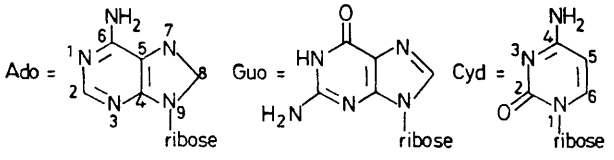
Interaction of *cis*-Diaminotolueneplatinum(II) with Nucleosides: Evidence for Guanosine O(6).N(7) Chelation by Platinum

By JEAN DEHAND and JEANNE JORDANOV
(*Laboratoire de Chimie de Coordination, 4, rue Blaise Pascal, 67008 Strasbourg Cedex, France*)

Summary The binding of the anti-tumour agent *cis*-[Pt(dat)Cl_2] (dat = 3,4-diaminotoluene) to nucleosides is reported; adenosine and cytidine act as monodentate ligands, *via* N(7) or N(3), respectively, and guanosine behaves as a bidentate ligand, the Pt atom being firmly bound at N(7) and weakly *via* O(6).

THE initial discovery[1] that certain Pt complexes may be very effective in the treatment of several different types of cancer has led to extensive studies of their possible mechanism of action. Some recent results[2,3] provide evidence for a specific binding of *cis*-[$Pt(NH_3)_2Cl_2$] to DNA rich in guanine and cytosine. An unusual Pt–guanosine chelate has been proposed,[3] although few reports are known to date of Pt atoms being bound to a ketone group.[4,5]



To provide further evidence for the Pt binding sites on nucleosides, we report a study of the interaction of an active anti-tumour agent, [Pt(dat)Cl_2] (dat = 3,4-diaminotoluene)[6] with adenosine (Ado), cytidine (Cyd), and guanosine (Guo).

In the adenosine complex, the ν (C=N) i.r. vibrations either appear at lower frequencies, or are split upon co-ordination, while the NH_2 vibrations remain essentially the same. Moreover, the n.m.r. signal of H(8), close to N(7), is the only one to be shifted downfield. Thus adenosine appears to bind only through the N(7) ring nitrogen.

In the cytidine complex, the total disappearance of the ν (C=N) i.r. band at 1615 cm^{-1} suggests a co-ordination through the ring nitrogen atoms. In the n.m.r. spectrum, the shift of the H(5) doublet downfield is greater than that for H(6). This indicates that H(5) is closer to the co-ordination site; since N(1) is also sterically less accessible because of the ribose ring, N(3) appears as the most probable co-ordination site. The N(4)H_2 lone electron pair participates in π-bonding to the pyrimidine ring, and this lessens its co-ordinating ability as compared with the ring nitrogen atoms. It is therefore improbable that the amine is bound to the metal; this is confirmed by the NH_2 i.r. vibrations frequencies being unchanged (the amine protons shift is concentration dependent probably owing to some exchange with H_2O traces in the solvent).

On recrystallising [Pt(dat)Guo]Cl_2 from ethanol–diethyl ether, [Pt(dat)GuoCl]Cl was formed. In the former, the ν (C=O) vibration appears at a lower frequency (*ca.* 100 cm^{-1} lower), but its frequency increases after recrystallisation. The chemical shift of N(1)H also changed after recrystallization, indicating less electron withdrawal from N(1) in the

TABLE

	^{1}H-n.m.r. and i.r. spectral data[a]					
	N(1)H	NH_2	H(a)	H(b)	ν (C=O)/cm^{-1}	ν (C=N)/cm^{-1}
Ado	—	7·37	8·39	8·20	—	1608, 1576, 1478
[Pt(dat)Ado_2]Cl_2	—	7·34	8·60	8·20	—	1595, 1570, 1490 1470
Cyd	—	7·13	7·83 (J_{H-H} 7·3 Hz)	5·65 (J_{H-H} 7·4 Hz)	1660	1615
[Pt(dat)Cyd_2]Cl_2	—	7·60	8·00	5·90	1725, 1680	—
Guo	10·68	6·46	7·93	—	1740	1630, 1576
[Pt(dat)Guo]Cl_2	10·82	6·62	8·04	—	1645	1570 sh
[Pt(dat)GuoCl]Cl	10·70	6·52	8·06	—	1685	1620, 1590, 1543

[a] Chemical shifts (δ values); H(a) = H(8) for Ado and Guo, H(6) for Cyd; H(b) = H(2) for Ado, H(5) for Cyd.

The solid nucleosides (N) react with [Pt(dat)Cl_2] (2:1) in $HCONMe_2$ at 60 °C, to give reddish-brown solutions. The complexes, of general formulae [Pt(dat)N_2]Cl_2 (where N = Ado or Cyd) and [Pt(dat)Guo]Cl_2, are precipitated by addition of acetone–ether (1:1). Their elemental analysis (C,H,N) are satisfactory. All the complexes are extremely soluble in water and ethanol.

The i.r. and ^{1}H-n.m.r. spectra of the compounds were recorded, respectively, for KBr pellets and $(CD_3)_2SO$ solutions (Me_4Si; Bruker WH 90). KBr did not displace the nucleosides from Pt, since the analogous brominated products gave the same spectra in the 4000—400 cm^{-1} range. However, some metathesis of the chlorine substituents cannot be excluded.

recrystallised complex. These results suggest an initial complex chelated through N(7) and O(6), with a subsequent release of the ketone group. The chlorine substituents were replaced by PF_6^-, and [Pt(dat)Guo]PF_6 and Pt(dat)-GuoCl]PF_6, respectively, were obtained. This confirms that guanosine initially chelates to the Pt atom, as postulated by Goodgame *et al.*[5] in their discussion of the most likely attack on double-stranded DNA by *cis*-[$Pt(NH_3)_2Cl_2$]. The Pt–O bond is unstable however and the co-ordinated species is formed, where the ketone group is no longer bound to the metal.

This latter observation may be explained by the following considerations: the two chlorine anions in the chelate species are probably interacting with the amine hydrogens

of the dat unit, and the polar solvent for recrystallisation enhances the separation of these pairs of ions. The amine hydrogen atoms are then free to interact, through hydrogen bonding with the guanosine ketone group, and this is enough to induce cleavage of the labile Pt←O=C bond. This is confirmed by the crystal structure of an analogous cation, $[Pt(NH_2CH_2CH_2NH_2)Guo_2]^{2+}$, where the carbonyl oxygen at C(6) is hydrogen bonded to an ethylenediamine nitrogen atom at a distance of 2·84 Å.

The isolation of an O(6)·N(7) guanosine chelate with $[Pt(dat)Cl_2]$, even if not a stable one, should mean that the guanosine oxygen is no longer available to form the necessary hydrogen bonds with cytidine in the replication process. The Pt–guanosine chelate may thus play a very important role in the inhibition of DNA replication by Pt drugs.

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[1] B. Rosenberg, *Naturwiss.*, 1973, **60**, 399 and references therein.
[2] P. J. Stone, A. D. Kelman, and F. M. Sinex, *Nature*, 1974, **251**, 736.
[3] M. M. Millard, J. P. Macquet, and T. Theophanides, *Biochim. Biophys. Acta*, 1975, **402**, 166.
[4] C. A. McAuliffe, personal communication (to be published).
[5] D. M. L. Goodgame, I. Jeeves, F. L. Phillips, and A. C. Skapski, *Biochim. Biophys. Acta*, 1975, **378**, 153.
[6] J. Dehand, J. Jordanov, and J. P. Beck, *Chem. Biol. Interactions*, 1975, **11**, 605.
[7] P. C. Kong and F. D. Rochon, *J.C.S. Chem. Comm.*, 1975, 600; P. C. Kong and T. Theophanides, *Inorg. Chem.*, 1974, **13**, 1981.
[8] R. W. Gellert and R. Bau, *J. Amer. Chem. Soc.*, 1975, **97**, 7379.