The Crystal Structure of the Antimalarial Chloroquine Diphosphate Monohydrate

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Summary The crystal structure of the antimalarial chloroquine phosphate reveals columns of $H_2PO_4^{2-}$ ions bridged by the 4-aminoquinoline group and enwrapped by the side-chain.

THE antimalarial chloroquine phosphate has been shown to form adducts with nucleic acids[1] and to inhibit the incorporation of ^{32}P orthophosphates into the nucleic acids of certain *Plasmodia*.[2] Allison, O'Brien, and Hahn suggested[3] that the 1,4-diaminopentane side-chain of chloroquine interacts with the acidic phosphate groups of DNA. In order to examine the binding "potential" of the chloroquine molecule, we have determined the crystal structure of chloroquine phosphate, and we propose to examine the structures of both metal complexes and organic phosphate salts of chloroquine.

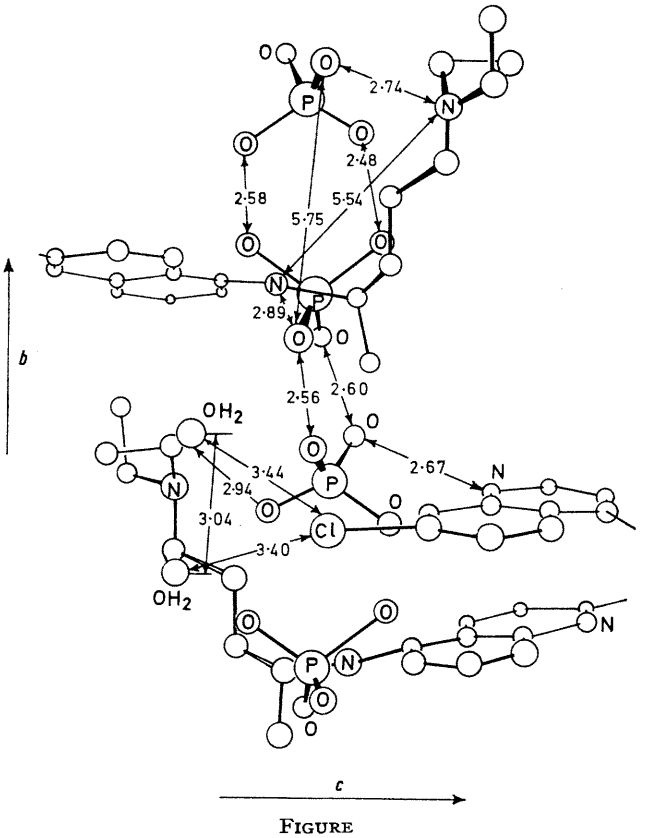
Colourless, hygroscopic crystals were grown by diffusion of acetone into an aqueous solution of chloroquine phosphate The crystals of $C_{18}H_{26}ClN_3,2H_3PO_4,H_2O$ were monoclinic prisms, space group $P2_1/a$, with $a = 15{\cdot}741(13)$, $b = 16{\cdot}865(9)$, $c = 9{\cdot}815(2)$ Å, $\beta = 105{\cdot}58(2)°$, $U = 2509{\cdot}8$ Å^3, $D_m = 1{\cdot}40$ (by flotation), $Z = 4$, $D_c = 1{\cdot}412$. The intensities of 4300 independent reflections ($2\theta < 45°$) were recorded with niobium-filtered Mo-K radiation, on an automated General Electric XRD-6 Diffractometer; a combination of 2θ scans and stationary crystal-stationary counter data was used.[4]

The co-ordinates of carbon, nitrogen, oxygen (except the water oxygen) and phosphorus atoms were obtained from

an '*E*' map which used phases determined by direct methods.[5] Full-matrix least-squares refinement of positional and isotropic thermal parameters of the non-hydrogen atoms yielded a residual of 0·131. Anisotropic refinement, *via* approximately 100 * 100 blocks,[6] proceeded to a residual of 0·081, with two-thirds of the hydrogen atoms included. Further refinement is in progress.

The structure (Figure) reveals columns of phosphate ions parallel to the crystallographic *b* axis. Independent $H_2PO_4^-$ groups are separated by very short O · · · · · O distances similar to those found in H_3PO_4.[7] The quinoline ring system lies almost perpendicular to the *b* axis and, *via* the heterocyclic nitrogen on one side, and the 4-amino-nitrogen on the other side, acts as a bridge between adjacent columns of phosphate groups. Each side chain wraps around a phosphate column with the two aliphatic nitrogens H-bonded to neighbouring phosphates. A helix-like arrangement of side-chains about the phosphate columns is generated by the two-fold screw axis.

Singh, Stein, and Biel[8] suggested that the best interval between the two side-chain N atoms would be 7·5 Å. In this study we observe aliphatic nitrogen atoms 5·54 Å apart interacting with phosphate oxygen atoms 5·75 Å apart. Large N · · · · · N distances (6·21, 6·24 Å) may be calculated for the 1,4-diaminopentane segments of independent spermidine cations, using the parameters of the structure analysis of spermidine phosphate trihydrate.[9] However, it appears to be impossible for the N · · · · · N separation in N–C–C–C–C–N to exceed 6·5 Å, in any conformation.



FIGURE

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