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PREPARATION, STABILITY AND ACIDITY OF DIFLUOROMETHYLENE BIS PHOSPHONIC ACID

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SUMMARY

Hydrolysis of difluoromethylene phosphonate esters quantitatively yields difluoromethylene bis phosphonic acid as a dihydrate. In vacuo drying leads to either the monohydrate or the anhydrous acid. Titration of either the free acid or its disodium salt and computer fit of the data gives all four pKa s. The disodium salt and the free acid are thermally stable, and the disodium salt is extremely stable even to strong base.

INTRODUCTION

Methylene bis phosphonic acids and derivatives thereof have recently become of interest as selective chelating agents and as analogues of pyrophosphoric acid for modification of the properties of biological substrates [1]. A wide variety of these bis phosphonic acids have been investigated, and the introduction of electron-withdrawing substituents on the methylene carbon has been shown to enhance the selectivity of the bis phosphonic acid analogue.

The normal mode of preparation of the bis phosphonic acid precursor (the phosphonate ester) is via halogenation of the intermediate phosphonate ylide (Scheme 1). From our work with related phosphonates [2] and the facile formation of the -P(O)F group, we anticipated that fluorination of such an intermediate phosphonate or phosphonate ylide would be difficult to control and particularly difficult to avoid degradation processes or non-selective fluorination processes. Thus, our approach was to develop an alternative route to the required difluoromethylene bis phosphonate precursor in high yield from readily available starting materials. Recently,

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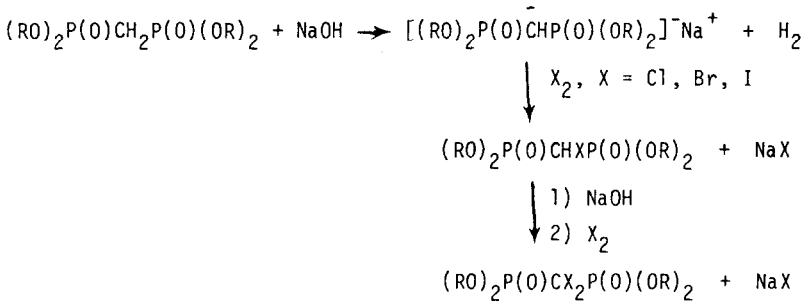
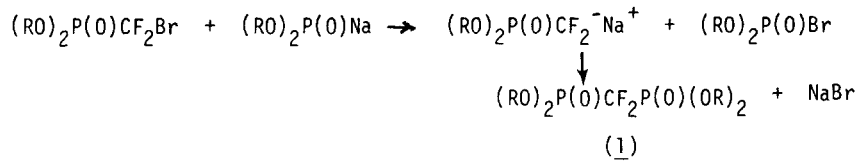


SCHEME 1

we reported such a preparative route [3] starting from the readily available bromo-F-methyldialkyl phosphonates [2], (Scheme 2). Obviously, hydrolysis of (1) would yield the desired difluoromethylene bis phosphonic acid (2).



SCHEME 2

We have successfully carried out the preparation of (2) and reported its chelation ability in bone reabsorption studies with ^{45}Ca [4]. Related work on the details of the preparation and stability of this acid has also been recently reported [5]. The recent report by Blackburn and co-workers [6] on the preparation of this acid via our procedure prompts this report on our more detailed studies of (2) and its acidity constants.

RESULTS AND DISCUSSION

The bis phosphonate obtained via the sequence outlined in Scheme 2 contains small amounts of acidic impurities. We have found that best results for the preparation of (2) are obtained if these impurities are first removed. This can be readily accomplished via extraction in ether solution of (1) with 0.1 M aqueous Na_2CO_3. Stronger base, such as NaOH, is to be avoided, as (1) is readily cleaved by the strong base.

$$(1) + NaOH \xrightarrow{H_2O} (RO)_2P(O)CF_2H + (RO)_2PO_2Na$$

The acid free (1) was then treated with Me_3SiBr (no solvent) for five hours at room temperature followed by heating at 50°C for ten hours to give a quantitative yield of the bis silyl ester of (1) as a pale yellow oil. Subsequent reaction of the bis silyl ester with water at 0°C was followed by stirring at room temperature for twenty hours. The aqueous solution of (2) was then washed with ether; concentration of the aqueous layer gave a quantitative yield of crude (2), (Scheme 3).

$$(EtO)_2P(O)CF_2P(O)(OEt)_2 + 4\ Me_3SiBr \xrightarrow[2)\ 50°C/\ 10\ hrs]{1)\ R.T.} (Me_3SiO)_2P(O)CF_2P(O)(OSiMe_3)_2$$

~ 100%

$$\downarrow \begin{matrix} 1)\ H_2O,\ 0°C \\ 2)\ R.T./20\ hrs. \end{matrix}$$

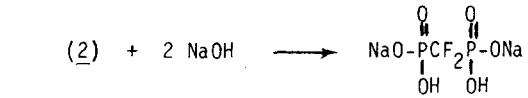
$$(HO)_2P(O)CF_2P(O)(OH)_2$$

(2), ~ 100%

SCHEME 3

Titration of this material gave three breaks; the first and third ones are distinct breaks while the second is poorly defined. The stoichiometry was 2:1:1 indicative of the four acidic protons in (2). The molecular weight of 249 from this titration indicated this material was a dihydrate (Calcd. M.W. for the dihydrate is 248). Thus, this yellow oil was dried in vacuo at 60°C (2 1/2 hrs.) followed by titration again. A molecular weight of 230 was obtained - indicative of a monohydrate (Calcd. M.W. for a monohydrate of (2) is 230). Additional drying in vacuo at 80°C (4 hrs.) gave a sample which exhibited a molecular weight of 212 via titration, corresponding to the anhydrous free acid (Calcd. M.W. for the anhydrous acid (2) is 212). The anhydrous acid (2) melted at 124°C and was thermally stable at 120°C without any detectable decomposition. A typical pH titration curve for anhydrous (2) is shown in Figure 1.

Titration of the free acid with two equivalents of NaOH was carried out to give the disodium salt (3). Evaporation of the water gave snow-white crystals of (3). Titration of this material gave two breaks with a



(3)

1:1 stoichiometry. The first break was poorly defined while the second was well defined. A typical pH titration curve for anhydrous (3) is shown in Figure 2. Molecular weight determination gave a value of 275, corresponding to the monohydrate (Calcd. M.W. for a monohydrate of (3) is 274). If the initial crystalline material is heated to 100°C in vacuo, anhydrous (3), mp 230-235°C, is obtained. Molecular weight determination of this material gave a value of 256 (Calcd. M.W. for anhydrous (3) is 256). Anhydrous (3) is extremely hygroscopic - much more so than anhydrous (2), and if exposed to the atmosphere it rapidly reverts back to a dihydrate. Since (3) is the anticipated form for biological utility of (2), we evaluated its stability at physiological pH, at pH 7.4 (phosphate buffer), (3) was found to be stable at room temperature up to 15 hours - we could detect no hydrolysis or decomposition (detectability levels of 0.1%) of (3). Even at pH 11.3, no detectable hydrolysis or decomposition was observed over three days at room temperature or 1/2 hour at 80°C.

Ionization constants for (2) were determined from titration curves (similar to Figs. 1 and 2) obtained from several independent titrations of (2) and its disodium salt (3). The titrations were carried out in a CO_2 free atmosphere at a constant temperature of 25°C and a constant ionic strength of 0.10 M (NaCl). A titration function, which describes how $[H^+]$ of a solution of acid (2) changes as a function of added strong base, was derived in terms of Ka_1, Ka_2, Ka_3, and Ka_4. A fit of the experimental pH data to this titration function via a non-linear least-squares program [7] yields the ionization constants. pKa_1 and pKa_2 were obtained from eight repetitive titrations of (2), while pKa_3 and pKa_4 were obtained from ten repetitive titrations of either (2) or (3). Table I summarizes these values. The larger error in Ka_1 is due to its strong acidity and similarity to Ka_2.

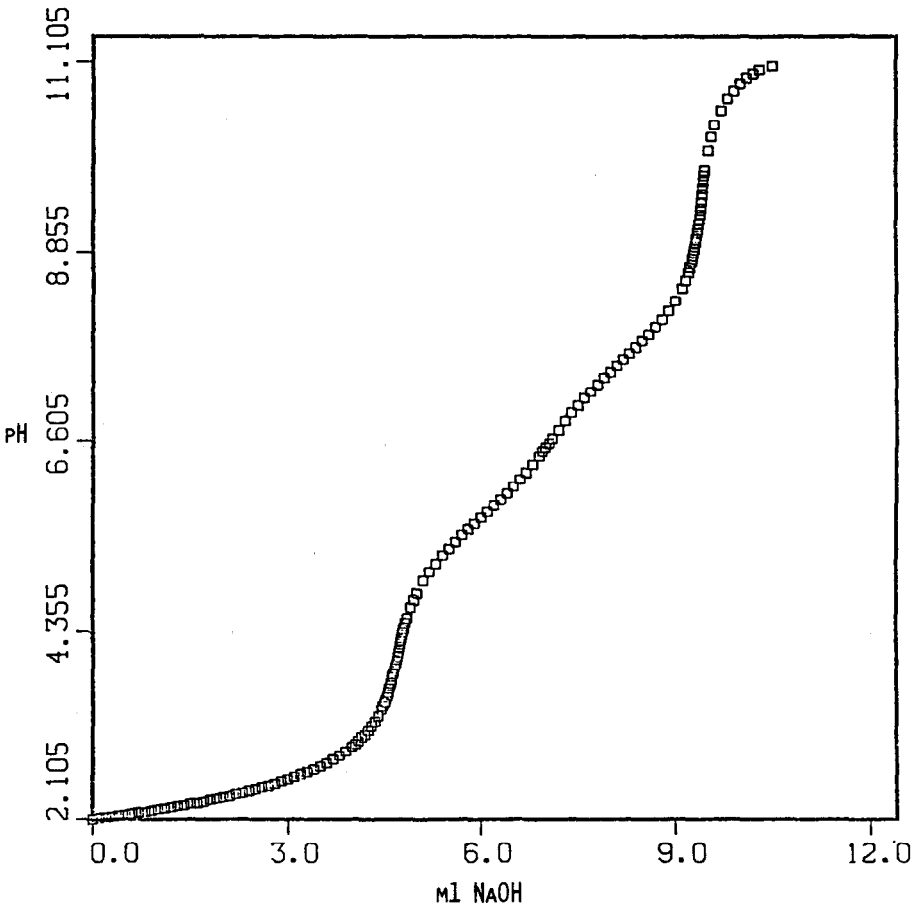


FIG. 1. TITRATION OF 47.20 MG OF $(HO)_2P(O)CF_2P(O)(OH)_2$ WITH 0.0939M NaOH.

TABLE 1

Acidity constants* of $(HO)_2P(O)CF_2P(O)(OH)_2$, 25°C, μ = 0.10 M

pKa_1	pKa_2	pKa_3	pKa_4
1.44 $\pm$ 0.15	2.11 $\pm$ 0.04	5.66 $\pm$ 0.02	7.63 $\pm$ 0.02

*Standard deviation for pKa_1 and pKa_2 are from eight pK values; pKa_3 and pKa_4 from ten pK values.

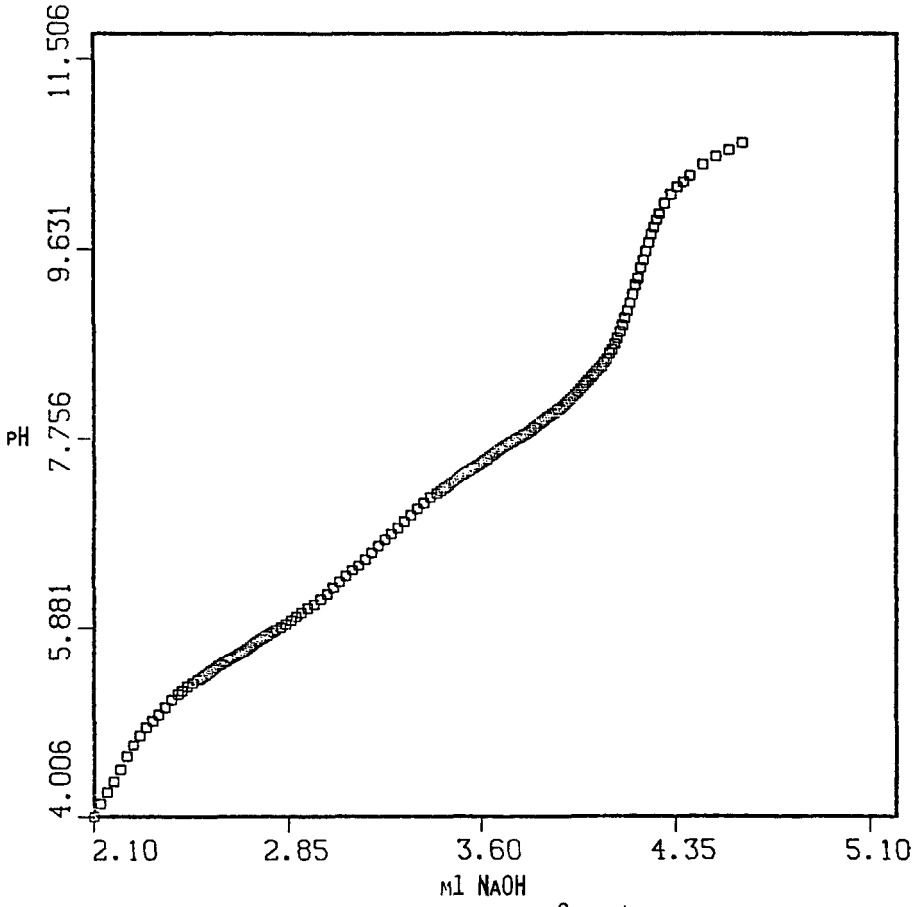


FIG. 2. TITRATION OF 18.50 MG OF $(HO_3PCF_2PO_3H)^{2-}2Na^+$ WITH 0.0939M NaOH.

EXPERIMENTAL

The fluorinated bis phosphonates were prepared by the method of Burton and Flynn [3,8]. pH titrations of anhydrous (2) and its disodium salt (3) were carried out with an Orion Research Microprocessor Ionalyzer Model 901 pH meter, using an Orion Research Model 91-01 glass electrode and an Orion Research Model 90-01 single junction reference electrode calibrated with standard buffers between pH 3 and 8. The titration apparatus consisted of a water-jacketed 180 ml beaker fitted with a stopper in which appropriately located holes allowed the insertion of a microburet, a pair of electrodes, and a nitrogen gas inlet tube. Titrations were carried out in a carbon

dioxide free atmosphere by bubbling nitrogen gas slowly through and maintaining an atmosphere of nitrogen above the solution. Water from a constant temperature bath maintained at 25°C was circulated through the jacketed beaker. A 10 ml Manostat microburet was used to add standard sodium hydroxide to the titration vessel. The sodium hydroxide was standarized with primary standard potassium hydrogen phthalate.

Anhydrous (2) or (3) were either quickly weighed into the titration flask or a carefully measured aliquote of an aqueous solution of (2) or (3) of known weight/volume was added to the flask, NaCl was added to maintain the ionic strength at 0.100 M, the volume was adjusted to exactly 40 ml, and the resulting solution was titrated with standard sodium hydroxide.

Typical purification of $(EtO)_2P(O)CF_2P(O)(OEt)_2$ (4)

The bis phosphonate (10 g) was dissolved in 40 ml of anhydrous diethyl ether and equilibrated in a separatory funnel with 0.1 M aqueous Na_2CO_3 (2 x 10 ml). The ether layer was dried over anhydrous $MgSO_4$ overnight and filtered twice to insure complete removal of fine particles of the drying agent. Rotoevaporation of the ether gave bis phosphonate suitable for further elaboration.

A 0.1 M $NaHCO_3$ solution was also found to be suitable for removal of acidic impurities from the bis phosphonate.

Initial attempts to remove acidic contaminents by extraction with a 1% aqueous NaOH solution gave rapid hydrolysis. For example, (4) gave $(EtO)_2P(O)CF_2H$; ^{19}F NMR, d,d at 137.5 ppm ($J_{P,F}$ = 90 Hz and $J_{F,H}$ = 49 Hz), ^{31}P NMR, d,d at 4 ppm.

Preparation of $(Me_3SiO)_2P(O)CF_2P(O)(OSiMe_3)_2$

Bis phosphonate (4) (6.5 g, 0.02 mole) was charged to a 50 ml dry round bottom flask equipped with a septum inlet and reflux condenser and maintained under a nitrogen atmosphere. To (4) was slowly added (10 minutes), via syringe, 15.3 g (0.10 mole) of Me_3SiBr (Aldrich) at room temperature. After the addition of the bromosilane was completed, the reaction mixture was stirred at room temperature for 5 hours and at 50°C for 10 hours. Then, the crude product was concentrated in vacuo to give the bis silyl ester as a pale yellow liquid; ^{19}F NMR, t at 124.2 ppm ($J_{P,F}$ = 89 Hz), ^{31}P NMR, t at 13.3 ppm.

Preparation of (2)

The crude bis silyl ester from the above reaction was cooled to 0°C and 10 ml of water was slowly added via syringe. The reaction mixture was stirred at room temperature for 20 hours followed by extraction with diethyl ether (3 x 10 ml).

Excess water was removed by rotoevaporation at 50°C to give 4.1 g of (2) as a pale yellow viscous oil. Compound (2) in D_2O/acetone (1/1) shows a triplet in the ^{19}F NMR spectrum at 123.3 ppm (J = 86.5 Hz) and a triplet at -2.38 ppm in the ^{31}P NMR spectrum.

Titration of crude (2) with standard NaOH indicated this material to be a dihydrate. After drying in vacuo at 60°C for 2 1/2 hours, titration indicated a monohydrate. After drying in vacuo at 80°C for 4 hours anhydrous (2), mp 124°C, was obtained.

Thermal stability of anhydrous (2)

Anhydrous (2) was heated to 120°C in a vacuum oven for 4 hours. Titration data and NMR data of this sample indicated that no detectable decomposition had occurred at this temperature.

Preparation of (3)

The disodium salt (3) was prepared from anhydrous (2) by addition of half the number of equivalents of NaOH required to neutralize a complete sample of the free acid (2). The aqueous solution was then concentrated as much as possible by rotoevaporation. The remaining water was removed in a vacuum oven by gradual reduction of the pressure and elevation of the temperature to 80°C. Crude (3) was isolated as snow white crystals. Titration of the material indicated it to be a monohydrate. Additional drying at 100°C in a vacuum oven gave anhydrous (3), mp 230-235°C, as snow white crystals.

Stability of (3) at base

Anhydrous (3) (61.1 mg) was dissolved in 6 ml of 0.09 M NaOH (pH = 11.3). At intervals of 17 1/2, 41, and 63 1/2 hours, the ^{19}F and the ^{31}P

spectra of this solution showed only the signals for (3). After 63 1/2 hours, the sample was heated to 80°C. After 1/2 hour, the ^{19}F and ^{31}P NMR spectra again exhibited signals only for (3). No signals for the $P(O)CF_2H$ group were detected. Similar results were observed when the experiments were repeated at pH = 7.4.

Control experiments indicated that the cleavage products could be detected in the ^{19}F and/or ^{31}P spectra at levels of 0.1% and 0.2%, respectively.

CONCLUSIONS

Difluoromethylene bis phosphonic acid and its disodium salt can be readily prepared from the difluoromethylene bis phosphonates available by the method of Burton and Flynn. These materials are initially isolated as hydrates, but the anhydrous substrates can be readily obtained. The bis phosphonic acid is a strong acid; the disodium salt is a weak acid. These materials are quite stable thermally and remarkably stable to base compared to the bis phosphonate precursor, which is readily cleaved by base.

Our work continues with these interesting materials and future reports will detail chelation studies of (2) and (3).

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