Reaction of $PtCl_4^{2-}$ with Theophylline: *X*-Ray Crystal Structures of Bis(theophyllinium) Tetrachloroplatinate(II) and Theophyllinium Trichlorotheophyllineplatinate(II)

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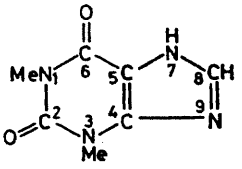
Summary The crystal structures of bis(theophyllinium) tetrachloroplatinate(II) (**A**) and theophyllinium trichlorotheophyllineplatinate(II) (**B**) have been determined; the Pt^{II} atom is bound to N(9) in the complex (**B**).

THE INTERACTION of metal ions with nucleic acids, nucleosides, and nucleotides has been an active area of inorganic and structural chemistry during the last few years and a number of recent reviews exist on the subject.[1-3] In part, this interest and activity arises from the success of certain platinum compounds, particularly *cis*-diaminedichloroplatinum(II) (DDP), in the inhibition and remission of neoplastic growth.[4] It is generally conceded that Pt compounds function as chemotherapeutic agents by binding to guanine-rich portions of DNA and thereby inhibiting transcription, translation, and replication.[5] The structure of $[\{cis\text{-(inosine monophosphate)}_2(NH_3)_2Pt^{II}\}^{2-}]_2$ has been reported[6] and models have been proposed for the interaction of DDP with DNA.[2,6] Theophylline (I) is an analogue of guanine, more precisely xanthine, in which methyl groups block the nitrogen atoms on the six-membered ring and sterically inhibit N(9) on the pyrimidine ring from reactions. It is thus of interest to investigate steps

in the reaction of $PtCl_4^{2-}$ with theophylline and we report here the isolation and structure of an intermediate (**A**) and one product (**B**) of this reaction. The latter compound contains an unexpected Pt–N(9) bond.



(I)

0·09 g of theophylline was dissolved in 40 ml of 0·5 M HCl and 10 ml of a solution containing 0·10 g of K_2PtCl_4 was added to it at 60 °C. The initial brownish colour of the mixture faded after *ca.* 30 min, but heating was continued for another 15 min. It was then allowed to stand at room temperature.

Rosy-red square plates of the intermediate (**A**) were deposited after 1—2 days which dissolved again if allowed to stand in the mother liquor. Light yellow needles of compound (**B**) were deposited after 2—4 days along with trace amounts of an amorphous pale yellow material. If allowed to evaporate to dryness, the yield of (**B**) was essentially stoicheiometric, except for the trace material.

Crystal data: (**A**), Bis(theophyllinium) tetrachloroplatinate(II), $[C_7H_9N_4O_2]_2[PtCl_4]$, monoclinic, space group $P2_1/c$, $a = 11{\cdot}716(4)$, $b = 8{\cdot}914(3)$, $c = 10{\cdot}838(5)$ Å, $\beta = 95{\cdot}84(1)°$, $Z = 2$, $D_c = 2{\cdot}16$, $D_m = 2{\cdot}15(2)$ g cm^{-3}, Zr-filtered Mo-K_α radiation ($\lambda = 0{\cdot}71068$ Å), $N = 2138$ (N = number of independent *hkl* intensities used in structure refinement), $\mu = 75{\cdot}7$ cm^{-1}. (**B**),Theophyllinium trichlorotheophyllineplatinum(II), $C_{14}H_{17}Cl_3N_8O_4Pt$, monoclinic, space group $P2_1/n$, $a = 10{\cdot}699(1)$, $b = 29{\cdot}774(1)$, $c = 6{\cdot}502(1)$ Å, $\beta = 101{\cdot}79(3)°$, $Z = 4$, $D_c = 2{\cdot}17$, $D_m = 2{\cdot}15(2)$ g cm^{-3}, unfiltered Mo-K_α radiation ($\lambda = 0{\cdot}71068$ Å), $N = 1532$, $\mu = 76{\cdot}4$ cm^{-1}.

Intensity data for both compounds were collected on a computer controlled Picker diffractometer to $2\theta \leqslant 60°$. Absorption corrections were made. The structures were solved by standard heavy atom methods and refined by full-matrix least-squares with anomalous dispersion corrections. Refinement with anisotropic temperature factors for all atoms (excluding hydrogen) proceeded to a conventional $R = 0{\cdot}033$ and weighted $R = 0{\cdot}0293$ for (**A**), and to conventional $R = 0{\cdot}0365$ and weighted $R = 0{\cdot}0368$ for (**B**).†

The structure of (**A**) is readily described in terms of packing of planar $PtCl_4^{2-}$ (M) and planar protonated theophylline (T) rings in a sequence ···MTTMTTM··· in the *a* direction with base stacking between protonated theophylline rings. The Pt–Cl distances and angles are normal (Figure 1).

The structure of (**B**) may be described as isolated theophyllinium cations and trichlorotheophyllineplatinum(II) anions. The Pt atom is bound to the five-membered

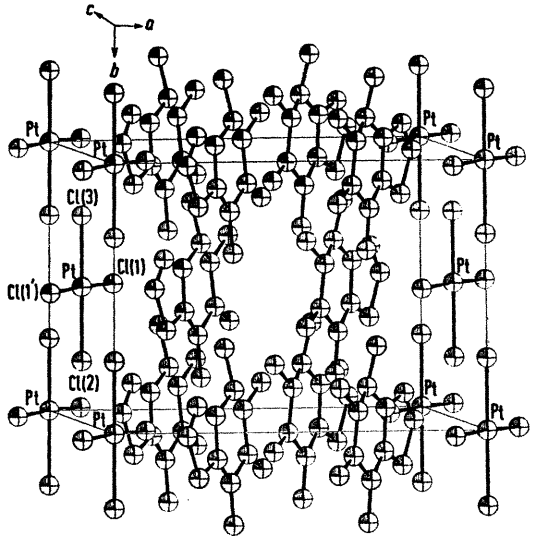


FIGURE 1. An ORTEP drawing of the packing of isolated theophyllinium cations and $PtCl_4^{2-}$ anions showing stacking of the planar ions in (**A**). The centre of the $PtCl_4^{2-}$ ion is on a centre of symmetry. Pt–Cl distances and Cl–Pt–Cl angles are normal.

pyrimidine ring at N(9) which has not earlier been found to be utilized as a metal co-ordination site for theophylline either as an anion[7] or as a neutral species.[8] The cation is essentially the same as in (**A**). The Pt–Cl and Pt–N distances and angles have the expected values.

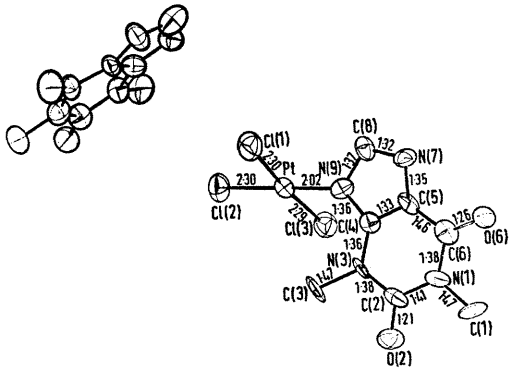


FIGURE 2. An ORTEP drawing of an isolated theophyllinium cation and a $PtCl_3$-theophylline anion in (**B**). The e.s.d.'s are: Pt–Cl distance, ±0·002; and the purine ring distances, ±0·02. The purine ring cation is essentially identical to that found in (**A**). It is to be noted that the C(2)–O(2) distance corresponds to a >C=O distance.

The mechanism of the reaction thus appears to involve purine protonation leading to (**A**) followed by attack of the theophyllinium cation on $PtCl_4^{2-}$ resulting in the formation

† 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.

of the Pt–N(9) bond and deprotonation, yielding compound (**B**). Apparently, protonation of the purine ring sufficiently alters the electron density of the pyrimidine ring so that N(9) is the point of metal attachment rather than N(7) as might be expected in spite of the steric hindrance.

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[1] D. J. Hodgson, *Progr. Inorg. Chem.*, 1977, **23**, 211; L. G. Marzilli, *ibid.*, p. 255.
[2] S. J. Lippard, *Accounts Chem. Res.*, 1978, **11**, 211.
[3] L. G. Marzilli and T. J. Kistenmacher, *Accounts Chem. Res.*, 1977, **10**, 146.
[4] For a recent review, see J. M. Hill, E. Loeb, A. MacLellan, N. O. Hill, A Khan, and J. J. King, *Cancer Chemother. Rep.*, 1975, **59**, 647.
[5] B. Rosenberg, *Cancer Chemother. Rep.*, 1975, 589; F. K. V. Leh and W. Wolf, *J. Pharm. Sci.*, 1976, **65**, 315.
[6] D. M. L. Goodgame, I. Jeeves, F. L. Phillips, and A. C. Skapski, *Biochim. Biophys. Acta*, 1975, **378**, 153.
[7] T. J. Kistenmacher and D. J. Szalda, *Acta Cryst.*, 1975, **31**, 90; L. G. Marzilli, T. J. Kistenmacher, and C. H. Chang, *J. Amer. Chem. Soc.*, 1973, **95**, 7507; T. J. Kistenmacher, *Acta Cryst.* (B), 1975, **31**, 85; D. J. Szalda, T. J. Kistenmacher, and L. G. Marzilli, *Inorg. Chem.*, 1976, **15**, 2783; T. J. Kistenmacher, D. J. Szalda, and L. G. Marzilli, *ibid.*, 1975, **14**, 1686; D. J. Szalda, T. J. Kistenmacher, and L. G. Marzilli, *J. Amer. Chem. Soc.*, 1976, **98**, 8371; T. Sorrell, L. G. Marzilli, and T. J. Kistenmacher, *ibid.*, p. 2181.
[8] B. L. Kindberg, E. A. H. Griffith, E. L. Amma, and E. R. Jones, Jr., *Cryst. Struct. Comm.*, 1976, **5**, 533.