Crystal and Molecular Structure of $K_2(PdCl_3)_2 \cdot 4$(1-propylthymine)

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Summary The crystal and molecular structure of an unusual complex between K_2PdCl_4 and 1-propylthymine, [$K_2Pd_2Cl_6 \cdot 4$(1-propylthymine)], has been determined by *X*-ray diffraction and shown to contain the structural features of Watson–Crick base stacking, significant hydrogen bonding, $K^+ \cdots O$ interactions connecting the bases, and a $Pd_2Cl_6^{2-}$ dimer.

SINCE their initial discovery[1] compounds of certain heavy metals have been found effective in the treatment of some animal and human carcinomas. These compounds bind to the acid insoluble fraction of the cell,[2] and hence their effectiveness is thought to be due primarily to inhibition of DNA replication.[3] Several mechanisms for this have been proposed, such as specific base binding,[4] disruption of hydrogen bonding and base stacking in the double helix,[5] and cross strand linkages[5,6] Investigation of the interaction between Pt^{2+} and Pd^{2+} compounds and nucleotide bases is therefore of considerable interest.

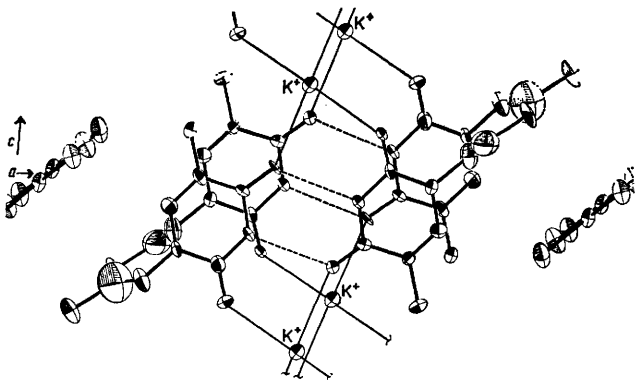

FIGURE 1. An ORTEP drawing of $K_2Pd_2Cl_6 \cdot 4$(1-propylthymine) showing a section of one ribbon and the surrounding $Pd_2Cl_6^{2-}$ dimers end on. This view shows the base stacking between pyrimidine rings. Hydrogen bonding between rings is shown by dotted lines and the light solid lines indicate the O—K interactions. The $Pd_2Cl_6^{2-}$ ions lie in channels surrounded by the hydrophobic propyl and methyl groups of the pyrimidines.

Since Pt^{II} is considered as a soft metal it probably binds to the pyrimidine or purine bases rather than the phosphate oxygen atoms or sugar groups. The nucleosides and nucleotides are also difficult to crystallize. We have blocked the site of sugar attachment on the purine and pyrimidine bases with alkyl group and treated these 'blocked bases' with Pt^{II} or Pd^{II} compounds. Similar compounds are formed with both metal ions and where feasible the Pd^{2+} compound is used for structure analysis. We report here the unusual structure of a reaction product.

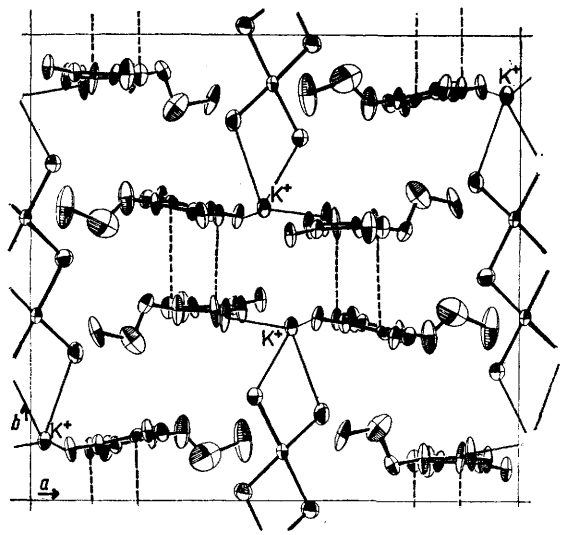

FIGURE 2. An ORTEP drawing of the structure of $K_2Pd_2Cl_6 \cdot 4$-(1-propylthymine). The $Pd_2Cl_6^{2-}$ ions are seen as double X's. The base stacking within the two ply ribbons is shown by dotted lines. The light solid lines show the K—O interactions. This view, perpendicular to that in Figure 1, shows the sides of the hydrophobic channel containing the $Pd_2Cl_6^{2-}$ ion.

1-propylthymine was prepared as previously described.[7] A solution of 0·016 g of this blocked pyrimidine in 10 ml H_2O was mixed with 10 ml of an aqueous solution containing 0·021 g K_2PdCl_4. Slow evaporation of the resulting 3:2 solution gave red parallelepipeds. Preliminary *X*-ray photographic data showed the crystals of $K_2(PdCl_3)_2 \cdot 4$(1-propylthymine) to be monoclinic, $P2_1/n$, $a = 17{\cdot}018(1)$, $b = 15{\cdot}975(4)$, $c = 8{\cdot}437(2)$ Å, $\beta = 91{\cdot}09°(1)$; $D_c = 1{\cdot}705$ g

cm^{-3}, $D_m = 1.70$ g cm^{-3}, respectively. An identical reaction was carried out with K_2PtCl_4 and although products were isolated, no diffraction-quality crystals were obtained.

A crystal 0·6 × 0·4 × 0·3 mm, mounted in a thin-walled glass capillary gave 8000 reflections on a Picker automated diffractometer with unfiltered Mo-K_α radiation. Of these, 4161 were statistically above background and were used to solve and refine the structure. Axial and zonal reflections were remeasured with Zr-filtered Mo-K_α radiation. Absorption corrections were made with $\mu = 13.504$ cm^{-1}, and minimum and maximum transmission coefficients were 0·662 and 0·725, respectively. The structure was solved by standard heavy-atom techniques and has been refined by full-matrix least-squares with anisotropic temperature factors to a current $R = 0.089$. Hydrogen atom contributions were not included.

The structure consists of two ply ribbons of blocked bases propagating in the *c* direction and separated by $Pd_2Cl_6^{2-}$ dimers (Figure 1). There is no direct dimer–base binding. The layers of the ribbon, each made up of hydrogen-bonded base pairs interconnected *via* oxygen co-ordination to K^+ (Figure 2), are held together by DNA-type base stacking between the plies and a long (3·3 Å) axial $K^+ \cdots O$ interaction. The ribbons are weakly connected by $K^+ \cdots Cl$ interactions with the terminal chlorines of the dimer, so that the net result is a seven-co-ordinate K^+. The hydrophobic portions of the 1-propylthymine groups are directed toward the $Pd_2Cl_6^{2-}$ ion, forming a cylindrical pocket open at each end. These openings allow the $Pd_2Cl_6^{2-}$ to interact with the ribbons *via* a $Cl^- \cdots K^+ \cdots O$ interaction. Thus, the cumulative effect of ring–ring hydrogen bonding, base stacking, and formation of the potassium interactions must be sufficient to stabilize the structure without metal–base binding.

The 1-propylthymine rings are planar and have distances and angles close to those found in 1-methylthymine[8] and thymine monohydrate.[9] Hydrogen bonding in these structures is quite similar.

The first step in the proposed mechanism is the hydrolysis of one chloride to form $[Pt(NH_3)_2(OH_2)Cl]^+$ or $[Pt(NH_3)_2(OH)Cl]$,[5] followed by electrophilic attack by Pt on sites of DNA. Here, $PdCl_4^{2-}$ has undergone the first step, but the blocked pyrimidine is not a sufficiently strong base for further reaction in competition with Cl^-, and the dimer results. Extrapolation of this result indicates the reason for lack of reactivity of $[Pt(NH_3)_2Cl_2]$ with polyuridylic acid and polythymidylic acid.[10] Several investigators[11] have postulated dimer or polymer formation in the reaction of $[Pt(NH_3)_2Cl_2]$ with nucleic acids. This structure strongly supports that possibility.

Structure analyses involving other blocked bases and Pt^{II}, should clarify the Pt^{II}–base interaction.

We thank the American Cancer Society for an Institutional Grant and the National Institutes of Health for financial support.

(*Received*, 3rd *December* 1974; *Com.* 1467.)

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