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The first isolable dialkyl iodophosphates

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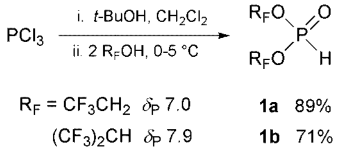
The synthesis and characterization of the first dialkyl iodophosphates to be isolated in a pure state is described; $(CF_3CH_2O)_2P(O)I$ and $[(CF_3)_2CHO]_2P(O)I$ have electronegative fluoro-ester groups and can be distilled under vacuum.

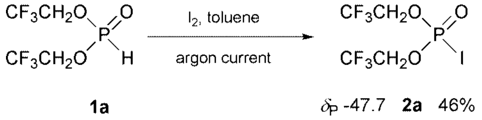
The study of derivatives of phosphoric acid is one of the oldest branches of organic chemistry. In 1868, Wichelhaus isolated the first member of the dialkyl halophosphate series, diethyl chlorophosphate $(CH_3CH_2O)_2P(O)Cl$.[1] Later work led to the fluorophosphate $(CH_3CH_2O)_2P(O)F$[2] and the bromophosphate $(CH_3CH_2O)_2P(O)Br$; the latter is unstable and decomposes after 3 days at room temperature.[3] The corresponding iodophosphate $(CH_3CH_2O)_2P(O)I$, like all known iodophosphates, decomposes extremely easily and has not been obtained out of solution.[4–6] In continuation of our studies on fluoroalkyl phosphoryl compounds,[7,8] we now describe the synthesis and characterization of the first isolable dialkyl iodophosphates (and the first such molecules containing fluoro-ester groups). Our results indicate that the presence of electronegative fluorine atoms[9] significantly enhances thermal stability.

We prepared bis(fluoroalkyl) phosphites **1a** and **1b** in good yield by treating the intermediate from tertiary butanolysis of phosphorus trichloride, namely $Cl_2P(O)H$, with two molar equivalents of trifluoroethanol or hexafluoroisopropanol (Scheme 1).† The synthesis of compound **1a** this way was reported by Gibbs and Larsen; modification of their procedure[10] gave the new phosphite **1b**. Both bis(fluoroalkyl) phosphites can be stored in glass vials in a refrigerator for many months without change.



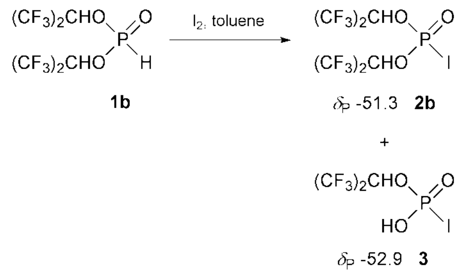
Scheme 1

Treatment of bis(trifluoroethyl) phosphite **1a** with a solution of iodine in toluene,[11] with argon blowing through the mixture to help remove hydrogen iodide, gave iodophosphate **2a** (Scheme 2). It was purified by vacuum distillation (bp 40 °C/0.02 mmHg).‡ This is the first time iodination of a dialkyl phosphite has permitted the isolation of a pure iodophosphate: the reaction with diethyl phosphite is complicated by dealkylation of diethyl iodophosphate by hydrogen iodide, and pure product cannot be obtained.[4] The greater ease of dealkylation of the CH_3CH_2O– group compared to the CF_3CH_2O– group is because the ethoxy oxygen is more basic than the trifluoroethoxy oxygen, and thus more easily converted into a leaving group by protonation, and also because the α-carbon of the CH_3CH_2O– group is a softer acid than that of the CF_3CH_2O– group, making it more vulnerable to attack by iodide ion, itself a soft base.



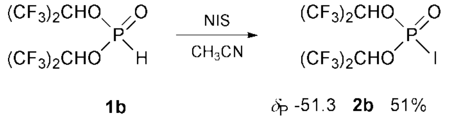
Scheme 2

Iodination of bis(hexafluoroisopropyl) phosphite **1b**, without argon blowing through the reaction mixture, gave a 1 : 2 ratio of iodophosphate **2b** and iodo acid **3** (Scheme 3), as shown by multinuclear NMR experiments. The iodo acid arises from dealkylation of the iodophosphate by resident hydrogen iodide; the by-product $(CF_3)_2CHI$ was not detected, but most likely escaped due to its volatile nature.



Scheme 3

Although bis(fluoroalkyl) iodophosphates resist dealkylation more than their unfluorinated counterparts, hydrogen iodide formation is best avoided during their synthesis. Treatment of bis(hexafluoroisopropyl) phosphite **1b** with *N*-iodosuccinimide (NIS), a convenient source of ‘positive’ iodine, led to good conversion to the iodophosphate, as shown by GC-MS analysis of the reaction mixture (Scheme 4). Iodophosphate **2b** was purified by vacuum distillation (bp 46 °C/2 mmHg).§



Scheme 4

Iodophosphates **2a–b** are pale yellow liquids that deposit traces of black solid on storage in a refrigerator. In line with other dialkyl halophosphates,[1] the iodophosphates might be expected to be colourless. The yellow colour is probably attributable to contamination by iodine vapour during distillation; the deposit during storage is assumed to be precipitated iodine. The phosphorus chemical shifts in deuteriochloroform for bis(trifluoroethyl) iodophosphate **2a** and bis(hexafluoroisopropyl) iodophosphate **2b** are −47.7 and −51.3 ppm. Values for $(CH_3CH_2O)_2P(O)I$ and $(CCl_3CH_2O)_2P(O)I$ in chloroethane are −41 and −50 ppm respectively.[6]

In summary, we have developed routes to two dialkyl iodophosphates that comprise the first such species to have been isolated and characterized properly. This discovery, which lags behind the first isolation of a pure dialkyl phosphorochloridate by over 130 years, opens up new frontiers in organic phosphorus and iodine chemistry. Further studies relating to the synthesis of

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a range of bis(fluoroalkyl) phosphites and their reactions with halogens will be reported in due course.

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Notes and references

† *Materials and methods:* trifluoroethanol and hexafluoroisopropanol were purchased from Apollo Scientific Ltd UK. Analytical information was obtained using documented instrumentation and techniques: see C. M. Timperley, M. Bird, I. Holden and R. M. Black, *J. Chem. Soc., Perkin Trans. 1*, 2001, 26. NMR data were recorded in $CDCl_3$ solution.

‡ *Bis(trifluoroethyl) iodophosphate* **2a**: a solution of iodine (5.08 g, 0.02 mol) in toluene (100 cm^3) was added dropwise to bis(trifluoroethyl) phosphite (4.92 g, 0.02 mol) in toluene (75 cm^3) at 0–5 °C with stirring and passage of argon through the solution. After addition, the purple solution was left for 2 h. Residual iodine was removed by filtration through a small plug of silica gel. Removal of toluene and double distillation of the residue gave **2a** as a pale yellow liquid (3.42 g, 46%). Bp 40 °C/0.02 mmHg. δ_H (500 MHz) 4.45 (4H, m, OCH_2); δ_C (125 MHz) 121.4 (dq, J = 13 and 278 Hz, CF_3), 69.4 (dq, J = 5 and 37 Hz, OCH_2); δ_F (470 MHz) −74.1 (6F, t, J = 7 Hz, CF_3); ν_{max}/cm^{-1} (film) 1454, 1421, 1296 (P=O), 1174, 1070, 962, 883, 849; m/z (CI) 373 (M + 1), 353 (M − F), 245 (M − I); HRMS (+ve ion EI): Calc. for $C_4H_4F_6IO_3P$ 371.939 ($[M - HF]^+$ = 351.933), found 351.933 (error 0.7).

§ *Bis(hexafluoroisopropyl) iodophosphate* **2b**: a solution of *N*-iodosuccinimide (2.62 g, 11.65 mmol) in acetonitrile (20 cm^3) was added dropwise by cannula to a stirred solution of bis(hexafluoroisopropyl) phosphite (4.45 g, 11.65 mmol) in acetonitrile (30 cm^3). After 2 h, GC-MS analysis showed good conversion to product. Removal of solvent and double distillation of the oily residue gave **2b** as a pale yellow liquid (3 g, 51%). Bp 46 °C/2 mmHg. δ_H (500 MHz) 5.28 (2H, dsep, J = 5 Hz, OCH); δ_C (125 MHz) 119.9 (dq, J = 6 and 282 Hz, CF_3), 71.9 (dsep, J = 7 and 37 Hz, OCH); δ_F (470 MHz) −72.3 (6F, m, CF_3), −73.2 (6F, m, CF_3); ν_{max}/cm^{-1} (film) 1379, 1300 (P=O), 1280–1205 (strong bands), 1117, 1068, 904, 879, 854; m/z (CI) 509 (M + 1), 489 (M − F), 381 (M − I); HRMS (+ve ion EI): Calc. for $C_6H_2F_{12}IO_3P$ 507.933 ($[M - HF]^+$ = 487.927), found 487.926 (error 1.6).

1 Refer to G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley & Sons, New York, 1950, p. 242.

2 Diethyl fluorophosphate $(CH_3CH_2O)_2P(O)F$ was first prepared in 1932 by W. Lange and G. von Krüger, *Chem. Ber.*, 1932, **65**, 1598. For a review of the history of this ‘nerve agent’, see C. M. Timperley, *Highly Toxic Fluorine Compounds*, in: R. E. Banks (Ed.), *Fluorine Chemistry at the Millennium: Fascinated by Fluorine*, Elsevier, Oxford, UK, 2000, pp. 499–538.

3 H. Goldwhite and B. C. Saunders, *J. Chem. Soc.*, 1955, 3564.

4 H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 1945, 921.

5 A. Skowronska, M. Pakulski, J. Michalski, D. Cooper and S. Trippett, *Tetrahedron Lett.*, 1980, **21**, 321.

6 Although the synthesis of $(CH_3CH_2O)_2P(O)I$ and the chloro analogue $(CCl_3CH_2O)_2P(O)I$ have been prepared by iodination of the respective trialkyl phosphites at −40 °C, their purification and full characterization has not been carried out. See J. Michalski, M. Pakulski and A. Skowronska, *J. Chem. Soc., Perkin Trans. 1*, 1980, 833.

7 C. M. Timperley, J. F. Broderick, I. Holden, I. J. Morton and M. J. Waters, *J. Fluorine Chem.*, 2000, **106**, 43.

8 C. M. Timperley, I. Holden, I. J. Morton and M. J. Waters, *J. Fluorine Chem.*, 2000, **106**, 153.

9 The hexafluoroisopropoxy group is more electron-withdrawing than the trifluoroethoxy group: pK_a values for $(CF_3)_2CHOH$ and CF_3CH_2OH are 9.3 and 12.4 respectively (compare these with 17.1 for isopropanol and 15.9 for ethanol). See M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Ellis Horwood, London, 2nd Edition, 1992, p. 550.

10 D. E. Gibbs and C. Larsen, *Synthesis*, 1984, 410. The reaction mixture from tertiary butanolysis of phosphorus trichloride was left for 1 h at 0–5 °C and hexafluoroisopropanol was added dropwise over 30 mins. After standing for 12 h at rt, the mixture was heated under reflux for 3 h, the solvent removed and the residue distilled to give bis(hexafluoroisopropyl) phosphite **1b** as a mobile colourless liquid (71%). Bp 62 °C/8 mmHg.

11 The solubility of iodine in g kg^{-1} of solvent at 25 °C decreases in the order: toluene 1875 > diethyl ether 337 > benzene 164; see *Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, New York, 3rd Edition, 1978, vol. 13, p. 652. Toluene is therefore the best choice of solvent for the iodination reaction.