Cyclic Oligophosphonic Anhydrides Stable in Aqueous Media

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Abstract

Amides, Phosphonylation, 1-Alkylaminoalkane-1,1,3,3-tetrayl-tetrakis-phosphonic Anhydrides, Cyclic Dimeric Anhydrides, 1-Aminoalkylidene-1,1-bis-phosphonic Acids

Depending on reaction conditions, the phosphonylation of N-alkylacetamides with H₃PO₃–PCl₃ in B–HCl media (B = Py, Bu₃N) gives either 1-alkylaminoethylidene-1,1-bis-phosphonic acids (1a–e) or previously unknown 1-alkylaminobutane-1,1,3,3-tetrayl-tetrakis-phosphonic dianhydrides (2a–e). The latter convert into monocyclic forms (3a–e) under mild acidic hydrolysis. Acyclic forms (4a–e) cannot be isolated. In the presence of higher N,N-dialkylamides the phosphorylation of acetamides affords the higher dianhydrides (2f–h). Strong acidic hydrolysis of 2 or 3 yields 3,3-diphosphonocarboxylic acids (5a–c). Reacting with H₃PO₃–PHal₃ in B–HHal (Hal = Cl, Br), the amides R’CONHR₂ (R₁ = H, Me; R₂ = Alk, H) give both N-alkyl- (or N-unsubstituted) 1-aminoalkylidene-1,1-bis-phosphonic acids (6a–j) and their cyclic dimeric anhydrides (7a–g, i, j).

Oligophosphonates have many applications owing to their chelating ability [1]. The phosphorylation of carboxylic acids [2, 3] or their nitrogen-containing derivatives (amides, nitriles) [4, 5] with H₃PO₃–PHal₃ systems is the most applicable method for the synthesis of two important classes of oligophosphonates, namely 1-hydroxy- and 1-aminoalkylidene-1,1-bis-phosphonic acids. The main feature of these related reactions is the necessity for dehydrating conditions (the reaction mixtures should be capable of binding ≥ 1 mol of water per 1 mol of trivalent phosphorus entered into the reaction, otherwise, the yields of the bis-phosphonic acids decrease dramatically, cf. [5]). As a result, polycondensation of the reaction products occurs, leading to thickening and even to solidification of the reaction mixtures. Ineficient mixing of reactants does not allow high yields of the phosphorylation products to be obtained. Dilution of the reaction mixtures with an excess (from 2- to 3-fold over the stoichiometric ratio) of acyl-containing component is only successful in the phosphorylation of some lower carboxylic acids, but fails in the case of amides.

Previously [6], we proposed the use of amine hydrohalides (salts of tri- and dialkylamines, pyridine, etc.) as diluents of reaction mixtures in the phosphorylation of carboxylic acids and formamides. The use of amine hydrohalides (from 30 to 300% by weight relative to the acyl-containing component) was shown to prevent the solidification of the reaction mixtures and to increase the yields of the desired bis-phosphonic acids. No unusual products were observed. In contrast, the application of this method to amides other than formamides gave a series of unexpected products.

Results

The reaction with amides was carried out at 80–100 °C using molar ratios (H₃PO₃+PHal₃):amide ≥ 2.5:1 (to ensure sufficient excess of trivalent P) and PHal₃:H₃PO₃ close to 0.85:1 (to create the necessary dehydrating ability of reaction mixtures). As a rule, PCl₃ was used (and amine hydrochlorides, respectively), but in some special cases it was replaced by PBr₃ (and amine hydrobromides). Mostly, the reaction mixtures with PBr₃ showed much weaker activity in the phosphorylation than those with PCl₃, except of the cases which required higher acidity. Hydrohalides of pyridine or tributylamine (from 150 to 500 g per 1 mol of amide) were preferably used, chlorobenzene or o-dichlorobenzene being introduced as additional diluents to further reduce the viscosity of the reaction mixtures. When the reaction was complete, the mixtures were hydrolyzed with an excess of water to destroy the unstable polycondensated products and were analyzed using ³¹P NMR. Yields of the phosphorylation products were calculated for the amides based on the data of NMR spectroscopic analysis.

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The phosphonylation of N-monoalkylacetamides with \( \text{H}_3\text{PO}_3 - \text{PCl} \) under relatively mild conditions (at 80–85 °C) gives after hydrolysis the expected 1-alkylaminothiophenol 1,1-bis-phosphonic acids (1a–e) in high yields. However, an insignificant raise of temperature (by ca. 10 °C) leads to dimerization of 1a–e followed by loss of one alkylamino group and the formation of a bicyclic 1-alkylaminobutane–1,1,1,3,3-tetrayl-tetrakis-phosphonic 1,3,1,3-dianhydrides (2a–e). Under controlled acidic hydrolysis, the latter are converted into the monocyclic forms (3a–e). Both 2 and 3 are stable in neutral or slightly alkaline aqueous solutions and may be isolated either as free acids or as salts.

It should be stressed that not free acids 1, but their oligomeric anhydrides (existing under dehydrating reaction conditions) are the precursors of 2 in this dimerizing phosphonylation of acetamides. Non-anhydride forms of 1 are rather stable compounds and do not change even at much higher temperatures. The tendency to the dimerization grows with increasing steric hindrance created by the N-substituent R. Under the same conditions (83–85 °C, 4 h), N-methyl- and N-butylacetamides form only 1a and 1b, respectively, N-dodecylacetamide gives nearly equal amounts of 1d and 2d, whereas N-cyclohexylacetamide yields almost only 2c. An additional excess of trivalent P is necessary to avoid the formation of 2 in two last cases.

In order to account for this unexpected reaction route, we propose that imine \( \text{CH}_3\text{C}(\text{POX}_2) = \text{NR} \) (POX = means anhydridized POH) is the major intermediate. This imine may form due to both the phosphorylation of acetamide and the reverse dephosphorylation of 1. Tautomerization gives the C-nucleophilic enamine \( \text{CH}_2 = \text{C}(\text{POX}_2) - \text{NHR} \) whereas protonation affords the C-electrophile. Their interaction leads to the formation of a new C–C bond and ultimately yields 2. This supposition is consistent with the above-mentioned influence of the N-substituent on the reaction pathway. Bulky groups R shift the equilibrium of the phosphorylation towards the imine and, hence, increase the rate of dimerization. As one would expect, no C–C bond formation was found to accompany the phosphorylation of N-unsubstituted acetamide.

The rôle of amine hydrochloride appears to be to lower the acidity of the reaction medium, thus favouring the formation of the enamine. The unusual sensitivity of the reaction to the raise of temperature may be explained by the same reason. Heating the reaction mixtures (even by 10 °C) significantly decreases the concentration of dissolved HCl, thus lowering the acidity and activating the conversion of 1 into 2. High molar concentrations of amine hydrochlorides appreciably accelerate the dimerizing phosphorylation and increase the yields of 2. Pyridine hydrochloride seems to be the best medium for this reaction because of its low molecular mass and high liquidizing ability. The replacement of PCl3 by PBr3 increases the acidity and prevents the dimerization of 1.

When N-alkylacetamides are introduced into the reaction in the presence of higher N,N-dialkylamides (which cannot yield any stable phosphorylation products without C–N bond rupture), the latter provide the major part of C-electrophilic species. Therefore, the higher cyclic anhydrides (2f–h) become the main products.
obtained using two-stage heating. At the first stage the mixtures should be kept at lower temperatures, which exclude formation of 2. The temperature ought to be raised only after complete conversion of the N-alkylacetamide into the corresponding 1.

The reaction of N-butylacetamide with equimolar amounts of various N,N-dialkylcaprylamides is found to depend also on the radicals R² and R³. Under the best found reaction conditions, the molar ratio 2f:2b is 14:1 for R²=R³=(CH₂)₄, 3:1 for R²=R³=Me and 1:1 for R²=R³=(CH₂)₅. Both phenomena are in agreement with our suggestions concerning the reaction mechanism. Complete conversion of N-alkylacetamide into 1 decreases the concentration of the imine to the equilibrious one, thus retarding the formation of 2b, e to a greater extent than that of 2f-h. Sterically unhindered N-acylpyrrolidine affords the most reactive C-electrophilic species.

Similarly to the lower homologues 2a-e, the anhydrides 2f-h undergo hydrolysis to the monocyclic forms (3f-h), but significantly (by ca. an order of magnitude) slower. This is apparently due to relative stabilization of the bicyclic form when both the radicals R and R¹ are rather bulky. When only the N-substituent is bulky (e.g. for 2d), the hydrolysis is not retarded appreciably.

The ³¹P(¹H) decoupled NMR spectra of 2 (Table I) show a picture typical of AA'BB' systems, which may be approximately described as two dd, with several small peaks being neglected. The spectra of 3 (Table II) exhibit four sorts of ³¹P and three marked coupling constants. Assignment of ³¹P signals in both cases is based on proton couplings. The ³¹P signals coupled with the greater

### Table I. ³¹P NMR data for 2a-h

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R¹</th>
<th>δ [ppm]</th>
<th>J[Hz]</th>
<th>AB</th>
<th>AB'</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>+15.1</td>
<td>21</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>Bu</td>
<td>Me</td>
<td>+14.8</td>
<td>21</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>cyclo-C₆H₁₃</td>
<td>Me</td>
<td>+14.8</td>
<td>21</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>C₆H₁₅</td>
<td>Me</td>
<td>+14.7</td>
<td>21</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2e</td>
<td>PhCH₂</td>
<td>Me</td>
<td>+14.1</td>
<td>22</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>Bu</td>
<td>C₆H₁₅</td>
<td>+13.5</td>
<td>23</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2g</td>
<td>Bu</td>
<td>C₁₁H₁₃</td>
<td>+13.3</td>
<td>23</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2h</td>
<td>PhCH₂</td>
<td>C₆H₁₅</td>
<td>+13.5</td>
<td>23</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

* Compound was not isolated; ³¹P chemical shifts depend on Et₂NH quantity, variations up to 0.5 ppm are possible.

### Table II. ³¹P NMR data for 3a-h

<table>
<thead>
<tr>
<th>Compound</th>
<th>δ [ppm]</th>
<th>p²</th>
<th>p³</th>
<th>p⁴</th>
<th>J[Hz]</th>
<th>p¹p³</th>
<th>p¹p²</th>
<th>p¹p⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>+20.9</td>
<td>+19.1</td>
<td>+8.5</td>
<td>+8.1</td>
<td>27</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>+21.5</td>
<td>+19.0</td>
<td>+8.9</td>
<td>+8.1</td>
<td>27</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>+21.3</td>
<td>+19.5</td>
<td>+7.7</td>
<td>+9.0</td>
<td>27</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>+21.8</td>
<td>+19.1</td>
<td>+9.0</td>
<td>+8.1</td>
<td>27</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>+22.5</td>
<td>+18.8</td>
<td>+9.2</td>
<td>+7.7</td>
<td>25</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>+21.3</td>
<td>+19.1</td>
<td>+9.1</td>
<td>+8.3</td>
<td>25</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3g</td>
<td>+21.3</td>
<td>+18.9</td>
<td>+9.1</td>
<td>+8.5</td>
<td>25</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3h</td>
<td>+21.8</td>
<td>+19.1</td>
<td>+9.2</td>
<td>+8.1</td>
<td>25</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Compound was not isolated; ³¹P variations up to 0.7 ppm.
number of protons are assigned to the atoms in 3-position relative to the amino group. Only one of the two possible diastereomers is detected in the spectra of both pure 3 and their reaction mixtures.

The phosphorylation of N-dodecylacetoacetamide with H₃PO₄ − PCl₃ has been found to give 2d in a high yield. This eliminates all doubts concerning the structure of anhydrides 2 and 3. However, it is hardly probable for N-alkylacetamide to be precursors of 2 in the dimerizing phosphorylation. N-Alkylation amides fail to dimerize when being heated with H₃PO₄ − PCl₃ under conditions similar to those of their reaction with H₃PO₄ − PCl₃. Evidently, the phosphorylation of acetamides really precedes the formation of a new C−C bond.

In acidic media the anhydrides 3a−e undergo reversible ring-opening, giving non-anhydride forms (4a−e). Rough estimations show that the equilibrium ratios of 4:3 hardly exceed 1:4. An excess of KOH gives rise to practically a full conversion of 3a into 4a, but at lower pH reverse cyclization occurs. Evidently, none of 4 can be isolated. ³¹P NMR data for 4a−e (Table III) have been obtained from the spectra of their mixtures with corresponding 3. Higher anhydrides 3f−h produce negligible amounts of acyclic forms.

Hydrolysis of 2 or 3 with refluxing azeotropic HCl or HBr leads to the elimination of alkylamine and two H₃PO₄ molecules, which yields 3,3-diphosphonocarboxylic acids (5a−c).

Formation of 5 is accompanied by a side reaction, giving H₂PO₄ and unidentified reduction products (probably 1-alkylaminoalkane-1,3,3-triyphosphonic acids). The latter are resistant to hydrolysis and complicate the subsequent isolation of 5. The more bulky R and the less bulky R', the higher the yields of 5 in destruc­tion of 3 is most likely due to rapid debenzylation of the latter under the reaction conditions. Solely 5a is isolated, the formation of 5b, c is detected only by NMR.

So far, all attempts to introduce N-monoalkylamides of other aliphatic carboxylic acids into reactions similar to the dimerizing phosphorylation of acetamides have failed. Reactions of

Table III. ³¹P NMR data for 4a−e.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>δ [ppm] (multiplicity, Jₚₚ [Hz])</th>
<th>P¹</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Me</td>
<td>+24.2 (sext., 15) +12.9 (t, 13)</td>
<td>+24.0 (sext., 15) +13.1 (t, 12)</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>Bu</td>
<td>+24.1 (sext., 14) +13.1 (t, 12)</td>
<td>+24.0 (sext., 14) +13.6 (t, 12)</td>
<td></td>
</tr>
<tr>
<td>4c</td>
<td>cyclo-C₆H₄</td>
<td>+24.0 (sext., 15) +12.5 (t, 12)</td>
<td>+24.0 (sext., 15) +12.8 (t, 12)</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>C₆H₅</td>
<td>+24.0 (sext., 15) +12.5 (t, 12)</td>
<td>+24.0 (sext., 14) +12.8 (t, 12)</td>
<td></td>
</tr>
<tr>
<td>4e</td>
<td>PhCH₂</td>
<td>+24.0 (sext., 14) +12.8 (t, 12)</td>
<td>+24.0 (sext., 14) +12.8 (t, 12)</td>
<td></td>
</tr>
</tbody>
</table>

Table IV. Strong acidic hydrolysis of 2 and 3 to 5a−c.

<table>
<thead>
<tr>
<th>Starting compound</th>
<th>Azeotropic HHal (volume a [mL])</th>
<th>Time of refluxing [h]</th>
<th>Product (yield)</th>
<th>³¹P NMR for 5 δ [ppm] (Jₚₚ [Hz])</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a · Py</td>
<td>HCl (14)</td>
<td>31</td>
<td>5a (73%)</td>
<td>+23.5 (sext., 15)</td>
</tr>
<tr>
<td>3a · Py</td>
<td>HBr (10)</td>
<td>14</td>
<td>5a (78%)</td>
<td></td>
</tr>
<tr>
<td>3b · 3 H₂O</td>
<td>HBr (10)</td>
<td>14</td>
<td>5a (92%)</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>HCl (14)</td>
<td>6.5</td>
<td>5a (97%)</td>
<td></td>
</tr>
<tr>
<td>2f · PhNH₂ · 3 H₂O</td>
<td>HBr (25)</td>
<td>30</td>
<td>5b (79%)</td>
<td>+23.1 (quint., 14)</td>
</tr>
<tr>
<td>2g</td>
<td>HBr (40)</td>
<td>30</td>
<td>5c (80%)</td>
<td>+23.0 (quint., 14)</td>
</tr>
<tr>
<td>3h · 3 H₂O</td>
<td>HBr (40)</td>
<td>30</td>
<td>5b (52%)</td>
<td></td>
</tr>
</tbody>
</table>

a Per 1 g of starting compound; b solvate with i-PrOH (M = 536.0); c non-stoichiometric PhNH₂ salt (M = 780).
these, and also of the aromatic N-monoalkylamides with H₃PO₃–PBr₃, afford oligomeric anhydrides of ordinary 1-alkylaminoalkylidene-1,1-bis-phosphonic acids. However, in most cases hydrolysis of the reaction mixtures gives only low yields of monomers (6a–h), the major products being previously unknown cyclic dimers (7a–g) stable to hydrolysis. None of other phosphorylation products are formed under mild reaction conditions. The yields of 7 (Table V) depend on both R¹ and R². Despite the limited number of tested amides, some regularities may be marked. Small R² and relatively large R¹ favour the formation of 7. When the length of R² is more than a certain critical value, no 7 forms. E.g., N-hexylvaleramide yields mainly dimer 7g, whereas N-octylvaleramide gives only monomeric 6h. The critical length of R² should, clearly, depend on R¹. Since such dimeric anhydrides have never been observed in the mentioned reaction mixtures of acetamides, for R¹=Me the length of any substituent R² already exceeds the critical value.

![Chemical structure diagram](image)

Under dehydrating reaction conditions, N-unsubstituted amides transform into nitriles. With the exception of lower homologues, the latter are hardly capable of phosphorylation with H₃PO₃–PBr₃ due to low acidity of the reaction medium. The use of the H₃PO₃–PBr₃ system succeeds in phosphorylation of higher unsubstituted amides or nitriles and gives dimers (7i, j) in high yields. The reaction time should be long enough, otherwise the known monomeric acids (6i, j) become the major products. Propionamide and propionitrile form none of the expected lower dimeric anhydrides, the known 1-aminopropylidene-1,1-bis-phosphonic acid being the only detectable product. As regards the phosphorylation of N-alkylacetamides, the system H₃PO₃–PBr₃ shows much weaker reactivity as compared to H₃PO₃–PBr₃, giving lower yields of dimers 7a–g.

The formation of dimers 7 in the previously rather well studied reaction [7] requires some explanations. We suppose that two sorts of 1-amino-1-N-alkylaminoalkylidene-1,1-bis-phosphonic anhydrides may exist under dehydrating conditions of the phosphorylation. In aqueous medium one of them undergoes rapid hydrolysis to monomeric 6, whereas another (namely 7) remains unchanged. The ratio between these two sorts of anhydrides seems to be under thermodynamic con-

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Table V. Phosphonylation of the N-alkylamides R¹CONHR² with H₃PO₃–PBr₃ and 3¹P NMR data for the reaction products.

<table>
<thead>
<tr>
<th>Starting amide R¹</th>
<th>R²</th>
<th>Products (yields²)</th>
<th>³¹P NMR data δ [ppm] (multipl.³, Jₚₚ [Hz]) for monomer</th>
<th>for dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>Me</td>
<td>6a (10%)</td>
<td>7a (85%)⁴</td>
<td>+12.0 (t, 13) +6.3 (m)</td>
</tr>
<tr>
<td>Bu</td>
<td>Me</td>
<td>6b (8%)</td>
<td>7b (88%)⁴</td>
<td>+11.8 (t, 11) +6.7 (m)</td>
</tr>
<tr>
<td>C₃H₅</td>
<td>Me</td>
<td>6c (9%)</td>
<td>7c (89%)⁴</td>
<td>+12.2 (t, 11) +7.0 (m)</td>
</tr>
<tr>
<td>C₆H₁₃</td>
<td>Me</td>
<td>6d (7%)¹</td>
<td>7d (91%)⁴</td>
<td>+12.4 (t, 11) +7.2 (m)</td>
</tr>
<tr>
<td>2-Me–C₆H₄</td>
<td>Me</td>
<td>6e (5%)</td>
<td>7e (82%)⁴</td>
<td>+13.4 (s) +7.0 (s)</td>
</tr>
<tr>
<td>Bu</td>
<td>Bu</td>
<td>6f (11%)</td>
<td>7f (85%)⁴</td>
<td>+11.6 (t, 12) +6.4 (m)</td>
</tr>
<tr>
<td>Bu</td>
<td>C₃H₁₃</td>
<td>6g (25%)</td>
<td>7g (70%)⁴</td>
<td>+12.2 (t, 12) +6.9 (m)</td>
</tr>
<tr>
<td>Bu</td>
<td>C₆H₁₇</td>
<td>6h (94%)</td>
<td>–</td>
<td>+12.5 (t, 12) –</td>
</tr>
</tbody>
</table>

² Based on ³¹P NMR analysis; ³ with ¹H decoupled all signals are singlets; ⁴ only 6h was isolated; ⁴ additionally, the probable minor isomer (3%) is observed at 4.4 ppm; ⁴ probable minor isomer (< 2%) at 4.5 ppm; ³ only precipitate was analyzed.
control. Probably, high concentrations of amine hydrohalides increase the stability of 7. Low viscosity of the reaction media accelerates the rearrangement of the labile sort into the stable one.

The water solubility of free acids 7 and their salts is significantly lower than that of corresponding 6. The $^{31}$P NMR spectra of 7 indicate the equivalency of all P atoms, the $^{31}$P signals (at 6–7 ppm for $7a$–$g$ and 11–12 ppm for $7i$, $j$) being shifted by ca. 5 ppm upfield relative to those of 6 with the same substituents. Mainly one of the two possible diastereomers of 7 is realized. Probably, the minor diastereomers exist in the reaction mixtures of 7a–c (additional $^{31}$P signals at 4–5 ppm), but in negligible amounts.

The anhydrides 7 remain unchanged for at least 5 h at 100 °C in aqueous solutions as the free acid forms and also as salts, even in the presence of 1 M KOH. The relatively soluble 7f undergoes rapid hydrolysis to 6f on refluxing in azeotropic HCl. This method, however, fails for most of the anhydrides 7, which are practically insoluble in HCl. Hydrolysis to $\text{KOH}$. The relatively soluble 7f undergoes rapid formation and also as salts, even in the presence of 1 M equiv.

Diastereomers exist in the reaction mixtures of 7. Probably, the minor diastereomers of 7 is realized. Probably, the minor diastereomers exist in the reaction mixtures of 7a–c (additional $^{31}$P signals at 4–5 ppm), but in negligible amounts.

The structure of 7 as cyclic anhydrides of 6 is reasonably demonstrated by the data given. As regards their dimeric composition, the only convincing proof comes from pH-metric titration which points to the absence of low-acidic phosphonate protons and to the presence of ammonium protons of two types with different acidities; the high-acidic phosphonate protons and each type of ammonium protons are in a 2:1:1 ratio.

**Experimental**

$^1$H and $^{31}$P NMR spectra were obtained with a JEOL FX-90Q or (when necessary) with a Bruker AM-250 spectrometer (for $^{31}$P 36.27 and 101.25 MHz, respectively). To attain reproducible results, all the $^{31}$P NMR spectra were recorded in $\text{D}_2\text{O}/\text{H}_2\text{O}$ with $\text{Et}_2\text{NH}$ buffer at pH = 10.5–11.5, reference $\text{H}_3\text{PO}_4$, downfield shifts being positive. Small amounts (5–10 mg) of EDTA or CyDTA complexes were introduced into the samples to avoid the broadening of $^{31}$P signals by occasional paramagnetic cations.

TLC of 2, 3 (except of lower homologues) and 7 was performed on the Silufol plates in a mixture of $\text{n-C}_6\text{H}_{13}\text{OH}$, water, $\text{Et}_2\text{NH}$ and Py (equal volumes), spots were detected by spraying with a mixture of water (50 ml), Xylenolorange indicator (40 mg), FeCl$_3•6\text{H}_2\text{O}$ (10 mg) and $\text{CCl}_3\text{COOH}$ (0.5 g). For lower 2 and 3 the method [8] (solvent 1) was usually more suitable. The only method found for TLC analysis of 5a was PC according to Thilo [9] in the acidic solvent C. The melting points were determined only in some cases since this method was found to be inappropriate to characterize the majority of compounds. An additional proof of the oligophosphonate structures was obtained from pH-meter titration, a difference of <2% was permitted between the alkali equivalents found and those calculated.

Phosphorylation mixtures of $\text{H}_3\text{PO}_3$, amine hydrohalides and PHal$_3$, were prepared from the corresponding amounts of conc. aqueous HHal, free amines and PHal$_3$. Caution! To avoid the disproportionation of $\text{H}_3\text{PO}_3$ and the formation of a pyrophorous yellow polymer with a red phosphorus like structure, it is necessary to maintain the mixtures always strong acidic. An additional organic solvent was added prior to other components to diminish PHal$_3$ loss and self-heating of the reaction mixtures. The phosphorus losses were determined and taken into account in the NMR spectroscopic analysis. Usually, they were within the range 1–12%.

**N-Dodecylacetatoacetamide**

The compound was prepared according to [10], m.p. 86–87 °C.

$^1$H NMR (CDCl$_3$): δ 0.83 [distorted t, 3 H, CH$_3$ (chain), $J = 5$], 1.21 [m, 20 H, CH$_2$ (chain)], 2.22 (s, 3 H, CH$_3$CO), 3.20 (q, 2 H, NHCH$_3$, $J = 6$), 3.35 (s, 2 H, COCH$_3$CO), 6.95 (br. m, 1H, NH).

**1-Methylaminomethylen-1,1-bis-phosphonic acid (1a)**

A phosphorylation mixture prepared from PhCl (7 ml), 34.4%–HCl (4.56 g containing 2.99 g, 166.0 mmol of water), Py (10.6 g, 133.9 mmol), and PCl$_3$ (9.34 g, 68.0 mmol) was saturated with HCl at 25 °C. N-Methylacetamide (2.92 g, 40.0 mmol) was added, the mixture was heated to 75–85 °C, and the second portion of PCl$_3$ (4.70 g, 34.2 mmol) was dropped in during 0.5 h under intensive stirring. After 4 h stirring at 83–85 °C, water (40 ml) was added, PhCl was removed by steam distillation simultaneously with the hydrolysis of unstable products at 95–100 °C for 2 h, the mixture was filtered and analyzed using $^{31}$P NMR, the result being 34 mmol (85%) of 1a. The filtrate was treated with a cation exchanger of Dowex-50* type (H$^+$ form), the eluate was evaporated in vacuo, and MeOH (45 ml) was added to the residue. After overnight standing, the crystals were filtered off, washed with MeOH, and dried, yield 7.52 g (83%)
of 1a. The product was recrystallized from water-
Et₃N with an excess of HCl and then with EtOH,
m. p. 235–240 °C (decomp.). In [3] no data for 1a
are given to be compared.

1H NMR (D₂O + Na₂CO₃, pH = 6): δ 1.4 (t, 3 H,
CH₃CP₂, J = 14), 2.7 (s, 3 H, NHCH₃). 3¹P NMR:
δ +12.7 (q, J = 13).

C₉H₁₅NO₆P₂ (295.2)
Calcd C 36.62 H 5.12%,
Found C 36.56 H 5.31%.

1-Butylaminoethylidene-1,1-bis-phosphonic acid
(1b)

N-Butylacetamide (4.61 g, 40.0 mmol) was sub­
tected to the abovementioned procedure to yield
37 mmol (92%) of 1b according to ³¹P NMR.
After cation exchange, the evaporated eluate was
crystallized with i-PrOH (55 ml) to give 9.40 g
(90%) of 1b. The product was recrystallized from
water with Me₂CO and dried in vacuo at 90 °C,
m. p. 204–206 °C (decomp.).
³¹P NMR: δ +12.9 (q, J = 13).

C₉H₁₇NO₆P₂ (261.2)
Calcd C 27.59 H 6.56%,
Found C 27.74 H 6.67%.

1-Cyclohexylaminoethylidene-1,1-bis-phosphonic
acid (1c)

N-Cyclohexylacetamide (4.24 g, 30.0 mmol) was
added to a phosphorylation mixture prepared
from PhCl (4 ml), 34.4%-HCl (4.56 g, containing
2.99 g, 166.0 mmol of water), Bu₃N (7.42 g,
40.0 mmol) and PCl₃ (9.34 g, 68.0 mmol). The sec­
ond portion of PCl₃ (4.70 g, 34.2 mmol) was added
dropwise at 75–80 °C during 0.5 h. The mixture
was stirred at 79–81 °C for 3.5 h and, after cool­
ing, hydrolyzed as above with removal of PhCl.
A 33%-Me₂NH aqueous solution (50 ml) was added
to the hydrolyzate, the mixture was extracted with
CHCl₃, the excess of Me₂NH was removed from
the aqueous layer by concentration in vacuo.
The yield of 1c determined by ³¹P NMR was 24 mmol
(80%). A treatment similar to that for 1b gave
6.92 g (78%) of 1c (purification as for 1a). M. p.
225–227 °C (decomp.).
³¹P NMR: δ +12.6 (q, J = 13).

C₉H₁₉NO₆P₂ (287.2)
Calcd C 33.46 H 6.67%,
Found C 33.29 H 6.76%.

1-Dodecylaminoethylidene-1,1-bis-phosphonic acid
(1d)

The reaction components were mixed as in the
synthesis of 1c. N-Dodecylacetamide (6.82 g,
30 mmol) was used, PhCl was replaced by
o-C₆H₄Cl₂ (10 ml). After 4 h stirring at 80–82 °C
and subsequent cooling, water (40 ml) was added,
the mixture was hydrolyzed at 85–95 °C for 5 h,
then diluted with water (300 ml) and 33%-Me₂NH
(150 ml). Higher amines and o-C₆H₄Cl₂ were
extracted with CHCl₃, MeOH (150 ml) being intro­
duced to accelerate separation of the emulsion.
The aqueous layer was concentrated to 200 ml to
remove MeOH and the excess of Me₂NH. Accord­
ing to ³¹P NMR, the solution contained 27 mmol
(90%) of 1d. It was acidified with 35%-HCl
(80 ml), the suspension was refluxed for ca. 1 min
and allowed to stand overnight. The crystals were
filtered off, washed with 5%-HCl, water and
Me₂CO to yield after drying 9.75 g (87%) of 1d.
The product was recrystallized from EtOH –
conc. HCl (20:1 by volume), dried in vacuo at
90 °C, and kept over a saturated NaCl solution to
a. 1D monohydrate, m. p. 207–209 °C
(decomp.).
³¹P NMR: δ +12.8 (q, J = 13).

C₉H₁₉NO₆P₂ (391.4)
Calcd C 42.96 H 9.01%,
Found C 43.14 H 9.16%.

1-Benzylaminoethylidene-1,1-bis-phosphonic acid
(1e)

The phosphorylation mixture was prepared as
for the synthesis of 1a, PhCl being replaced by
o-C₆H₄Cl₂ (8 ml). N-Benzylacetamide (4.48 g,
30.0 mmol) was added, the second portion of PCl₃
(4.70 g, 34.2 mmol) was added dropwise at
75–80 °C during 0.5 h, and the mixture was stirred
at 79–81 °C for 4 h. After cooling, the mixture
was hydrolyzed as in the synthesis of 1a with re­
moval of o-C₆H₄Cl₂. The crystals of 1e were dis­
solved by addition of Et₂NH (45 ml), the solution
was evaporated in vacuo. The residue was diluted
with water and filtered through Polyamide Woelm
TLC®. According to ³¹P NMR, the filtrate con­
tained 22.5 mmol (75%) of 1e. A treatment similar
to that for 1b yielded 6.59 g (74%) of 1e, which
was purified analogously to 1a, m. p. 232–235 °C
(decomp.).

¹H NMR (D₂O + Na₂CO₃, pH = 7): δ 1.6 (t, 3 H,
CH₃, J = 13), 4.4 (s, 2 H, CH₂), 7.4 (s, 5 H, C₆H₅).
³¹P NMR: δ +14.6 (q, J = 13).

C₉H₁₉NO₆P₂ (295.2)
Calcd C 36.62 H 5.12%,
Found C 36.56 H 5.31%.
Bicyclic 1-cyclohexylaminobutane-1,1,3,3-tetrayl-tetrakis-phosphonic anhydride (2c)

N-Cyclohexylacetamide (5.65 g, 40.0 mmol) was added to the phosphorylation mixture similar to that for the synthesis of 1a, the second PC1 portion (4.70 g, 34.2 mmol) was dropped in at 75–80 °C during 0.5 h, the mixture was stirred at 82–84 °C for 6 h, and allowed to cool to 25 °C. Water (150 ml) was added, the mixture was immediately neutralized with Et₂NH (50 ml). PhCl, Py and excess of Et₂NH were removed by evaporation in vacuo. The residue was dissolved in water and filtered. The ³¹P NMR analysis detected 18.4 mmol (92%) of 2c. The filtrate (68 g) was cooled to 0 °C, acidified with cold 35%-HCl (29 ml), diluted with i-PrOH (125 ml) and allowed to stand at 0 °C for crystallization, yielding 8.73 g (81%) of 2c solvate with i-PrOH (M = 536.0 according to pH-metric titration). The product was dissolved in a minimum amount of water, the solution was concentrated in vacuo to 1/4 of the initial volume. The precipitate was filtered off, washed with small portions of water and air-dried to give 2c trihydrate.

C₁₀H₂₅N₂O₈P₄ (493.2)
Calcd C 24.35 H 5.52%,
Found C 24.23 H 5.53%.

Monocyclic 1-methylaminobutane-1,1,3,3-tetrayl-tetrakis-phosphonic anhydride (3a)

N-Methylacetamide (2.92 g, 40.0 mmol) was introduced into the reaction as in the synthesis of 1a. The second portion of PC₁ (4.70 g, 34.2 mmol) was added at 80–93 °C during 0.5 h. The mixture was stirred at 91–93 °C for 9.5 h, hydrolyzed with water (40 ml) at 90–97 °C for 1.5 h, with PhCl being removed, and filtered. The ³¹P NMR spectroscopic analysis detected 18.2 mmol (91%) of 3a and 1.4 mmol (7%) of 4a. The filtrate was evaporated in vacuo up to the end of distillation (bath up to 80 °C). The residue was dissolved in MeOH (50 ml) at 50–60 °C, the crystallization being initiated by rubbing. After continuous standing at 20–25 °C, the crystals were filtered off, washed with MeOH and dried to yield 7.84 g (84%) of 3a monopyridinium salt. The product was reprecipitated from water with Me₂CO and dried in vacuo at 40–50 °C.

C₅H₁₅N₂O₄P₄ (485.2)
Calcd C 19.80 H 5.61%,
Found C 19.79 H 5.80%.

Monocyclic 1-benzylaminobutane-1,1,3,3-tetrayl-tetrakis-phosphonic anhydride (3e)

The reaction of N-benzylacetamide (5.97 g, 40.0 mmol) was carried out similarly to that in the synthesis of 3a. According to ³¹P NMR, 16.6 mmol (83%) of 3e and 2.4 mmol (12%) of 4e were obtained. The isolation (analogous to that for 3b) yielded 7.02 g (67%) of 3e solvate with EtOH (by ¹H NMR, EtOH : 3e = 0.6; according to pH-metric titration, M = 522.0). The product was reprecipitated from water with EtOH, then dissolved in water, and slowly dried up to the crystallization, giving 3e trihydrate.

¹H NMR (D₂O + Na₂CO₃, pH = 9): δ 1.3 (dd, 3H, CH₃, J₁ = 16, J₂ = 13), 2.0–3.0 (br. m, 2H, CP₃CH₂CH₂P), 4.7 and 5.0 (two d, 1H and 1H, diastereotopic NHCH₃ protons, J = 13), 7.4–7.7 (m, 5H, C₆H₅).

C₁₃H₂₅N₂O₄P₄ (519.2)
Calcd C 25.45 H 4.85%,
Found C 25.22 H 4.79%.

Bicyclic (2d) and monocyclic (3d) 1-dodecylaminobutane-1,1,3,3-tetrayl-tetrakis-phosphonic anhydrides

N-Dodecylacetamide (9.09 g, 40.0 mmol) was added to the phosphorylation mixture prepared...
similarly to that for the synthesis of 1a. The second portion of PCl₃ (4.70 g, 34.2 mmol) was added dropwise at 80–96 °C during 0.5 h. The frothy mixture was stirred at 94–96 °C for 10 h and allowed to cool to 25 °C. The reaction mass was suspended in water (200 ml) and CHCl₃ (450 ml), 33%-Me₂NH (250 ml) was added, the aqueous layer was separated and additionally extracted with CHCl₃. The excess of Me₂NH was removed by concentration in vacuo. According to ³¹P NMR, the solution contained 20 mmol (100%) of 2d.

To isolate 2d, the solution (172 g) was cooled to 10 °C, acidified with 35%-HCl (172 ml), and allowed to stand at 15–20 °C for 0.5 h. The voluminous precipitate was filtered off, washed with 18%-HCl, then with Et₂O, and dried over KOH to remove the rest of HCl and water. The cake was suspended in Me₂CO to give 10.14 g (93%) of 2d monoclonal after filtration. The product was reprecipitated from a mixture i-ProOH-water-CF₃COOH (14:2.7:0.7 by volume) with EtOAc and dried in vacuo at 70–80 °C.

C₁₆H₃₇N₂O₁₅P₄ (543.4)
Calcd C 35.37 H 6.86%,
Found C 35.50 H 6.81%.

To isolate 3d, the solution was diluted with water to 1.5 l and treated with a cation exchanger. The eluate (1.9 l) was hydrolyzed at 100 °C for 3.5 h (attaining the full conversion of 2d into 3d) and concentrated to 149 g. After addition of 36%-HCl (86 ml), the mixture was allowed to stand at 20–25 °C for several days. The crystals were filtered off and washed as in the isolation of 2d. The product was dried in vacuo at 50–55 °C and kept over a saturated NaCl solution to yield 10.49 g (88%) of 3d trihydrate.

C₁₆H₄₃N₂O₁₅P₄ (597.4)
Calcd C 32.16 H 7.27%,
Found C 32.20 H 7.38%.

Phosphonylation of N-dodecylacetocetamide

N-Dodecylacetocetamide (5.39 g, 20.0 mmol) was added at 25 °C to a phosphonylation mixture prepared from PhCl (7 ml), 34.4%-HCl (4.56 g containing 2.99 g, 166.0 mmol of water), Py (6.87 g, 86.8 mmol) and PCl₃ (9.34 g, 68.0 mmol). The second portion of PCl₃ (4.70 g, 34.2 mmol) was added dropwise at 85–92 °C during 15 min and the mixture was stirred at 91–93 °C for 6 h. After cooling, the reaction mass was suspended in water (200 ml), mixed with 33%-Me₂NH (250 ml), and extracted with CHCl₃. The aqueous layer was concentrated in vacuo to remove excess Me₂NH and analyzed by ³¹P NMR, the yield being 18.4 mmol (92%) of 2d. The product was isolated as mentioned above.

**Bicyclic 1-butylaminodecane-1,1,3,3-tetratetrakis-phosphonic anhydride (2f)**

The phosphonylation mixture was prepared as in the synthesis of 1a, PhCl being replaced with o-C₆H₄Cl (7 ml). N-Butylacetamide (2.31 g, 20.0 mmol) and N-caprylypyrrolidine (3.95 g, 20.0 mmol) were added simultaneously, the second portion of PCl₃ (4.70 g, 34.2 mmol) at 75–82 °C during 20 min. The reaction mixture was stirred at 81–82 °C for 4 h, then at 91–92 °C for 6 h, and allowed to cool to 25 °C. Water (200 ml) and 33%-Me₂NH (150 ml) were added, the emulsion was extracted with CHCl₃. The aqueous layer was concentrated in vacuo to remove excess Me₂NH and analyzed by ³¹P NMR, the solution contained 14.6 mmol (73%) of 2f and 1.0 mmol (10% calculated on N-butylicetamide) of 2b. To the solution (83 g) a mixture of PhNH₂ (36 ml), water (72 ml) and 35%-HCl (26 ml) was added at 40–45 °C, and the suspension was allowed to stand overnight. The precipitate was filtered off and washed portion-wise with a mixture of PhNH₂ (16 ml), water (25 ml) and 35%-HCl (10 ml). The cake was suspended in a mixture of i-ProOH (50 ml) and PhNH₂ (1 ml), filtered off and washed with i-ProOH to give 10.99 g of crude 2f anilinie salt, which was dissolved in a hot mixture of i-ProOH (160 ml), water (75 ml) and PhNH₂ (25 ml). After cooling to 50–60 °C, the solution was acidified with 35%-HCl (26 ml) and allowed to stand overnight at 20–25 °C for crystallization, to yield 7.63 g (53%) of pure 2f anilinie salt with the molar ratio 2f:PhNH₂ close to 1:2 (M = 715.6 according to pH-metric titration). The product was recrystallized from EtOH-water-PhNH₂ (20:4:1 by volume), dried in vacuo at 110 °C to attain the equimolar 2f:PhNH₂ ratio and kept over a saturated NaCl solution, giving 2f monoanilinie salt trihydrate.

³¹H NMR (D₂O+Na₂CO₃, pH = 8): δ 0.9 [distorted t, 3H, CH₃ (heptyl chain), J = 6]; 1.0 [t, 3H, CH₃ (butyl chain), J = 6]; 1.2–1.8 [m, 16H, CH₂ (aliphatic)], 1.9–2.9 (br. m, 2H, CP₂CH₂CP₂), 3.4 (t, 2H, NHCH₂, J = 7), 6.8–7.4 (m, 5H, C₆H₅).

C₁₂H₄₄N₂O₁₅P₄ (644.5)
Calcd C 37.27 H 6.88%,
Found C 37.07 H 7.12%.
Bicyclic 1-butylaminotetradecane-1,1,3,3-tetrayltetrakis-phosphonic anhydride (2g)

The cross-phosphonylation of N-butylacetamide (2.31 g, 20.0 mmol) with N-laurylpyrrolidine (5.07 g, 20.0 mmol) was carried out as in the synthesis of 2f, the time of stirring at 91–92 °C being reduced to 4 h. The solution of Me$_2$NH salts was obtained as above and analyzed by $^{31}$P NMR, which detected 15.4 mmol (77%) of 2g and 1.9 mmol (19%) on N-butylacetamide of 2b. To the solution (110 g) a mixture of water (150 ml), PhNH$_2$ (47 ml) and 35%-HCl (41 ml) was added, the suspension was allowed to stand for a day at 20–25 °C. The precipitate was filtered off, washed portionwise with a mixture of water (150 ml), PhNH$_2$ (30 ml) and 35%-HCl (26 ml), then with water and Et$_2$O to give 12.66 g of crude 2g aniline salt. The product was refluxed for 1 h with a mixture of i-PrOH (217 ml), water (43 ml) and PhNH$_2$ (14 ml), then hot-filtered to remove any insoluble impurity. The filtrate was acidified with CF$_3$COOH (15 ml) and hot-filtered to remove any insoluble impurity. The precipitate was filtered off, washed with 18%-HCl and with hexane, air-dried, and finally washed with Me$_2$CO to give 5.90 g (49%) of pure 2g aniline salt (non-stoichiometric, M = 780 according to pH-metric titration). The hydrolyzate was evaporated in vacuo, and the residue was treated with Et$_2$O, dried in vacuo at 110 °C, and kept over a saturated NaCl solution, giving 2g monoaniline salt dihydrate.

C$_{24}$H$_{59}$N$_2$O$_3$P$_4$ (682.6)
Calcd C 42.23 H 7.38%,
Found C 42.05 H 7.16%.

Monocyclic 1-benzylaminodecane-1,1,3,3-tetrayltetrakis-phosphonic anhydride (3h)

The cross-phosphonylation of N-benzylacetamide (2.99 g, 20.0 mmol) with N-caprylylpyrrolidine (3.95 g, 20.0 mmol) was carried out as in the synthesis of 2f, the time of stirring at 91–92 °C being reduced to 4 h. The solution of Me$_2$NH salts was obtained as above and analyzed by $^{31}$P NMR, which detected 15.4 mmol (77%) of 2h and 1.2 mmol (12% on N-benzylacetamide) of 2e. The mixture was diluted with water to 0.5 l and treated with a cation exchanger. The eluate was evaporated in vacuo, and the residue refluxed with water (250 ml) for 15 h up to the complete conversion of 2h into 3h. After cooling, the solution was filtered, concentrated to 168 g and mixed with 35%-HCl (210 ml). The mixture was allowed to stand for 3 days with periodic stirring. The precipitate was filtered off, washed with 18%-HCl and with hexane, air-dried, and finally washed with Me$_2$CO to give 3.12 g (96%) of 3h trihydrate. An additional portion of the product (0.50 g, 4%) was obtained from the concentrated HCl-water filtrate. The product was purified using a procedure analogous to that for 2e.

C$_{17}$H$_{37}$NO$_4$P$_4$ (603.4)
Calcd C 33.84 H 6.18%,
Found C 33.85 H 6.54%.

3,3-Diphophonobutyric acid (5a)

Unpurified 2e solvate with i-PrOH (5.00 g, 9.33 mmol) was refluxed with azeotropic HCl (70 ml) for 6.5 h to yield 97% of 5a according to $^{31}$P NMR. The hydrolyzate was evaporated in vacuo to remove water and HCl as fully as possible (bath up to 85 °C). After partial crystallization, the residue was treated with Et$_2$O (100 ml) and allowed to stand for several days with periodic stirring. The precipitate was filtered off, washed with Et$_2$O, and suspended in i-PrOH (35 ml) to yield, after standing up to the end of crystallization, 3.12 g (96%) of 5a cyclohexylammonium salt. The product was reprecipitated from water with Me$_2$CO, dried in vacuo at 70 °C, and kept over a saturated NaCl solution, giving a monohydrate, m.p. 136–138 °C.

$^1$H NMR (D$_2$O, NH$_2$-salt, pH = 6, cyclohexylamine removed): δ 1.1 (t, 3H, CH$_3$, J = 15), 2.4 (t, 2H, CH$_2$, J = 15).

C$_{16}$H$_{25}$NO$_9$P$_2$ (365.3)
Calcd C 32.88 H 6.90%,
Found C 33.04 H 6.92%.

Phosphonylation of N-alkylamides to 6 and 7

N-Alkylamide (40.0 mmol) was added to the phosphonylation mixture prepared as for the reaction of N-dodecylacetocetamide. The second portion of PCl$_3$ (4.70 g, 34.2 mmol) was added dropwise at 75–87 °C during 15–30 min. The mixture was stirred at 87–89 °C for 2 h, diluted with water (50–250 ml), and hydrolyzed at 90–98 °C for 2 h, with PhCl being removed. The precipitate was dissolved by addition of a suitable amine, the solution was analyzed by $^{31}$P NMR. When N-methylauramide was phosphonylated, the precipitate was filtered off, washed with 5%-HCl, water, Me$_2$CO, and analyzed separately. Yields and $^{31}$P NMR data for 6, 7 are given in Table V.

Cyclic dimeric 1-methylaminopropylidene-1,1-bis-phosphonic anhydride (7a)

The phosphorylation of N-methylpropionamide (3.48 g, 40.0 mmol) was carried out as above, Py
(40 ml) being added to dissolve the precipitate of 7a. The filtered solution (335 g) was acidified with 35%-HCl (205 ml) at 70—80 °C and allowed to stand overnight. The precipitate was filtered off, washed with 10%-HCl, EtOH and Me2CO to give crude 7a hydrate (7.69 g), which contained as the only impurity (4%) the supposed minor isomer. The product was dissolved in water with an excess of MeNH2, and the solution was concentrated in vacuo to 25.5 g. The precipitate was filtered off, washed with small portions of water (total amount 4.5 ml) and with Me2CO to give 7.59 g of the pure 7a MeNH2 salt. It was dissolved in water (85 ml), the solution was acidified with 35%-HCl (26 ml), the suspension was heated on a steam bath for 0.5 h and allowed to cool to 20—25 °C. The precipitate was filtered off, washed with 5%-HCl and with Me2CO, dried in vacuo at 50—60 °C, and kept over a saturated NaCl solution, to yield 6.01 g (62%) of 7a trihydrate.

\[ \text{Cyclic dimeric 1-methylaminooctylidene-1,1-bis-phosphonic anhydride (7b)} \]

The phosphonylation of N-methylvaleramide (4.61 g, 40.0 mmol) was carried out as above, 25%-MeNH2 (60 ml) being used to dissolve the precipitate of 7b. The filtered solution (300 ml) was concentrated to 65 g, the precipitate was filtered off, washed with a minimum amount of water and with Me2CO to give 8.97 g of 7b MeNH2 salt. It was dissolved in water (250 ml) with 25%-MeNH2 (15 ml), the solution was acidified with 35%-HCl (75 ml). The treatment analogous to that for 7a yielded 8.62 g (80%) of 7b trihydrate.

\[ \text{Cyclic dimeric 1-methylaminooctylidene-1,1-bis-phosphonic anhydride (7c)} \]

With the exception of the replacement of MeNH2 with Me2NH, the procedure was analogous to that used for the preparation of 7b, yield 9.71 g (80%) of 7c dihydrate.

\[ \text{C18H46N2O13P4 (624.5)} \]

Calcd C 35.65 H 7.64%.

Found C 36.03 H 7.78%.

\[ \text{Cyclic dimeric 1-methylaminododecylidene-1,1-bis-phosphonic anhydride (7d)} \]

Crude 7d (14.25 g) was obtained as above from N-methylauramide (8.53 g, 40.0 mmol). The substance contained the only phosphorus-bearing impurity of 6d (7%). It was dissolved in water (8 l) with addition of 33%-Me2NH (60 ml), the filtered solution was concentrated to 270 g. The precipitate was filtered off, washed with water and with Me2CO to give 12.26 g of pure 7d Me2NH salt. The product was suspended in water (375 ml) and acidified with 35%-HCl (112 ml). The suspension was heated on a steam bath for 0.5 h with stirring and allowed to stand for a day. The precipitate was filtered off, washed with 10%-HCl, with water, with Me2CO, and air-dried to yield 10.50 g (73%) of 7d dihydrate.

\[ \text{C26H62N2O13P4 (718.7)} \]

Calcd C 43.45 H 8.69 N 3.90 P 17.2%.

Found C 43.14 H 8.59 N 3.74 P 17.5%.

\[ \text{Cyclic dimeric p-tolyl(methylamino)methylene-bis-phosphonic anhydride (7e)} \]

The procedure was similar to that used for the synthesis of 7c, yield 7.86 g (65%) of 7e trihydrate.

\[ \text{C18H46N2O13P4 (608.4)} \]

Calcd C 35.54 H 5.47%.

Found C 35.60 H 5.51%.

\[ \text{Cyclic dimeric 1-butylaminopentylidene-1,1-bis-phosphonic anhydride (7f)} \]

The phosphonylation of N-butylvaleramide (6.29 g, 40.0 mmol) was carried out as above, 33%-Me2NH (60 ml) being used to dissolve 7f precipitate. The solution was evaporated in vacuo, the residue was dissolved in water and filtered through Polyamide Woelm TLC®. The filtrate (140 g) was acidified with 35%-HCl (40 ml) at 80—90 °C and allowed to cool to 20—25 °C. The crystals were filtered off, washed with 8%-HCl and with Me2CO to yield 8.24 g (66%) of 7f trihydrate. The product was reprecipitated from water-Me2NH with an excess of HCl.

\[ \text{C18H46N2O13P4 (624.5)} \]

Calcd C 34.62 H 7.75%.

Found C 34.21 H 7.63%.
Cyclic dimeric 1-hexylaminopentylidene-1,1-bis-phosphonic anhydride (7g)
The synthesis, isolation and purification of the compound were the same as for 7f to yield 8.26 g (59%) of 7g tetrahydrate.

\[ \text{Cyclic dimeric 1-hexylaminopentylidene-1,1-bis-phosphonic anhydride (7g)} \]

Cyclic dimeric 1-aminoctylidene-1,1-bis-phosphonic anhydride (6h)
N-Octylvaleramide (8.54 g, 40.0 mmol) was phosphonylated as above, 33%-Me_2NH (60 ml) being used to dissolve 6h precipitate. The solution (250 ml) was extracted with CHCl_3, the aqueous layer being concentrated to 140 g and acidified with 35%-HCl (60 ml) at 80—90 °C. When rubbing, the resinous precipitate gradually transformed into a crystalline product. The suspension was heated on a steam bath for 5 min and allowed to stand for a day. The crystals were filtered off, washed with 5%-HCl, water and Me_2CO to yield 1,1-bis-phosphonic anhydride (7g) of 7.77 g of crude 7i. According to 31P NMR, the product contained 91% of 7i (70% on amide) and 9% of 6i (7% on amide). The product was purified analogously to 7d, to yield 6.25 g (62%) of 7i dihydrate.

\[ \text{Cyclic dimeric 1-aminoctylidene-1,1-bis-phosphonic anhydride (6h)} \]

1-Octylaminopentylidene-1,1-bis-phosphonic acid (6h)
N-Octylvaleramide (8.54 g, 40.0 mmol) was phosphonylated as above, 33%-Me_2NH (60 ml) being used to dissolve 6h precipitate. The solution (250 ml) was extracted with CHCl_3, the aqueous layer being concentrated to 140 g and acidified with 35%-HCl (60 ml) at 80—90 °C. When rubbing, the resinous precipitate gradually transformed into a crystalline product. The suspension was heated on a steam bath for 5 min and allowed to stand for a day. The crystals were filtered off, washed with 5%-HCl, water and Me_2CO to yield 3.75 g (57.8% of 7g tetrahydrate).

\[ \text{Cyclic dimeric 1-aminoctylidene-1,1-bis-phosphonic acid (6h)} \]

Cyclic dimeric 1-aminododecylidene-1,1-bis-phosphonic anhydride (7j)
A phosphonylation mixture was prepared from PhCl (8 ml), 46.4%-HBr (4.84 g containing 2.59 g, 144.0 mmol of water), Bu_3N (3.11 g, 16.8 mmol) and PBr_3 (16.51 g, 61.0 mmol). The second portion of PBr_3 (7.88 g, 29.1 mmol) was added at 90—95 °C during 15 min, and the mixture was stirred at 90—100 °C for 15 h. The hydrolysis and the subsequent filtration (analogous to those for the synthesis of 7j) gave 10.92 g of crude 7j, which contained 94% (85% on nitrile) of 7j and 6% (5% on nitrile) of 7j according to 31P NMR. The product was purified similarly to 7d, Et_3NH being used instead of Me_2NH. The yield of 7j dihydrate was 7.64 g (63%).

\[ \text{Cyclic dimeric 1-aminododecylidene-1,1-bis-phosphonic anhydride (7j)} \]

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