Uracil quartet formation through non-covalent interaction with a neutral metal ammine complex

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Cocrystallization of 1-methyluracil (Hmura) and *trans*-[PtCl₄(NH₃)₂] yields an adduct of composition [PtCl₄(NH₃)₂·2 Hmura with two types of uracil quartets, one of which is relevant to that formed in tetraplex RNA.

Nucleobase quartets, in particular of guanine (G), have been the subject of considerable interest.[1] More recently, the existence of uracil (U)[2] and thymine (T)[3,4] quartets in four-stranded RNA and DNA helices has been demonstrated applying NMR spectroscopy. Both G_4 and T_4 quartets require the presence of alkali- or alkaline-earth metal cations in their center for stabilization. Although probably more stable than T_4 quartets owing to the absence of the 5-methyl group, U_4 quartets appear not to have been considered intrinsically stable entities. Their formation in RNA is certainly aided by an existing $(G_4)_n$ core, with U_4 layered on top.

Here we report the X-ray crystal structure analysis of a 1-methyluracil (Hmura) adduct of the neutral metal complex *trans*-[PtCl₄(NH₃)₂]† which reveals the presence of two types of uracil quartet structures.‡ There are two crystallographically independent Pt^{IV} entities, Pt(1) (on a fourfold axis) and Pt(1′) (on a S4 axis), the structures of which are normal (Fig. 1). Both octahedral metal complexes are sandwiched between two uracil quartets (I, II), each in such a way that the NH₃ groups form hydrogen bonds to four exocyclic oxygen atoms of the Hmura bases. Specifically, in quartet I N(7) and N(8) ammine protons of two Pt units form hydrogen bonds with four O(2) oxygens (Fig. 2). In quartet II N(7′) ammine protons are hydrogen bonded to four O(4) oxygens (Fig. 3). In both cases, the four oxygens form a square [dimensions 3.643(4) × 3.643(4) Å between O(2) sites in I; 3.443(5) × 3.443(5) Å between O(4) sites in II]. Distances between the ammine N atoms and these
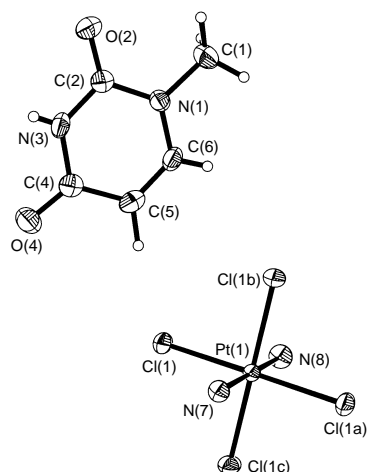
oxygens are 3.052(4) Å [N(7)–O(2)] and 3.149(5) Å [N(8)–O(2)] for I, as well as 2.948(4) and 3.047(4) Å [N(7′)–O(4)] for II. Although protons at the NH₃ ligands were not located, the scenario, NH₃ group above a square of acceptor sites, probably indicates dynamically disordered H atoms of the NH₃ groups.[5] Both quartets are strongly non-planar. Quartet I has roughly the shape of a cup, with O(2) atoms representing its bottom, while quartet II is saddle-shaped. Only II displays the four cyclic H bonds between N(3) and O(4) sites of adjacent nucleobases [3.059(6) Å] seen in RNA uracil quartets and therefore can be considered a model of it.[6] It is to be noted that each Hmura takes part in both types of quartets.
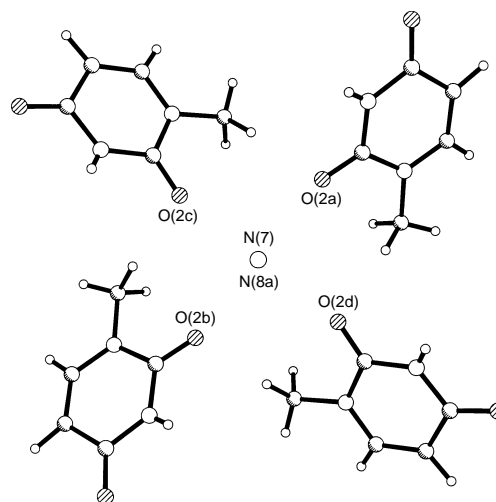

Fig. 2 View of quartet I; N(7) and N(8) ammine groups are 1.636(7) Å above and 1.810(7) Å below the plane formed by the four O(2) oxygen atoms
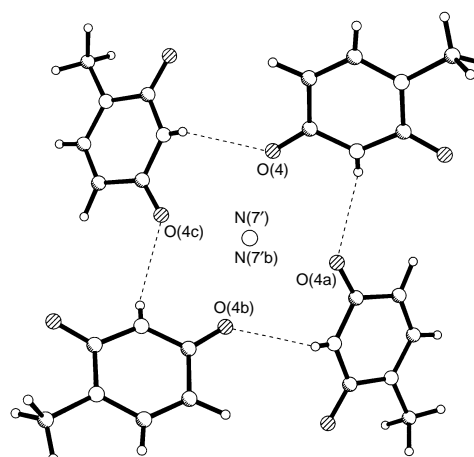

Fig. 1 Molecular structure of the *trans*-[PtCl₄(NH₃)₂] entity and of the Hmura ring. Selected bond lengths (Å) and angles (°) for the Pt complex: Pt(1)–N(7) 2.069(6), Pt(1)–N(8) 2.064(7), Pt(1)–Cl(1) 2.3137(10), N(7)–Pt(1)–N(8) 180.000(1), N(7)–Pt(1)–Cl(1) 89.85(3), N(8)–Pt(1)–Cl(1) 90.15(3). The geometry of the Hmura ring does not differ significantly from published data.[7]

Fig. 3 View of quartet II with cyclic N(3)H···O(4) hydrogen bonds indicated. The N(7′) ammine groups of Pt(1) are 1.751(5) Å each below and above the plane formed by the four O(4) oxygen atoms. The four uracil bases are markedly non-planar and form angles of 44° between each other.
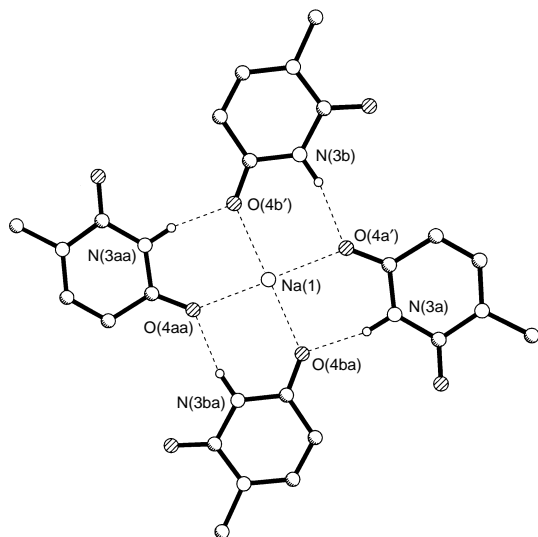
Fig. 4 View of quartet III as found in [Na(Hmura)₄][AuCl₄]. The four Hmura bases are coplanar with Na(1). The protons at the N(3) sites are at calculated positions. Selected interatomic distances (Å): O(4a′)···N(3b) 2.83(2), O(4a′)···O(4b′) 3.28(2), O(4a′)···Na(1) 2.336(7), O(4b′)···Na(1) 2.301(8).

The difference in hydrogen-bond formation between Hmura [pairwise N(3)H···O(4) hydrogen bonds of 2.814(2) Å][7] and that observed in [PtCl₄(NH₃)₂]·2Hmura is also reflected in differences in the IR spectra.§

In the course of this work, it occurred to us that we had, without recognizing it then,[8] prepared a planar uracil quartet III already two years prior to the first report of U₄ in a RNA tetraplex.[2] In [Na(Hmura)₄][AuCl₄][8] (Fig. 4) the four O(4) oxygens form a square of 3.28 Å and four hydrogen bonds, between N(3) and O(4) sites of *ca.* 2.83 Å, with Na⁺ in the center.

In summary, the apparent ease of quartet formation of Hmura in the presence of suitable partners (Pt–NH₃ groups, Na⁺) suggests that U₄ structures in RNA may be more readily formed than generally anticipated. Stabilization may not only be brought about by a G₄ support and/or alkali-metal ion binding, but also by additional hydrogen bonding. The NH₃⁺ group of lysine, which is ubiquitous in many nucleic acid binding proteins, could be a candidate in this respect. Finally, [PtCl₄(NH₃)₂]·2Hmura represents, to the best of our knowledge, the first example of a neutral metal ammine complex interacting with a nucleobase in a specific manner. Hydrogen bonding of cationic metal complexes, *e.g.* of [Co(NH₃)₆]³⁺ with DNA is known to have dramatic effects on the DNA stucture.[9]

Footnotes

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† *trans*-[PtCl₄(NH₃)₂]·2Hmura was obtained in two ways: (*a*) *trans*-[Pt(NH₃)₂(mura-*N*³)₂] (0.65 mmol; obtained from *trans*-[Pt(NH₃)₂(H₂O)₂][NO₃]₂ and 2–3 equiv. of Hmura in a similar way to the *cis*-isomer)[10] was suspended in water (10 ml) at 40 °C; 4 M HCl (4 ml) was added dropwise until all the solid was dissolved. Heating was continued for 1 h and a pale yellow precipitate {*trans*-[PtCl₂(NH₃)₂] identified by IR spectroscopy} was removed by filtration. Slow evaporation of the filtrate at room temp. gave crystals of *trans*-[PtCl₄(NH₃)₂]·2Hmura in 12% yield. Oxidation has apparently been brought about by air. Satisfactory elemental analyses were obtained for C, H and N {*trans*-[PtCl₄(NH₃)₂]·2Hmura, C₁₀H₁₈Cl₄N₆O₄Pt. Found (Calc.) C, 19.1 (19.27); H, 2.9 (2.91); N, 13.5 (13.49)%}.

(*b*) To a solution of *trans*-[PtCl₄(NH₃)₂][11] (0.3 mmol) in water (10 ml) was added Hmura (0.6 mmol); the mixture was briefly heated until all solid material had dissolved. Slow evaporation at room temp. gave crystals of *trans*-[PtCl₄(NH₃)₂]·2Hmura (identified by IR spectroscopy) in 93% yield.

‡ *Crystal data*: $C_{10}H_{18}Cl_4O_4N_6Pt$; $M = 623.19$, tetragonal, space group $P4/n$, $a = b = 15.496(2)$, $c = 7.580(2)$ Å, $U = 1820.2(6)$ Å³, $Z = 4$, $F(000) = 1192$; $D_c = 2.274$ Mg m⁻³; μ(Mo-Kα) = 8.326 mm⁻¹ yellow cube; size, $0.15 \times 0.15 \times 0.15$ mm. Data collection and processing: Enraf-Nonius-Mach3 diffractometer (graphite-monochromated Mo-Kα radiation), $T = 293(2)$ K; ω–2θ scans; θ range 2.63–24.97°; index ranges $-13 \leq h \leq 18$, $-13 \leq k \leq 18$, $0 \leq l \leq 9$; 3280 reflections measured, 1600 independent ($R_{int} = 0.0259$); 1356 observed [$F_o > 4\sigma(F_o)$]. Structure solution and refinement: Patterson syntheses (SHELXS-86[12]), full-matrix least squares on F^2 (SHELXL-93[13]); hydrogen atoms found in difference Fourier synthesis and refined isotropically, all other atoms anisotropic; 140 parameters refined; empirical absorption correction (ψ-scans); min., max. corrections 0.5515, 0.9972; $R_1 = 0.0306$; $wR_2 = 0.0496$ (all data); max., min. residual electron density 0.596, -0.764 e Å⁻³. Atomic coordinates, bond length and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number 182/505.

§ The IR spectrum of *trans*-[PtCl₄(NH₃)₂]·2Hmura (KBr pellet; Bruker FTIR spectrometer IFS 28) and that of Hmura[14] differ, as expected, but the former is not a simple superposition of spectra of Hmura and *trans*-[PtCl₄(NH₃)₂].[15] This is particularly well seen in the 900–700 cm⁻¹ region, *e.g.* Hmura: 870s (br), 805s, 757s, 722m; *trans*-[PtCl₄(NH₃)₂]: 878m (br); *trans*-[PtCl₄(NH₃)₂]·2Hmura: 823s, 782s, 758m, 738w, 719m. Similarly, in the Raman spectra (solid state; Jobin Yvon, T 64000; Spectra Physics laser, $\lambda = 514.5$ nm) both the intense ν(Pt–Cl) and ν(Pt–N) modes[15] of *trans*-[PtCl₄(NH₃)₂] and the characteristic Hmura ring modes have undergone shifts as compared to the pure components.

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6 From a strictly geometrical point of view, I could be considered a model of a T quartet. If atoms are interchanged, *e.g.* N(1)CH₃ is considered a C(5)CH₃ group of T, O(2) a O(4) in T *etc.,* the resulting entity would correspond to T₄ with the methyl groups pointing to the center of the quartet and no hydrogen bonds between the four thymines; *cf.* also discussions in ref. 3.

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