C-fluorinated phosphate analogues

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Abstract

C-fluorinated phosphinic acid derivatives $RP(O)(OEt)CF_2Br$ (R = Ph, Me) **2a, b** and $[RP(O)(OR^1)]_2CF_2$ (R = Ph, R^1 = Et, H) **3**, **4** have been prepared via a Michaelis–Arbuzov reaction. The signs of the scalar coupling constants in the AMX spin system of $(EtO)_2P(O)CHFCOOEt$ (**5**) formed by the P, F and H of the P–C(H)F unit were determined using spin-tickling techniques.

Introduction

C-fluorinated derivatives of phosphonic acids have attracted widespread interest because of their ability to take part in cell metabolism [1–3]. Various acids and esters have recently been prepared to investigate their properties as chelating and antiviral agents, as well as substrate analogues in biochemistry and medicine [4–7].

Replacing one OH group in phosphonic acids by alkyl or aryl substituents leads to the monobasic phosphinic acids:

$$R{-}\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle OH}{|}}{P}}}{-}\overset{\displaystyle X}{\overset{|}{\underset{\underset{\displaystyle Y}{|}}{C}}}{-}R^1 \qquad (X, Y = F;\ R, R^1 = \text{aryl, alkyl})$$

To date, compounds of this type are found rarely in the literature due to the more tedious synthesis of phosphinic acids in comparison to that of phosphonates. The first part of this work is concerned with phosphinic acid derivatives while the second part includes some new NMR data on a phosphonic acid.

Results and discussion

Following the studies of Burton and Flynn [8], we have investigated the preparation of C-fluorinated phosphinic acids via a Michaelis–Arbuzov reaction and the properties of the acids thus obtained. The ethyl esters of phenyl **1a** (R = Ph) and methyl phosphonous acid **1b** (R = Me) were prepared according to the following scheme [9, 10] (DMA = *N,N*-dimethylaniline):

$$R{-}P\langle^{Cl}_{Cl} + 2EtOH + 2DMA \xrightarrow{<0\ ^\circ C} R{-}P\langle^{OEt}_{OEt} + 2DMA\cdot HCl \qquad (1)$$

(1a, b)

Compounds **1a, b** reacted readily with halogenated alkanes such as CH_2Br_2 and even faster with fluorinated derivatives like CF_2Br_2, when toluene or diethyl ether were used as solvents:

$$\underset{\textbf{(1a, b)}}{R{-}P\langle^{OEt}_{OEt}} + CF_2Br_2 \xrightarrow{0\text{–}5\ ^\circ C} \underset{\textbf{(2a, b)}}{R{-}\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle OEt}{|}}{P}}}{-}CF_2{-}Br} + EtBr \qquad (2)$$

Since compounds **2a** and **2b** could not be distilled without decomposition (a behaviour which is in contrast to that of the corresponding phosphonates), both compounds were used without further purification. Even at a stoichiometric ratio $\mathbf{1a}/CF_2Br_2 = 1{:}1$, small amounts of a bis-phosphinate **3** were formed as a by-product of the above-mentioned reaction. This was identified by $^{31}P\{^1H\}$ and ^{19}F NMR spectroscopy.

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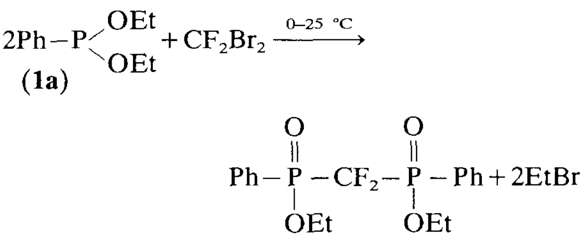
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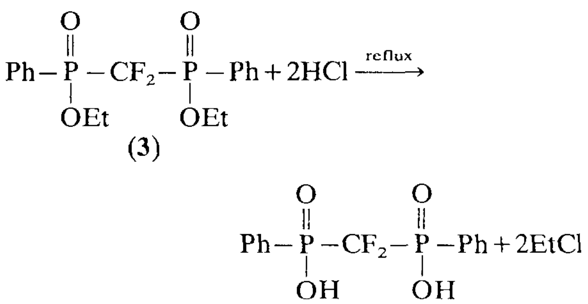
The $^{31}P\{^1H\}$ and ^{19}F NMR spectra of **2a** and **2b** showed ABX-type spin systems, as expected in view of the proximity of a chiral centre at phosphorus and the resulting diastereotopicity of the fluorine atoms. Surprisingly, the spin system of **3** was of the A_2X_2 type implying a local symmetry in the molecule. Compound **3**, a mossy green resin, could neither be purified by distillation nor by recrystallization; for this reason, it was transformed into the corresponding acid **4** by hydrolysis with aqueous hydrochloric acid.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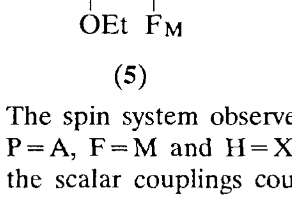
Titration of acid **4** with NaOH showed only one inflection point. Because of the high acidity of C-fluorinated phosphonic and phosphinic acids, the first proton is already dissociated when the acid is dissolved in water. This result is in accordance with previous investigations of difluoromethylene bisphosphonic acid by Burton and co-workers [11]. Dissociation constants were determined from the titration curves using GENOPT, an iterative computer program [12], as $pK_{a1} = 0.94 \pm 0.01$ and $pK_{a2} = 1.88 \pm 0.02$.

Further investigations concerned an NMR spectroscopic study of the ethyl ester of the monofluorinated phosphonoacetic acid **5** which was prepared according to the method of Elkik and Imbeaux [13].



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The spin system observed was of the AMX type with P = A, F = M and H = X; for this reason, the signs of the scalar couplings could not be taken directly from the spectra. Therefore, we used selective excitation of certain transitions with weak radiofrequency power, known as 'spin tickling' [14–16], to achieve this purpose.

All theoretically possible permutations of the signs of the coupling constants served as a basis for the calculation of eigenvalues, energies and transition frequencies [17]. The resulting energy-level diagrams revealed a network of progressive, regressive and non-connected transitions which could be used for the interpretation of the experimental data.

Two double-resonance experiments, $^1H\{^{31}P\}$ and $^{19}F\{^1H\}$, were performed. Comparison of the experimental results and the theoretical solutions showed that the $^2J_{PF}$ and $^2J_{FH}$ coupling constants have the same sign, which is opposite to that of $^2J_{PH}$. The correct values for the scalar couplings are as follows: $J_{AM} = {}^2J_{PF} = +71.8$ Hz; $J_{AX} = {}^2J_{PH} = -12.5$ Hz; and $J_{MX} = {}^2J_{FH} = +47.0$ Hz.

Experimental

General

NMR spectra were recorded on a Bruker AM 200 spectrometer operating at 200 MHz for protons. ^{19}F NMR spectra are referenced against external $CFCl_3$, ^1H NMR spectra against internal tetramethylsilane and $^{31}P\{^1H\}$ NMR spectra against external 85% H_3PO_4. $CDCl_3$ and D_2O were used as an internal lock. The concentrations employed were 4% for ^1H and ^{19}F spectra and 10% for ^{31}P spectra. All solvents were dried according to literature procedures [18]. Melting points were determined using a Büchi apparatus and were not corrected.

Preparation of phosphonous acid diethylester (1)

A 2 l round-bottomed flask equipped with mechanical stirrer, Claisen adapter, dropping funnel, reflux condenser, thermometer and nitrogen bubbler was charged with freshly distilled *N,N*-dimethylaniline (187.8 g, 1.55 mol) and dry ethanol (71.4 g, 1.55 mol) in pentane (500 ml). The mixture was cooled in an N_2 isopropanol bath. Over a period of 90 min, dichlorophosphine (132.5 g, 0.74 mol) was added under a nitrogen atmosphere. During this time the temperature was kept below 0 °C. Subsequently, the mixture was stirred for 30 min at room temperature. After filtration of *N,N*-dimethylaniline hydrochloride and removal of the solvent, the product was distilled *in vacuo*. Compound **1a** (140 g, 95.5%) was a colourless liquid, b.p. 98–105 °C/0.09 Torr. $^{31}P\{^1H\}$ NMR δ: 154.3 ppm. Compound **1b** (97.9 g, 90%) was a colourless liquid, b.p. 50–52 °C/60 Torr. $^{31}P\{^1H\}$ NMR δ: 176.4 ppm.

Preparation of bromodifluoromethylene phosphinic acid monoethylester (2)

A 500 ml round-bottomed flask was equipped with a dropping funnel, reflux condenser, thermometer, Teflon-coated spin bar and nitrogen bubbler. Phosphonous acid diethylester (**1a, b**) (**1a**: 70.0 g, 0.353 mol; **1b**: 48.1 g, 0.353 mol) was dissolved in 250 ml of dry toluene and cooled down to 0–5 °C. To this solution dibromodifluoromethane (74.1 g, 0.353 mol) was added slowly to avoid a vigorous exothermic reaction. After stirring the mixture for some hours at room temperature and removal of the solvent, the residue was purified using a falling-film distillation apparatus (KDL, Leybold) at 100 °C and 0.1 Torr.

Compound **2a**: $^{31}P\{^1H\}$ NMR δ: 19.78 (X part of ABX system, $^2J_{PF}$=85.7 Hz and 78.3 Hz) ppm. ^{19}F NMR δ: 63.18, 62.74 (AB part of ABX system, $^2J_{FF}$=195.2 Hz) ppm. ^1H NMR δ: 1.39 (dt, CH_3, $^3J_{HH}$=7.0 Hz, $^4J_{PH}$=0.3 Hz); 4.40 (dqt, CH_2, $^3J_{PH}$=8.2 Hz); 7.50 (m C_6H_5) ppm.

Compound **2b**: $^{31}P\{^1H\}$ NMR δ: 35.55 (X part of ABX system, $^2J_{PF}$=82.5 Hz and 79.1 Hz) ppm. ^{19}F NMR δ: 63.89, 64.33 (AB part of ABX system, $^2J_{FF}$=196.7 Hz) ppm. ^1H NMR δ: 1.41 (t, CH_3, $^3J_{HH}$=7.1 Hz); 4.36 (dqt, CH_2, $^3J_{PH}$=7.5 Hz); 1.74 (td, CH_3–P, $^2J_{PH}$= −16.3 Hz, $^4J_{FH}$=0.8 Hz) ppm.

*Preparation of difluoromethylene-bis(*P*-phenylphosphinic acid) diethylester (3)*

This compound was formed as a by-product (mossy green resin) during the synthesis of compound **2a**. $^{31}P\{^1H\}$ NMR δ: 26.09 (t, $^2J_{PF}$=82.5 Hz) ppm. ^{19}F NMR δ: −120.66 (t) ppm.

*Preparation of difluoromethylene-bis(*P*-phenyl phosphinic acid) (4)*

Cleavage of the bis-ester **3** with aqueous HCl yielded this compound as violet needles, m.p. 256–258 °C. $^{31}P\{^1H\}$ NMR δ: 18.54 (t, $^2J_{PF}$=76.6 Hz) ppm. ^{19}F NMR δ: −120.72 (t) ppm. Analysis: Calc. for $C_{13}H_{12}O_4P_2F_2 \cdot H_2O$: C, 44.6; H, 4.03; P, 17.69; F, 10.85%. Found: C, 43.4; H, 4.26; P, 18.0; F, 10.25%.

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