figure 8a corresponds to an antiparallel orientation of the third strand (G′) with respect to the strand containing G, and Figure 8b to a parallel orientation of the third strand.

As outlined above, introduction of a linear metal entity into these G′ × G pairs (Figure 8c,d) causes relatively minor geometrical changes, as seen from a comparison of distances between C atoms, which in nucleic acids correspond to C1′ of sugars. The increase in glycosidic bond separations between the two guanine bases in the platinated species **1a** and **2** (Figure 8c) as well as **4** (Figure 8d) is relatively modest (0.7−1 Å). There are two more possibilities (Figure 8e,f) of metalated G′ × G·C triplexes, which have, however, no counterparts in their unmetalated forms due to the absence of suitable H-bonding interactions. In Figure 8e, the third G′ is cross-linked to the G·C duplex via a N7′−M−N7 bond and the two guanine bases adopt a *head*−*tail* orientation, as found in *trans*-$[(CH_3NH_2)Pt(9\text{-EtGH})_2]Cl_2$, for example.[53] The *head*−*head* orientation of the metal cross-linked G′,G bases (Figure 8f) is likewise possible, as seen in model compounds obtained by us more recently.[54] It needs to be noted that the general orientation of the residues at the N9 (N9′) positions of G (G′) in Figure 8e and Figure 8f corresponds to those of Figure 8c and Figure 8d, respectively, but that there are differences in mutual distances of these sites. On the basis of these distances it is evident that, compared to the two triplets that contain exclusively H bonds (Figure 8a,b), introduction of a metal of linear coordination geometry leads either to an increase in interglycosidic distances (if N7,N1 cross-linking takes place) or a reduction (if N7,N7 cross-linking occurs). Changes in either direction are on the order of 0.7−1.2 Å, hence ≤10% of the glycosidic bond separation of the triplets, and are presumably tolerable by the backbone.

Acidity Constants of 1 and 2. 9-Alkylguanine derivatives may usually accept a proton at N7 and release one from the N1H site. In both complexes **1** and **2** the N1′ and N7′ positions of the 7,9-DimeG residue are blocked by Pt^{II} or a methyl group, respectively. In the 9-EtGH ligand, the N7 position is occupied by the metal center, so that only one deprotonation site (and hence also only a single equilibrium) has to be considered in each of the two compounds. The results obtained from ^1H NMR measurements are listed in Table 3. For each complex it was possible to evaluate chemical shifts of HC8 and H_2C91 resonances, which were most affected by a change in pD; for both complexes the agreement of the two individual results is excellent. In Figure 9, the change of chemical shifts of HC8 in **1** and **2** is shown. It is noticed that in complex **1** (i.e., with

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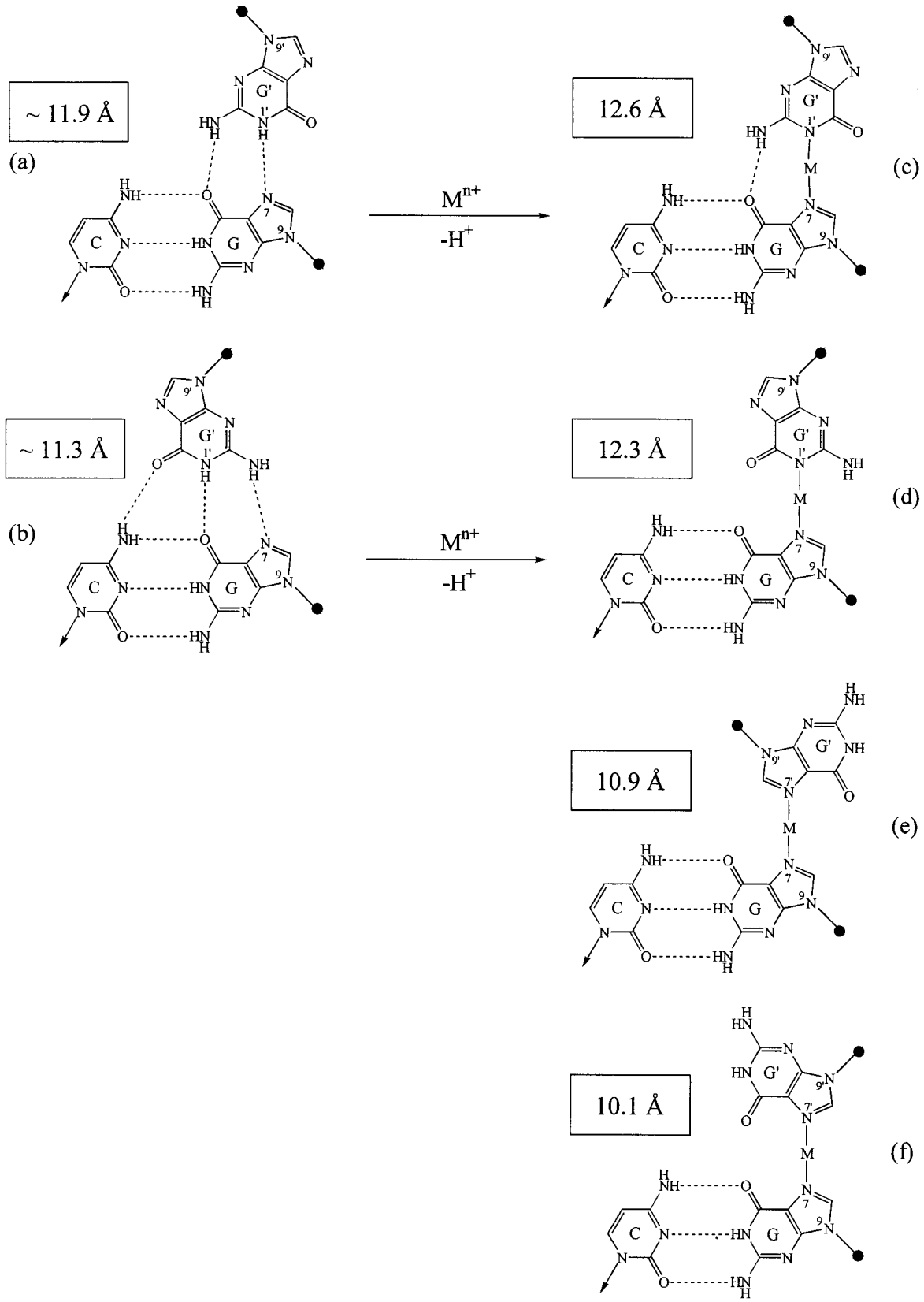

Figure 8. Four principal variants of metalated G′ × G·C base triplets (a, b) containing G′−N1, G−N7 (c, d) and G′−N7, G−N7′ (e, f) metal cross-links. Distances given refer to separations of the C1′ atoms in the glycosidic bonds of the two guanines (indicated by dots).

NH_3 ligands at the Pt^{II}) the curve of HC8 is slightly upfield shifted by about 0.1 ppm as compared to **2** (which has CH_3-NH_2 ligands at the Pt^{II}), and also the $\Delta\delta$ is slightly larger with **2**; the same is true for H_2C91, but the upfield shift is much smaller. pK_a values obtained are 8.22 ± 0.03 for **1** and 8.24 ± 0.07 for **2**. This shows that methylation of the amine ligands at Pt^{II} has an effect on the chemical shifts, yet not on the acid−base properties of such complexes within the error limits. For free 9-EtGH, pK_a = 9.57 ± 0.04 has been measured;[34] thus platination at N7 results in a decrease of 1.35 ± 0.05 or 1.33 ±

Table 3. ^{1}H NMR Data and Acidity Constants for **1** and **2**[a]

complex		δ_{GH} (ppm)	δ_G (ppm)	$\Delta\delta$ (ppm)	pK^*_{a/D_2O}	pK_{a/D_2O}	pK_{a/H_2O}
1	HC8	8.380 ± 0.001	8.204 ± 0.001	0.176 ± 0.001	8.789 ± 0.008	8.788 ± 0.001	8.22 ± 0.03
	H_2C91	4.194 ± 0.001	4.159 ± 0.001	0.035 ± 0.001	8.767 ± 0.026		
2	HC8	8.483 ± 0.002	8.282 ± 0.002	0.201 ± 0.003	8.802 ± 0.025	8.809 ± 0.023	8.24 ± 0.07
	H_2C91	4.221 ± 0.001	4.185 ± 0.001	0.036 ± 0.001	8.869 ± 0.072		

[a] Chemical shifts of the HC8 and H_2C91 of the 9-EtGH residue for protonated (i.e., deuterated) and deprotonated *trans*-[$(NH_3)_2$Pt(7,9-DimeG)(9-EtGH)]$^{2+}$ (**1**) and *trans*-[$(CH_3NH_2)_2$Pt(7,9-DimeG)(9-EtGH)]$^{2+}$ (**2**) as determined in D_2O (20 °C; I = 0.1 M, $NaNO_3$) by ^{1}H NMR are given in columns 3 and 4. These chemical shifts were calculated by using the average value of the acidity constant (column 7) together with its error limit; the range of error given with the calculated shifts is twice the standard deviation. in column 5 the shift differences $\Delta\delta$, resulting from deprotonation of the species, are listed: $\Delta\delta = \delta_{GH} - \delta_G$. Values for p$K^*_{a/D_2O}$ of the individual protons (column 6) are given with one standard deviation (1σ). The result for pK_{a/D_2O} (column 7) is the weighted mean with one standard deviation (1σ) of the individual values obtained from the various protons; this result is transformed to aqueous solution (H_2O) by applying eq 1 to give the final result for pK_{a/H_2O} (column 8). The error range given here is at least three times the standard error of the mean value.

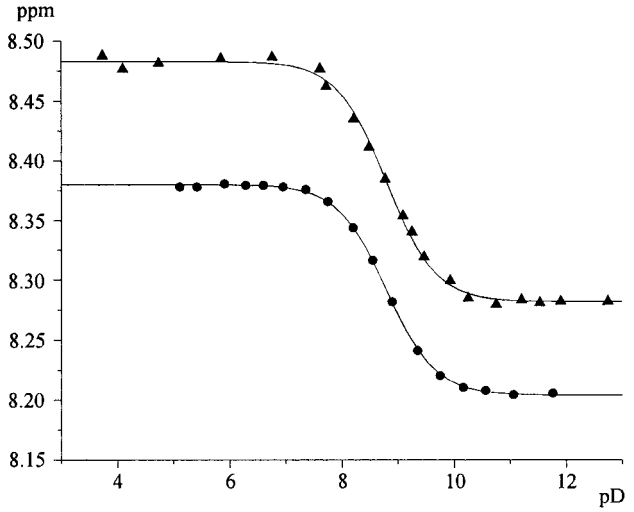

Figure 9. pH dependence of the ^{1}H chemical shifts of C8H of **1** (●) and **2** (▲). For the exact chemical shifts of the protonated and deprotonated complexes, see also Table 3.

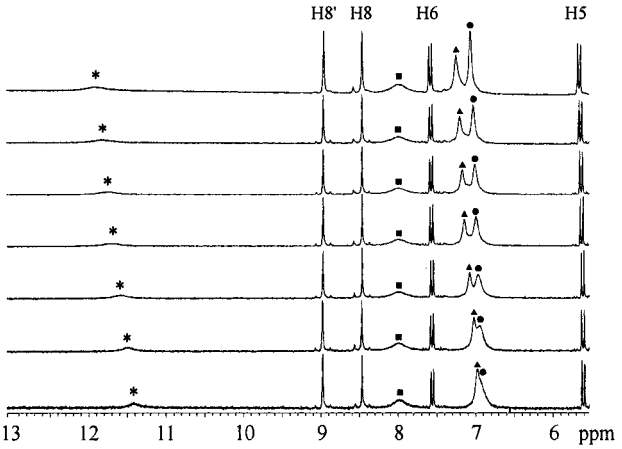

Figure 10. Stack plot of the aromatic part of the ^{1}H NMR spectrum (5.5−13 ppm) of an equimolar mixture of **2** and 1-MeC in DMSO-d_6 upon dilution. Carbon protons are labeled. The other resonances are, from left to right, N1H (*), H_2N2′ (■), N2H_2 (▲), and N4H_2 (cyt) (●). Concentrations from the top are 77.72, 51.81, 38.86, 31.09, 15.54, 8.29, and 4.97 mM.

0.08 pK_a units, which is slightly larger, but still on the same order as has been found before for several guanine derivatives where metal ions are coordinated to N7.[34]

However, the acidifying effect of about 1.34 pK_a units in **1** and **2** means that the N1H site is transformed to an even better hydrogen donor suitable for hydrogen bonding as for example in the G′ × G·C triplet (see below).

A Platinated G′ × G•C Triplet in Solution. The existence of platinated G′ × G·C triplets in solution can be demonstrated by ^{1}H NMR dilution experiments in DMSO-d_6.[55] Figure 10 shows a stackplot of the aromatic part of the ^{1}H NMR spectra of equimolar mixtures of **2** and 1-methylcytosine. It can be easily noticed that only three resonances are affected by the change in concentration, i.e., N1H and N2H_2 of the 9-EtGH residue and N4H_2 of the free 1-MeC. All other resonances of complex **2** and also of 1-MeC remain unaffected, which proves that there is no other kind of association (such as stacking, for example) occurring in solution. It also shows that a Watson−Crick pair between 9-EtGH and 1-MeC is formed because only this sort of base pairing involves all these (and only these) hydrogen donor sites. A pairing scheme as found in the solid state structure of *trans*-[$(CH_3NH_2)_2$Pt(7,9-DimeG)$_2$]$(ClO_4)_2$·(1-MeC)$_2$,[56] where N2′H_2 and N3′ of 7,9-DimeG on the one side and N4H_2 and N3 of 1-MeC on the other side are involved, is to be excluded, because in this case the resonance of N1H of the 9-EtGH ligand should remain unaffected. Thus, a triplet structure as shown in Figure 8c or 8d is postulated. The NMR data do not reveal if there is an intramolecular H bond between N2′H_2 and O6 as found in the solid state structures of **1a** and **1b**, hence if 7,9-DimeG is in a fixed position or is rotating fast around the Pt−N1′ bond. There is definitely no slow rotation (on the NMR time scale), since this should lead to two sets of (at least) the H8 and H8′ protons.

As expected, the downfield shift of the N1H resonance is approximately twice that of the two NH_2 signals, consistent with the involvement of only one of the two NH_2 resonances each in the Watson−Crick base pair and averaging due to fast rotation of the exocyclic amino group around the C−N bond.

Ab Initio Calculations of the Platinated G′ × G•C Triplet. The geometry of the platinated G′ × G·C triplet was established by ab initio HF SCF calculations applying nonalkylated nucleobases for simplicity. The result is shown in Figure 11. The orientation of the two guanine bases corresponds to that seen in **1a**, **1b**, and **2** and the platinated triplet is of the type shown in Figure 8c, with a normal Watson−Crick pair between G and C. Taking into account an elongation of the bond lengths typical for such calculations,[57] the geometry around the platinum atom compares reasonably well with the experimental data (Supporting Information). One of the interesting aspects of the ab initio structure is the involvement of the ammine ligands in intramo-

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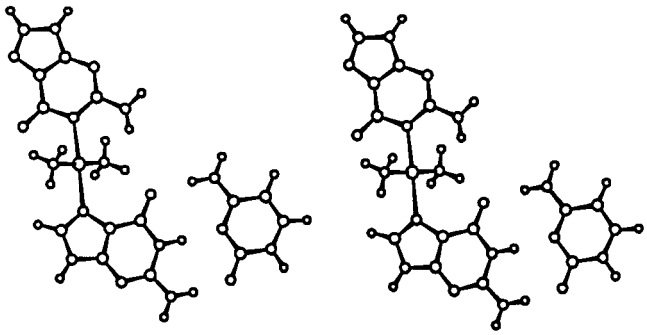

Figure 11. Stereoview of the ab initio optimized structure of *trans*-$[(NH_3)_2Pt(G\text{-}N1)(HG\text{-}N7)]^+$·C triplet (HG = unsubstituted guanine; G = anion of unsubstituted guanine; C = unsubstituted cytosine).

lecular hydrogen bonds with the exocyclic O6 oxygen atoms of both guanine moieties. The N(am1)···O6(G′) and N(am2)···O6(G) distances are 2.753 and 2.950 Å, respectively. As a result, the ammine ligands remain closer to the plane of the triplet and the whole system is "flattened" as opposed to the solid state structures of **1a**, **1b**, and **2**, where the am(m)ine ligands are almost perpendicular to the bases. Also, the dihedral angle between the guanine bases (5.7°) is significantly smaller than the corresponding angles in the X-ray structures (10.9−17.1°). However, it should be noted that in the solid state structures the am(m)ine moieties are involved in intermolecular hydrogen-bonding interactions, rather than the intramolecular system observed in the ab initio structure which refers to the gas phase.

Conclusions

As part of our research on cross-linking products of metal ions with nucleobases, we have described here mixed-nucleobase complexes of *trans*-Pt^{II} containing the purine bases 9-EtGH and 7,9-DimeG. The two bases are bound to Pt^{II} via *different* donor atoms, N7 and N1, respectively. As demonstrated by ^{1}H NMR spectroscopy for compound **2**, the N7-platinated 9-EtGH forms a Watson−Crick pair with 1-MeC, thereby producing an example of a metalated base triplet of the pu × pu·pym type.

Metalated base triplets or, more generally, metalated DNA triplex structures appear to be of interest in at least two respects: First, metal ions can induce formation of intramolecular DNA triplexes, and second, metal ions may be applied to generate triplex structures by linking a third oligonucleotide strand to a duplex. As to the first possibility, intramolecular GGC triples formation within runs of poly(dG)·poly(dC) of a DNA by metal ions is well established.[14b,58,59] It has been hypothesized[60] that metal binding to N7 of guanine in the third strand could increase the strength of H bonds between the two guanines as a consequence of a polarizing effect of the metal ion. On the basis of our structural work it would appear that an alternative scenario—cross-linking of the two guanine bases via N1 and N7 by a metal entity—is feasible as well. There would be no need to cross-link two guanines in *all* triplets. Rather a single metal ion, e.g., Zn^{II} or Cd^{II}, cross-linking base triplets once in a while, may be sufficient. We propose that cross-links of this type could stabilize a triplex to a considerably higher extent than simple polarizing effects of the metal. From model work with hexacoordinated bis(nucleobase) complexes of Pt^{IV} it is quite clear that a coplanar arrangement of two trans-orientated bases is possible.[61] The orientation of the other ligands, e.g., four water molecules about an octahedral metal ion, is in fact favorable for additional H bond formation with bases above and below the cross-link. For NH_3 groups we have recently been able to demonstrate this feature in the solid state.[32] The question of how capable a metal ion is of binding to N1 of guanine (rather than guanine methylated at N7 as in our case) is more difficult to answer. It should, however, be kept in mind that the relatively high pK_a value of N1H of guanine is by no means an obstacle for metal binding to this site. There are a number of cases known by now where metal ions substitute weakly acidic imino protons of nucleobases (pK_a 9−10) and even amino protons (pK_a 16−17), giving either the respective metalated anion[62,63] or the metalated neutral base in a rare tautomeric structure.[62,64]

As to the second aspect raised, formation of intermolecular DNA triplexes, we propose that metal cross-linking between a purine-containing oligonucleotide and a DNA duplex analogously to that of pyrimidine-containing oligonucleotides[5a] is possible in principle. It might be yet another gene-silencing strategy within the antigene technology which involves the use of metalated oligonucleotides.[52] The model compounds studied in this work provide a good basis to pursue this aspect further.

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Supporting Information Available: X-ray crystallographic files, in CIF format, of compounds **1a**, **1b**, **2**, and **4**, numbering scheme of ab initio optimized structure, Cartesian coordinates, and comparison of structural parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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