Mixed Adenine, Guanine Nucleobase Quartets: Metal-Modified Forms of an Open U and a Closed Rectangle

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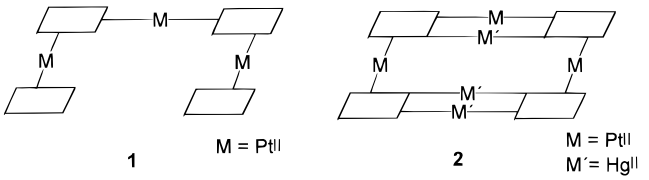
Nucleobase quartet structures are an emerging aspect of nucleic acids chemistry. Originally discovered as a distinct feature of guanine association[1] and later recognized as part of the telomeres of eukaryotic chromosome ends,[2] nucleobase quartet structures have been established since then for other bases such as isoguanine,[3] 7-deazaisoguanine,[4] thymine,[5] and uracil.[6] Interestingly, guanine quartets are also present in DNA[7] and RNA[8] aptamers. Heteronucleobase quartets are known motifs of DNA duplex interactions in the solid state,[9] and have been implicated in genetic recombination.[10]

Nucleobase quartet formation seems to require the presence of metal cations, which frequently are centrally located between pairs of quartets. Our interest in "metal-modifications" of nucleobase associates in general[11] has recently led us to prepare nucleobase quartets linked by metal ions and/or H bonds. Apart from closed quartet structures,[12−14] an S-shaped structure[15] was also established. Here we report on an open, U-shaped purine nucleobase quartet (**1**) and a closed quartet structure (**2**), derived from the former.



In continuation of previous work,[16,17] two cations *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$^{2+}$ (9-MeA = 9-methyladenine; 9-MeGH = 9-methylguanine) were cross-linked by a *trans*-$Pt^{II}(CH_3NH_2)_2$ entity via the available N1 positions of 9-MeA to give trinuclear *trans*,*trans*,*trans*-{$(CH_3NH_2)_2$Pt(*N1*-9-MeA-*N7*)$_2$-[$(NH_3)_2$Pt(9-MeGH-*N7*)]$_2$}$(NO_3)_6$·6.25H_2O (**1**).[18] One of two crystallographically independent cations of **1** is shown in Figure 1.[19] The cations are not flat: while the adenine and guanine planes (bound to Pt1,Pt2 and Pt2,Pt3) form a small dihedral angle only (13.3(4) and 6.5(4)°, respectively), the two adenines are propeller-twisted by 17.2(4)°. The respective values for the second cation are 5.7(5), 2.4(5), and 20.9(4)°. If viewed from the side, the two halves of the cations resemble slightly opened

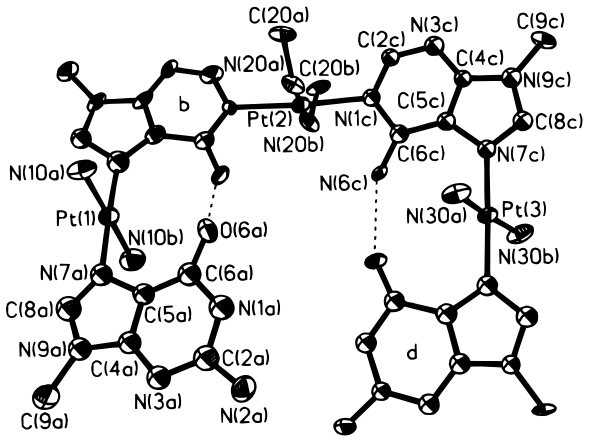


Figure 1. View of one of the two crystallographically independent cations of the open nucleobase rectangle *trans*,*trans*,*trans*-{$(CH_3NH_2)_2$Pt(*N1*-9-MeA-*N7*)$_2$[$(NH_3)_2$Pt(9-MeGH-*N7*)]$_2$}$(NO_3)_6$·6.25H_2O (**1**). Intramolecular H bonds are 2.77(1) Å (N6c−O6d) and 2.90(2) Å (N6b−O6a). For clarity, atoms of the second adenine ring (b) and the second guanine ring (d) are not numbered.

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(18) Synthesis of **1**: *trans*-$(NH_2CH_3)_2PtCl_2$ (123 mg, 0.38 mmol) was suspended in H_2O (10 mL) and stirred with $AgNO_3$ (126 mg, 0.74 mmol) for 24 h at 35 °C with daylight excluded. After the mixture was cooled to 4 °C, AgCl was removed by filtration and *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2$·H_2O[16] (500 mg, 0.76 mmol), dissolved in water (50 mL), was added. The solution was stirred for 6 days at 35 °C. After filtration from an unidentified dark precipitate the filtrate was concentrated to a 20 mL volume. Unreacted *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2$·H_2O, which precipitated during evaporation, was removed by filtration, and the yellowish filtrate was further concentrated to a 5 mL volume. Crystalline **1** precipitated as colorless cubes. X-ray crystallography showed the presence of 6.25 water molecules in contrast to elemental analysis (2H_2O). The yield was 24%. Anal. Calcd for $C_{26}H_{54}N_{32}Pt_3O_{22}$: C, 17.8; H, 3.1; N, 25.6. Found: C, 17.6; H, 2.9; N, 25.7.
(19) Crystal data for **1**: $C_{52}H_{125}O_{52.5}N_{64}Pt_6$, colorless cubes, triclinic, $P\bar{1}$, a = 15.161(3) Å, b = 16.085(3) Å, and c = 24.972 (3) Å, α = 85.89(3)°, β = 74.96(3)°, and γ = 75.39(3)°, V = 5690.9(19) Å^3, Z = 2, D_x = 2.135 g cm^{-3}, T = 193(2) K, $R(F)$ = 6.08%, $R(wF^2)$ = 10.37%.

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pairs of scissors. As in the starting compound,[16] there is intramolecular H bonding between the exocyclic N6 and O6 groups of the two purines (O6a−N6b, 2.90(1) Å and O6d−N6c, 2.77(1) Å). Within the second cation (same orientation) these distances are 2.91(1) and 2.72(1) Å. Intermetallic distances within **1** are as follows: Pt1−Pt2, 6.477(2) Å; Pt2−Pt3, 6.401(2) Å; Pt1−Pt3, 10,427(3) Å; and in the second cation, these values are 6.471(2), 6.466(2), and 10.850(3) Å. Pt−N distances are in the normal range. We have previously noticed,[17,20] that in *N7*,*N1*-diplatinated purine nucleobases the Pt−N vectors are almost at right angle and that deviations from 90° are essentially due to the "softness" of the external ring angles at *N7*, viz. C5−N7−Pt and C8−N7−Pt, and interactions involving the exocyclic groups of the purine.[15] In the present case, these angles vary between 80.8(4)° (adenine ring c in Figure 1) to 91.6(4)° in the adenine ring f (not shown). In solution, the solid-state structure is not retained, but rather **1** exists in an equilibrium between U and S form, with rotation about the Pt2−adenine−N1 bonds.[21]

Addition of $Hg(NO_3)_2$ (3.5 equiv) to an aqueous solution of **1** yielded quantitatively *trans*,*trans*,*trans*-$\{(CH_3NH_2)_2PtHg(H_2O)_2[(N1,N6\text{-}9\text{-}MeA^-\text{-}N7)(NH_3)_2Pt(N7\text{-}9\text{-}MeG^{2-}\text{-}N1,N2)]_2Hg_2(ONO_2)\}(NO_3)_5\cdot 13H_2O$ (**2**) (9-MeA$^-$ = 9-methyladenine anion; 9-MeG^{2-} = 9-methylguanine dianion). Prior to verification by X-ray crystallography, the following observations indicated that cyclization had occurred: First, the ^{1}H NMR spectrum was consistent with a single rotamer.[22] Second, the significant drop in pH during the reaction from 6 to 1.2 proved nucleobase deprotonation. Third, the ^{195}Pt NMR resonance of Pt1[23] as compared to **1** suggested the vicinity of a Hg^{II} and cross-linking of the deprotonated exocyclic amino groups of the two 9-MeA ligands, very much as in related complexes of 1-methylcytosine.[14,24] Fourth, EPXMA (electron probe X-ray microanalysis) of the isolated product **2** gave a Pt/Hg ratio of 1:1.

X-ray crystallography[25] of **2** (Figure 2) confirmed the above conclusions and revealed at the same time a number of interesting details: (i) Hg^{II} cross-linking occurs, with deprotonation, via the *N6* positions of 9-MeA, giving monoanionic 9-methyladeninato ligands, and 2-fold via the *N1* positions of 9-methylguanine *and* the *N2* positions of this ligand, leading to dianionic 9-methylguaninato ligands. To the best of our knowledge, this is the first unambiguously proven case of metal ion binding to the exocyclic amino group of a guanine nucleobase and definitely the first example of simultaneous metal binding to *N1*, *N2*, and *N7* of a *N9* blocked guanine. (ii) Intramolecular H bonding between the

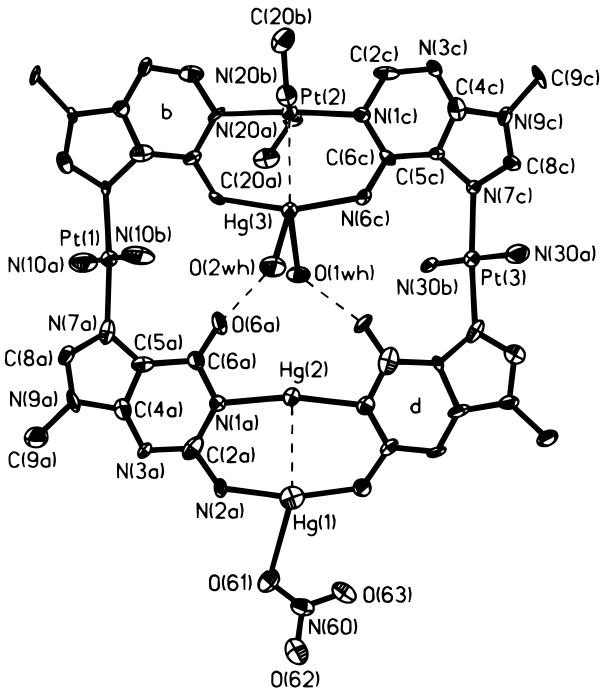

Figure 2. View of the cation of *trans*,*trans*,*trans*-$\{(CH_3NH_2)_2PtHg(H_2O)_2[(N1,N6\text{-}9\text{-}MeA^-\text{-}N7)(NH_3)_2Pt(N7\text{-}9\text{-}MeG^{2-}\text{-}N1,N2)]_2Hg_2(ONO_2)\}(NO_3)_5\cdot 13H_2O$ (**2**) with atom-numbering scheme. For clarity, atoms of the second adenine ring (b) and of the second guanine ring (d) are not numbered.

N6 positions of the adeninato and the *O6* positions of the guaninato ligands as seen in **1** is lost (N6b−O6a, 3.52(2) Å; N6c−O6d, 3.53(2) Å) and Pt−N vectors form angles of 89.1(5)° (adenine b) and 91.2(5)° (adenine c). (iii) The aqua groups bound to Hg3 are H-bonded to the O6 positions of the two guaninato ligands (O2wh−O6a, 2.75(2) Å; O1wh−O6d, 2.82(2) Å). (iv) Intermetallic distances are as follows: Pt2−Hg3, 2.795(1) Å; Hg1−Hg2, 2.835(1) Å. As with the 1-methylcytosinato compounds,[14,24] the former contact may reflect a weak attraction[26] between the Pt^{II} and Hg^{II}, therefore explaining the mentioned downfield shift in the ^{195}Pt NMR of the corresponding resonance.

Ignoring the extra Hg^{II} ions bound to the exocyclic groups of the nucleobases (Hg1, Hg3), Pt1, Pt2, Pt3, and Hg2 form the previously[20] postulated molecular rectangle of dimensions 10.107(5) Å (Pt1−Pt3) × 8.000(3) Å (Pt2−Hg2), which represents a variant of those molecular squares[14,27] that utilize the right angles of *cis*-L_2M^{II} (M = Pd, Pt) entities and the collinearity of suitable ligands.

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Supporting Information Available: Tables of X-ray data (crystal data, atomic coordinates and isotropic displacement parameters, anisotropic displacement parameters, distances and angles, H coordinates, and isotropic displacement parameters, torsional angles), ^{1}H and ^{195}Pt NMR spectra, figures of both independent cations of **1** (42 pages). Ordering information is given on any current masthead page.

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(21) ^{1}H NMR data for **1** (200 MHz, D_2O, room temperature, 0.02 M, δ, ppm): 9.36, 9.32 (H2 of 9-MeA with relative intensities 4:1); 9.02 (H8 of 9-MeA); 8.42, 8.41 (H8 of 9-MeGH with relative intensities 1:4); 4.08 (CH_3 of 9-MeA); 3.84 (CH_3 of 9-MeGH); 2.34, 2.32, 2.31, 2.28 ($(CH_3NH_2)_2$−Pt). ^{195}Pt NMR data for **1** (43.02 MHz, D_2O, room temperature, 0.02 M, δ, ppm): −2474 ((9-MeA-*N7*-Pt-*N7*-9-MeGH)$_2$); −2659, −2681 (9-MeA-*N1*-Pt-*N1*-9-MeA with relative intensities of 1:4).

(22) ^{1}H NMR data for **2** (200 MHz, D_2O, room temperature, 0.02 M, δ, ppm): 8.85, 8.84 (H2, H8 of 9-MeA$^-$); 8.37 (H8 of 9-MeG^{2-}); 4.01 (CH_3 of 9-MeA$^-$); 3.83 (CH_3 of 9-MeG^{2-}); 2.34 ($(CH_3NH_2)_2$-Pt).

(23) ^{195}Pt NMR data for **2** (43.02 MHz, D_2O, room temperature, 0.02 M, δ, ppm): −2364 (9-MeA$^-$-*N1*-Pt-*N1*-9-MeA$^-$); −2470 ((9-MeA$^-$-*N7*-Pt-*N7*-9-MeG^{2-})$_2$) with relative intensities of 1:2.

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(25) Crystal data for **2**: $C_{26}H_{74}O_{35}N_{32}Pt_3Hg_3$, colorless columns, triclinic, $P\bar{1}$, a = 15.295(3) Å, b = 15.674(3) Å, and c = 16.835 (3) Å, α = 63.99(3)°, β = 78.59(3)°, and γ = 64.93(3)°, V = 3285.1(11) Å^3, Z = 2, D_x = 2.611 g cm^{-3}, T = 183(1) K, $R(F)$ = 5.03%, $R(wF^2)$ = 12.82%. The crystal used for X-ray crystallography was isolated from the NMR tube.

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