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Combining four different model nucleobases (uracil, adenine, guanine, cytosine) *via* metal binding and H bond formation in a single compound

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A cyclic arrangement of the four model nucleobases 1-methyluracilate (mura), 9-ethyladenine (eade), 9-ethylguanine (Hegua) and 1-methylcytosine (mcyt), held together by two metal entities [*trans*-$(NH_3)_2Pt^{II}$ and *trans*-$(MeNH_2)_2Pt^{II}$] and multiple H bond interactions, is presented.

Complementary and likewise non-complementary nucleobases can be cross-linked by suitable (usually linear or *trans*-square-planar) metal ions to give ‘metal-modified’ base pairs,[1,2] triples,[2] or quartets.[3] If combined with H bond formation, many variants are possible.[4] Here we report on an example of a nucleobase quartet which combines models of all four RNA bases uracil (U), adenine (A), guanine (G) and cytosine (C) in a single compound. In {*trans,trans*-[$(NH_3)_2$Pt(mura-N^3)(eade-N^7,N^1)Pt$(MeNH_2)_2$(Hegua-N^7)•mcyt]}$_2$[mcyt•Hmcyt][ClO_4]$_{4.5}$-[NO_3]$_{2.5}$•8.7H_2O **5** (Fig. 1) the four bases are joined *via* two linear metal entities and multiple H-bonding interactions. These include a Watson–Crick pair between Hegua and mcyt, which is reinforced by a fourth H-bond between the second amino proton of mcyt and a carbonyl oxygen atom of mura. In addition there is hemiprotonated 1-methylcytosine [mcyt•Hmcyt]$^+$ present in the lattice, displaying the well-known[5] threefold H bonding scheme.

The title compound was prepared in a stepwise fashion from *trans*-[$(NH_3)_2$Pt(mura-N^3)Cl] **1** as outlined in Scheme 1. Intermediates **2**–**4** have been isolated.‡ The title compound **5** was crystallized from an aqueous solution of **4** (20 mg, 0.0167 mmol dissolved in 3 mL of water), to which an excess of mcyt (6.27 mg, 0.05 mmol) had been added, with the pH adjusted to 5.3 with HNO_3. Colourless crystals of **5** suitable for X-ray crystallography§ were obtained upon slow evaporation of the solvent at 22 °C.

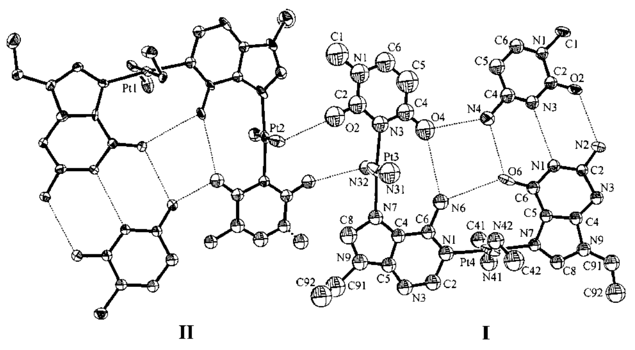


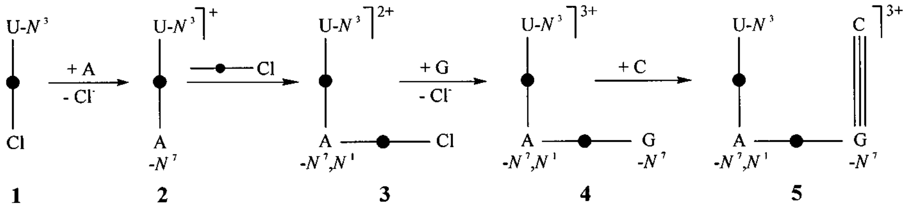
Fig. 1 View from the top of the two crystallographically independent cations **I** and **II** in **5**. The ellipsoids are drawn at 30% probability.

Compound **5** crystallizes with two crystallographically independent cations (**I**, **II**) in the asymmetric unit, which display two slightly different quartets. In the first one (**I**), the four bases give, despite moderate dihedral angles between each other, the picture of an essentially coplanar base quartet. In contrast, in cation **II** the guanine, cytosine entity on one hand, and the uracil, adenine entity on the other are markedly propeller-twisted about the Hegua-N^7–Pt^1–eade-N^1 bonds, thereby making in particular the two pyrimidine bases markedly non-coplanar (Table 1). This feature is reminiscent of the situation with an open base quartet consisting of four purine bases (A_2, G_2) and three metal ions (Pt^{II}).[3] In the present case (**II**) disorder (60 : 40) of the uracil base about the Pt^2–N^3-mura bond facilitates this feature: If, as is the case in the predominant rotamer, O^2 of mura participates in H bonding within the quartet, the CH_3 group of mura is pointing toward mcyt, thereby causing repulsion between C^5H (mcyt) and CH_3 (mura). Another effect is stacking of the guanine nucleobases of two cations **II** (3.2 Å, symmetry operation $-x + 2$, $-y + 1$, $-z + 2$).

As expected from relative orientations of the three platinated bases, exocyclic groups are involved in weak H bonding interactions (Table 1). Geometries of the Watson–Crick pairs in **I** and **II** are normal.[6] **I** and **II** are joined by two additional H bonds between NH_3 groups of Pt^2 and Pt^3 as well as O^2 and O^4/O^2 of mura ligands (Fig. 1).

We have previously observed[7] that Pt–N vectors in diplatinated adenine bases are close to perpendicular, and found that in mixed di- or tri-nuclear purine complexes this feature is likewise confirmed.[1–3] As evident from the data of **5**, addition of the pyrimidine base mura causes a marked deviation toward smaller angles. For example, in **I** this angle is 84.4(7)° and in **II** it is even smaller, 80.7(5)°. Considering the relatively large errors in nucleobase angles, it is not possible to relate this fact to a unique structural feature, *e.g.* variations in external ring angles at the sites of metal coordination.

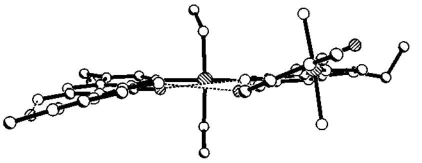
In conclusion, a compound (**5**) has been prepared which combines four different model RNA nucleobases in a single compound. It displays simultaneously a metal-modified Hoogsteen pairing scheme (A, U), a metal-modified mispair (A, G), and a Watson–Crick pair (G, C). In principle, a corresponding quartet containing the DNA bases G, C, A and T (T = thymine) of type **II** is feasible. The (nearly) coplanar arrangement of the three metalated nucleobases in **5** contrasts that of a compound with three different bases (G, A, C) combined in a mononuclear complex, with the nucleobases arranged mutually perpendicu-



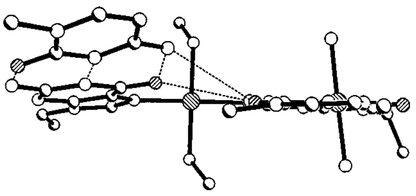
Scheme 1

Table 1 Selected dihedral angles (°) and H-bonding distances (Å) in the two independent cations **I** and **II** in **5**

	I	**II**
U/A	17.9(10)	6.1(5)
A/G	14.0(7)	11.6(3)
G/C	14.7(9)	14.0(6)
C/U	5.9(9)	26.1(7)
$O^6(G)\cdots N^6(A)$	3.18(3)	3.21(2)
$N^6(A)\cdots O^4(U)$	3.31(4)	—
$N^6(A)\cdots O^4/O^2(U)$	—	3.09(2)
$O^4(U)\cdots N^4(C)$	2.82(4)	—
$O^4/O^2(U)\cdots N^4(C)$	—	3.15(2)
$N^2(G)\cdots O^2(C)$	2.80(2)	2.83(2)
$N^1(G)\cdots N^3(C)$	2.95(3)	2.89(2)
$O^6(G)\cdots N^4(C)$	2.86(3)	2.89(2)
$N^7(G)$–$N^1(A)$/Pt^3–$N^7(A)$	84.4(7)	—
$N^7(G)$–$N^1(A)$/Pt^2–$N^7(A)$	—	80.7(5)



I



II

Fig. 2 View from the side of the two crystallographically independent cations **I** and **II** in **5**.

lar.[8] Considering the ever increasing number of RNA tertiary structures,[9] **5** represents a unique example of an interplay between nucleobases, metal ions and H bonds. Preliminary solution studies indicate clearly that H bonding between the metalated G base and the C model nucleobase is not only taking place in the solid state but also in solution.

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Notes and references

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‡{*trans,trans*-[$(NH_3)_2$Pt(mura-N^3)(eade-N^7,N^1)Pt$(MeNH_2)_2$(Hegua-N^7)•mcyt]}$_2$ [mcyt•Hmcyt][ClO_4]$_{4.5}$[NO_3]$_{2.5}$•8.7H_2O **5** was synthesized as follows: compounds **1** and **2** have been synthesized according to ref. 1, where 1-methylthymine was used instead of mura. The yields were 68% for *trans*-[$(NH_3)_2$Pt(mura-N^3)Cl] **1** and 63% for *trans*-[$(NH_3)_2$Pt(mura-N^3)(eade-N^7)]NO_3 **2**.

To a 20 mM aqueous solution of **2**, 1.2 equiv. of *trans*-[$(MeNH_2)_2PtCl_2$] were added and stirred for 36 h at 45 °C. Precipitated excess of *trans*-[$(MeNH_2)_2PtCl_2$] was filtered off and the solution concentrated at room temperature to 3 mL. After addition of 4 equiv. of $NaClO_4$ and cooling at 4 °C for 24 h, *trans,trans*-[$(NH_3)_2$Pt(mura-N^3)(eade-N^7,N^1)Pt$(MeNH_2)_2$Cl]-[ClO_4]$_2$•3 H_2O (**3**) could be isolated as a white powder in 61% yield. Anal. Calc. for $C_{14}H_{30}N_{11}O_{10}Cl_3Pt_2$: C, 15.8; H, 3.4; N, 14.5. Found: C, 15.8; H, 3.2; N, 14.5 %.

To a 8 mM aqueous solution of **3**, 0.95 equiv. of $AgNO_3$ were added and stirred at 40 °C in the dark overnight. After removal of AgCl, 1.2 equiv. of Hegua were added and the solution (pH 4.0, HNO_3) stirred at 40 °C for 36 h. The solution (pH 7.1, NaOH) was slowly concentrated at room temperature and precipitated excess of Hegua removed. The residue was recrystallized from water to give **4** in its hemideprotonated form {*trans,trans*-[$(NH_3)_2$Pt(mura-N^3)(eade-N^7,N^1)Pt$(MeNH_2)_2$($H_{0.5}$egua)]-[ClO_4]$_{2.5}$•1.25 H_2O}$_2$ in 28% yield. Anal. calc. for $C_{42}H_{77}N_{32}O_{26}Cl_5Pt_4$: C, 20.6; H, 3.4; N, 18.3. Found: C, 20.7; H, 3.4; N, 18.5%.

To a 5 mM aqueous solution of **4** (pH 5.3, HNO_3), 3 equiv. of mcyt were added and the solution evaporated to dryness at room temperature, which gave yellow crystals of **5** suitable for X-ray crystallography.

§ *Crystal data* for **5**: $C_{62}H_{122.4}O_{44.2}N_{46.5}Cl_{4.5}Pt_4$, M_r = 3166.55, triclinic, space group $P\,\bar{1}$, a = 15.004(3), b = 17.795(4), c = 21.662(4) Å, α = 97.81(3), β = 103.21(3), γ = 92.16(3)°, U = 5564.2(20) Å^3, Z = 2, D_c = 1.890 g cm^{-3}, μ(Mo-Kα) = 5.226 mm^{-1}, T = 126(2) K, Enraf–Nonius–KappaCCD[10] with graphite monochromator, ω-scans, 10 299 independent reflections, R_{int} = 0.043, structure solved by standard Patterson methods[11] and refined by full matrix least squares on F^2 using SHELXL-93.[12] Only a few non hydrogen atoms were refined anisotropically, because of the poor reflection to parameter ratio. Hydrogens were placed at calculated positions and no further refined. The methyl group of the uracil molecule of cation **II** is disordered over two positions (occupancy factors 0.6 and 0.4) and also the oxygens of three perchlorate anions and some of the water molecules show disorder. Another half occupied perchlorate anion shares the same position with a 25% occupied nitrate anion. 981 refined parameters gave R_1 = 0.0670 and wR_2 = 0.1697 for 6896 reflections with $I \geq 2\sigma(I)$ and R_1 = 0.1062 and wR_2 = 0.1947 for all data, minimum and maximum features in the difference Fourier map were −2.786 and 2.479 e Å^{-3} (near Pt). CCDC 182/1087. See http://www.rsc.org/suppdata/cc/1999/19/ for crystallographic files in .cif format.

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