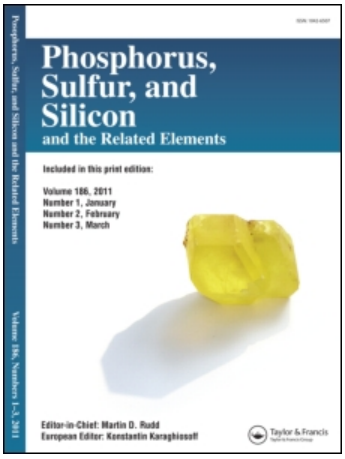

Phosphorus, Sulfur, and Silicon and the Related Elements

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SYNTHESIS OF NEW POLYPHOSPHONIC ACIDS

Carine Viornery,[a] *Péter Péchy,*[a] *Mickaël Boegli,*[a,†] *Björn-O. Aronsson,*[b] *Pierre Descouts,*[b] *and Michael Grätzel*[a]
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A general method for the synthesis of new polyphosphonic acids is described. The hexaisopropyl alkane-1,1,n-triphosphonates (n = 4–5) are formed by the reaction of the salt of tetraisopropyl methylenediphosphonate with diisopropyl n-bromoalkanephosphonates (n = 3–4) while the hexaisopropyl alkane-2,2,n-triphosphonates (n = 5–6) are formed by the reaction of the salt of tetraisopropyl ethane-1,1-diphosphonate with diisopropyl n-bromoalkanephosphonates (n = 3–4). The esters are then hydrolyzed with HCl to give the corresponding phosphonic acids.

Keywords: Bone formation; phosphonic acids; synthesis

INTRODUCTION

Organophosphorus compounds containing a P—C—P linkage have found several applications and have gained increasing interest. They are of considerable biological, industrial, and chemical importance.[1,2] Thus, the diphosphonates are widely used as analogues of pyrophosphates and nucleotides since the P—C—P bond shows a greater inertness to enzymatic hydrolysis than the P—O—P linkage.[3] Phosphonates play an important role as chelating agents of divalent metals. As a result, they are used as detergents,[4–6] sequestrates,[7–9] in the treatment of Paget's disease, tumor induced hypercalcemia and osteoporosis.[10–14] Labelled derivatives have found applications in bone scintigraphy.[15] They also

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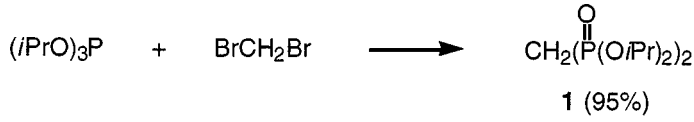
enter in the composition of fixing agents in the photographic process,[16] insecticides and herbicides.[17–19]

The described methods to generate the P—C—P linkage are principally based on phosphonoalkylation of chlorophosphates[20] or employ Michaelis-Arbuzov[21–25] and Michaelis-Becker reactions.[26–28] Several books[19,29–32] and reviews[33,34] discuss these reactions.

The aim of the work presented here was to synthesize new polyphosphonic acid molecules in order to modify titanium disks with the objective of increasing the chemical interaction between the implant and bone tissue instead of a mechanical interaction. Phosphonic acid groups were shown to bind strongly to TiO_2 in a large pH range (from 1 to 9)[35] and to hydroxyapatite.[36] In order to find the best system, several different and new polyphosphonic acids were synthesized by varying the number and the position of phosphonic acid groups and the length of the hydrocarbon chain.

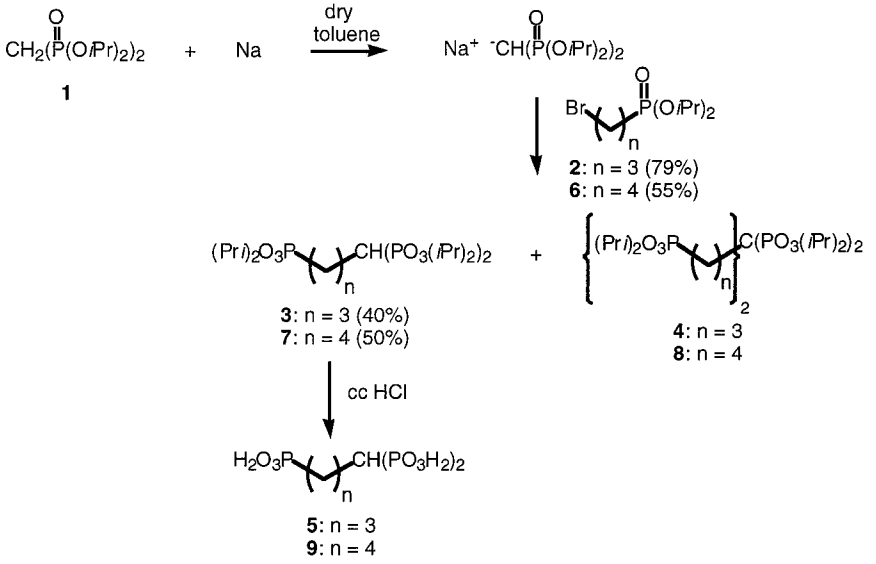
RESULTS AND DISCUSSION

All the final polyphosphonic acid molecules started with the same reagent, which was the tetraisopropyl methylenediphosphonate **1**. **1** was synthesized according to the classical Michaelis-Arbuzov reaction by reacting dibromomethane with triisopropylphosphite (Scheme 1).



SCHEME 1

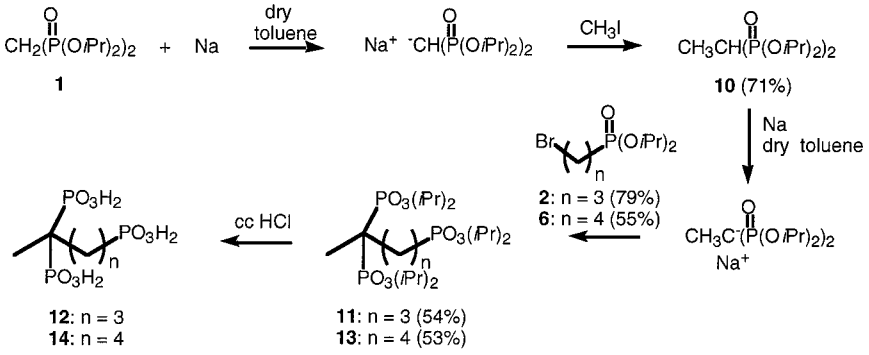
Then the butane-1,1,4-triphosphonic acid **5** and its methylene homologue, the pentane-1,1,5-triphosphonic acid **9** (Scheme 2) was synthesized. The first step consisted of making the carbanion of **1** by reacting the ester with a dispersion of sodium, and the course of the reaction was followed by ^1H and ^{31}P NMR. The ^{31}P NMR spectrum showed the formation of the carbanion (^{31}P NMR (C_6D_6), $\delta = 42$ ppm), but some starting material still remained (about 10–15% for this step) which had not reacted with the sodium. Once the evolution of heat ceased, the bromophosphonate (diisopropyl 3-bromopropylphosphonate **2** or diisopropyl 4-bromobutylphosphonate **6**) was added and the mixture was refluxed for 24 hours. A white precipitate of NaBr salt rapidly formed. The hexaisopropyl butane-1,1,4-triphosphonate **3** and the hexaisopropyl pentane-1,1,5-triphosphonate **7** were formed and were separated



SCHEME 2

from NaBr by extraction. Purification by column chromatography gave the pure products. Formation of by-products identified by ^{1}H and ^{31}P NMR spectroscopy as octaisopropyl heptane-1,4,4,7-tetraphosphonate **4** and octaisopropyl nonane-1,5,5,9-tetraphosphonate **8** contributed to lower their yields, which were 40.2% (**3**) and 49.6% (**7**) respectively. The by-products are also interesting new multiphosphonates. The esters **3** and **7** were then hydrolyzed with an excess of HCl to give **5** and **9**.

To prevent the substitution of the methine proton in $(P_2)CH$ by blocking it with a methyl terminal group, two new molecules were synthesized, which were the pentane-2,2,5-triphosphonic acid **12** and the hexane-2,2,6-triphosphonic acid **14** (Scheme 3). The first step was identical to the previous one. Once the carbanion formed, iodomethane was added and then the mixture was heated to 80°C. The mixture rapidly became white as the Nal salt formed. The tetraisopropyl ethane-1, 1-diphosphonate **10** was formed and separated from NaI by perforation. Purification by column chromatography gave the pure product. The following step was the formation of another carbanion. The sodium base pulled out the most acidic proton of **10** and the carbanion immediately reacted with the bromophosphonate (**2** or **6**). The mixture was brought to reflux. A white precipitate of NaBr salt rapidly formed. The hexaisopropyl pentane-2,2,5-triphosphonate **11** and the hexaisopropyl hexane-2,2,6-triphosphonate **13** were formed and separated from NaBr



SCHEME 3

by extraction; their purification was difficult. They were purified twice by flash chromatography. **11** and **13** were then hydrolyzed with an excess of HCl to give **12** and **14**.

Because phosphonate esters are oils, their purification was difficult, due to their viscosity. Solvents and impurities also were difficult to remove. Moreover they are hygroscopic compounds, but less than their corresponding acids, and due to their hygroscopicity, some water was present in our phosphonates (see experimental section, elemental analysis results).

CONCLUSION

In summary, six new phosphonate esters and four new phosphonic acids (the butane-1,1,4-triphosphonic acid, the pentane-1,1,5-triphosphonic acid, the pentane-2,2,5-triphosphonic acid and the hexane-2,2,6-triphosphonic acid) were successfully synthesized. Their structure was proven by ^{1}H, ^{31}P and ^{13}C NMR, MS and elemental analysis except for two of them (the octaisopropyl heptane-1,4,4,7-tetraphosphonate and the octaisopropyl nonane-1,5,5,9-tetraphosphonate), which were characterized with ^{1}H and ^{31}P NMR.

EXPERIMENTAL

The NMR spectra were performed on an AC-P200 Bruker spectrometer (200 MHz ^{1}H, 81 MHz ^{31}P and 50 MHz ^{13}C). Chemical shifts were referred to tetramethyl silane (TMS) for ^{1}H and ^{13}C and 85% aqueous H_3PO_4 for ^{31}P.

The mass spectra were performed on two different spectrometers. The phosphonates were characterized using chemical ionization with

NH_3 on a Nermag R-10–10 quadrupole spectrometer at the Department of Chemistry of the University of Lausanne while the phosphonic acids were characterized using electronspray ionization on a Finnigan MAT ion trap mass LCQ spectrometer at the Department of Pharmacy of the University of Lausanne.

Elemental analysis was performed at the Microanalytical Laboratory in Kronach (Ilse Beetz, Germany).

All equipment was dried at 150°C for at least three hours before being assembled under nitrogen.

All liquid compounds were purified by standard procedures before being used; toluene was dried, distilled, and stored over sodium.

Column chromatography was performed using silica gel 60 (0.040–0.063 mm) and a gradient of solvents (ethyl acetate or ethyl acetate/ether/methanol).

Tetraisopropyl Methylenediphosphonate 1

Tetraisopropyl methylenediphosphonate was synthesized according to Quimby.[4] ^{31}P NMR ($CDCl_3$), $\delta = 17.71$ (s, 2 P, PCH_2P); ^{13}C NMR $\delta = 71.25$–71.12 (t, $J = 2.7$ Hz, $CH(CH_3)_2$), 30.55–25.06 (t, $J = 137$ Hz, PCH_2P), 24.13–23.87 (m, $CH(CH_3)_2$); ^1H NMR $\delta = 4.90$–4.62 (m, 4 H, $CH(CH_3)_2$), 2.46–2.22 (t, $J = 19.5$ Hz, 2 H, PCH_2P), 1.40–1.27 (m, 24 H, $CH(CH_3)_2$); MS (chemical ionization, NH_3): $m/z = 345$ (100, M + 1); 303 (30.0, M−C_3H_6 + 1); 261 (20.8, M-2C_3H_6 + 1); 219 (20.9, M-3C_3H_6 + 1); 177 (48.5, M-4C_3H_6 + 1).

Diisopropyl 3-bromopropylphosphonate 2

Triisopropylphosphite (5.21 g, 0.025 mol) was added to 1,3-dibromopropane (20.19 g, 0.1 mol) and then refluxed for 4 h. The reaction mixture was cooled and purified by a slow distillation under vacuum (10 mmHg, bath temperature 130°C). Chromatography of the residue on silica gel eluted with ethyl acetate gave the pure product with a yield of 79%. ^{31}P NMR ($CDCl_3$), $\delta = 28.69$ (s, 1 P, CH_2P); ^{13}C NMR $\delta = 70.22$–70.09 (d, $J = 6.5$ Hz, $CH(CH_3)_2$), 33.81–33.43 (d, $J = 19$ Hz, $BrCH_2$), 27.24–26.28 (d, $J = 48.5$ Hz, CH_2CH_2P), 26.19–24.39 (d, $J = 90$ Hz, CH_2P), 24.05–23.97 (d, $J = 4$ Hz, $CH(CH_3)_2$); ^1H NMR $\delta = 4.82$–4.59 (m, 2 H, $CH(CH_3)_2$), 3.52–3.44 (td, $J = 6.49$ and 1 Hz, 2 H, $BrCH_2$), 2.22–2.04 (m, 2 H, $BrCH_2CH_2$), 1.95–1.77 (m, 2 H, CH_2P), 1.34–1.31 (d, $J = 6$ Hz, 12 H, $CH(CH_3)_2$); MS (chemical ionization, NH_3): $m/z = 287$, (90.8, M + 1); 289, (92.9, M + 3); 245 (49.9, M−C_3H_6 + 1), 247 (46.3, M−C_3H_6 + 3); 203 (98.5, M-2C_3H_6 + 1),

205 (100, M-2C_3H_6+3); 165 (10.3, M—C_3H_6—Br), 123 (76.2, M-2C_3H_6—Br).

Hexaisopropyl butane-1,1,4-triphosphonate 3

The following description is mentioned as a general procedure.

To a dispersion of sodium (0.17 g, 7.3×10^{-3} mol) in dry toluene (10 ml) was added dropwise at room temperature **1** (2.51 g, 7.3×10^{-3} mol). **2** (2.08 g, 7.3×10^{-3} mol) was then added dropwise. The mixture was gently refluxed for 24 h. Toluene was evaporated and the residue was extracted with water (30 ml) and dichloromethane (2×20 ml). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. **3** was the major product, and a small quantity of octaisopropyl heptane-1,4,4,7-tetraphosphonate **4** was also formed. Column chromatography of the residue over silica gel using a gradient of ethyl acetate/ether/methanol (three times) gave pure **3** (40.2% yield). ^{31}P NMR ($CDCl_3$), $\delta = 29.85$ (s, 1 P, CH_2CH_2P), 21.80 (s, 2 P, $P_2C(H)CH_2$); ^{13}C NMR $\delta = 71.29$–70.96 (t, $J = 7.5$ Hz, $CH(CH_3)_2$), 69.94–69.80 (d, $J = 6.5$ Hz, $CH(CH_3)_2$), 41.04–35.64 (t, $J = 134.5$ Hz, $P_2C(H)CH_2$), 28.52–25.67 (d, $J = 141.5$ Hz, CH_2CH_2P), 27.31–26.93 (dt, $J = 20$ and 5.3 Hz, CH_2CH_2P), 24.22–23.85 (m, $CH(CH_3)_2$), 22.62–22.38 (td, $J = 7$ and 4.5 Hz, $P_2C(H)CH_2$); ^{1}H NMR $\delta = 4.88$–4.59 (m, 6 H, $CH(CH_3)_2$), 2.30–1.59 (m, 7 H, $P_2CHCH_2CH_2CH_2P$), 1.38–1.31 (m, 36 H, $CH(CH_3)_2$); MS (chemical ionization, NH_3): $m/z = 551$ (100, M + 1); 509 (10.5, M—C_3H_6 + 1); 467 (8.6, M-2C_3H_6 + 1); 385 (6.1, M—$PO_3(C_3H_7)_2$); 343 (4.5, M—$PO_3(C_3H_7)_2$—C_3H_7 + 1); Anal. (calculated; with 1/2 H_2O) found: C (47.98%; 47.21%) 47.30%; H (8.99%; 8.84%) 8.86%; P (16.87%; 16.60%) 16.54%.

Octaisopropyl heptane-1,4,4,7-tetraphosphonate 4

Octaisopropyl heptane-1,4,4,7-tetraphosphonate was separated from **3** by column chromatography **4** came in the last fractions of the column after **3**. NMR and MS showed that approximately 5% of **3** remained. ^{31}P NMR ($CDCl_3$), $\delta = 29.86$ (s, 2 P, CH_2CH_2P), 24.37 (s, 2 P, $P_2C(CH_2)_2$); ^{13}C NMR $\delta = 71.14$–71.02 (d, $J = 6$ Hz, $CH(CH_3)_2$), 69.86–69.74 (d, $J = 6$ Hz, $CH(CH_3)_2$), 48.78–43.44 (t, $J = 133.5$ Hz, $P_2C(CH_2)CH_2$), 29.40–26.58 (d, $J = 141$ Hz, CH_2CH_2P), 32.75–32.45 (dt, $J = 20$ and 5 Hz, CH_2CH_2P), 24.18–23.78 (m, $CH(CH_3)_2$), 18.40–18.10 (quadruplet (td), $J = 5$ Hz, $P_2C(CH_2)CH_2$); ^{1}H NMR $\delta = 4.93$–4.59 (m, 8 H, $CH(CH_3)_2$), 2.01–1.57 (m, 12 H, $P_2C(CH_2CH_2CH_2P)$ $CH_2CH_2CH_2P$), 1.38–1.31 (m, 48 H, $CH(CH_3)_2$); MS (chemical ionization, NH_3): $m/z = 757$ (100, M + 1); 715 (6.7, M—C_3H_6 + 1); 592

(26.9, M—$PO_3(CH_3H_7)_2 + 1$); 591 (32.4, M—$PO_3(C_3H_7)_2$); 549 (13.8, M—$PO_3(C_3H_7)_2$—$C_3H_7 + 1$); 384 (4.0, M-2PO_3 $(C_3H_7)_2$—$C_3H_7 + 1$.

Butane-1,1,4-triphosphonic acid 5

The hydrolysis is described as a general procedure.

Hexaisopropyl butane-1,1,4-triphosphonate was hydrolyzed with a 75% molar excess of HCl (32%) under reflux for 4 h. To remove traces of HCl, the acidic solution was distilled three times with H_2O (3 × 30 ml). **5** was obtained and dried under vacuum (10 mmHg, room temperature (r.t.)) over P_2O_5. ^{31}P NMR (D_2O), $\delta = 30.64$ (s, 1 P, CH_2CH_2P), 21.59 (s, 2 P, $P_2C(H)CH_2$); ^{13}C NMR $\delta = 37.95$–36.28 (t, $J = 124.2$ Hz, $P_2C(H)CH_2$), 26.40–25.50 (d, $J = 141.5$ Hz, CH_2CH_2P), 25.97–25.83 (dt, $J = 18.3$ and 4.2 Hz, CH_2CH_2P), 22.04–21.96 (m, $P_2C(H)CH_2CH_2$); ^{1}H NMR $\delta = 2.33$–1.65 (m, 7 H, $P_2CHCH_2CH_2CH_2P$); MS (electron spray): $m/z = 297.1$ (100, M-1); 278.9 (5.0, M—H_2O-1).

Diisopropyl 4-bromobutylphosphonate 6

Triisopropylphosphite (8.4 g, 0.04 mol) was added to 1,4-dibromobutane (30.5 g, 0.15 mol) and then refluxed for 4 h. The reaction mixture was cooled and purified by a slow distillation under vacuum (10 mmHg, bath temperature 140°C). Chromatography of the residue on silica gel eluted with ethyl acetate gave the pure product with a yield of 55.4%. ^{31}P NMR ($CDCl_3$), $\delta = 29.58$ (s, 1 P, CH_2P); ^{13}C NMR $\delta = 70.01$–69.87 (d, $J = 7$ Hz, $CH(CH_3)_2$), 33.34–33.01 (d, $J = 16.5$ Hz, CH_2CH_2P), 32.75 (s, $BrCH_2$), 27.49–24.64 (d, $J = 142.5$ Hz, CH_2P), 24.08–24.01 (d, $J = 3.5$ Hz, $CH(CH_3)_2$), 21.43–21.33 (d, $J = 5$ Hz, $BrCH_2CH_2$); ^{1}H NMR $\delta = 4.80$–4.58 (m, 2 H, $CH(CH_3)_2$), 3.43–3.38 (t, $J = 6.8$ Hz, 2 H, $BrCH_2$), 2.04–1.89 (m, 2 H, CH_2P), 1.81–1.59 (m, 4 H, $BrCH_2CH_2CH_2$), 1.34–1.30 (d, $J = 6.8$ Hz, 12 H, $CH(CH_3)_2$); MS (chemical ionization, NH_3); $m/z = 301$, (100, M + 1), 303 (99.5, M + 3); 259 (22.7, M—$C_3H_6 + 1$), 261 (20.6, M—$C_3H_6 + 3$); 217 (22.8, M–2$C_3H_6 + 1$), 219 (20.0, M–2$C_3H_6 + 3$); 179 (10.1, M—C_3H_6—Br); 137 (52.8, M–2C_3H_6—Br + 1).

Hexaisopropyl Pentane-1,1,5-triphosphonate 7

The same general procedure was used as with **3**. **7** was the major product and a small quantity of octaisopropyl nonane-1,5,5,9-tetraphosphonate **8** was also formed. Column chromatography of the residue over silica gel using a gradient of ethyl acetate/methanol gave pure **7** (49.6% yield). ^{31}P NMR ($CDCl_3$), $\delta = 30.38$ (s, 1 P, CH_2CH_2P), 22.14 (s, 2 P, $P_2C(H)CH_2$); ^{13}C NMR $\delta = 71.11$–70.81 (t, $J = 7$ Hz, $CH(CH_3)_2$),

69.80–69.67 (d, $J = 7$ Hz, $CH(CH_3)_2$), 40.98–35.60 (t, $J = 134$ Hz, $P_2C(H)CH_2$), 30.52–29.65 (dt, $J = 18.3$ and 6.5 Hz, $P_2C(H)CH_2CH_2CH_2CH_2P$), 28.23–25.41 (d, $J = 141.5$ Hz, CH_2CH_2P), 25.51–25.41 (t, $J = 4.8$ Hz, $P_2C(H)CH_2CH_2$), 24.23–23.84 (m, $CH(CH_3)_2$), 22.57–22.47 (d, $J = 5$ Hz, CH_2CH_2P); ^{1}H NMR $\delta = 4.83$–6.64 (m, 6 H, $CH(CH_3)_2$), 1.64 (large peak, 9 H, $P_2CHCH_2CH_2CH_2CH_2P$), 1.36–1.26 (m, 36H, $CH(CH_3)_2$); MS (chemical ionization, NH_3): $m/z = 565(100, M + 1)$; 523 (11.3, M–$C_3H_6 + 1$); 481 (5.4, M–$2C_3H_6 + 1$); 399 (15.2, M–$PO_3(C_3H_7)_2$); 357 (7.0, M–$PO_3(C_3H_7)_2$–C_3H_6); 315 (3.1, M–$PO_3(C_3H_7)_2$–$2C_3H_6$); Anal. (calculated; with 1/4H_2O) Found: C (48.92%; 48.53%) 48.62%; H (9.12%; 9.05%) 9.08%; P (16.45%; 16.32%) 16.29%.

Octaisopropyl Nonane-1,5,5,9-tetraphosphonate 8

From a later fraction **8** was isolated. NMR and MS analysis showed that approximately 30% of **7** remained. ^{31}P NMR ($CDCl_3$), $\delta = 30.27$ (s, 2 P, CH_2CH_2P), 25.07 (s, 2 P, $P_2C(CH)_2)_2$).

Pentane-1,1,5-triphosphonic acid 9

The same hydrolysis procedure was used as with **5**. ^{31}P NMR (D_2O), $\delta = 31.48$ (s, 1 P, CH_2CH_2P), 21.92 (s, 2 P, $P_2C(H)CH_2$); ^{13}C NMR $\delta = 40.63$–35.68 (t, $J = 123.5$ Hz, $P_2C(H)CH_2$), 30.52–30.05 (dt, $J = 17$ and 6.5 Hz, $P_2C(H)CH_2CH_2$), 28.00–25.34 (d, $J = 132.5$ Hz, CH_2CH_2P), 25.46 (t (unresolved), $P_2C(H)CH_2CH_2$), 22.70–22.61 (d, $J = 5$ Hz, CH_2CH_2P); ^{1}H NMR $\delta = 2.39$–2.02 (tt, 1 H, $J = 23.3$ and 5.8 Hz, $P_2CHCH_2CH_2CH_2CH_2P$), 1.99–1.40 (m, 8 H, $P_2CHCH_2CH_2CH_2CH_2P$); MS (electron spray); $m/z = 311.1$ (100, M-1);293.1 (35.0,M–H_2O-1); 275.2 (18.0, M–2H_2O-1).

Tetraisopropyl Ethane-1,1-diphosphonate 10

Tetraisopropyl ethane-1,1-diphosphonate was synthesized according to Menge et al.[37] ^{31}P NMR ($CDCl_3$), $\delta = 22.48$ (s, 2 P, $CH_3C(H)P_2$); ^{13}C NMR $\delta = 71.02$–70.84 (d, $J = 1.5$ Hz, $CH(CH_3)_2$), 70.88–70.84 (d, $J = 1.5$ Hz, $CH(CH_3)_2$), 35.35–29.89 (t, $J = 136.5$ Hz, $CH_3C(H)P_2$), 24.23–24.16 (d, $J = 3.5$ Hz, $CH(CH_3)_2$), 23.97–23.84 (d, $J = 5.5$ Hz, $CH(CH_3)_2$), 10.59–10.47 (t, $J = 6$ Hz, $CH_3C(H)P_2$); ^{1}H NMR $\delta = 4.88$–4.69 (m, 4 H, $CH(CH_3)_2$), 2.41–2.13 (m, 1 H, $P_2C(H)CH_3$), 1.56–1.42 (m, 3 H, $P_2C(H)CH_3$), 1.40–1.31 (d, 24 H, $J = 6.1$ Hz, $CH(CH_3)_2$); MS (chemical ionization, NH_3); $m/z = 359$ (100, M + 1); 317 (28.0, M–$C_3H_6 + 1$); 275 (21.7, M–$2C_3H_6 + 1$); 233 (13.1, M–$3C_3H_6 + 1$); 191 (13.8, M–$4C_3H_6 + 1$).

Hexaisopropyl Pentane-2,2,5-triphosphonate 11

The following experimental part is mentioned as a general procedure. To a dispersion of sodium (0.055 g, 2.4×10^{-3} mol) dry toluene (10 ml) was added dropwise at room temperature **10** (0.86 g, 2.4×10^{-3} mol). **2** (0.685 g, 2.4×10^{-3} mol) was then added dropwise. The mixture was gently refluxed for 24h. Toluene was evaporated and the residue was extracted with water (20 ml) and dichloromethane (2×15 ml). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. Column chromatography of the residue over silica gel using a gradient of ethyl acetate/ether/methanol (twice) gave pure **11** (53.6% yield). ^{31}P NMR ($CDCl_3$), $\delta = 30.01$ (s, 1 P, $(CH_2))_3P$), 25.31 (s, 2 P, $CH_3C(P_2)(CH_2)_3$); ^{13}C NMR $\delta = 71.06$–70.93 (t, $J = 3.5$ Hz, $CH(CH_3)_2$), 69.83–69.70 (d, $J = 6.5$ Hz, $CH(CH_3)_2$), 43.68–38.32 (t, $J = 134$ Hz, $CH_3C(CH)_2P_2$), 35.18–34.78 (dt, $J = 20$ and 4.5 Hz, $CH_3C(P_2)CH_2CH_2CH_2P$), 29.31–26.49 (d, $J = 141$ Hz, CH_2P), 24.40–23.84 (m, $CH(CH_3)_2$), 18.49–18.17 (quadruplet (td), $J = 5.5$ Hz, $CH_3C(P_2)CH_2$), 17.34–17.12 (t, $J = 5.5$ Hz, $CH_3C(CH_2)P_2$); ^{1}H NMR $\delta = 4.89$–4.61 (m, 6 H, $CH(CH_3)_2$), 1.94–1.52 (m, 9 H, $CH_3C(P_2)CH_2CH_2CH_2P$), 1.37–1.29 (t, 36 H, $CH(CH_3)_2$); MS (chemical ionization, NH_3): $m/z = 565$ (100.0, M + 1); 523 (24.0, M–C_3H_6 + 1); 481 (7.8, M-2C_3H_6 + 1); 399 (18.3, M–$PO_3(C_3H_7)_2$); Anal. (calculated; with 1/4H_2O) Found: C (48.92%; 48.53%) 48.64%; H (9.12%; 9.05%) 9.09%; P (16.45%; 16.32%) 16.30%.

Pentane-2,2,5-triphosphonic acid 12

The same hydrolysis procedure was used as with **5**. ^{31}P NMR (D_2O), $\delta = 30.78$ (s, 1 P, $(CH_2)_3P$), 25.74 (s, 2 P, $CH_3C(P_2)(CH_2)_3$); ^{13}C NMR $\delta = 42.54$–37.53 (t, $J = 125.5$ Hz, $CH_3C(P_2)CH_2$), 34.48–34.10 (dt, $J = 19$ and 4 Hz, $CH_3C(P_2)CH_2CH_2CH_2P$), 29.01–26.34 (d, $J = 133.5$ Hz, CH_2CH_2P), 19.05–18.69 (quadruplet (td), $J = 5$ Hz, $CH_3C(P_2)CH_2$), 16.81–16.63 (t, $J = 4.5$ Hz, $CH_3C(CH_2)P_2$); ^{1}H NMR $\delta = 2.01$–1.62 (m, 6 H, $CH_3(P_2)CCH_2CH_2CH_2P$), 1.45–1.29 (t, $J = 16$ Hz, 3 H, $CH_3(P_2)CCH_2CH_2CH_2P$); MS (electron spray): $m/z = 313.2$ (100, M + 1); 295.2 (4.3, M–H_2O + 1).

Hexaisopropyl Hexane-2,2,6-triphosphonate 13

The same general procedure was used as with **11**. **13** (52.7% yield). ^{31}P NMR ($CDCl_3$), $\delta = 29.99$ (s, 1 P, $(CH_2)_4P$), 25.31 (s, 2 P, $CH_3C(P_2)(CH_2)_4$); ^{13}C NMR $\delta = 70.89$ (d (unresolved), $CH(CH_3)_2$), 69.78–69.65 (d, $J = 6.5$ Hz, $CH(CH_3)_2$), 43.47–38.10 (t, $J = 134$ Hz, $CH_3C(P_2)CH_2$), 33.40–33.25 (t, $J = 4$ Hz, $P_2CCH_2CH_2$), 28.39–25.58

(d, $J = 140.5$ Hz, $CH_2CH_2P_2$), 26.20–25.58 (dt, $J = 24.5$ and 5.5 Hz, $(P_2)CCH_2CH_2CH_2CH_2P$), 24.34–23.76 (m, $CH(CH_3)_2$), 23.45–23.35 (d, $J = 5$ Hz, $CH_2CH_2P_2$), 17.33–17.11 (t, $J = 5.5$ Hz, $CH_3C(P_2)CH_2$); ^{1}H NMR $\delta = 4.86$–4.60 (m, 6 H, $CH(CH_3)_2$), 1.86–1.51 (m, 11 H, $CH_3C(P_2)CH_2CH_2CH_2CH_2P$), 1.36–1.28 (m, 36 H, $CH(CH_3)_2$); MS (chemical ionization, NH_3): $m/z = 579$ (100.0, M + 1); 537 (17.1, M—C_3H_6 + 1); 495 (5.8, M-2C_3H_6 + 1); 413 (12.5, M—$PO_3(C_3H_7)_2$); Anal. (calculated; with 1/4H_2O) Found: C (49.81%; 49.42%) 49.48%; H (9.25%; 9.18%) 9.20%; P (16.05%; 15.93%) 15.83%.

Hexane-2,2,6-triphosphonic acid 14

The same hydrolysis procedure was used as with **5**.^{31}P NMR (D_2O), $\delta = 31.64$ (s, 1 P, $(CH_2)_4P$), 26.18 (s, 2 P, $CH_3C(P_2)(CH_2)_4$); ^{13}C NMR $\delta = 42.55$–37.56 (t, $J = 125$ Hz, $CH_3C(P_2)CH_2$), 32.96 (unresolved triplet, $CH_3(P_2)CCH_2CH_2$), 28.09–25.43 (d, $J = 133$ Hz, $CH_2CH_2P_2$), 26.38–25.82 (dt, $J = 16$ and 6 Hz, $(P_2)CCH_2CH_2CH_2CH_2$), 23.67–23.58 (d, $J = 4.5$ Hz, $CH_2CH_2P_2$), 16.97–16.88 (t, $J = 4.5$ Hz, $CH_3C(P_2)CH_2$); ^{1}H NMR $\delta = 2.00$–1.53 (m, 8 H, $CH_3(P_2)CCH_2CH_2CH_2CH_2P$), 1.48–1.32 (t, $J = 16$ Hz, 3 H, $CH_3(P_2)CCH_2CH_2CH_2CH_2P$); MS (electron spray): $m/z = 327.6$ (100, M + 1); 309.6 (2.8, M—H_2O + 1).

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