A Novel Metal Binding Mode of Cytosine Nucleobases: N(3),N(4) Chelation

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The formation and crystal structure of the first example of an anionic 1-methylcytosine [deprotonated at the exocyclic amino group N(4)] acting as a chelating ligand for *trans*-$(NH_3)_2Pt^{IV}$ through N(3) and N(4), *trans,trans*-diamminebis(1-methylcytosinato)platinum(IV) dinitrate dihydrate, is reported.

Metal ion–nucleobase interactions are of significance with respect to changes in nucleic acid structure[1] and the possible biological consequences.[2] Cytosine is a particularly versatile ligand with several types of metal binding known (Figure 1). Neutral cytosines [N(1) position blocked] have been shown to bind metals in the majority of cases through N(3), (I), but also through O(2), (II), or simultaneously through both atoms, either bridging, (III), or chelating (IV).[3] Two modes of metal co-ordination to anionic cytosine residues [deprotonated at the exocyclic amino group N(4)] have been reported to date: monofunctional binding, (V)[4] and N(3),N(4) bridging, (VI).[5] Certainly the most striking aspect of metal binding to the deprotonated amino group is the fact that it occurs in weakly basic or even moderately acidic media, despite the rather weak acidity of the amino proton ($pK_a \approx 16.7$).[6] As has previously been suggested by ourselves,[3b] this finding could be explained by the fact that deprotonation of the amino group and subsequent metallation takes place in a condensation reaction between the NH_2 group and a M–OH moiety. The results presented in this communication, N(3),N(4) chelate formation, (VII), strongly support this interpretation.

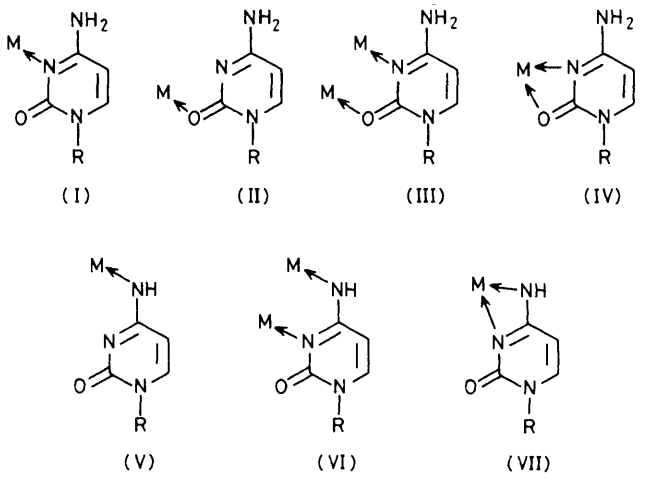

Figure 1. Crystallographically confirmed metal co-ordination modes to N(1)-substituted cytosines.

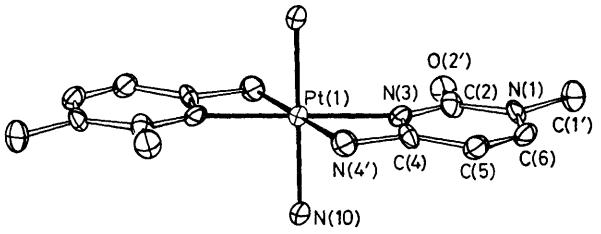

Figure 2. Molecular cation of *trans,trans*-$[Pt(NH_3)_2(C_5H_6N_3O)_2]$-$(NO_3)_2 \cdot 2H_2O$.

trans,trans-Diamminebis(1-methylcytosinato-N^3,N^4)platinum(IV) dinitrate dihydrate, *trans,trans*-$[Pt(NH_3)_2(C_5H_6N_3O)_2](NO_3)_2 \cdot 2H_2O$, was prepared from *trans*-$[Pt(NH_3)_2(C_5H_7N_3O)_2](NO_3)_2$ [7] ($C_5H_7N_3O$ = neutral 1-methylcytosine) which was oxidized by H_2O_2 to give the Pt^{IV} complex *trans,trans,trans*-$[Pt(NH_3)_2(C_5H_7N_3O)_2(OH)_2](NO_3)_2 \cdot 2H_2O$.† Brief warming (50—60 °C) of an acidified (HNO_3) aqueous solution of this compound (150 mg in 10 ml H_2O, colourless, pH 2.6—3) resulted in formation of a yellow solution. On slow evaporation, several crops of yellow cubic crystals of *trans,trans*-$[Pt(NH_3)_2(C_5H_6N_3O)_2](NO_3)_2 \cdot 2H_2O$ were obtained. The crystals were washed with a small amount of water and dried in air. Total yield 90 mg.‡ (At a later stage of the crystallization process, a second, as yet unidentified, complex was isolated.)

The centrosymmetric cation of this compound is shown in Figure 2.§ Pt co-ordination is through N(3) of the cytosine ring and through the deprotonated amino group N(4), leading to two four-membered chelate rings about Pt. The Pt co-ordination is completed by two mutually *trans* NH_3 groups, which are at right angles to the chelate rings. Details of the chelate ring structure are given in Figure 3.

The Pt–N(3) and Pt–N(4′) distances are short and identical, in contrast to most N(3),O(2) chelates, which have one short [M–N(3)] and one considerably longer bond [between the metal atom and O(2)]. These Pt–N distances are close to those observed for Pt^{IV} complexes of neutral 1-methylcytosine [2.061(6)—2.082(5) Å].[8] Chelation causes enormous deviations in the bond angles about Pt from the normal 90°: 64° for N(3)–Pt–N(4′) and 116° for N(3)–Pt–N(4′*). Several ring angles are also affected: while monodentate Pt^{IV} co-ordination to neutral 1-methylcytosine leads to the expected angles close to 120° about N(3) and C(4),[8] chelate formation

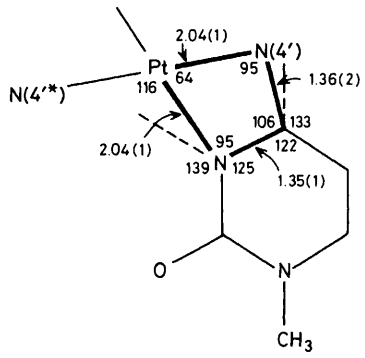

Figure 3. Geometry of the Pt^{IV}-containing chelate ring. Dotted lines indicate orientations of Pt–N(3) and C(4)–N(4) vectors in complexes of monodentate N(3)–Pt^{IV} binding. Bond lengths in Å, bond angles in °.

severely disturbs this regularity (*cf.* Figure 3). The four-membered chelate ring is approximately planar, as is the heterocyclic ring. Maximum deviations from the best plane of the 1-methylcytosinato ligand are 0.03 Å for N(1) and 0.02 Å for both N(4′) and Pt.

In conclusion, this complex, which represents the first crystallographically confirmed example of N(3),N(4) chelation of a metal to a cytosine nucleobase, demonstrates that N(4) deprotonation and metal binding occur in a condensation reaction involving a hydroxo ligand, even in acidic media as well as exemplifying the enormous angular strain Pt^{IV} can withstand in order to accomplish chelate formation. Whether or not our finding is of any relevance to the co-ordination chemistry of Pt^{IV} antitumour agents of the type *cis,cis,trans*-$Pt(a)_2Cl_2(OH)_2$ (a = NH_3 or $Me_2CH_2NH_2$)[9] remains to be seen.

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† The identity of this compound was established by elemental analysis, ^1H n.m.r. spectroscopy, and *X*-ray crystallography.[8]

‡ Satisfactory C, H, N elemental analyses were obtained.

§ *Crystal data:* $C_{10}H_{22}N_{10}O_{10}Pt$, M = 637.42, monoclinic, space group $P2_1/c$, a = 7.230(3), b = 10.576(4), c = 13.186(2) Å, β = 100.92(3)°, U = 990.0 Å^3, Z = 2, D_m = 2.13, D_c = 2.138 g cm^{-3}, λ = 0.71069 Å. Crystal size *ca.* 0.1 × 0.1 × 0.1 mm. Data were collected at room temperature up to θ = 27°. Lorentz, polarisation, and empirical absorption corrections were applied. 2165 Independent reflections were obtained and the 1419 reflections with $F_o \geq 2\sigma(F_o)$ were used for the calculations. The structure was solved by the Patterson method. Refinement using anisotropic temperature factors led to R = 0.048, R_{wF} = 0.056. Hydrogen atoms were ignored during the structure calculations.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.