Monofluoro- and Difluoro-methylenebisphosphonic Acids: Isopolar Analogues of Pyrophosphoric Acid

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Summary New syntheses are described for the preparation of monofluoromethylenebisphosphonic and difluoromethylenebisphosphonic acids whose physical properties show them to be good isopolar analogues of pyrophosphoric acid of significant biological potential.

PHOSPHONATES have been widely investigated as models for phosphate esters because they have an approximately isosteric relationship and because the C–C–P linkage is more stable to hydrolysis than is the C–O–P linkage. Their successful application as biological models has been of limited value,[1] even though significant progress has been achieved in the efficient synthesis of such compounds.[2,3] This limitation has been attributed in part to the failure of the α-CH_2 group in a phosphonate adequately to reflect the electronegativity of oxygen and its consequent impaired influence on the adjacent phosphorus atom in a phosphate ester.[4]

We have shown that α-fluorination of alkylphosphonic acids and their esters heightens their similarity to the corresponding phosphoric acid esters.[5] We here describe novel syntheses for fluoromethylene- and difluoromethylenebisphosphonic acid esters and their smooth conversion into the parent acids. The physical properties of these acids show that they can be well described as isopolar analogues of pyrophosphoric (diphosphoric) acid.

While the direct halogenation of tetra-alkyl methylenebisphosphonates, as their carbanions, is a proven method for the preparation of mono- and di-chloro, -bromo, and -iodo derivatives,[6] we have experienced considerable difficulty in attempting to reproduce a reported synthesis of the corresponding fluoromethylene esters using fluorine in

toluene solution.[7] In our hands, fluorine gas, perfluoropiperidine, or perfluoro-2,6-dimethylpiperidine each led to partial fluorine substitution for hydrogen at all possible sites in tetraethyl methylenebisphosphonate.[8] We therefore turned to perchloryl fluoride as an electrophilic fluorinating agent[9] which has been used in a synthesis of triethyl 2-phosphonofluoroacetate.[10]

Treatment of the sodium salt of tetraisopropyl methylenebisphosphonate (**1**) with an excess of perchloryl fluoride in tetrahydrofuran (THF) at −20 °C results in the formation in good yield of tetraisopropyl monofluoromethylenebisphosphonate (**2a**) mixed with some difluoromethylenebisphosphonate (**3a**). While these products co-distil in high vacuum, they can be separated readily by partition between hexane and water and purified by distillation. The ratio of the products depends on the choice of conditions and is usually about 4:1 (Scheme 1).

$$\underset{(\mathbf{1})}{CH_2(PO_3Pr^i_2)_2} \xrightarrow{i,\ ii} \underset{(\mathbf{2})}{CHF(PO_3R_2)_2} + \underset{(\mathbf{3})}{CF_2(PO_3R_2)_2}$$

i, NaH, PhMe; ii, $ClFO_3$, THF.

a, R = Pr^i; **b**, R = H; **c**, R = Me_3Si

SCHEME 1.

The separated esters (**2a**) and (**3a**) are both transformed by means of iodotrimethylsilane[3] into the corresponding acids (**2b**) and (**3b**) which afford stable, highly crystalline salts with cyclohexylamine or with anisidine.† The reaction of bromotrimethylsilane[2] with (**2a**) and (**3a**) is sluggish at ambient temperature and less useful for the preparation of the free acids.

We have achieved a more satisfactory synthesis of the difluoromethylene-bisphosphonic acid (**3b**) from bromodifluoromethylphosphonate esters (**4**), themselves readily prepared by a Michaelis–Becker reaction using dibromodifluoromethane.[8,11] The ester (**4a**) reacts smoothly with the sodium salt of dibutyl phosphite (**5a**) at −40 °C in hexane to give difluoromethylenebisphosphonic acid as the tetra-alkyl ester (**4**) in good yield (Scheme 2).

High resolution ^{19}F n.m.r. analysis of the partially purified product (**6**) formed from (**4a**) and (**5a**) shows the presence of three different tetra-alkyl esters, identified as (**6a**), (**6b**), and (**6c**). It follows that, in addition to the transfer of a bromonium ion from (**4**) to (**5**) proposed by Burton,[12] the formation of these esters involves either the

$$\underset{(\mathbf{4})}{BrCF_2P(O_3R^1_2)} + \underset{(\mathbf{5})}{NaP(O_3R^2_2)} \xrightarrow{i} \underset{(\mathbf{6})\ 45\%}{(R^1_2O_3)PCF_2P(O_3R^2_2)} + NaBr$$

i, hexane, −40°C

a, R^1 = Et, R^2 = Bu; **b**, R^1 = R^2 = Bu; **c**, R^1 = R^2 = Et.

SCHEME 2.

generation of difluorocarbene or a process equivalent to its exchange between phosphorus anions. The mixed esters (**6**), are smoothly and quantitatively dealkylated by iodotrimethylsilane[3] to give the tetrakistrimethylsilyl ester (**3c**), which on methanolysis affords the parent acid (**3b**).

The relationship between (**2b**), (**3b**), and other methylene analogues of pyrophosphoric acid and their esters is shown by a comparison of spectroscopic and physical data (Table). The general rising trend of P=O vibrational frequency is characteristic of phosphoryl groups bonded to increasingly electronegative ligands.[13] The downfield shift effect of fluorination is clearly evident in the ^{13}C n.m.r. data and this corresponds with an upfield shift for the ^{31}P n.m.r. signal. This latter is suggestive of an increased symmetry in electronegativity for the four ligands around phosphorus[14] for which difluoromethylenebisphosphonic acid makes the closest approach to pyrophosphoric acid. Lastly, the third and fourth dissociation constants of the tetrabasic acids show a progressive increase in acid strength in the series $X = CH_2 < CCl_2 \leqslant CHF < C(OH)_2 < O \leqslant CF_2$. Because both of these ionisations operate within the 'physiological' range of pH, the excellent correlation of acidity for (**3b**) and pyrophosphoric acid is particularly significant.

It is thus apparent that while methylenebisphosphonic acid can be described as an isosteric analogue of pyrophosphate, the latter has a superior relationship to the mono- and di-fluoromethylenebisphosphonic acids. For all the physical properties described here, this feature is attributable to the disparity in electronegativity between –O– and the $–CH_2–$ groups which is made good partially for the –CHF– and more extensively for the $–CF_2–$ functions. There is good evidence that in biological systems, the steric analogy of phosphonates to their phosphate prototypes is of lesser importance than features relating to electronic distribution.[4] We believe that this quality of relationship is best emphasised by the description of (**2b**) and (**3b**) as 'isopolar' analogues of pyrophosphoric acid.

TABLE. Physical properties of bisphosphoryl compounds $R_2O_3PXPO_3R_2$.[a]

	Tetra-alkyl ester (R = alkyl)			Free acid (R = H)			
X	$\nu_{P=O}/cm^{-1}$	δ (^{13}C)	δ (^{31}P)	δ (^{31}P)	pK_{a2}	pK_{a3}	pK_{a4}
CH_2	1255	+20·4	+17·5	(+18·5)	(2·87)	(7·45)	(10·96)
CCl_2	—	—	(+6·5)	(+7·5)	—	(6·11)	(9·78)
$C(OH)_2$	—	—	—	(+14·5)	[b]	(5·81)	(8·42)
CHF	1260	+84·5	+9·5	+9·5	<2·7	6·15	9·35
CF_2	1275	+116·1	+3·35	+3·54	<2·6	5·80	8·00
O	(1280)	—	(−12·5)	(−10·6)	(2·36)	(5·77)	(8·22)

[a] ^{31}P Data in p.p.m. relative to external 85% phosphoric acid at 40·48 MHz in D_2O for disodium salts and in $CDCl_3$ for fully esterified species. ^{13}C Data in p.p.m. relative to tetramethylsilane at 25·19 MHz. pK_a values determined at zero ionic strength and 20 °C (c = 5 mM). Literature values in parentheses. [b] Unstable in acid solution.

† All new compounds described have been fully characterised by elemental and spectroscopic analysis.

Studies on the biological activity of these species and the synthesis of nucleotide analogues derived from them will be reported elsewhere.

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[1] R. Engel, *Chem. Rev.*, 1977, **77**, 349.
[2] C. E. McKenna, M. T. Higa, N. H. Cheung, and M.-C. McKenna, *Tetrahedron Lett.*, 1977, 155; C. E. McKenna and J. Schmidthauser, *J. Chem. Soc., Chem. Commun.*, 1979, 739.
[3] G. M. Blackburn and D. Ingleson, *J. Chem. Soc., Chem. Commun.*, 1978, 870; *J. Chem. Soc., Perkin Trans.* 2, 1980, 1150.
[4] G. M. Blackburn, *Chem. Ind. (London)*, 1981, 134.
[5] G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Chem. Commun.*, 1981, 511.
[6] O. T. Quimby, J. D. Curry, D. A. Nicholson, J. B. Prentice, and C. H. Roy, *J. Organomet. Chem.*, 1968, **13**, 199.
[7] Proctor and Gamble Co., Brit. P. 1,026,366, April 20, 1966 (*Chem. Abstr.*, 1966, **65**, 5685c).
[8] D. A. England, Ph.D. Thesis, Sheffield University, 1981.
[9] M. R. C. Gerstenberger and A. Haas, *Angew. Chem., Int. Ed. Engl.*, 1981, in the press; M. Schlosser and G. Heinz, *Chem. Ber.*, 1969, **102**, 1944.
[10] W. Grell and H. Machleidt, *Leibigs Ann. Chem.*, 1966, **693**, 134.
[11] D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, 1977, **10**, 392.
[12] D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, 1980, **15**, 263.
[13] L. C. Thomas and R. A. Chittenden, *Spectrochim. Acta*, 1964, **20**, 467.
[14] J. R. van Wazer, and J. H. Letcher, 'Topics in Phosphorus Chemistry,' eds. E. J. Griffith and M. Grayson, Wiley, New York, 1967, Vol. 5, pp. 173ff.

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