Cyclic Oligophosphonic Anhydrides Stable in Aqueous Media

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Depending on reaction conditions, the phosphonylation of N-alkylacetamides with $\text{H}_3\text{PO}_3\text{--PCl}_3$ in $\text{B}\cdot\text{HCl}$ media ($\text{B} = \text{Py}, \text{Bu}_3\text{N}$) gives either 1-alkylaminoethylidene-1,1-bis-phosphonic acids (**1a–e**) or previously unknown 1-alkylaminobutane-1,1,3,3-tetraol-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-di-alkylamides the phosphonylation of acetamides affords the higher dianhydrides (**2f–h**). Strong acidic hydrolysis of **2** or **3** yields 3,3-diphosphonocarboxylic acids (**5a–c**). Reacting with $\text{H}_3\text{PO}_3\text{--P}(\text{H})\text{Hal}_2$ in $\text{B}\cdot\text{H}(\text{Hal})$ ($\text{Hal} = \text{Cl}, \text{Br}$), the amides R^1CONHR^2 ($\text{R}^1 \neq \text{H}, \text{Me}$; $\text{R}^2 = \text{Alk}, \text{H}$) 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 phosphonylation of carboxylic acids [2, 3] or their nitrogen-containing derivatives (amides, nitriles) [4, 3] with $\text{H}_3\text{PO}_3\text{--P}(\text{H})\text{Hal}_2$ 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. Inefficient mixing of reactants does not allow high yields of the phosphonylation 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 phosphonylation 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 phosphonylation of carboxylic acids and formam-

ides. 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 $(\text{H}_3\text{PO}_3 + \text{P}(\text{H})\text{Hal}_2) : \text{amide} \geq 2.5:1$ (to ensure sufficient excess of trivalent P) and $\text{P}(\text{H})\text{Hal}_2 : \text{H}_3\text{PO}_3$ close to 0.85:1 (to create the necessary dehydrating ability of reaction mixtures). As a rule, PCl_3 was used (and amine hydrochlorides, respectively), but in some special cases it was replaced by PBr_3 (and amine hydrobromides). Mostly, the reaction mixtures with PBr_3 showed much weaker activity in the phosphonylation than did those with PCl_3 , 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 ^{31}P NMR. Yields of the phosphonylation products were calculated for the amides based on the data of NMR spectroscopic analysis.

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The phosphonylation of N-monoalkylacetamides with $\text{H}_3\text{PO}_3\text{--PCl}_3$ under relatively mild conditions (at 80–85 °C) gives after hydrolysis the expected 1-alkylaminoethylidene-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 bicyclic 1-alkylaminobutane-1,1,3,3-tetraol-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 dimerizing phosphonylation 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_2 means anhydridized PO_3H_2) is the major intermediate. This imine may form due to both the phosphonylation of acetamide and the reverse dephosphonylation 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 phosphonylation towards the imine and, hence, increase the rate of dimerization. As one would expect, no C–C bond formation was found to accompany the phosphonylation 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 phosphonylation 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 PCl_3 by PBr_3 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 phosphonylation 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.

It is clear that the lower homologues **2b** or **2e** must form simultaneously. In spite of the structural similarity, **2f–h** and **2b, e** may be distinguished using ³¹P NMR. Thus, the yields of both the higher and the lower homologues may be determined. It is found that the maximum yields of **2f–h** and, respectively, the minimum yields of **2b, e** can be at-

tained 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 **2f:2b** ratio in the reaction of N-butylacetamide with equimolar amounts of various N,N-dialkylcaprylamides is found to depend also on the radicals R^2 and R^3 . Under the best found reaction conditions, the molar ratio **2f:2b** is 14:1 for $R^2-R^3=(CH_2)_4$, 3:1 for $R^2=R^3=Me$ and 1:1 for $R^2-R^3=(CH_2)_5$. 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 equilibrant one, thus retarding the formation of **2b, e** to a greater extent than that of **2f-h**. Sterically unhindered N-acyl-

pyrrolidine 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 R^1 are rather bulky. When only the N-substituent is bulky (*e.g.* for **2d**), the hydrolysis is not retarded appreciably.

The $^{31}P\{^1H\}$ 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 ^{31}P and three marked coupling constants. Assignment of ^{31}P signals in both cases is based on proton couplings. The ^{31}P signals coupled with the greater

Compound	R	R^1	δ [ppm] ^b P^1	P^2	J [Hz] AB	AB'
2a ^a	Me	Me	+15.1	+10.3	21	8
2b ^a	Bu	Me	+14.8	+10.3	21	8
2c	<i>cyclo</i> -C ₆ H ₁₁	Me	+14.8	+10.4	21	8
2d	C ₁₂ H ₂₅	Me	+14.7	+10.3	21	8
2e ^a	PhCH ₂	Me	+14.7	+10.0	22	7
2f	Bu	C ₇ H ₁₅	+13.5	+ 9.7	23	8
2g	Bu	C ₁₁ H ₂₃	+13.3	+ 9.8	23	8
2h ^a	PhCH ₂	C ₇ H ₁₅	+13.5	+ 9.4	23	8

$$\begin{array}{c} HO(O)P^1 - O - P^2(O)OH \\ | \qquad \qquad | \\ R^1 - C - CH_2 - C - NHR \\ | \qquad \qquad | \\ HO(O)P^1 - O - P^2(O)OH \end{array}$$

Table I. ^{31}P NMR data for **2a-h** (AA'BB' systems with 1H decoupled).

^a Compound was not isolated; ^b chemical shifts depend on Et₂NH quantity, variations up to 0.5 ppm are possible.

Compound	δ [ppm] ^b P^1	P^2	P^3	P^4	J [Hz] P^1P^3	P^1P^2	P^3P^4
3a	+20.9	+19.1	+8.5	+8.1	27	5	5
3b	+21.5	+19.0	+8.9	+8.1	27	6	5
3c ^a	+21.3	+19.5	+7.7	+9.0	27	5	6
3d	+21.8	+19.1	+9.0	+8.1	27	6	5
3e	+22.5	+18.8	+9.2	+7.7	25	6	4
3f ^a	+21.3	+19.1	+9.1	+8.3	25	5	4
3g ^a	+21.3	+18.9	+9.1	+8.5	25	5	4
3h	+21.8	+19.1	+9.2	+8.1	25	6	5

$$\begin{array}{c} HO(O)P^1 - O - P^3(O)OH \\ | \qquad \qquad | \\ R^1 - C - CH_2 - C - NHR \\ | \qquad \qquad | \\ H_2O_3P^2 \qquad P^4O_3H_2 \end{array}$$

Table II. ^{31}P NMR data for **3a-h**.

^a Compound was not isolated; ^b 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 $\text{H}_3\text{PO}_3\text{--PCl}_3$ 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-alkylacetoacetamides to be precursors of **2** in the dimerizing phosphorylation. N-Alkylacetamides fail to dimerize when being heated with $\text{H}_3\text{PO}_4\text{--POCl}_3$ under conditions similar to those of their reaction with $\text{H}_3\text{PO}_3\text{--PCl}_3$. 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. ^{31}P NMR data for **4a–e** (Table III) have been ob-

tained 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 H_3PO_3 molecules, which yields 3,3-di-phosphonocarboxylic acids (**5a–c**).

Formation of **5** is accompanied by a side reaction, giving H_3PO_4 and unidentified reduction products (probably 1-alkylaminoalkane-1,3,3-triyl-tris-phosphonic acids). The latter are resistant to hydrolysis and complicate the subsequent isolation of **5**. The more bulky R and the less bulky R^1 , the higher the yields of **5** (Table IV) and the faster the hydrolysis. The lowest yield of **5b** in destruction of **3h** is most likely due to rapid debenzoylation 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-mono-alkylamides of other aliphatic carboxylic acids into reactions similar to the dimerizing phosphorylation of acetamides have failed. Reactions of

Table III. ^{31}P NMR data for **4a–e**.

Compound	R	δ [ppm] (multiplicity, J_{PH} [Hz])
		P^1 P^2
4a	Me	+24.2 (sext., 15) +12.9 (t, 13)
4b	Bu	+24.1 (sext., 14) +13.1 (t, 12)
4c	<i>cyclo</i> - C_6H_{11}	+24.0 (sext., 15) +13.6 (t, 12)
4d	$\text{C}_{12}\text{H}_{25}$	+24.0 (sext., 15) +12.5 (t, 12)
4e	PhCH_2	+24.0 (sext., 14) +12.8 (t, 12)

$$\begin{array}{c} \text{H}_2\text{O}_3\text{P}^1 \quad \text{P}^2\text{O}_3\text{H}_2 \\ | \quad \quad | \\ \text{CH}_3\text{--C--CH}_2\text{--C--NHR} \\ | \quad \quad | \\ \text{H}_2\text{O}_3\text{P}^1 \quad \text{P}^2\text{O}_3\text{H}_2 \end{array}$$

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

Starting compound	Azeotropic HHal (volume ^a [ml])	Time of refluxing [h]	Product (yield)	^{31}P NMR for 5 δ [ppm] (J_{PH} [Hz])
3a ·Py	HCl (14)	31	5a (73%)	+23.5 (sext., 15)
3a ·Py	HBr (10)	14	5a (78%)	
3b ·3 H_2O	HBr (10)	14	5a (92%)	
2c ^b	HCl (14)	6.5	5a (97%)	
2f · PhNH_2 ·3 H_2O	HBr (25)	30	5b (79%)	+23.1 (quint., 14)
2g ^c	HBr (40)	30	5c (80%)	+23.0 (quint., 14)
3h ·3 H_2O	HBr (40)	30	5b (52%)	

^a Per 1 g of starting compound; ^b solvate with *i*-PrOH ($M = 536.0$); ^c non-stoichiometric PhNH_2 salt ($M = 780$).

these, and also of the aromatic N-monoalkylamides with $\text{H}_3\text{PO}_3\text{--PCl}_3$, 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 R^1 and R^2 . Despite the limited number of tested amides, some regularities may be marked. Small R^2 and relatively large R^1 favour the formation of **7**. When the length of R^2 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 R^2 should, clearly, depend on R^1 . Since such dimeric anhydrides have never been observed in the mentioned reaction mixtures of acetamides, for $\text{R}^1=\text{Me}$ the length of any substituent R^2 already exceeds the critical value.

Under dehydrating reaction conditions, N-unsubstituted amides transform into nitriles. With the exception of lower homologues, the latter are hardly

capable of phosphorylation with $\text{H}_3\text{PO}_3\text{--PCl}_3$ due to low acidity of the reaction medium. The use of the $\text{H}_3\text{PO}_3\text{--PBr}_3$ 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 $\text{H}_3\text{PO}_3\text{--PBr}_3$ shows much weaker reactivity as compared to $\text{H}_3\text{PO}_3\text{--PCl}_3$, 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- or 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-

Table V. Phosphorylation of the N-alkylamides R^1CONHR^2 with $\text{H}_3\text{PO}_3\text{--PCl}_3$ and ^{31}P NMR data for the reaction products.

Starting amide R^1	R^2	Products (yields ^a) monomer ^c	dimer	^{31}P NMR data δ [ppm] (multipl. ^b , J_{PH} [Hz]) for monomer	for dimer
Et	Me	6a (10%)	7a (85%) ^d	+12.0 (t, 13)	+6.3 (m)
Bu	Me	6b (8%)	7b (88%) ^e	+11.8 (t, 11)	+6.7 (m)
C_7H_{15}	Me	6c (9%)	7c (89%)	+12.2 (t, 11)	+7.0 (m)
$\text{C}_{11}\text{H}_{23}$	Me	6d (7%) ^f	7d (91%) ^f	+12.4 (t, 11)	+7.2 (m)
<i>p</i> -Me- C_6H_4	Me	6e (5%)	7e (82%)	+13.4 (s)	+7.0 (s)
Bu	Bu	6f (11%)	7f (85%)	+11.6 (t, 12)	+6.4 (m)
Bu	C_6H_{13}	6g (25%)	7g (70%)	+12.2 (t, 12)	+6.9 (m)
Bu	C_8H_{17}	6h (94%)	—	+12.5 (t, 12)	—

^a Based on ^{31}P NMR analysis; ^b with ^1H decoupled all signals are singlets; ^c only **6h** was isolated; ^d additionally, the probable minor isomer (3%) is observed at 4.4 ppm; ^e probable minor isomer (<2%) at 4.5 ppm; ^f only precipitate was analyzed.

trol. 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.

The structure of **7** as cyclic anhydrides of **6** is sufficiently 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

^1H 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 Et_2NH buffer at pH = 10.5–11.5, reference – H_3PO_4 , downfield shifts being positive. Small amounts (5–10 mg) of EDTA or CyDTA complexons 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 *n*- $\text{C}_6\text{H}_{13}\text{OH}$, water, Et_2NH and Py (equal volumes), spots were detected by spraying with a mixture of water (50 ml), Xylenolorange indicator (40 mg), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (10 mg) and CCl_3COOH (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-metric titration, a difference of <2% was permitted between the alkali equivalents found and those calculated.

Phosphonylation mixtures of H_3PO_3 , amine hydrohalides and $\text{P}(\text{H}_2\text{Al})_3$ were prepared from the corresponding amounts of conc. aqueous $\text{H}(\text{H}(\text{Al}))$, free amines and $\text{P}(\text{H}_2\text{Al})_3$. Caution! To avoid the disproportionation of H_3PO_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 $\text{P}(\text{H}_2\text{Al})_3$ 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-Dodecylacetoacetamide

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

^1H 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_3CO), 3.20 (q, 2 H, NHCH_2 , $J = 6$), 3.35 (s, 2 H, COCH_2CO), 6.95 (br. m, 1 H, NH).

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

A phosphonylation 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 reprecipitated 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* = 14).

C₃H₁₁NO₆P₂ (219.1)

Calcd C 16.45 H 5.06%,

Found C 16.40 H 5.27%.

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

N-Butylacetamide (4.61 g, 40.0 mmol) was subjected 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 reprecipitated 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).

C₆H₁₇NO₆P₂ (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 second 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 cooling, 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).

C₈H₁₉NO₆P₂ (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 introduced to accelerate separation of the emulsion. The aqueous layer was concentrated to 200 ml to remove MeOH and the excess of Me₂NH. According 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 give **1d** monohydrate, m. p. 207–209 °C (decomp.).

³¹P NMR: δ +12.8 (q, *J* = 13).

C₁₄H₃₅NO₇P₂ (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 removal of *o*-C₆H₄Cl₂. The crystals of **1e** were dissolved 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 contained 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).

C₉H₁₅NO₆P₂ (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 PCl_3 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 Et_3NH (50 ml). PhCl , Py and excess of Et_3NH were removed by evaporation *in vacuo*. The residue was dissolved in water and filtered. The ^{31}P 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.

$\text{C}_{10}\text{H}_{27}\text{NO}_{13}\text{P}_4$ (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 PCl_3 (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 ^{31}P 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 Me_2CO and dried *in vacuo* at 50–55 °C.

^1H NMR (D_2O): δ 1.3 (t, 3H, CH_3C , $J = 15$), 1.8–2.8 (br. m, 2H, CH_2), 2.8 (s, 3H, NHCH_3), 7.8–8.6 (m, 5H, pyridinium H).

^{13}C NMR (75.47 MHz, D_2O): δ 24.5 (t, CH_3CP_2 , $J = 4$), 33.8 (NHCH_3), 40.7 (t with small additional couplings, CH_3CP_2 , $J = 112$), 43.0 (CH_2), 63.6

(dd, NHCP_2 , $J_1 = 125$, $J_2 = 111$), 127.2 (pyridinium 3- C), 140.2 (pyridinium 4- C), 151.5 (pyridinium 2- C).

$\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_{11}\text{P}_4$ (468.2)

Calcd C 25.65 H 4.31 N 5.98 P 26.5%,

Found C 25.39 H 4.39 N 5.82 P 25.9%.

Monocyclic 1-butylaminobutane-1,1,3,3-tetrayl-tetrakis-phosphonic anhydride (3b)

The phosphorylation of N-butylacetamide (4.61 g, 40.0 mmol) and the hydrolysis of the reaction mixture were carried out the same as in the synthesis of **3a**. The ^{31}P NMR spectroscopic analysis detected 15.7 mmol (78%) of **3b** and 2.6 mmol (13%) of **4b**. The filtrate was treated with a cation exchanger, the eluate was evaporated *in vacuo* (bath up to 70 °C), the residue was dissolved in EtOH (60 ml). The crystallization was complete only after continuous standing at 20–25 °C, yielding 6.98 g (72%) of **3b** trihydrate. The product was reprecipitated from water with Me_2CO and dried *in vacuo* at 40–50 °C.

$\text{C}_8\text{H}_{27}\text{NO}_{14}\text{P}_4$ (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 ^{31}P 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, $\text{EtOH}:\text{3e} = 0.6$; 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 ($\text{D}_2\text{O} + \text{Na}_2\text{CO}_3$, pH = 9): δ 1.3 (dd, 3H, CH_3 , $J_1 = 16$, $J_2 = 13$), 2.0–3.0 (br. m, 2H, $\text{CP}_2\text{CH}_2\text{CP}_2$), 4.7 and 5.0 (two d, 1H and 1H, diastereotopic NHCH_2 protons, $J = 13$), 7.4–7.7 (m, 5H, C_6H_5).

$\text{C}_{11}\text{H}_{25}\text{NO}_{14}\text{P}_4$ (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 PCl_3 (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 CHCl_3 (450 ml), 33%- Me_2NH (250 ml) was added, the aqueous layer was separated and additionally extracted with CHCl_3 . The excess of Me_2NH was removed by concentration *in vacuo*. According to ^{31}P 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 Et_2O , and dried over KOH to remove the rest of HCl and water. The cake was suspended in Me_2CO to give 10.14 g (93%) of **2d** monohydrate after filtration. The product was reprecipitated from a mixture *i*-PrOH-water- CF_3COOH (14:2.7:0.7 by volume) with EtOAc and dried *in vacuo* at 70–80 °C.

$\text{C}_{16}\text{H}_{37}\text{NO}_{11}\text{P}_4$ (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.

$\text{C}_{16}\text{H}_{43}\text{NO}_{14}\text{P}_4$ (597.4)

Calcd C 32.16 H 7.27%,

Found C 32.20 H 7.38%.

Phosphonylation of *N*-dodecylacetoacetamide

N-Dodecylacetoacetamide (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 PCl_3 (9.34 g, 68.0 mmol). The second portion of PCl_3 (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%- Me_2NH (250 ml), and extracted with CHCl_3 . The aqueous layer was

concentrated *in vacuo* to remove excess Me_2NH and analyzed by ^{31}P NMR, the yield being 18.4 mmol (92%) of **2d**. The product was isolated as mentioned above.

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

The phosphonylation mixture was prepared as in the synthesis of **1a**, PhCl being replaced with *o*- $\text{C}_6\text{H}_4\text{Cl}_2$ (7 ml). *N*-Butylacetamide (2.31 g, 20.0 mmol) and *N*-caprylylpyrrolidine (3.95 g, 20.0 mmol) were added simultaneously, the second portion of PCl_3 (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%- Me_2NH (150 ml) were added, the emulsion was extracted with CHCl_3 . The aqueous layer was concentrated *in vacuo* to remove excess Me_2NH and analyzed by ^{31}P NMR, showing 14.6 mmol (73%) of **2f** and 1.0 mmol (10% calculated on *N*-butylacetamide) of **2b**. To the solution (83 g) a mixture of PhNH_2 (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 portionwise with a mixture of PhNH_2 (16 ml), water (25 ml) and 35%-HCl (10 ml). The cake was suspended in a mixture of *i*-PrOH (50 ml) and PhNH_2 (1 ml), filtered off and washed with *i*-PrOH to give 10.99 g of crude **2f** aniline salt, which was dissolved in a hot mixture of *i*-PrOH (160 ml), water (75 ml) and PhNH_2 (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** aniline salt with the molar ratio **2f**: PhNH_2 close to 1:2 ($M = 715.6$ according to pH-metric titration). The product was recrystallized from EtOH-water- PhNH_2 (20:4:1 by volume), dried *in vacuo* at 110 °C to attain the equimolar **2f**: PhNH_2 ratio and kept over a saturated NaCl solution, giving **2f** monoaniline salt trihydrate.

^1H NMR ($\text{D}_2\text{O} + \text{Na}_2\text{CO}_3$, pH = 8): δ 0.9 [distorted t, 3H, CH_3 (heptyl chain), $J = 6$], 1.0 [t, 3H, CH_3 (butyl chain), $J = 6$], 1.2–1.8 [m, 16H, CH_2 (aliphatic)], 1.9–2.9 (br. m, 2H, $\text{CP}_2\text{CH}_2\text{CP}_2$), 3.4 (t, 2H, NHCH_2 , $J = 7$), 6.8–7.4 (m, 5H, C_6H_5).

$\text{C}_{20}\text{H}_{44}\text{N}_2\text{O}_{13}\text{P}_4$ (644.5)

Calcd C 37.27 H 6.88%,

Found C 37.07 H 7.12%.

Bicyclic 1-butylaminotetradecane-1,1,3,3-tetrahydro-2H-tetrakis-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, and the solution of Me_2NH salts was obtained according to the procedure used for **2f**. ^{31}P NMR showed 13.2 mmol (66%) of **2g** and 1.9 mmol (19% on N-butylacetamide) of **2b**. To the solution (110 g) a mixture of water (105 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_2O 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_3COOH (15 ml) and allowed to stand for 2 days. The crystals were filtered off and washed with *i*-PrOH to yield 6.92 g (44%) of pure **2g** aniline salt (non-stoichiometric, $M = 780$ according to pH-metric titration). The product was recrystallized from *i*-PrOH-water (6:1 by volume), dried *in vacuo* at 110 °C, and kept over a saturated NaCl solution, giving **2g** monoaniline salt dihydrate.

$\text{C}_{24}\text{H}_{50}\text{N}_2\text{O}_{12}\text{P}_4$ (682.6)

Calcd C 42.23 H 7.38%,
Found C 42.05 H 7.16%.

Monocyclic 1-benzylaminodecane-1,1,3,3-tetrahydro-2H-tetrakis-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_2NH 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_2CO to give 5.90 g (49%) of **3h** trihydrate. An additional por-

tion 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 **2c**.

$\text{C}_{17}\text{H}_{37}\text{NO}_{14}\text{P}_4$ (603.4)

Calcd C 33.84 H 6.18%,
Found C 33.85 H 6.54%.

3,3-Diphosphonobutyric acid (5a)

Unpurified **2c** 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_2O (100 ml) and allowed to stand for several days with periodic stirring. The precipitate was filtered off, washed with Et_2O , 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_2CO , dried *in vacuo* at 70 °C, and kept over a saturated NaCl solution, giving a monohydrate, m. p. 136–138 °C.

^1H NMR (D_2O , NH_4 -salt, pH = 6, cyclohexylamine removed): δ 1.1 (t, 3H, CH_3 , $J = 15$), 2.4 (t, 2H, CH_2 , $J = 15$).

$\text{C}_{10}\text{H}_{25}\text{NO}_9\text{P}_2$ (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-dodecylacetoacetamide. 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-methyl-lauramide was phosphonylated, the precipitate was filtered off, washed with 5%-HCl, water, Me_2CO , 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 phosphonylation 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.

¹H NMR (D₂O+Py): δ 1.0 (t, 3H, CH₃CH₂, *J* = 7), 1.7–2.3 (m, 2H, CH₂), 2.7 (s, 3H, NHCH₃).

¹³C NMR (50.31 MHz, D₂O+Py): δ 8.2 (CH₃CH₂), 20.4 (CH₂), 28.9 (NHCH₃), 63.4 (additionally coupled t, CP₂, *J* = 139).

C₈H₂₈N₂O₁₃P₄ (484.2)

Calcd C 19.84 H 5.41 N 5.79 P 25.6%,
Found C 19.44 H 5.63 N 5.93 P 26.1%.

Cyclic dimeric 1-methylaminopentylidene-1,1-bis-phosphonic anhydride (7b)

The phosphorylation 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.

C₁₂H₃₆N₂O₁₃P₄ (540.3)

Calcd C 26.67 H 6.72%,
Found C 26.85 H 6.87%.

Cyclic dimeric 1-methylaminoctylidene-1,1-bis-phosphonic anhydride (7c)

With the exception of the replacement of MeNH₂ with Me₂NH, the procedure was analo-

gous to that used for the preparation of **7b**, yield 9.71 g (80%) of **7c** dihydrate.

C₁₈H₄₆N₂O₁₂P₄ (606.5)

Calcd C 35.65 H 7.64%,
Found C 36.03 H 7.78%.

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.

C₂₆H₆₂N₂O₁₂P₄ (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%.

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.

C₁₈H₃₂N₂O₁₃P₄ (608.4)

Calcd C 35.54 H 5.47%,
Found C 35.60 H 5.51%.

Cyclic dimeric 1-butylaminopentylidene-1,1-bis-phosphonic anhydride (7f)

The phosphorylation 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.

C₁₈H₄₈N₂O₁₃P₄ (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.

$C_{22}H_{58}N_2O_{14}P_4$ (698.6)

Calcd C 37.82 H 8.37%,

Found C 37.75 H 8.28%.

1-Octylaminopentylidene-1,1-bis-phosphonic acid (6h)

N-Octylvaleramide (8.54 g, 40.0 mmol) was phosphonylated as above, 33%-Me₂NH (60 ml) being used to dissolve **6h** precipitate. The solution (250 ml) was extracted with CHCl₃, 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 Me₂CO to yield after drying 10.19 g (71%) of **6h**. The product was recrystallized from azeotropic HCl and dried *in vacuo* at 60 °C.

$C_{13}H_{31}NO_6P_2$ (359.3)

Calcd C 43.45 H 8.70%,

Found C 43.68 H 9.12%.

Cyclic dimeric 1-aminooctylidene-1,1-bis-phosphonic anhydride (7i)

A phosphonylation mixture was prepared from PhCl (8 ml), 46.4%-HBr (4.84 g containing 2.59 g, 144.0 mmol of water), Bu₃N (3.11 g, 16.8 mmol) and PBr₃ (16.35 g, 60.4 mmol). Caprylamide (5.01 g, 35.0 mmol) was added at 25 °C, the mixture was heated to 85–90 °C and the second portion of PBr₃ (8.01 g, 29.6 mmol) was added dropwise during 20 min with intense stirring. The frothy mixture was stirred at 100–102 °C for 11 h and allowed to cool to 30 °C. Water (50 ml) was

poured on and the mixture was hydrolyzed at 90–98 °C for 3 h, with PhCl being removed. The precipitate was filtered off, washed with 10%-HCl and Me₂CO to give 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.

³¹P NMR: δ +12.1 (m, with ¹H decoupled – s).

$C_{16}H_{42}N_2O_{12}P_4$ (578.4)

Calcd C 33.22 H 7.32%,

Found C 33.21 H 7.40%.

Cyclic dimeric 1-aminododecylidene-1,1-bis-phosphonic anhydride (7j)

Lauroitrile (6.35 g, 35.0 mmol) was added at 25 °C to a phosphonylation mixture of PhCl (7 ml), 45.8%-HBr (5.94 g containing 3.22 g, 178.7 mmol of water), Bu₃N (3.11 g, 16.8 mmol), and PBr₃ (16.51 g, 61.0 mmol). The second portion of PBr₃ (7.88 g, 29.1 mmol) was added at 90–96 °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 **7i**) gave 10.92 g of crude **7j**, which contained 94% (85% on nitrile) of **7j** and 6% (5% on nitrile) of **6j** according to ³¹P NMR. The product was purified similarly to **7d**, Et₂NH being used instead of Me₂NH. The yield of **7j** dihydrate was 7.64 g (63%).

³¹P NMR: δ +12.0 (m, with ¹H decoupled – s).

$C_{24}H_{58}N_2O_{12}P_4$ (690.6)

Calcd C 41.74 H 8.46 N 4.06 P 17.9%,

Found C 41.48 H 8.48 N 4.00 P 16.9%.

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