Metal-Modified Nucleobase Pairs: Mixed Adenine, Thymine Complexes of *trans*-a_2Pt^{II} (a = NH_3, CH_3NH_2) with Watson-Crick and Hoogsteen Orientations of the Bases

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Abstract: Replacement of a weakly acidic N-H proton of a H bond between two nucleobases (neutral or hemiprotonated) by a metal species of suitable geometry generates metal-modified nucleobase pairs. Depending upon the combination of bases and/or respective donor sites involved in metal binding, these adducts can be divided in metal analogues of (i) homopyrimidine and homopurine pairs, (ii) Watson-Crick pairs, (iii) Hoogsteen pairs, (iv) pairs between noncomplementary bases, and (v) non-nucleobase, nucleobase pairs. Representative examples of (ii)-(v) have been prepared and are reported. In three cases, (ii), (iii), and (v), X-ray crystallography has been used to determine structural details. *trans*-[$(CH_3NH_2)_2$Pt(1-MeT-*N3*)(9-MeA-*N1*)]ClO_4·3.25H_2O (**4'**) crystallizes in the triclinic space group $P\bar{1}$ (No. 2) with a = 6.410(1) Å, b = 12.227(1) Å, c = 16.212(3) Å, α = 79.80(1)°, β = 81.40(1)°, γ = 84.13(1)°, Z = 2. *trans*-[$(NH_3)_2$Pt(1-MeT-*N3*)(9-MeA-*N7*)]ClO_4·2.5H_2O (**5**) crystallizes in the same space group $P\bar{1}$ (No. 2) with a = 13.527(3) Å, b = 19.264(5) Å, c = 9.383(1) Å, α = 91.24(1)°, β = 103.03(1)°, γ = 74.94(2)°, Z = 4. *trans*-[$(NH_3)_2$Pt(2-NH_2-py)(9-MeGH-*N7*)]$(NO_3)_2$ (**10**) (2-NH_2-py = 2-aminopyridine) crystallizes in the monoclinic space group $P2_1/c$ (No. 14) with a = 14.265(6) Å, b = 9.264(4) Å, c = 15.321(6) Å, β = 108.25(3)°, Z = 4. In **4'**, the two complementary bases 1-methylthymine (deprotonated at N3) and 9-methyladenine are arranged in a Watson-Crick fashion, while in **5** they adopt a Hoogsteen arrangement. In both cases a (partial) disorder of the 1-MeT ligand cannot be excluded from X-ray data. With **5**, variable temperature ^{1}H NMR spectroscopy in DMF-d_7 has been applied to demonstrate the existence of rotamers (Hoogsteen and reversed Hoogsteen arrangement of the nucleobases) in solution. Common structural features of **4'**, **5**, and **10** are an approximately coplanar arrangement of the two heterocyclic ligands, a marked nonlinearity of the base-Pt-base' angle (deviation as much as 173.4(2)° in **4'**), and H bonding between the two bases. This H bonding occurs between exocyclic groups of the bases intramolecularly in **5** and **10** and via a water molecule in **4'**. Structural changes of the adenine, thymine base pair upon metal modifications are discussed in detail, extended to other metals (Ag^I, Hg^{II}), and generalized to other possible metal coordination geometries. The formation of metal-modified base pairs, with regard to DNA cross-linking and related topics, is discussed.

Hydrogen bonding between the four common nucleobases guanine (G), adenine (A), cytosine (C), and thymine (T) or uracil (U) can occur in a variety of ways. With the assumption of at least two hydrogen bonds between two bases, 28 different ways of arrangement exist.[2] In DNA and double-stranded RNA, the complementary bases (G,C and A,T(U)) usually pair in the Watson-Crick fashion.

Occasionally, e.g. in drug-modified DNA,[3] complementary A,T and G,CH^+ bases may also adopt a Hoogsteen arrangement. In triple-stranded DNA, both Watson-Crick and Hoogsteen base pairing patterns coexist,[4] and in telomeric DNA, a completely different H-bonding pattern between four guanines exists.[5] While the existence of odd base pairs in tRNAs or the G,T wobble base pair[6] has been known for a long time, more recently, additional base pairing schemes have been verified, e.g. G,A mismatches in DNA (G(*anti*), A(*anti*)[7] and G(*anti*), A(*syn*)[8]) or pairing between neutral and anionic (G,C^-),[9] neutral and protonated (CH^+,C;[10] CH^+,A[11]), and two protonated nucleobases (AH^+,AH^+ [12]). With rare nucleobase tautomers allowed, the number of feasible base pairing schemes further increases.[13,14] They are possibly relevant to the questions of spontaneous and induced mutations.[15] Very recently, the introduction of nonstandard base pairs in nucleic acids and their processing by natural polymerases have been demonstrated[16] and the role of nucleobase analogs with respect to mutagenesis and possible medical applications has been reviewed.[17]

In all the above mentioned examples, hydrogen bonding is responsible for holding two (or three) bases together. The linkage

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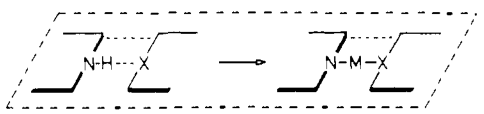
Chart I



between two nucleobases becomes considerably stronger as H bonds are replaced by covalent bonds. Covalent binding can be achieved by a variety of groups,[18-20] including a metal of suitable coordination chemistry.[21] As to the latter, formally a proton in a base pair may be replaced by a *linear* metal entity, giving a "metal-modified base pair" (Chart I). Depending on the donor sites involved, additional H bonds may be formed between the two bases. Even without any additional H bonding, the essential feature of a base pair—planar or nearly planar orientation of the bases—may be maintained when substituting a proton by a metal. Metal ions with a preference for linear coordination geometries such as Ag(I) and Hg(II) or metal entities like *trans*-L_2M (e.g. M = Pt^{II}, Pd^{II}; L = ligand) are expected to form metal-modified base pairs. In fact Ag(I) and Hg(II) have been shown to produce ordered helical structures with certain polynucleotides,[22,23] and binary model compounds for such interactions have been described.[24] As ternary systems (metal and two *different* nucleobases) are studied,[24] their model character, at least with regard to metal–DNA interactions, will further improve.

In this paper we describe complexes of composition *trans*-$[a_2Pt^{II}L_1L_2]^{n+}$ (a = NH_3 or NH_2CH_3) containing two different heterocyclic ligands L_1 and L_2 which either represent two complementary or two noncomplementary model nucleobases or a pyridine and a purine base.[25] Particular attention will be paid to mixed adenine, thymine compounds. We consider the complexes models for temporary or permanent cross-linking products of metal ion with two nucleic acid strands, possibly relevant to (i) metal-induced mutations, (ii) metal-induced renaturation processes of denatured DNA, and (iii) irreversible interstrand cross-linking by a metal. Applications with respect to antisense oligonucleotide chemistry[21] seem feasible.

Experimental Section

Preparation. Starting materials (9-MeA,[26] 9-MeA-d_8,[27] 1-MeTH,[28] K(1-MeT),[29] *trans*-$(NH_3)_2PtCl_2$,[30] *trans*-$(CH_3NH_2)_2PtCl_2$[31]) were prepared as described or obtained from commercial sources (9-MeGH, 2-OH-py, 2-NH_2-py).

^1H NMR and IR data of the compounds prepared are given in the supplementary material.

***trans*-a_2PtLCl Compounds.** The L = 1-MeT compounds **1** and **1′** were prepared by treating *trans*-$[a_2Pt(DMF)Cl]^+$, obtained *in situ* from *trans*-a_2PtCl_2 and $AgNO_3$ in DMF upon filtration of AgCl, with 1 equiv of K(1-MeT). After 3–6 days at 22 °C, *trans*-$(NH_3)_2Pt(1\text{-MeT})Cl$ (**1**) was filtered off, washed with DMF and acetone, and dried at 70 °C. The yield was ≥80%. **1** is poorly soluble in H_2O. Attempts to recrystallize it from H_2O or 0.01 N HCl failed. Although *trans*-$(NH_3)_2Pt(1\text{-MeT})_2$ is also extremely insoluble in water, the IR spectra of both compounds are sufficiently different to exclude the presence of the latter in detectable quantities. Anal. Calcd for $Pt(NH_3)_2(C_6H_7N_2O_2)Cl{\cdot}0.5H_2O$ (**1**): C, 17.46; H, 3.43; N, 13.57. Found: C, 17.7; H, 3.3; N, 13.5. *trans*-$(CH_3NH_2)_2Pt(1\text{-MeT})Cl$ (**1′**) was prepared in a similar way in ca. 50% yield (reaction time 2 days). On the basis of ^1H NMR evidence, the product always contained a few percent of *trans*-$(CH_3NH_2)_2Pt(1\text{-MeT})_2$. Recrystallization from 0.01 N HCl gave **1′** in low yield but pure form according to ^1H NMR spectroscopy and elemental analysis. Anal. Calcd for $(CH_3NH_2)_2Pt(C_6H_7N_2O_2)Cl{\cdot}0.5H_2O$ (**1′**): C, 21.79; H, 4.11; N, 12.71. Found: C, 21.9; H, 4.0; N, 12.6. For the preparation of the mixed nucleobase complexes, separation of the bis(1-MeT) product proved unnecessary.

trans-$(NH_3)_2Pt(2\text{-OH-py})Cl]NO_3$ (**2**) was prepared from *trans*-$(NH_3)_2PtCl_2$ and $AgNO_3$ (2 mmol each) in water (40 mL), filtration of AgCl, and addition of 2-hydroxypyridine (2 mmol). After 2 days at 50 °C, unreacted *trans*-$(NH_3)_2PtCl_2$ was filtered off and the slightly yellow solution was allowed to slowly evaporate. Yellow crystals of **2** were isolated in 20% yield. Anal. Calcd for $[(NH_3)_2Pt(C_5H_5NO)Cl]NO_3$ (**2**): C, 14.24; H, 2.62; N, 13.28. Found: C, 14.3; H, 2.6; N, 13.1.

trans-$[(NH_3)_2Pt(2\text{-NH}_2\text{-py})Cl]NO_3$ (**3**) was prepared in analogy to **2** from *trans*-$(NH_3)_2PtCl_2$, $AgNO_3$, and 2-aminopyridine and isolated in 33% yield. Anal. Calcd for $[(NH_3)_2Pt(C_5H_6N_2)Cl]NO_3$: C, 14.27; H, 2.87; N, 16.64. Found: C, 14.4; H, 2.7; N, 16.6.

Mixed Ligand Complexes. *trans*-$[(NH_3)_2Pt(1\text{-MeT})(9\text{-MeA-}N^1)]ClO_4{\cdot}4H_2O$ (**4**) and *trans*-$[(NH_3)_2Pt(1\text{-MeT})(9\text{-MeA-}N^7)]ClO_4{\cdot}4H_2O$ (**5**) were synthesized by treating *trans*-$[(NH_3)_2Pt(1\text{-MeT})(H_2O)]^+$, obtained from **1** and $AgClO_4$ *in situ*, with 1 equiv of 9-MeA in water (typically 2–3 mmol in 150 mL) for 2 days at 60 °C. Upon fractional crystallization, **4** and **5** were obtained in pure form, whereas a third compound, *trans*-$[(NH_3)_2(1\text{-MeT})Pt(9\text{-MeA-}N^1,N^7)Pt(1\text{-MeT})(NH_3)_2](ClO_4)_2{\cdot}nH_2O$ (**6**), was not analytically pure. Isolated yields were *ca.* 50% (**4**), 30% (**5**), and 10% (**6**). Anal. Calcd for $[Pt(NH_3)_2(C_6H_7N_2O_2)(C_6H_7N_5)]ClO_4{\cdot}4H_2O$ (**4**), (**5**): C, 20.92; H, 4.11; N, 18.29. Found (**4**): C, 20.6; H, 4.2; N, 18.6. Found (**5**): C, 20.7; H, 4.1; N, 18.9. In the course of attempts to separate **4** and **5** by fractional crystallization from mixtures of **4**, **5**, and **6**, we noticed that occasionally colorless needles **7** formed which, according to ^1H NMR spectroscopy, contained **4** and **5** in a 1:1 ratio.[32] According to X-ray crystallography, the crystal of **5** used for the study contained $2.5H_2O$ only.

The CH_3NH_2 analogs of **4**–**6** and **4′**–**6′** were prepared in a similar way. Upon concentration of the solution, **4′** crystallized as the first product (35% yield). Anal. Calcd for $[(CH_3NH_2)_2Pt(C_6H_7N_2O_2)(C_6H_7N_5)]ClO_4{\cdot}3.25H_2O$ (**4′**): C, 23.90; H, 4.38; N, 17.92. Found: C, 23.6; H, 4.4; N, 17.3. Attempts to separate the 9-MeA-N^7 linkage isomer **5′** and the 9-MeA-bridged compound **6′** in analytically pure forms via ion exchange chromatography or chromatography over Sephacryl (Pharmacia) from the remaining solution were not fully successful. However, the assignment on the basis of ^1H NMR spectroscopy in all cases was unambiguous (cf. text).

trans-$(CH_3NH_2)_2Pt(1\text{-MeT})(9\text{-MeG-}N^7)$ (**8b′**) was prepared as follows: *trans*-$[(CH_3NH_2)_2Pt(1\text{-MeT})(H_2O)]NO_3$ and 9-MeGH were allowed to react for 28 h at 50 °C in water (pH 5–6). After filtration from unreacted 9-MeGH and a small amount of *trans*-$(CH_3NH_2)_2Pt(1\text{-MeT})_2$, the solution was concentrated to a small volume, passed across a Sephadex column, and eluted with NaCl solution. Attempts to crystallize *trans*-$[(CH_3NH_2)_2Pt(1\text{-MeT})(9\text{-MeGH})]Cl$ (**8′**) or, upon titration with NaOH, the corresponding neutral species $(CH_3NH_2)_2Pt(1\text{-MeT})(9\text{-MeG})$ (**8b′**) without NaCl were not successful, although ^1H NMR spectroscopy confirmed the composition and the C:N ratio obtained from elemental analysis (Found: C, 18.8; N, 14.0) was consistent with this formulation.

trans-$[(NH_3)_2Pt(2\text{-OH-py})(9\text{-MeGH-}N^7)](NO_3)_2$ (**9**) was prepared from **2** and $AgNO_3$ after filtration of AgCl and subsequent reaction with 9-MeGH (48 h, 50 °C). The almost clear solution (pH 3.6) was allowed

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(25) Abbreviations used: 1-MeTH = neutral 1-methylthymine, $C_6H_8N_2O_2$; 1-MeT = 1-methylthymine anion; 1-MeC = 1-methylcytosine; 9-MeGH = neutral 9-methylguanine; 9-MeHyxaH = 9-methylhypoxanthine; 7,9-Dime-Hyxa = 7,9-dimethylhypoxanthine; 2-OH-py = 2-hydroxypyridine; 2-NH_2-py = 2-aminopyridine; ps = parallel standed; aps = antiparallel stranded. If unspecified, bases are also abbreviated according to their first letter, e.g. T for thymine.

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(32) It is feasible that **7** is a H-bonding adduct of **4** and **5**, which could involve N7 and N6H or 9-MeA in **4** and the N1 and N6H positions of 9-MeA in **5**.

Table I. Crystal Data and Experimental Details for **4'**, **5**, and **10**

	4'	5	10
A. Crystal Data			
empirical formula	$PtClO_{9.25}N_9C_{14}H_{30.5}$	$PtClO_{8.50}N_9C_{12}H_{25}$	$PtO_7N_{11}C_{11}H_{19}$
formula wt	703.49	661.93	612.43
cryst color, habit	colorless, plate	colorless, plate	colorless, needle
cryst dimens (mm)	0.390 × 0.320 × 0.210	0.410 × 0.29 × 0.120	0.420 × 0.240 × 0.200
cryst system	triclinic	triclinic	monoclinic
lattice params:	a = 6.410(1) Å b = 12.227(1) Å c = 16.212(3) Å α = 79.80(1)° β = 81.40(1)° γ = 84.13(1)° V = 1232.7(6) Å^3	a = 13.527(3) Å b = 19.264(5) Å c = 9.383(1) Å α = 91.24(1)° β = 103.03(1)° γ = 74.94(2)° V = 2299(2) Å^3	a = 14.265(6) Å b = 9.264(4) Å c = 15.321(6) Å β = 108.25(3)° V = 1923(2) Å^3
space group	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$P2_1/c$ (No. 14)
Z value	2	4	4
D_{calc} (g/cm^3)	1.895	1.913	2.115
μ(Mo Kα)	59.19	63.40	74.31
B. Intensity Measurements			
diffractometer	Enraf-Nonius CAD-4	Siemens/Nicolet P3m	Rigaku AFC6S
radiation	Mo Kα (λ = 0.710 69 Å)	Mo Kα (λ = 0.710 73 Å)	Mo Kα (λ = 0.710 69 Å)
temp (°C)	−120	25	−120
scan type	ω–2θ	ω–2θ	ω–2θ
2θ_{max} (deg)	50	46	50.0
no. of rflns measured	total: 4759 unique: 4337 (R_{int} = 0.017)	total: 6717 unique: 6408 (R_{int} = 0.032)	total: 3763 unique: 3611 (R_{int} = 0.014)
corr	Lorentz polarization absorption (trans. factors: 0.92–1.17)	Lorentz polarization absorption (trans. factors: 0.81–1.12)	Lorentz polarization absorption (trans. factors: 0.53–1.00) secondary extinction (coefficient: 0.31138 × 10^{-6})
C. Structure Solution and Refinement			
structure solution	Patterson method	direct methods (SIR88)	patterson method
refinement	full-matrix least squares	full-matrix least squares	full-matrix least squares
function minimized	$\sum w(\lvert F_o\rvert - \lvert F_c\rvert)^2$	$\sum w(\lvert F_o\rvert - \lvert F_c\rvert)^2$	
no. of observations ($I > 3.00\sigma(I)$)	3853	5355	2591
no. of variables	310	559	348
rfln/param ratio	12.43	9.58	7.45
residuals: R; R_w	0.041; 0.058	0.045; 0.069	0.020; 0.026
goodness of fit indicator	1.91	1.90	1.19
max peak in final diff map	1.78 e/Å^3 (near Pt atom)	3.70 e/Å^3 (near Pt2 atom)	0.71 e/Å^3

to slowly evaporate at 40 °C. Colorless crystals of cubic shape were isolated in 37% yield. Anal. Calcd for *trans*-$[(NH_3)_2Pt(C_5H_5NO)(C_6H_7N_5O)](NO_3)_2$ (**9**): C, 21.53; H, 2.95; N, 22.83. Found: C, 21.8; H, 3.0; N, 22.6.

trans-$[(NH_3)_2Pt(2\text{-}NH_2\text{-py})(9\text{-MeGH-}N^7)](NO_3)_2$ (**10**) was prepared in analogy to **9** (72 h, 50 °C and 24 h, 22 °C). The yield was 45%. Crystals suitable for X-ray crystallography were grown by slow evaporation of an aqueous solution of **10** at 40 °C. Anal. Calcd for *trans*-$[(NH_3)_2Pt(C_5H_6N_2)(C_6H_7N_5O)](NO_3)_2$: C, 21.57; H, 3.12; N, 25.15. Found: C, 21.4; H, 3.2; N, 25.0.

Spectra. ^{1}H NMR spectra were recorded on the following instruments: Joel JNM-FX 60, Bruker AC 200, and Bruker AM 300. Given shifts are relative to TMS (TSP or NMe_4^+ as internal standard in D_2O, TMS in DMF-d_7 and DMSO-d_6). The use of DMSO-d_6 as solvent for the bis(nucleobase) complexes did not cause any problems such as ligand displacement. pK_a values (in D_2O) were determined by plotting ^{1}H NMR chemical shifts vs the uncorrected pH (pH*). IR spectra (KBr) were recorded on a Perkin-Elmer 580B spectrometer.

X-ray Crystallography. All X-ray data were collected using Mo Kα radiation. Pertinent crystallographic parameters and refinement data are listed in Table I. All calculations were performed on a VAXstation 3520 computer by using the TEXSAN 5.0 crystallographic software package.[33]

Compound 4'. A crystal of dimensions 0.39 × 0.32 × 0.21 mm was mounted on a glass fiber and quickly transferred to the cold stream (−120 °C) of an Enraf-Nonius CAD4 diffractometer. The unit cell dimensions were determined by least-squares refinement of the setting angles for 25 high-angle reflections. The intensities of three standard reflections were measured every 3 h of X-ray exposure, showing no significant changes. The intensities were corrected for absorption by applying the program DIFABS.[34] The transmission factors ranged from 0.92 to 1.17. The structure was solved by heavy-atom techniques (Patterson and Fourier maps). Full-matrix least-squares refinement with anisotropic thermal displacement parameters for all non-hydrogen atoms except the O atoms of the disordered ClO_4^- ion yielded then the final R of 0.041 (R_w = 0.058). The perchlorate ion was found to exist in two orientations related by a rotation of ca. 30° around the Cl-O(1P) bond. The H atoms were found in difference Fourier maps and were included without further refinement. The final difference map showed one peak 1.78 e/Å^3 high in the vicinity of the Pt atom.

Compound 5. The X-ray data for a crystal of dimensions 0.41 × 0.29 × 0.12 mm were collected on a Siemens/Nicolet P3m diffractometer at room temperature (25 °C). Several attempts to collect data at low temperature failed because of crystal cracking. Preliminary measurements and cell reduction calculations indicated a triclinic unit cell. The unit cell parameters were determined by the application of least-squares refinement to the setting angles of 25 high-angle reflections. Three standard reflections monitored throughout the data collection showed no significant changes in intensity. The data were corrected for absorption by using the program DIFABS,[34] with the transmission factors ranging from 0.81 to 1.12. The structure was solved by direct methods (SIR88).[35] Full-matrix least-squares refinement with the anisotropic displacement parameters for all non-H atoms except the Cl and O atoms of the perchlorate ions gave the final R factor of 0.045 (R_w = 0.069). The ClO_4^- ions were found disordered. One of the ions (Cl1) showed two different orientations of the O atoms around the central Cl1 atom. The other perchlorate ion was disordered between two locations characterized by the positions of the Cl2 and Cl2A central atoms. All the atoms belonging to the perchlorate ions were refined with isotropic thermal displacement parameters. The H atoms were included in calculated

(33) *TEXSAN*: *Single Crystal Structure Analysis Software*; Version 5.0; Molecular Structure Corporation: The Woodlands, TX 77381, 1989.

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Table II. Positional Parameters and B(eq) for **4′**

atom	x	y	z	B(eq)
Pt	−0.21956(4)	0.16731(2)	−0.20788(2)	2.42(2)
Cl	0.1803(4)	0.3933(2)	0.2465(1)	3.7(1)
O(1P)	0.267(2)	0.475(1)	0.1846(8)	9.2(3)
O(1W)	0.201(1)	0.2596(5)	0.6359(4)	3.7(4)
O(2T)	−0.399(1)	0.1647(5)	−0.0263(4)	3.2(3)
O(2W)	0.255(1)	0.0492(5)	0.9467(4)	3.7(4)
O(3W)	0.853(3)	0.506(1)	0.443(1)	9(1)
O(4T)	0.177(1)	0.2959(5)	−0.2001(4)	3.2(3)
O(4W)	0.427(5)	0.405(1)	0.462(1)	12(2)
O(2P1)	0.036(3)	0.346(1)	0.202(1)	7.6(3)
O(2P2)	0.161(4)	0.298(2)	0.213(2)	4.2(4)
O(3P1)	0.024(3)	0.451(2)	0.295(1)	10.1(5)
O(3P2)	0.401(5)	0.389(3)	0.276(2)	6.6(7)
O(4P1)	0.298(4)	0.302(2)	0.278(1)	11.9(6)
O(4P2)	0.118(6)	0.399(3)	0.337(2)	7.1(7)
N(1)	−0.060(1)	0.0183(6)	−0.1657(4)	2.9(4)
N(1T)	−0.195(1)	0.2278(6)	0.0226(5)	3.4(4)
N(1A)	−0.348(1)	0.0902(6)	−0.2888(4)	2.6(4)
N(2)	−0.371(1)	0.3175(6)	−0.2505(5)	3.1(4)
N(3T)	−0.121(1)	0.2377(6)	−0.1175(4)	2.7(4)
N(3A)	−0.640(1)	−0.0191(5)	−0.2844(4)	2.3(3)
N(6A)	−0.051(1)	0.0965(6)	−0.3912(4)	2.7(3)
N(7A)	−0.263(1)	−0.0734(5)	−0.4611(4)	2.2(3)
N(9A)	−0.576(1)	−0.1323(5)	−0.3963(4)	2.0(3)
C(1)	−0.179(1)	−0.0843(7)	−0.1478(5)	3.2(5)
C(2)	−0.346(2)	0.3548(8)	−0.3435(6)	3.8(5)
C(2T)	−0.244(1)	0.2225(7)	−0.0408(5)	2.9(4)
C(2A)	−0.544(1)	0.0535(7)	−0.2567(5)	3.0(4)
C(4T)	0.058(1)	0.2925(6)	−0.1321(5)	2.6(4)
C(4A)	−0.526(1)	−0.0565(6)	−0.3527(5)	2.0(4)
C(5T)	0.105(1)	0.3475(6)	−0.0672(5)	2.2(4)
C(5A)	−0.333(1)	−0.0185(6)	−0.3926(4)	2.2(4)
C(6T)	−0.023(1)	0.3380(6)	0.0071(5)	2.5(4)
C(6A)	−0.242(1)	0.0570(6)	−0.3592(4)	2.1(4)
C(7T)	−0.336(2)	0.2670(8)	0.1049(5)	3.5(5)
C(8T)	0.291(1)	0.4141(7)	−0.0829(5)	3.3(5)
C(8A)	−0.412(1)	−0.1388(6)	−0.4606(4)	2.2(4)
C(9A)	−0.760(1)	−0.1988(8)	−0.3762(5)	3.1(5)

positions without further refinement. The final difference Fourier map showed a peak 3.7 e/Å^3 close to the Pt2 atom.

Compound 10. A crystal of dimensions 0.42 × 0.24 × 0.20 mm was placed in the cold stream (−120 °C) of a Rigaku AFC6S diffractometer. The previously described procedures were applied during the unit cell determination and data collection. The empirical absorption corrections were based on ψ scans of several reflections with the χ angles close to 90°. The transmission factors were between 0.53 and 1.00. The structure was solved by heavy-atom techniques. Full-matrix refinement yielded the final R of 0.020 (R_w = 0.026). The H atoms were found in difference Fourier maps and refined with isotropic thermal displacement parameters. The final difference map was essentially featureless.

Atomic positional parameters and temperature factors are listed in Tables II–IV.

Results

Reaction of *trans*-[a$_2$Pt(1-MeT)(H$_2$O)]$^+$ with 9-MeA. From ^{1}H NMR spectroscopy and preparative work, it became evident that *trans*-[a$_2$Pt(1-MeT)(H$_2$O)]$^+$, when reacted with 9-MeA in 1:1 ratio (water, pH ~ 5.5), gave three products: *trans*-[a$_2$Pt(1-MeT)(9-MeA-N^1)]$^+$ (**4**, **4′**), *trans*-[a$_2$Pt(1-MeT)(9-MeA-N^7)]$^+$ (**5**, **5′**), and *trans*-{[a$_2$Pt(1-MeT)]$_2$(9-MeA-N^1,N^7)}$^{2+}$ (**6**, **6′**). According to ^{1}H NMR spectroscopy, the distribution of the three compounds is *ca.* 1:0.7:0.4 after 48 h at 60 °C. The signal assignment of the individual products was based on differences in ^{195}Pt–^{1}H coupling[27,36–38] (**4**, **4′**, coupling with H2; **5**, **5′**, coupling with H8; **6**, **6′**, coupling with both H2 and H8; ^3J values of *ca.* 20–23 Hz each, observed in spectra recorded at 60 MHz only), the application of C8-deuterated 9-MeA,[27] the pD dependence of the nonexchangeable protons, and vibrational spectroscopy. A noticeable difference between NH$_3$ and CH$_3$NH$_2$ compounds is the 1:1 splitting of the 9-MeA resonances at lowest field in the methylamine complexes (H2 in **4′**, H8 in **5′**, H2 in **6′**), observed

Table III. Positional Parameters and B(eq) for **5**

atom	x	y	z	B(eq)
Pt(1)	0.17611(2)	0.94111(2)	0.13626(4)	2.50(2)
Pt(2)	0.59419(3)	0.65951(2)	0.72953(5)	4.07(3)
Cl(1)	0.7299(3)	0.4745(2)	0.3786(4)	5.77(7)
Cl(2)	0.0815(5)	0.2258(4)	0.108(1)	5.4(1)
Cl(2A)	0.0608(9)	0.2477(7)	0.034(1)	8.5(2)
O(1W)	0.5803(8)	0.3350(6)	0.712(1)	7.0(6)
O(2W)	0.4989(9)	0.0593(6)	0.600(1)	7.3(7)
O(3W)	0.425(1)	0.2883(7)	0.798(1)	9.2(8)
O(4W)	0.620(1)	0.4627(7)	0.812(2)	10(1)
O(5W)	0.263(2)	0.401(1)	0.902(2)	9(2)
O(6W)	0.298(1)	0.135(1)	0.393(3)	9(2)
O(11)	0.685(2)	0.550(1)	0.355(2)	5.8(4)
O(11A)	0.740(4)	0.551(3)	0.374(6)	18(1)
O(12)	0.025(1)	0.2001(7)	−0.035(1)	8.6(3)
O(21)	0.665(2)	0.453(2)	0.451(4)	10.2(7)
O(2T1)	−0.0205(6)	0.9816(5)	0.2733(8)	4.3(4)
O(21A)	0.823(3)	0.427(2)	0.363(5)	13(1)
O(22)	0.038(2)	0.228(2)	0.213(3)	9.2(7)
O(2T2)	0.7904(8)	0.5373(7)	0.845(1)	8.2(7)
O(22A)	0.077(5)	0.195(4)	0.180(7)	19(1)
O(31)	0.757(2)	0.444(2)	0.247(4)	10.8(8)
O(31A)	0.655(2)	0.437(2)	0.342(4)	10.7(7)
O(32)	0.188(2)	0.195(2)	0.135(3)	8.3(6)
O(32A)	0.168(3)	0.229(2)	0.054(4)	10.9(8)
O(41)	0.832(2)	0.459(1)	0.480(3)	8.6(6)
O(4T1)	0.2507(6)	0.7895(4)	0.250(1)	4.5(4)
O(41A)	0.753(3)	0.473(2)	0.543(4)	14(1)
O(4T2)	0.6790(8)	0.7245(6)	0.506(1)	7.4(7)
O(42)	0.122(4)	0.295(3)	0.075(5)	14(1)
O(42A)	0.026(3)	0.309(2)	0.072(4)	12.7(9)
N(1A1)	0.4940(6)	0.8737(5)	−0.064(1)	3.5(4)
N(1A2)	0.3049(6)	0.8754(5)	0.5973(9)	3.5(4)
N(3A1)	0.4412(8)	0.9910(6)	−0.181(1)	4.0(5)
N(3A2)	0.2128(6)	0.8315(5)	0.7501(9)	3.5(4)
N(6A1)	0.4026(6)	0.8354(5)	0.083(1)	3.6(4)
N(6A2)	0.4644(7)	0.8137(5)	0.554(1)	4.7(5)
N(7A1)	0.2458(6)	0.9881(4)	0.0107(8)	2.8(4)
N(7A2)	0.4486(6)	0.6970(5)	0.765(1)	3.6(4)
N(9A1)	0.2840(7)	1.0629(5)	−0.126(1)	3.7(5)
N(1T1)	−0.0010(7)	0.8771(6)	0.411(1)	4.6(5)
N(11)	0.0860(6)	0.9092(5)	−0.0432(9)	3.2(4)
N(9A2)	0.3079(6)	0.7130(5)	0.8540(9)	3.3(4)
N(1T2)	0.9079(8)	0.5519(9)	0.719(2)	8.3(8)
N(12)	0.5416(8)	0.5921(6)	0.580(1)	5.0(6)
N(21)	0.2646(8)	0.9739(6)	0.323(1)	4.4(5)
N(22)	0.6477(8)	0.7245(7)	0.886(2)	6.7(7)
N(3T1)	0.1169(6)	0.8868(5)	0.2632(8)	3.0(4)
N(3T2)	0.7365(7)	0.6277(6)	0.685(1)	5.5(6)
C(2A1)	0.5025(8)	0.9261(7)	−0.150(1)	3.7(6)
C(2A2)	0.2251(8)	0.8806(6)	0.660(1)	3.5(5)
C(4A1)	0.3590(7)	1.0032(5)	−0.120(1)	2.8(5)
C(4A2)	0.2948(7)	0.7717(6)	0.771(1)	2.9(5)
C(5A1)	0.3378(7)	0.9542(5)	−0.033(1)	2.6(4)
C(6A1)	0.4100(7)	0.8868(5)	0.001(1)	2.9(5)
C(5A2)	0.3810(7)	0.7624(6)	0.714(1)	3.3(5)
C(6A2)	0.3853(8)	0.8178(6)	0.620(1)	3.3(5)
C(8A1)	0.2168(8)	1.0531(6)	−0.048(1)	3.7(5)
C(8A2)	0.4004(8)	0.6694(6)	0.847(1)	3.8(5)
C(9A1)	0.275(1)	1.1346(6)	−0.203(1)	4.7(6)
C(9A2)	0.229(1)	0.6974(7)	0.928(1)	4.8(7)
C(2T1)	0.0284(7)	0.9189(6)	0.313(1)	2.9(5)
C(2T2)	0.810(1)	0.572(1)	0.753(2)	7(1)
C(4T1)	0.1744(8)	0.8147(6)	0.298(1)	3.4(5)
C(4T2)	0.755(1)	0.671(1)	0.577(2)	7(1)
C(5T1)	0.1376(7)	0.7768(5)	0.384(1)	3.4(5)
C(5T2)	0.854(1)	0.6485(9)	0.530(2)	6.0(8)
C(6T1)	0.0510(9)	0.8099(6)	0.443(1)	4.0(6)
C(6T2)	0.923(1)	0.594(1)	0.607(2)	8(1)
C(7T1)	0.191(1)	0.6998(7)	0.416(2)	6.6(8)
C(7T2)	0.882(2)	0.684(1)	0.427(4)	12(2)
C(8T1)	−0.085(1)	0.9122(8)	0.486(1)	4.9(7)
C(8T2)	0.985(2)	0.487(2)	0.791(2)	13(2)

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Table IV. Positional Parameters and B(eq) for **10**

atom	x	y	z	B(eq)
Pt	0.80180(1)	0.08186(2)	0.64032(1)	1.264(9)
O(6G)	0.6121(3)	0.2793(4)	0.6461(2)	2.1(2)
O(11)	0.7222(3)	0.0751(5)	0.0148(3)	2.8(2)
O(12)	0.0993(3)	0.0769(4)	0.5849(3)	2.4(1)
O(21)	0.7201(4)	0.1640(5)	–0.1154(3)	3.8(2)
O(22)	0.2268(3)	0.1610(5)	0.6910(3)	3.1(2)
O(23)	0.0890(3)	0.2786(5)	0.6542(3)	3.2(2)
O(31)	0.6281(4)	–0.0187(6)	–0.1094(3)	4.7(2)
N(1G)	0.4790(3)	0.3061(5)	0.5173(3)	1.7(2)
N(1P)	0.9167(3)	0.1235(5)	0.7530(3)	1.5(2)
N(1)	0.7354(4)	–0.0120(6)	0.7259(3)	1.8(2)
N(2)	0.8717(4)	0.1726(7)	0.5566(4)	2.1(2)
N(2G)	0.3372(4)	0.3406(6)	0.3948(4)	2.2(2)
N(2P)	0.8350(4)	0.3250(6)	0.7815(3)	2.0(2)
N(3G)	0.4514(3)	0.1750(5)	0.3775(3)	1.6(2)
N(7G)	0.6834(3)	0.0562(5)	0.5284(3)	1.5(2)
N(9G)	0.5866(3)	0.0131(5)	0.3868(3)	1.5(2)
N(11)	0.6901(4)	0.0722(6)	–0.0702(3)	2.3(2)
N(12)	0.1379(3)	0.1742(5)	0.6437(3)	1.9(2)
C(2G)	0.4237(4)	0.2716(6)	0.4283(4)	1.8(2)
C(2P)	0.9137(4)	0.2362(6)	0.8077(3)	1.5(2)
C(3P)	0.9945(4)	0.2616(7)	0.8871(4)	2.1(2)
C(4P)	1.0747(4)	0.1739(7)	0.9087(4)	2.4(2)
C(4G)	0.5398(4)	0.1154(6)	0.4225(3)	1.5(2)
C(5P)	1.0780(5)	0.0591(7)	0.8511(4)	2.4(2)
C(5G)	0.5991(4)	0.1408(6)	0.5103(3)	1.3(2)
C(6P)	0.9976(4)	0.0380(7)	0.7753(4)	2.0(2)
C(6G)	0.5702(4)	0.2432(6)	0.5669(3)	1.5(2)
C(8G)	0.6726(4)	–0.0191(6)	0.4527(4)	1.8(2)
C(9G)	0.5521(5)	–0.0465(8)	0.2926(4)	2.2(3)
H(1G)	0.454(4)	0.370(6)	0.547(4)	2(1)
H(1A)	0.681(4)	–0.058(6)	0.702(3)	1(1)
H(1B)	0.720(4)	0.052(6)	0.764(4)	1(1)
H(1C)	0.783(7)	–0.09(1)	0.764(6)	7(2)
H(2PA)	0.831(4)	0.379(6)	0.824(3)	1(1)
H(2A)	0.921(4)	0.205(6)	0.582(4)	1(1)
H(2GA)	0.321(4)	0.415(6)	0.427(4)	2(1)
H(2B)	0.882(5)	0.117(7)	0.515(5)	3(1)
H(2GB)	0.308(5)	0.340(7)	0.338(5)	3(1)
H(2PB)	0.771(4)	0.301(6)	0.737(4)	2(1)
H(2C)	0.836(5)	0.251(8)	0.524(5)	5(1)
H(3P)	0.990(3)	0.336(5)	0.923(3)	1(1)
H(4P)	1.130(5)	0.199(7)	0.962(4)	4(1)
H(5P)	1.134(4)	0.001(5)	0.865(3)	1(1)
H(6P)	0.995(4)	–0.039(6)	0.743(4)	2(1)
H(8G)	0.722(4)	–0.074(6)	0.445(4)	2(1)
H(9GA)	0.564(5)	0.021(8)	0.252(5)	4(1)
H(9GB)	0.588(5)	–0.134(8)	0.287(4)	4(1)
H(9GC)	0.490(6)	–0.079(8)	0.284(5)	5(1)

at ambient temperature and tentatively attributed to hindered rotation about a Pt–nucleobase bond.[39]

Protonation processes at the 9-MeA ligands of **4** and **4′** and of **5** and **5′**, as determined by ^{1}H NMR spectroscopy, occur with pK_a values close to those established for related Pt(II) complexes of the two linkage isomers (*ca.* 1.2 for **4**; *ca.* 3 for **5**).[36–38,40] Protonation of the 1-MeT ligands takes place in strongly acidic medium only (pK_a ~ 0), very similar to the situation in *trans*-$(NH_3)_2$Pt(uridine)$_2$,[41] and eventually leads to ligand displacement.

The assignment of Pt-binding sites of 9-MeA in **4** and **5** was further confirmed by vibrational spectroscopy (IR, Raman) using characteristic marker bands in the 700–800-cm^{-1} range.[38,42]

Description of the Crystal Structure of 4′. Figure 1 depicts the molecular cation of *trans*-[$(CH_3NH_2)_2$Pt(1-MeT-N^3)(9-MeA-N^1)]ClO_4·3.25H_2O, **4′**. Selected interatomic distances and angles are given in Table V. Pt coordination is through the N3 position of the deprotonated thymine ring and through N1 of the adenine ring. Thus, **4′** represents only the second example[38] of a structurally characterized Pt complex with the metal coordinating exclusively via N1 of an adenine.

The coordination geometry of Pt is roughly square-planar with only the N1A–Pt–N3T angle deviating more strongly (173.4(2)°) from the ideal 180°. Pt–N distances are normal and compare well with distances observed in other methylamine[31,43,44] and related 1-methyluracil[45] and 1-methylthymine[46] complexes of Pt(II). As evident from Figure 1, the two methyl groups of

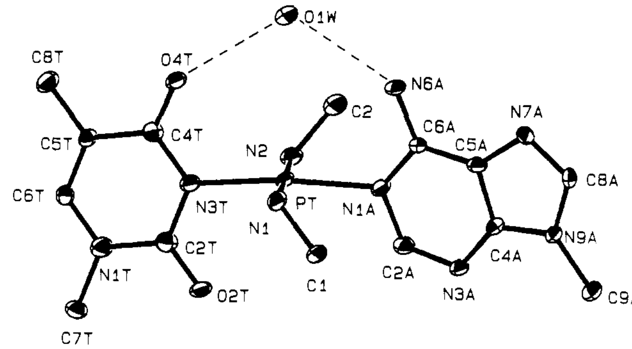

Figure 1. ORTEP drawing (30% probability ellipsoids) and atom-numbering scheme of the cation of *trans*-[$(CH_3NH_2)_2$Pt(1-MeT-N^3)(9-MeA-N^1)] ClO_4·3.25H_2O (**4**) with the water molecule (O1W) which forms H bonds to O4T and N6A.

Table V. Selected Bond Lengths (Å) and Angles (deg) for **4′**

Pt–N1	2.055(7)	N3T–C4T	1.36(1)
Pt–N1A	2.051(7)	N3A–C2A	1.30(1)
Pt–N2	2.045(8)	N3A–C4A	1.35(1)
Pt–N3T	2.032(7)	N6A–C6A	1.36(1)
O2T–C2T	1.25(1)	N7A–C5A	1.39(1)
O4T–C4T	1.24(1)	N7A–C8A	1.30(1)
N1–C1	1.50(1)	N9A–C4A	1.35(1)
N1T–C2T	1.41(1)	N9A–C8A	1.37(1)
N1T–C6T	1.36(1)	N9A–C9A	1.47(1)
N1T–C7T	1.49(1)	C4T–C5T	1.43(1)
N1A–C2A	1.37(1)	C4A–C5A	1.39(1)
N1A–C6A	1.34(1)	C5T–C6T	1.35(1)
N2–C2	1.49(1)	C5T–C8T	1.48(1)
N3T–C2T	1.36(1)	C5A–C6A	1.37(1)
N1–Pt–N1A	89.2(3)	O2T–C2T–N1T	120.0(7)
N1–Pt–N2	178.5(2)	O2T–C2T–N3T	122.3(8)
N1–Pt–N3T	90.3(3)	N1T–C2T–N3T	117.7(7)
N1A–Pt–N2	91.6(3)	N1A–C2A–N3A	126.6(7)
N1A–Pt–N3T	173.4(2)	O4T–C4T–N3T	121.1(7)
N2–Pt–N3T	88.9(3)	O4T–C4T–C5T	120.7(7)
Pt–N1–C1	117.8(6)	N3T–C4T–C5T	118.2(7)
C2T–N1T–C6T	119.6(7)	N3A–C4A–N9A	128.5(7)
C2T–N1T–C7T	118.3(7)	N3A–C4A–C5A	124.4(7)
C6T–N1T–C7T	122.1(7)	N9A–C4A–C5A	107.0(6)
Pt–N1A–C2A	113.7(5)	C4T–C5T–C6T	118.7(7)
Pt–N1A–C6A	125.1(5)	C4T–C5T–C8T	119.7(7)
C2A–N1A–C6A	120.0(7)	C6T–C5T–C8T	121.5(7)
Pt–N2–C2	116.7(6)	N7A–C5A–C4A	109.1(7)
Pt–N3T–C2T	114.8(5)	N7A–C5A–C6A	131.7(7)
Pt–N3T–C4T	122.2(5)	C4A–C5A–C6A	119.2(7)
C2T–N3T–C4T	123.0(7)	N1T–C6T–C5T	122.4(7)
C2A–N3A–C4A	112.7(6)	N1A–C6A–N6A	119.1(7)
C5A–N7A–C8A	104.2(6)	N1A–C6A–C5A	116.8(7)
C4A–N9A–C8A	105.8(6)	N6A–C6A–C5A	124.0(7)
C4A–N9A–C9A	127.1(6)	N7A–C8A–N9A	114.0(6)
C8A–N9A–C9A	127.0(6)		

(39) The CH_3 resonances of the methylamine groups show no signs of signal splitting at 200 MHz. However, prior to complete isotopic exchange of NH_2 *vs* ND_2 in D_2O, the CH_3 resonance displays three components separated by 5.65 Hz. With isotopic exchange complete, only a single resonance with ^{195}Pt satellites (^3J ~ 37 Hz) remains. See also: Pesch, F. J.; Preut, H.; Lippert, B. *Inorg. Chim. Acta* **1990**, *169*, 185.

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(46) A trend to a somewhat shorter Pt–N3T distance (1.973(10) Å) is observed with *cis*-$(NH_3)_2$Pt(1-MeT)Cl: Schöllhorn, H.; Thewalt, U.; Lippert, B. *Inorg. Chim. Acta* **1985**, *106*, 177.

the CH_3NH_2 groups are pointing away from the 1-MeT ligand toward 9-MeA. In principle, an alternating arrangement of the CH_3 groups as obtained by rotation about the Pt–NH_2CH_3 bond could have been expected as well.

There are no peculiarities in the geometries of the two model nucleobases. Compared to the free bases (1-MeTH,[47] 9-MeA[47b,48]), the expected[49] trends in changes of ring angles are observed for thymine only, namely, a compression of the internal ring angle at N3T (127.0(6)° in neutral thymines[47b] *vs* 123.0-(7)° in **4′**) on metal substitution of the proton. In contrast, the expected widening of the internal angle at N1A is below the level of significance (118.8(8)° [47b] *vs* 120.0(7)° in **4′**). Possibly this finding is related to the fact that, unlike for the 1-MeT ring, Pt is substantially out of the coordination plane of 9-MeA (deviation 0.60 Å), which in turn might be a consequence of steric interference between the methyl group C2 and the 9-MeA ring.

The orientation of the two nucleobases shown in Figure 1 is that of the Watson-Crick base pair between A and T(U) with N–CH_3 groups arranged *cis* relative to each other. We are aware that, due to the pseudo-2-fold axis through N3 and C6 of 1-MeT, N1 and C5 as well as C2 and C4 and O2 and O4 might be interchanged in principle; hence, a reversed Watson-Crick arrangement with N–CH_3 groups *trans* to each other or a mixture of both arrangements might be realized in **4′**. Similarly, both Hoogsteen and reversed Hoogsteen pairing are observed in the 1-MeTH, 9-MeA[50] as well as the related 1-Me-5-BrUH, 9-EtA adduct.[51] In the case of **4′**, crystallography does not provide a definitive answer in that switching of N1T and C5T leads to no change in *R* values but very slight changes in temperature factors of several atoms of the 1-MeT ring. On the basis of the solid-state structure, it would seem likely that there is indeed the possibility of rotation of 1-MeT about the Pt–N3T bond in solution, although it may be slow due to steric interference (or H bonding) between the NH_2 protons of CH_3NH_2 and the exocyclic oxygens of 1-MeT (cf. also NMR discussion above). Considering the possibility of reversed Watson-Crick base pairing in parallel-stranded DNA (psDNA),[52] the model character of compound **4′** is maintained in any case.

Cations of **4′** are arranged in pairs (Figure 2) with intermolecular H bonding between N6A and N7A, very much as in adenine hydrochloride.[53] Other intermolecular contacts below 3 Å are between the following sites: exocyclic groups of 1-MeT (O2T, O4T) and water or N2 of CH_3NH_2, N6A of 9-MeA and water, and between water molecules (see supplementary material). Among these H bonds, two involving the water molecule O1W are of particular interest in that they connect the two nucleobases, namely, N6A···OH_2, 2.822(9) Å, and O4T···HOH, 2.751(8) Å. Although the distance between Pt and O1W (3.538(6) Å) is too long to be considered a bond, other features (angles at O1W, 116.4(3)°; O1W roughly coplanar with *trans*-PtTA entity) clearly support the view that this water molecule is of importance in stabilizing the orientation of the two nucleobases. The situation thus is similar to that observed in *trans*-$Cl_2Pt(creat)_2 \cdot 2H_2O$ (creat = creatinine).[54]

Description of the Crystal Structure of 5. *trans*-$[(NH_3)_2Pt$-(1-MeT-N^3)(9-MeA-N^7)]$ClO_4 \cdot 2.5H_2O$ (**5**) crystallizes with two independent molecules in the unit cell as shown in Figure 3. Selected interatomic distances and angles are listed in Table VI. In both cations Pt coordination occurs via N3 of 1-MeT and N7 of 9-MeA. The coordination geometries about Pt are square-planar, with some deviations of the N3T–Pt–N7A angles from 180° (175.2(3)° and 176.4(4)° for molecules 1 and 2, respectively), however. This bending facilitates intramolecular H-bond formation between O4T and N6A, values being 3.15(1) and 3.09-(1) Å, respectively. The deviation from linearity is comparable to that observed in *trans*-$[(NH_3)_2Pt$(1-MeC-N^3)(9-MeA-N^7)]$^{2+}$ (175.6(3)°),[37] but smaller than that in *trans*-$[(CH_3NH_2)_2Pt$(1-MeC-N^3)(9-MeGH-N^7)]$^{2+}$ (172.5(3)°).[21] In both cases, H

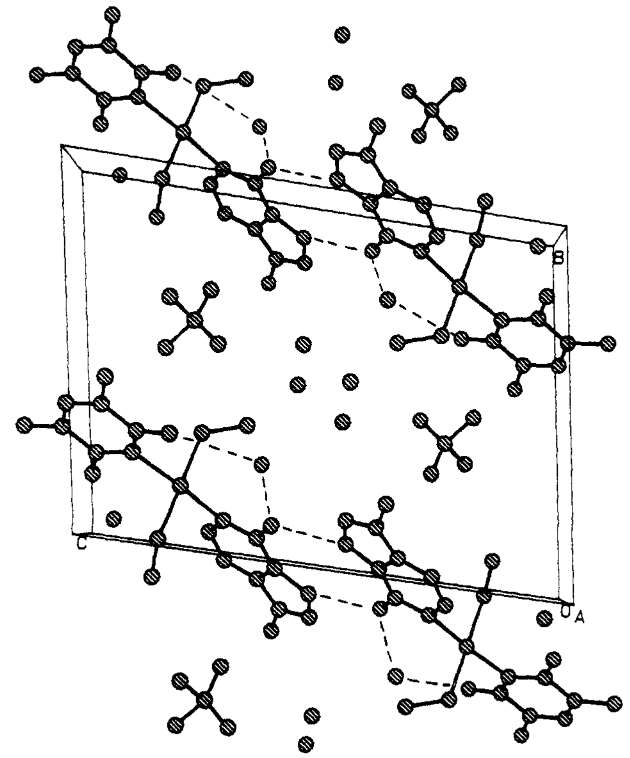

Figure 2. Unit cell packing diagram of **4** with H bonding between adjacent adenines indicated in addition to H bonding with O1W.

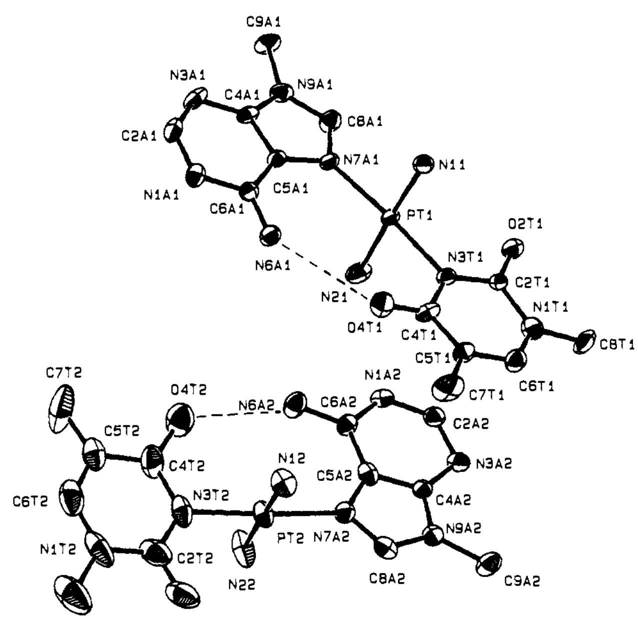

Figure 3. ORTEP drawing (30% probability ellipsoids) and atom-numbering scheme of the two independent cations of *trans*-$[(NH_3)_2Pt$-(1-MeT-N^3)(9-MeA-N^7)]$ClO_4 \cdot 2.5H_2O$ (**5**). Intramolecular H bonds between an exocyclic oxygen of 1-MeT and the amino group 6 of 9-MeA are indicated.

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(53) Kistenmacher, T. J.; Shigematsu, T. *Acta Crystallogr., Sect. B* **1974**, *B30*, 166.
(54) Beja, A. M.; Paixao, J. A. C.; Gil, J. M.; Salgado, M. A. *Acta Crystallogr., Sect. C* **1991**, *C47*, 2333.

Table VI. Selected Interatomic Distances (Å) and Angles (deg) in **5**

Pt1–N7A1	2.022(7)	N1T1–C2T1	1.42(1)
Pt1–N11	2.029(8)	N1T1–C6T1	1.31(2)
Pt1–N21	2.07(1)	N1T1–C8T1	1.48(2)
Pt1–N3T1	2.019(8)	N1T2–C2T2	1.38(2)
Pt2–N7A2	2.015(8)	N1T2–C6T2	1.43(2)
Pt2–N12	2.03(1)	N1T2–C8T2	1.46(3)
Pt2–N22	2.04(1)	N3T1–C2T1	1.37(1)
Pt2–N3T2	1.997(9)	N3T1–C4T1	1.41(1)
		N3T2–C2T2	1.31(2)
N1A1–C2A1	1.35(1)	N3T2–C4T2	1.43(2)
N1A1–C6A1	1.37(1)	C4T1–C5T1	1.35(1)
N1A2–C2A2	1.33(1)	C4T2–C5T2	1.46(2)
N1A2–C6A2	1.32(1)	C5T1–C6T1	1.40(1)
N3A1–C2A1	1.31(2)	C5T1–C7T1	1.47(2)
N3A1–C4A1	1.33(1)	C5T2–C6T2	1.30(3)
N3A2–C2A2	1.35(1)	C5T2–C7T2	1.36(3)
N3A2–C4A2	1.36(1)		
N6A1–C6A1	1.31(1)	O4T1–C4T1	1.21(1)
N6A2–C6A2	1.34(1)	O4T2–C4T2	1.32(2)
N7A1–C5A1	1.39(1)	O2T1–C2T1	1.24(1)
N7A1–C8A1	1.30(1)	O2T2–C2T2	1.23(2)
N7A2–C5A2	1.37(1)		
N7A2–C8A2	1.31(1)	N7A1–Pt1–N11	91.5(3)
N9A1–C4A1	1.31(1)	N7A1–Pt1–N21	89.9(3)
N9A1–C8A1	1.34(1)	N7A1–Pt1–N3T1	175.2(3)
N9A1–C9A1	1.54(1)	N11–Pt1–N21	178.3(3)
N9A2–C4A2	1.33(1)	N11–Pt1–N3T1	89.0(3)
N9A2–C8A2	1.33(1)	N21–Pt1–N3T1	89.7(3)
N9A2–C9A2	1.50(1)	N7A2–Pt2–N12	90.2(4)
		N7A2–Pt2–N22	89.6(4)
C4A1–C5A1	1.38(1)	N7A2–Pt2–N3T2	176.4(4)
C4A2–C5A2	1.36(1)	N12–Pt2–N22	177.9(5)
C5A1–C6A1	1.40(1)	N12–Pt2–N3T2	90.3(4)
C5A2–C6A2	1.42(1)	N22–Pt2–N3T2	90.1(4)

bonding between exocyclic groups of the two bases also takes place. The difference in H-bond lengths within the two independent cations of **5** obviously arises from differences in dihedral angles between the bases, 4.5° for cation 1 and 12.0° for cation 2. The only other significant differences between the two cations appear to be the tilting of the nucleobases with respect to the Pt coordination plane and the deviations of Pt from the 9-MeA plane. For molecule 1, both bases are essentially perpendicular to the PtN_4 plane (dihedral angles 89.1° for T, 92.8° for A), and Pt1 is essentially in the planes of both nucleobases (deviation maximum 0.07 Å from 9-MeA plane). In molecule 2, only T is at a right angle (89.0°), while A is substantially tilted (78.1°). At the same time, Pt is clearly out of the 9-MeA plane by 0.22 Å. Neither feature is unusual.

The general difficulty in differentiating exocyclic groups of 1-MeT, and hence establishing the correct orientation of the 1-MeT rings with respect to 9-MeA, also holds up for **5**. A detailed analysis of alternative 1-MeT orientations was inconclusive, and attempts to get low-temperature X-ray data failed (cf. Experimental Section). Results from ^1H NMR spectra (*vide infra*) suggest that the existence of different orientations in the solid state, Hoogsteen and reversed Hoogsteen like, is indeed feasible.

Variable Temperature ^1H NMR Spectra of 5. Sharp, single resonances of the nonexchangeable protons of **5** as well as a broad resonance due to the NH_3 groups (with ^{195}Pt satellites of *ca.* 55 Hz) are observed in the ^1H NMR spectra recorded in DMSO-d_6 at ambient temperature. Signals due to the NH_2 protons of the 9-MeA ligand are seen at higher or lower temperature only. For example, in DMSO, this resonance starts to reappear above 40 °C at *ca.* 8.65 ppm, while below 10 °C (DMF) it is split into two components (8.5–9 ppm and 9.5–10 ppm, respectively), with one of these further split below −5 °C (Figure 4). We attribute this behavior (i) to a fast rotation of the amine group about the C6–N6 bond at higher temperatures (rate constants $k = (\pi/2^{1/2})\,\Delta\nu = 410\ s^{-1}$), (ii) to a freezing out of this rotation below 10 °C, and (iii) to a freezing out of a nucleobase (probably 1-MeT) rotation about the Pt–N vector below −5 °C. While freezing out of NH_2 rotors of nucleobases on hydrogen-bond formation[55–57] or metal binding to an adjacent donor site[58,59] are well-known phenomena, additional splitting of the low-field component in this case is satisfactorily explained only if two different hydrogen-bond acceptors for one of the two amino protons are assumed. Logically, the presence of two different rotamers (Chart II) with O4 and O2 being the respective acceptor sites could account for this fact. This interpretation is supported by the concomitant splitting of H8 and CH_3 resonances of 9-MeA below −5 °C. On the basis of the relative intensities of both the low-field NH components and the CH resonances of 9-MeA, it appears that the distribution of the two rotamers is approximately 45:55.

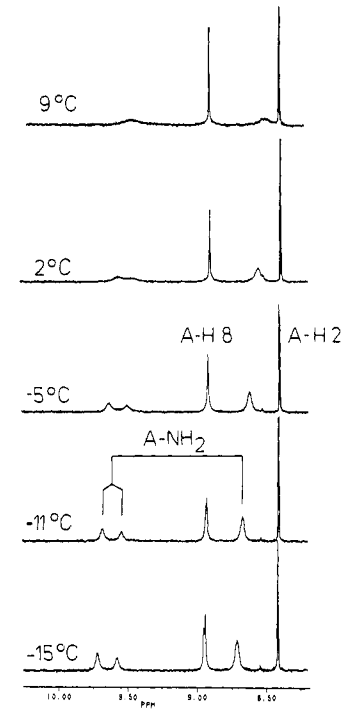
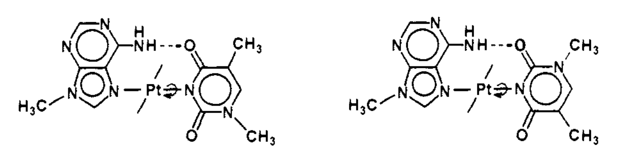


Figure 4. ^1H NMR spectra (DMF-d_7, TMS, low-field region only) of **5** at different temperatures. At room temperature, the NH_2(6) resonance of 9-MeA is not observable.

Chart II



A B

Other Combinations. (i) Noncomplementary Bases. Linking of the two noncomplementary bases thymine and guanine by *trans*-a_2Pt^{II} leads to a complex, *trans*-[(CH_3NH_2)Pt(1-MeT-N^3)-(9-MeGH-N^7)]$^+$ (**8′**), in which the two bases are expected to be close to parallel yet not connected via any intramolecular hydrogen bonding.[60] Since we considered the possibility that a protonated form of **8′**, *trans*-[$(CH_3NH_2)_2$Pt(1-MeTH-N^3)(9-MeGH-N^7)]$^{2+}$,

(55) (a) Shoup, R. R.; Miles, H. T.; Becker, E. D. *Biochem. Biophys. Res. Commun.* **1966**, *23*, 194. (b) Shoup, R. R.; Becker, E. D.; Miles, H. T. *Biochem. Biophys. Res. Commun.* **1971**, *43*, 1350. (c) Raszka, M.; Kaplan, N. O. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 2025.
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(60) This assumption excluded the theoretical possibility that the platinated guanine might be present in an iminol tautomeric form. The IR spectrum of **8** and comparison with related 9-MeG complexes of Pt^{II} do not substantiate this possibility.

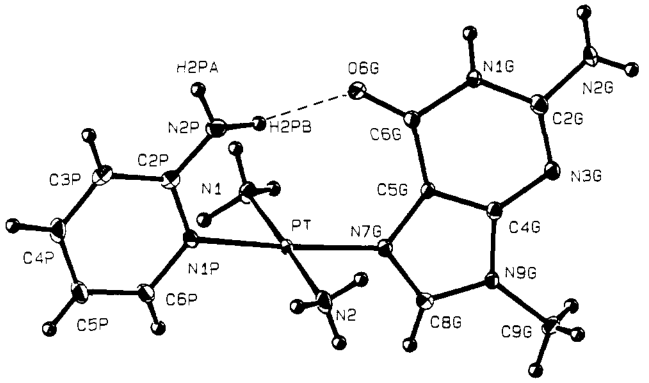
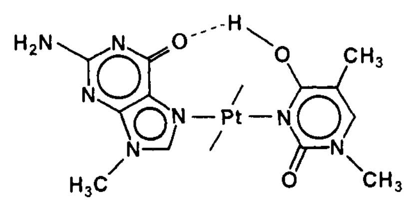


Figure 5. ORTEP drawing (30% probability ellipsoids) and atom-numbering scheme of the cation of *trans*-$[(NH_3)_2Pt(2\text{-}NH_2\text{-py})(9\text{-}MeGH\text{-}N^7)](NO_3)_2$ (**10**) with the intramolecular H bond indicated.

Chart III



8a′, with a hydrogen bond between the two bases (Chart III) might exist, we determined the acid/base equilibria of **8′** in the pH range 0–11.5. pH-dependent ^1H NMR spectra of **8** indicated the following equilibria with $pK_{a1} \sim 0$ and $pK_{a2} = 8.6$.

$$8a' \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} 8' \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} 8b'$$

$$K_1 \qquad K_2$$

The difficulty in protonating **8′** in moderately acidic solution most likely relates to the O4(O2)T···O6G separation (estimated at 3.0–3.1 Å) which, compared to related complexes of *cis*-a_2-Pt^{II},[61] is too long to stabilize a protonated form appreciably. Attempts to isolate **8a′** from solutions of pH <0 have failed so far and instead led to partial displacement of 1-MeTH from the compound.

Deprotonation of the platinated guanine in **8′**, giving *trans*-a_2Pt(1-MeT)(9-MeG), **8b′**, occurs in the typical pH range.[42]

(ii) Pyridine, Purine Base Pairs. The replacement of a pyrimidine nucleobase (1-MeT or 1-MeC) in a metal-modified base pair by a suitable substituted pyridine heterocycle again leads to compounds in which the two bases are arranged in a (nearly) coplanar fashion. The pyridine ligands applied were L = 2-hydroxypyridine and 2-aminopyridine, and the purine base was 9-MeGH, giving *trans*-$[(NH_3)_2Pt(2\text{-}OH\text{-py})(9\text{-}MeGH\text{-}N^7)](NO_3)_2$ (**9**) and *trans*-$[(NH_3)_2Pt(2\text{-}NH_2\text{-py})(9\text{-}MeGH\text{-}N^7)](NO_3)_2$ (**10**). Pt binding through the pyridine ring nitrogen was clearly established by ^1H NMR spectroscopy (^3J coupling of ^{195}Pt with H6 of pyridine (*ca.* 49 Hz (**2**, **9**); *ca.* 45 Hz (**3**, **10**)) and, in the case of **10**, by X-ray crystallography.

(iii) Description of X-ray Structure of 10. The molecular cation of **10** is depicted in Figure 5. Interatomic distances and angles are compiled in Table VII. The overall structure of the cation of **10** is similar to that of *trans*-$[a_2Pt(1\text{-}MeC\text{-}N^3)(9\text{-}EtGH\text{-}N^7)]^{2+}$.[21,62] Specifically, the N7G–Pt–N1py vector is markedly nonlinear (angle at Pt 175.5(2)°) and there is a weak H-bond interaction between O6 of the guanine and the exocyclic amino group of the pyridine ligand (3.235(6) Å). The distance from the amino proton H2PA to O6G is 2.27(6) Å, which is considerably shorter than that between H2PA and Pt (2.63(5) Å). The latter is therefore not considered to be a H bond, even though in complexes of Pd, such contacts (2.66(2) Å);[63] 2.86(7) Å[64]) have been interpreted in terms of weak metal–hydrogen bonds (cf. also ref 44b for discussion on Pt···HN contacts). The Pt is essentially within the plane of the aminopyridine ring but clearly out of the 9-MeGH plane. The planes of the heterocyclic rings are tilted with respect to the PtN_4 plane, 99.8° for aminopyridine and 70.3° for 9-methylguanine, and the angle between the two heterocycles is 14.1°.

Table VII. Selected Interatomic Distances (Å) and Angles (deg) in **10**

Pt–N1P	2.011(4)	N2G–C2G	1.341(7)
Pt–N1	2.038(5)	N2P–C2P	1.347(7)
Pt–N2	2.037(5)	N3G–C2G	1.325(7)
Pt–N7G	2.009(4)	N3G–C4G	1.351(7)
O6G–C6G	1.219(6)	N7G–C5G	1.388(7)
O11–N11	1.238(6)	N7G–C8G	1.321(7)
O12–N12	1.271(6)	N9G–C4G	1.368(7)
O21–N11	1.253(6)	N9G–C8G	1.356(7)
O22–N12	1.255(6)	N9G–C9G	1.478(7)
O23–N12	1.232(6)	C2P–C3P	1.409(7)
O31–N11	1.233(6)	C3P–C4P	1.357(8)
N1G–C2G	1.381(7)	C4P–C5P	1.392(9)
N1G–C6G	1.410(7)	C4G–C5G	1.368(7)
N1P–C2P	1.348(7)	C5P–C6P	1.367(8)
N1P–C6P	1.352(7)	C5G–C6G	1.430(7)
N1P–Pt–N1	87.0(2)	O22–N12–O23	120.8(5)
N1P–Pt–N2	91.9(2)	N1G–C2G–N2G	116.1(5)
N1P–Pt–N7G	175.5(2)	N1G–C2G–N3G	123.6(5)
N1–Pt–N2	178.4(2)	N2G–C2G–N3G	120.3(5)
N1–PT–N7G	93.6(2)	N1P–C2P–N2P	118.3(5)
N2–Pt–N7G	87.6(2)	N1P–C2P–C3P	119.3(5)
C2G–N1G–C6G	125.6(5)	N2P–C2P–C3P	122.3(5)
Pt–N1P–C2P	120.4(3)	C2P–C3P–C4P	120.7(6)
Pt–N1P–C6P	120.4(4)	C3P–C4P–C5P	119.8(5)
C2P–N1P–C6P	119.2(5)	N3G–C4G–N9G	125.0(5)
C2G–N3G–C4G	112.2(4)	N3G–C4G–C5G	128.5(5)
Pt–N7G–C5G	123.2(3)	N9G–C4G–C5G	106.5(5)
Pt–N7G–C8G	130.4(4)	C4P–C5P–C6P	117.5(6)
C5G–N7G–C8G	105.5(4)	N7G–C5G–C4G	109.2(5)
C4G–N9G–C8G	107.2(4)	N7G–C5G–C6G	130.5(5)
C4G–N9G–C9G	126.5(5)	C4G–C5G–C6G	120.2(5)
C8G–N9G–C9G	126.3(5)	N1P–C6P–C5P	123.7(6)
O11–N11–O21	119.3(5)	O6G–C6G–N1G	120.3(5)
O11–N11–O31	119.9(5)	O6G–C6G–C5G	129.8(5)
O21–N11–O31	120.8(5)	N1G–C6G–C5G	109.8(4)
O12–N12–O22	118.4(5)	N7G–C8G–N9G	111.6(5)
O12–N12–O23	120.8(5)		

Among the many intermolecular contacts (cf. supplementary material), only two are below 3 Å, between the guanine amino group N2G and a nitrate oxygen (2.845(7) Å) and between the guanine N1 and a nitrate oxygen (2.991(7) Å).

Discussion

Classification of Metal-Modified Base Pairs. Depending on the nucleobases involved and the respective metal-binding sites, metal-modified base pairs can be classified as follows:

(i) Homopyrimidine and Homopurine Base Pairs. *trans*-$[(NH_3)_2Pt(1\text{-}MeC\text{-}N^3)_2]^{2+}$,[65] *trans*-$[(NH_3)_2Pd(1\text{-}MeC\text{-}N^3)_2]^{2+}$,[66] *trans*-$Cl_2Pd(1\text{-}MeC\text{-}N^3)_2$,[63] *trans*-$[(CH_3NH_2)_2Pt(9\text{-}EtGH\text{-}N^7)_2]^{2+}$,[67] and $[Ag(9\text{-}MeHyxa\text{-}N^7)_2]^+$ [68] are analogs of the

(61) (a) Schöllhorn, H.; Thewalt, U.; Lippert, B. *J. Am. Chem. Soc.* **1989**, *111*, 7213. (b) Lippert, B. *Inorg. Chem. Acta* **1981**, *55*, 5.

(62) A preliminary report for the a = NH_3 compound has appeared: Hitchcock, A. P.; Lock, C. J. L.; Pratt, W. M. C.; Lippert, B. In *Platinum, Gold, and Other Metal Chemotherapeutic Agents*; Lippard, S. J., Ed.; ACS Symposium Series 209; American Chemical Society: Washington, DC, 1983; pp 209–227.

(63) Sinn, E.; Flynn, C. M., Jr.; Martin, R. B. *Inorg. Chem.* **1977**, *16*, 2403.

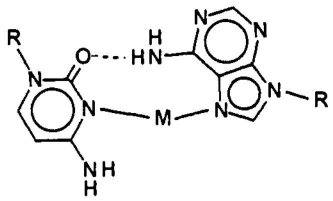
(64) Dehand, J.; Fischer, J.; Pfeffer, M.; Mitschler, A.; Zinsius, M. *Inorg. Chem.* **1976**, *15*, 2675.

(65) (a) Lippert, B.; Lock, C. J. L.; Speranzini, R. A. *Inorg. Chem.* **1981**, *20*, 808. (b) Brown, B. E.; Lock, C. J. L. *Acta Crystallogr., Sect. C* **1988**, *C44*, 611.

(66) Krumm, M.; Mutikainen, I.; Lippert, B. *Inorg. Chem.* **1991**, *30*, 884.

(67) Pesch, F. J.; Wienken, M.; Preut, H.; Tenten, A.; Lippert, B. *Inorg. Chim. Acta* **1992**, *197*, 243.

Chart IV



respective hemiprotonated nucleobase $[CH]^+ \equiv C$[10] and $[GH_2]^+$—GH.[69] Similarly, *trans*-$[(NH_3)_2Pt(7,9\text{-DimeHyxa-}N^1)_2]^{2+}$,[70] Hg(1-MeT-$N^3$)$_2$,[71] Ag(1-MeU),[72] and Ag(1-MeT)[73] (as far as the central AgL_2^- entity is concerned) can be considered metal analogs of the hemideprotonated forms of the respective nucleobases $[LHL]^-$.

(ii) Complementary Bases in a Watson-Crick or Reversed Watson-Crick Arrangement. *trans*-$[(CH_3NH_2)_2Pt(1\text{-MeT-}N^3)(1\text{-MeA-}N^1)]^+$ (**4′**) represents the first and, so far, only example of a metal-modified base pair involving two complementary bases in an orientation as found in a Watson-Crick base pairing scheme (*cis* or *trans*). The other possibility, *trans*-$[a_2Pt(C\text{-}N^3)(G\text{-}N^1)]^+$, has not been realized as yet.

(iii) Complementary Bases in Hoogsteen and Reversed Hoogsteen Arrangement. In *trans*-$[(NH_3)_2Pt(1\text{-MeT-}N^3)(9\text{-MeA-}N^7)]$[5] (**5**), the linear Pt(II) entity connects the two sites which, in Hoogsteen and reversed-Hoogsteen A,T base pairing schemes, are involved in H bonding. The second H bond, between the exocyclic amino group of A and O4(O2) of T, is maintained, albeit it is considerably longer in the metal analog.

A metal analog of the Hoogsteen pair between guanine and protonated cytosine is *trans*-$[a_2Pt(1\text{-MeC-}N^3)(9\text{-RGH-}N^7)]^{2+}$ (a = CH_3NH_2, R = Me;[21] a = NH_3, R = Et[62]). Again, H bonding between $NH_2(4)$ of cytosine and O(6) of guanine is maintained, although it becomes weaker as compared to G≡CH⁺.

(iv) Noncomplementary Bases. A and C as well as G and T(U) are noncomplementary bases, which in nucleic acid normally do not pair via H-bond formation (for a compilation of mismatches see refs 5–12 and 74). However, when linked by a suitable metal, base pair analogs are produced in which planarity of the two bases is maintained. Both in the *trans*-$[(NH_3)_2Pt(1\text{-MeC-}N^3)(9\text{-MeA-}N^7)]^{2+}$ [37] and in $[Ag(1\text{-MeC-}N^3)(9\text{-MeA-}N^7)(H_2O)]^+$,[24] hydrogen bonds between C-O2 and A-N6 are formed (Chart IV), at the expense of the linearity of the (C-N^3)–M–(A-N^7) bond (M = Pt, 175.6°; M = Ag, 165.8°).

In *trans*-$[(NH_3)_2Pt(1\text{-MeC-}N^3)(9\text{-MeA-}N^1)]^+$,[37] which has not been characterized by X-ray crystallography, and likewise in Hg(thymidine-N^3)(guanosine-N^1),[75] the two noncomplementary bases are arranged in a fashion similar to that found in Watson-Crick pairs in that the N3 positions of the pyrimidine and N1 of the purine are involved in metal binding. As in the case of **4′**, intramolecular H-bonding interactions between the bases are excluded because of the large separation, estimated at 3.8–4 Å.

(v) Pyridine Heterocycles and Purine Nucleobases. Ortho-substituted pyridines such as α-aminopyridine, α-hydroxypyridine, or α-pyridonate can mimic a nucleobase in a metal-modified base pair as far as its role in H bonding with a purine nucleobase in a Hoogsteen-like fashion is concerned.

(68) Bélanger-Gariépy, F.; Beauchamp, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 3461.
(69) Mandel, G. S.; Marsh, R. E. *Acta Crystallogr., Sect. B* **1975**, *B31*, 2862.
(70) Orbell, J. D.; Wilkowski, K.; Marzilli, L. G.; Kistenmacher, T. J. *Inorg. Chem.* **1982**, *21*, 3478.
(71) Kosturko, L. D.; Folzer, C.; Stewart, R. F. *Biochemistry* **1974**, *13*, 3949.
(72) Aoki, K.; Saenger, W. *Acta Crystallogr., Sect. C* **1984**, *C40*, 775.
(73) Guay, F.; Beauchamp, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 6260.
(74) For a review on base pair mismatches, see: Kennard, O. In *Nucleic Acids and Molecular Biology*; Eckstein, F., Lilley, D. M. J., Eds.; Springer: Heidelberg, 1987; Vol. 1, pp 25–52.
(75) Buncel, E.; Boone, C.; Joly, H. *Inorg. Chim. Acta* **1986**, *125*, 167.

Table VIII. Comparison of Geometrical Features (Å, deg) of AT Base Pairs and Situations in **4′** and **5**

	Watson-Crick base pair[a]	4′ [b]
N3T···N1A	2.82 Å	4.08 Å
O4T···N6A	2.95 Å	4.74 Å
C9A···C7T	10.44 Å	11.22 Å
N9A–C9A–C7T[c]	56.2°	59.9°
N1T–C7T–C9A[c]	57.4°	64.0°
angle between bases	12°	16.4° [d]
	Hoogsteen base pair[e]	**5[b]**
N3T···N7A	2.93 Å	4.04(1), 4.01(1) Å
O4T···N6A	2.86 Å	3.15(1), 3.09(1) Å
C9A···C8T[c]	8.65 Å	10.50(2), 10.33(2) Å
N9A–C9A–C8T[c]	44°	39.4(6)°, 37.9(7)°
N1T–C8T–C9A	56°	52.7(6)°, 49.8(6)°
angle between bases	0° [f]	4.5°, 12.0°

[a] Reference 59. [b] This work. [c] Angles refer to N(base)–C1′–C1′ in nucleosides and nucleotides. [d] Cf. text. [e] Reference 50a. [f] Cf. 9° in ref 60.

Comparison of the Geometries of Watson-Crick, Hoogsteen, and Metal-Modified Base Pairs. Irrespective of any disorder of the 1-MeT rings in **4′** and **5**, basic structural features of the base pairs in the absence or presence of bound metal can be compared (Table VIII and Figure 6). Reference is made to the Watson-Crick pair found in the ApU dinucleotide[76] and the Hoogsteen arrangement in thymine, adenine model nucleobase pairs.[50,77]

Insertion of the linear *trans*-a_2Pt^{II} entity in the Watson-Crick AT pair causes the following changes: (i) The two bases are pulled apart, by 1.79 Å (O4T···N6A), 1.26 Å (N3T···N1A), and 0.78 Å (C7T···C9A). Thus, while the effect on the interglycoside bond separation (C1′ atoms of sugars) is surprisingly small, the H bond between O4T and N6A is lost. Whether the indirect bonding interaction via a water molecule, as observed in **4′**, is a general phenomenon in these types of compounds is not clear at present. The possibility exists that H bonding via H_2O molecules is equally important in stabilizing metal-modified base pairs in the absence of any other ligands at the metal (amines in **4′**) as it is in nucleobase mismatches.[78] With metal ions adopting a more flexible coordination geometry than Pt^{II}, e.g. Ag^I or Hg^{II} (distorted linear or trigonal-planar), relative magnitudes of distance changes may be reversed, up to the situation where the O4T···N6A hydrogen bond is maintained and the interglycoside distance becomes considerably longer (see also discussion in ref 24). (ii) The pseudosymmetry of the Watson-Crick base pair is lost since N(base)–C1′–C1′ angles become markedly different. (iii) Angles between the two bases cannot always be compared directly since for AT they refer to a propeller-twist, whereas in A–Pt–T they refer to the tilt between two bases. Only in cases where Pt is coplanar with *both* bases does the difference in dihedral angles between the nucleobase and the Pt coordination plane correspond to a propeller-twist. To a first approximation, the bases can be considered close to coplanar, however.

Characteristics of the AT Hoogsteen pair geometry upon insertion of *trans*-a_2Pt^{II} are as follows: (i) Changes in distances between the two bases are inverted as compared to the Watson-Crick orientation, with a substantial widening of the interglycoside bonding distance (1.68–1.85 Å) and a minor widening (0.25–0.39 Å) of the O4T···N6A separation. The N3T···N7A widening (1.1 Å) is similar to that in the Watson-Crick case. Thus, the H bond between the exocyclic groups of A and T is maintained, but clearly weaker than in the absence of *trans*-a_2Pt^{II}. It appears to be (at least in part) responsible for the pronounced nonlinearity of the N3T–Pt–N7A vector. (ii) The N(base)–C1′–C1′ angles,

(76) Seeman, N. C.; Rosenberg, J. M.; Suddath, F. L.; Kim, J. J. P.; Rich, A. *J. Mol. Biol.* **1976**, *104*, 109.
(77) Sakore, T. D.; Tavale, S. S.; Sobell, H. M. *J. Mol. Biol.* **1969**, *43*, 361.
(78) See, e.g.: (a) Poltev, V. I.; Steinberg, S. V. *J. Biomol. Struct. Dyn.* **1987**, *5*, 307. (b) Hunter, W. N.; Brown, T.; Kneale, G.; Anand, N. N.; Rabinovich, G.; Kennard, O. *J. Biol. Chem.* **1987**, *262*, 9962. (c) Hunter, W. N.; Brown, T.; Anand, N. N.; Kennard, O. *Nature* **1986**, *320*, 552.

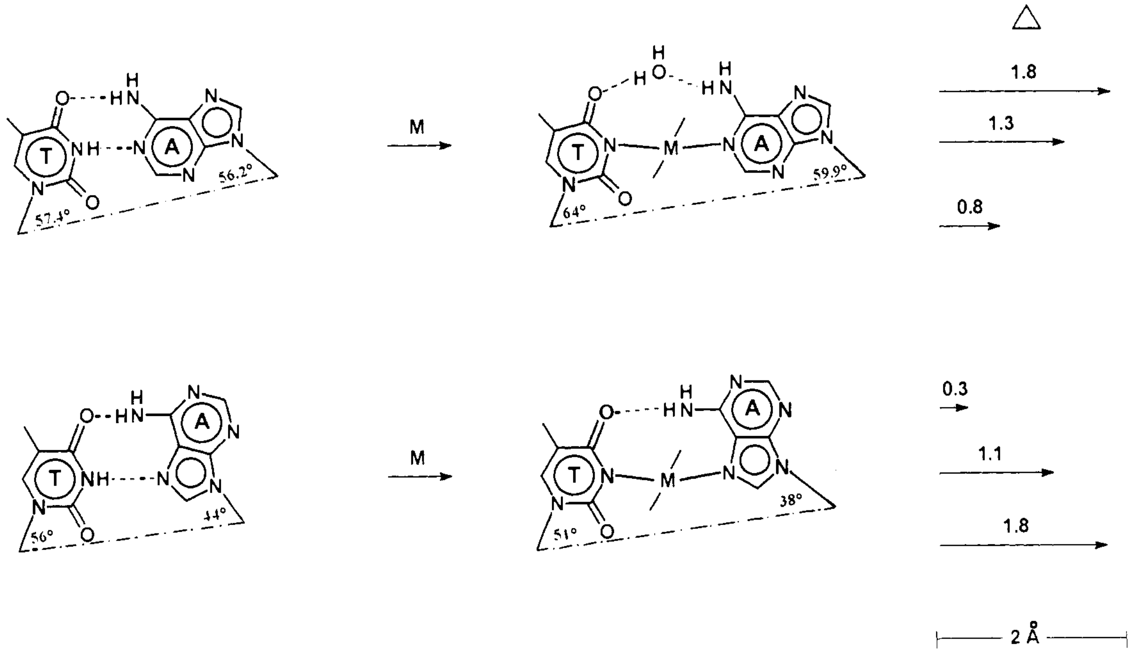
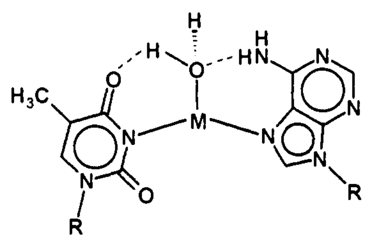


Figure 6. Comparison of Watson-Crick and Hoogsteen AT base pairs with their metalated forms as seen in **4′** and **5**. The increase in interatomic distances (O4T···N6A, N3T···N1A, C1′T···C1′A in Watson-Crick pairs; O4T···N6A, C1′T···C1′A in Hoogsteen pairs) upon *trans*-(am)$_2$Pt^{II} binding are schematically indicated.

Chart V



which in the AT Hoogsteen base pair are already different, are smaller by 3°–6° upon Pt binding but show the same trend as in the absence of the metal. (iii) The metalated bases are close to planar.

Similar changes occur in the G=CH$^+$ Hoogsteen pair upon substitution of H$^+$ by *trans*-a$_2$Pt^{II}.[21,62]

With more flexible ions such as Ag^I or Hg^{II} (see above), the H-bond length between the exocyclic groups at the 6-position (purine) and the 4-position (pyrimidine) could be comparable to that found in the unmetalated Hoogsteen pairs, at the expense of a further slight increase of the interglycoside bond separation. Alternatively, introduction of a ligand already bound to Ag^I or Hg^{II} and capable of H bonding, e.g. H$_2$O, would cause the interglycosidic bond separation to diminish while reshaping the H-bonding situation (Chart V).

Requirements for Coplanar Arrangement of Bases. The (nearly) coplanar arrangement of the heterocyclic rings in **4**, **5**, and **10** as well as *trans*-[a$_2$PtC(GH-*N*^{7})]$^{2+}$ [21,62] and *trans*-[a$_2$PtC(A-*N*^{7})]$^{2+}$ [37] is forced in part by the two *trans*-positioned amine ligands at Pt,[79] but clearly reinforced by *direct* intramolecular H-bond formation (e.g. in **5**, **10**, *trans*-[a$_2$PtC(GH-*N*^{7})]$^{2+}$, and *trans*-[a$_2$PtC(A-*N*^{7})]$^{2+}$) or *indirect* intramolecular H bonding via a water molecule (**4**).

Coplanar arrangement of two nucleobases in the coordination sphere of a metal, with the metal binding through an *endocyclic* donor atom, is restricted to the following geometries: linear (MLL′), square-planar *trans*-X$_2$MLL′, and octahedral *trans*-X$_4$MLL′ (L, L′ = nucleobases, X = other ligands). For steric reasons (bulk of exocyclic groups of nucleobases, interference of these groups with ligands X), it is not possible for any of the other common coordination geometries (trigonal-planar,[80] tetrahedral, *cis*-square planar, *cis*-octahedral) to accommodate two bases in a coplanar fashion. This statement is in accord with presently available X-ray data of metal nucleobase complexes[81] and in particular with the large number of X-ray structures of square-planar bis(nucleobase) complexes *cis*-a$_2$Pt^{II}.[42] There, nucleobases are always substantially (70°–90°) tilted with respect to the metal coordination plane but never coplanar with each other and the Pt plane. If the antitumor activity of *cis*-a$_2$Pt^{II} and the inactivity of the *trans*-isomer is related to a steric distortion of DNA, then this basic difference of the two isomers may be very important.[82] Only if metal binding of at least one of two nucleobases via an *exocyclic* group (e.g. deprotonated amino group, carbonyl oxygen) is allowed, the other common coordination geometries (trigonal-planar, tetrahedral, *cis*-square planar, *cis*-octahedral) are possible. For example, it is even possible to put four uracil nucleobases in a plane and bind them to a central cation, provided binding occurs through the exocyclic oxygens O4.[83]

Relevance: Interstrand DNA Cross-Linking, Antisense Oligonucleotide Chemistry, and DNA Triplexes. The model nucleobase complexes reported in this work could be relevant to the chemistry of *trans*-a$_2$Pt^{II} with A,T-rich regions of DNA. On the other hand, the distribution of *trans*-a$_2$Pt^{II}–DNA adduct has not been studied to the same extent as that of the antitumor agent *cis*-a$_2$Pt^{II},[84] and work with poly(dA-dT) has not been fully conclusive as far as binding patterns are concerned.[85] Studies of reactions of *trans*-a$_2$Pt^{II} with oligonucleotides so far have centered predominantly on reactions with guanine-*N*^{7},[86] even though in one case an *AXG*

(79) This effect is even more pronounced in octahedral complexes of composition *trans,trans,trans*-a$_2$Pt(OH)$_2$L$_2$. See, e.g.: (a) Schöllhorn, H.; Beyerle-Pfnür, R.; Thewalt, U.; Lippert, B. *J. Am. Chem. Soc.* **1986**, *108*, 3680. (b) Dieter, I.; Lippert, B.; Schöllhorn, H.; Thewalt, U. *Z. Naturforsch.* **1990**, *45b*, 731.

(80) Refers to ideal or only weakly distorted trigonal-planar geometry, not to a linear geometry distorted *toward* trigonal-planar as reported in ref 24.

(81) Lusty, J. R., Wearden, P., Moreno, V., Eds. *Handbook of Nucleobase Complexes*; CRC Press: Boca Raton, 1992; Vol. II.

(82) This statement does not refer to long-range 1,*n* cross-links ($n \geq 2$).

(83) Fischer, B.; Preut, H.; Lippert, B.; Schöllhorn, H.; Thewalt, U. *Polyhedron* **1990**, *9*, 2199.

(84) Eastman, A.; Jennerwein, M. M.; Nagel, D. L. *Chem.-Biol. Interact.* **1988**, *67*, 71.

(85) Canuel, L. L.; Teo, B.-K.; Patel, D. J. *Inorg. Chem.* **1981**, *20*, 4003.

(86) (a) van der Veer, J. L.; Ligtvoet, G. J.; van den Elst, H.; Reedijk, J. *J. Am. Chem. Soc.* **1986**, *108*, 3860. (b) Gibson, D.; Lippard, S. J. *Inorg. Chem.* **1987**, *26*, 2275. (c) Lepre, C. A.; Chassot, L.; Costello, C. E.; Lippard, S. J. *Biochemistry* **1990**, *29*, 811.

Chart VI

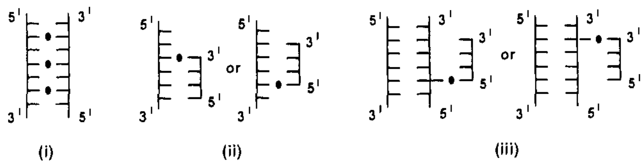
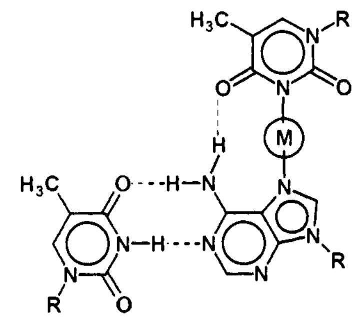


Chart VII



adduct has been studied[87] and a remarkable switch from a *C*G*C*G cross-link to a *CG*C*G* adduct has been reported.[88]

X-ray data of our compounds provide details of steric conditions of cross-links of metal species with a linear (or nearly linear) coordination geometry. These data are therefore relevant also to other metal species such as *trans*-X_2Ni^{II}, *trans*-X_2Pd^{II},Au^{I}, Ag^{I}, or Hg^{II}, for example. The latter metal ion incidentally has a pronounced affinity for A,T sequences in DNA.[89] As evident from our data, cross-linking of A and T bases can occur either in a Watson-Crick or Hoogsteen fashion. In the first case, the metal would generate a slight bulge in DNA due to a moderate increase in the glycosyl bond separation of the two bases, from 10.44 to 11.22 Å. The bulge would be smaller than that caused by the G_{anti}, A_{syn} mismatch (12.5 Å),[5] however, which is readily accommodated in a duplex. In contrast, the metalated Hoogsteen pair (10.33, 10.50 Å) almost exactly fits the requirements of normal DNA as far as interglycosyl distances are concerned. The formation of this cross-link would require only an *anti* → *syn* switch of the N^7-metalated A and subsequent metal binding to N^3 of T, very similar to the case of the corresponding G,C adduct.[62] These considerations have ignored the possible role of other X ligands at the metal, specifically amine ligands in the case of Pt^{II}. While accommodation of two methylamine ligands (as in **4**) in the interior of DNA represents a problem (unless considerable steric distortion is anticipated), NH_3 ligands would probably fit, even though also at the expense of some local structural disturbance.[90] This question will be subject of future work.

The model compounds reported here and previously[21,62] suggest several applications, which we are presently studying in our laboratory (Chart VI): (i) the formation of M-DNA, in which metals (M) adopting a linear geometry substitute protons of a H bond between complementary nucleobases in a highly regular fashion;[91] (ii) metalated oligonucleotides applicable to antisense strategy with a single-stranded target molecule; and (iii) metalated nucleotide triplexes, in which a metalated oligonucleotide acts as the third strand of a duplex. As to points ii and iii, it is the hypothesis that the unmetalated bases of the metal–oligonucleotide accomplish (fast) recognition of the target, while the metal is responsible for irreversible cross-linking. With *trans*-$(NH_3)_2$-Pt^{II}, any steric effect of the ammonia ligands should be minimal if the platinated base is either at the 3′ or 5′ end of the metalated oligonucleotide. Compound **5** can therefore also be regarded a model for the interaction of a platinated T within an oligonucleotide with A of an AT base pair, similar to the situation in the CG–Pt–C base triple (Chart VII).[21] This strategy complements other attempts to irreversibly bind a designed oligonucleotide to a target RNA or DNA via photochemistry,[92] alkylation,[93] or the use of Pt.[94,95]

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Asta Medica (loan of K_2PtCl_4). We wish to thank M. Lutterbeck for the preparation of the drawings and S. Menzer for the low-temperature spectra of **5**.

Supplementary Material Available: Listings of positional and thermal displacement parameters of **4′**, **5**, and **10**, intramolecular distances and angles of **5**, intermolecular distances and angles of **4′**, **5**, and **10**, tables of least-squares planes, unit cell packing diagrams of **5** and **10**, and selected IR and ^{1}H NMR data of compounds (32 pages); listing of observed and calculated structure factors for **4′**, **5**, and **10** (80 pages). Ordering information is given on any current masthead page.

(87) Lepre, C. A.; Strothkamp, K.-G.; Lippard, S. J. *Biochemistry* **1987**, *26*, 5651.
(88) Comess, K. M.; Costello, C. E.; Lippard, S. J. *Biochemistry* **1990**, *29*, 2102.
(89) Nandi, U. S.; Wang, J. C.; Davidson, N. *Biochemistry* **1965**, *4*, 1687.
(90) Any major distortion could be eased by H bonding between NH_3 and donor sites of the base pairs below and above the cross-link.
(91) For related work, see, e.g.: (a) Shin, Y. A.; Eichhorn, G. L. *Biopolymers* **1980**, *19*, 539. (b) Daune, M.; Dekker, C. A.; Schachman, H. K. *Biopolymers* **1966**, *4*, 51.
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