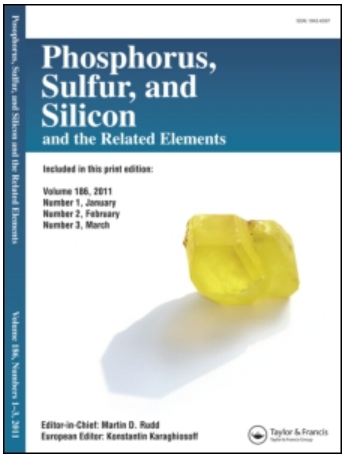

Phosphorus, Sulfur, and Silicon and the Related Elements

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DESIGN AND SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS WITH ANTIVIRAL AND OTHER BIOACTIVITIES

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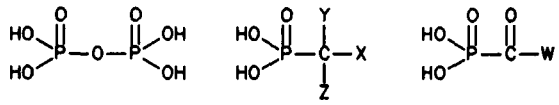
Abstract Investigations of phosphonates and related biophosphate analogues as inhibitors of viral nucleic acid polymerases are summarized. General syntheses of α-halo phosphonoacetic acid (PAA) and methanediphosphonic acid (MDP) derivatives have been extended to preparation of seven α-halo phenyl(phosphonomethyl)phosphinates (PhMpP). Two phosphonates containing potentially reactive α-keto groups, oxophosphonoacetate (phosphonoglyoxalate, COPAA) and oxomethanediphosphonate (carbonyldiphosphonate, COMDP) are discussed. A convenient, two-step synthesis of trisodium thiophosphonoformate (TPFA) from trimethyl phosphonoformate (Me_3PFA) [via Me_3TPFA] is presented. TPFA selectively inhibits HIV-1 reverse transcriptase (RT) relative to both human DNA polymerase α (pol α) and four herpesvirus DNA polymerases. The significance of membrane Na^+/Pi cotransport inhibition by phosphonates is briefly addressed.

INTRODUCTION

There is growing interest in phosphonate analogues of biophosphates as probes of enzymes or biological systems and as potential anti-viral agents. Ultimate understanding of why particular analogues exhibit potency and specificity as inhibitors requires detailed structural knowledge of the active site involved in binding the inhibitor. In the absence of such information, correlations of inhibitor structure with accessible biochemical properties such as binding affinities are of value. At present, the effects of structural variation on the ability of phospho no analogues of pyrophosphate (I) to inhibit viral nucleic acid polymerases are poorly understood. This paper summarizes part of our research in this area, including some recent work.



I II III

VIRAL POLYMERASE INHIBITORS

α-Halo Phosphonates

A range of combined polar and steric modifications can be produced by systematic halogen substitution at the α-carbon of PAA (II, X = CO_2H: Y, Z = H, F, Cl, Br, CH_3) and MDP (II, X = PO_3H_2; Y, Z = H, F, Cl, Br).[1] The compounds are easily made from the corresponding esters[2,3] via hydrolysis using HCl or BTMS/H_2O.[3-5] With dihalo (Y, Z = Cl, Br) PAA, HCl hydrolysis conditions must be adjusted to minimize product decarboxylation to the corresponding dihalomethylphosphonic acid. BrPAA is converted to ClPAA in refluxing HCl, but in this case HBr is a good alternative to BTMS.[6]

Several α-halo PAA derivatives inhibit HSV-1 and other herpesvirus DNA polymerases, whereas all the α-halo MDP derivatives are inactive.[1] The viral polymerases tested differed significantly in their sensitivity to these inhibitors.[1,6] PAA, MDP and a selected group of their α-halo derivatives fail to exhibit significant potency against HIV-1 RT.

α-Halo Phosphonophosphinates

The methods cited above were readily extended to prepare (via the ethyl esters) seven α-halo phenyl-MpP derivatives: II, X = $P(Ph)O_2H$; Y, Z = H,F; F,F; H,Cl; Cl,Cl; H,Br; Br,Br; Cl,Br. As the starting material used, Et_3PhMpP, was racemic, racemic dihalo products and diastereomeric monohalo racemate mixtures were obtained. The presence of the phenyl group may improve membrane transport or affect other hydrophobic interactions in these MDP-like analogues. Testing of the compounds as inhibitors of several enzymes is currently in progress.

Functionally Reactive Phosphonates

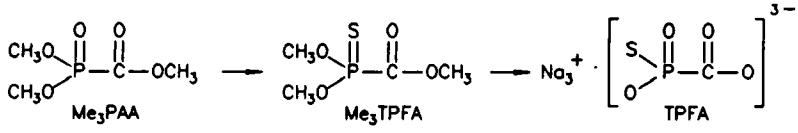
Examples of phosphonates containing a reactive functionality are the α-keto phosphonates COPAA[7] (III, W = CO_2H) and COMDP (III, W = PO_3H_2). These compounds have a $(HO)_2P(O)$-C(O) fragment in common with phosphonoformate (PFA). However, both have a 1-carbon 'spacer' between their anionic groups as do PAA and MDP, and both are ketones capable of adding

nucleophiles; their keto electrophilicity varies inversely with anionic charge and hence with pH.[6,7]

Both compounds appear to inhibit HIV-1 RT with significantly greater potency than their parent analogues, PAA and MDP, although neither is as active as PFA.[6]

Thiophosphonoformate (TPFA)

A convenient, two-step conversion of Me_3PFA into trisodium TPFA can be accomplished by selective thiation of Me_3PFA with Lawesson's reagent, giving thiono Me_3TPFA in good yield, followed by direct (NaOH) or indirect (ITMS/Na_2CO_3) hydrolysis.



The ester and salt were characterized by ^{31}P, ^{13}C, ^{1}H (ester) NMR; IR; UV (salt); elemental analysis; and high resolution MS (ester). The existence of trisodium TPFA primarily in thiolo form in solution (D_2O) is indicated by its ^{31}P chemical shift (δ 37.7 compared to δ 64.8 for the thiono ester). Of analytical note is the UV absorbance of TPFA (ϵ_{254} = 1 x 10^3 at pH 8, >20x greater than the ϵ_{254} of PFA).

TABLE I Polymerase inhibition.

	IC_{50} (μM)	
Enzyme	TPFA	PFA
Human DNA pol α	>100	31
HIV-1 RT	1	0.7
HSV-1,2 DNA pol	12	0.7
EBV DNA pol	70	1
HV-6 DNA pol	70	1

TPFA is markedly less inhibitory than PFA to four herpesvirus DNA polymerases tested, but is comparably potent against HIV RT; it is the weaker inhibitor of human pol α (Table I). In an earlier report,[8] similar HSV-1 DNA pol IC_{50} values were found for PFA and TPFA. The inhibition of HIV-1 replication in H9 cell culture by added TPFA, which

approximates that of PFA (A. Bodner and R. Kilkuskie, unpublished), is under investigation.

OTHER BIOACTIVITIES

The use of phosphonates as bioprobes is not limited to nucleic acid polymerase inhibition, as illustrated by Dousa's recent discovery that Na^+/Pi cotransport in renal brush border cortical membrane is inhibited by PFA and, to a lesser extent, PAA.[9] Subsequent evaluation of our complete α-halo PAA group has revealed that ClBrPAA blocks cotransport 4x more strongly than PFA.[10] ClBrPAA has little or no activity against viral polymerases[1,6] but is also a significantly weaker human pol α inhibitor than PFA,[1] i.e. it is at once more potent and more selective than PFA in this cross-system activity comparison.

ACKNOWLEDGMENT

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