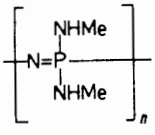
Antitumour Agents Synthesized from K_2PtCl_4 and Polymeric or Cyclic Phosphazenes

By H. R. ALLCOCK,* R. W. ALLEN, and J. P. O'BRIEN
(*Department of Chemistry, The Pennsylvania State University University Park, Pennsylvania* 16802)

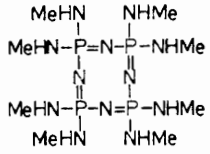
Summary The phosphazenes $[NP(NHMe)_2]_n$, $[NP(NHMe)_2]_4$, and $[NPMe_2]_4$, react with K_2PtCl_4 in organic media to yield square-planar Pt complexes of the type $(NPR_2)_x$-$PtCl_2$, and in aqueous acid media to yield salts of the type, $[H_2N_4P_4R_8]^{2+}[PtCl_4]^{2-}$; moreover, these compounds have shown significant antitumour behaviour in preliminary testing.

THE anticancer activity of *cis*-dichlorodiammine Pt compounds is now widely recognized.[1] The principal drawback of these materials is their capacity to cause serious side effects, such as kidney damage, due to their rapid rate of excretion.

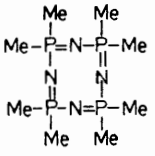


(I)

(*ca.*10,000)

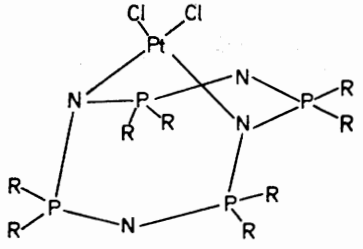


(II)



(III)

Our objective was to prepare a complex between a square-planar Pt unit and a polymeric ligand. It was anticipated that the excretion of a polymer-bound Pt complex would be prevented or retarded by the inability of the macromolecules to pass through semipermeable membranes. A polymer chosen by us for this purpose was poly[bis(methylamino)phosphazene] (I), a water-soluble compound synthesized earlier in our laboratories.[2] This polymer possesses both skeletal and side group N atoms as possible binding sites for Pt.



(IV)

The interaction of (I) with K_2PtCl_4 in $CHCl_3$ in the presence of 18-crown-6 ether yielded a light yellow polymeric precipitate. Pt could not be removed from the polymer by dialysis in water, a result which indicates a strong binding of Pt to the polymer. Microanalysis indicated a composition in which $PtCl_2$ residues were bound to

the polymer. This compound has proved to be particularly active as an antitumour agent in preliminary screening tests.†‡

In order to provide a model for bonding analysis, a similar complex was prepared from octakis(methylamino)-cyclotetraphosphazene (II), K_2PtCl_4, and 18-crown-6 ether in $CHCl_3$. The yellow crystals formed were shown by microanalysis to have the composition $[NP(NHMe)_2]_4PtCl_2$. A single-crystal *X*-ray analysis of this material§ has shown that the square-planar Pt is bonded in a transannular fashion to two 2,6-skeletal N atoms, as shown in (IV). Because of the spectral similarities between the complexes formed by (I) and (II), it is assumed that the polymer (I) also binds through its skeletal N atoms. Complex (IV) is less active than the complex from (I) in preliminary anticancer tests but, nevertheless, it displayed some tumour inhibitory properties.¶ A complex formed from $(NPMe_2)_4$ (III) [presumed to retain the square-planar metal centre as does (IV)] shows an anticancer activity comparable to that displayed by the complex formed from (I).

Finally, we report that (II) and (III) react with K_2PtCl_4 in aqueous acidic media to yield the platinate salts, $[H_2N_4P_4(NHMe)_8]^{2+}[PtCl_4]^{2-}$ and $[H_2N_4P_4Me_8]^{2+}[PtCl_4]^{2-}$. Both compounds were active in the Erlich Ascites screening test (78 and 91% inhibition, respectively). This, to our knowledge, is the first time that a charged platinum complex has been shown to display antitumour activity.

This work was supported in part by the U.S. Army Research Office.

(*Received*, 14*th June* 1976; *Com.* 667.)

† A high activity was shown against P388 lymphocytic leukaemia (max T/C = 130) and against Ehrlich Ascites mouse tumours (86% inhibition).

‡ The P388 lymphocytic leukaemia tests were conducted by National Institutes of Health, Division of Cancer Treatment (a T/C value over 125 is considered to be significant), and the Ehrlich Ascites inhibition tests were carried out by Dr. Iris H. Hall, Division of Medicinal Chemistry, University of North Carolina.

§ *Crystal data*: monoclinic cell, $a = 10{\cdot}351$, $b = 15{\cdot}619$, $c = 14{\cdot}327$, $\beta = 92{\cdot}385$, space group $P2_1/n$, $Z = 4$. The structure was refined to an *R* factor of 0·049. The details of this structure will be published elsewhere.

¶ A maximum T/C of 127 was found in the P388 survival test and a 61% inhibition in the Ehrlich Ascites screen.

[1] B. Rosenberg, L. Van Camp, J. E. Trosko, and V. H. Mansour, *Nature*, 1969, **222**, 385.
[2] H. R. Allcock, W. J. Cook, and D. P. Mack, *Inorg. Chem.*, 1972, **11**, 2584.