Metalated Nucleobase Quartets: Dimerization of a Metal-Modified Guanine, Cytosine Pair of *trans*-$(NH_3)_2Pt^{II}$ and Formation of CH···N Hydrogen Bonds

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Abstract: The X-ray crystal structures of two complexes of the composition *trans*-[$Pt(NH_3)_2$(9-EtG-*N7*)(1-MeC-*N3*′)]X·nH_2O (**1**) with 9-EtG = 9-ethylguaninate and 1-MeC = 1-methylcytosine are reported. **1b** (X = picrate, $n = 1$) crystallizes to produce a dimetalated base quartet, held together by H-bonding interactions between pairs of cations. This feature essentially corresponds to the solution structure previously proposed by us on the basis of ^{1}H NMR and ESI-MS, with a H-bonding interaction between the aromatic H5′ proton of 1-MeC and the deprotonated N1 position of 9-EtG. **1c** (X = trifluoromethanesulfonate, $n = 0$) crystallizes in a radically different fashion as a consequence of nucleobase rotation about the Pt−N bond, leading to a reversed Hoogsteen arrangement without any intracomplex H bonding between the two bases. In the solid-state structure of **1b** short intermolecular H bonds exist between the exocyclic NH_2 group of 1-MeC and O6 of 9-EtG (2.715(7) Å). Considerably longer intra- (N4′(1-MeC)···O6(9-EtG), 3.229(6) Å) and intermolecular (C5′(1-MeC)···N1(9-EtG), 3.548(7) Å) H bonds are primarily a consequence of considerable base twisting, presumably caused by stacking between the guanine residues and the picrate anions. In DMSO-d_6 solution, the cyclic base quartet structure is favored, regardless of the nature of the anion X (X = picrate, trifluoromethanesulfonate, perchlorate, nitrate). An association constant $K_D = 44.1 \pm 3.2$ M^{-1} for the dimerization has been determined.

Introduction

Substitution of a proton involved in H bonding between two nucleobases by a metal entity of suitable geometry generates complexes that are to be considered "metal-modified base pairs".[1,2] These pairs can be converted into base triplets, either by H bonding to a third base[3] or by additional "metal-modification"[4] (Chart 1, i and ii). As we have recently found, "metal-modified base pairs" can also self-associate via H bond formation to give open[5] or cyclic[6] base quartets (Chart 1, iii and iv). The latter situation is of particular interest since it relates to nucleobase quartets and tetrastranded nucleic acid structures.[7] The role of metal ions in stabilizing tetrastranded DNA[7] or RNA[7] is to bind to carbonyl oxygen atoms of four or eight bases, as also seen in model systems,[8] rather than to cross-link bases as in the present case. There is reason to believe that even more ways to stabilize nucleobase quartets are possible, e.g. by ammine ligands bound to a metal.[8]

Situation (iv) had been encountered by us for *trans*-[$Pt(NH_3)_2$(9-EtG-*N7*)(1-MeC-*N3*′)]ClO_4 (**1a**) according to ^{1}H NMR data obtained in DMSO-d_6 solution and ESI mass spectrometry of a MeOH solution.[6,9] The most intriguing feature of the metalated cyclic base quartet was the existence of two H bonds between the aromatic H5′ proton of 1-MeC and the deprotonated ring nitrogen atom N1 of 9-EtG each. To the best of our knowledge, this had been the first report of this type of H bonding between two nucleobases. Attempts to grow single crystals of **1a** suitable for X-ray crystallography had been unsuccessful for a long time. We finally were able to obtain crystals of the picrate (**1b**), the trifluoromethanesulfonate (**1c**), and the nitrate salt (**1d**). Eventually, only **1b** and **1c** permitted full structure determinations.

Experimental Section

Preparations. 9-Ethylguanine (9-EtGH) was purchased from Chemogen, Konstanz (Germany) and 1-methylcytosine was prepared

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(9) Abbreviations used: 9-MeA = 9-methyladenine; 9-EtGH = 9-ethylguanine; 9-EtG = 9-ethylguaninate anion (deprotonated at N1); 7,9-DimeG = 7,9-dimethylguanine; 1-MeC = 1-methylcytosine; 1-MeU = 1-methyluracil anion; Pt donor sites are indicated by *N7*, *N3*, etc.; ESI-MS = electrospray ionization mass spectrometry.

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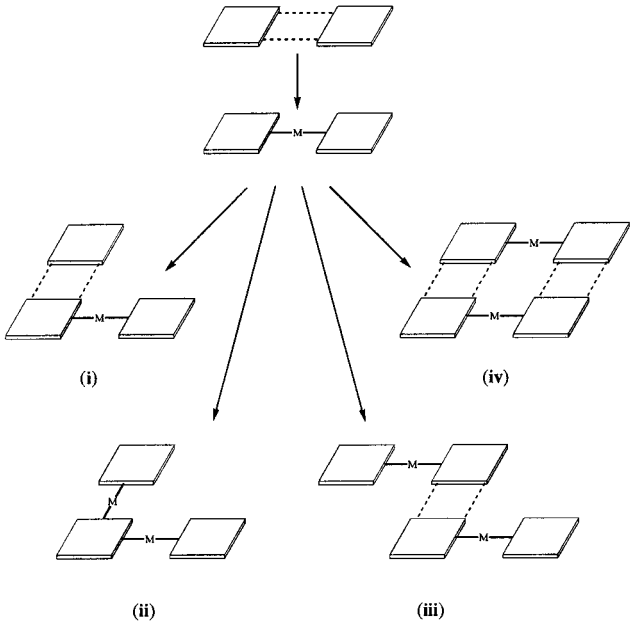
Chart 1



according to ref 10. *trans*-$[(NH_3)_2PtCl_2]$ was synthesized according to the method of Kauffman and Cowan[11] from K_2PtCl_4 (Degussa (Germany)). The synthesis of *trans*-$[Pt(NH_3)_2$(9-EtG-*N7*)(1-MeC-*N3′*)$]ClO_4$ (**1a**) from *trans*-$[Pt(NH_3)_2$(9-EtGH-*N7*)(1-MeC-*N3′*)$](ClO_4)_2$[5a] has been reported.[6]

***trans*-[Pt(NH$_3$)$_2$(9-EtG-*N7*)(1-MeC-*N3′*)](C$_6$H$_2$N$_3$O$_7$)·H$_2$O (1b)** was prepared by combining aqueous solutions of *trans*-$[Pt(NH_3)_2$(9-EtGH-*N7*)(1-MeC-*N3′*)$](NO_3)_2$ (15 mL, c = 10 mM) and of picric acid (15 mL, c = 10 mM), both brought to pH 10.7 (NaOH). The orange precipitate that formed immediately was redissolved by stirring the mixture at 80 °C under N_2. The solution was slowly cooled to room temperature and kept for several weeks under exclusion of air, before the orange microcrystalline powder that had formed was filtered off, washed with water, and dried at 40 °C. The yield of **1b** was 82%. Recrystallization from a dilute ethanolic solution and slow evaporation of the alcohol gave larger crystals which were suitable for X-ray analysis. Anal. Calcd (found) for $C_{18}H_{25}N_{13}O_{10}Pt$: C 27.77 (27.6); H 3.24 (3.3); N 23.39 (23.4).

***trans*-[Pt(NH$_3$)$_2$(9-EtG-*N7*)(1-MeC-*N3′*)](CF$_3$SO$_3$) (1c).** *trans*-$[Pt(NH_3)_2$(9-EtGH-*N7*)(1-MeC-*N3′*)$](ClO_4)_2$ (217 mg, 0.3 mmol) was dissolved in water (20 mL) and passed over an anion exchange column that had been loaded with chloride. The eluate was evaporated to dryness to give *trans*-$[Pt(NH_3)_2$(9-EtGH-*N7*)(1-MeC-*N3′*)$]Cl_2$ (167 mg). To an aqueous solution of *trans*-$[Pt(NH_3)_2$(9-EtGH-*N7*)(1-MeC-*N3′*)$]Cl_2$ (8 mL, c = 16.5 mM) was added $AgCF_3SO_3$ (0.95 equiv), and the mixture was stirred in the dark at room temperature overnight. After removal of AgCl, the solution was brought to pH 10.7 with 1 M NaOH and then allowed to evaporate slowly at room temperature under N_2. A small amount of crystalline platelets of **1c** suitable for X-ray analysis was isolated.

***trans*-[Pt(NH$_3$)$_2$(9-EtG-*N7*)(1-MeC-*N3′*)](NO$_3$)·*x*H$_2$O (1d).** *trans*-$[Pt(NH_3)_2$(9-EtGH-*N7*)(1-MeC-*N3′*)$](NO_3)_2 \cdot H_2O$ (26 mg, 39 μmol) was dissolved in water (3 mL) and brought to pH 10.7 (NaOH). Slow evaporation of the solution at room temperature under N_2 gave a few crystals of **1d** of poor quality which allowed no full structure determination.

Instrumentation. ^{1}H NMR spectra were recorded at 20 °C on a Bruker AC 200 FT NMR spectrometer with DMSO-d_6 (with TMS as internal standard) as solvent without suppression of solvent signals. The NOESY spectrum was recorded on a Bruker DRX 400 spectrometer at 400.13 MHz and processed with standard software (uxnmr by Bruker). Elemental analysis was performed with a Carlo Erba Model 1106 Strumentazione Element-Analyzer. The stability constant was calculated on an IBM-compatible PC with a curve fitting procedure that used a nonlinear Newton−Gauss least-squares program (see also below).

Determination of the Association Constant. The experimental conditions of the dilution experiment were the same as described in ref 6. At different concentrations of **1a** in DMSO-d_6, the chemical shifts of H5′, H6′, and the two hydrogen atoms at N4′ of 1-MeC were evaluated for the calculation of the stability constant for the dimerization by application of eq 1, which provides the relationship for the observed

$$\delta_{obs} = \delta_D + (\delta_D - \delta_o)\frac{1 - (8K_D[A] + 1)^{1/2}}{4K_D[A]} \quad (1)$$

chemical shift (δ_{obs}) and the various concentrations of the cation **1**[A]. Equation 1 was derived in analogy to ref 12 where the self-association of nucleosides and nucleotides was investigated. δ_o represents the chemical shift of the protons at infinite dilution (i.e., when only monomers are present in solution), δ_D represents the shift of the dimer, and K_D is the association constant as defined in eqs 2a and 2b.

$$A + A \rightleftharpoons A_2 \quad (2a)$$

$$K_D = [A_2]/[A]^2 \quad (2b)$$

The unknown parameters were determined by starting an iterative calculation with estimated values and varying them until the standard deviation reaches a minimum (nonlinear Newton−Gauss least-squares regression).

Distance Calculation in Solution. The NOESY spectrum was taken at a spectral width of 4802 Hz with a mixing time of 400 ms. The sample concentration was 17 mM, corresponding to a dimerization degree of 41.1 ± 2.1%. 256 FIDs of 1 K data points each were recorded in a phase-sensitive mode using the TPPI method.[13] Data were zero-filled to a final size of 2 K × 1 K data points and multiplied by a 90° shifted, squared sine bell window function prior to Fourier transformation. A fifth order polynomial baseline correction in both dimensions was performed before integration. Integrals of cross-peaks between $N2H_2$/H5′, $N2H_2$/H6′, and H5′/H6′, respectively, were computed by adding all signal intensities within manually chosen integration regions (uxnmr). Distances between the $N2H_2$ protons of guanine and the H5′ and H6′ protons of cytosine were calculated with eq 3[14]

$$r_1 = r_{H5'-H6'}\left(I_{H5'-H6'}\frac{x_D}{I}\right)^{1/6} \quad (3)$$

on the basis of a r^6 dependency of the cross-peak integrals I, using the H5′−H6′ distance of cytosine ($r_{H5'-H6'}$ = 2.4 Å) and the integral of the cytosine H5′/H6′ cross-peak $I_{H5'-H6'}$ as references and taking into account that only dimers give rise to $N2H_2$/H5′ and $N2H_2$/H6′ cross-peaks, while all molecules contribute to the H5′/H6′ cross-peak. x_D corresponds to the molar fraction of cations **1** forming dimers.

X-ray Structure Determination of 1b and 1c. All X-ray data were collected on an Enraf-Nonius-KappaCCD diffractometer[15] with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). Preliminary orientation matrixes and unit cell parameters were obtained from the peaks of the first 10 frames, respectively, and refined by using the whole data set of 360 frames. Frames were integrated and corrected for Lorentz and polarization effects by using DENZO.[16] The scaling as well as the global refinement of crystal parameters was performed by SCALEPACK.[16] Reflections, which were partly measured on previous and following frames, are used to scale these frames on each other.

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Table 1. Crystallographic Data for *trans*-[Pt(NH_3)$_2$(9-EtG-*N7*)(1-MeC-*N3′*)]($C_6H_2N_3O_7$)·H_2O (**1b**) and *trans*-[Pt(NH_3)$_2$(9-EtG-*N7*)(1-MeC-*N3′*)](CF_3SO_3) (**1c**)

	1b	**1c**
formula	$C_{18}H_{25}N_{13}O_{10}Pt$	$C_{13}H_{21}N_{10}O_5SF_3Pt$
fw (g mol^{-1})	778.60	681.55
crystal system	triclinic	monoclinic
space group	$P\bar{1}$ (No. 2)	$P2_1$ (No. 4)
crystal color	red	colourless
crystal habit	block	columns
a (Å)	8.884(2)	10.562(2)
b (Å)	10.670(2)	7.291(1)
c (Å)	15.620(3)	15.259(3)
α (deg)	74.23(3)	
β (deg)	76.75(3)	106.81(3)
γ (deg)	67.19(3)	
V (Å^3)	1300.6(5)	1124.8(3)
Z	2	2
data/obsd[a]/params.	34933/3399/396	31561/2574/266
R_1(obsd data)[b]	0.0301	0.0380
wR_2(obsd data)[c]	0.0595	0.0792
GOF[d]	1.016	1.086

[a] Observation criterion $I > 2\sigma(I)$. [b] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$. [d] GOF $= [\sum w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$, with n = number of reflections and p = number of parameters.

This procedure in part eliminates absorption effects and also considers a crystal decay if present.

All structures were solved by standard Patterson methods[17] and refined by full-matrix least-squares based on F^2, using the SHELXTL PLUS[18] and SHELXL-93 programs.[19]

1b: Data collection was performed with a collecting time of 50 s per frame. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrical calculated positions except for the aromatic hydrogens of the nucleobases, which were found with difference Fourier syntheses, and refined with a common isotropic temperature factor.

1c: The collection time of the intensity data was 60 s per frame. The non-hydrogen atoms were refined anisotropically, except for the disordered ethyl group, which was modeled with occupancies of 0.44 (C92A) and 0.56 (C92B), and the atoms of the anion except for sulfur. Hydrogen atoms were included at calculated positions but not refined.

Crystal data and data collection parameters are summarized in Table 1.

Results and Discussion

Solution Behavior. All four compounds **1a**−**1d** behave identically in DMSO-d_6 solution as far as the concentration dependency of the H5′ proton and of one of the 4′-amino protons of the 1-MeC is concerned (Figure 1). This clearly indicates that the monomer ⇌ dimer equilibrium postulated for **1a** does not depend on the anion. The concentration-independent shift of the picrate proton resonance of **1b** (8.59 ppm; 0.6−30.5 mM) further confirms this conclusion. Comparison of the chemical shifts (DMSO-d_6) of H5′ and H6′ cytosine resonances of **1a**-**1d** with *trans*-[Pt(CH_3NH_2)$_2$(1-MeC)$_2$]$^{2+}$ [20] reveals the following: At concentrations where the H5′ chemical shift is more or less constant (≥0.1 M; δ(H5′) ≈ 7.2 ppm), this resonance is downfield by 1.2 ppm in **1**, whereas the H6′ resonances in the compounds differ very slightly only. This is so despite the fact that as a consequence of guanine deprotonation in **1**, actually a slight upfield shift of the 1-MeC resonances as compared to *trans*-[Pt(CH_3NH_2)$_2$(1-MeC)$_2$]$^{2+}$ might have been expected. As to the resonance of the amino group of 1-MeC, it is split in a 1:1 ratio at the lowest concentration applied and at concentrations ≥10 mM (Figure 1). Splitting of this resonance is to be attributed to either of the three following reasons or combinations thereof: (i) binding of a Pt electrophile at N3′, which increases the double bond character of the C4′−N4′ bond and hence makes fast rotation of the amino group more difficult, (ii) anion binding to the amino proton,[21] or (iii) H bonding in general. In the present case, it is to be considered a combination of (i) and (iii). Clearly, the concentration dependency of one of the two components reflects its involvement in *intermolecular* association. The second component of the NH_2 resonance, downfield from the former only at very low concentrations but otherwise little affected (9.1−9.2 ppm), has to be due to an *intramolecularly* H bonded proton (viz. to O6 of 9-EtG, as seen in the solid-state structure of **1b**). Only if H bonded can the relatively large downfield shift of this resonance be explained.[22] For example, in cases with no intramolecular H bond formation possible, such as in *trans*-[Pt(CH_3NH_2)$_2$(1-MeC)Cl]Cl, the amino protons of 1-MeC resonate at considerably higher field, at 8.29 and 8.72 ppm.[23] The NH_2 resonance of 9-EtG is almost concentration-independent and therefore practically does not participate in the association process.

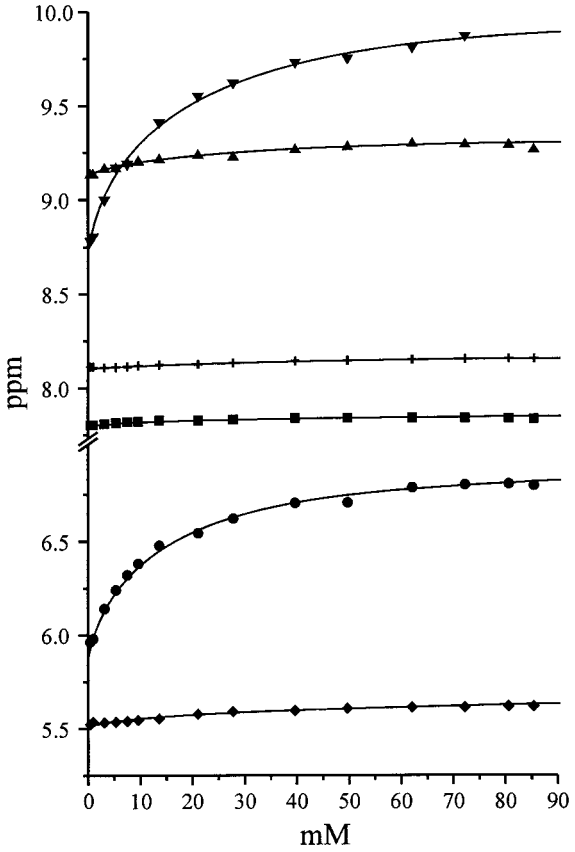

Figure 1. Concentration dependency of the chemical shifts of **1** in DMSO-d_6 in the concentration range 0−85 mM. The data from top to bottom correspond to N4′H^2 (▼) and N4′H^1 (▲) of 1-MeC, H8 (+) of 9-EtG, H6′ (■) and H5′ (●) of 1-MeC, and N2H$_2$ (◆) of 9-EtG.

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Table 2. Individual Results Obtained from the Curve Fitting Procedure Based on Eq 1 for the Dimerization of **1** in DMSO-d_6 (20 °C)[a]

	δ_0 [ppm]	δ_∞ [ppm]	K_D* [M^{-1}]	K_D [M^{-1}]
H5′	5.911 ± 0.012	7.213 ± 0.013	45.8 ± 4.5	44.1 ± 3.2
H6′	7.799 ± 0.002	7.853 ± 0.002	45.3 ± 11.5	
N4′H^2	8.695 ± 0.013	10.419 ± 0.018	41.7 ± 5.1	

[a] δ_0 corresponds to the calculated chemical shift of the monomer whereas δ_∞ is the calculated shift of the dimer species. Both protons involved directly in dimerization (H5′ and N4′H^2) as well as the neighboring proton H6′ (all from the cytosine moiety) were evaluated giving three individual results for the association constant K_D*. The final association constant K_D (see eqs 2a and 2b) in the column to the right corresponds to the weighted mean of the four results in the fourth column with two times the error limit. All other error limits correspond to one standard deviation.

For determination of the association constant the data sets of the 1-MeC resonances H5′, H6′, and N4′H$_2$ (the proton of the amino group of 1-MeC, which is directly involved in the *intermolecular* H bond) were evaluated. The individual association constants (K_D*), which are given in Table 2, were calculated by applying eq 1. The concentration range of the cation **1** was between 0.47 and 72.2 mM for all three protons used for evaluation because at larger concentrations only the H5′ and H6′ resonances yet not the one from the amino proton could be detected. The concentration dependency is much larger with H5′ and the amino group than with H6′. However, this finding is not surprising because the latter one itself is not involved in hydrogen bonding. Still, the value obtained agrees excellently with the values obtained for H5′ and the amino proton. The final constant for the dimerization

$$K_D = 44.1 \pm 3.2\ M^{-1}$$

as it is defined by eqs 2a and 2b, corresponds to the weighted mean of the three individual constants K_D* obtained for H5′, H6′, and N4′H$_2$. The error given is two times the standard deviation. It should be noted that all data sets could be fitted with this final result by keeping K_D constant and varying only δ_0 and δ_∞, which correspond to the calculated chemical shifts of the monomer or the dimer, respectively. The calculated results for δ_0 and δ_∞, obtained with K_D, are shown in Table 2.[24]

The other amino proton of 1-MeC which itself is involved in the *intramolecular* H bond and also the data sets of H8 and the amino group of 9-EtG could be fitted with this result as well, even though the resonances are only slightly affected in these cases by the dimerization.

The value $K_D = 44.1 \pm 3.2\ M^{-1}$ obtained for the dimerization of **1** compares with $K = 3.7 \pm 0.6\ M^{-1}$ for the Watson−Crick pair between guanosine and cytidine at 32 °C in the same solvent[25] and with $K = 6.7 \pm 0.2\ M^{-1}$ (30 °C) for a 2:1 mixture of DMSO and methanol.[26] Provided compound **1** could be derivatized to make it soluble in aprotic solvents, very high association constants could indeed be expected.

X-ray Crystal Structure of 1b: A Diplatinated Nucleobase Quartet. A view of the cation, anion, and water molecule of *trans*-[Pt(NH$_3$)$_2$(9-EtG-*N7*)(1-MeC-*N3*′)](C$_6$H$_2$N$_3$O$_7$)·H$_2$O (**1b**) is depicted in Figure 2. Selected interatomic distances and angles of **1b** are listed in Table 3 and compared with those of the trifluoromethanesulfonate salt **1c**. In **1b** the two bases are bound to Pt via the guanine *N7* and cytosine *N3*′ positions and adopt a Hoogsteen arrangement with the *N3*′ proton of cytosinium replaced by the *trans*-(NH$_3$)$_2$Pt^{II} residue, very much like the two bases of the parent compound *trans*-[(NH$_3$)$_2$Pt(9-EtGH)(1-MeC)]$^{2+}$.[5a] As far as the overall geometry of the complex is concerned, there are several differences between the parent compound (isolated as two slightly different modifications) and **1b**: Among these, the *N7*(guanine)-Pt-*N3*′(cytosine) angle (178.4(2)° in **1b**, but 175.0(2)° in one of the two modifications of the parent complex[5a]) and the considerably higher propeller twist between the two bases in **1b** (20°) as compared to the starting compound (5.5° and 6.3°) need to be mentioned. Both features add up to a considerably longer intramolecular O6···N4′ separation in **1b** (3.229(6) Å) as compared to *trans*-[Pt(NH$_3$)$_2$(9-EtGH)(1-MeC)](ClO$_4$)$_2$·*n*H$_2$O (3.00(2) and 3.11(1) Å)[5a] or related mixed purine-*N7*, pyrimidine-*N3*′ nucleobase complexes of *trans*-(NH$_3$)$_2$Pt^{II}.[1,3,5,27] We are aware that the angles at the Pt coordination sites, e.g., Pt−N7−C5, Pt−N7−C8 and Pt−N3′−C2′, Pt−N3′−C4′, likewise have an influence on this intracomplex distance.[5b,28] Another difference refers to the intramolecular ring angle at N1 of guanine, which is significantly smaller in **1b** (120.0(5)°) as compared to the starting compound (127.3(7)° and 128(1)°) or neutral guanine in general,[29,30] and reflects deprotonation of the N1 position in **1b**.[31] It appears that the propeller twist of the two bases in **1b** is primarily caused by the picrate anion, which

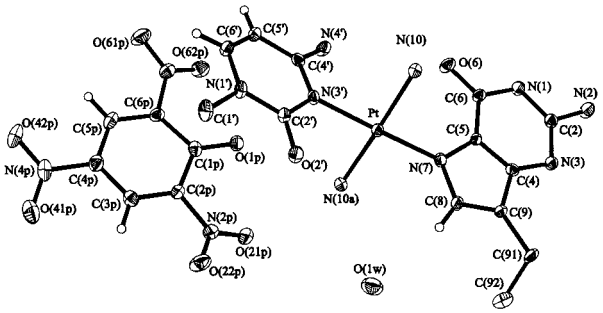

Figure 2. Cation *trans*-[Pt(NH$_3$)$_2$(9-EtG-*N7*)(1-MeC-*N3*′)]$^+$, picrate anion, and water molecule of compound **1b** with atom numbering scheme. Ellipsoids are at the 50% probability level.

Table 3. Selected Dihedral Angles (deg) and H-Bonding Distances (Å) in the Crystal Structures of **1b** and **1c**

	1b	**1c**
N7−Pt−N3′	178.4(2)	174.2(4)
C6−N1−C2	120.0(5)	120(1)
G/C	20.2(3)	6.0(4)
Pt−N7	2.008(4)	1.986(8)
Pt−N3′	2.024(4)	2.022(8)
N4′···O6a	2.715(7)	
N4′···O6	3.229(6)	
O2···O6		4.35(1)
C5′···N1	3.548(7)	
N4′···N1		2.80(1)
N2···N3a	3.229(6)	
N10···O2′		2.91(3)/2.95(3)
N10···O6		2.92(3)/2.86(3)

(24) The previously[6] obtained association constant ($K_D = 59.1 \pm 1.0\ M^{-1}$) is sligthly higher than the one calculated now, but has been calculated with a different method.

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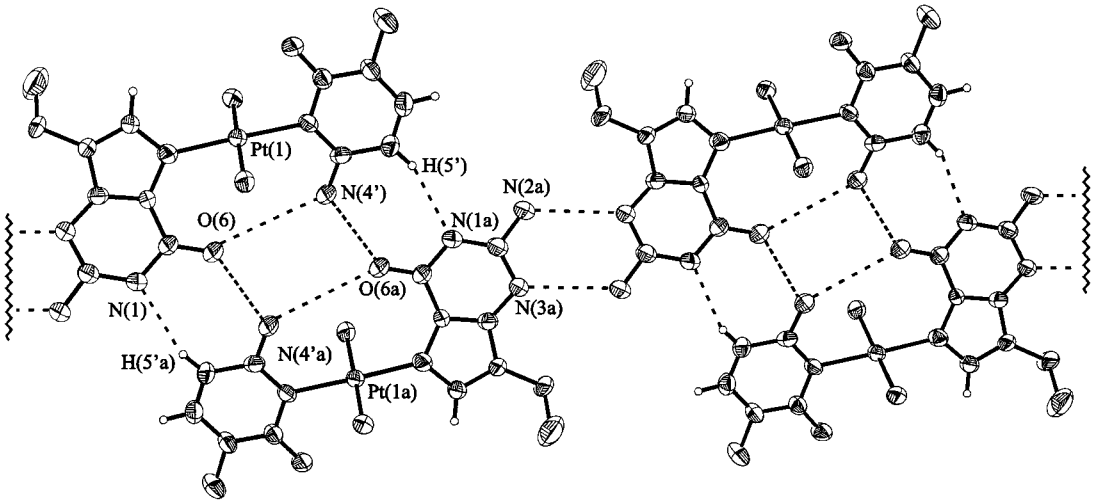


Figure 3. Association of quartets of **1b**. Hydrogen atoms are not found in the Fourier-difference map; the water molecules as well as the picrate anions are omitted for clarity.

stacks on top of the guanine base. The guanine moiety and the aromatic ring of the picrate anion are nearly coplanar (deviation 2°) and 3.5 Å apart.

A view of the way cations of **1b** are associated via H bonds is given in Figure 3. Essentially the arrangement deduced by ^{1}H NMR spectroscopy is verified. The two *trans*-[Pt(NH$_3$)$_2$(9-EtG)(1-MeC)]$^+$ cations are connected by two short intermolecular H bonds between O6 sites of guanine and N4′ sites of cytosine. The length, 2.715(7) Å, is definitely at the lower end of H bonds typically found between nucleobases.[32] On the other hand the two separations between C5′ of the cytosine and N1 of guanine are rather long, 3.548(7) Å. Since the proton at C5′ was located in the difference Fourier synthesis, details of this contact can be quantified: C5′−H5′, 0.88(5) Å, H5′−N1, 2.71(6) Å, and C5′−H5′−N1, 160(5)°. The H5′···N1 separation of 2.71(6) Å is slightly shorter than the sum of the van der Waals radii of H (1.20 Å) and N (1.55 Å,[33] 1.60 Å[34,35]), but it has to be taken into account that the radius for a negatively charged N atom, as present here, is expected to be even larger. Compared to typical CH···N hydrogen bonds,[35] which have proton−nitrogen separations between 2.3 and 2.7 Å,[33a,35] this value should then still be considered a H bond. Again, inspection of a model reveals that a reduction in nucleobase propeller twist within the mononuclear entities brings about a shortening of both the intramolecular O6−N4′ and the intermolecular C5′−N1 distance if the intermolecular O6−N4′ separation is kept constant. If a slight lengthening of the intermolecular H bonds between O6 and N4′ is allowed, and coplanarity of the four bases assumed, all six H bonds can be within the usual 2.9−3.2 Å margin typically seen in nucleobase associates. We therefore propose that the two "long" distances are essentially a consequence of the mentioned stacking effect of the counterion.

It is to be noted that involvement of H5′ of cytosine in H bonding has some precedence: Protonated cytosine model nucleobases crystallize with ClO_4^- and NO_3^- anions in such a way that H5′ and one of the two NH_2 protons make H bonding contacts to two oxygen atoms of the anion.[21] C5′···O contacts

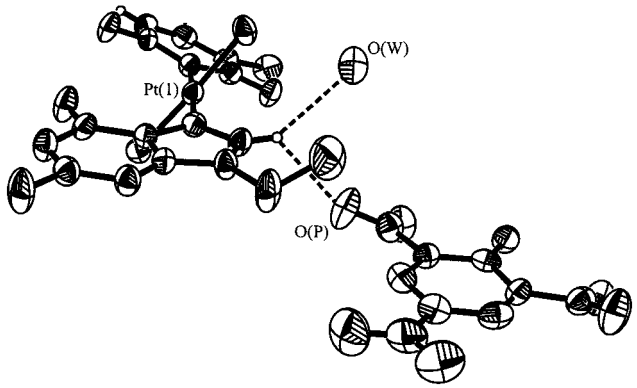
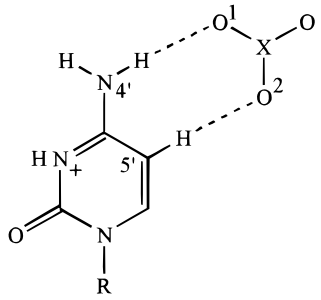


Figure 4. Involvement of H8 proton of 9-EtG in **1b** in H bonding with a water molecule and an oxygen atom of the picrate anion, respectively.

Chart 2



are 3.373(5) Å and 3.318(4) Å, clearly longer than the N4′···O separations (2.980(5), 2.992(4) Å) (Chart 2).

There are at least two additional interesting features of the crystal packing. First, nucleobase quartets are linked by pairs of weak H bonds of 3.229(6) Å between respective N2 and N3 sites of adjacent guanines, which are related by an inversion center as shown in Figure 3. This pattern is similar to that seen in the parent compound (2.95(1) Å)[5a] and in [9-EtGH$_2$]$_2$[PtCl$_4$] (3.05 Å)[36] and it corresponds to that realized in homoguanine pairs of parallel DNA.[37] Second, the guanine H8 proton of the

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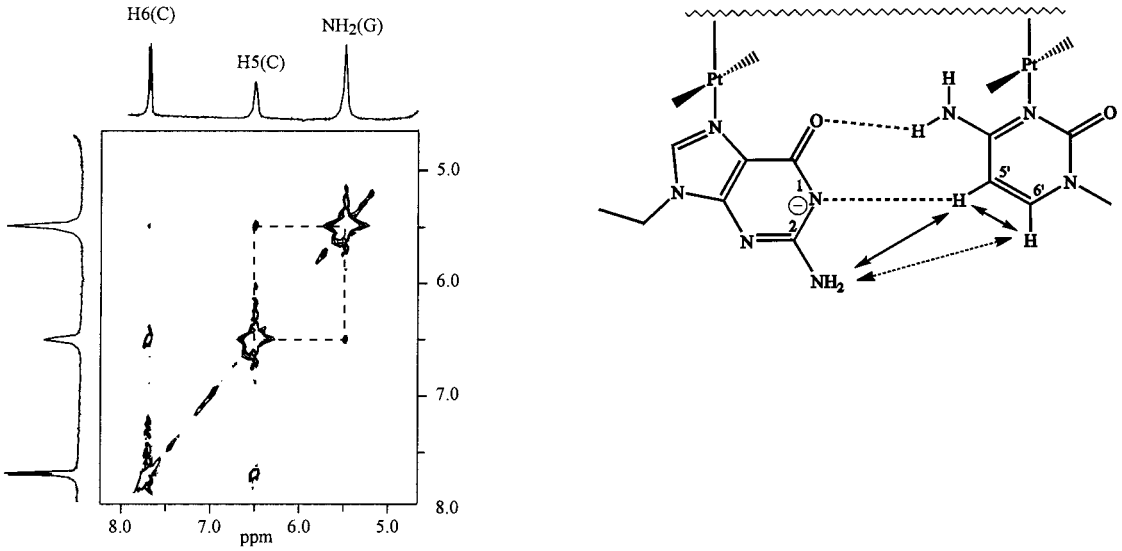

Figure 5. Aromatic part of the NOESY spectrum of **1** in DMSO-d_6 solution (left) with crosspeaks due to through-space coupling between H5′ of 1-MeC and NH_2 of 9-EtG indicated by broken lines, and scheme of relevant NOE contacts (right).

9-EtG ligand is involved in a bifurcated H bond with oxygen atoms of a water molecule (3.274(9) Å) and of a picrate anion (3.272(8) Å) (Figure 4). The two angles C8−H8−O are 142(5)° and 130(5)° and the O−H8−O angle is 87(2)°. Similar contacts between aromatic nucleobase protons and oxygen acceptor atoms have been experimentally verified in a number of cases[21,38] and are presently subject to speculations concerning their possible role in nucleic acid recognition.[39]

Nucleobase Quartet Structure: Comparison of Solid State and Solution Structure. The NOESY cross-peak observed between cytosine-H5′ and guanine-N2H_2 in DMSO-d_6 solution was clearly supportive of the postulated quartet structure. Calculation of the intramolecular distances in solution with the aid of eq 3 gave 2.8 Å for the N2H_2−H5′ and 3.5 Å for the N2H_2−H6′ distance, respectively. These two values compare with the situation in the solid state where distances of 3.24(6) (N2H_2−H5′) and 3.94(5) Å (N2H_2−H6′) are found. This difference is readily rationalized if one assumes that the propeller twist of the nucleobases in the crystal structure of **1b** is lost in solution, leading to coplanarity of the four nucleobases.

It should be noted that the resulting distances between N2H_2 and H5′/H6′ in solution are only rough estimates for the following reasons. First, as the molecule is very small, a mixing time as high as 400 ms had to be chosen. Therefore, spin diffusion and relaxation may affect cross-peak intensities. Second, at the high sample concentration chosen for our measurements (to achieve a satisfying degree of dimerization), nonspecific intermolecular interactions may contribute to the investigated cross-peaks.[40] Nevertheless, no unexpected cross-peaks indicative of nonspecific interactions have been detected in the spectrum. Third, it has to be mentioned that the N2H_2 resonance of guanine is an average signal of two amino protons having different distances to the aromatic cytosine protons. In our calculations, we have neglected the contribution of the second amino proton pointing away from the cytosine ring. This proton is about 1.7 Å further apart from the aromatic cytosine protons than the amino proton (pointing toward the cytosine ring). Therefore, we have estimated the contribution of the second proton to the cross-peak integral to be less than 6%.

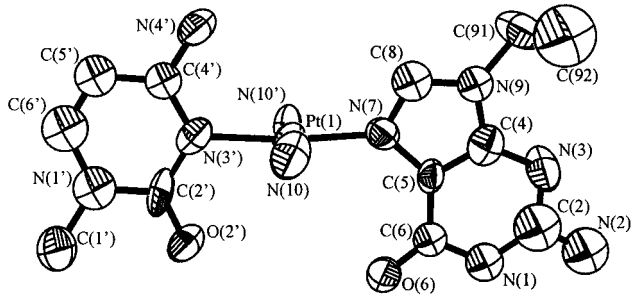

Figure 6. Cation of *trans*-[Pt(NH_3)$_2$(9-EtG-*N7*)(1-MeC-*N3*′)](CF_3SO_3) (**1c**) with atom numbering scheme. Ellipsoids are at the 50% probability level.

X-ray Crystal Structure of 1c: A Metalated Base Pair (only). The solid-state structure of *trans*-[Pt(NH_3)$_2$(9-EtG-*N7*)(1-MeC-*N3*′)](CF_3SO_3) (**1c**) is radically different from that of **1b** in that the two bases adopt a reversed Hoogsteen arrangement with the exocyclic oxygen atoms of the two bases facing each other (Figure 6). Selected interatomic distances and angles of **1c** are included in Table 3. As can be seen, the separation between guaninate-O6 and cytosine-O2′ is large (4.35(1) Å) and in agreement with the deviation from linearity of the Pt−N(nucleobase) vectors (*N3*′−Pt−*N7*, 174.2(4)°). The orientation of the two nucleobases contrasts that of all presently known metal complexes containing mixed pyrimidine-*N3*′, purine-*N7* combinations (cytosine/guanine,[5a] cytosine/adenine,[27] thymine/adenine[1]) of linearly coordinated metal ions, since it avoids intracomplex H bonding between the 6-position of the purine and the 4′- or 2′-positions of the pyrimidine base. As a consequence of this orientation in **1c** a cyclic quartet structure is excluded. Differences in cation−anion contacts are probably responsible for this fact. The resulting cation−cation interactions of **1c** are depicted in Figure 7: There are two motifs recognized. First, pairs of cations stack (ca. 3.4 Å) and form pairs of H bonds between the NH_3 groups and O6 of the 9-EtG

(38) See, e.g.: (a) Wahl, M. C.; Rao, S. T.; Sundaralingam, M. *Nature Struct. Biol.* **1996**, *3*, 24−31. (b) Wahl, M. C.; Sundaralingam, M. *TIBS* **1997**, *22*, 98−102. (c) Leonard, G. A.; McAuley-Hecht, K.; Brown, T.; Hunter, W. N. *Acta Crystallogr.* **1995**, *D51*, 136−139. (d) Beyerle-Pfnür, R.; Jaworski, S.; Lippert, B.; Schöllhorn, H.; Thewalt, U. *Inorg. Chim. Acta* **1985**, *107*, 217−222. (e) Szalda, D. J.; Kistenmacher, T. J.; Marzilli, L. G. *Inorg. Chem.* **1975**, *14*, 2623−2629.

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(40) Experiments with shorter mixing times or lower concentrations of the complex gave no cross-peaks which were distinct enough for integration and distance calculation.

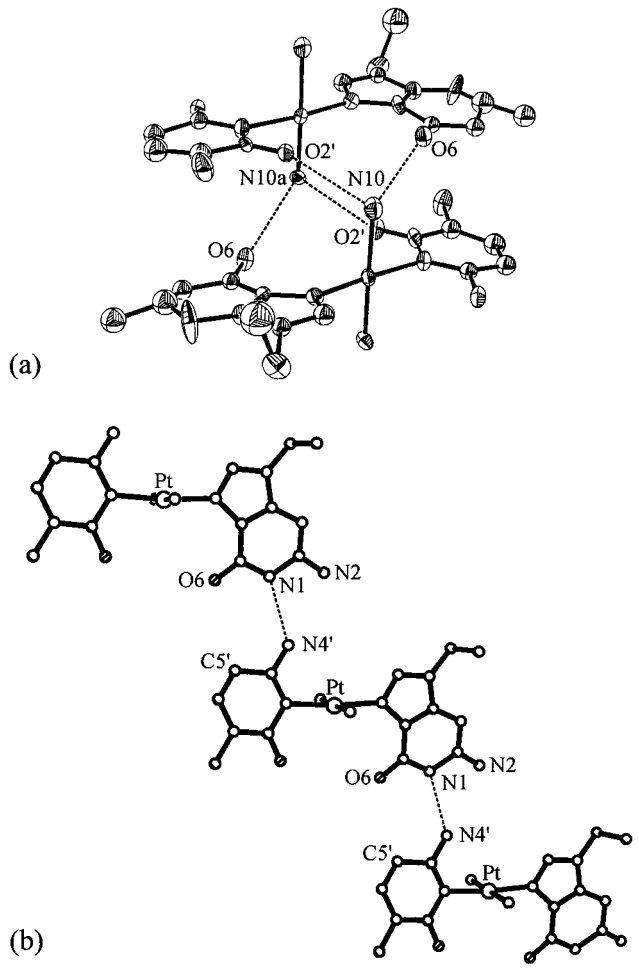

Figure 7. (a) Two cations *trans*-[Pt(NH$_3$)$_2$(9-EtG-*N7*)(1-MeC-*N3′*)]$^+$ of **1c**, forming a H bonded dimer (symmetry operation $x - 1/y/z$). Ellipsoids are at the 50% probability level. (b) Cation association via hydrogen bond formation between N4′H$_2$ of 1-MeC and N1 of 9-EtG (symmetry operations $x - 1/y/z$ and $x + 1/y/z$).

(2.86(3) Å and 2.92(3) Å) as well as O2′ of the 1-MeC ligands (2.95(3) Å and 2.91(3) Å) (Figure 7a). This pattern appears to be a recurring motif of bis(nucleobase) complexes of *trans*-Pt^{II}(NH$_3$)$_2$ and has been observed, among others, in *trans*-[Pt(NH$_3$)$_2$(1-MeC-*N3′*)(7,9-DimeG-*N1*)]$^{2+}$ [28] as well as in the protonated form and in a heteronuclear derivative of *trans*-Pt(NH$_3$)$_2$(1-MeU)$_2$.[41] Second, pairs of stacked cations are connected by a single short H bond (2.80(1) Å) between N4′ of 1-MeC and N1 of 9-EtG (Figure 7b). There is also a long contact between C5′ of 1-MeC and O6 of 9-EtG of 3.66(2) Å. This separation is probably too long to be considered a CH$\cdots$O hydrogen bond. Typically, C$\cdots$O distances in these H bonds are in the range of 2.9−3.3 Å.[33a] However, if a favorable geometry of the H bond is realized, values of up to 3.9−4.1 Å are still considered (weak) H bonds.[42]

Irrespective of such considerations and even assuming that in solution the C5′(1-MeC)−O6(9-EtG) separation becomes sufficently short to get the two positions into reach for H bonding (Figure 8), such an arrangement appears to be unlikely to explain the solution behavior for the following reasons: (i) Associates with two H bonds only are virtually never detected in DMSO-d_6 solution, (ii) the involvement of the second proton of N4′H$_2$ of 1-MeC in H bonding is not accounted for (cf. above), and (iii) the ESI-MS spectrum (recorded in MeOH) gives no hint for oligomers, yet clear evidence for a quartet.[6]

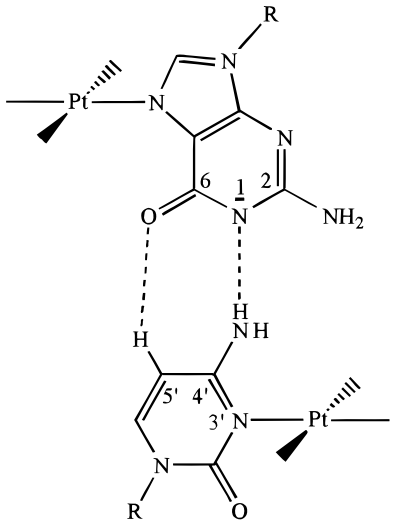

Figure 8. Hypothetical H bonding alternative to quartet formation based on the X-ray crystal structure of **1c**. ^{1}H NMR data do not support such an arrangement.

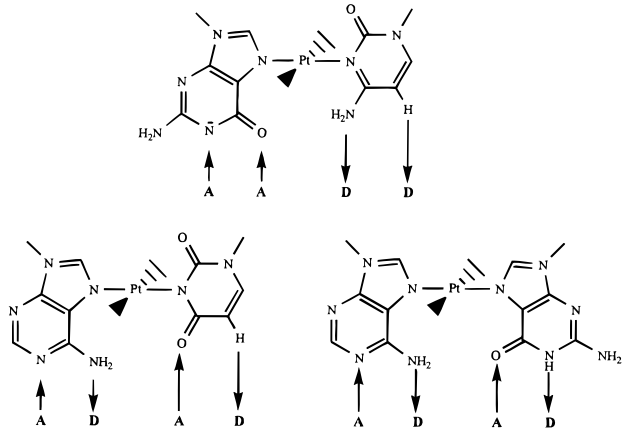

Figure 9. Sequence of H bond donor (D) and acceptor (A) sites as found in the diplatinated quartet formed by *trans*-[Pt(NH$_3$)$_2$(9-EtG-*N7*)(1-MeC-*N3′*)](C$_6$H$_2$N$_3$O$_7$)·H$_2$O (**1b**) (AADD, above) and in *trans*-[Pt(NH$_3$)$_2$(9-MeA-*N7*)(9-MeGH-*N7*)]$^{2+}$ and *trans*-[Pt(NH$_3$)$_2$(1-MeU-*N3′*)(9-MeA-*N7*)]$^+$ (ADAD each, below). No quartet formation is observed for the sequence ADAD.

Related Systems. In the course of our studies on "metal-modified base pairs" we have prepared also compounds of the type *trans*-[Pt(NH$_3$)$_2$(9-MeA-*N7*)(9-MeGH-*N7*)]$^{2+}$ [4a] and *trans*-[Pt(NH$_3$)$_2$(1-MeU-*N3′*)(9-MeA-*N7*)]$^+$.[43] On steric grounds these compounds should likewise be capable of forming metalated base quartets (Figure 9). However, neither ^{1}H NMR spectra in DMSO-d_6 nor presently available X-ray crystal structure analyses provide any hint for a dimerization as seen with **1b**. At least in the case of the mixed uracil, adenine complex charge repulsion cannot account for this difference, since both cations carry the same +1 charge. What is different between **1b** and the two other complexes, however, is the sequence of donor (D) and acceptor (A) sites within the mononuclear entities: While it is AADD in **1b**, it is ADAD in the two other compounds. As has been pointed out by Jorgensen et al.,[44]

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favorable secondary electrostatic interactions in the quartet structure of **1b**, possible between H5′ of 1-MeC and O6 of 9-EtG as well as between the intermolecularly bound NH of 1-MeC and N1 of 9-EtG, might account for an extra stabilization.

Conclusions

Metal complexes which lead through H bonding interactions to supramolecular ensembles are receiving increased attention, for reasons such as crystal engineering, molecular recognition, or energy transfer.[45] Our interest in such systems[3,5b,8,46] stems largely from biological aspects such as the effects of binding of heavy metal ions to nucleobases to their H bonding properties with respect to mispairing patterns or the stabilization of nucleobase associates by an interplay of metal coordination and H bonding. The here described complex **1b** is unique in that it displays an H-bonding pattern unprecedented in nucleic acid chemistry involving a CH donor and a negatively charged N acceptor. It extends the list of H bonds of type NH···N and NH···O commonly found in nucleic acids as well as the rather novel CH···O hydrogen bond[38a,b] now to CH···N. Whether or not such H bonds involving deprotonated bases are biologically relevant (e.g., in multistranded nucleic acids; during genetic recombination; during forced duplex association under the influence of cross-linking metal ions, etc.) is admittedly unclear. However, the strength of the association of the base quartet, which exceeds that of the Watson−Crick pair between guanosine and cytidine by far, is quite remarkable and needs to be emphasized.

Acknowledgment. The authors acknowledge support of this research by the Swiss National Science Foundation and the Swiss Federal Office for Education and Science (TMR fellowship to R.K.O.S.; No. 83EU-046320), by the Fonds der chemischen Industrie (fellowship for S.M.), by the Deutsche Forschungsgemeinschaft, and by Asta Medica.

Supporting Information Available: Tables listing atomic coordinates, temperature factors, bond lengths and angles, and torsion angles and details of the refinement of the X-ray crystallographic data for compounds **1b** and **1c** (18 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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