Axial guanine binding to a diplatinum(III) core

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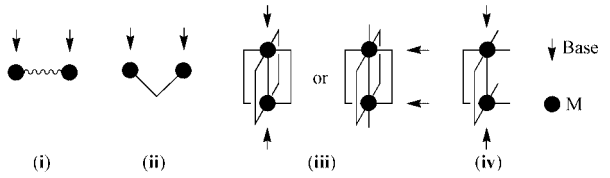
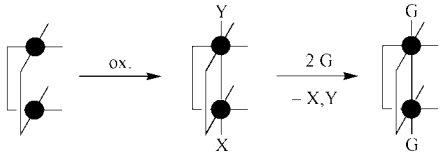
The preparation, crystal structure and NMR spectroscopic properties of a cisplatin-derived diplatinum(III) complex is reported which contains two bridging 1-methylcytosinato nucleobases in mutual *head–tail* orientation and in addition two axially bound 9-ethylguanine nucleobases.

Reactions of di-, rather than mononuclear metal antitumor complexes with nucleobases or DNA, in which the integrity of the dimetal core is retained, have recently attracted attention. Examples are nucleobase adducts of dinuclear Pt(II) complexes with flexible aliphatic (**i**)[1] or rigid heterocyclic linkers (**ii**),[2] and



'lantern' type dirhodium(II) tetracarboxylates (**iii**).[3] In the latter case nucleobase binding can occur both through the axial positions[4] or with replacement of two bridging ligands.[5] Here we report on a diplatinum(III) complex (**iv**) which binds two guanine nucleobases with high efficiency through the two axial positions of the dimetal core. The novelty of (**iv**) relates to Pt binding through guanine-N^7, a pattern ruled out in the case of dimetal tetracarboxylates (**iii**) because of repulsive interactions between O^6 of guanine and the four oxygen donor atoms in the metal plane.[6] In contrast, axial binding of adenine nucleobases (*via* N^7) was rationalized on the basis of favourable H bonding interactions with the MO_4 plane.[3–5] The observation by Aoki *et al.*[7] on axial theophylline-N^7 binding to a mixed-valence tetrakis(μ-acetamidato)rhodium(II)-rhodium(III) cation was a logical consequence of the partial replacement of O atoms by NH functions and the possibility of interligand H bond formation. Consistent with this view, the presence of three H donor sites (NH, two NH_3) in the MN_4 faces of the diplatinum(III) core applied in this study proved particularly advantageous for guanine binding.

The title compound was prepared as follows: The diplatinum(II) precursor *cis*-[{$Pt(NH_3)_2$(μ-mcyt-N^3-N^4)}$_2$]$^{2+}$ (**1**)[8] con-



taining two bridging 1-methylcytosinato (mcyt) model nucleobases in *head–tail* arrangement was oxidized to the diplatinum(III) complex *cis*-[X$Pt(NH_3)_2$(μ-mcyt-N^3-N^4)$_2$-$Pt(NH_3)_2$Y](Z)$_n$ (**2**).[9] Subsequently, the axial ligands X and Y were replaced by 9-ethylguanine (Hetgua) by adding this nucleobase to an aqueous solution of **2** (pH ≃ 2) to give *cis*-[{$Pt(NH_3)_2$(Hetgua-N^7)(mcyt-N^3-N^4)}$_2$]$^{4+}$ (**3**). The cation of the title compound **3** $[ClO_4]_4 \cdot 5H_2O$[10,11] is depicted in Fig. 1. Salient structural features are as follows: the Pt–Pt bond length of 2.5868(8) Å is in the typical range for single bonds of diplatinum(III) complexes derived from cisplatin.[12] The two Pt planes form an angle of 20.3(1)°, and the torsional angle about the Pt–Pt vector is 26.9(2)° (N(3C)–Pt–Pt–N(4C)) and 33.2(2)° (N2–Pt–Pt–N1). Pt–N distances in the Pt plane are normal [Pt–N(4C), 2.002(5); Pt–N(3C), 2.043(5); Pt–N(2), 2.056(5) Å] or only slightly elongated [Pt–N(1), 2.070(5) Å]. However, the Pt–N^7 bond [2.189(6) Å] is markedly longer than those typically seen in Pt(II)[13] and Pt(IV)[14] complexes of guanine. The guanine ligand is oriented in such a way, that O^6 escapes any steric clash with O^2 of the mcyt ligand by H bond formation with the two NH_3 groups (N1···O6G, 2.854(8); N2···O6G, 3.101(7) Å; angles: N1–H1A···O6G, 159.8(4); N2–H2B···O6G, 144.2(4)°].

Compound **3** is stable in aqueous solution for at least 7 d. The ^{195}Pt NMR signal at −816 ppm is consistent with a Pt(III) oxidation state and the singlet indicates that the two Pt centers have identical environments. A ^{195}Pt ^{1}H HMQC experiment reveals ^4J coupling between ^{195}Pt and H5 of mcyt (9.2 Hz), ^5J coupling between ^{195}Pt and H6 of mcyt (8.3 Hz), as well as ^3J coupling between ^{195}Pt and H8 of Hetgua (5.2 Hz). While coupling with the cytosine protons are in the expected range,[15] it is noted that ^3J coupling to guanine H8 is rather small as compared to guanine bases bonded to Pt(II) (20–32 Hz[16]) and even to Pt(IV) (12 Hz[14]). It is a consequence of the apparent weak binding of the axial guanine ligands. This situation contrasts the strong binding of a single, C^5 bonded 1-methyluracilyl entity to a diplatinum(III) core,[17] which has some

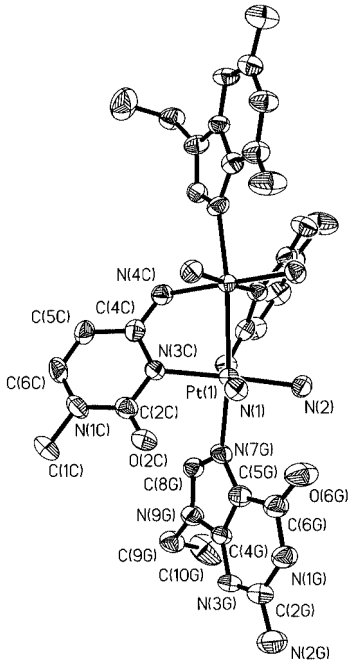


Fig. 1 Crystal structure of cation of *cis*-[{$Pt(NH_3)_2$(Hetgua-N^7)(mcyt-N^3-N^4)}$_2$][$ClO_4]_4 \cdot 5H_2O$(**3**).

structural similarity with the present case as it is another example of a diplatinum(III) complex carrying a nucleobase in an axial position.

The affinity of **2** for the guanine model nucleobase is retained in reactions with the corresponding nucleoside 2′-deoxyguanosine and the nucleotide 5′-dGMP. Binding occurs rapidly, as evident from ^{1}H NMR spectroscopy. Doubling of most resonances is consistent with formation of diastereomers upon combination of the chiral *head–tail* species **2** with the chiral nucleoside/nucleotide.[15] The guanosine adduct is stable in aqueous solution for approximately 1 d, whereas the 5′-GMP compound is stable for at least one week (*e.g.* ^{195}Pt NMR resonance at δ −804 ppm for 5′-dGMP complex). Afterwards the ^{1}H NMR spectra of both species become quite complicated. It is unclear at present whether oxidative degradation processes of either the purine skeleton and/or the sugar moieties take place similarly to the situations encountered with Au(III)[21] and high valent Mn,[22] Ni,[23] or Ru[24] species.

Attempts to bind model nucleobases other than guanine, *e.g.* 1-methylcytosine, 1-methyluracil or 9-methyladenine to **2** under comparable conditions, failed. Thus **2** appears to be highly selective for guanine nucleobases. Whether this feature may be exploited to generate a chemical probe for guanine in nucleic acids remains to be seen.

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9 **2a**: X = NO_2^-, Y = H_2O, Z = ClO_4^-, n = 3; **2b**: X = Y = ONO_2^-, Z = NO_3^-, n = 2; **2c**: X = Y = H_2O, Z = ClO_4^-, n = 4. All three compounds have been characterized by X-ray crystallography. Details will be reported elsewhere. Oxidation of **1** was achieved by any of the following oxidants: HNO_3, $HClO_4$, or $K_2S_2O_8$. In a typical experiment, **1** (82.26 mg; 0.095 mmol) is dissolved in concentrated $HClO_4$ (1.5 ml), the orange solution then diluted with 3.5 ml H_2O and allowed to slowly evaporate. Orange crystals of **2a** are collected in *ca.* 72% yield. ^{1}H NMR (200 MHz, D_2O, δ/ppm) of **2a**: 7.35 (d, ^3J = 7.4 Hz H6), 7.31 (d, ^3J = 7.4 Hz H6), 6.04 (d, ^3J = 7.4 Hz H5), 5.91 (d, ^3J = 7.4 Hz H5), 3.40 (s, CH_3), 3.33 (s, CH_3). ^{195}Pt-NMR (42.998 MHz, D_2O δ/ppm): −1000, −445.

10 Synthesis:10.9 mg (0.06 mmol) of 9-ethylguanine is added to a solution of 32.9 mg (0.03 mmol) of **2a** in water (1 ml). Upon slow evaporation compound **3** crystallizes and is collected as several fractions to give 26 mg (0.017 mmol, 58% yield) **3**. Anal. calcd. for **3**, $C_{24}H_{52}N_{20}O_{25}Cl_4Pt_2$ (1552.84 g mol^{-1}): C 18.57; H 3.38, N 18.04%; found: C 18.8, H 3.1, N 18.2%.

11 Crystal data for **3**: $C_{24}H_{52}N_{20}O_{25}Cl_4Pt_2$ M_r = 1552.84, monoclinic, space group $C2/m$, a = 17.574(4), b = 20.356(4), c = 13.815(3), β = 91.69(3), V = 4940(2) Å^3, Z = 8, D_c = 2.088 g cm^{-3}, μ(Mo-Kα) = 5.978 mm^{-1}, T = 293(2) K, Enraf–Nonius–KappaCCD[18] with graphite monochromator, φ-scans, 6661 independent reflections, R_{int} = 0.044, structure solved by standard Patterson methods[19] and refined by full matrix least squares on F^2 using SHELXL-97[20]. All non-hydrogen atoms were refined anisotropically. Hydrogens were placed at calculated positions and not further refined. One perchlorate is heavily disordered. 368 refined parameters gave R_1 = 0.0428 and wR_2 = 0.1104 for 4665 reflections with $I \geqslant 2\sigma(I)$ and R_1 = 0.0673 and wR_2 = 0.1163 for all data, minimum and maximum features in difference Fourier map were 2.61 and −2.19 e Å^{-3} (near Cl3). CCDC 157798.

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