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Association Patterns of Platinated Purine Nucleobases in Metal-Modified Pairs and Triples

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Blocking of Watson–Crick or Hoogsteen edges in purine nucleobases by a metal entity precludes involvement of these sites in interbase hydrogen bonding, thereby leaving the respective other edge or the sugar edge as potential H bonding sites. In mixed guanine, adenine complexes of *trans*-a_2Pt^{II} (a = NH_3 or CH_3NH_2) of composition *trans*-$[(NH_3)_2Pt(9\text{-EtA-}N1)(9\text{-MeGH-}N7)](NO_3)_2$ (**1a**), *trans*-$[(NH_3)_2Pt(9\text{-EtA-}N1)(9\text{-MeGH-}N7)](ClO_4)_2$ (**1b**), and *trans*,*trans*-$[(CH_3NH_2)_2(9\text{-MeGH-}N7)Pt(N1\text{-}9\text{-MeA-}N7)Pt(9\text{-MeGH-}N7)(CH_3NH_2)_2](ClO_4)_4\cdot 2H_2O$ (**2**) (with 9-EtA = 9-ethyladenine, 9-MeA= 9-methyladenine, 9-MeGH = 9-methylguanine), this aspect is studied. Thus, in **1b** pairing of two adenine ligands via Hoogsteen edges and in **2** pairing of two guanine bases via sugar edges is realized. These situations are compared with those found in a series of related complexes.

Introduction

Hydrogen-bond formation is a major structure-determining feature in biology, supramolecular chemistry, and crystal engineering.[1−3] Others[3c,4] and ourselves[5−9] have been engaged for quite some time in studies on molecular architectures of metal−heterocycle complexes, specifically in studies of the interplay of coordinative bonds between metal entities and the heterocycle (which in our systems frequently is a nucleobase) and hydrogen bonds between the ligands. In a number of cases,[5,6,8,9] we have followed the simple concept of replacing protons involved in hydrogen-bond formation between nucleobases or other heterocycles by linear metal entities ("metal-modified" base pairs, Scheme 1), frequently by the kinetically robust *trans*-a_2Pt^{II} unit (a = NH_3 or CH_3NH_2).[10] This approach in a way extends earlier work, in which kinetically labile metal species with a pronounced tendency for linear coordination geometries have been applied to study or model DNA cross-linking by these metal ions.[11] Metal binding to some of the hydrogen-bonding sites of nucleobases usually does not exclude the others from becoming involved in H bond formation, and as a result,

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(1) (a) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinheim, Germany, 1995. (b) Neidle, S., Ed.; *Oxford Handbook of Nucleic Acid Structure*; Oxford University Press: Oxford, UK, 1999. (c) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond*; Oxford University Press: Oxford, 1999.

(2) (a) Linton, B.; Hamilton, A. D. *Chem. Rev.* **1997**, *97*, 1669. (b) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383. (c) Prins, L. J.; Hulst, R.; Timmerman, P.; Reinhoudt, D. N. *Chem. Eur. J.* **2002**, *8*, 2288 and refs cited.

(3) (a) Braga, D.; Grepioni, F.; Desiraju, G. R. *Chem. Rev.* **1998**, *98*, 1375. (b) Proceedings of the Dalton Discussion "Inorganic Crystal Engineering". *J. Chem. Soc., Dalton Trans.* **2000**, 3705−3998. (c) Aakeröy, C. B.; Beatty, A. M. *Aust. J. Chem.* **2001**, *54*, 409 and refs cited.

(4) See, for example: (a) Burrows, A. D.; Chan, C. W.; Chowdry, M. M.; McGrady, J. E.; Mingos, D. M. P. *Chem. Soc. Rev.* **1995**, *24*, 329. (b) James, S. L., Mingos, M. P.; Xu, X.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1998**, 1335. (c) Xu, X.; James, S. L.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **2000**, 3873. (d) Shipman, M. A.; Price, C.; Gibson, A. E.; Elsegood, M. R. J.; Clegg, W.; Houlton, A. *Chem. Eur. J.* **2000**, *6*, 4371. (e) Price, C.; Shipman, M. A.; Rees, N. H.; Elsegood, M. R. J.; Edwards, A. J.; Clegg, W.; Houlton, A. *Chem. Eur. J.* **2001**, *7*, 1194. (f) Gianneschi, N. C.; Tiekink, E. R. T.; Rendina, L. M. *J. Am. Chem. Soc.* **2000**, *122*, 8474. (g) Breuning, E.; Ziener, U.; Lehn, J.-M.; Wegelius, E.; Rissanen, K. *Eur. J. Inorg. Chem.* **2001**, 1515.

(5) (a) Lüth, M. S.; Freisinger, E.; Lippert, B. *Chem. Eur. J.* **2001**, *7*, 2104. (b) Sigel, R. K. O.; Thompson, S. M.; Freisinger, E.; Glahé, F.; Lippert, B. *Chem. Eur. J.* **2001**, *7*, 1968. (c) Rother, I. B.; Freisinger, E.; Erxleben, A.; Lippert, B. *Inorg. Chim. Acta* **2000**, *301−302*, 339. (d) Freisinger, E.; Meier, S.; Lippert, B. *J. Chem. Soc., Dalton Trans.* **2000**, 3274. (e) Rother, I. B.; Willermann, M.; Lippert, B. *Supramol. Chem.* **2002**, *14*, 189.

(6) Navarro, J. A. R.; Freisinger, E.; Lippert, B. *Inorg. Chem.* **2000**, *39*, 1059.

(7) Freisinger, E.; Schimanski, A.; Lippert, B. *J. Biol. Inorg. Chem.* **2001**, *6*, 378.

(8) (a) Sigel, R. K. O.; Freisinger, E.; Lippert, B. *J. Biol. Inorg. Chem.* **2000**, *5*, 287. (b) Brüning, W.; Sigel, R. K. O.; Freisinger, E.; Lippert, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3397.

(9) Müller, J.; Drumm, M.; Boudvillain, M.; Leng, M.; Sletten, E.; Lippert, B. *J. Biol. Inorg. Chem.* **2000**, *5*, 603.

(10) Lippert, B. *J. Chem. Soc., Dalton Trans.* **1997**, 3971 and refs. cited.

(11) (a) Sundaralingam, M.; Carrabine, J. A. *J. Mol. Biol.* **1971**, *61*, 287. (b) Shin, Y. A.; Eichhorn, G. L. *Biopolymers* **1980**, *19*, 539. (c) Kistenmacher, T. J.; Rossi, M.; Marzilli, L. G. *Inorg. Chem.* **1979**, *18*, 240. (d) Bélanger-Gariépy, F.; Beauchamp, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 3461.

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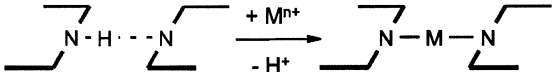
Scheme 1



various architectures can form, e.g. metal-containing base triples,[5a,12] base quartets,[5a,5c,13,14] or larger aggregates.[5b]

Our previous studies have revealed that intrabase hydrogen bonding, viz. H bonding between two or more bases in a metal complex, and interbase hydrogen bonding, viz. H-bond formation between individual metal complexes, is frequently predictable, yet not always. For example, the mixed purine complex *trans*-$[a_2Pt(A\text{-}N7)(GH\text{-}N7)]^{2+}$ (A = 9-alkyladenine, GH = 9-alkylguanine) displays the expected intramolecular H bond between the exocyclic amino group of A and the exocyclic oxo group of GH, but there is no intermolecular nucleobase association of the cations, despite the self-complementarity of H-bond donor and acceptor sites.[15] On the other hand, the mixed adenine, hypoxanthine analogue, *trans*-$[a_2Pt(A\text{-}N7)(HxH\text{-}N7)]^{2+}$ (HxH = 9-methylhypoxanthine) undergoes both intra- and interbase H-bond formation to give a base quartet, provided the anion is ClO_4^-.[5c] With NO_3^- being the counterion, intermolecular base pairing is absent, however, and rather the cations undergo base stacking (Scheme 2).[5e] It thus appears that in particular in cases where favorable secondary electrostatic interactions between H donor (D) and H acceptor (A) sites[16] are absent, the effects of counterions and solvent molecules become increasingly important. Finally, in these compounds rotational isomerism about Pt−N bonds may also strongly affect H-bonding interactions.

In continuation of our systematic studies, we report here on a metal-modified base pair and a metal-modified base triplet containing exclusively purine bases. The first compound, *trans*-$[(NH_3)_2Pt(A\text{-}N1)(GH\text{-}N7)]^{2+}$, is a linkage isomer of the above-mentioned mixed adenine, guanine complex,[15] while the second one, *trans,trans*-$[(CH_3NH_2)_2(GH\text{-}N7)Pt(N1\text{-}A\text{-}N7)Pt(GH\text{-}N7)(CH_3NH_2)_2]^{4+}$, is a methylamine analogue of the previously reported complex containing NH_3 groups at the two Pt's.[5c] As will be shown, this seemingly minor modification has a dramatic effect on the association pattern.

Experimental Section

Starting Compounds. *trans*-$(NH_3)_2PtCl_2$ was prepared according to the method of Kauffman and Cowan from K_2PtCl_4,[17] which was purchased from Heraeus. 9-MeGH was obtained from Chemogen. 9-EtA,[18] 9-MeA,[19] and the complexes *trans*-$[(NH_3)_2Pt(9\text{-}MeGH\text{-}N7)Cl]Cl$ [20] and *trans,trans*-$[Cl(CH_3NH_2)_2Pt(N1\text{-}9\text{-}MeA\text{-}N7)Pt(CH_3NH_2)_2Cl](ClO_4)_2$ [21] were prepared according to the literature method.

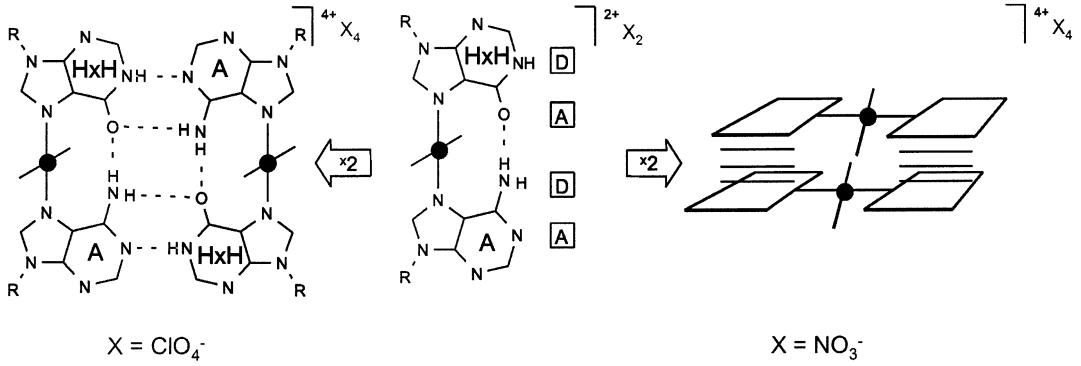
Synthesis of *trans*-$[(NH_3)_2Pt(9\text{-}EtA\text{-}N1)(9\text{-}MeGH\text{-}N7)]X_2\cdot nH_2O$ [X = NO_3, *n* = 3 (1a); X = ClO_4, *n* = 2 (1b)]. *trans*-$[(NH_3)_2Pt(9\text{-}MeGH\text{-}N7)Cl]Cl\cdot 1.5H_2O$ (246.1 mg, 0.5 mmol) and 9-EtA (163.2 mg, 1.0 mmol) were suspended in 50 mL of water. After addition of $AgNO_3$ (152.9 mg, 0.9 mmol), the pH was adjusted to 6.5 by means of 1 N KOH. The mixture was stirred at 37 °C for 4 days in the dark and cooled to 4 °C, and the precipitated AgCl was removed by filtration. The filtrate was evaporated to dryness (composition according to ^{1}H NMR was **1a**:*trans*-$[(NH_3)_2Pt(9\text{-}EtA\text{-}N7)(9\text{-}MeGH\text{-}N7)](NO_3)_2$:9-EtA ≈ 1:1:2), taken up with methanol (75 mL), stirred for 24 h at room temperature, and concentrated to 15 mL. After cooling at 4 °C for 24 h, the precipitate (which consisted of mainly *trans*-$[(NH_3)_2Pt(9\text{-}EtA\text{-}N7)(9\text{-}MeGH\text{-}N7)](NO_3)_2$) was removed by centrifugation, and the remaining solution was evaporated to dryness, taken up in 800 μL of water, acidified with nitric acid to pH 1, and stirred for 1 h. After centrifugation, the remaining solid was washed with 4 × 100 μL of water and dried at 40 °C. The isolated yield of colorless **1a** was 48 mg (13%). Crystals suitable for X-ray analysis were obtained upon recrystallization from water. Anal. Calcd for $C_{13}H_{22}N_{14}O_7Pt\cdot 3H_2O$: C, 21.2; H, 3.8; N, 26.7. Found: C, 21.7; H, 3.8; N, 26.4. Recrystallization of **1a** (10 mg) in the presence of 10 μL of 10 N $NaClO_4$ yielded crystals of **1b** which proved suitable for X-ray crystallography and showed the composition *trans*-$[(NH_3)_2Pt(9\text{-}EtA\text{-}N1)(9\text{-}MeGH\text{-}N7)](ClO_4)_2\cdot 2H_2O$. ESI MS: Signals due to isotopomers of cations of **1a** centered at *m*/*z* 556.2 and fragments (loss of one and both NH_3 ligands) at 539.2 and 522.1, among others.

Synthesis of *trans,trans*-$[(CH_3NH_2)_2(9\text{-}MeGH\text{-}N7)Pt(N1\text{-}9\text{-}MeA\text{-}N7)Pt(9\text{-}MeGH\text{-}N7)(CH_3NH_2)_2](ClO_4)_4\cdot H_2O$ (2). *trans,trans*-$[Cl(CH_3NH_2)_2Pt(N1\text{-}9\text{-}MeA\text{-}N7)Pt(CH_3NH_2)_2Cl](ClO_4)_2$ (250 mg, 0.26 mmol) was suspended in water (50 mL), $AgClO_4$ (0.52 mmol, dissolved in 3.1 mL of water) and 9-MeGH (85.8 mg, 0.52 mmol, dissolved in 15 mL of aqueous $HClO_4$, pH 2.5) were added, and the reaction mixture was stirred for 36 h at 50 °C in the dark. After cooling to 4 °C, AgCl was filtered off, and the solution was concentrated in a stream of N_2 until colorless prisms of **2** appeared. The yield of crystalline **2** was 35%. Anal. Calcd for $C_{22}H_{45}N_{19}O_{20}Cl_4Pt_2$: C, 18.7; H, 3.1; N, 18.9. Found: C, 18.5; H, 3.2; N, 18.6.

NMR Spectroscopy. ^{1}H NMR spectra were recorded on a Varian Mercury 200 FT NMR spectrometer or on a Varian Inova AS600, respectively. Sodium 3-(trimethylsilyl)propanesulfonate (TSP; δ = 0.00 ppm) was used as an internal standard in aqueous solutions, while spectra recorded in DMSO-d_6 were calibrated to the signal of partially nondeuterated solvent. Spectra recorded in DMF-d_7 were likewise referenced against solvent peaks. ^{195}Pt NMR spectra were recorded in D_2O on a Bruker AM-300 FT NMR spectrometer using sodium hexachloroplatinate (δ = 0 ppm) as an external standard. Signal assignment was achieved by selective 1D ^{1}H NOE spectroscopy,[22] performed on a Varian Inova AS600 FT-NMR spectrometer. pD values were determined by means of a glass electrode and addition of 0.4 units to the meter reading.[23]

(12) Dieter-Wurm, I.; Sabat, M.; Lippert, B. *J. Am. Chem. Soc.* **1992**, *114*, 358.
(13) (a) Metzger, S.; Lippert, B. *J. Am. Chem. Soc.* **1996**, *118*, 12467. (b) Sigel, R. K. O.; Freisinger, E.; Metzger, S.; Lippert, B. *J. Am. Chem. Soc.* **1998**, *120*, 12000.
(14) Meiser, C.; Freisinger, E.; Lippert, B. *J. Chem. Soc., Dalton Trans.* **1998**, 2059.
(15) (a) Schreiber, A.; Lüth, M. S.; Erxleben, A.; Fusch, E. C.; Lippert, B. *J. Am. Chem. Soc.* **1996**, *118*, 4124. (b) Lüth, M. S.; Freisinger, E.; Glahé, F.; Müller, J.; Lippert, B. *Inorg. Chem.* **1998**, *37*, 3195.
(16) (a) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810. (b) Jorgenson, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 209. (c) Murray, T. J.; Zimmermann, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010. (d) Sartorius, J.; Schneider, H.-J. *Chem. Eur. J.* **1996**, *2*, 1446.
(17) Kauffman, G. B.; Cowan, D. O. *Inorg. Synth.* **1963**, *7*, 239.
(18) Nowick, J. S.; Chen, J. S.; Noronha, G. *J. Am. Chem. Soc.* **1993**, *115*, 7636.
(19) Krüger, G. Z. *Physiol. Chem.* **1893**, *18*, 434.
(20) (a) Raudaschl, G.; Lippert, B. *Inorg. Chim. Acta* **1983**, *80*, L49. (b) Aletras, V.; Hadjiliadis, N.; Lippert, B. *Polyhedron* **1992**, *11*, 1359.
(21) Schreiber, A.; Hillgeris, E. C.; Lippert, B. *Z. Naturforsch.* **1993**, *48b*, 1603.
(22) Stoff, K.; Keeler, J.; Van, Q. N.; Shaka, J. J. *J. Magn. Res.* **1997**, *125*, 302.

Scheme 2



Vibrational Spectra. IR spectra (KBr pellets) were recorded on a Bruker IFS 28 instrument. The Raman spectrum (sample in glass capillary) was recorded on a Codberg T800 spectrometer applying an Ar^+ laser, $\lambda = 514.5$ nm (Spectra Physics).

ESI-MS. ESI-mass spectra of **1a** were recorded on a Thermo Quest TSQ spectrometer. The aqueous solution of the sample was introduced into the ESI source with a flow rate of 10 μL·min^{-1}. The spray voltage was 4.5 kV.

X-ray Crystallography. Crystal data for compounds **1a**, **1b**, and **2** were collected at room temperature on an Enraf-Nonius-KappaCCD diffractometer[24] using graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). For data reduction and cell refinement, the programs DENZO and SCALEPACK were used.[25] The structures were solved by conventional Patterson methods and subsequent Fourier syntheses and refined by full-matrix least squares on F^2 using the SHELXTL PLUS, SHELXL-93, and SHELXL-97 programs.[26] Except for some of the disordered perchlorate oxygen atoms and water molecules of crystallization in **1b** and **2**, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated geometrically and given fixed isotropic thermal parameters (**1a**) or refined isotropically (**1b**, **2**). Crystallographic data and details of refinement are reported in Table 1.

pK_a Values. pK_a values were determined by means of pD dependent ^{1}H NMR spectroscopy. The resulting curves in a plot of δ vs pD were fitted by equations given in the Supporting Information.[27] The pK_a values for D_2O, obtained by this method, were then calculated for H_2O.[28]

Results and Discussion

Solid-State Structures of Mixed Adenine, Guanine Complexes. Cations of *trans*-[$(NH_3)_2$Pt(9-EtA-*N1*)(9-MeGH-*N7*)]X_2·*n*H_2O (X = NO_3, *n* = 3 (**1a**); X = ClO_4, *n* = 2 (**1b**)) are depicted in Figures 1 and 2, respectively. The two compounds belong to the relatively small class of X-ray structurally characterized examples of adenine complexes with N1 metal coordination.[29] Guanine is bonded through the N7 position, which is most common in complexes of Pt^{II}.[30] As expected, significant differences in the metal coordination spheres of **1a** and **1b** are not seen (Table 2). Differences refer, however, to (i) the mutual orientation of the two bases (head−head in **1a**, head−tail in **1b**), (ii) dihedral angles between the purine bases [7.9(4)° in **1a**, 11.6(4)° in **1b**], (iii) relative orientations of the NH_3 ligands [almost perpendicular to base planes in **1a**, 85.9(2)° av; substantially tilted in **1b**, 62.0(1)°], and (iv) the absence of an intramolecular H bond between O(6G) and N(6A) in **1b**. This hydrogen bond is in **1a** [3.28(1) Å] clearly considerably longer than the corresponding H bond seen in the linkage isomer with adenine platinated at N7 [2.94(3) Å,[15a] 3.04(1) Å[15b]], as further confirmed by a direct comparison with the situation in the Pt base triplet *trans*,*trans*-[$(NH_3)_2$(9-MeGH-*N7*)Pt(*N1*-9-MeA-*N7*)Pt(9-MeGH-*N7*)$(NH_3)_2$]$^{4+}$ with head−head arrangements of the three bases.[5c] In this compound distances of 3.257(8) Å (between O6 of guanine and N6 of N1 platinated adenine) vs 2.944(8) Å (between O6 of guanine

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

	1a	**1b**	**2**
formula	$C_{13}H_{28}N_{14}O_{10}Pt$	$C_{13}H_{26}Cl_2N_{12}O_{11}Pt$	$C_{22}H_{43}Cl_4N_{19}O_{19}Pt_2$
M_r	735.58	792.45	1409.73
crystal system	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$C2/c$	$P2_1/n$
a (Å)	9.888(1)	47.399(1)	19.394(4)
b (Å)	10.627(1)	8.080(2)	8.876(2)
c (Å)	12.598(1)	13.853(3)	26.690(5)
α (deg)	83.40(1)		
β (deg)	88.58(1)	98.78(3)	107.78(3)
γ (deg)	74.06(1)		
V (Å^3)	1264.4(2)	5243(2)	4375(2)
Z	2	8	4
ρ_{calcd} (g cm^{-3})	1.932	2.008	2.140
ind reflns	3405	6122	7462
obsd reflns [$I > 2\sigma(I)$]	2955	3994	4248
R1 [$I > 2\sigma(I)$][a]	0.029	0.029	0.031
wR2 [$I > 2\sigma(I)$][b]	0.083	0.049	0.047

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$. $w^{-1} = \sigma^2(F_o^2) + (aP)^2$. $P = (F_o^2 + 2F_c^2)/3$. $a = 0.0802$ for **1a**, 0.0087 for **1b**, and 0.0064 for **2**.

(23) Lumry, R.; Smith, E. L.; Glantz, R. R. *J. Am. Chem. Soc.* **1951**, *73*, 4330.
(24) KappaCCD package, Nonius, Delft, The Netherlands, 1997.
(25) Otwinowsky, Z.; Minor, W. DENZO and SCALEPACK. *Methods Enzymol.* **1997**, *276*, 307.
(26) Sheldrick, G. M. *SHELXTL-PLUS (VMS)*, Siemens Analytical X-ray Instruments, Inc. Madison, WI, 1990; *SHELXL-93, Program for crystal structure refinement*; University of Göttingen, 1993; *SHELXL-97, Program for the Refinement of Crystal Structures*; University of Göttingen, 1997.
(27) Tribolet, R.; Sigel, H. *Eur. J. Biochem.* **1987**, *163*, 353.
(28) Martin, R. B. *Science* **1963**, *139*, 1198.
(29) (a) McCall, M. J.; Taylor, M. R. *Biochim. Biophys. Acta* **1975**, *390*, 137. (b) Olivier, M. J.; Beauchamp, A. L. *Inorg. Chem.* **1980**, *19*, 1064. (c) Beyerle-Pfnür, R.; Brown, B.; Faggiani; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1985**, *24*, 4001. (d) Schwarz, F.; Schöllhorn, H.; Thewalt, U. *Inorg. Chim. Acta* **1980**, *176*, 114. (e) Arpalahti, J.; Klika, K. D.; Molander, S. *Eur. J. Inorg. Chem.* **2000**, 1007. (f) Schmidt, K. S.; Reedijk, J.; Weisz, K.; Basilo Janke, E. M.; Sponer, J. E.; Sponer, J.; Lippert, B. *Inorg. Chem.* **2002**, *41*, 2855.
(30) Lippert, B. *Coord. Chem. Rev.* **2000**, *200*−*202*, 487 and refs. cited.

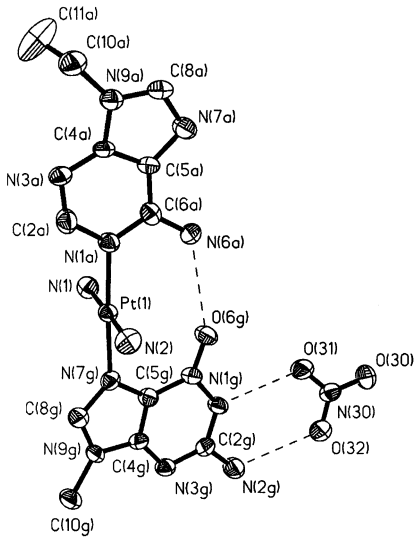


Figure 1. Cation of **1a** with one of the two nitrate anions hydrogen bonded to the guanine base. The two bases adopt a head−head orientation and are connected through a weak intramolecular H bond of 3.28(1) Å.

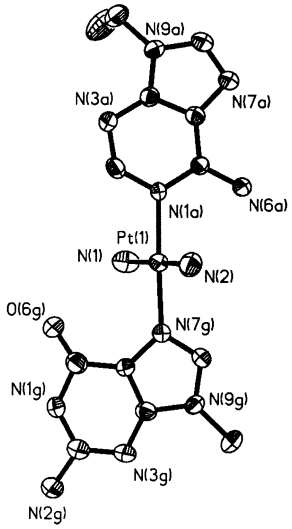


Figure 2. Cation of **1b**. The two bases adopt a head−tail orientation, ruling out any H bond formation within the cation.

Table 2. Selected Bond Lengths (Å) and Angles (deg) in **1a** and **1b**

bond length	**1a**	**1b**	bond angle	**1a**	**1b**
Pt(1)−N(1)	2.046(8)	2.035(3)	N(1)−Pt(1)−N(1a)	89.3(3)	90.5(1)
Pt(1)−N(2)	2.065(9)	2.052(3)	N(1)−Pt(1)−N(7g)	91.1(3)	89.7(1)
Pt(1)−N(1a)	2.026(8)	2.012(3)	N(2)−Pt(1)−N(1a)	90.9(4)	90.6(1)
Pt(1)−N(7g)	2.013(8)	1.999(3)	N(2)−Pt(1)−N(7g)	88.9(4)	89.4(1)

and N6 of N7 platinated adenine) are observed. This marked difference immediately suggests that rotation of the guanine about the Pt−N7 bond trans to adenine-*N1* should be relatively facile, certainly more facile than rotation of guanine about the bond trans to adenine-*N7*.

In **1a**, one of the two nitrate counterions [N(30)] is essentially coplanar with the guanine base (Figure 1), forming two H bonds of 2.85(1) Å [with N(1G)] and 2.90(1) Å [with N(2G)]. O(30) of this NO_3^- is hydrogen bonded to a water molecule, which in turn is bonded to a second one, thus

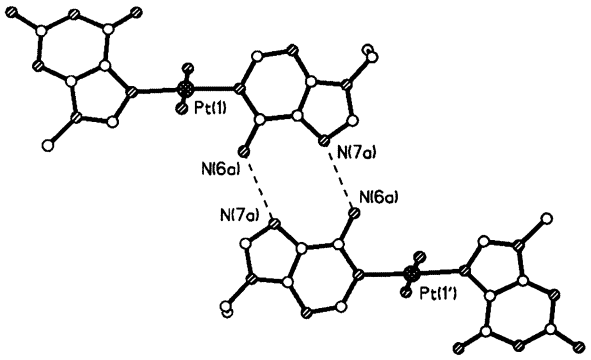


Figure 3. Centrosymmetric pair of cations of **1b**. Pairing occurs via the Hoogsteen edges of the two adenine bases.

bridging to guanine O6 of an adjacent cation. As a consequence, this nitrate anion is layered between guanine and adenine bases of two neighboring cations. There is no direct H-bonding interaction between nucleobases of adjacent cations possible, because this nitrate anion is blocking potential guanine H bonding sites at the Watson−Crick edge.

Cations of **1b** form centrosymmetric dimers via pairs of H bonds of 2.976(5) Å between N(7A) and symmetry-related N(6A) sites (Figure 3). This hydrogen-bonding pattern is reminiscent of that observed in double-stranded $[polyAH^+]_2$,[31] in which formally a proton at N1 of adenosine phosphate replaces the Pt^{II} entity of **1b**. There are numerous other H bonds or contacts between nucleobase sites and water molecules as well as oxygen atoms of the ClO_4^- anions, yet none of these is particularly short. The shortest one [2.81(1) Å] is between N(1)H of guanine and a water molecule.

It is to be noted that the metal coordination sites of Pt^{II} *and* the head−tail orientation of the two purine bases in **1b** are identical with those observed in an interstrand cross-link of *trans*-$(NH_3)_2Pt^{II}$ with a DNA 12/11-mer.[32] The combination of guanine-*N7* and adenine-*N1* is also realized, albeit with *cis*-$(NH_3)_2Pt^{II}$, in a complex with the RNA dinucleotide r(GpA).[33]

X-ray Crystal Structure of Platinated Base Triplet. Figure 4 gives a view of the platinated purine base triple *trans*,*trans*-$[(CH_3NH_2)_2$(9-MeGH-*N7*)Pt(*N1*-9-MeA-*N7*)Pt(9-MeGH-*N7*)$(CH_3NH_2)_2](ClO_4)_4 \cdot H_2O$ (**2**). Selected bond lengths and angles are listed in Table 3. The composition of this compound is analogous to the previously reported triplet with NH_3 ligands instead of the methylamines in **2**,[5c] with distinct differences in structural features, however. Thus, in **2** the central adenine base and the terminal guanine across the N1 position of adenine are head−tail, unlike in the NH_3 compound. As a consequence, there is no H bond between the exocyclic groups in 6-positions of the two purines, very much as in **1b**. The second terminal guanine, that across the adenine-*N7* site, retains its head−head orientation with respect to the adenine and is involved in a short intramo-

(31) Rich, A.; Davies, D. R.; Crick, F. H. C.; Watson, J. D. *J. Mol. Biol.* **1961**, *3*, 71.
(32) Andersen, B.; Bernal-Méndez, E.; Leng, M.; Sletten, E. *Eur. J. Inorg. Chem.* **2000**, 1201.
(33) (a) Van Hemelryck, B.; Girault, J.-P.; Chottard, G.; Valadon, P.; Laoui, A.; Chottard, J.-C. *Inorg. Chem.* **1987**, *26*, 787. (b) Inagaki, K.; Alink, M.; Nagai, A.; Kidani, Y.; Reedijk, J. *Inorg. Chem.* **1990**, *29*, 2183.

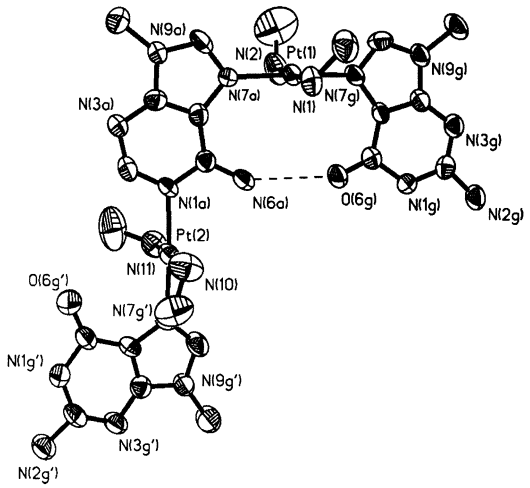
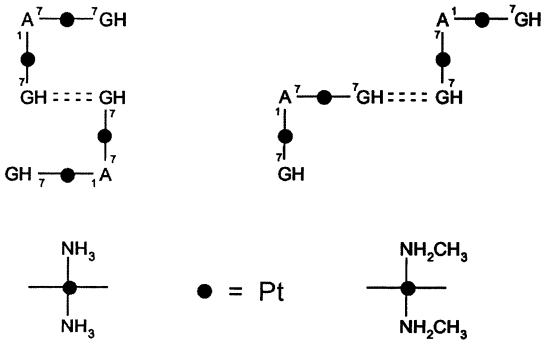


Figure 4. View of cation of compound **2** and atom numbering scheme. The terminal guanine base opposite to N1 of adenine adopts a head−tail orientation with respect to the latter, while the guanine across N7 of the central adenine is oriented in a way that a head−head arrangement results.

Table 3. Selected Bond Lengths (Å) and Angles (deg) in **2**

	Bond Lengths		
Pt(1)−N(1)	2.044(5)	Pt(2)−N(10)	2.041(5)
Pt(1)−N(2)	2.031(5)	Pt(2)−N(11)	2.054(5)
Pt(1)−N(7a)	2.008(5)	Pt(2)−N(1a)	2.046(5)
Pt(1)−N(7g)	1.999(4)	Pt(2)−N(7g′)	2.014(5)
	Bond Angles		
N(1)−Pt(1)−N(7a)	90.4(2)	N(10)−Pt(2)−N(1a)	88.8(2)
N(1)−Pt(1)−N(7g)	89.2(2)	N(10)−Pt(2)−N(7g′)	91.4(2)
N(2)−Pt(1)−N(7a)	90.9(2)	N(11)−Pt(2)−N(1a)	92.2(2)
N(2)−Pt(1)−N(7g)	89.5(2)	N(11)−Pt(2)−N(7g′)	87.6(2)

Chart 1



lecular H bond [N(6a)···O(6g), 2.867(6) Å], as expected. As in the NH_3 analogue, the Pt−N vectors of the adenine base in **2** are close to perpendicular [89.4(2)°], hence the 9-MeA represents a building block with a right angle, as previously reported by us.[5,21] The three nucleobases are close to coplanar, with angles of 5.6(2)° between adenine and guanine opposite to N1 and 14.0(2)° between adenine and guanine opposite to N7. The second major difference between **2** and the NH_3 analogue refers to the association pattern of two cations (Chart 1). In **2**, pairs of N3 and N(2)-H_2 of the guanine bases opposite to adenine-*N7* form weak, centrosymmetric hydrogen bonds [3.437(8) Å, Figure 5], whereas in the NH_3 analogue the guanine bases opposite to adenine-*N1* form pairs of short H bonds involving N(1)H and O6 sites [2.882(9) Å]. Moreover, in **2** the six bases are roughly coplanar, whereas in the NH_3 analogue the two halves form a step with partial stacking of guanines. We note that guanine/guanine pairing involving N3 and N(2)H_2 groups is not uncommon in cases where the N7 position is carrying a metal ion[34] or a proton,[35] and that in general the lengths of these hydrogen bonds are substantially shorter (2.9−3.2 Å) than in the present case. Even the Watson−Crick pair between 9-ethylguanine and 1-methylcytosine displays in addition this H bonding pattern (3.010 Å).[36]

Formation and Isolation of 1. The reaction of *trans*-[$(NH_3)_2$Pt(9-MeGH-*N7*)Cl]Cl with $AgNO_3$ and subsequent reaction with 9-EtA in water leads to a mixture of *trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)(9-MeGH-*N7*)]$^{2+}$, *trans*-[$(NH_3)_2$Pt(9-EtA-*N1*)(9-MeGH-*N7*)]$^{2+}$ (**1**), and the dinuclear base triplet *trans*,*trans*-[$(NH_3)_2$(9-MeGH-*N7*)Pt(*N1*-9-EtA-*N7*)Pt$(NH_3)_2$-(9-MeGH-*N7*)]$^{4+}$. Formation of the latter product is suppressed if an excess of 9-EtA is applied. The ratio of the two mononuclear linkage isomers is strongly influenced by pH. At low pH (<4.5), when the N1 position of 9-EtA becomes protonated, the N7 linkage isomer is formed preferentially, and this strategy has previously been applied to prepare the compound.[15] In the present case, the reaction was carried out at pH 6.5 and gave the expected mixture. The N7 and N1 linkage isomers can be differentiated by pD-dependent ^{1}H NMR spectroscopy (Figure 6 for **1a**) as a consequence of the markedly different pK_a values of the adeninium ligands of the two isomers. pK_a values were found to be ca. 0.2 for protonated **1a** and ca. 1.8 for the protonated adenine in the N7 linkage isomer (calculated for water, cf. the Experimental Section). The two linkage isomers were also differentiated by ^{195}Pt NMR spectroscopy (D_2O, pD 7), with resonances appearing at −2628 ppm (**1a**) and −2570 ppm (N7 linkage isomer), respectively.

The separation of the two linkage isomers was based, in part, on the feature of different charges of the two isomers at pH 1. Thus, the N7 linkage isomer is largely protonated at this pH (charge +3), whereas only a fraction of **1a** is protonated at this pH. The somewhat better solubility of the +3 charged species permits these species to become extracted from a mixture of both linkage isomers. Although this method did not permit a complete separation of the two isomers, it greatly assisted it.

The ^{1}H NMR spectrum of **1a** in D_2O (pD 7) is given in Figure 7. In addition to the pD dependence mentioned, a straightforward assignment of the aromatic resonances is achieved by a selective 1D ^{1}H NOE experiment.[22] Thus, irradiation of the methyl resonance of the guanine base permits identification of guanine H8, while irradiation of the singlet at 8.27 ppm identifies this resonances as the H8 of 9-ethyladenine due to the NOE with the CH_3CH_2 resonance.

The assignment of the individual ^{1}H NMR resonances of **1a** in DMSO-d_6 was achieved by a series of 1D NOE experiments and is as follows (δ ppm, 600 MHz): 1.46 (t, CH_3CH_2-A), 3.73 (s, CH_3-GH), 4.28 (s, H_3N−Pt), 4.30 (q, CH_3CH_2-A), 6.98 (s, H_2N-GH), 8.37 (s, H(8)-GH), 8.44 (s,

(34) Lüth, M. S.; Freisinger, E.; Lippert, B. Unpublished results.
(35) Schimanski, A.; Freisinger, E.; Erxleben, A.; Lippert, B. *Inorg. Chim. Acta* **1998**, *283*, 223.
(36) O'Brien, E. J. *Acta Crystallogr.* **1967**, *23*, 92.

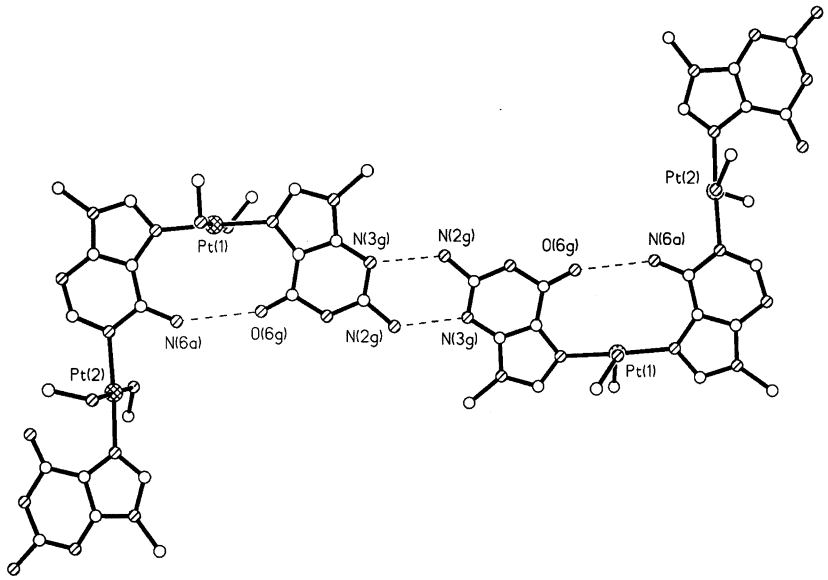


Figure 5. Pair of platinated base triplets **2** (anions and water of crystallization omitted). The six nucleobases are essentially coplanar. The sugar edges of two guanine bases are engaged in intermolecular H bonding.

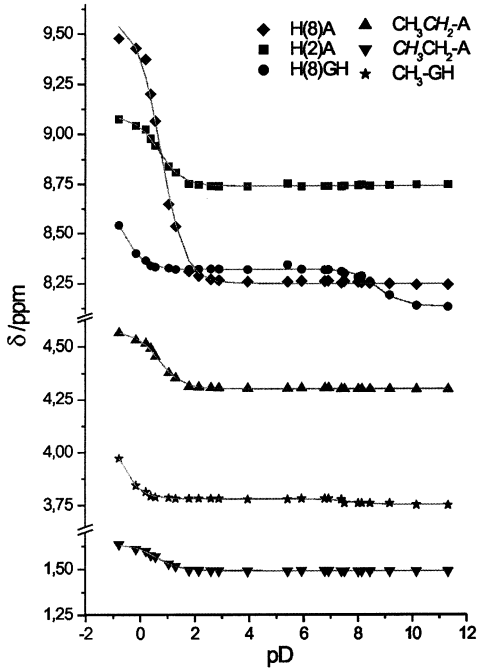


Figure 6. pD dependence of chemical shifts of ^{1}H resonances of **1a**.

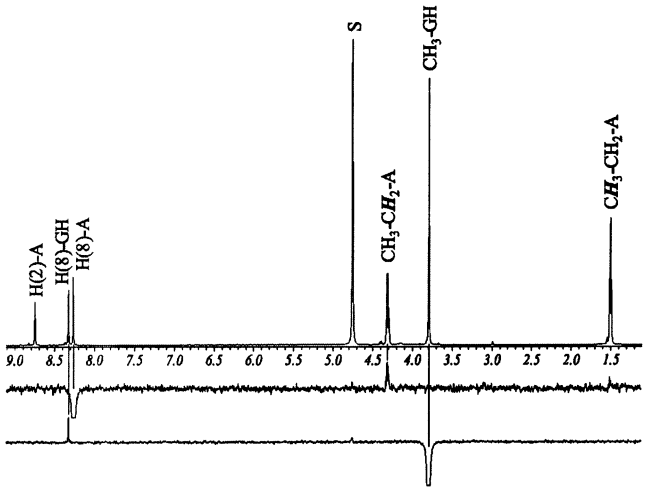


Figure 7. ^{1}H NMR spectrum (600 MHz, D_2O, pD 7) of **1a** (top) and two selective 1D ^{1}H NOE spectra (below) which were used to assign the H8 resonances of 9-MeA and 9-MeGH. S = solvent peak.

H(2)-A), 8.46 (s, H(8)-A), 8.76, 9.15 (s, s, H_2N-A), 11.48 (s, HN(1)-GH).

A concentration dependence of **1a** in DMSO-d_6 was carried out in the range 0.2−60 mM in order to investigate whether any self-association of **1a** is taking place. After all, the cation in its head−head orientation is partial self-complementary $[DADA]_2$, provided the NH_2 group of guanine is not involved in pairing. The NMR results gave no indication for any self-association, however, very much as also observed for the linkage isomer with adenine-*N7* metal binding.[15b]

Vibrational Spectra of 1a. We have previously reported that selected Raman bands in the 700−800 cm^{-1} range of 9-methyladenine containing Pt complexes can be indicative of the Pt binding pattern.[37] A comparison with the Raman spectrum (solid state) of the 9-ethyladenine complex **1a** reveals an intense ring deformation mode at 728 cm^{-1}, which is very close to the values observed in two 9-MeA complexes with Pt binding through N1 (Supporting Information).

Solution Behavior of 2. The ^{1}H NMR spectra of **2** in D_2O and DMSO-d_6 at 293 K are rather simple: For the bridging 9-MeA ligand, single sets of proton resonances are observed in both solvents with the exception of the split NH_2 resonance in DMSO-d_6 (9.91 and 9.75 ppm). Its chemical shift is in the expected range[5c,15a,b] for adenine bases platinated at N1 and N7. The nonequivalency of the two 9-MeGH bases is reflected only by the existence of two C(8)H singlets, while all other resonances coincide when the solvent is either D_2O or DMSO-d_6. However, in DMF-d_7 (291 K), the N(1)H resonances of the two nonequivalent guanine bases are distinguishable, yet the $N(2)H_2$ resonances still coincide

(37) Lippert, B. *Prog. Inorg. Chem.* **1989**, *37*, 1.

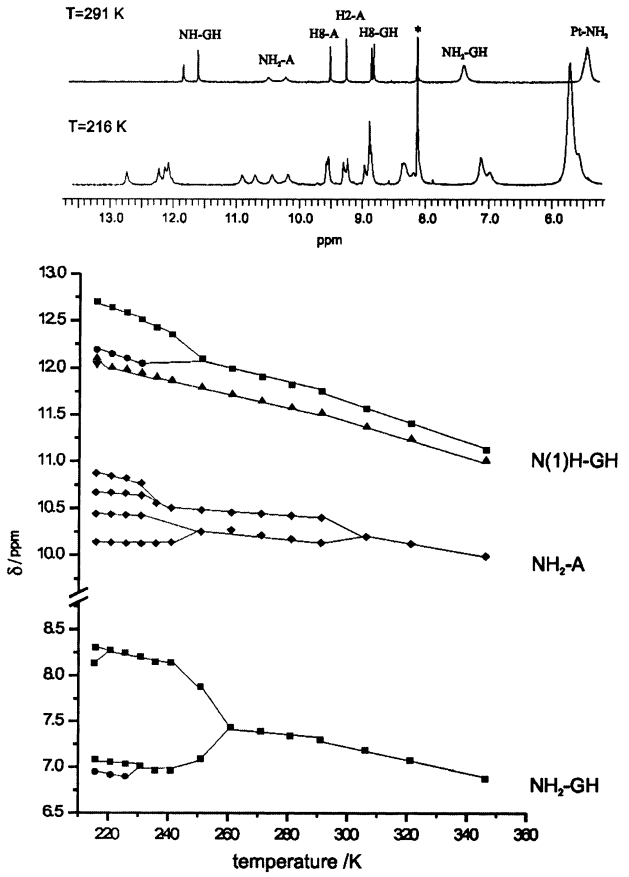


Figure 8. Section of ^{1}H NMR spectra of **2** in DMF-d_7 at different temperatures (top) and temperature dependence of NH and NH_2 resonances of the purine bases in DMF-d_7 (bottom).

(Figure 8, top). At 216 K, four distinct N(1)H resonances in the 12−13 ppm range are clearly discernible, and most of the other resonances have at least doubled. While an assignment of the resonances to individual species is not possible, at least from the appearance of four individual N(1)H resonances of the two guanine bases, it is evident that four different rotamers exist at low temperature. These are expected to be (i) the head−head−tail rotamer, as seen in the solid-state structure of **2**; (ii) the head−head−head rotamer, as observed in the solid-state structure of the NH_3 analogue of **2**;[5c] (iii) the tail−head−tail rotamer; and (iv) the tail−head−head rotamer (Supporting Information). This observation suggests that at higher temperatures, when a single N(1)H resonance is observed only (e.g. DMSO-d_6, 293 K), rotation about the Pt−N (guanine) bonds is rapid on the NMR time scale. The situation with the NH_2 resonances of the two bases is further complicated by the fact that rotation about the C−NH_2 bond is slowed and eventually frozen at low temperatures.

In DMSO-d_6 (ambient temperature) two ^{195}Pt NMR resonances are observed, at −2553 and −2594 ppm. They are in the expected range for PtN_4 coordination spheres and occur at similar shifts as the NH_3 analogue (−2470, −2530 pm).[5c]

The +4 cation of **2** can be successively deprotonated, namely at the N1 positions of the two guanine bases and eventually also at the exocyclic amino group of the adenine.

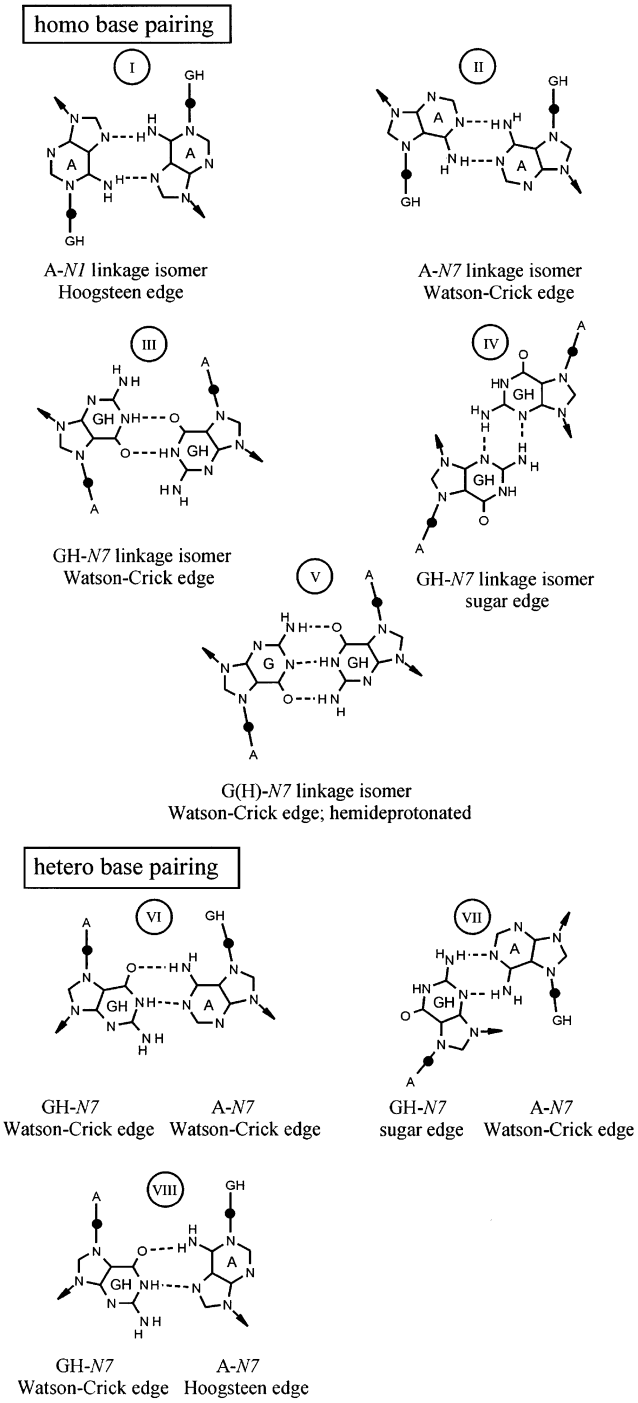
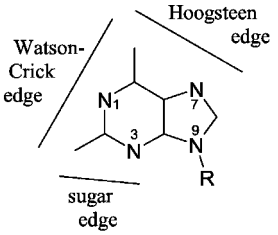


Figure 9. Homo-base- (top) and hetero-base-pairing patterns (bottom) in mixed adenine (A), guanine (GH) complexes of *trans*-a_2Pt^{II}. Pairing patterns involving the sugar edge [N(3) and C(2)H] of adenine are not shown, even though they are possible, in principle.

An average pK_a value of ca. 8.5 (D_2O) was deduced from pD-dependent ^{1}H NMR spectra for the two guanines (with no distinction possible due to signal overlap). Deprotonation at the 9-methyladenine base occurred with a pK_a of ca. 11.6 (D_2O). These values are in good agreement with expectations.[29d,38,39]

(38) Song, B.; Zhao, J.; Griesser, R.; Meiser, C.; Sigel, H.; Lippert, B. *Chem. Eur. J.* **1999**, *5*, 2374.

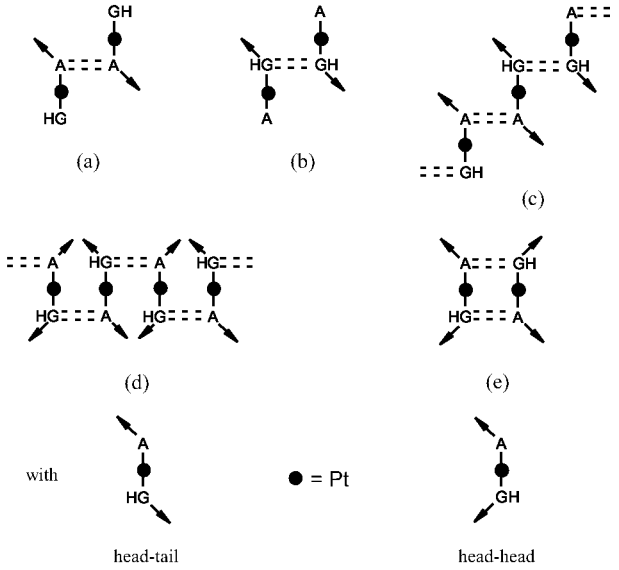
Chart 2



Association Patterns of *trans*-a_2Pt^{II}-Modified Purine Nucleobases. Usually double-stranded DNA contains complementary base pairs (GC, TA) only. However, it is also possible to synthesize DNA molecules with mismatches (e.g. AG, GG).[40] There is a good chance that such mispairs are relevant to mutagenesis. In RNA structures many more than the canonical Watson−Crick pairs between complementary bases are realized, including the above-mentioned hetero- and homopurine pairs.[41] Early ab initio calculations have shown that a number of non-Watson−Crick pairs are energetically more favorable than the Watson−Crick AT pair.[42]

Metal binding to nucleobases automatically reduces the number of H-bonding interactions between bases, yet it does not necessarily weaken these. On the contrary, both theoretical[43] and experimental data[44] support the view that due to electrostatic and polarization effects the H-bonded associate becomes stronger. With purine bases, to which this discussion is restricted, the location of a metal ion at either the Watson−Crick edge (e.g. N1), the Hoogsteen edge (e.g. N7), or the sugar edge (e.g. N3)[45,46] (Chart 2) will prevent H bonding via this edge. Clearly, linkage isomers can therefore display different interbase hydrogen-bonding schemes. As pointed out in Figure 9, complexes of composition *trans*-[a_2Pt(A-*N1*)(GH-*N7*)]$^{2+}$ or *trans*-[a_2Pt(A-*N7*)(GH-*N7*)]$^{2+}$, hence two of several linkage isomers, can associate in at least eight different ways. This number does not even include possible H bonding via the sugar edge of adenine and hence involvement of the C(2)H proton, as seen in a group I ribozyme structure.[47] Several of these different H-bonding patterns have been observed in this work, e.g. I in **1b** and IV in **2**, or have been previously reported for related compounds, e.g. II,[44c] V,[44b] and VI.[44c] It is obvious that cation−anion interactions, as seen in **1a**, for example, and blocking of H-bonding sites by solvent molecules are also crucial for the extent of interbase hydrogen bonding. If these competing interactions are absent, in principle, also polymeric or closed structures are feasible (Chart 3). For example, if both A,A (a) and GH,GH (b) homo base pairing is realized simultaneously, a stair structure could form (c), and if hetero base pairing A,GH is envisaged, either a meander structure (d) or a closed quartet structure (e) is possible. It needs to be emphasized that situations d and e apply to both A-*N1* and A-*N7* linkage isomers and that in both cases the major difference refers to the mutual orientation of adenine and guanine bases, namely head−tail for d and head−head for e.

Chart 3



Work is in progress to investigate under which conditions the feasible association patterns are realized.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support. We dedicate this paper to Professor Dieter Naumann, University of Köln, on the occasion of his 60th Birthday.

Supporting Information Available: Three crystallographic files, in CIF format. pK_a values for **1a**, IR and Raman spectra of **1a**, possible rotamers of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(39) Inagaki, K.; Kuwayama, M.; Kidani Y. *J. Inorg. Biochem.* **1982**, *16*, 59.
(40) See, for example: (a) Brown, T.; Hunter, W. N. *Biopolymers* **1997**, *44*, 91 and refs cited. (b) Kennard, O. In *Nucleic Acids and Molecular Biology*; Eckstein, F.; Lilley, D. M. L.; Eds.; Springer: Berlin, 1987; p 25. (c) Chou, S.-H.; Reid, B. R. In *Oxford Handbook of Nucleic Acid Structure*; Neidle, S.; Ed.; Oxford University Press: Oxford, 1999; p 331.
(41) Leontis, N. B.; Westhof, E. *RNA* **2001**, *7*, 499.
(42) Hobza, P.; Sandorfy, C. *J. Am. Chem. Soc.* **1987**, *109*, 1302.
(43) See, for example: (a) Basch, H.; Krauss, M.; Stevens, W. J. *J. Am. Chem. Soc.* **1985**, *107*, 7267. (b) Anwander, E. H. S.; Probst, M. M.; Rode, B. M. *Biopolymers* **1990**, *29*, 757. (c) Burda, J. V.; Sponer, J.; Leszczynski, J.; Hobza, P. *J. Phys. Chem. B* **1997**, *101*, 9670.
(44) (a) Sigel, R. K. O.; Lippert, B. *Chem. Commun.* **1999**, 2167. (b) Sigel, R. K. O.; Freisinger, E.; Lippert, B. *J. Biol. Inorg. Chem.* **2000**, *5*, 287. (c) Brüning, W.; Sigel, R. K. O.; Freisinger, E.; Lippert, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3397.
(45) For term "sugar edge", see ref 41.
(46) N3 purine metal coordination is not considered in this work, but we are aware that many of the arguments raised apply to this binding pattern as well. See, for example, refs 4d and 4e.
(47) Cate, J. H.; Gooding, A. R.; Podell, E.; Zhon, K.; Golden, B. L.; Kundrot, C. E.; Cech, T. R.; Doudna, J. A. *Science* **1996**, *237*, 1678.