Fluorine-containing phosphonates and phosphonic acids are described. The method of preparation is a reaction of trialkylphosphites with dihalodifluoromethanes or a reaction of the salts of dialkylphosphites with halodifluoromethylphosphonates. The corresponding phosphonic acids are prepared by hydrolysis of the phosphonates.

1 Claim, No Drawings
BIS(PHOSPHONIC ACID) DIFLUOROMETHANE

The invention described herein was made in the course of work under a grant or award from the Department of Health, Education and Welfare.

SUMMARY OF THE INVENTION

The present invention relates to fluorine-containing phosphonates and phosphonic acids and methods of preparing same. In particular, the fluorine-containing phosphonates are characterized by the formula:

\[ \text{(RO)}_2\text{PCF}_2\text{P(OR')}_2 \]

wherein R is an alkyl group from 1 to 16 carbon atoms, preferably from 1 to 6 carbon atoms.

These compounds are diphosphonates and have been prepared by one of two methods.

Thus, the compounds of the invention may be prepared by the following sequence:

\[ \text{(RO)}_2\text{PCF}_2\text{P(OR')}_2 + \text{(RO)}_2\text{PCF}_2\text{X} \rightarrow \text{(RO)}_2\text{PCF}_2\text{P(OR')}_2 \]

wherein M is an alkali metal, preferably Na or K.

X is a halogen, preferably Cl, Br, or I.

As an alternative, the compounds may be prepared thusly

\[ \text{(RO)}_2\text{PCF}_2\text{P(OR')}_2 + \text{CF}_2\text{XY} \rightarrow \text{(RO)}_2\text{PCF}_2\text{P(OR')}_2 \]

wherein X is a halogen as before defined, and Y is halogen, preferably Cl, Br, and I; and M and R as defined above.

The corresponding acid is made by hydrolysis of the phosphonate compound by known means.

Typically, the reaction between (BuO)\text{2}P(O)CF\text{2}Br and (BuO)\text{2}PONa in hexane was found to yield tetrabutyl difluoromethylene bis(phosphonate) (1) in 47% isolated yield. A 27% yield of the reduced dibutyl monophosphonate was also isolated. The spectral and analytical data of the bis (phosphonate) were entirely compatible with the structural assignment. (Bu is butyl)

\[ \text{(BuO)}_2\text{PCF}_2\text{Br} + \text{(BuO)}_2\text{PONa} \rightarrow \text{(BuO)}_2\text{PCF}_2\text{P(OBu)}_2 \]

Similarly, the reaction between (EtO)\text{2}P(O)CF\text{2}Br and sodium diethyl phosphite in hexane afforded tetraethyl difluoromethylene bis(phosphonate) (2) in 13% isolated yield. (Et is ethyl). The considerable difference in yields between (1) and (2) can probably be ascribed to the solubility differences of their corresponding sodium dialkyl phosphites. Sodium dibutyl phosphite is freely soluble in hexane, whereas sodium diethyl phosphite is much less soluble. No effort has been made to entirely optimize either of these reactions and high isolated yields are undoubtedly possible. The mechanism for these reactions can be viewed as abstraction of positive bromine from the initial phosphonate followed by recombination.

\[ \text{(BuO)}_2\text{PCF}_2\text{Br} + \text{(BuO)}_2\text{PONa} \rightarrow \text{(BuO)}_2\text{PCF}_2\text{P(OR')}_2 \]

The mechanism is, however, more complex. The reaction between sodium dibutyl phosphate and (EtO)\text{2}P(O)CF\text{2}Br afforded three bis(phosphonates) as observed in the 19\text{F} nmr spectrum in a 1:2:1 ratio.

Generally, the reaction is carried out in an inert, hydrocarbon, non-protic solvent. This reduces the amount of reduction product formed in the reaction. Particularly good results were obtained using toluene.

Two of these bis(phosphonates) were identified as (1) and (2) by enhancement of their respective signals in the 19\text{F} nmr spectrum upon addition of authentic samples of each. The remaining triplex was assigned the mixed bis(phosphonate) structure (3). Fortunately, (2) was both considerably more water soluble and lower boiling than either (1) or (3) and was entirely removed in the workup of the reaction mixture. The unsymmetrical bis(phosphonate) (3) could not be separated entirely from (1). The 19\text{F} nmr spectrum of the mixture showed two triplets: \( \delta = 121.7 \text{ J} = 87 \text{ Hz} \) (3) and \( \delta = 121.4 \text{ J} = 87 \text{ Hz} \) (1). The 31\text{P} nmr spectrum showed only a triplet. The 1\text{H} nmr spectrum clearly indicated the presence of an ethyl group. Finally, the 31\text{C} nmr spectrum revealed all seven carbons for the alkyl groups of (3) as well as a (t.t) for the difluoromethyl ene carbon atom. The butyl carbons of (3) did, however, overlap with the butyl carbons of (1). A rationale for the observations of the three bis-(phosphonates) is shown in the equation below:
Mechanistic scheme for the reaction between (BuO)₂PONa and (EtO)₂PCF₂Br:

(BuO)₂PONa + (EtO)₂PCF₂Br → (BuO)₂PBr + (EtO)₂PCF₂Na + Δ → (BuO)₂PCF₂P(OEt)₂

In path [A], the recombination of the phosphonate ylide and the acid bromide lead directly to the mixed phosphonate 3. If, instead of recombination, the ylide were to collapse to [CF₂] and (EtO)₂PONa, two alternate pathways arise. In path [B], the (EtO)₂PONa can react directly with the precursor phosphonate to afford 2. In path [C], the [CF₂] can be trapped by the (BuO)₂PONa to afford the dibutyl ylide which can then react further with the acid bromide to give 1.

An attempt to intercept an ylide intermediate in this reaction by carrying out the synthesis in the presence of trifluoroacetophene failed, since sodium dibutyl phosphite was found to react readily with the ketone. The ¹⁹F nmr and ³¹P nmr spectral data suggest that the product of this reaction is the enol phosphate.

(BuO)₂PONa + CF₂COPh → (BuO)₂P═O═O

¹⁹F nmr: Fₙ₂ = 95.2 (d, J(F,F) = 55 Hz, J(P,F) = 7.8 Hz)
Fₙ₂ = 108.0 (d, d, J(P,F) = 55 Hz, J(P,F) = 10.9 Hz)
³¹P nmr: δ = 3.8 (d, d, J(P,F) = 5.6 Hz, J(P,F) = 9.4 Hz)

A more direct synthesis of the bis(phosphonates) would be from the reaction of (RO)₂PONa with CF₂Br₂. Sodium dibutyl phosphate reacted rapidly with the evaluation of heat with CF₂Br₂ in hexane. When an excess of CF₂Br₂ was employed both (BuO)₂P(O)CF₂Br and (1) were formed in a 1:4.1 ratio. The use of a 2:1 stoichiometry of phosphate anion to CF₂Br₂ again resulted in the formation of (BuO)₂P(O)CF₂Br and (1) in approximately the same ratio. Any inert, non-protic solvent may be used, although good results are obtained using toluene.

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Detailed Description of the Invention

The following examples serve to illustrate the invention.
5

**EXAMPLE 1**

\[ (\text{BuO}_2\text{PCF}_3\text{P(OBu)}_2) \]

To a solution of

\[ (\text{BuO}_2\text{PCF}_3\text{Br}(6.5 \text{ g}, 0.02 \text{ mole}) \] in dry hexane (40 ml) cooled in an ice water bath was added slowly via syringe a solution of (BuO)₂PONA in hexane (25 ml, 0.02 mole). The (BuO)₂PONA solution was prepared by the reaction of Na metal (2 g, 0.087 mole) and (BuO)₂POH (16.8 g, 0.087 mole) in 80 ml dry hexane. This afforded a solution of concentration approximately 0.8 M. After stirring for four hours, the mixture was poured into water (50 ml) and dried over anhydrous Na₂SO₄. The hexane was removed at room temperature via rotary evaporation at reduced pressure and the residue distilled to give 4.1 g (47%) of

\[ (\text{BuO}_2\text{PCF}_3\text{P(OBu)}_2) \] (bp 152-165/0.1 mm Hg)

as well as 1.3 g (27%) (BuO)₂PCF₃H (bp 170°/3.6 mm Hg).

**EXAMPLE 2**

\[ (\text{EtO}_2\text{PCF}_3\text{P(OEt)}_2) \]

Diethyl phosphite (9.0 g, 0.065 mole) was syringed into a mixture of sodium metal (1.5 g, 0.065 mole) in dry hexane (50 ml). After the initial vigorous reaction had subsided, the solution was heated to reflux until the sodium metal had completely dissolved. The mixture was cooled in an ice bath and

\[ (\text{EtO}_2\text{PCF}_3\text{Br} (17.4 \text{ g}, 0.065 \text{ mole}) \]

added slowly via syringe. The reaction was rapid and the white solid dissolved and was replaced by a gray-green precipitate. After stirring for one hour at room temperature, water (50 ml) was added and three layers formed. The middle aqeous layer was separated and discarded; the top and bottom layers were combined and dried over anhydrous sodium sulfate. The hexane

was removed by rotary evaporation at aspirator pressure and the residue distilled to yield 2.7 g (13%) of

\[ (\text{EtO}_2\text{PCF}_3\text{P(OEt)}_2) \] (bp 115-118°/0.4 mm Hg)

as well as a forerun (3 g) consisting of a 1:1 mixture of (EtO)₂PCF₃Br and (EtO)₂PCF₃H (bp 46.5-47.5°/0.4 mm Hg).

The ¹⁹F nmr spectrum of

\[ (\text{EtO}_2\text{PCF}_3\text{P(OEt)}_2) \]

\[ \delta = 122.0 \text{ (t)} \text { J = 87 Hz; } \] ¹H nmr: \[ \delta = 1.40 \text{ (t) J = 7 Hz (CH₃)}; \delta = 4.39 \text{ (d)} \text { J (H,H)} = 7 \text{ Hz, J(H,P)} = 3.8 \text{ Hz (CH₂O)}; \text{ ³¹P nmr: } \delta = -3.5 \text{ (t) J = 86 Hz; } \] ¹³C nmr: \[ \delta = 16.4 \text{ (s) (CH₂)}; \delta = 65.3 \text{ (d) J = 2.9 Hz; } \delta = 116.2 \text{ (t,t) J(C,P)} = 187 \text{ Hz, J(C,F)} = 279 \text{ Hz.} \]

Analysis: Calculated for C₉H₂₀F₂O₄P₂: %C = 33.33% H = 6.17.

Found: %C = 33.41 %H = 6.32.

**EXAMPLE 3**

Dibutyl phosphite (6.26 g, 0.032 mole) was added to sodium metal (0.74 g, 0.032 mole) in dry hexane (30 ml) and the mixture stirred overnight under an inert atmosphere. After dissolution of the sodium, the solution was transferred to a 60 ml constant addition funnel and added slowly dropwise to an ice cold solution of

\[ (\text{EtO}_2\text{PCF}_3\text{Br} (8.6 \text{ g}, 0.032 \text{ mole}) \]

in hexane. A check of the ¹⁹F nmr spectrum of the solution after completion of the addition revealed that all of

\[ (\text{EtO}_2\text{PCF}_3\text{Br} ) \]

had been consumed and that three triplets were present at

\[ \delta = 122.2 \text{ (BuO)₂PCF₃Br(OBu)}_2, \delta = 122.4 \text{ (EtO)₂PCF₃Br(OEt)}_2, \delta = 122.7 \text{ ppsr (EtO)₂PCF₃P(OEt)}_2 \]

Water (50 ml) was added to the reaction mixture and the organic layer was separated and washed again with water. The two aqeous layers were combined and examined by ¹⁹F nmr. The ¹⁹F nmr spectrum revealed that the aqeous layers contained
as the only fluorine containing compound. The organic layer was dried over anhydrous MgSO4, the hexane removed via rotary evaporation at aspirator pressure and the residue distilled to yield two fractions. The first contained

\[
\text{O} \quad \text{O} \\
\quad (\text{BuO})_2\text{PCF}_2\text{P(OBu)}_2
\]

and the unsymmetrical bis (phosphonate)

\[
\text{O} \quad \text{O} \\
\quad (\text{EtO})_2\text{PCF}_2\text{P(OBu)}_2
\]

in about a 3:1 ratio (bp 126° -136°/0.2 mm Hg). The second fraction contained the same products in a 1:2 ratio (bp 147-153/0.2 mm Hg); no

\[
\text{O} \quad \text{O} \\
\quad (\text{EtO})_2\text{PCF}_2\text{P(OEt)}_2
\]

was observed. \(^1\text{H} \text{nmr}: \) butyl protons of

\[
\text{O} \quad \text{O} \\
\quad (\text{BuO})_2\text{PCF}_2\text{P(OBu)}_2 \text{ and}
\]

\[
\text{O} \quad \text{O} \\
\quad (\text{EtO})_2\text{PCF}_2\text{P(OBu)}_2 \text{ overlap, CH}_3\text{CH}_2\text{O} (\text{EtO})_2\text{PCF}_2\text{P(OBu)}_2;
\]

\[
\delta = 1.38 \text{ (t) } J = 7 \text{ Hz; } ^{19}\text{F nmr (EtO)}_2\text{PCF}_2\text{P(OBu)}_2:
\]

\[
\delta = 121.7 \text{ (t) } J = 87 \text{ Hz; } ^{31}\text{P nmr: } \delta = -3.7 \text{ (t) } J = 86 \text{ Hz (overlap of}
\]

\[
\text{O} \quad \text{O} \\
\quad (\text{BuO})_2\text{PCF}_2\text{P(OBu)}_2 \text{ and (EtO)}_2\text{PCF}_2\text{P(OBu)}_2; \text{ } ^{13}\text{C nmr;}
\]

\[
\text{O} \quad \text{O} \\
\quad \text{(butyl carbons of (BuO)}_2\text{PCF}_2\text{P(OBu)}_2 \text{ and}
\]

\[
\text{O} \quad \text{O} \\
\quad (\text{EtO)}_2\text{PCF}_2\text{P(OBu)}_2 \text{ overlap:}
\]

\[
\delta = 13.5 \text{ (s), } \delta = 186 \text{ (s), } \delta = 32.5 \text{ (t) } J = 3 \text{ Hz, } \delta = 68.9 \text{ (t) } J
\]

3 Hz (butyl carbons); \( \delta = 16.4 \text{ (t) } J = 3 \text{ Hz (CH}_3\text{CH}_2\text{O),} \delta = 65.4 \text{ (d) } J = 3 \text{ Hz (CH}_3\text{CH}_2\text{O); } \delta = 116.2 \text{ (t,t) } J
\]

(\text{C,F})=188 \text{ Hz, } J (\text{C,F})=279 \text{ Hz. The assignments of the butyl carbons and the ethyl carbons was made by comparison to the spectral data of}

\[
\text{O} \quad \text{O} \\
\quad (\text{BuO)}_2\text{PCF}_2\text{P(OBu)}_2 \text{ and (EtO)}_2\text{PCF}_2\text{OEt)}_2 \text{ respectively.}
\]

Using the same reaction procedure as set forth in the examples it is possible to make compounds of the formula

\[
\text{O} \quad \text{O} \\
\quad (\text{RO})_2\text{PCF}_2\text{P(OR)}_2
\]

wherein R is 1 to 12 carbons, preferably 1 to 6. These compounds can be used in the following ways: as detergents and as chelating agents for ions.

We claim:

I. The compound:

\[
\text{O} \quad \text{O} \\
\quad (\text{HO)}_2\text{PCF}_2\text{P(OH)}_2
\]

* * * * *