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Fluorinated phosphorus compounds Part 2. The synthesis of some bis(fluoroalkyl) alkylphosphonates

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Abstract

Twenty bis(fluoroalkyl) alkylphosphonates of structure $(R_FO)_2P(O)R$ were prepared in 28–69% yields by treatment of alkylphosphonic dichlorides $Cl_2P(O)R$ [R=Me, Et, *n*-Pr, i-Pr] with fluoroalcohols R_FOH [R_F=CF_3CH_2, $H(CF_2)_2CH_2$, $C_2F_5CH_2$, $C_3H_7CH_2$, $(CF_3)_2CH$] in diethyl ether in the presence of triethylamine. Reactions of isopropylphosphonic dichloride with two molar equivalents of alcohols and fluoroalcohols were compared. After 12 h at room temperature, the alcohols EtOH, *n*-PrOH, i-PrOH and *n*-BuOH gave mixtures of monoesters and diesters, except isopropanol, which gave the monoester exclusively. Electronic and steric effects caused by the alkoxy substituents satisfactorily account for the product ratios. With the fluoroalcohols CF_3CH_2OH, $C_2F_5CH_2OH$, $C_3F_7CH_2OH$ and $(CF_3)_2CHOH$, the diesters predominated. Here the electronic effects of the fluoroalkoxy substituents stabilise the intermediate phosphoranes, eg. $Cl_2(R_FO)P(OH)$i-Pr and $Cl(R_FO)_2P(OH)$i-Pr, and drive the reactions to completion. Steric effects are clearly much less important in the case of attack by fluorinated alcohols.

Keywords: Alkylphosphonic dichlorides; Bis(fluoroalkyl) alkylphosphonates; Fluorinated phosphonates; Fluoroalcohol; Phosphonate

1. Introduction

The synthesis of fluoroalkoxy phosphorus compounds was pioneered by F. Swarts. In 1909, he described the preparation of tris(2,2-difluoroethyl) phosphate, $(HCF_2CH_2O)_3P$=O, the first phosphorus molecule to contain a fluoroalkoxy group [1]. Since then, relatively few fluoroalkoxy phosphorus compounds have been made, and little attention has been paid to their physical and chemical properties. As part of a study of fluorinated phosphorus compounds in progress in this laboratory [2,3], the synthesis of bis(fluoroalkyl) alkylphosphonates of general structure $(R_FO)_2P(O)R$ became of interest.[1] Few substances of this type are described in the literature. The main reason for this is that classical routes to dialkyl alkylphosphonates work poorly for fluorinated systems [4–9].

One of the commonest routes to dialkyl phosphonates is the Arbusov reaction of trisubstituted esters of phosphorous acid with alkyl halides [10]. Trivalent phosphorus compounds having fluorine bound to phosphorus, or fluorine within an ester group, enter such reactions with difficulty due to their reduced nucleophilicity. For example, triisopropyl phosphite $(i\text{-PrO})_3P$ reacts readily with boiling methyl iodide to give diisopropyl methylphosphonate $(i\text{-PrO})_2P(O)Me$ in 95% yield [11], but diisopropyl phosphorofluoridite $(i\text{-PrO})_2PF$ requires a temperature of 100°C for 7 h in a sealed tube to produce a 44% yield of isopropyl methylphosphonofluoridate (i-PrO)P(O)MeF [12]. The presence of one *β*-fluorine atom in trialkyl phosphites also retards profoundly the rate of the Arbusov reaction. Whereas triethyl phosphite isomerises quantitatively to diethyl ethylphosphonate in boiling ethyl iodide [11], diethyl 2-fluoroethyl phosphite reacts only on heating to 130°C for 5 h in a sealed tube, giving ethyl 2-fluoroethyl ethylphosphonate (*pathway a*) and diethyl ethylphosphonate (*pathway b*) [9].

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[1] Organic phosphorus compounds are named after the corresponding parent acids. The compounds described in this paper are diesters of alkylphosphonic acids $(HO)_2P(O)R$ and are therefore called dialkyl alkylphosphonates. Similarly, compounds of type $Cl_2P(O)R$ are called alkylphosphonic dichlorides, and those of type $Cl(R'O)P(O)R$ are called alkyl alkylphosphonochloridates.

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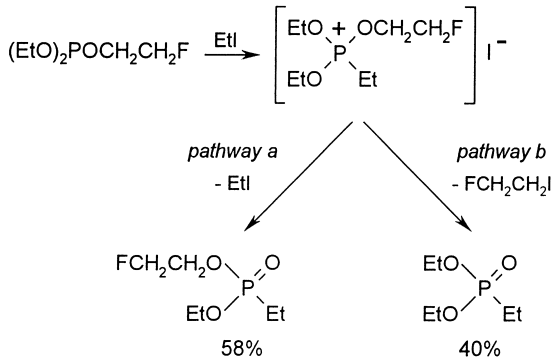


Some methods that have been used to make bis(fluoroalkyl) alkylphosphonates are shown in Fig. 1. The harsh conditions necessary for the Arbusov reactions of polyfluorinated phosphites (route A) render this chemistry unsuitable for routine use. Other approaches are often low yielding and

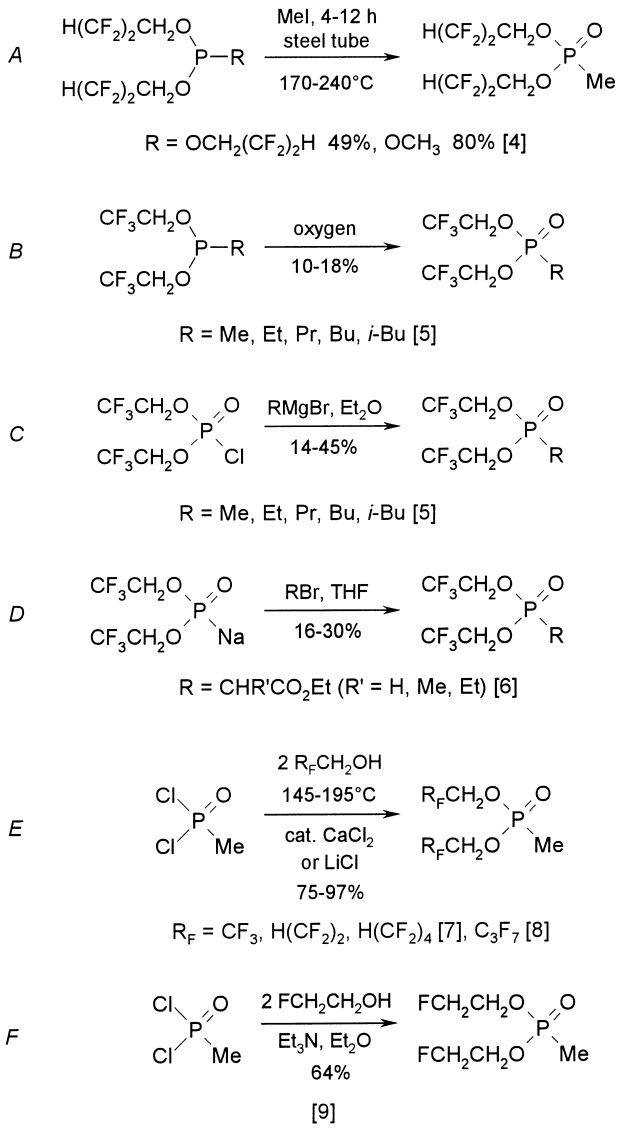


Fig. 1. Literature routes to bis(fluoroalkyl) alkylphosphonates.

these include the oxidation of phosphonites (route B), the substitution of phosphorochloridates by Grignard reagents (route C), and the Michaelis–Becker reaction of sodium dialkyl phosphonates with alkyl halides (route D). Some improved approaches involve the reactions of alkylphosphonic dichlorides with fluoroalcohols promoted by metal chloride catalysts (route E) or by tertiary amines (route F). The last two methods have been applied only to methylphosphonic dichloride.

In this paper, we report the reactions of various alkylphosphonic dichlorides $Cl_2P(O)R$ [R=Me, Et, *n*-Pr, i-Pr] with fluoroalcohols and triethylamine. Stereoelectronic influences on the reaction pathway were studied by treating isopropylphosphonic dichloride with the alcohols EtOH, *n*-PrOH, *n*-BuOH and i-PrOH, and the fluoroalcohols CF_3CH_2OH, $C_2F_5CH_2OH$, $C_3F_7CH_2OH$ and $(CF_3)_2CHOH$.

2. Results and discussion

2.1. Synthesis of bis(fluoroalkyl) alkylphosphonates

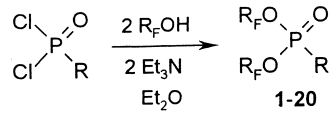
Bis(fluoroalkyl) alkylphosphonates **1**–**20** (Table 1) were prepared by fluoroalcoholysis of methyl, ethyl, propyl or isopropylphosphonic dichloride. They were isolated as mobile colourless liquids; some of them solidified to low-melting white solids on standing in a refrigerator. Yields and physical constants are presented in Table 2 and spectroscopic data in Tables 3–6.

2.2. NMR spectra of bis(hexafluoroisopropyl) alkylphosphonates

The fluorine spectra of the bis(hexafluoroisopropyl) alkylphosphonates **5**, **10**, **15** and **20** in deuterated chloroform are complex (assignments are given in Tables 3–6). For bis(hexafluoroisopropyl) *n*-propylphosphonate **15**, two broad resonances having fine structure were observed at about $\delta=-72.6$ and -72.8 (Fig. 2). In the proton spectrum, the methine resonance appeared as a doublet of septets corresponding to $^3J_{HP}$ and $^3J_{HF}$. The fluorine spectrum in d8-tetrahydrofuran gave a simple doublet at $\delta=-72.2$ with a coupling constant of 5 Hz (Fig. 2). Dissolution of the compound in d4-dichlorobenzene, and heating to a maximum of 120°C, caused a gradual loss of fine structure in the fluorine spectrum, but no coalescence. Additionally the fluorine spectra showed the same chemical shift difference when recorded at a frequency of 470 or 282 MHz.

Bis(hexafluoroisopropyl) alkylphosphonates probably exist in chloroform in a high-energy state, with the ester groups conformationally locked due to high intramolecular repulsive forces: either two pairs of non-equivalent trifluoromethyl groups, or one pair of non-equivalent hexafluoroisopropyl groups, are present. The repulsive forces are expected to be reduced in tetrahydrofuran, the solvent perhaps hydrogen bonding to the hexafluoroisopropoxy

Table 1

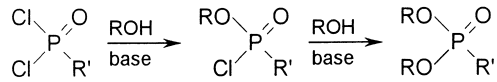


R	Fluoroalkyl group R_F	Compound	Fluoroalkyl group R_F	Compound	Fluoroalkyl group R_F	Compound
Me	CF_3CH_2	**1**	$HCF_2CF_2CH_2$	**2**	$C_2F_5CH_2$	**3**
	$C_3F_7CH_2$	**4**	$(CF_3)_2CH$	**5**		
Et	CF_3CH_2	**6**	$HCF_2CF_2CH_2$	**7**	$C_2F_5CH_2$	**8**
	$C_3F_7CH_2$	**9**	$(CF_3)_2CH$	**10**		
n-Pr	CF_3CH_2	**11**	$HCF_2CF_2CH_2$	**12**	$C_2F_5CH_2$	**13**
	$C_3F_7CH_2$	**14**	$(CF_3)_2CH$	**15**		
i-Pr	CF_3CH_2	**16**	$HCF_2CF_2CH_2$	**17**	$C_2F_5CH_2$	**18**
	$C_3F_7CH_2$	**19**	$(CF_3)_2CH$	**20**		

protons; many highly-fluorinated branched alcohols form strong hydrogen bonds with ether or other substrates that contain oxygen atoms [13].

2.3. Factors affecting the alcoholysis of alkylphosphonic dichlorides

The interaction of alkylphosphonic dichlorides with oxygen nucleophiles proceeds with formation of alkyl alkylphosphonochloridates that react further to give disubstituted products. In both stages, the alcohol adds to a phosphorus chloride to give a trigonal bipyramidal phosphorane intermediate that eliminates HCl (S_N2P mechanism) [14].



The structures of the alkylphosphonic dichloride and intermediate chloridate, and the nature of the alcohol, are some of the features that affect the reaction pathway. Although steric and electronic influences on the process have been elucidated for alcohols [15], the relative contribution of such effects for fluoroalcohols is unknown.

The inductive effect of the alkyl group on phosphorus varies little in going from methyl through to isopropyl [16] and therefore all the alkylphosphonic dichlorides studied are similar electronically. However, the role of steric factors in

Table 2
Experimental data for bis(fluoroalkyl) alkylphosphonates $RP(O)(OR_F)_2$

Compound	R	R_F	Yield (%)	Bp (°C/mmHg)
1	Me	CF_3CH_2	69	55/4 (mp 22°C)[a]
2	Me	$H(CF_2)_2CH_2$	58	97/0.015[b]
3	Me	$C_2F_5CH_2$	37	45/1 (mp 15°C)
4	Me	$C_3F_7CH_2$	52	73/0.02 (mp 20°C)[c]
5	Me	$(CF_3)_2CH$	48	38/2.5
6	Et	CF_3CH_2	67	59/4[d]
7	Et	$H(CF_2)_2CH_2$	58	98/0.015
8	Et	$C_2F_5CH_2$	28	35/0.1 (mp 19°C)
9	Et	$C_3F_7CH_2$	49	73/0.015
10	Et	$(CF_3)_2CH$	52	41/0.15
11	*n*-Pr	CF_3CH_2	66	47/1[e]
12	*n*-Pr	$H(CF_2)_2CH_2$	48	95/0.015
13	*n*-Pr	$C_2F_5CH_2$	39	49/0.5
14	*n*-Pr	$C_3F_7CH_2$	48	80/0.015
15	*n*-Pr	$(CF_3)_2CH$	67	34/0.3
16	i-Pr	CF_3CH_2	69	57/0.04
17	i-Pr	$H(CF_2)_2CH_2$	57	91/0.015
18	i-Pr	$C_2F_5CH_2$	35	64/3
19	i-Pr	$C_3F_7CH_2$	40	71/0.02
20	i-Pr	$(CF_3)_2CH$	54	46/0.8

[a] 51–52°C/4 mmHg [5] or 70–71°C/8 mmHg [7].
[b] 102–103°C/3 mmHg [4], 114–115°C/6 mmHg [7] (these figures are too high and suggest either impure products or wrong pressure readings).
[c] 92–93°C/9 mmHg [8].
[d] 41°C/1 mmHg [5].
[e] 50–53°C/1 mmHg [5].

Table 3
Spectroscopic data for bis(fluoroalkyl) methylphosphonates $(R_FO)_2P(O)Me$ (NMR data measured in $CDCl_3$)

Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ, J (Hz)	^{31}P NMR δ	IR ν (cm^{-1})	HRMS analysis
1	4.39 (4H, complex m, OCH_2), 1.68 (3H, d, J=19, P–CH_3)	122.3 (dq, J=9, 278, CF_3), 61.7 (dq, J=6, 37, OCH_2), 11.1 (d, J=148, P–CH_3)	−74.4 (6F, t, J=7, CF_3)	33.5	1403, 1296 (P=O), 1252, 1175, 1108, 1077, 966, 923, 903, 845	Calculated $C_5H_7F_6O_3P$ 260.004, found 259.996 (error 29.1 ppm)
2	5.91 (2H, tt, J=4, 53, CF_2H), 4.42 (4H, br m, OCH_2), 1.65 (3H, d, J=18, P–CH_3)	113.7 (dtt, J=7, 29, 250, CF_2), 109 (tt, J=37, 251, CF_2H), 61.1 (dt, J=6, 30, OCH_2), 11.1 (d, J=148, P–CH_3)	−137.1 (4F, d, J=53, CF_2H), −124.3 (4F, t, J=13, CF_2)	33.2	1460, 1420, 1321 (P=O), 1255, 1236, 1211, 1109, 1065, 920, 903, 831	Calculated $C_7H_9F_8O_3P$ 324.016 ($[M-HF]^+$=304.010), found 304.010 (error 0.8 ppm)
3	4.46 (4H, br m, OCH_2), 1.67 (3H, d, J=18, P–CH_3)	118.2 (tq, J=34, 286, CF_3), 111.7 (dqt, J=7, 45, 255, CF_2), 60.9 (dt, J=6, 28, OCH_2), 11 (d, J=147, P–CH_3)	−123.8 (4F, t, J=13, CF_2), −82.7 (6F, m, CF_3)	33.5	1460, 1407, 1376, 1355, 1320 (P=O), 1267, 1204, 1157, 1110, 1069, 1028, 936, 921, 839	Calculated $C_7H_7F_{10}O_3P$ 359.997, found 359.996 (error 2.3 ppm)
4	4.50 (4H, m, OCH_2), 1.65 (3H, d, J=18, P–CH_3)	117–105 (complex m, J obscured, $CF_2CF_2CF_3$), 61.1 (dt, J=5, 28, OCH_2), 11.1 (d, J=148, P–CH_3)	−127.2 (4F, m, CF_2), −121.3 (4F, m, CH_2CF_2), −80.6 (6F, m, CF_3)	33.7	1460, 1408, 1358, 1321 (P=O), 1300, 1230, 1186, 1132, 1080, 1018, 966, 926, 841	Calculated $C_9H_7F_{14}O_3P$ 459.991, found 459.991 (error 0.6 ppm)
5	5.18 (2H, dsep, J=6 each, OCH), 1.84 (3H, d, J=18, P–CH_3)	120 (dq, J=20, 284, CF_3), 70 (dsep, J=7, 38, OCH), 11.9 (d, J=146, P–CH_3)	−73.9 (6F, br, CF_3), −73.7 (6F, J=6–7, CF_3)	36.5	1383, 1324 (P=O), 1305, 1262, 1230, 1202, 1130, 1091, 931, 870	Calculated $C_7H_5F_{12}O_3P$ 395.978, found 395.979 (error −0.8 ppm)

Table 4
Spectroscopic data for bis(fluoroalkyl) ethylphosphonates $(R_FO)_2P(O)Et$ (NMR data measured in $CDCl_3$)

Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ, J (Hz)	^{31}P NMR δ	IR ν (cm^{-1})	HRMS analysis
6	4.38 (4H, complex m, OCH_2), 1.93 (2H, dq, J=19, 8, P–CH_2), 1.23 (3H, dt, J=19, 8, CH_3)	122.8 (dq, J=7, 272, CF_3), 62 (dq, J=5, 37, OCH_2), 19.2 (d, J=144, P–CH_2), 6.05 (d, J=6, CH_3)	−74.4 (6F, t, J=8, CF_3)	36.1	1462, 1419, 1288 (P=O), 1255, 1174, 1109, 1080, 1036, 1016, 964, 845	Calculated $C_6H_9F_6O_3P$ 274.019, found 274.017 (error 7.3 ppm)
7	5.91 (2H, tt, J=4, 53, CF_2H), 4.42 (4H, br m, OCH_2), 1.91 (2H, dq, J=19, 8, P–CH_2), 1.21 (3H, dt, J=19, 8, CH_3)	113.7 (dtt, J=7, 28, 251, CF_2), 109.1 (tt, J=36, 251, CF_2H), 61.1 (dt, J=5, 23, OCH_2), 18.7 (d, J=143, P–CH_2), 5.9 (d, J=7, CH_3)	−136.6 (4F, d, J=53, CF_2H), −123.8 (4F, t, J=11, CF_2)	35.5	1462, 1411, 1291 (P=O), 1258, 1232, 1212, 1109, 1069, 1034, 964, 950, 864	Calculated $C_8H_{11}F_8O_3P$ 338.032, found 338.032 (error 0.1 ppm)
8	4.48 (4H, m, OCH_2), 1.93 (2H, dq, J=19, 8, P–CH_2), 1.22 (3H, dt, J=19, 8, CH_3)	118.1 (tq, J=35, 286, CF_3), 111.6 (dqt, J=7, 38, 256, CF_2), 60.8 (dt, J=6, 29, OCH_2), 18.8 (d, J=44, P–CH_2), 5.5 (d, J=8, CH_3)	−123.8 (4F, br t, CF_2), −82.7 (6F, m, CF_3)	36.2	1464, 1410, 1375, 1355, 1302 (P=O), 1270, 1201, 1158, 1111, 1073, 1029, 957, 866	Calculated $C_8H_9F_{10}O_3P$ 374.013, found 374.013 (error 0.4 ppm)
9	4.5 (4H, m, OCH_2), 1.94 (2H, dq, J=19, 8, P–CH_2), 1.22 (3H, dt, J=19, 8, CH_3)	117–109 (complex m, J obscured, $CF_2CF_2CF_3$), 60.9 (dt, J=5, 28, OCH_2), 18.6 (d, J=143, P–CH_2), 5.6 (d, J=7, CH_3)	−126.6 (4F, m, CF_2), −120.7 (4F, m, CH_2CF_2), −79.9 (6F, m, CF_3)	36.3	1464, 1410, 1356, 1300 (P=O), 1230, 1186, 1132, 1082, 1014, 966, 924, 864	Calculated $C_{10}H_9F_{14}O_3P$ 474.007, found 474.007 (error −0.8 ppm)
10	5.17 (2H, dsep, J=6, OCH), 2.07 (2H, dq, J=23, 8, P–CH_2), 1.28 (3H, dt, J=23, 8, CH_3)	120 (dq, J=11, 286, CF_3), 70 (dsep, J=6, 35, OCH), 19.5 (d, J=140, P–CH_2), 5.5 (d, J=8, CH_3)	−73.9 (6F, d, J=66, CF_3), −73.7 (6F, d, J=66, CF_3)	38.8	1466, 1383, 1294 (P=O), 1234, 1203, 1130, 1113, 1093, 1038, 1018, 903, 866	Calculated $C_8H_7F_{12}O_3P$ 409.994, found 409.994 (error 0.5 ppm)

Table 5
Spectroscopic data for bis(fluoroalkyl) propylphosphonates $(R_FO)_2P(O)n$-Pr (NMR data measured in $CDCl_3$)

Compound	^{1}H NMR δ, J (Hz)[a]	^{13}C NMR δ, J (Hz)	^{19}F NMR δ, J (Hz)	^{31}P NMR δ	IR ν (cm^{-1})	HRMS analysis
11	4.36 (4H, m, J∼8, OCH_2), 1.91 (2H, m, J∼8, P–CH_2), 1.69 (2H, m, J∼8, CH_2), 1.06 (3H, dt, J=2, 8, CH_3)	122.5 (dq, J=7, 277, CF_3), 61.8 (dq, J=6, 37, OCH_2), 27.5 (d, J=140, P–CH_2), 15.6 (d, J=5, CH_2), 14.9 (d, J=18, CH_3)	−74.4 (6F, t, J=7, CF_3)	35.2	1412, 1293 (P=O), 1261, 1239, 1174, 1109, 1070, 1042, 965, 872	Calculated $C_7H_{11}F_6O_3P$ 288.035, found 288.035 (error 1 ppm)
12	5.9 (2H, tt, J=4, 53, CF_2H), 4.4 (4H, m, J∼8, OCH_2), 1.85 (2H, br m, J∼8, P–CH_2), 1.67 (2H, br m, J∼8, CH_2), 1.05 (3H, dt, J=1, 7, CH_3)	113.8 (dtt, J=8, 29, 247, CF_2), 109.1 (tt, J=36, 251, CF_2H), 61.1 (dt, J=6, 25, OCH_2), 27.6 (d, J=140, P–CH_2), 15.6 (d, J=6, CH_2), 14.9 (d, J=18, CH_3)	−137.1 (4F, d, J=52, CF_2H), −124.3 (4F, t, J=13, CF_2)	34.6	1460, 1408, 1290 (P=O), 1263, 1236, 1213, 1109, 1063, 951, 935, 870, 835	Calculated $C_9H_{13}F_8O_3P$ 352.047, found 352.046 (error 3 ppm)
13	4.47 (4H, m, J∼7, OCH_2), 1.68 (2H, m, J∼7, P–CH_2), 1.90 (2H, m, J∼7, CH_2), 1.05 (3H, dt, J=2, 7, CH_3)	118.3 (qt, J=286, 34, CF_3), 111.8 (dqt, J=7, 38, 255, CF_2), 60.8 (dt, J=6, 29, OCH_2), 27.5 (d, J=141, P–CH_2), 15.4 (d, J=6, CH_2), 14.7 (d, J=18, CH_3)	−124.4 (4F, t, J=7, CF_2), −83.3 (6F, m, CF_3)	35.0	1462, 1408, 1354, 1306 (P=O), 1275, 1209, 1157, 1128, 1066, 1028, 958, 935, 872	Calculated $C_9H_{11}F_{10}O_3P$ 388.029, found 388.029 (error −1.8 ppm)
14	4.55 (4H, m, J∼8, OCH_2), 1.92 (2H, dt, J=10, 8, P–CH_2), 1.69 (2H, m, J∼8, CH_2), 1.05 (3H, dt, J=2, 8, CH_3)	117.4 (qt, J=287, 33, CF_3), 113.6 (dtt, J=7, 31, 257, CH_2CF_2), 108.5 (qt, J=266, 34, CF_2), 61 (dt, J=5, 27, OCH_2), 27.6 (d, J=141, P–CH_2), 15.5 (d, J=6, CH_2), 14.8 (d, J=18, CH_3)	−126.6 (4F, m, CF_2), −120.7 (4F, m, CH_2CF_2), −80 (6F, m, CF_3)	35.0	1462, 1408, 1356, 1300 (P=O), 1230, 1186, 1132, 1072, 1016, 966, 924, 870	Calculated $C_{11}H_{11}F_{14}O_3P$ 488.022, found 488.022 (error 0 ppm)
15	5.17 (2H, dsep, J=6 each, OCH), 2.03 (2H, m, J∼8, P–CH_2), 1.73 (2H, tq, J=8, CH_2), 1.08 (3H, dt, J=2, 8, CH_3)	120.1 (dq, J=16, 285, CF_3), 69.9 (dsep, J=6, 37, OCH), 28 (d, J=137, P–CH_2), 15.3 (d, J=6, CH_2), 14.7 (d, J=19, CH_3)	−73.9 (6F, br, CF_3), −73.7 (6F, complex m, J∼6, CF_3)[b]	37.5	1462, 1382, 1300 (P=O), 1272, 1243, 1206, 1129, 1077, 1043, 904, 883, 866	Calculated $C_9H_9F_{12}O_3P$ 424.010, found 424.009 (error 0.9 ppm)

[a] The P–OCH_2 proton resonances are second order; hence coupling constants are only approximate.
[b] ∼80 Hz apart at 470 MHz and ∼44 Hz apart at 282 MHz.

Table 6
Spectroscopic data for bis(fluoroalkyl) isopropylphosphonates $(R_FO)_2P(O)i\text{-}Pr$ (NMR data measured in $CDCl_3$)

Compound	^{1}H NMR δ, J (Hz)[a]	^{13}C NMR δ, J (Hz)	^{19}F NMR δ, J (Hz)	^{31}P NMR δ	IR ν (cm^{-1})	HRMS analysis
16	4.38 (4H, dq, J=8, OCH_2), 2.15 (1H, dsep, J=19, 7, P–CH), 1.25 (6H, dd, J=7, 20, CH_3)	122.7 (dq, J=7, 277, CF_3), 62 (dq, J=3, 38, OCH_2), 26.6 (d, J=43, P–CH), 15.5 (d, J=5, CH_3)	−74.4 (6F, t, J=7, CF_3)	37.7	1421, 1287 (P=O), 1240, 1174, 1110, 1094, 1075, 1046, 964, 868	Calculated $C_7H_{11}F_6O_3P$ 288.035, found 288.035 (error −1.1 ppm)
17	5.9 (2H, tt, J=4, 53, CF_2H), 4.41 (4H, br m, J∼8, ∼13, OCH_2), 2.13 (1H, dsep, J=19, 7, P–CH), 1.24 (6H, dd, J=7, 19, CH_3)	113.8 (dtt, J=7, 27, 251, CF_2), 109.1 (tt, J=37, 251, CF_2H), 61.3 (dt, J=6, 29, OCH_2), 26 (d, J=42, P–CH), 15.5 (d, J=6, CH_3)	−137.1 (4F, d, J=52, CF_2H), −124.3 (4F, t, J=13, CF_2)	37.4	1471, 1292 (P=O), 1234, 1213, 1109, 1065, 1043, 951, 935, 891, 864, 837	Calculated $C_9H_{13}F_8O_3P$ 352.047, found 352.048 (error −0.1 ppm)
18	4.46 (4H, m, OCH_2), 2.15 (1H, dsep, J=21, 7, OCH), 1.25 (6H, dd, J=7, 19, CH_3)	118.2 (tq, J=34, 285, CF_3), 111.8 (dqt, J=7, 38, 256, CF_2), 61 (dt, J=6, 29, OCH_2), 25.9 (d, J=42, OCH), 15.2 (d, J=3, CH_3)	−123.8 (4F, br m, CF_2), −82.7 (6F, m, CF_3)	37.7	1471, 1395, 1375, 1354, 1297 (P=O), 1270, 1205, 1156, 1127, 1070, 1043, 958, 936, 892, 865, 823	Calculated $C_9H_{11}F_{10}O_3P$ 388.029, found 388.029 (error −0.6 ppm)
19	4.5 (4H, m, J∼8, OCH_2), 2.15 (1H, dsep, J=19, 7, P–CH), 1.25 (6H, dd, J=7, 19, CH_3)	117.4 (tq, J=34, 287, CF_3), 113.7 and 108[a] (m, CF_2CF_2), 61.2 (dt, J=8, 44, OCH_2), 26.3 (d, J=44, P–CH), 15.3 (d, J=5, CH_3)	−126.6 (4F, m, CF_2), −120.7 (4F, m, CH_2CF_2), −79.9 (6F, m, CF_3)	37.8	1471, 1356, 1296 (P=O), 1230, 1184, 1132, 1076, 1016, 966, 924, 891, 862	Calculated $C_{11}H_{11}F_{14}O_3P$ 488.022, found 488.023 (error −0.8 ppm)
20	5.17 (2H, dsep, J=6 each, OCH), 2.26 (2H, dsep, J=21 and 7, P–CH), 1.32 (6H, dd, J=7, 21, CH_3)	120.1 (dq, J=16, 284, CF_3), 70 (dsep, J=7, 37, OCH), 27 (d, J=138, P–CH), 15.1 (d, J=5, CH_3)	−73.6 (12F, d, J=66, CF_3)	39.9	1471, 1375, 1292 (P=O), 1246, 1205, 1128, 1113, 1086, 1047, 891, 877, 854	Calculated $C_9H_9F_{12}O_3P$ 424.010, found 424.009 (error 1.8 ppm)

[a] Coupling constants obscured because of CF_2 overlap.

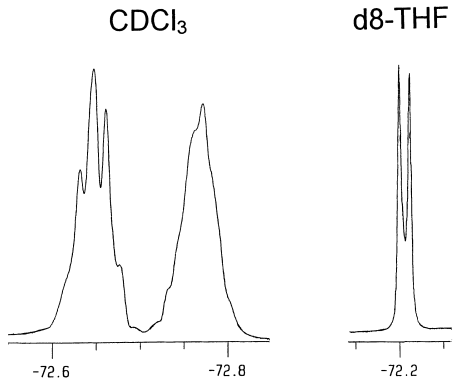
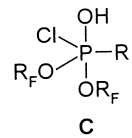


Fig. 2. The ^{19}F spectra of bis(hexafluoroisopropyl) *n*-propylphosphonate $[(CF_3)_2CHO]_2P(O)n$-Pr **15**, showing the signals corresponding to the trifluoromethyl groups; recorded in deuterated chloroform (left) and tetrahydrofuran (right) at 470 MHz; the chemical shift on the horizontal axis is relative to external $CFCl_3$ standard.

determining their reactivity is profound. For example, $MeP(O)Cl_2$ hydrolyses five times faster than $EtP(O)Cl_2$ or n-$PrP(O)Cl_2$, and over a hundred times faster than i-$PrP(O)Cl_2$ in ice-cold acetone containing 5% water [17]. Isopropylphosphonic dichloride was the least reactive of the alkylphosphonic dichlorides investigated and is the best model for studying differences in the rates of alcoholysis. The reactivities of some alcohols and fluoroalcohols towards isopropylphosphonic dichloride were therefore compared.

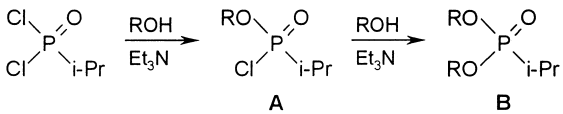
After 12 h at room temperature, two molar equivalents of alcohol reacted to give mixtures of mono and disubstituted products **A** and **B** (Table 7), but in the case of isopropanol, one product only. The increase in monosubstituted product with lengthening of the alkyl chain of the alcohols can be ascribed to electron release to the phosphorus atom (in agreement with pK_a values), reducing the reactivity of the phosphonochloridate towards further nucleophilic attack. However, the steric effect of the newly formed ester function is also important, particularly in the case of the isopropoxy group. A similar interplay between steric and electronic effects accounts for differences in the rates of hydrolysis of alkyl alkylphosphonochloridates. For example, in the methylphosphonochloridate series Cl(RO)P(O)Me, the methyl ester hydrolyses twice as fast as the ethyl ester and four times faster than the isopropyl ester [20]. In the ethylphosphonochloridate series Cl(RO)P(O)Et, the methyl ester hydrolyses about three times faster than the ethyl ester, but almost 13 times faster than the isopropyl ester [20]. Similarly, Cl(n-PrO)P(O)n-Pr hydrolyses one and a half times faster, and Cl(n-PrO)P(O)i-Pr approximately two times faster, than the corresponding isopropyl esters [21].

Fluoroalcohols are more reactive towards alkylphosphonic dichlorides than their hydrogen counterparts owing to the ability of fluorine to stabilise the alkoxide form, which is a better nucleophile, and to increase inductively the electrophilicity of the intermediate phosphonochloridates. Fluoroalcoholysis of isopropylphosphonic dichloride led to almost exclusive production of bis(fluoroalkyl) isopropylphosphonates of type **B**. The low percentage or absence of any intermediate phosphonochloridates must be a consequence of the unusually rapid rate of the second substitution. This phenomenon is anomalous as products of type **A** and **B** (Table 7) were formed when unfluorinated primary alcohols reacted with isopropylphosphonic dichloride. The product differences in the two cases can be ascribed to a difference in the electronic effect of a fluoroalkoxy group (electron-withdrawing) relative to an alkoxy group (electron-donating). A kinetic acceleration of the second substitution occurs for fluoroalkyl phosphonochloridates $Cl(R_FO)P(O)R'$ but not for alkyl phosphonochloridates $Cl(RO)P(O)R'$. Alternatively, thermodynamic stabilisation of the intermediate phosphorane **C**, formed in the fluoroalcoholysis reactions, could lead to the same phenomenon.



C

Table 7
Composition of reaction mixtures after 12 h at 25°C as determined by GC-MS



A **B**

Alcohol	pK_a[a]	%**A**	%**B**	Fluoroalcohol	pK_a[a]	%**A**	%**B**
MeOH	15.1	29	70				
EtOH	15.9	50	48	CF_3CH_2OH	12.4	5	94
n-PrOH	16.1	68	29	$C_2F_5CH_2OH$	–	5	93
n-BuOH	16.1	75	23	$C_3F_7CH_2OH$	11.4	–	98
i-PrOH	17.1	98	–	$(CF_3)_2CHOH$	9.3	–	98

[a] pK_a values for alcohols obtained from [18] and for fluoroalcohols from [19].

It is well established that the stabilities of pentacoordinate phosphorus compounds increase with the electronegativity of the ligand (e.g. PF_5 is very stable, PCl_5 dissociates, and PH_5 and PMe_5 are unknown) [22]. Consequently reaction intermediates with the most electronegative ligands are the most stable; the slightly higher rate of hydrolysis of (i-$PrO)_2P(O)F$ compared to (i-$PrO)_2P(O)Cl$ has been attributed to the greater stability of the intermediate (i-$PrO)_2P(OH)_2F$ versus (i-$PrO)_2P(OH)_2Cl$ [23]. Fluoroalkoxy groups also stabilise the pentavalent state. For example, the fluoroalkoxyphosphoranes $(CF_3CH_2O)_3P(CN)_2$ [24] and $(HCF_2CF_2CH_2O)_3P(CN)_2$ [25] are liquids of relatively high stability - they can be distilled without decomposition unlike related alkoxyphosphoranes which usually undergo rapid Arbusov rearrangement. The hexafluoroisopropyl group is

particularly good at stabilising the pentavalent state. Its strong electron-acceptor ability and bulkiness hinder transformation of dihalophosphoranes by the Arbusov reaction, and stable covalent derivatives of structure $[(CF_3)_2CHO]_3PX_2$ (X=F, Cl or Br) can be isolated [26]. Such a stabilising effect may explain why bis(hexafluoroisopropyl) isopropylphosphonate $[(CF_3)_2CHO]_2P(O)$i-Pr **20** formed exclusively in the reaction between hexafluoroisopropanol and isopropylphosphonic dichloride. On steric grounds, only monosubstitution to give $Cl[(CF_3)_2CHO]$-P(O)i-Pr was expected, hexafluoroisopropanol being assumed to be roughly the same size as 2,4-dimethyl-3-pentanol $(i\text{-}Pr)_2CHOH$; the trifluoromethyl group is considerably larger than a methyl group and is estimated to be at least as large as an isopropyl group [27]. Thermodynamic stabilisation of the phosphorane intermediate to account for the formation of bis(hexafluoroisopropyl) isopropylphosphonate **20** is supported by the steric congestion of the molecule, as indicated by NMR studies (refer to Section 2.2), and the finding that disubstitution of isopropylphosphonic dichloride with an excess of isopropanol could not be achieved with triethylamine as base, even on prolonged reflux in ether (see Section 4.2).

3. Conclusion

The base-promoted reaction of fluoroalcohols with alkylphosphonic dichlorides is one of the best methods available for the synthesis of bis(fluoroalkyl) alkylphosphonates. Unlike most literature methods, this approach is mild and of general applicability. Now that bis(fluoroalkyl) alkylphosphonates can be prepared in good yield, the path is laid for a systematic study of their chemistry.

4. Experimental details

All reagents were of commercial quality: fluoroalcohols were purchased from Apollo Scientific Ltd (Derbyshire, UK). Methylphosphonic dichloride was purified by distillation; bp 163°C (lit. bp 163°C [28]). Ethyl and *n*-propylphosphonic dichlorides were purchased from Aldrich (the latter was of technical grade, i.e. 95% pure). Isopropylphosphonic dichloride was obtained from the Friedel–Crafts reaction between isopropyl chloride and phosphorus trichloride [29,30]; bp 80°C/15 mmHg (lit. bp 77–79°C/14 mmHg [30]). Anhydrous ether and triethylamine (distilled from CaH_2 and stored over CaH_2) were used for the alcoholysis experiments. NMR spectra were obtained on a JEOL Lambda 500 instrument (operating at 500 MHz for ^1H, 125 MHz for ^{13}C, 470 MHz for ^{19}F, and 202 MHz for ^{31}P spectra) or a JEOL instrument (operating at 300 MHz for ^1H, 75 MHz for ^{13}C, 282 MHz for ^{19}F, and 121.5 MHz for ^{31}P spectra) as solutions in $CDCl_3$, with internal reference $SiMe_4$ for ^1H and ^{13}C, external $CFCl_3$ for ^{19}F and external $(MeO)_3P$ (δ=140 ppm) for ^{31}P spectra. Data in Tables 3–6 are recorded as follows: chemical shifts in ppm from reference on the δ scale, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and sep=septet; br=broad), coupling constant (Hz) and assignment. IR spectra were recorded as liquid films on a Nicolet SP210 instrument using Omnic software. Reaction mixtures were monitored by gas chromatography-mass spectrometry (GC-MS) using a Finnigan MAT GCQ instrument and chemical ionisation (CI) using methane as reagent gas. Molecular masses of pure products were confirmed with methane +ve CI data. Elemental analysis was carried out on the largest stable fragment ion, using high resolution mass spectrometry (HRMS) on a Micromass Autospec SQ Double Focusing Magnetic Sector instrument. Mode: +ve ion electron impact, magnet scan *m/z* 400 to 100 s per decade, resolution 2900. Inlet: septum (160°C), 0.2 ml introduced. Source conditions: temperature 200°C, electron energy 70 eV, and accelerating voltage 8000 V.

4.1. General method for bis(fluoroalkyl) alkylphosphonates

A solution of fluoroalcohol (0.14 mol) and triethylamine (0.14 mol) in diethyl ether (50 ml) was added dropwise to a magnetically stirred solution of alkylphosphonic dichloride (0.07 mol) in diethyl ether (50 ml) at 0–5°C. After addition, the mixture was refluxed for 2 h. Analysis by GC-MS indicated that the reaction had gone to completion. The precipitate was removed by filtration and the filtrate concentrated to an oil. Fractionation under reduced pressure (0.015–4 mmHg) gave the title compounds as colourless mobile liquids. Yields and physical constants are given in Table 2 and spectroscopic data in Tables 3–6. In the reactions of $H(CF_2)_2CH_2OH$ with the alkylphosphonic dichlorides, i.e. for the synthesis of **2**, **7**, **12** and **17**, the procedure differed: the reaction mixture was treated with water (100 ml), the organic layer separated, dried ($MgSO_4$) and concentrated to a mobile oil which was then fractionated under reduced pressure.

4.2. Reactions of alcohols with isopropylphosphonic dichloride

The molar ratios of reactants were as before but the reaction mixtures were left for 12 h at room temperature, then analysed by GC-MS. The product/s that formed are given in Table 7. The reaction between isopropylphosphonic dichloride and isopropanol yielded only isopropyl isopropylphosphonochloridate Cl(i-PrO)P(O)i-Pr. This could be isolated by filtration, evaporation of the filtrate to an oil and fractionation under reduced pressure (bp 42–44°C/0.1 mmHg). Alternatively, refluxing for several days produced a 2:1 mixture of isopropyl isopropylphosphonochloridate, Cl(i-PrO)P(O)i-Pr, and diisopropyl isopropylphosphonochloridate, $(i\text{-}PrO)_2P(O)$i-Pr.

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