Direct Approach to α-Hydroxyphosphonic and α,ω-Dihydroxyalkane-α,ω-bisphosphonic Acids by the Reduction of (Bis)acylphosphonic Acids

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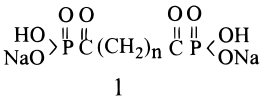
Acylphosphonic and bisacylphosphonic acid sodium salts were directly reduced by sodium borohydride to the corresponding hydroxyphosphonates and dihydroxyalkanebisphosphonates. The solution conformation of the (bis)hydroxyphosphonic acid sodium salts, elucidated from the homonuclear and heteronuclear coupling constants of the proton adjacent to the hydroxy and the phosphonic groups, was identical with the solid-state conformation as determined for 1-hydroxy-2-phenylethylphosphonic acid, a representative compound, by X-ray crystallography.

In previous papers it was reported from our laboratory that α,α′-difunctionalized long-chain bisphosphonates such as bisacylphosphonates[1] **1** and α,α′-bishydroxyiminophosphonates[2] **2** are biologically active in calcium-related disorders such as hydroxyapatite formation and dissolution. This is in contrast to alkane-α,ω-bisphosphonates which are devoid of any activity.[3] To elucidate the roles of the functional groups in α positions for biological activity, we have undertaken a systematic study of synthesizing variously difunctionalized long-chain bisphosphonates. This paper describes the development of a practical method for the synthesis of α,ω-dihydroxyalkane-α,ω-bisphosphonic acids **3** which are also suitable for the synthesis of simple α-hydroxyphosphonic acids **5**.



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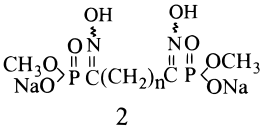

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α-Hydroxyphosphonate esters have been obtained previously by the Abramov and Pudovik reactions which consist of adding phosphites to carbonyl compounds[4] or by the reduction of acylphosphonate diesters using various reducing agents. Thus dialkyl acylphosphonates have been reduced to α-hydroxyphosphonates by sodium borohydride,[5,6] aluminum isopropoxide,[7] activated zinc in acetic acid,[7a] diborane in tetrahydrofuran,[8] and by lithium triethylborodeuteride.[9]

Attempted synthesis of α,ω-dihydroxyalkane-α,ω-bisphosphonic acids **3** by reduction of tetramethyl bisacylphosphonates to the corresponding dihydroxyalkanebisphosphonate tetramethyl esters, followed by bromotrimethylsilane-induced demethylation to the corresponding bisphosphonic acids, gave rise in our hands to impure products which were difficult to purify because of their highly polar nature.

We considered that since both acylphosphonic and α-hydroxyphosphonic acids, as well as their salts, are far more stable than the esters[10] (α-hydroxyphosphonate diesters fragment easily to the corresponding carbonyl compound by eliminating dialkyl hydrogen phosphonate[7]), direct reduction of bisacylphosphonic acids might lead to the desired α-hydroxy and α,α′-dihydroxyalkane-α,ω-bisphosphonic acids more efficiently.

Results

Reduction of Acylphosphonates. Addition of sodium borohydride to an aqueous solution of monosodium benzoylphosphonate or phenylacetylphosphonate gave immediate reduction to the corresponding α-hydroxyphosphonic acid. The progress of the reaction could conveniently be monitored by ^{31}P NMR spectroscopy. In contrast to the signal of the starting materials at approximately −1 ppm, the products resonate at around 20 ppm in the ^{31}P NMR spectrum. The products could be isolated in good yields by the addition of an organic solvent, miscible with water, such as dioxane or methanol. Reduction of bisacylphosphonates to α,ω-dihydroxyalkane-α,ω-bisphosphonic acids could be carried out equally conveniently. The latter were isolated by the

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(4) Engel, R. *Synthesis of Carbon−Phosphorus Bonds*; CRC Press: Boca Raton, FL, 1988; pp 77−136.

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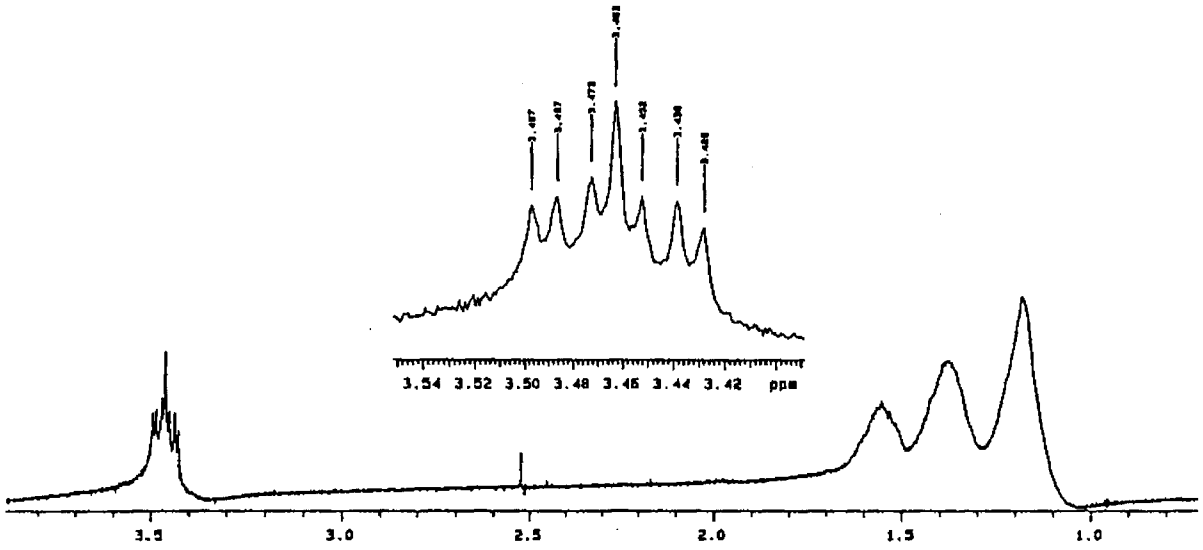
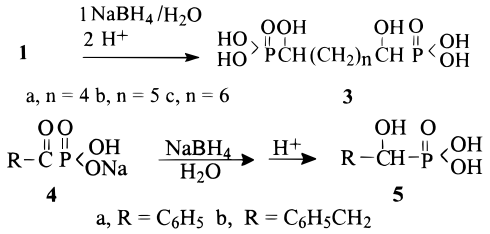


Figure 1.

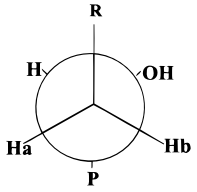
addition of methanol to the aqueous reaction mixtures. The sodium salts were converted to the free acids by passing through a cation-exchange column.



Structures of α-Hydroxyphosphonates. Examination of the ^{1}H NMR spectra of both mono- and bishydroxyphosphonates revealed the presence of characteristic septets at low field as that shown for disodium 1,8-dihydroxyoctane-1,8-bisphosphonate in Figure 1.

The septet shown clearly originates from the protons in position α relative to the phosphorus and oxygen atoms. Its splitting pattern indicates that the α proton is split by the phosphorus and *unequally* by the two diastereotopic protons on the adjacent methylene group. The various coupling constants were determined by the following decoupling techniques. Irradiation of the methylene protons in the region of 1.4−1.6 ppm caused collapse of the septet at 3.5 ppm to a doublet which gave the $^2J_{PH} = 6.5$ Hz. Irradiation of the phosphorus transformed the septet at 3.5 ppm into a double doublet with coupling constants of $^3J_{HH} = 2.4$ and 10.4 Hz. Next the septet was irradiated causing the phosphorus signal to change from a quartet to a triplet with $^3J_{PH} = 6.65$ Hz. Using the Karplus curves,[11] the coupling constants determined allow to postulate the dihedral angles and thus the conformations of the bishydroxyphosphonates in aqueous solution. Of the three possible staggered rotational conformations, only the structure shown in Chart 1 satisfies all the coupling constants, which require equal dihedral angles between the P atom and the β protons and, at the same time, different dihedral angles between the α proton and the two β protons.

Chart 1



Similar treatment of 1-hydroxy-2-phenylethylphosphonic acid (**5b**) gave the following coupling constants: $^2J_{HaHb,gem} = 14.4$ Hz, $^3J_{HbH} = 9.6$ Hz, $^3J_{HbP} = 7.8$ Hz, $^3J_{HaH} = 3.1$ Hz, $^3J_{HaP} = 3.4$ Hz, $^2J_{PH} = 7.5$ Hz. Using these values together with the Karplus curves, we arrive at a conformation in which the phenyl and the phosphorus moieties are anti and the β H−P dihedral angles are distorted from the 60° required for the ideal staggered structure. Compound **5b** afforded high-quality crystals which allowed a single-crystal X-ray analysis. This confirmed the above postulated distorted staggered structure having a torsional angle of 165° for the Ph−C−C−P group.

Experimental Section[12]

Synthesis of Starting Sodium Salts of Acylphosphonates 1 and 4. Carboxylic or dicarboxylic acid chlorides were subjected to the Arbuzov reaction with trimethyl phosphite to yield dimethyl acylphosphonates and tetramethyl bisacylphosphonates, which were dealkylated using excess bromotrimethylsilane to yield the corresponding trimethylsilyl esters, which in turn were converted to the sodium salt **1** or **4** by treatment with methanolic sodium hydroxide solution (see ref 1a for bisacylphosphonates and ref 13 for acylphosphonates.

General Procedure for the Synthesis of α,ω-Dihydroxyalkane-α,ω-Bisphosphonic Acids (3). Sodium borohydride (0.001 45 mol) was added to a solution of disodium dihydrogen bisacylphosphonate (0.001 45 mol) dissolved in distilled water (7 mL), and the reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by ^{31}P NMR spectroscopy to ensure complete

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(12) Instruments and general techniques are described in ref 1.

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conversion of the bisacylphosphonate ($\delta_P \approx -1$ ppm) to bis-α,α′-dihydroxyphosphonate ($\delta_P \approx 20$ ppm). If the reaction was incomplete, an additional 0.3 equiv of $NaBH_4$ was added. After completion of the reaction, the product as sodium salt was precipitated by the addition of methanol (50 mL) to the reaction mixture. The free α,ω-dihydroxyalkane-α,ω-bisphosphonic acids could be isolated by passing the aqueous solutions of the sodium salts through a Dowex-50W cation-exchange column, followed by lyophilization of the eluted solutions.

1,6-Dihydroxyhexane-1,6-bisphosphonic acid (3a): yield 95%, mp 160−165 °C dec; NMR (D_2O) ^1H, δ 1.20−1.36 (m, 2H), 1.40−1.51(m, 4H), 1.52−1.59 (m, 2H), 3.64−3.71 (septet, 2H, $^2J_{(PH)} = 6.6$ Hz, $^3J_{(HaH)} = 2.4$ Hz, $^3J_{(HbH)} = 10.4$ Hz); ^{31}P, δ 25.36 (q, $^2J_{(PH)} = 6.6$ Hz, $^3J_{(PH)} = 6.6$ Hz); $^{13}C-\{^1H\}$, δ 26.5 (d, $^2J_{(CP)} = 12.8$ Hz), 26.6 (d, $^2J_{(CP)} = 12.8$ Hz), 32.5 (s), 32.5 (s), 70.36 (d, $^1J_{(CP)} = 155.4$ Hz), 70.41 (d, $^1J_{(CP)} = 155.4$ Hz); IR (Nujol) ν = 3193w, 2988s, 2847s, 2313w, 1463s, 1377m, 1230w, 1002m, 943m; mol wt calcd 278; FAB MS [M + H] = 279.1, [M − H] = 277.4. Anal. Calcd for $C_6H_{16}O_8P_2$: C, 25.91; H, 5.80. Found: C, 25.41; H, 5.67.

1,7-Dihydroxyheptane-1,7-bisphosphonic acid (3b): yield 87%, mp 170−175 °C dec; NMR (D_2O) ^1H, δ 1.26 (m, 4H), 1.43−1.53 (m, 4H), 1.60−1.62 (m, 2H), 3.64−3.71 (septet, 2H, $^2J_{(PH)} = 6.6$ Hz, $^3J_{(HaH)} = 2.4$ Hz, $^3J_{(HbH)} = 10.4$ Hz); ^{31}P, δ 24.96 (dd, $^2J_{(PH)} = 6.6$ Hz, $^3J_{(PH)} = 6.6$ Hz); $^{13}C-\{^1H\}$, δ 26.81 (d, $^2J_{(CP)} = 12.1$ Hz), 26.85 (d, $^2J_{(CP)} = 12.1$ Hz), 29.40 (s), 29.46 (s), 32.62 (s), 70.76 (d, $^1J_{(CP)} = 154$ Hz); IR (Nujol) ν = 3190w, 2924s, 2855s, 2288w, 1463m, 1377m, 1174w, 1006s, 983m, 940s; mol wt calcd 292; FAB MS [M + H] = 293.2, [M − H] = 291.4. Anal. Calcd for $C_7H_{18}O_8P_2 \cdot H_2O$: C, 27.11; H, 6.50. Found: C, 27.58; H, 6.04.

1,8-Dihydroxyoctane-1,8-bisphosphonic acid (3c): yield 93%, mp 180−185 °C dec; NMR (D_2O) ^1H, δ 1.25 (m, 6H), 1.46−1.54 (m, 4H), 1.61−1.63 (m, 2H), 3.66−3.73 (septet, 2H, $^2J_{(PH)} = 6.6$ Hz, $^3J_{(HaH)} = 2.4$ Hz, $^3J_{(HbH)} = 10.4$ Hz); ^{31}P, δ 24.24 (dd, $^2J_{(PH)} = 6.6$ Hz, $^3J_{(PH)} = 6.6$ Hz); $^{13}C-\{^1H\}$, δ 26.66 (d, $^2J_{(CP)} = 12.8$ Hz), 29.52 (s), 32.45 (s), 70.55 (d, $^1J_{(CP)} = 155.5$ Hz); IR (Nujol) ν = 3190w, 2925s, 2854s, 2348w, 1460m, 1224m, 1007s, 963s, 915m. Anal. Calcd for $C_8H_{20}O_8P_2$: C, 31.37; H, 6.59. Found: C, 31.20; H, 6.30.

α−Hydroxybenzylphosphonic Acid (5a) Sodium borohydride (362 mg, 0.0096 mol) was added to a solution of sodium hydrogen benzoylphosphonate[13] (2 g, 0.0096 mol) dissolved in distilled water (10 mL). After completion of the reaction, dioxane (150 mL) was added to the reaction causing precipitation of the sodium salt, which was converted to the free acid using the same method as that used for bishydroxyphosphonates: yield 57%, mp 171−173 °C; NMR (D_2O) ^1H, δ 4.83 (d, 1H, $^2J_{(PH)} = 12.0$ Hz), 7.23 (dd, 1H, $^3J_{(HH)} = 5.6$ Hz), 7.29 (dd, 2H, $^3J_{(HH)} = 7.4$ Hz), 7.37 (dd, 2H, $^3J_{(HH)} = 7.4$ Hz); ^{31}P, δ 19.30 (d, $^2J_{(PH)} = 11.5$ Hz); $^{13}C-\{^1H\}$, δ 71.52 (d, $^1J_{(CP)} = 151.5$ Hz), 126.85 (d, $^3J_{(CP)} = 4.9$ Hz), 127.2 (s), 128.0 (s), 139.1 (s); IR (Nujol) ν = 3211m, 2918s, 2855s, 2317w, 1467s, 1377m, 1287w, 1248m, 1218m, 1004s, 963s. Anal. Calcd for $C_7H_9O_4P$: C, 44.68; H, 4.82. Found: C, 44.41; H, 4.80.

1-Hydroxy-2-phenylethylphosphonic acid (5b). Sodium borohydride (102 mg, 0.0027 mol) was added to a solution of sodium hydrogen phenylacetylphosphonate (0.5 g, 0.002 25 mol) dissolved in distilled water (7 mL). After completion of the reaction, methanol (50 mL) was added to the reaction causing precipitation of the sodium salt, which was converted to the free acid using the same method as used for the bishydroxyphosphonates: yield 75%, mp 165 °C; NMR (D_2O) ^1H, δ 2.66 (ddd, 1H, $^2J_{(HaHb,gem)} = 14.4$ Hz, $^3J_{(HbH)} = 9.6$ Hz, $^3J_{(HbP)} = 7.8$ Hz), 3.07 (dt, 1H, $^2J_{(HaHb,gem)} = 14.4$ Hz, $^3J_{(HaH)} = 3.1$ Hz, $^3J_{(HaP)} = 3.4$ Hz), 3.77 (ddd, 1H, $^2J_{(PH)} = 7.5$ Hz, $^3J_{(HaH)} = 3.1$ Hz, $^3J_{(HbH)} = 9.6$ Hz), 7.22−7.27 (m, 1H), 7.27−7.30 (m, 4H); ^{31}P, δ 18.22 (m, $^2J_{(PH)} = 6.9$ Hz); $^{13}C-\{^1H\}$, δ 37.82 ($^2J_{(CP)} = 3.1$ Hz), 70.39 (d, $^1J_{(CP)} = 151.3$ Hz), 126.0 (s), 128.2 (s), 128.9 (s), 139.73 (d, $^3J_{(CP)} = 15.6$ Hz); IR (Nujol) ν = 3220m, 2921s, 2866s, 1459s, 1378m, 1308w, 1260m, 1060m, 999s, 946s. Anal. Calcd for $C_8H_{11}O_4P$: C, 47.53; H, 5.48. Found: C, 46.64; H, 5.46.

Crystallization of 5b for X-ray Crystallography. 5b was allowed to crystallize from methanol by slow evaporation to yield large and well-formed crystals.

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Supporting Information Available: X-ray crystallographic data of 1-hydroxy-2-phenylethylphosphonic acid **(5b)** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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