A Convenient Synthesis of Phosphonic Anhydrides − Trimers $[RPO_2]_3$ (R = *tert*-Butyl, 2-Methylphenyl, 2,4,6-Trimethylphenyl): Their Structures and Reaction Products

Klaus Diemert, Wilhelm Kuchen*, Wolfgang Poll, and Frank Sandt

Institut für Anorganische Chemie und Strukturchemie der Heinrich-Heine-Universität,
Universitätsstraße 1, D-40225 Düsseldorf, Germany

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By reaction of $RP(O)Cl_2$ with $RP(O)(OSiMe_3)_2$, phosphonic anhydrides $(RPO_2)_3$ (R = *t*Bu, 2-methylphenyl, 2,4,6-trimethylphenyl) **1a−c** are conveniently obtained. In contrast to **1b** and **1c**, compound **1a** is remarkably stable against protolysis. Intermediates of hydrolysis of **1a**, namely tris(*tert*-butyl)triphosphonic acid (**2**) and bis(*tert*-butyl)diphosphonic acid (**3**), can also be isolated in good yield. The structures of **1−3** were determined mainly by NMR spectroscopy (^1H, ^{13}C, ^{31}P). Assuming an energetic preference for the chair conformations in solution, and considering the steric requirements of the bulky substituents R, configurations Ia (point group C_s, two R in equatorial positions) for **1a** and **b**, and IIa (point group C_{3v}, all R equatorial) for **1c** are suggested. − Reaction of **1a** with *N*-benzyloxycarbonylglycine (**4**) in methanol affords strong evidence that in the first step of peptide synthesis with $(RPO_2)_3$, a mixed anhydride of triphosphonic acid and the *N*-protected amino acid is formed. − The crystal structure of **1a** (monoclinic, space group $P2_1/n$) widely corresponds to the suggested configuration Ia, but reveals an envelope conformation for the six-membered ring with a P_3O_2 plane in the crystal. In the crystal structure of the octahydrate of the disodium salt of **2** (monoclinic, space group $P2_1/c$), it can be seen that the polar end groups of the anions $[tBu_3P_3O_7]^{2-}$ together with the water molecules and the Na^+ cations form hydrogen-bonded double-layers, strictly separated from each other by the non-polar *tert*-butyl groups of the anions.

Introduction

A variety of methods have been reported in the literature for the preparation of phosphonic anhydrides $(RPO_2)_n$. These methods usually result in mixtures of oligomers which are difficult to separate[1][2][3].

Compounds of this composition were also obtained when the corresponding cyclophosphanes were oxidized with dry oxygen (R = CF_3, average number $\bar{n}$ = 3−4[4], R = Ph, $\bar{n}$ = 5[5]).

Thermolysis and flash vacuum pyrolysis of $tBuP(O)(OSiMe_3)X$ (X = Cl, Br) afforded the trimer $(tBuPO_2)_3$[6].

Among other alkylphosphonic anhydrides, compound $(PrPO_2)_3$, which is commercially available, is recommended as a condensation reagent in the synthesis of peptides[7].

As phosphinic anhydrides $R_2P(O){-}O{-}P(O)R_2$ are readily accessible by treating $R_2P(O)Cl$ and silyl esters $R_2P(O)(OSiMe_3)$ with elimination of Me_3SiCl[8], we now used the analogous reaction between phosphonoyl chlorides $RP(O)Cl_2$ and silyl phosphonates $RP(O)(OSiMe_3)_2$ for the synthesis of the title compounds. By this method we obtained, in excellent yield and purity, alkyl compounds $(RPO_2)_n$ as highly viscous, colorless oils that are readily hydrolyzable. They can be distilled under vacuum, and some of them gradually crystallize after standing at room temperature. According to cryoscopic measurements in benzene, $\bar{n}$ varied from 11 (R = Pr) to 6 (R = Bu, Pentyl) within a wide range of concentrations[9].

In case of bulky substituents R, we isolated well-defined trimers **1a−1c**. Their configurations and some of their reactions are discussed in the following sections[10].

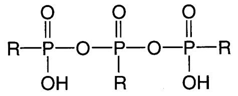
Trimeric Phosphonic Anhydrides 1a−1c

On heating equimolar quantities of $RP(O)Cl_2$ and $RP(O)(OSiMe_3)_2$, **1a−1c** are obtained as colorless crystals with sharp melting points. While **1a** and **1b** are readily soluble in toluene, benzene, $CHCl_3$, or CH_2Cl_2, **1c** is fairly soluble only in the latter two solvents. **1b** and **1c** are rapidly dissolved by methanol or H_2O, with the formation of phosphonic acid esters $RP(O)(OMe)OH$ or phosphonic acids $RP(O)(OH)_2$.

$(RPO_2)_3$

1

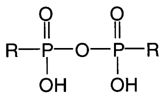
a: R = *t*Bu
b: R = 2-methylphenyl
c: R = 2,4,6-trimethylphenyl



$R{-}P(=O)(OH){-}O{-}P(=O)(R){-}O{-}P(=O)(OH){-}R$

2

R = *t*Bu
2a: Disodium salt · 2 H_2O
2b: Disodium salt · 8 H_2O



$R{-}P(=O)(OH){-}O{-}P(=O)(OH){-}R$

3

R = *t*Bu
3a: Disodium salt · 3 H_2O

1a, however, is remarkably stable in this respect. As shown by NMR spectroscopy, solutions of **1a** in methanol

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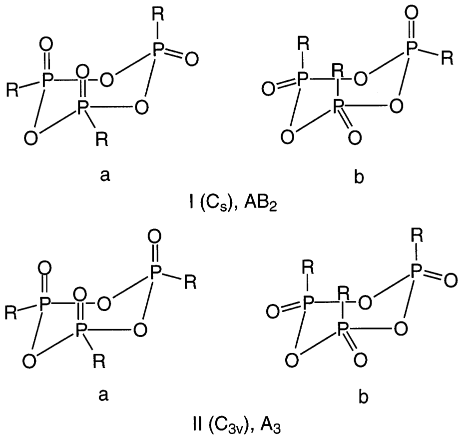
or ethanol remain unchanged even after boiling for several hours. Hydrolysis is so slow that it is possible (as is shown later) to isolate intermediates of this reaction.

While in the mass spectra of **1b** and **1c**, abundant peaks for the molecular ions are observed, the signal for $M^{+\cdot}$ in the spectrum of **1a** is of low intensity. The spectrum of the latter compound is characterized by a successive loss of C_4H_8 from the molecular ion. A peak m/z = 192 (19%) corresponding to $[HPO_2]_3^{+\cdot}$ indicates that this process can occur without fragmentation of the six-membered ring.

NMR Spectra

Assuming a six-membered ring structure for **1**, and an energetic preference for the chair conformations, structures I and II, both with conformations a and b, have to be considered (Figure 1).

Figure 1. Possible structures of cyclic trimers **1** (chair conformations), point groups, and $^{31}P\{^1H\}$ spin systems



These should give rise to AB_2 or A_3 spin systems in their $^{31}P\{^1H\}$-NMR spectra, and we did in fact observe AB_2 systems for **1a** and **1b** and an A_3 system for **1c**. The correspondence of the observed spectra given in the Experimental Section with spectra simulated with parameters ν_A = 1912.3 Hz, ν_B = 1824.1 Hz, J_{AB} = 50.9 Hz (**1a**) and ν_A = 163.5 Hz, ν_B = −33.1 Hz, J_{AB} = 42.6 Hz (**1b**) is excellent. Considering the steric requirements of the bulky substituents R, structure Ia is therefore suggested for **1a** and **1b**, while structure IIa appears to be the most probable one for **1c**. In the crystal, **1a** adopts an envelope conformation with point group C_s and a P_3O_2 plane.

The ^1H-NMR spectra are in accordance with the suggested structures for **1a** and **1b**. The spectrum of the *tert*-butyl compound shows two doublets of relative intensity 1:2, a ratio that has also been found for the methyl protons in the spectrum of the 2-methylphenyl compound **1b**. The spectrum of **1c**, however, is more complex as several broad resonance signals for methyl groups and aromatic protons are observed.

Tris(*tert*-butyl)triphosphonic Acid (2), Bis(*tert*-butyl)diphosphonic Acid (3), and Their Disodium Salts 2a, 2b, and 3a

By reaction of equimolar quantities of **1a** and H_2O in ethanol at 50−60°C for 3.5 h, **2** is obtained as colorless crystals that are soluble in $CHCl_3$, methanol, or ethanol, and melt at 152°C. **2** is a strong dibasic acid (in water at room temperature: pK_{a1} not determinable, pK_{a2} = 2.29). Aqueous solutions of **2** were found to be stable for at least 10 h at room temperature. The $^{31}P\{^1H\}$-NMR spectrum corresponds to an AB_2 spin system (with close approximation to AX_2), and the $^1H\{^{31}P\}$-NMR spectrum shows two resonance signals (intensity ratio 2:1) for the *tert*-butyl groups, as well as one signal in the range of acidic protons. Neutralisation of **2** by NaOH affords **2a**, the dihydrate of its disodium salt. The octahydrate **2b** is obtained by diffusion-controlled precipitation from aqueous solutions of **2a** with acetone. **2b** forms large transparent leaflets, the crystal structure of which is reported.

Bis(*tert*-butyl)diphosphonic acid (**3**) is formed together with *tert*-butylphosphonic acid when the triphosphonic acid (**2**) is heated with concentrated hydrochloric acid for 1 h. After 4 h, tBuP(O)(OH)$_2$ is the sole reaction product. Reaction of **1a** with EtONa (molar ratio 1:4) in refluxing ethanol for 1 h affords the disodium salt of acid **3**. Both compounds were isolated as hydrates of composition $\mathbf{3}\cdot 1.5\ H_2O$ and **3a**. They form colorless needles, which loose their water of crystallization on heating at 80−100°C. Compound **3**, m.p. 198−200°C, is soluble in water or acetone, **3a** readily dissolves only in water.

Reaction of (tBuPO$_2$)$_3$ (1a) with an *N*-Protected Amino Acid

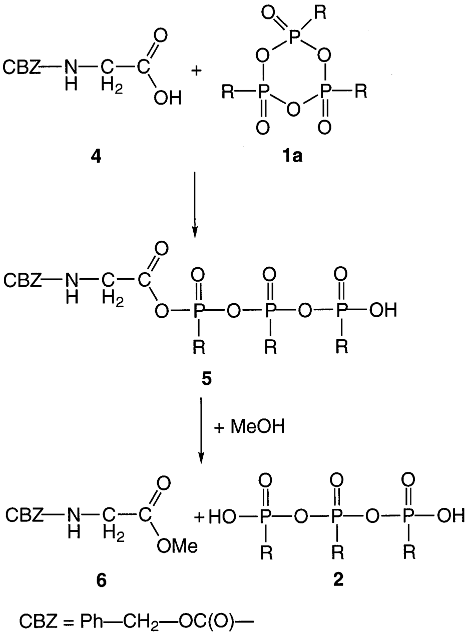
Considering the general methods for peptide synthesis with other phosphorus compounds[11] it can be assumed that with $(PrPO_2)_3$ for example, the first step of the reaction is ring opening and formation of a mixed anhydride of the corresponding triphosphonic acid, and an *N*-protected amino acid. In a subsequent step, the mixed anhydride is thought to react with a carboxyl-protected amino acid, affording triphosphonic acid and the peptide.

Since **1a**, as well as the triphosphonic acid **2**, have been found to be stable against methanolysis, we tried to substantiate the opening step of this peptide synthesis by treating equimolar amounts of **1a** and the *N*-protected amino acid *N*-benzyloxycarbonylglycine (**4**) in methanol. After 3 h at 65°C, the reaction was complete. The reaction product, a colorless, highly viscous oil, was investigated by NMR spectroscopy and GC-MS. The conclusions drawn from the results are shown in Scheme 1, and may be summarized as follows:

The $^{31}P\{^1H\}$-NMR spectrum ($CDCl_3$) of the reaction mixture reveals the presence of one AX_2 system and several strongly overlapping multiplets at δ = 21−23, 30−31, and 32−34. The parameters of the AX_2 system (δ_A = 21.30 (t); δ_X = 31.30 (d); J_{AX} = 49.3 Hz) correspond well with those of the triphosphonic acid **2**. Moreover, a precipitate obtained by adding hexane to the methanolic solution of the reaction product was clearly identified as **2**.

P,P-COSY reveals the presence of 2 AMX spin systems with the following parameters: δ_A = 22.10 (t); δ_M = 30.40 (d); δ_X = 33.70 (d); J_{AM} = 48.3 Hz; J_{AX} = 46.9 Hz and δ_A = 21.80 (t); δ_M = 30.60 (d); δ_X = 33.10 (d); J_{AM} = 47.7 Hz; J_{AX} = 47.2 Hz. The AMX systems possibly result from

Scheme 1. Suggested reaction of **1a** with *N*-benzyloxycarbonylglycine (**4**) (methanol, 65°C, 3 h), R = *t*Bu



the two pairs of diastereomers expected for the mixed anhydride **5** in Scheme 1. According to this scheme, acid **2** and the methyl ester **6**, detected by GC-MS, are formed by methanolysis of **5**. Alternatively, reaction of **4** with **5**, with formation of the anhydride of **4** followed by methanolysis, may be regarded as the source of **6** and **2**.

The ^{1}H-NMR spectrum ($CDCl_3$) of the reaction product shows groups of resonance signals that correspond to protons of the compounds in Scheme 1. They can be assigned as follows:

$\delta(\mathrm{PCC}H_3)$ = 1.06–1.56; $\delta(\mathrm{C}H_2\mathrm{COOH})$ = 3.51–3.80; $\delta(\mathrm{COC}H_3)$ = 4.00–4.06; $\delta(\mathrm{C_6H_5C}H_2)$ = 5.17; $\delta(\mathrm{C_6}H_5\mathrm{CH_2})$ = 7.24–7.53; $\delta(\mathrm{O}H)$ = 9.50–9.70 (s, br.).

Thus, there is strong evidence that mixed anhydrides of phosphonic acids and *N*-protected amino acids (in Scheme 1 represented by **5**) are intermediates in peptide synthesis with $(RPO_2)_n$.

Crystal Structures

In the molecular structure of **1a** in the crystal, trimeric units of $t\mathrm{BuPO_2}$ form six-membered rings of P_3O_3, with two *tert*-butyl groups directed to one side of the ring and one group to the other (Figure 2). In slight contrast to the assumed chair conformation used for the interpretation of the NMR data in solution, the P_3O_3 ring takes on an envelope conformation in the crystal, with the oxygen atom O23 as an apex with a deviation of 0.43 Å from the least-squares plane defined by the other five ring atoms. Although the observed deviations from the furthermore assumed symmetry (C_S) of the molecule are small (C_S asymmetry parameters for atoms P1 and O23 are only 2°), their significance is supported by the molecule lying in general position 4e of space group $P2_1/n$.

All bond lengths and angles are in good agreement with common values, and no intermolecular contacts less than the sum of the corresponding van der Waals radii occur. Remarkable geometrical parameters are the angles P1–O12–P2 and P1–O13–P3 with 136.2 and 136.0° respectively, in contrast to the more common value of 130.3° for P2–O23–P3. Also, a distortion of the tetrahedral coordination of the phosphorus atoms is observed, insofar as all bond angles involving the P=O bonds are widened [O*n*–P*n*–C*n* 116.0–116.5°, O*n*–P*n*–O(ring) 111.6–114.6°], and the remaining angles reduced [O(ring)–P*n*–O(ring) 101.0–102.8°, O(ring)–P*n*–C*n* 105.1–106.3° with *n* = 1, 2, or 3, respectively].

The molecular structure of **2b** consists of one anion $[t\mathrm{Bu_3P_3O_7}]^{2-}$, two Na^+ cations, and eight water molecules, with all atoms in general positions 4e of space group $P2_1/c$. While most geometrical parameters of the anion (Figure 3) agree well with usual values, the oxygen atoms of the two configurations P1–O21–P2 and P2–O23–P3 are significantly shifted towards the central phosphorus atom P2 [mean bond lengths 1.574(3) Å for P2(central)–O and 1.641(2) Å for P1/P3(terminal)–O]. These discrepancies in the four formally equivalent single P–O bonds may be in correlation with the fact that the double bonded O22 at the central P atom is the only atom of the anion coordinating

Figure 2. Molecular structure of **1a** in the crystal[14], thermal ellipsoids represented on a 25% probability scale, hydrogen atoms with fixed radii of 0.15 Å

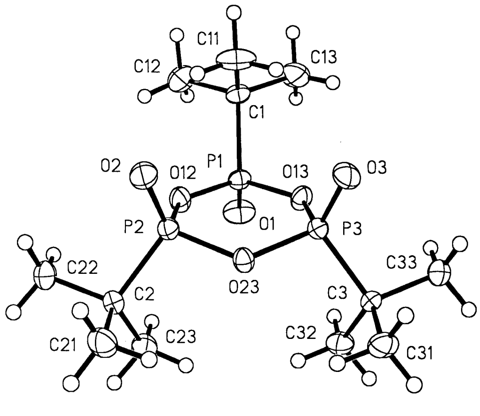
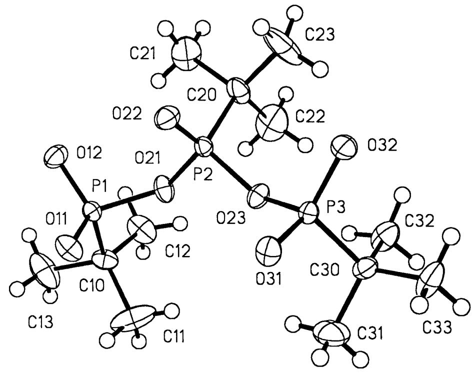


Figure 3. Anion $[t\mathrm{Bu_3P_3O_7}]^{2-}$ of **2b** in the crystal[14], thermal ellipsoids represented on a 40% probability scale, hydrogen atoms with fixed radii of 0.17 Å



one of the sodium atoms. The other oxygen atoms O11, O12, O31, and O32 accept two or three hydrogen bonds donated by seven of the eight water molecules.

Atom Na1 is hexacoordinated by five water molecules and atom O22 in the form of a distorted octahedron. The coordination of Na2 is made up by five water molecules only, best described as a highly distorted square-based pyramid, sharing one edge with the octahedron of Na1. These two concatenated polyhedra are expanded to a unit of four edge-connected polyhedra by a crystallographic inversion center lying on another edge of the Na1 octahedron.

The complete connectivity of cations, anions, and water molecules making up the crystal structure is very complex (if only because of 16 different hydrogen bonds). In summary it can be said that the anions and seven of the eight water molecules form a hydrogen-bonded layer parallel to the *ac* plane. Two of these layers are concatenated by the eighth water molecule and the two Na^+ cations to form a double layer with all polar parts of the crystal structure (water, Na^+, end groups PO_2^-) on the inside and the non-polar *tert*-butyl groups on the outside of such a double layer. By this arrangement of the anions, any further connectivity between those layers to form a three-dimensional framework is prevented, and only van der Waals contacts between methyl groups of neighbouring layers are observed.

Experimental Section

The silyl esters, and compounds **1** were prepared and handled under inert conditions. − Melting points (uncorrected) were determined in sealed tubes with a melting-point apparatus 510 H (Büchi, Switzerland). − ^1H-, ^{13}C-, and ^{31}P-NMR spectroscopy: Bruker AM 200, TMS (^1H), sodium salt of 3(trimethylsilyl)propionic acid (^1H, ^{13}C) as internal and 85% H_3PO_4 (^{31}P) as external reference. Downfield shifts are positive and given in parts per million, and coupling constants are expressed in Hz. − EI-MS: Varian Mat 311 A (IE 70 eV). − GC-MS: GC 5890−MSD 5970 (Hewlett Packard). Only the main peaks are listed. − Cryoscopy: Cryoscopic unit A 0284 (Knaur, Berlin). − Osmometry: Osmometric unit 11.00, $T = 37°C$ (Knaur, Berlin). − Thermogravimetry: Mettler TA 1. − pK_a values: Potentiometric titration with NaOH using hardware of Schott, Hofheim and the program system MINI T401 and ITERAX[12]. − Elemental analysis: C,H,N: Analyzer 2400 (Perkin−Elmer). P: Photometrically[13] after decomposition with conc. HNO_3 in a stainless steel bomb, type DAB II (Berghof, D-72800 Emingen).

X-ray Crystallographic Study of **1a**: $C_{12}H_{27}O_6P_3$; formula mass 360.25 g mol^{-1}; monoclinic space group $P2_1/n$ (no. 14); a = 7.590(3), b = 27.06(1), c = 8.926(3) Å; β = 95.16(3)°; V = 1826(1) Å^3; Z = 4; $d_{calcd.}$ = 1.310 Mg m^{-3}; μ(Mo-K_α) = 0.346 mm^{-1}; $F(000)$ = 768. Siemens P3 (upgraded Syntex P2$_1$) diffractometer, Mo-K_α radiation (λ = 0.71073 Å), graphite monochromator. Data collection at room temperature in ω/2Θ mode (4° ≤ 2Θ ≤ 55°) on a colorless crystal of about 0.5 × 0.6 × 0.9 mm yielded 4460 reflections, which after merging the symmetry equivalents, gave 4169 independant reflections with 3150 observations with $I > 2\sigma(I)$[14]. After solving the structure by direct methods[15] a final full-matrix least-squares refinement against F^2 [16] of all 4169 reflections resulted in $wR2$ = 0.1773 and $R1$ (obs. refl. only) = 0.0526 for 199 variables, using a "riding" model for the hydrogen atoms with $U(H) = 1.3U_{eq}(C)$. A final difference Fourier map gave min./max. residual electron densities of −0.72/0.50 e Å^{-3}[17].

X-ray Crystallographic Study of **2b**: $C_{12}H_{43}Na_2O_{15}P_3$; formula mass 566.35 g mol^{-1}; monoclinic space group $P2_1/c$ (no. 14); a = 10.869(1), b = 31.139(4), c = 9.123(1) Å; β = 114.59(1)°; V = 2807.7(5) Å^3; Z = 4; $d_{calcd.}$ = 1.340 Mg m^{-3}; μ(Mo-K_α) = 0.301 mm^{-1}; $F(000)$ = 1208. Siemens P3 (upgraded Syntex P2$_1$) diffractometer, Mo-K_α radiation (λ = 0.71073 Å), graphite monochromator. Data collection at room temperature in ω/2Θ mode (4° ≤ 2Θ ≤ 55°) on a colorless crystal of about 0.2 × 0.5 × 0.6 mm yielded 6791 reflections which after merging the symmetry equivalents gave 6405 independant reflections with 4930 observations with $I > 2\sigma(I)$[14]. After solving the structure by direct methods[15] a final full-matrix least-squares refinement against F^2 [18] of all 6405 reflections resulted in $wR2$ = 0.1190 and $R1$ (obs. refl. only) = 0.0404 for 362 variables. For the H atoms of the methyl groups, a riding model with $U(H) = 1.3U_{eq}(C)$ was used, while the H atoms of the water molecules, all being involved in hydrogen bonds, were refined independently with isotropic temperature factors. A final difference Fourier map gave min./max. residual electron densities of −0.67/1.50 e Å^{-3}[17].

Starting materials were mostly prepared according to methods reported in the literature: $(Me_3SiO)_3P$[19], tBuP(O)Cl_2[20][21], 2-$MeC_6H_4P(O)Cl_2$[22][23][24], 2,4,6-$Me_3C_6H_2P(O)Cl_2$[24][25], tBuP(O)(O-$SiMe_3)_2$[26], *N*-benzyloxycarbonylglycine[27].

Bis(trimethylsilyl) 2-Methylphenylphosphonate: Following the procedure of Issleib et al.[28] 16 mmol of $(Me_3SiO)_3P$ was added dropwise with stirring to a mixture of 16 mmol of 2-bromotoluene and 0.8 mmol of anhydrous $NiCl_2$ at 160°C. The Me_3SiBr formed in the reaction was continuously distilled off and the residue distilled in vacuo. Colorless, hydrolyzable liquid, b.p. 94°C/0.2 Torr; yield 57%. − $C_{13}H_{25}O_3PSi_2$ (316.5): calcd. C 49.34, H 7.96; found: C 48.95, H 7.86. − EI-MS; *m/z* (%): 316 (30). − $^{31}P\{^1H\}$ NMR (neat): δ = 0.52 (s). − ^1H NMR (C_6D_6): δ = −0.63 (d, $^4J_{PH}$ = 1.16, OSi*Me*$_3$), 1.79 (s, C_6H_4*Me*), 6.24 (m, C_6*H*$_4$Me), 7.37 (m).

Bis(trimethylsilyl) 2,4,6-Trimethylphenylphosphonate: Preparation as before from 21 mmol of $(Me_3SiO)_3P$, 21 mmol of 2,4,6-$Me_3C_6H_2Br$, and 1 mmol of $NiCl_2$; yield 41%. Colorless, hydrolyzable liquid, b.p. 91°C/0.15 Torr, m.p. 39°C. − $C_{15}H_{29}O_3PSi_2$ (344.5): calcd. C 52.29, H 8.48; found C 52.08, H 7.51. − EI-MS; *m/z* (%): 344 (34). − $^{31}P\{^1H\}$ NMR (toluene): δ = 4.5 (s). − ^1H NMR (C_6D_6): δ = 0.45 (s, OSi*Me*$_3$), 2.24 (s, C_6H_2*Me*$_3$), 3.06 (s) (intensity ratio 1:2), 6.98 (d, C_6H_2).

tert-Butylphosphonic Anhydride **1a**: A mixture of 50 mmol of tBuP(O)Cl_2 and 50 mmol of tBuP(O)$(OSiMe_3)_2$ was heated for 8 h at 170−180°C and the Me_3SiCl formed was continually distilled off. Subsequently, the reaction product was heated for another 3 h at 110°C in vacuo in order to remove unreacted starting materials, and crystallized from toluene/pentane; yield 46%. Colorless crystals, m.p. 166°C, 150−152°C[6]; 194−195°C[3]. − $C_{12}H_{27}O_6P_3$ (360.3): calcd. C 40.01, H 7.55, P 25.79; found C 39.89, H 7.56, P 25.71. − Mol. mass (cryoscopic in benzene): 358 (0.031 molal), 375 (0.089 molal). − EI-MS; *m/z* (%): 360 (3), 304 (80), 248 (67), 192 (19), 57 (100). − $^{31}P\{^1H\}$ NMR ($CDCl_3$): AB_2 spin system, δ_A = 24.23, δ_B = 23.83, $J_{AB} = {}^2J_{PP}$ = 50.6, δ = 24.12 (s, $CDCl_3$)[6], 31.16 (s, C_6D_6)[3]. − $^1H\{^{31}P\}$ NMR (C_6D_6): δ = 1.43 (s), 1.32 (s), intensity ratio 1:2.

2-Methylphenylphosphonic Anhydride (**1b**): 13 mmol of 2-Me-$C_6H_4P(O)(OSiMe_3)_2$ and 13 mmol of 2-$MeC_6H_4P(O)Cl_2$ in 40 ml of toluene were heated so that the Me_3SiCl which formed and small amounts of toluene were continually distilled off. At the end of the reaction the distillate consisted solely of toluene. After concentrating the solution, **1b** was precipitated by slow addition of ligroin (100−140°C); yield 97%. Colorless, very hydrolyzable crystals, m.p.

123−125°C. − $C_{21}H_{21}O_6P_3$ (462.3): calcd. C 54.65, H 4.58, P 20.10; found C 54.34, H 4.38, P 19.90. − Mol. mass (cryoscopic in benzene): 458 (0.085 molal), 462 (0.112 molal). − EI-MS; *m/z* (%): 462 (100), 309 (19), 155 (28). − $^{31}P\{^1H\}$ NMR (C_6D_6): AB_2 spin system, $\delta_A = 1.99$, $\delta_B = -0.46$; $J_{AB} = {}^2J_{PP} = 42.6$. − ^1H NMR (C_6D_6): δ = 2.72 (s, CH_3), 3.01 (s), intensity ratio 2:1; 7.04 (m, C_6H_4), 8.25 (m), 8.65 (m).

2,4,6-Trimethylphenylphosphonic Anhydride (**1c**): Preparation as mentioned before from 20 mmol of $2,4,6\text{-}Me_3C_6H_2P(O)(OSiMe_3)_2$ and 20 mmol of $2,4,6\text{-}Me_3C_6H_2P(O)Cl_2$ in 70 ml of toluene. The anhydride formed is only sparingly soluble in toluene, and was thus precipitated in the course of the reaction as colorless hydrolyzable crystals that could be used without further purification; yield 58%, m.p. 250°C. − $C_{27}H_{33}O_6P_3$ (546.5): calcd. C 59.34, H 6.09, P 17.00; found C 59.02, H 5.83, P 17.00. − EI-MS; *m/z* (%): 546 (100), 364 (38), 183 (40). − $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 1.48 (s). − ^1H NMR ($CDCl_3$): δ = 2.34, 2.59, 2.81 (intensity ratio 2:4:3, CH_3); 6.97, 7.04 (C_6H_2), (in all cases broad signals).

Tris(tert-butyl)triphosphonic Acid (**2**): A solution of 40 mmol of **1a** in 150 ml of ethanol, containing 40 mmol of H_2O, was heated at 60°C for 3 h. After evaporation of the solvent, the residue is washed with ligroin (100−140°C) and dried in vacuo; yield 54%. Colorless, crystalline powder, soluble in $CHCl_3$, MeOH, EtOH, or water, m.p. 152°C. − $C_{12}H_{29}O_7P_3$ (378.3): calcd. C 38.01, H 7.73, P 24.56; found C 38.02, H 7.87, P 24.30. − The acid is associated via hydrogen bonds. − IR (KBr): $\tilde{\nu} = 2663\ cm^{-1}$, $2298\ cm^{-1}$, $1654\ cm^{-1}$. − Mol. mass (osmometric in $CHCl_3$, 37°C): 609 (0.063 molal, 672 (0.123 molal). − $^{31}P\{^1H\}$ NMR (C_6D_6): AB_2 spin system, $\delta_A = 20.31$, $\delta_B = 31.05$; $J_{AB} = {}^2J_{PP} = 49.3$. − ^1H NMR ($CDCl_3$): δ = 1.30 (d, $^3J_{PH} = 18.2$, PCMe), 1.36 (d, $^3J_{PH} = 19.6$), intensity ratio 2:1, 11.84 (s, OH).

Disodium Salts of Tris(tert-butyl)triphosphonic Acid, Dihydrate (**2a**) *and Octahydrate* (**2b**): After neutralization of 5 mmol of **2** in 10 ml of H_2O with 1 M NaOH, the resulting sodium salt was precipitated by adding acetone. Crystallization from acetone/water and drying at 20°C in vacuo afforded **2a** as shiny small leaflets that are readily soluble in water; yield practically quantitative. **2b** was obtained as transparent plates, m.p. > 300°C, from a concentrated solution of the disodium salt in H_2O by diffusion-controlled precipitation with acetone, and drying in vacuo at 20°C. − $C_{12}H_{27}Na_2O_7P_3 \cdot 2\ H_2O$ (458.3): calcd. C, 31.45; H, 6.82; P, 20.28; found C, 31.17; H, 6.63; P, 20.05. − $C_{12}H_{27}Na_2O_7P_3 \cdot 8\ H_2O$ (566.4): calcd. C, 25.45; H, 7.65; found C, 25.60; H, 7.58. − According to the results of thermogravimetric measurements, both hydrates loose their water of crystallization completely between 80−100°C. − $^{31}P\{^1H\}$ NMR (D_2O): AB_2 spin system, $\delta_A = 19.80$, $\delta_B = 29.50$; $J_{AB} = {}^2J_{PP} = 49.7$. − ^1H NMR (D_2O): δ = 1.16 (d, $^3J_{PH} = 16.9$, PC*Me*), 1.27 (d, $^3J_{PH} = 18.91$), intensity ratio 2:1.

Bis(tert-butyl)diphosphonic Acid (**3**): After heating 2.6 mmol of **2** with 10 ml of conc. hydrochloric acid for 1 h, the clear solution was cooled to room temperature. The resulting precipitate was filtered off and dried in vacuo at 20°C. Crystallization from toluene afforded colorless needles, m.p. 198−200°C that are soluble in acetone and sparingly soluble in H_2O; yield 23%. − $C_8H_{20}O_5P_2 \cdot 1.5\ H_2O$ (285.2): calcd. C 33.68, H 8.07, P 21.73; found C 33.28, H 8.16, P 21.45. − EI-MS; *m/z* (%): 459 (11), 259 (22), 202 (100), 146 (33), 138 (51), 123 (12), 83 (20), 57 (83). − $^{31}P\{^1H\}$ NMR ([D$_6$]acetone): δ = 32 (s). − ^1H NMR ([D$_6$]acetone): δ = 1.40 (m, PCMe); 4.55 (s, br., POH).

tert-Butylphosphonic Acid can be isolated from the filtrate by concentration and crystallization of the residue from toluene; yield 72%; colorless needles, m.p. 188−190°C (see ref.[30] 191°C), soluble in H_2O or acetone. − $^{31}P\{^1H\}$ NMR ([D$_6$]acetone): δ = 39.50 (see ref.[30] 37.00, [D$_6$]acetone).

Disodium Salt **3a**: A solution of EtONa from 28.4 mmol of Na in 20 ml of EtOH was added dropwise to 7.1 mmol of **1a** in 20 ml of EtOH. After heating for 1 h, the sodium salt formed was filtered off and dried in vacuo at 20°C; yield 57%. Colorless needles from water/acetone, m.p. > 320°C. Loss of weight between 80−110°C: 15.5% (TG), calcd.: 15.16%. − $C_8H_{18}Na_2O_5P_2 \cdot 3\ H_2O$ (356.2): calcd. C 26.98, H 6.79, P 17.39; found C 26.78, H 6.82, P 17.39. − $^{31}P\{^1H\}$ NMR (D_2O): 26.30 (s). − ^1H NMR (D_2O): $[AX_9]_2$ spin system centered at δ = 1.13. − ^{13}C NMR (D_2O): X-part of an AA′X spin system centered at δ = 33.91, coupling constants obtained according to ref.[29]: $^2J_{PP} = 48.6$; $^1J_{PC} = 144.5$; $^3J_{PC'} = 2.0$.

Reaction of **1a** *with N-Benzyloxycarbonylglycine* (**4**): 10 mmol of **4** in 20 ml of methanol was added to a heated solution of 10 mmol of **1a** in 10 ml of methanol. After boiling the mixture for 3 h, the solvent was removed in vacuo at room temperature. The residue was a highly viscous, colorless liquid. − $^{31}P\{^1H\}$ NMR ($CDCl_3$): AX_2 spin system $\delta_A = 21.30$ (t); $\delta_X = 31.30$ (d); $J_{AX} = 49.3$; two AMX spin systems $\delta_A = 22.10$ (t); $\delta_M = 30.40$ (d); $\delta_X = 33.70$ (d); $J_{AM} = 48.3$; $J_{AX} = 46.9$ and $\delta_A = 21.80$ (t); $\delta_M = 30.60$ (d); $\delta_X = 33.10$ (d); $J_{AM} = 47.7$; $J_{AX} = 47.2$ Hz. − ^1H NMR ($CDCl_3$): δ = 1.06−1.56 ($PCCH_3$); 3.51−3.80 (C*H*$_2$COOH); 4.00−4.06 ($COCH_3$); 5.17 (C_6H_5C*H*$_2$); 7.24−7.53 (C$_6$*H*$_5$CH$_2$); 9.50−9.70 (s, br., OH). − GC-MS of **6**; *m/z* (%): 223(9), 108(80), 91(100).

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