If Watson–Crick and Hoogsteen sites of guanine are blocked, hydrogen bonding with cytosine is *via* N^2 and N^3

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A novel hydrogen bonding scheme between cytosine and guanine nucleobases is observed if both N^1 and N^7 positions of the guanine are blocked by a metal entity and a methyl group, respectively.

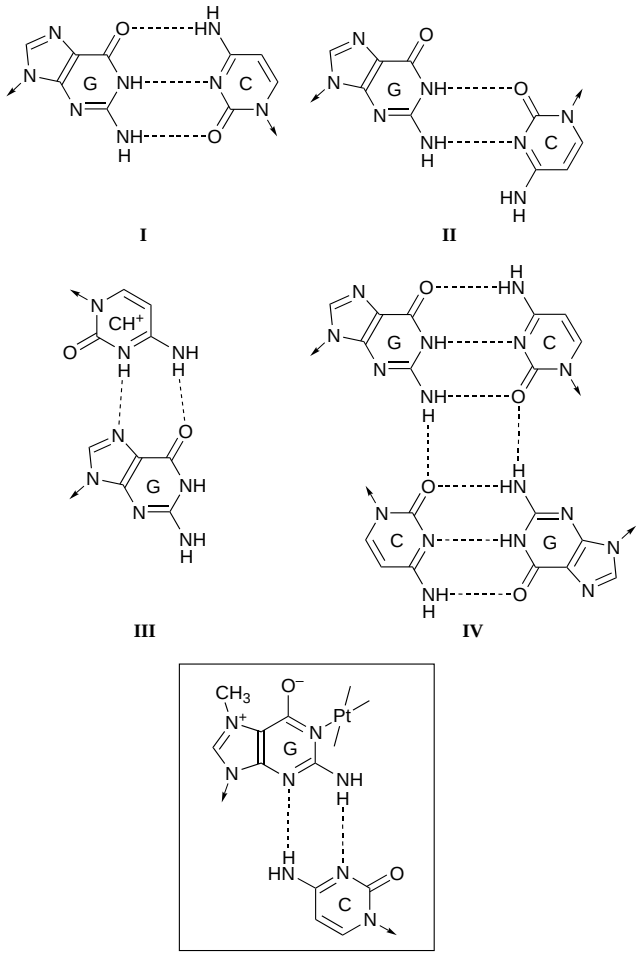
Chemical modification of nucleobases can result in severely altered hydrogen bonding patterns as far as base selectivity and/or hydrogen bonding sites are concerned. When occurring in DNA, potentially dangerous consequences can be expected, as known in the case of guanine methylated at the 6-position.[1] Here we demonstrate, on a model nucleobase level, that the complementary nucleobases guanine (G) and cytosine (C) associate in a hitherto unknown fashion if both Watson–Crick, and Hoogsteen hydrogen bonding sites are blocked.

Base pairing between G and C is predominantly according to the Watson–Crick scheme (Scheme 1, **I**), and very rarely, *e.g.* between G_{15} and C_{48} in yeast $tRNA^{Phe}$, of the reversed Watson–Crick type (**II**).[2] With protonated cytosine, and possibly also with neutral cytosine in a rare tautomeric form,[3] pairing is of the Hoogsteen type (**III**). In addition to these principal hydrogen bonding patterns, there is also the possibility of association to quartet structures through dimerization of two Watson–Crick pairs *via* hydrogen bonds (**IV**).[4]

Metal binding at the N^7 site of G still permits types **I** and **IV** hydrogen bonding patterns.[5,6] Alternatively it can lead to a 'metal-modified' Hoogsteen pattern[5] or, upon guanine deprotonation at N^1, to either mispairing with free guanine[7] or formation of a quite unusual nucleobase quartet.[8] Additional blockage at N^1 leads to the pattern **V** hereafter.

7,9-Dimethylguanine (7,9-dmgua), a model of the rare nucleobase 7-methylguanosine, forms 2:1 complexes with *trans*-$Pt^{II}am_2$ (am = NH_3 or NH_2Me) of composition *trans*-$[Ptam_2(7,9\text{-dmgua-}N^1)_2]X_2{\cdot}nH_2O$. Recently we have published the X-ray structure analyses for the combination am = NH_2Me, X = NO_3^-, n = 0.[9] With am = NH_2Me, X = ClO_4^- cocrystallization with the model nucleobase 1-methylcytosine (mcyt) from water† gave crystals suitable for X-ray crystallography.‡

As can be seen in Fig. 1, each mcyt molecule forms two strong hydrogen bonds; one to a coplanar 7,9-dmgua ligand, N(3a′)···N(2) 2.881(8) Å, and the second one to the amine group of NH_2Me of another cation lying below the pyrimidine [O(2′)···N(10) 2.878(6) Å]. Furthermore the pyrimidine rings are stacking (3.4 Å) with the platinated purine ligands leading to an arrangement like tiles of a roof. These strong intermolecular interactions bring the exocyclic amino group of mcyt in relatively close proximity to N(3) of 7,9-dmgua [N(3)···N(4a′) 3.194(8) Å] leading to an arrangement as shown in Fig. 2. Although the latter distance is at the upper end of a hydrogen bond, the sum of the van der Waals radii of H and N (1.20 Å + 1.55 Å = 2.75 Å)[10] is still larger than the distance between the H and the acceptor N [2.340(8) Å], so it can still be considered as such,[11] especially in view of the near-coplanarity of the two bases [dihedral angle 2.3(3)°].



Scheme 1

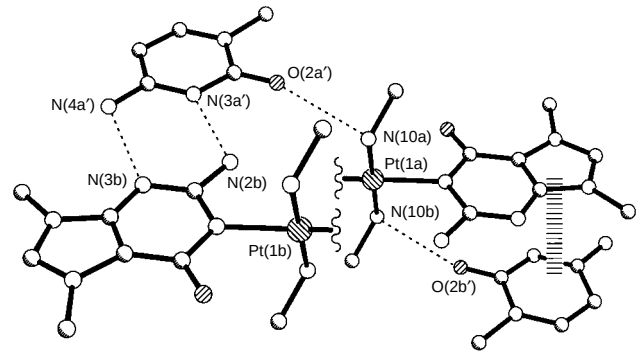


Fig. 1 Section of packing of cations and mcyt in the crystal lattice of *trans*-$[Pt(MeNH_2)_2(7,9\text{-dmgua-}N^1)_2][ClO_4]_2{\cdot}2$mcyt. There is stacking between 7,9-dmgua ligands and mcyt (distance 3.4 Å), one hydrogen bond of 2.878(6) Å between O(2a′) of the free mcyt and N(10a) of the NH_2Me group and another short hydrogen bond between N(3a′) and N(2b) [2.881(8) Å]. At each cation one 7,9-dmgua ligand is omitted for clarity.

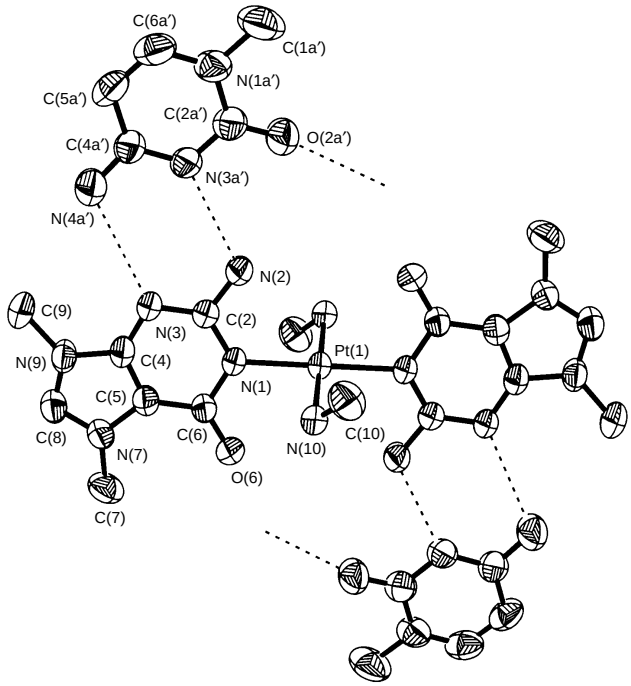


Fig. 2 Hydrogen bonding scheme between 7,9-dmgua and mcyt in *trans*-[Pt(MeNH$_2$)$_2$(7,9-dmgua-*N*^{1})$_2$][ClO$_4$]$_2$·2mcyt with two hydrogen bonds, N(2)···N(3′) 2.881(8) Å and N(3)···N(4′) 3.194(8) Å, between the two nucleobases. Hydrogen bond formation between O(2) sites and N(10) groups is schematically shown.

Involvement of guanine N^2 and N^3 sites in hydrogen bonding with another nucleobase has some precedence, although not with cytosine. In one of the four types of GA mispairs found in RNA,[12] as well as in a base quartet formed as a consequence of crystal packing, the guanine N^3 positions act as hydrogen bond acceptors.[13]

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Footnotes and References

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† *trans*-[Pt(MeNH$_2$)$_2$(7,9-dmgua-*N*^{1})$_2$][ClO$_4$]$_2$·2mcyt was obtained from a 10 mM aqueous solution of *trans*-[Pt(MeNH$_2$)$_2$(7,9-dmgua-*N*^{1})$_2$[ClO$_4$]$_2$ with 2 equiv. of mcyt. After 5 d slightly yellow crystals, suitable for X-ray diffraction studies could be isolated in 38% yield. Anal. calc. for C$_{26}$H$_{42}$O$_{12}$N$_{18}$Cl$_2$Pt: C, 29.3; H, 4.0; N, 23.7. Found: C, 29.4; H, 4.1; N, 24.1%.

‡ *Crystal data for trans*-[Pt(MeNH$_2$)$_2$(7,9-dmgua-*N*^{1})$_2$][ClO$_4$]$_2$·2mcyt: C$_{26}$H$_{42}$N$_{18}$O$_{12}$Cl$_{12}$Pt, M = 1064.77, triclinic, space group $P\bar{1}$, a = 6.623(1), b = 9.819(2), c = 15.261(3) Å, α = 85.47(3), β = 82.85(3), γ = 79.73(3)°, U = 967.3(3) Å^3, Z = 2, D_c = 1.828 g cm^{-3}, μ(Mo-Kα) = 3.848 mm^{-1}, F(000) = 532, T = 293 K. The crystals were slightly yellow platelets with a size of 0.625 × 0.125 × 0.125 mm. Intensity data were collected on a Nonius KappaCCD with graphite-monochromated Mo-Kα radiation (λ = 0.710 69 Å). 3354 independent reflections were measured and 3012 reflections with $F_o > 4\sigma(F_o)$ were used in the refinement. Reflections which were partly measured on previous and following frames were used to scale these frames on each other. This procedure in part eliminates absorption effects and also considers crystal decay, if present. The structure was solved by Patterson method (SHELXS-86[14]) and refined on F_o^2 (SHELXS = 93[15]). Refinement and positional and anisotropic thermal parameters for all non-hydrogen atoms (276 parameters) converged to R_1 = 0.0365 and wR_2 = 0.0798. The final Fourier difference map showed residual electron density in the range of 2.612 to −0.752 e Å^{-3}. CCDC 182/676.

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