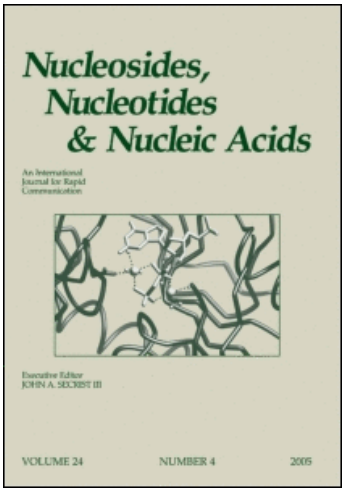

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Isopolar vs Isosteric Phosphonate Analogues of Nucleotides

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ISOPOLAR vs ISOSTERIC PHOSPHONATE ANALOGUES OF NUCLEOTIDES

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Summary A range of β,γ-bridged phosphonate analogues of ATP and of β,β'-bridged analogues of Ap_4A has been synthesised. Some of their metal binding characteristics and inhibition of enzymatic phosphoryl transfer processes can be described in terms of the relative importance of steric and electronic features of the nucleotide analogues.

The use of phosphonate analogues of biological phosphate monoesters has been governed primarily by the general stability of the P-C bond and by the adequate stereochemical correspondence between a divalent CH_2 group in the phosphonate and the ester oxygen of the parent phosphate.[1,2] The resulting emphasis on the *isosteric* character of the analogue has barely been justified by quantitative evaluations of their biological activity. For example, haemoglobin binds D-2,3-bisphosphoglyceric acid (1) ten times better than either D- or L- isomers of the analogue 2-carboxybutane-1,4-bisphosphonate (2).[2] We have therefore argued that isostericity may be less important than *isopolar* character and, to that end, have devised a variety of routes for the preparation of α-fluorophosphonic acids as analogues of phosphate monoesters.[3,4]

The ready availability of halo- and dihalo-methylenebisphosphonic acids (3) has enabled us to prepare β,γ-bridged analogues of ATP (4a) and GTP using the Moffatt-Khorana phosphomorpholidate coupling route.[5] We have also prepared the α,β-bridged ADP analogues by DCCD condensation of (3) with isopropylidene adenosine.[6] The physical properties of these *isosteric* ATP analogues (4b-e) show an increasing correspondence to those of ATP (4a) in the sequence $CH_2 < CHF \simeq CCl_2 < CF_2 \simeq NH < O$ for the

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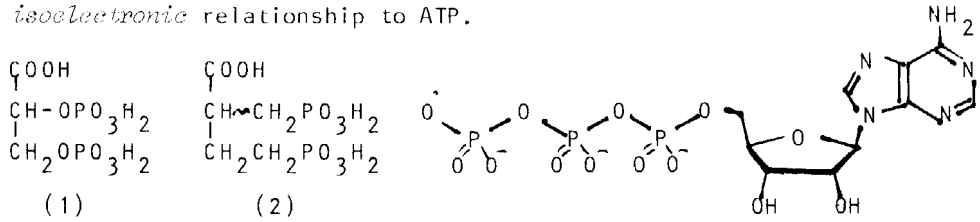
β,γ-bridged function and they bind calcium and magnesium ions as expected. These compounds thus describe a series of increasing *isoelectronic* relationship to ATP.



(1) (2)

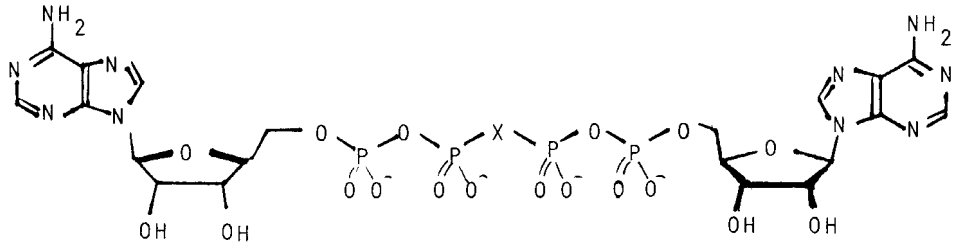
(3) X,Y=H,F,Cl

(4) a,X=O; b, X=CH_2; c, X=CFH; d,X=CCl_2; e,X=CF_2; f,X=C≡C; g,X=CH=CH; h,X=O-O.

The condensation of acetylenebisphosphonic acid and of *E*-ethylene-1,2-bisphosphonic acid with adenosine 5'-monophosphomorpholidate gives analogues of ATP (4f,g) which are not isosteric although their ^{31}P NMR spectra and general ionisation behaviour suggests that they are good isopolar analogues of ATP. An additional example of a more flexible, isoelectronic but non-isosteric ATP analogue has been provided by Leonard[7] through the incorporation of the labile peroxide linkage into the β,γ-bridge (4h).

These ATP analogues are substrates for adenylate enzymes such as adenylate cyclase and RNA polymerase. The latter shows a preference for size factors over electronegativity. The analogues are inhibitors of kinases, where hexokinase shows a preference for isopolarity.

When the condensation reaction for the synthesis of (4b-g) is carried out with an excess of adenosine 5'-monophosphomorpholidate, the major products are the β,β'-bridged phosphonate analogues of Ap_4A (5a). The centrosymmetric character of these compounds (5b-f) is readily seen in their ^{31}P NMR spectra. This property makes them ideal bisubstrate analogues to probe the nucleotide binding site of myokinase (EC 2.7.4.3). In the longer term, however, these analogues may be expected to show more potential for investigation of the range of cellular control functions regulated by Ap_4A, such as DNA synthesis[8] and cell proliferation.[9]



(5) a, X=O; b, X=CH_2; c, X=CCl_2;
d, X=CF_2; e, X=C≡C; f, X=CH=CH.

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