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Feasibility of a Two-Metal, Four-Purine Nucleobase Quartet Motif

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A mixed-purine nucleobase complex of composition *trans*-[$(NH_3)_2$Pt(9-EtA-*N1*)(9-MeHx-*N7*)]$(NO_3)_2 \cdot 2H_2O$ (**1**) (9-EtA = 9-ethyladenine; 9-MeHx = 9-methylhypoxanthine) has been prepared and characterized by X-ray crystallography. Cations of **1** are self-complementary as far as hydrogen bonding properties are concerned and form H bonded dimers, containing four intermolecular hydrogen bonds in addition to two intramolecular ones. The resulting mixed-purine square is considered a model compound for a putative mixed-purine tetrad consisting of two adenines and two guanines. In this model, the one-metal, four-nucleobase quartet motif, as seen in guanine or uracil quartets of nucleic acids, with the metal located in the center of the base tetrad, has been altered to a two-metal, four-nucleobase motif, with the two metal ions localized at the periphery.

The guanine quartet (G_4), which consists of four guanine bases in a cyclic arrangement, with the four bases interconnected by eight hydrogen bonds, is increasingly recognized as a central motif in stuctural nucleic acid chemistry.[1] It is found, among other places,[2] in the telomeres,[3] and in gene regulatory segments of DNA,[4] and it represents the core of larger nucleobase aggregates such as hexads,[5] heptads,[6] or even octads.[7] Its presence also facilitates the formation of other co-stacked base quartets, e.g., of T_4 [8] or U_4 [9] (with T = thymine, U = uracil). From a coordination chemistry point of view, the requirement of metal ions for proper stabilization (and partial charge neutralization) of these base tetrads is noteworthy. It is evident that in G_4, T_4, and U_4 the spatial orientation of the exocyclic oxygen donor functions within the tetrad is particularly favorable to bind a single metal ion, hence to generate a one-metal, four-nucleobase quartet motif with the metal ion in the center.[10,11] In contrast, the role of metal ions in A_4 or mixed GCGC and TATA tetrads (with A = adenine, C = cytosine) is less clear[1b] or even controversial.[12] As to the existence of mixed AGAG tetrads, neither their biological relevance nor the possible role of metal ions is fully clear at present.

It appears, however, that telomeres at the chromosome ends do not fold into mixed AGAG quartets,[13] consistent with results of X-ray structure determination of d[AGGG-$(TTAGGG)_3$].[3] This is surprising considering the fact that AG mismatches in DNA are remarkably stable and come in several variants.[14] A side-by-side alignment of two duplexes containing AG pairs is, however, feasible from a geometrical point of view, very much as in the case of formation of GCGC or TATA quartets through dimerization of the corresponding GC and TA pairs.

Here we wish to propose a novel metal binding pattern for mixed-purine quartets which implies the binding of two metal ions at the periphery of the base quartet. It leads to a coplanar arrangement of the four bases, as demonstrated in the model compound reported here, *trans*-[$(NH_3)_2$Pt(9-EtA-

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(10) We are aware that, depending on the size of the metal ion, it may reside either in the plane of the four nucleobases or may be sandwiched between parallel base tetrads.

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(12) The presence of a Na^+ in the vicinity of an A tetrad has been interpreted in terms of a "weaker interaction between N6(A) and Na^+", even though this seems unlikely considering the virtual complete lack of basicity of the exocyclic amino group (and delocalization of the lone pair into the heterocyclic ring): Pan, B.; Xiong, Y.; Shi, K.; Deng, D.; Sundarilingam, M. *Structure* **2003**, *11*, 815−823.

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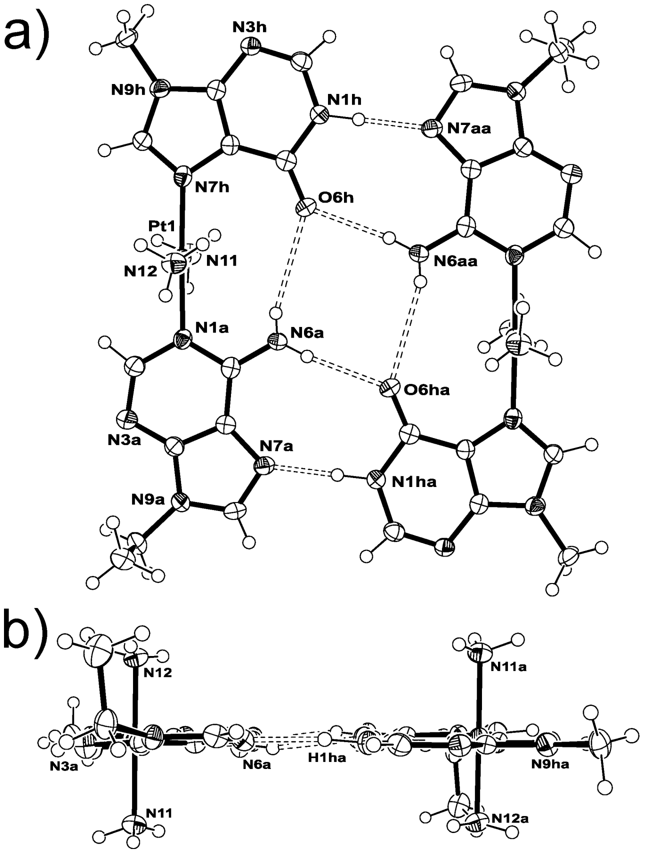

Figure 1. View of dinuclear, hydrogen bonded cation **1** with atom numbering scheme: (a) top view, (b) side view of the dimer.

N1)(9-MeHx-*N7*)]$(NO_3)_2$ (with 9-EtA = 9-ethyladenine, 9-MeHx = 9-methylhypoxanthine).[15,16] The use of hypoxanthine (Hx) instead of guanine is justified in that with the exception of the "sheared" AG mismatch, where the guanine amino group binds to N7 of a neighboring adenine, the three other mispairs $A_{anti}\cdot G_{anti}$, $A_{syn}\cdot G_{anti}$, and $AH^{+}_{anti}\cdot G_{syn}$ do not utilize the guanine amino group in the pairing schemes.[14]

The cation of the title compound crystallizes as a dimer (Figure 1a), held together by four coordinative Pt−nucleobase bonds and six hydrogen bonds. Intercationic hydrogen bonding is a consequence of the pattern of hydrogen donor (D) and acceptor (A) sites at the cation edge, which is self-complementary (DADA), and the near complementarity of the two purine bases within the cation. The hydrogen bonding scheme realized between A and Hx is that of the $A_{syn}\cdot G_{anti}$ type. The lengths of these H bonds are 2.77(1) Å for N(1)Hx$\cdots$N(7)A and 2.99(1) Å for O(6)Hx$\cdots$N(6)A between the two mononuclear halves, and 3.36(1) Å within the monomer (O(6)Hx$\cdots$N(6)A). Pt−nucleobase and Pt−NH_3 bond lengths are normal.[17] The metalated purine square is planar (Figure 1b) with dimensions of ca. 12.35 × 10.60 $Å^2$ (N(9)-methyl and methylene groups of bases).

Several hydrogen bonds are formed between NH_3 ligands and adjacent anions. Except for a hydrogen bond between N(3) of 9-MeHx and a water molecule, there are no short contacts between any atom of the square and anions or water of crystallization.

As outlined in Figure 2, $A_{anti}\cdot G_{anti}$ and $AH^{+}_{anti}\cdot G_{syn}$ mismatches can likewise be converted into quartets[18] and eventually into dimetalated quartets by cross-linking endocyclic ring N atoms by two metal ions. In fact, we have previously shown[19] that insertion of two linear metal entities between the four N7 positions of quartet $(I)_2$ is fully compatible with the quartet structure without disrupting the six existing hydrogen bonds. Furthermore, we have demonstrated that it is possible to substitute the imino protons of the two Hx ligands by metals of linear coordination geometry, thereby generating a M_2, M'_2, AHxAHx pair.[20]

On the basis of theoretical calculations,[21] it has been proposed that the AGAG tetrad derived from H bonding of two $G_{anti}\cdot A_{syn}$ mispairs, viz. of the kind seen in our complex, may not be important in tetraplexes due to its pronounced nonplanarity and V-shape structure. Although bonding within each AG pair is strong,[22] the two pairs interact weakly only, primarily as a result of the repulsive interaction between N1 of adenine and N7 of guanine. It is obvious that cross-linking of these two sites by a metal ion removes this obstacle. Even a separation of 4.02(1) Å between N(1A) and N(7H), as found in **1**, still allows for hydrogen bonding between N(6) of adenine and O(6) of hypoxanthine. Although we have applied, for the sake of stability and crystallization, linear *trans*-$(NH_3)_2Pt^{II}$ fragments as metal entities in the title compound, we believe that many more metal ions are, in principle, suited to become inserted into the base quartet, as long as the metal−N distances do not deviate too much from the ca. 2 Å length found in the present structure. Insertion of a proton between these positions, hence dimer formation of $AH^{+}_{anti}\cdot G_{syn}$ pairs,[23] should likewise lead to a compact

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(15) Synthesis: 653 mg (4.00 mmol) of 9-EtA, 900 mg (2.00 mmol) of *trans*-[$(NH_3)_2$Pt(9-MeHx-*N7*)Cl]Cl,[19] and 646 mg (3.80 mmol) of $AgNO_3$ were dissolved in 100 mL of H_2O, and the pH was adjusted to 6.5 with KOH. The mixture was stirred for 4 days at 37 °C and filtered from AgCl. Residual Cl^- ions were removed with a NO_3^--charged strongly basic anion exchanger. According to ^1H NMR spectroscopy, the mixture consists of approximately equal amounts of the title compound and the linkage isomer *trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)(9-MeHx-*N7*)]$^{2+}$. The solution was allowed to evaporate slowly at room temperature. Within several weeks, small crystals and a fine precipitate formed. The crystals were isolated by careful pipetting and recrystallized from H_2O, yielding 13.5 mg of colorless plates of **1**. ^1H NMR (D_2O, pD 5.0): δ 8.77, s, H(2A); 8.71, s, H(8H); 8.37, s, H(2H); 8.27, s, H(8A); 4.31, q, CH_2(A); 3.99, s, CH_3(H); 1.50, t, CH_3(A).

(16) Crystal data: $C_{13}H_{25}N_{13}O_9Pt$; fw = 702.54; crystal size (mm^3) 0.20 × 0.20 × 0.13; crystal system triclinic; cell parameters $a = 7.908(2)$ Å, $b = 10.940(2)$ Å, $c = 14.207(3)$ Å, $\alpha = 80.41(3)°$, $\beta = 84.22(3)°$, $\gamma = 72.12(3)°$; $V = 1151.7(4)$ $Å^3$; space group $P\bar{1}$; $d_{calcd} = 2.026$ $Mg\cdot m^{-3}$; $Z = 2$; data collection on a NONIUS KappaCCD apparatus; Mo Kα ($\lambda = 0.7107$ Å) radiation; graphite monochromator, θ range 3−27.5°; number of unique reflections 5254 (R(int) = 0.0346); number of parameters 427; $R_1(I > 2\sigma(I)) = 0.0278$; wR_2(all data) = 0.0652.

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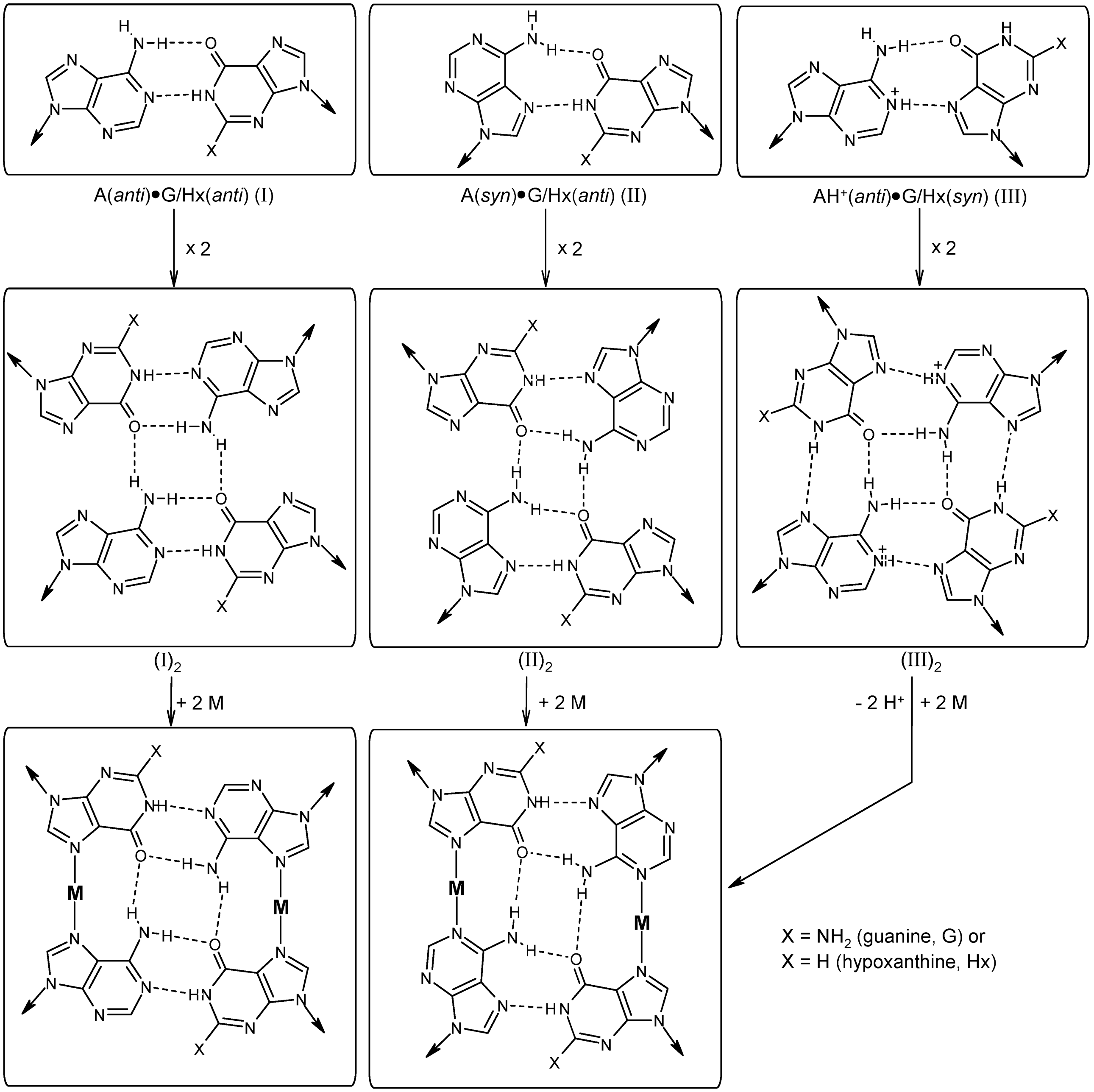

Figure 2. Three mispairs I−III between A and G or Hx (top), three feasible mixed-purine quartets $(I)_2$, $(II)_2$, $(III)_2$ (middle), and two metalated mixed-purine quartets (bottom). $M_2(I)_2$ has previously been described[19a] and can be converted into a $M_2M_2'(I)_2$ derivative upon deprotonation of the 6-oxopurine.[20] Quartet $(III)_2$ can be described either as a dimer of the $AH^+_{anti}{\cdot}G_{syn}$ pair or alternatively as a dimer of a $AH^+_{syn}{\cdot}G_{anti}$ pair.

quartet structure with eight cyclic hydrogen bonds. Work is in progress to evaluate if other metal ions and in particular physiologically relevant ones are suitable for this purpose.

The title compound described here adds to the list of metalated base quartets which we have been studying.[11,19,20,24] It is unique in the sense that it is (formally) derived from two different mispairs (II, III) and is a rare example for metal cross-linking of the N1 site of an adenine and N7 of a 6-oxopurine. The structure suggests that location of tetrad-stabilizing cations at the quartet periphery may lead a way out of the dilemma of having a metal ion in the center of a quartet in cases where exocyclic amino groups are directed towards this position.

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Supporting Information Available: X-ray crystallographic file in CIF format and description of pD dependent ^{1}H NMR chemical shifts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) If viewed from the other edge, the square is to be considered also as a dimer of two $AH^+_{syn}{\cdot}G_{anti}$ pairs.

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