Structural Studies on Bio-active Molecules. Part 17. Crystal Structure of 9-(2′-Phosphonomethoxyethyl)adenine (PMEA)[1,†]

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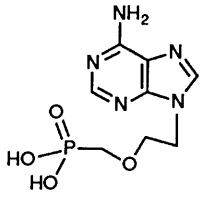
The crystal structure of the antiviral agent PMEA **1** has been determined to $R = 0.032$ and reveals a zwitterion whose side chain emerges in-plane from the adenine ring; the conformation is compared with that of crystal structures of acyclic nucleoside analogues and AMP **2**.

The acyclic nucleotide analogue, 9-(2′-phosphonomethoxyethyl)adenine **1** (PMEA) is currently undergoing further evaluation as a drug for the treatment of AIDS.[2] It is a potent and selective inhibitor of the human immunodeficiency virus (HIV), with an ED_{50} of 2 μmol dm^{-3} in MT-4 cells.[3] PMEA has shown stronger *in vivo* antiretrovirus activity than AZT against Moloney murine sarcoma virus-induced tumour formation.[4] PMEA is also active against a broad range of herpes viruses, including cytomegalovirus.[3,4] Following penetration into the cells, bisphosphorylation of PMEA is catalysed by host kinases.[5] The bisphosphate of PMEA has been shown to inhibit DNA polymerase,[6] ribonucleotide reductase,[7] and interestingly, reverse transcriptase.[5]



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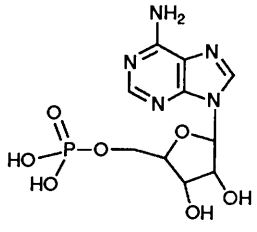

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As part of our efforts to synthesise prodrug forms, a sample of PMEA was prepared both as a starting material and as a standard for HPLC analysis. Crystals suitable for X-ray diffraction were formed, and it is the crystal structure of PMEA that is discussed.

The bis(trimethylsilyl) ester of PMEA was synthesised by the method described by Holy and Rosenberg.[8] From this compound, these workers formed the disodium salt; however, treatment of the ester with water[9] gave the free acid of PMEA. Crystallisation from water gave colourless laths, which were fully characterised spectroscopically and by elemental analysis.‡ The ^1H NMR spectrum showed that the protons in each methylene group are equivalent, suggesting a flexible conformation of the 'sugar moiety' in solution.

The unit cell of PMEA is shown in Fig. 1. PMEA was found to crystallise as the zwitterion protonated at N(1). The most unusual feature of this structure is the 'glycosidic' torsion angle.

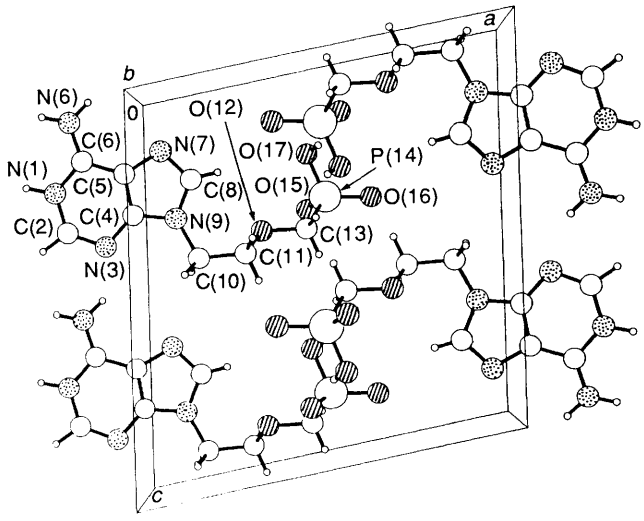

Fig. 1 PLUTO[15] drawing of the unit cell contents of PMEA. Nitrogen atoms are stippled and oxygen atoms hatched.

In 10 molecules[10] of acyclonucleosides for which C(1′) is secondary this torsion angle averages 96°, yet in PMEA C(8)–N(9)–C(10)–C(11) is only 3.3°. The close 1,4-contact that arises between C(8) and C(11) is relieved by expanding angle C(8)–N(9)–C(10) to a value 7.4(1)° greater than C(4)–N(9)–C(10). While *syn-anti* conversion has been recognised in acyclonucleosides,[11] the present structure provides a concrete representation of the likely intermediate. The remaining twist angles along the chain to the phosphonate group are *gauche*, *trans*, *trans* about C(10)–C(11), C(11)–O(12), O(12)–C(13) respectively.

Bond distances and angles in the adenine moiety resemble those in the standard model of protonated adenine[12] within 3σ except in the vicinity of N(6), where a hydrogen bond to an adjacent phosphonate oxygen and another to an inversion-related N(7) may perturb the geometry. A strong [2.610(2) Å] intermolecular hydrogen bond links N(1) and phosphonate O(15), and the screw axis creates columns of adenine rings while the phosphonates occupy separate domains (Fig. 1). P–O Bond lengths are correlated with the nature and number of other attachments to the O atoms: the longest bond is to O(17), which is protonated; the next longest, to O(15), which accepts two hydrogen bonds; and the shortest, to O(16), which accepts one.

PMEA can be regarded as an analogue of adenosine 5′-monophosphate **2** (AMP) in which O(1′) and C(4′) of the ribose unit have been interchanged and O(5′) has been omitted. The shortening of the path from N(9) to P(14) by one atom in PMEA is compensated by its more circuitous route in AMP, so that the N(9)···P distance of 5.31 Å in PMEA is similar to the 5.45 Å in the monoclinic form[13] of AMP monohydrate and

† Contribution from the Joint Crystallography Unit, Universities of Aston and Birmingham.

‡ M.p. 282–284 °C; $\delta_H(D_2O$, 300 MHz) 8.13 (1 H, s, 8-H), 8.11 (1 H, s, 2-H), 4.24 (2 H, t, J_{HH} Hz 4.9, C-CH_2-O), 3.72 (2 H, t, J_{HH} Hz 4.9, N-CH_2-C), 3.49 (2 H, d, J_{PH} Hz 8.8, O-CH_2-P); ^{31}P NMR (D_2O, 121.5 MHz) δ 20.0 ppm (s, ^1H decoupled), (t, J_{PH} Hz 8.8, ^1H coupled) (Found: C, 34.6; H, 4.4; N, 25.3. $C_8H_{12}N_5O_4P$ requires C, 35.16; H, 4.42; N, 25.62%).

longer than the 4.36 Å in the orthorhombic form.[14] When the adenine rings of PMEA and monoclinic AMP are superimposed, the P atoms are 2.28 Å apart. This separation can be reduced to *ca.* 1 Å simply by twisting the O(12)–C(13) bond of PMEA to make C(11)–O(12)–C(13)–P(14) *ca.* −100°. In the light of these results, further studies are planned on the conformational preferences of PMEA and its phosphorylated analogues as compared with AMP, ADP and ATP.

Crystal Data for $C_8H_{12}N_5O_4P$.—Monoclinic, space group $P2_1/c$, a = 11.935(3), b = 7.367(1), c = 12.943(2) Å, β = 100.80(1)°, Z = 4, D_c = 1.62 g cm^{-3}, μ(Mo-Kα) = 0.211 mm^{-1}. 4857 Reflections were collected to $2\theta_{max}$ = 54°, yielding 2433 independent reflections (R_{int} = 0.020) of which 2196 were considered observed with [$F_{obs} > 3\sigma(F_{obs})$]. The structure was solved by direct methods,[16] methylene H atoms were placed in calculated positions, and all other H atoms were located in a difference electron density map. Full-matrix least-squares refinement[16] of all atomic co-ordinates together with anisotropic thermal parameters for non-H atoms and isotropic temperature factors for H atoms converged at R = 0.032, R_g = 0.052. No peak on a final difference electron density map exceeded 0.33 eÅ^{-3}. Atomic co-ordinates, lengths and angles of covalent and hydrogen bonds are available, on request, from the Cambridge Crystallographic Data Centre: see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.

Acknowledgements

We thank Dr. W. J. Irwin and Baljit Ahitan for their interest, and the MRC AIDS Directed Programme for support, project grant number G 872331. S. F. is a Lister Fellow.

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Paper 0/04822D
Received 25*th October* 1990
Accepted 22*nd February* 1991