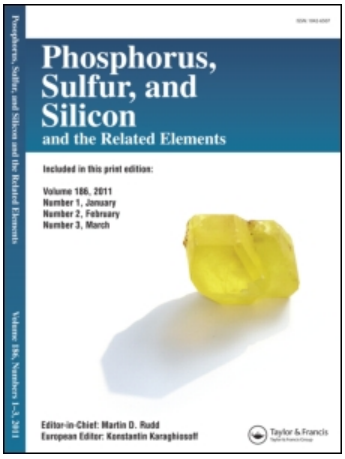

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THE DEHALOGENATION OF DIHALOGENOMETHYLENE-BISPHOSPHONATES

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Tetraesters of dihalogenomethylenebisphosphonic acids undergo nucleophilic dehalogenation with potassium fluoride or hydroxide in solution in acetonitrile in the presence of [18,6]-crown ether. Fluoride ion is the best nucleophile for dehalogenation and there is no evidence for nucleophilic displacement of halide ion by attack at the central atom of the methylenebisphosphonic esters. Conditions have been developed for the monodehalogenation of tetraisopropyl dibromo- and dichloromethylenebisphosphonates in good yield.

INTRODUCTION

Halogenomethylenebisphosphonic acids (e.g., 1, $R^1 = R^2 =$ Cl or Br) are better isosteres of inorganic pyrophosphoric acid than the parent compound (1, $R^1 = R^2 =$ H) as substitution of the bridge carbon atom with electronegative halogen atoms increases the acidity of the phosphonyl groups so that they more closely resemble the phosphoryl groups in pyrophosphoric acid.[1] Substitution of the bridge carbon atoms of (1, $R^1 = R^2 =$ H) with halogen atoms also affects the interaction of these compounds with metal ions. In general, the halogenated methylenebisphosphonic acids are better chelating agents than the parent compound.[2] The difference in metal chelating properties of the phosphonyl groups in halogenated methylenebisphosphonic acids and (1, $R^1 = R^2 =$ H) is reflected in their biological activities. For example, both (1, $R^1 = R^2 =$ Cl) and (1, $R^1 =$ Cl, $R^2 =$ H) inhibit the RNA transcriptase activity of influenza virus A while (1, $R^1 = R^2 =$ H) does not and their inhibitory properties can be related to their abilities to complex with zinc ions.[3] However, there are problems when using the highly charged methylenebisphosphonic acids in biological systems as they are not taken up well by cells. A solution to this problem would be to synthesise lipophilic methylenebisphosphonic acids that still carry a halogen atom on the bridge carbon atom, e.g., (1, $R^1 =$ Cl, $R^2 =$ alkyl). A synthetic route to the latter would be to alkylate the monoanion of the fully esterified acid (1, $R^1 =$ Cl, $R^2 =$ H) and then remove the protecting groups. Thus, this synthesis depends on the availability of monohalogenomethylenebisphosphonates. Dichloro- and dibromomethylenebisphosphonates are readily prepared by the direct halogenation of commercially available tetraisopropyl methylenebisphosphonate followed by hydrolysis of the substituted tetraesters with acid.[4] It is not easy to adapt this procedure for the preparation of the monohalogenomethylenebisphosphonates in high yield and it has been reported that treatment of tetraesters of dihalogenomethylenebisphosphonates with reducing agents, e.g., sodium

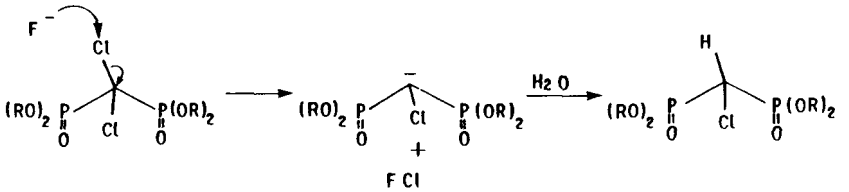
hydrosulphide can be used to obtain the monohalogenoderivatives in 25–50% yield but that the mechanism of displacement was not clear. In our hands this has not been a satisfactory synthetic route and we now wish to report studies on the nucleophilic dehalogenation of dihalogenomethylenebisphosphonates in dipolar aprotic solvents.

$(HO)_2P(O)CR^1R^2P(O)(OH)_2$ (1) $(C_4H_9O)_2P(O)CF_2Br$ (2)

RESULTS AND DISCUSSION

Dehalogenation of tetraesters of dihalogenomethylenebisphosphonates probably takes place by nucleophilic attack on a halogen atom to give the stable anion which is protonated during the work up to give (1, R^1 = Cl, R^2 = H) (Scheme 1). Nucleophilic dehalogenation of a compound that gives a stable anion as a reaction product has been observed with malononitrile,[5] and fully esterified malonic or phosphonoacetic acids.[4] Positive halogen abstraction has also been observed during the reaction between sodium diethyl phosphite and dibutyl bromodifluoromethylphosphonate (2),[6] a reaction that closely resembles that described here. Furthermore, treatment of the tetraethyl ester of (1, R^1 = R^2 = Cl) with one equivalent of butyllithium yields the tetraethyl ester (1, R^1 = Cl, R = H).[7]

We find that when the tetraisopropyl esters of (1, R^1 = R^2 = Cl) or (1, R^1 = R^2 = Br) are heated at 60° with one equivalent of potassium fluoride in solution in acetonitrile in the presence of [18,6]-crown ether, a slow reaction occurs and, when water is added to the solution to quench any anion formed, tetraisopropyl (1, R^1 = Cl, R^2 = H) or (1, R^1 = Br, R^2 = H) are obtained in high yield. The reaction, although slow, is very clean, the only other minor products observable by ^{31}P n.m.r. being readily removed by chromatography. There was no evidence by ^{31}P or ^{19}F n.m.r. for the formation of any C—F compounds by nucleophilic displacement at carbon. If an excess (4 equivalents) of potassium fluoride was used, the major product observed after the work up was tetraisopropyl (1, R^1 = R^2 = H). Of the nucleophiles tested, fluoride ion was the most effective under our conditions and no reaction was observed with bromide or chloride ions. It is of interest that fluoride ion as the naked anion in acetonitrile in the presence of [18,6]-crown ether is the most nucleophilic of the halide ions[8] and it is also the smallest, a factor that may be important in reactions of sterically hindered compounds. Furthermore, chlorine



SCHEME 1

monofluoride has the highest bond energy of the interhalogen compounds that contain chlorine.[9] Addition to the reaction of an excess of cyclohexene, which might be expected to remove any chlorine monofluoride formed, caused an initial increase in the rate of dehalogenation, but the yield of the tetraisopropyl (1, R^1 = Cl, R = H) did not increase beyond 40% after two days. Hydroxide ion under our reaction conditions did cause dehalogenation to take place but the yield of monohalogenated product was lower than with fluoride ion and the reaction was accompanied by de-esterification. Hydride ions (lithium triethylborohydride) also caused dehalogenation to occur but the reaction was slower than with fluoride ion and tetraisopropyl (1, R^1 = R^2 = H) was also formed. A number of other nucleophiles, e.g., cyanide ion, triphenylphosphine, 2-mercaptopyridine, gave complex mixtures of products which did not contain any monohalogenated methylenebisphosphonate esters. No similar reactions could be observed with the free acid (1, R^1 = R^2 = Cl), and for example, hydroxide ion reacted to give carbonylbisphosphonic acid.[10] No compounds that contained C—F bonds could be detected in the reaction between (1, R^1 = R^2 = Cl) and fluoride ion.

We therefore purpose that halogenation of tetraisopropyl dibromo- or dichloromethylenebisphosphonates by fluoride ion in solution in acetonitrile in the presence of [18,6]-crown ether is a simple and convenient method for the preparation of tetraesters of monohalogenomethylenebisphosphonates.

EXPERIMENTAL

Tetraisopropyl Monochloromethylenebisphosphonate. [18,6]-Crown ether (0.1 g) was dissolved in dry acetonitrile (5 ml) with stirring and dry potassium fluoride (0.17 g, 2.9 mmole) was slowly added over 30 minutes with stirring to ensure complete solution. Tetraisopropyl dichloromethylenebisphosphonate[12] (1 g, 2.4 mmole) was added and the mixture heated at 55–60°C with stirring. After a few minutes, the reaction turned pink and the colour intensified as the reaction proceeded. After seven days, water (20 ml) was added and the mixture extracted with chloroform (2 × 40 ml). The chloroform extracts were washed with water (3 × 25 ml) dried (Mg_2SO_4) and the solvent removed *in vacuo*. ^{31}P N.m.r. of the residue showed that tetraisopropyl monochloromethylenebisphosphonate (δ = 11.51 p.p.m. at 36.44 MHz) made up 70% of the phosphorus-containing products and no starting material remained. From the ^{31}P n.m.r. spectrum, five compounds in addition to the tetraester of (1, R^1 = Cl, R^2 = H) were present, the identities of these minor products were not determined. Tetraisopropyl (1, R^1 = Cl, R^2 = H) was isolated in 55% yield by chromatography on silica with elution by chloroform/40-60° petroleum ether (1 : 2 v/v). The 220 MHz ^{1}H n.m.r. spectrum of the product showed peaks at δ 1.4 (24 Hd, J = 2.5 Hz), 3.9 (1 Ht, J = 20 Hz) and 4.9 p.p.m. (4 Hm). The ammonia chemical ionisation mass spectrum[11] showed major peaks at m/z 379 and 381 in a ratio of 3 : 1. If cyclohexene (75 μl) was added to the reaction described above, ^{31}P n.m.r. indicated that the tetraester of monochloromethylenebisphosphonate was formed in 40% yield after 2 days and no starting material remained.

In a similar reaction tetraisopropyl monobromomethylenebisphosphonate (δ = 11.5 p.p.m.) was obtained from 1 equivalent of potassium fluoride and tetraisopropyl dibromomethylenebisphosphonate as 70% of the isolable phosphorus-containing material. The ammonia chemical ionisation mass spectrum of the product after chromatography (isolated yield 50%) showed two major peaks at m/z 422 and 424 in a ratio 1 : 1. When an excess of potassium fluoride (4 equivalents) was added to tetraisopropyl dichloromethylenebisphosphonate (1 equivalent) in acetonitrile in the presence of [18,6]-crown ether, ^{31}P n.m.r. indicated that tetraisopropyl methylenebisphosphonate (δ = 17.4 p.p.m.) was formed in 60% yield after seven days at 60°. When potassium hydroxide (1 equivalent) was used in place of potassium fluoride in the above reaction, ^{31}P n.m.r. indicated that tetraisopropyl monochloromethylenebisphosphonate was formed in 40% yield and that some de-esterification had occurred. When lithium triethylborohydride in tetrahydrofuran (1 M, 2.8 ml, 1 equivalent) was added to tetraisopropyl dichloromethylenebisphosphonate (1 g) after one week at room temperature ^{31}P n.m.r. showed that the tetraesters of monochloromethylene-(30%) and methylene-(10%)bisphosphonates were present.

No monochloromethylenebisphosphonate esters could be detected by ^{31}P n.m.r. for the reactions with tetraisopropyl dichloromethylenebisphosphonate at 60° in acetonitrile in the presence of [18,6]-crown ether and potassium chloride (1 equivalent, 3 days), potassium iodide (1 equivalent, 7 days) or lithium aluminium tri-*tert*-butoxyaluminium hydride (1 equivalent, 7 days). In all these reactions the starting material was unchanged. Complex mixtures of products, but no monochloromethylenebisphosphonate esters, were obtained with 1 equivalent in each case of 2-mercaptopyridine (3 days), triphenylphosphine (3 days), potassium cyanide/[18,6]-crown ether (3 days) or sodium dithionite/[18,6]-crown ether (2 days).

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