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Cyclic Oligophosphonic Anhydrides

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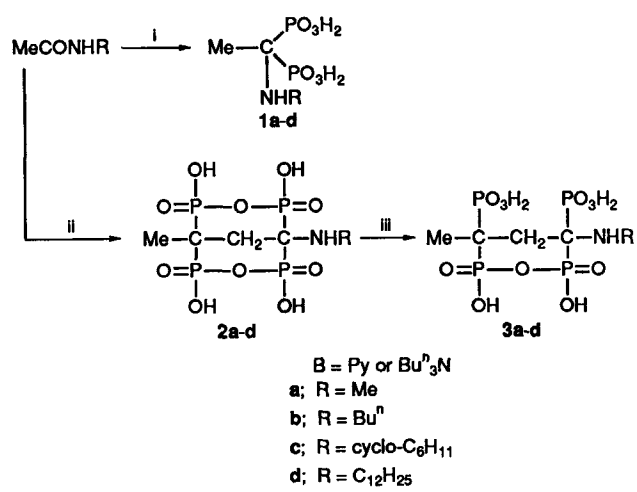
The previously unkown, water-stable, mono- and bi-cyclic anhydrides of oligophosphonic acids containing an amino group have been obtained by phosphonylation of amides using H_3PO_3–PX_3 systems in the presence of amine hydrohalides.

Oligophosphonates have many applications owing to their chelating ability.[1] The phosphonylation of amides (or nitriles) with H_3PO_3–PX_3 (X = Br, Cl) systems is a well-known method for the synthesis of an important class of oligophosphonates, namely the 1-aminoalkylidene-1,1-bis-phosphonic acids.[2] Previously,[3] we proposed the use of amine hydrohalides (amine = tri- and di-alkylamines, pyridine, *etc.*) as diluents of the reaction mixtures in a similar phosphonylation of carboxylic acids and formamides. The use of amine hydrohalides 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.

The reaction with amides was carried out at 80–110 °C using a molar ratio amide:H_3PO_3:PX_3 close to 1:1.4:1.2, PX_3 being either PCl_3 or PBr_3. Hydrohalides of pyridine or tributylamine were preferably used, chlorobenzene being introduced as an additional diluent to further reduce the viscosity of the reaction mixture. When the reaction was complete, the mixtures were hydrolysed with an excess of water to destroy the unstable polycondensed products, and were analysed using ^{31}P NMR.†

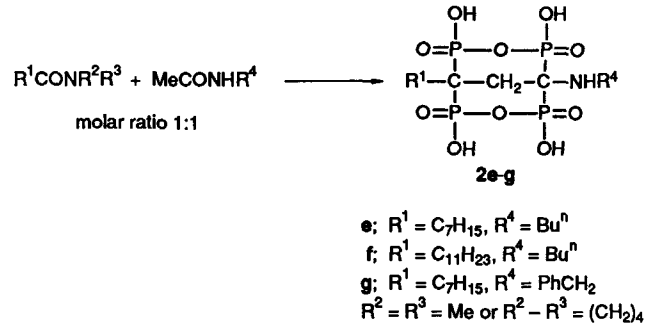
The phosphonylation of *N*-monoalkylacetamides with H_3PO_3–PCl_3 under these relatively mild conditions gives (after hydrolysis) products, which are assumed to be acids **1a–d** in high yields (Scheme 1).‡ However, the use of harsher reaction conditions leads to dimerization of **1a–d**, followed by the loss of one alkylamino group and the formation of bicyclic 1-alkylaminobutane-1,1,3,3-tetrayltetrakisphosphonic 1,3;1,3-dianhydrides **2a–d**. Under controlled acidic hydrolysis, the latter convert into the monocyclic forms **3a–d**. Both **2** and **3** are stable in neutral or slightly alkaline aqueous solutions and may be isolated either as free acids or as salts.



Scheme 1 *Reagents and conditions*: i, H_3PO_4, PCl_3–B·HCl, PhCl, 80–90 °C, 1–4 h (70–90%); ii, H_3PO_4, PCl_3–B·HCl, PhCl, 90–100 °C, 5–15 h (80–100%); iii, H_2O, H^+

† ^{31}P NMR spectra were recorded in D_2O–H_2O (Et_2NH buffer, pH = 10–12), reference H_3PO_4, shifts downfield are positive.

‡ Yields were calculated for the amides based on ^{31}P NMR spectroscopic analysis.



Scheme 2 *Reagents and conditions*: H_3PO_4, PCl_3–B·HCl, PhCl, 80–100 °C, 5–15 h (50–70%)

In order to account for this unexpected reaction route we propose that imine MeCX=NR (X is most likely an anhydridized PO_3H_2 group) is the major intermediate. Tautomerization gives the *C*-nucleophilic enamine CH_2=CX—NHR, whereas protonation affords the *C*-electrophile. Their interaction leads to the formation of a new C—C bond and ultimately yields compound **2**.

The role of the amine hydrochloride appears to be to lower the acidity of the reaction medium, which favours the formation of the enamine. The replacement of PCl_3 by PBr_3 increases the acidity and prevents the dimerization of **1**.

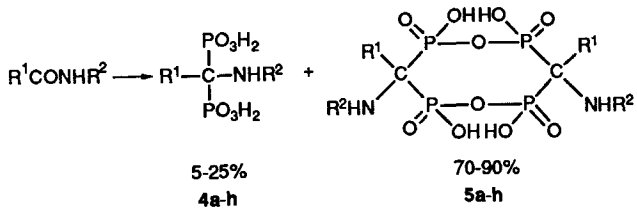
When *N*-alkylacetamides are introduced into the reaction in the presence of long chain *N,N*-dialkylamides (which cannot give any stable phosphonylation products without C–N bond rupture), the latter provide the major part of the electrophilic species. Therefore the cyclic anhydrides **2e–g** become the main products (Scheme 2).

The ^{31}P NMR spectra of **2** exhibit two sorts of ^{31}P (at δ 9.1–10.5 and 13.5–15.1, with ^1H decoupled both dd, $^1J_{PP}$ 21–23 Hz, $^2J_{PP}$ 7–9 Hz) whereas four sorts of ^{31}P are observed for **3** (at δ 7.5–9.0, 8.5–9.5, 18.5–19.5 and 20.9–22.1) with more complex couplings.

In acidic media compounds **3** undergo reversible ring-opening, giving non-anhydride forms in yields not exceeding 30%. An excess of KOH gives rise to practically a full conversion of **3a** into $MeC(PO_3K_2)_2CH_2C(PO_3K_2)_2NHMe$ [^{31}P NMR: δ 24.1 (sext., *J* 15 Hz, 2P), 13.1 (t, *J* 13 Hz, 2P)], but the lower pH results in reverse cyclization. Strong hydrolysis of **2** or **3** with azeotropic HCl or HBr (reflux, 20–40 h) leads to the elimination of alkylamine and two H_3PO_3 molecules, yielding 3,3-diphosphonocarboxylic acids. Thus heating **3a** under reflux for 40 h in azeotropic HCl gives an 85% yield of 3,3-diphosphonobutyric acid $MeC(PO_3H_2)_2CH_2CO_2H$ (^{31}P NMR: δ 23.5, sext., *J* 15 Hz).

The structures of **2** and **3** were demonstrated by both analytical and NMR spectroscopic methods and also by direct synthesis of **2c** from *N*-dodecylacetoacetamide and H_3PO_3–PCl_3 in 90% yield.

So far, all attempts to introduce *N*-monoalkylamides of other aliphatic carboxylic acids into reactions similar to the dimerizing phosphonylation of acetamides have failed. Reaction of these, and also of aromatic *N*-monoalkylamides, with H_3PO_3–PCl_3 affords oligomeric anhydrides of 1-alkylaminoalkylidene-bis-phosphonic acids. However, in most cases hydrolysis of the reaction mixtures gives only low yields of monomers **4a–h**. This is because the anhydrides consist of the



a; R^1 = Et, R^2 = Me
b; R^1 = Bu^n, R^2 = Me
c; R^1 = C_5H_{11}, R^2 = Me
d; R^1 = C_7H_{15}, R^2 = Me
e; R^1 = $C_{11}H_{23}$, R^2 = Me
f; R^1 = *p*-MeC_6H_4, R^2 = Me
g; R^1 = R^2 = Bu^n
h; R^1 = Bu^n, R^2 = C_6H_{13}

Scheme 3 *Reagents and conditions*: H_3PO_4, PCl_3–B·HCl, PhCl, 80–90 °C, 2–6 h

previously unknown cyclic dimers **5a–h** (Scheme 3), which are stable to hydrolysis. The yields of **5** seem to decrease with increasing length of R^2. thus all the *N*-methylamides tested provide *ca.* 90% yields of dimers **5**. In the series of *N*-alkylvaleramides the yields of **5** decrease from 90% to 70% as the size of R^2 increrases from Me to C_6H_{13}. When $R^2 = C_8H_{17}$, **5** is not obtained, the monomeric $Bu^nC(PO_3H_2)_2NHC_8H_{17}$ being the only product (95%).

N-Unsubstituted cyclic dimeric anhydrides **5i,k** (**i**;$R^1 = C_7H_{15}$, R^2 = H; *k*; $R^1 = C_{11}H_{23}$, R^2 = H) can be obtained by phosphonylation of unsubstituted amides (or nitriles) with H_3PO_3–PBr_3 in the presence of Bu_3N·HBr and PhCl (95 °C, 7–9 h, 70–75%). All the compounds **5** can be readily isolated, owing to their very low water solubility. The ^{31}P NMR spectra of **5** indicate the equivalency of all P atoms, the ^{31}P signals (at δ 6–7 for **5a–h** and δ 11–12 for **5i,k**) being shifted upfield relative to corresponding signals for compounds **4**. Mainly one of the two possible diastereoisomers of **5** is realized, on the whole.

The anhydrides **5** 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 mol dm^{-3} KOH. The relatively soluble **5g** undergoes rapid hydrolysis to **4g** on refluxing in azeotropic HCl. This method, however, fails for most of the anhydrides **5**, which are practically insoluble in HCl.

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