University of Groningen

Formation of Poly(ethylene phosphates) in Polycondensation of H3PO4 with Ethylene Glycol. Kinetic and Mechanistic Study

Pretula, Julia; Kaluzynski, Krzysztof; Wisniewski, Blazej; Szymanski, Ryszard; Loontjens, Ton; Penczek, Stanislaw

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

[Link to publication in University of Groningen/UMCG research database](#)

Formation of Poly(ethylene phosphates) in Polycondensation of H₃PO₄ with Ethylene Glycol. Kinetic and Mechanistic Study

JULIA PRETULA,[1] KRZYSZTOF KALUZYNSKI,[1] BLAZEJ WISNIEWSKI,[1] RYSZARD SZYMANSKI,[1] TON LOONTJENS,[2] STANISLAW PENCZEK[1]

[1]Department of Polymer Chemistry, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Lodz, Poland

[2]DSM Research, 6160 MD Geleen, The Netherlands

ABSTRACT: Conditions of synthesis of poly(ethylene phosphates) in reaction of H_3PO_4 with $HOCH_2CH_2OH$ (EG), the actual path of polycondensation, and structure of the obtained polymers (mostly oligomers) and kinetics of reaction are described. Preliminary kinetic information, based on the comparison of the MALDI-TOF-ms and $^{31}P\{^1H\}$ NMR spectra as a function of conversion is given as well. Because of the dealkylation process fragments derived from di- and triethylene glycols are also present in the repeating units. Structures of the end groups ($-CH_2CH_2OH$ or $-OP(O)(OH)_2$) depend on the starting ratio of $[EG]_0/[H_3PO_4]_0$, although even at the excess of EG the acidic end groups prevail because of the dealkylation process. In MALDI-TOF-ms products with P_n equal up to 21 have been observed. The average polymerization degrees (P_n) are lower and have been calculated from the proportion of the end groups. © 2007 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 46: 830–843, 2008
Keywords: diol; esterification; kinetics (polym.); MALDI; NMR; phosphoric acid; polycondensation; polyesters

INTRODUCTION

In this article, direct synthesis of poly(ethylene phosphate) based on reaction of ethylene glycol with phosphoric acid is described. The expression "direct" is used since some other methods of poly(alkylene phosphates) synthesis are known. Our Note[1] described already the principle and preliminary results. In this article some kinetic data of the principal versus side reaction (dealkylation) are described, and it has been shown for the first time that although H_3PO_4 has been taken for polycondensation, its dimer, namely pyrophosphoric acid (PP) is the actual phosphorylating agent. The first high-molecular weight polymers (M_n up to 10^5) with a repeating unit

$$-[(CH_2)_x-\overset{\overset{\textstyle O}{\|}}{O}PO]_n- \\ \underset{\textstyle OH}{|} \qquad (x = 2 \text{ or } 3) \qquad (1)$$
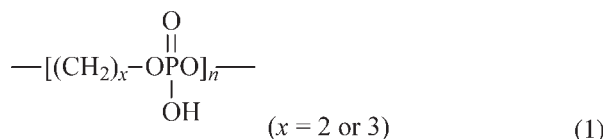
were prepared in our laboratory as early as in 1973, by ring-opening polymerization (ROP).[2–4] Even earlier Munoz and Majoral[5,6] polymerized 5- and 6-membered cyclic phosphates; the reported molar masses were $\leq 5 \times 10^3$. There are also articles on polycondensation of diols with dichloroalkyl(aryl) phosphates.[7] The molar

masses of poly(alkylene phosphates) prepared in our laboratory by ROP varied, depending on the monomer structures. Thus, for the 5-membered cyclic esters (e.g. 2-methoxy-2-oxo-1,3,2-dioxaphospholane) $M_n \sim 10^4$ could be reached [further dealkylation—removal of the CH_3 groups—leads to the poly(ethylene phosphate)],[8] whereas ROP of the 5- and 6-membered H-phosphonates gave even higher molar masses (up to 10^5). Oxidation of the resulting polymers allowed preparing of the poly(1,3-propylene phosphate), e.g.,

$$(2)$$
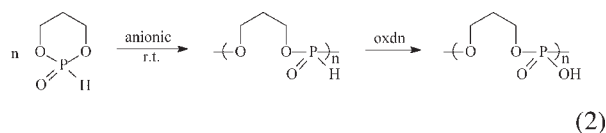
Transesterification of glycols with dialkyl H-phosphonates was also elaborated leading to the high-molar mass poly(alkylene phosphates) after oxidation of the first prepared poly(H-alkylene phosphonates).[9–11] Similar methods were used later in other laboratories.[12–14] More recently these approaches (including ROP) have successfully been used for preparation of polymers for the biomedical field (nerve guides, controlled drugs release), mostly by Leong and coworkers.[15–17]

In our laboratories and in cooperation with other research groups, liquid membranes were prepared which were able to separate Ca^{+2} and Mg^{+2} and other cations, taking advantage of the known ability of the derivatives of poly(1,2-glycerol phosphates) or poly(1,3-glycerol phosphates) to flux these ions through membranes in living organisms (teichoic acids).[18] Understanding of these transport processes has led to the development of poly(alkylene phosphates) capable in separating (as liquid membranes) cations such as Ni^{+2} and Co^{+2} (work in cooperation with the Copernicus University, Torun).[19] Finally, block copolymers, having two hydrophilic blocks—ionic and nonionic (in the repeating units of ionic blocks monoesters of H_3PO_4 were present)[20] have been used to control crystallization of inorganic salts (like $CaCO_3$). Polymeric phosphates and phosphonates of this structure are the most efficient bonding blocks, when compared with other polyanions.[21,22]

However, all the above described methods of synthesis are based on the nondirect synthetic methods.

Searching for the relevant literature revealed that there are contradicting information even on the synthesis of monoesters of phosphoric acid

and low-molar mass alcohols when H_3PO_4 is used as reactant. Cherbuliez[23] was studying reactions of ethyl and butyl alcohols with H_3PO_4 and came to an opinion that such a direct reaction is "practically" not possible. "Practically" means, that reaction is very slow and that the position of equilibrium

$$H_3PO_4 \;+\; ROH \;\rightleftharpoons\; ROP(O)(OH)_2 \;+\; H_2O \qquad (3)$$

is shifted very much to the left hand side. For an explanation, Cherbuliez[23] proposed that in contrast to the electronic structure of carboxylic acids, in phosphoric acid (actually, protonated phosphoric acid) there is an electronic octet, preventing phosphorous atom from the nucleophilic attack, that would lead to an ester formation as follows

$$(4)$$

However, in the more recent literature,[24] successful and high-yield formation of the monoesters of phosphoric acid in reaction of H_3PO_4 with alcohols (e.g. dodecyl alcohol) was reported.[25] The higher molar mass alcohol used allowed elimination of H_2O from the reaction mixture. In the same work only traces of diesters were however observed (diesters are needed whenever poly(alkylene phosphates) are considered).

The most comprehensive review of the literature on reactions of H_3PO_4, P_4O_{10}, pyro- (PP) and polyphosphoricacids (PPA) with alcohols is given in ref. 25.

There is no information, however, on the reaction of H_3PO_4 with glycols. Perhaps some information could be found in the abundant patent literature, although our search gave negative results.

Simple poly(alkylene phosphates) have backbones similar to the bare backbones of some biopolymers, namely nucleic and teichoic acids [poly(glycerol phosphates)]. Moreover, esters of phosphoric acids are used as surfactants, plasticizers, extractants, and fire retardants as well as in some other areas (e.g. food additives).[26] Any of these applications, to be practical, requires a simple synthetic method, based on inexpensive and easily available starting materi-

als, and the process with no side products formation. Thus, we started exploring reactions of H_3PO_4 with polyols.

In this article we describe reaction of EG and H_3PO_4, leading to short oligomers of the poly (ethylene phosphate) structure. This article also explains the chemistry of the process limiting the higher molar mass polymers formation. Preliminary Note on this method has been published in this Journal.[1]

EXPERIMENTAL

Polycondensation of EG with H_3PO_4

Reactions of H_3PO_4 with ethylene glycol were usually carried out without solvent (in mass) under normal pressure in the stirred homogeneous mixture of substrates and products (with or without added catalyst). H_2O was being removed from the system either in the stream of neutral gas at normal or reduced pressure. In some experiments H_2O was removed by heteroazeotrope with heptane, and the reaction was then kept under vigorous reflux (temperature range 98–120 °C) in a flask equipped with azeotropic receiver (similar to the Dean-Stark water trap). In bulk polycondensation temperatures until 150 °C were used. The progress of esterification was monitored by $^{31}P\{^1H\}$ NMR spectroscopy. A sample taken out from the system at the given time was cooled to the room temperature, dissolved in D_2O, alkalized with 10 N NaOH to pH ≈ 12, and $^{31}P\{^1H\}$NMR spectrum was immediately recorded. Some evidence of hydrolysis was observed only when NMR tubes were kept for a much longer time (more than 5 h). Larger samples taken out for different types of analysis [e.g. MALDI-TOF-ms (MTms)] were kept below 0 °C.

NMR Spectra

All NMR spectra were recorded on a Bruker AC-200 spectrometer. NMR tubes were filled with samples immediately before measurements. Standard acquisition parameters: 1s for ^1H, and 2s for $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR were applied for most of the spectra. $^{13}C\{^1H\}$ NMR spectra for quantitative estimation of various structures in the product were recorded with inverse gated proton decoupling and time delay between pulses equal to 30 s. 2D NMR experiment
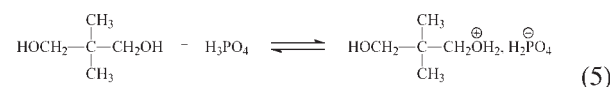
^{31}P-^1H GRASP HMBC was performed on the Bruker Avance TM DRX500 spectrometer with channel F1 and F2 frequencies, respectively, 500.13 and 202.46 MHz.
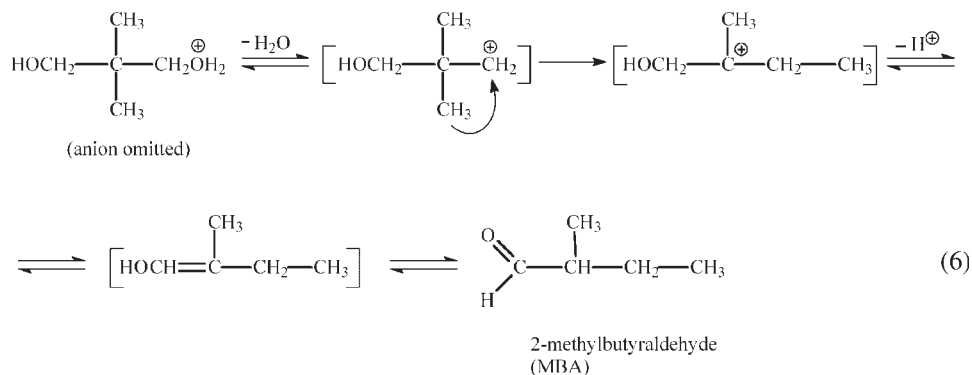
MALDI-TOF-ms Experiments

Spectra of polycondensation products were recorded either directly, dissolving the sample in the matrix [trihydroxy acetophenone (THA) with addition of ammonium citrate (AC)] or after conversion at first the acid groups into the ammonium salts. Negative and positive ionization spectra were recorded. Products methylated with diazomethane were also analyzed using THA/AC as the matrix; only spectra containing positive ions (MW+1) were recorded. Some of the MALDI-TOF mass spectroscopy (MTms) spectra were recorded using a Voyager-Elite (PerSeptive Biosystems), the other ones on the Bruker Reflex IV mass spectrometer. In all experiments the accelerating voltage 20 kV was used.

RESULTS AND DISCUSSION

The first experiments were performed with neopentyl glycol (2,2-dimethylpropanediol-1,3) (NPG). This glycol was first chosen since this compound does not contain H atoms attached to the C atom in the β-position to the terminal —OH group, therefore the dehydration could not take place. During reaction of NPG with H_3PO_4 at various conditions the only observed product was 2-methylbutyraldehyde (MBA), formed almost quantitatively (over 90 mol %). Thus, when H_3PO_4 and NPG were heated at (e.g.) 120 °C, then the organic reaction product that distilled off from the reaction mixture was almost exclusively MBA. The reaction path could be as shown below (schematically):

$$\text{HOCH}_2\text{—}\overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}}\text{—CH}_2\text{OH} \ - \ H_3PO_4 \ \rightleftharpoons \ \text{HOCH}_2\text{—}\overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}}\text{—CH}_2\overset{\oplus}{\text{OH}}_2. \, H_2\overset{\ominus}{P}O_4 \quad (5)$$

(whether reaction involves one molecule of H_3PO_4 or a dimer, in which after the proton transfer the anion is stabilized by the second molecule of acid, is not known).

$$\text{HOCH}_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\text{CH}_2\text{OH}_2^{\oplus} \underset{}{\overset{-\text{H}_2\text{O}}{\rightleftharpoons}} \left[\text{HOCH}_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\text{CH}_2^{\oplus}\right] \longrightarrow \left[\text{HOCH}_2-\overset{\overset{\displaystyle CH_3}{|}{\oplus}}{C}-\text{CH}_2-\text{CH}_3\right] \overset{-\text{H}^{\oplus}}{\rightleftharpoons}$$

(anion omitted)

$$\rightleftharpoons \left[\text{HOCH}=\overset{\overset{\displaystyle CH_3}{|}}{C}-\text{CH}_2-\text{CH}_3\right] \rightleftharpoons \overset{\displaystyle O}{\underset{\displaystyle H}{\diagdown}}\text{C}-\overset{\overset{\displaystyle CH_3}{|}}{C}\text{H}-\text{CH}_2-\text{CH}_3 \qquad (6)$$
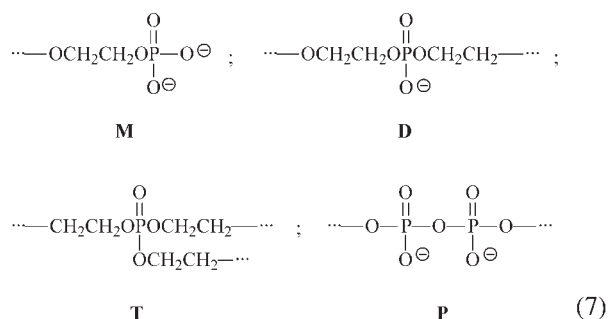
2-methylbutyraldehyde
(MBA)

The presented reaction path does not pretend to exactness, but shows in which way the aldehyde could be formed. The brackets indicate that some of the transient products that are formed could not be isolated. The identity of MBA was confirmed by ^{1}H and ^{13}C{^{1}H} NMR spectra, and formation of the MBA hydrazone in reaction with 2,4-dinitrophenylhydrazine. The hydrazone was identified by NMR spectra and T_m. The mass spectra gave molecular mass of MBA hydrazone equal to $m/z = 267$ in agreement with the calculated mass. Finally, the product was compared with the original MBA (Aldrich). Their bp were practically identical (equal to $\sim$90 °C); ^{1}H and ^{13}C{^{1}H} NMR were also the same.

H$_3$PO$_4$–HOCH$_2$CH$_2$OH Polycondensation

Polymer Structure

^{31}P NMR Spectra. This polycondensation was conducted either in bulk or in solvents, namely in 1,4-dioxane (giving a homogenous solution at the beginning of reaction; at the later stages polymer precipitates out from solution), or at heterogeneous conditions in hydrocarbon solvents as described in the Experimental section. In the hydrocarbon solvents EG, H$_3$PO$_4$, and reaction products are not soluble. The heterogeneous mixture was vigorously stirred at the boiling point, removing H$_2$O in the form of a hetero-azeotrope. In some polycondensations catalysts were used. The progress of reaction was studied by ^{1}H, ^{31}P{^{1}H}, and ^{13}C{^{1}H} NMR. Samples taken at certain time intervals were dissolved in H$_2$O at room temperature and brought to pH $\approx$ 12. It has been proven that during prolonged standing at these conditions (up to 10 h), proportions of the peak areas did not change. In agreement

with our earlier works,[27] chemical shifts of the analyzed products in the form of their salts (at pH $\approx$ 12) are as follows (in ppm δ from external H$_3$PO$_4$): H$_3$PO$_4$ 5.5–5.7, monoester (M) 3.9–4.3, diester (D) 0.0–1.2, triester (T) -1.4 to -0.5, and pyro (PP) -5 to -4.

$$\cdots-\text{OCH}_2\text{CH}_2\text{O}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O\ominus}{|}}{P}}-\text{O}^{\ominus} \quad ; \quad \cdots-\text{OCH}_2\text{CH}_2\text{O}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O\ominus}{|}}{P}}\text{OCH}_2\text{CH}_2-\cdots \quad ;$$

M   **D**

$$\cdots-\text{CH}_2\text{CH}_2\text{O}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_2CH_2-\cdots}{|}}{P}}\text{OCH}_2\text{CH}_2-\cdots \quad ; \quad \cdots-\text{O}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O\ominus}{|}}{P}}-\text{O}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O\ominus}{|}}{P}}-\text{O}-\cdots$$

T   **P**   (7)

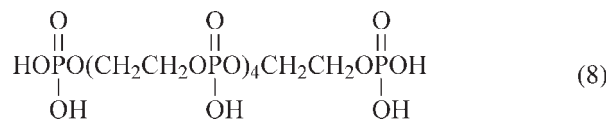Typical ^{31}P{^{1}H} NMR spectra taken at three different stages of polycondensation are given in Figure 1(a–c).

At the early stage of reaction at 150 °C in bulk ([EG]$_0$/[H$_3$PO$_4$]$_0$ = 1.59), when 12% of H$_3$PO$_4$ reacted there are only single peaks in the ^{31}P{^{1}H} NMR at 6.21 ppm (H$_3$PO$_4$), 4.86 ppm (M), and 1.45 ppm (D), [M]/[D] $\cong$ 2.0. At the further progress [Fig. 1(b)], at 70% of H$_3$PO$_4$ conversion, the ratio of [M]/[D] becomes equal to $\sim$1.6. Finally, at 96% conversion of H$_3$PO$_4$ there is an inverted ratio of [M]/[D] ($\sim$0.7), and some triesters are formed as well as a very small amount of pyrophosphorus compounds (not shown). Most probably at the 12% conversion of H$_3$PO$_4$ [Fig. 1(a)], when $\sim$15% of the —OH groups of EG reacted, the first reaction products are as follows: HOCH$_2$CH$_2$OP(O)(OH)$_2$ (M) and HOCH$_2$CH$_2$OP(O)(OH)OCH$_2$CH$_2$OH (D). As it will be shown later, at higher conversion the majority of macromolecules have mostly two
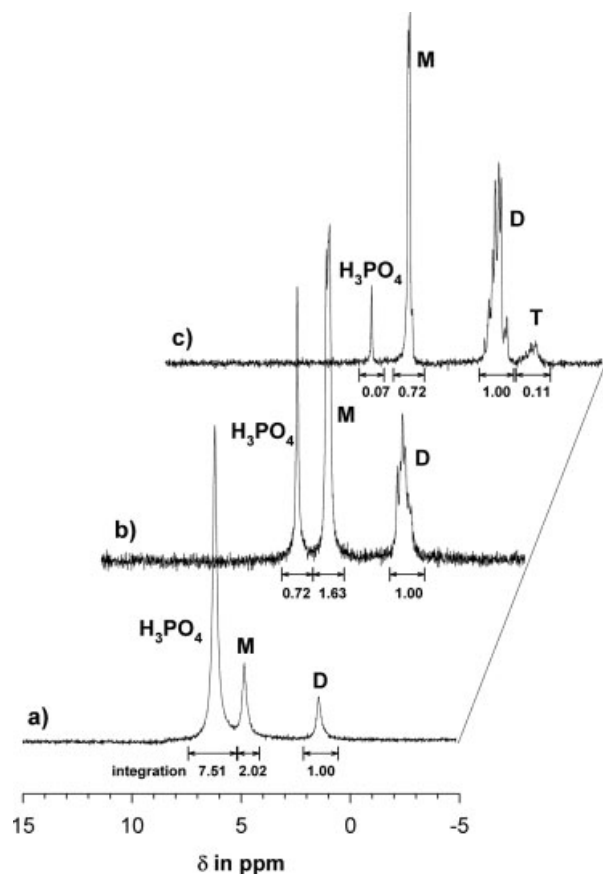
Figure 1. $^{31}P\{^1H\}$ NMR spectra (in D_2O, pH = 12) of the reaction mixture after 1.25 h (a), 11.0 h (b), and 17.5 h (c). Conditions: $[EG]_0/[H_3PO_4]_0 = 1.59$, 150 °C, reaction in bulk.

acidic end groups; thus one of the reaction product, with the ratio [D]/[M] units equal to 2 (this is the average ratio) could have the structure shown below:

$$\underset{\underset{OH}{|}}{\overset{\overset{O}{\|}}{HOPO}}(CH_2CH_2\underset{\underset{OH}{|}}{\overset{\overset{O}{\|}}{OPO}})_4CH_2CH_2\underset{\underset{OH}{|}}{\overset{\overset{O}{\|}}{OPOH}} \qquad (8)$$

Studies of the dependence of the determined signal integrals ratio [M]/[D] (ratio of the mono/diesters) on the acquisitions conditions applied to our samples ($^{31}P\{^1H\}$ NMR has been measured) indicated that nuclear overhauser effect (NOE) can be eliminated when the time delay equal to 10 s was used. This delay was further adopted for the quantitative integration.
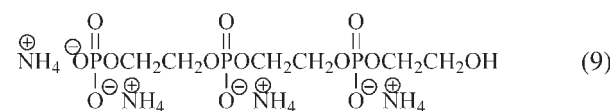
In all three regions of the $^{31}P\{^1H\}$ NMR spectrum, namely for M, D, and T, there is a number of single peaks, indicating nonequivalence of the

P-atoms in these groups. Several structures could be responsible for these differences. Some are described in the next section. However, in the M area (over 100 of the $^{31}P\{^1H\}$ NMR spectra were recorded) there are usually two singlets with small shoulders. The major peak with intensity increasing in time should be related to the "normal" end group: $—OCH_2CH_2OP(O)(OH)$ $OCH_2CH_2OP(O)(OH)_2$, the other one, decreasing with time could be related to the $(OH)_2P(O)OCH_2$- $CH_2OP(O)(OH)_2$ (ethylenediphosphate).
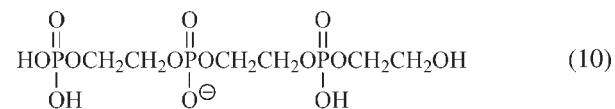
MALDI-TOF Mass Spectroscopy

The $^{31}P\{^1H\}$ NMR spectra shortly described in the previous section give only a general information on the structures of the reaction products. More detailed information could have been expected from the MALDI-TOF-ms studies. Analysis of the MTms data is difficult because ionic groups are present in the main chains as well as at the chain ends.

At first MTms was applied for polymers which converted into their ammonium salts, and mixture of trihydroxyacetophenone (THA) and ammonium citrate (AC) was used as a matrix. It is known that at such conditions cations are strongly complexed and the spectrum can be recorded with a negative ionization.[28] At these conditions the observed original mass peaks appear at the positions of molecules in their acidic forms, -1; e.g., for a molecule:

$$\underset{\underset{O^{\ominus}\ \overset{\oplus}{NH_4}}{|}}{\overset{\overset{O}{\|}}{\underset{\oplus}{NH_4}\ \overset{\ominus}{O}POCH_2CH_2}}\underset{\underset{O^{\ominus}\ \overset{\oplus}{NH_4}}{|}}{\overset{\overset{O}{\|}}{OPOCH_2CH_2}}\underset{\underset{O^{\ominus}\ \overset{\oplus}{NH_4}}{|}}{\overset{\overset{O}{\|}}{OPOCH_2CH_2OH}} \qquad (9)$$

with a molar mass equal to 442, the corresponding peak appears at the molar mass equal to 369 from an anion of a structure given below (or its isomers):

$$\underset{\underset{OH}{|}}{\overset{\overset{O}{\|}}{HOPOCH_2CH_2}}\underset{\underset{O^{\ominus}}{|}}{\overset{\overset{O}{\|}}{OPOCH_2CH_2}}\underset{\underset{OH}{|}}{\overset{\overset{O}{\|}}{OPOCH_2CH_2OH}} \qquad (10)$$

Then, it appeared that when the products are dissolved in the THA/AC matrix, conversion to the ammonium salts is not necessary, and both positive and negative ionization spectra can be recorded.

The MTms spectrum (positive ionization) of a sample prepared at $[EG]_0/[H_3PO_4]_0 = 1.1$ (composition of the product is given in the cap-
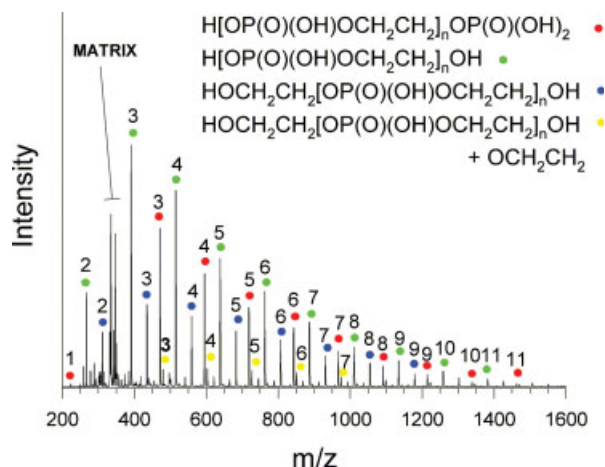
Figure 2. MTms spectrum of the polycondensation product, $[EG]_0/[H_3PO_4]_0 = 1.1$, reaction time 107 h, azeotropic removal of water (heptane, 98 °C), catalyst $Sc(OTf)_3$ 0.17 wt % (H_3PO_4:monoester:diester:triester = 2.8:28.0:59.1:10.1), matrix THA/AC, positive ionization, (the product indicated in red circle with $n = 2$ should have $m/z = 346.06$ and is masked by matrix by coincidence). Numbers over peaks are equal to n in the presented formulae.

tion of figure) is shown in Figure 2. The assignments of the corresponding peaks are given directly in the figure, whereas in Table 1 the comparison of the calculated (using a freeware program IsoPro 2.1 by MS/MS Software) and determined m/z are given for a part of spectrum, namely for m/z from 500 to 900 (shown in Fig. 2).

At the positive ionization the main series of peaks corresponds to oligomers with both types of the end groups, namely $-CH_2CH_2OH$ and $-CH_2OP(O)(OH)_2$. The other population of peaks, corresponding to oligomers with both end groups $-CH_2OP(O)(OH)_2$ is almost equally frequent and it seems to be much less of macromolecules with both $-CH_2CH_2OH$ end groups. There are some macromolecules with $-(CH_2 CH_2O)_n-$ units ($n = 2$ or 3; their origin is discussed in a section "Side reactions"..) and small population of macromolecules devoid of H_2O, that could contain cyclic structures from the end-to-end closure or containing cyclics "in the chain".

However, at the negative ionization contribution of signals of oligomers with both acidic groups is higher than contribution of chains with both types of the end groups. In Figure 3 fragments of the MTms spectra of the same sample in the same matrix, and differing only by the mode of ionization, are presented. The changes of the response coefficients of products differing by the end groups, when ionization mode is changed from positive to negative, are clearly visible. When ionization is changed from positive to negative, the detected intensity of peaks corresponding to chains with both acidic ends increases, and detected intensity of chains with hydroxyethyl groups (or mixed) at both ends decreases.

Thus, the ratio of the observed intensities does not necessarily correspond to the actual proportions of products at any of the two studied modes of ionization, and perhaps none of the modes of ionization gives the exact ratio. The average value of the two is maybe the closest to reality, although this assumption was not further studied.

Table 1. Comparison of Observed and Calculated Positions of Signals for the Polycondensation Products (m/z Range 500–900)

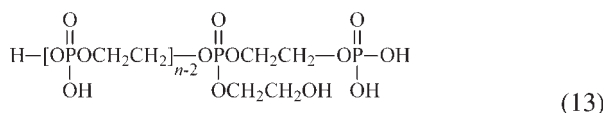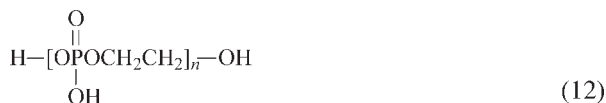| Structures (Isomers Not Shown)	m/z (Observed)	Computed (Expected Values)	
		Average	Peak Maximum
H[OP(O)(OH)OCH$_2$CH$_2$]$_4$OH	514.78	515.146	514.981
H[OP(O)(OH)OCH$_2$CH$_2$]$_4$OP(O)(OH)$_2$	594.71	595.126	594.947
HOCH$_2$CH$_2$[OP(O)(OH)OCH$_2$CH$_2$]$_4$OH	558.78	559.199	559.007
HOCH$_2$CH$_2$[OP(O)(OH)OCH$_2$CH$_2$]$_4$OH + [OCH$_2$CH$_2$]	602.76	603.252	603.033
H[OP(O)(OH)OCH$_2$CH$_2$]$_5$OH	638.68	639.179	638.973
H[OP(O)(OH)OCH$_2$CH$_2$]$_5$OP(O)(OH)$_2$	718.56	719.158	718.939
HOCH$_2$CH$_2$[OP(O)(OH)OCH$_2$CH$_2$]$_5$OH	682.65	683.232	682.999
HOCH$_2$CH$_2$[OP(O)(OH)OCH$_2$CH$_2$]$_5$OH + [OCH$_2$CH$_2$]	726.64	727.285	727.026
H[OP(O)(OH)OCH$_2$CH$_2$]$_6$OH	762.56	763.211	762.966
H[OP(O)(OH)OCH$_2$CH$_2$]$_6$OP(O)(OH)$_2$	842.51	843.192	842.932
HOCH$_2$CH$_2$[OP(O)(OH)OCH$_2$CH$_2$]$_6$OH	806.57	807.266	806.992
HOCH$_2$CH$_2$[OP(O)(OH)OCH$_2$CH$_2$]$_6$OH + [OCH$_2$CH$_2$]	850.56	851.319	851.018
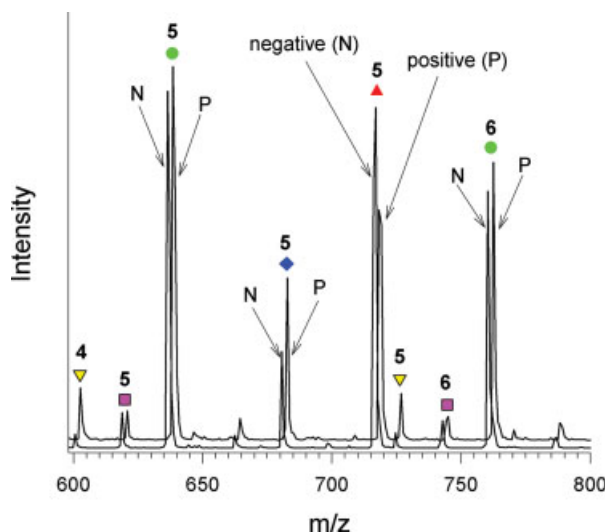
Figure 3. Fragments of the MALDI TOF spectra of the polycondensation product from Figure 2, at positive (P) (shifted slightly up) and negative (N) ionization. End groups: red triangle indicates both $-CH_2OP(O)(OH)_2$, green circle indicates $-CH_2CH_2OH$, and $-CH_2OP(O)(OH)_2$, blue diamond indicates both $-CH_2CH_2OH$, other structures: a yellow inverted triangle indicates $HOCH_2CH_2[OP(O)(OH)OCH_2CH_2]_nOH + OCH_2CH_2$ (oxyethylene unit can be incorporated either in the main chains or the end groups), purple square indicates $H[OP(O)(OH)OCH_2CH_2]_nOH - [H_2O]$ (cyclic?). Note the difference of 2 units between positions of peaks of the given oligomer at negative ($M_x - 1$) and positive ($M_x + 1$) ionization (M_x – molar mass of the oligomer).

In the observed structures of macromolecules (with identical, acidic or $-CH_2CH_2OH$ end groups, or with both types of the end groups) the branched units, i.e., triester ones like

$$\cdots\!-\!CH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_2CH_2-\cdots}{|}}{P}}CH_2CH_2-\cdots \tag{11}$$
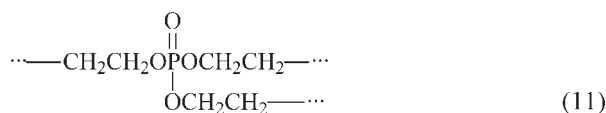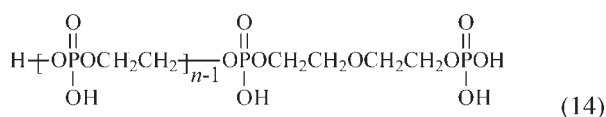
are usually not taken into account because they are formed only at high temperature and/or prolonged polycondensation. These triester structures cannot be distinguished in MTms from their linear isomers when the original macromolecules in their acidic forms are studied. Indeed, in formulae (12) and (13) compositions are identical, namely $P_nC_{2n}O_{4n+1}H_{6n+2}$.

Therefore, it is not clear, whether MTms signals ascribed to macromolecules of this composition belong to structures (12) or (13) or (most probably) both.
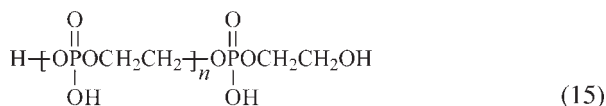
$$H-[O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}OCH_2CH_2]_n-OH \tag{12}$$

$$H-[O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}OCH_2CH_2]_{n-2}-O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_2CH_2OH}{|}}{P}}OCH_2CH_2-O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH \tag{13}$$

However, according to the $^{31}P\{^1H\}$ NMR spectra (cf. Fig. 1), the proportion of the triesters (13) is very low.
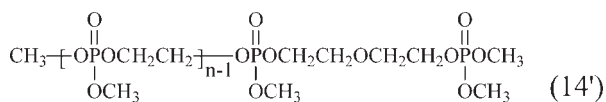
Another coincidence of similar compositions of macromolecules differing in structures is illustrated below [macromolecules (14) and (15)]:
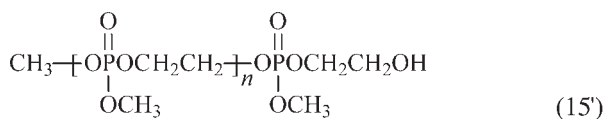
$$H\!+\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}OCH_2CH_2\!+_{\!n-1}\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}OCH_2CH_2OCH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}OH \tag{14}$$

or

$$H\!+\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}OCH_2CH_2\!+_{\!n}\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}OCH_2CH_2OH \tag{15}$$

Both (14) and (15) have the same composition, namely $P_{n+1}C_{n+2}O_{2(n+1)}H_{5n+7}$, and distinction on the basis of the $^{31}P\{^1H\}$ NMR spectra is more difficult. These two populations could, however, be distinguished in MTms after methylation, since into macromolecules (14) $n + 3$ methyl groups are introduced whereas into macromolecules (15) only $n + 2$. To make it clear the corresponding methylated structures are shown as (14′) and (15′).

$$CH_3\!+\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}OCH_2CH_2\!+_{\!n-1}\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}OCH_2CH_2OCH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}OCH_3 \tag{14′}$$

or

$$CH_3\!+\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}OCH_2CH_2\!+_{\!n}\!O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}OCH_2CH_2OH \tag{15′}$$

Thus, methylation allows distinguishing in MTms all three types of linear macromolecules, differing in the structures of the end groups.

The methylated samples are nonionic. Therefore, the usual influence of the degree of ionicity of our products on the MALDI-TOF-ms response coefficients disappears.

The MTms spectrum (only major peaks are shown) of the methylated product is given
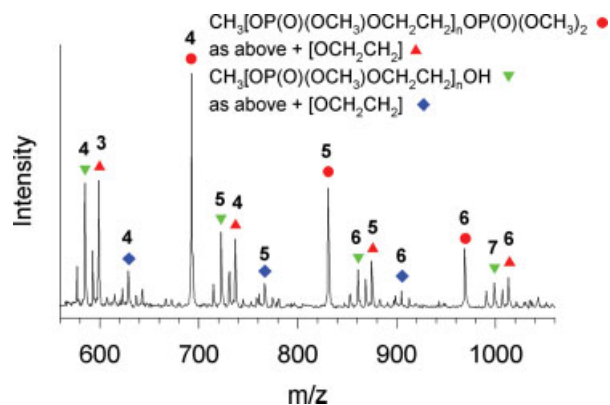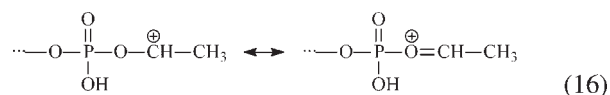
Figure 4. Fragment of the MTms spectrum of the polycondensation product from Figure 2, after methylation. Matrix THA/AC, positive ionization; $n = 3$–7. Macromolecules with both hydroxyl end groups are not shown (see text). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

in Figure 4. The dominating signals correspond to the chains having both acidic end groups.

Another example of the MTms spectrum of the methylated product, with negligible amount of triesters (according to the $^{31}P\{^1H\}$ NMR) is shown in Figures 5 and 6. Macromolecules of the highest molar mass that are clearly detected have polymerization degrees over 20 ($M_n \sim 3000$). Dominating structures are chains with both acidic end groups (here methylated), as described earlier. The expanded fragment of the spectrum (Fig. 6) shows that contribution of other structures is considerably lower.

In this spectrum signals of oligomers with vinyl end groups, formed as side products by dehydration are also visible. The contribution of this population of macromolecules is low (could not be seen in NMR). The relatively high-response coefficient of these signals in MTms could result from the relatively high stability of the protonated vinyl esters:

$$\cdots\text{—O—}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}\text{—O—}\overset{\oplus}{C}H\text{—}CH_3 \;\longleftrightarrow\; \cdots\text{—O—}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}\text{—}\overset{\oplus}{O}=CH\text{—}CH_3 \qquad (16)$$

formed during the MTms experiment.

Assuming that the response coefficients in MTms of the methylated oligomers do not depend on the polymerization degree, the P_n of the product shown in Figures 5 and 6 is equal to 5.4. Most probably the real P_n is higher, remembering that in the most known cases the response coefficient falls down with increasing P_n.

How Does the Reaction Proceed?

It is known, that phosphorylation of alcohols when H_3PO_4 is taken as the reagent is slow, whereas similar reaction with P_4O_{10} is fast. Therefore, an experiment was performed to determine the actual reaction path and to establish the role of pyrophosphoric acid (PP) that may be formed. In Figure 7 the course of this experiment is shown. First, H_3PO_4 was heated at $\sim$100 °C and water was removed azeotropically with heptane. PP (mostly) and some polyphosphoric acid (PPA, $\delta = -19$ to -20 ppm) were formed as it was evidenced from the $^{31}P\{^1H\}$ NMR spectrum. Approximately 20 mol % of the total amount of the phosphorus atoms were then found in the formed PP ($\delta = -5$ to -4 ppm). The corresponding amount of H_3PO_4 disappeared (accuracy of measurements $\leq 5\%$).

$$2\,H_3PO_4 \;\rightleftharpoons\; (HO)_2(O)P\text{-}O\text{-}P(O)(OH)_2 + H_2O \qquad (17)$$
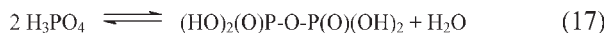
(in further discussion the formation and disappearance of the small amounts of the polyphosphoric acids (tri and four) are omitted).

When EG was introduced into this mixture at 100 °C, PP disappeared almost immediately and $\sim$10 mol % of phosphorus moved back to H_3PO_4. At the same time, M and D are formed. There should also be 10 mol % of phosphorus in these
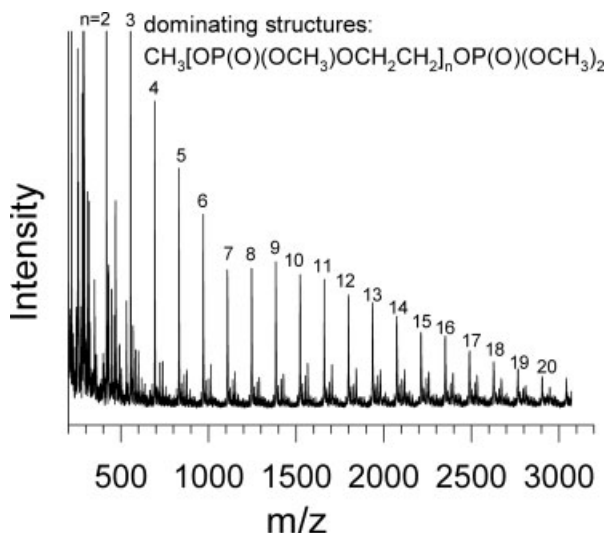
Figure 5. MTms spectrum of the methylated polycondensation product, $[EG]_0/[H_3PO_4]_0 = 1.62$, reaction time 209 h, azeotropic removal of water (heptane, 98 °C), catalyst $Sc(OTf)_3$ 0.15 wt % (H_3PO_4:monoester:diester:triester = 12.1:44.6:38.9:4.4). Matrix THA/AC, positive ionization.
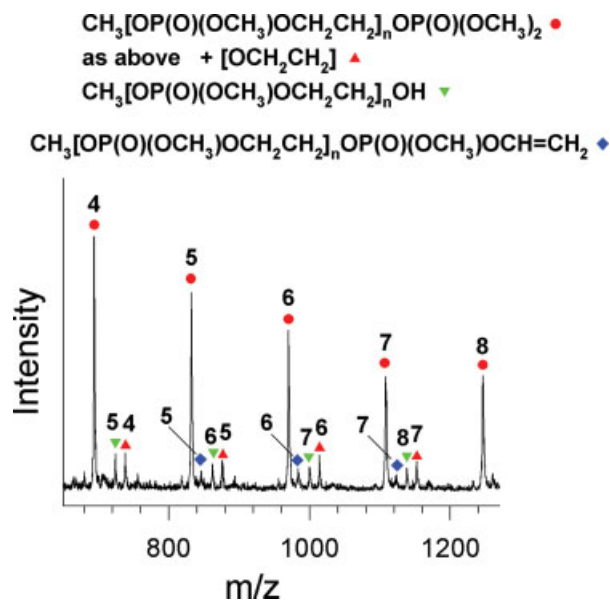
Figure 6. Expanded fragment of the MTms spectrum of the polycondensation product from Figure 5, showing signals related to various structures. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

esters, but due to the larger error in integration of the small peaks, it shows that there is less than 10 mol %. The 10 mol % of H_3PO_4 formed indicates, however, that PP was indeed used in the esterification of the corresponding amount of EG. If PP were reacting (in the discussed first stage) with H_2O introduced (as impurity) with EG, the same amount of phosphorus should appear in H_3PO_4 (i.e. 20%) as disappeared from PP. Then, further heating of the system has shown the usual reaction path in which more M and D are formed. The strict stoichiometry is observed at this period of reaction. When, e.g., 60% of H_3PO_4 reacted, there is in the system 30 mol % of each of the esters: M and D formed. No PP could be detected at this period of reaction.

Results shown in Figure 7 indicate that formation of PP is relatively slow but its reaction with EG is very fast. Besides, as long as EG is present in the system there is no detectable amount of PP. Therefore, it has experimentally been shown, in agreement with the Cherbuliez's[23] suggestion, that the true phosphorylating agent is not H_3PO_4 itself but PP, that is present at a certain (low) steady-state concentration throughout the process. Whether H_3PO_4 contributes to phosphorylation as such was not established.

## Conversion of H_3PO_4, Mono- and Diesters Formation as a Function of Time

"Kinetics of Polycondensation"

The change of concentrations of the individual molecules, monoesters, and diesters during the course of polycondensation could not be determined. The reason is explained in the section on the MTms studies, where it was indicated, that the response coefficient depends very much on the structure of the end groups. Moreover, positions of the corresponding individual peaks in the $^{31}P\{^1H\}$ NMR spectra change with the degree of H_3PO_4 conversion. Unfortunately, even having methylated samples taken at various stages of reaction and determining the $^{31}P\{^1H\}$ NMR spectra and MTms, this kind of exact analysis was not possible. Thus, although it has originally been planned to follow the fate of every individual separately, the present section describes much less ambitious work. It gives merely dependence on time of the concentrations of H_3PO_4, monoesters, and diesters, independently of the subtle structures. In other words, it gives the global ratio of the end groups to the repeating units as a function of time. At higher temperatures, e.g., at 150 °C, in bulk, and at $[EG]_0/[H_3PO_4]_0$ ratio equal to 1.6 the process is quite well reproducible and is illustrated by Figure 8. $[H_3PO_4]$ goes down to the measured ~4% of $[H_3PO_4]_0$, [M] goes through a maximum, and [D] increases steadily.
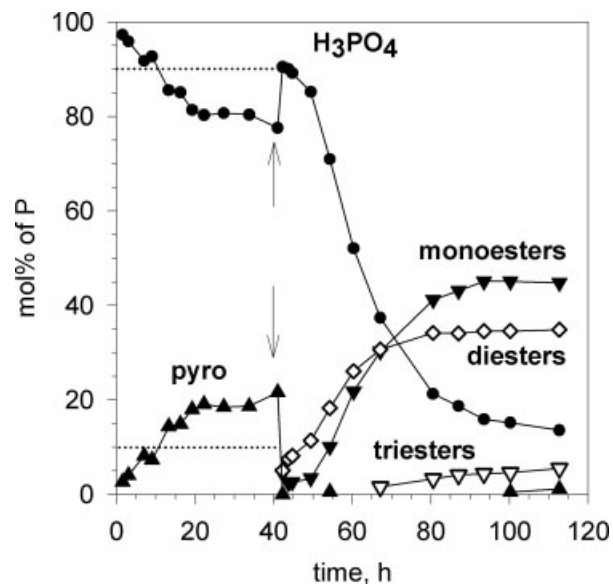

Figure 7. Kinetics of azeotropic (heptane, 98 °C) polycondensation of H_3PO_4 with EG. EG added at time = 41 h when about 20% of P atoms were in pyrophosphoric structures. Note fast addition of EG to pyro-compound.
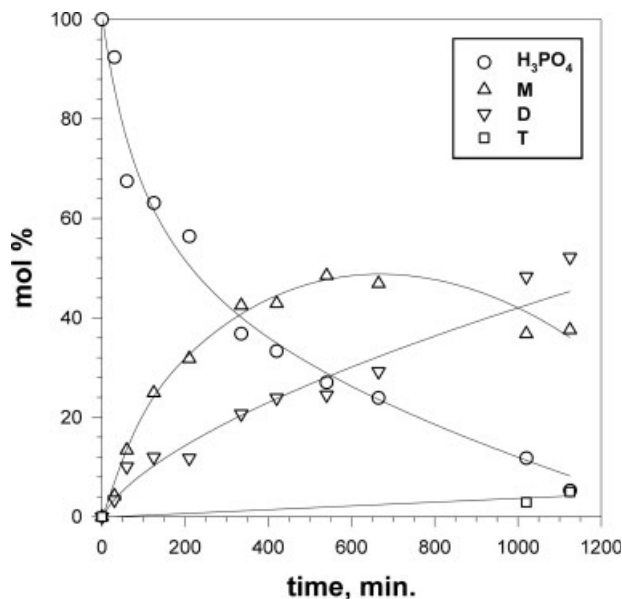
Figure 8. Kinetics of polycondensation carried out at 150 °C, argon stream flow, $[EG]_0/[H_3PO_4]_0 = 1.58$, reaction in bulk.
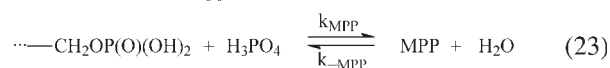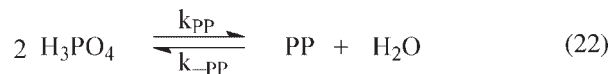
When polycondensation was conducted at the same starting $[EG]_0/[H_3PO_4]_0$ ratio, but at 100 °C, then formation of D becomes faster than formation of M (Fig. 9).

These results, together with data from Figure 8 allow proposing the following path of reaction:


$$(18)$$

$$(19)$$

$$(20)$$

$$(21)$$
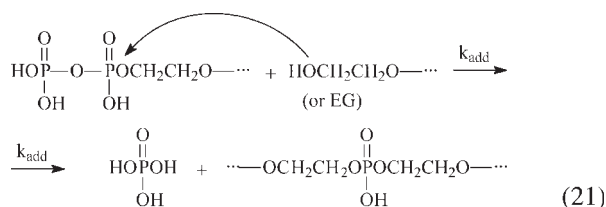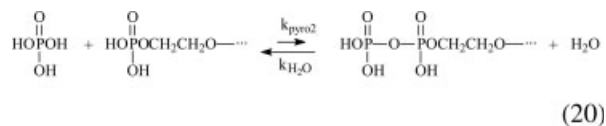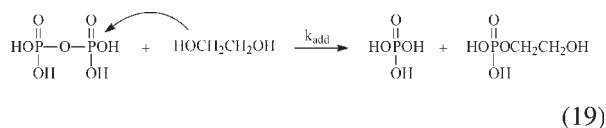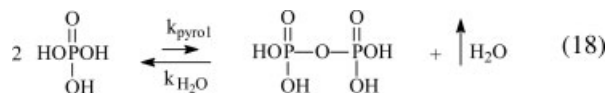
The rate-limiting steps for the first and further products formation is formation of the pyrostructures. However, the steady-state concentrations of PP and its monoester (MPP) apparently depend on temperature in a different way. Formation of D is faster than formation of M at 100 °C,

whereas at 150 °C the reverse order of rates is observed. There are two reactions responsible for the steady-state concentrations of PP and MPP (beside the reactions of PP and MPP with alcohol groups) namely formation and hydrolysis (back reaction). Thus, the resulting steady-state concentrations are described by equations below and the interplay of the forward and back reactions eventually give higher [PP] than [MPP] at 150 °C and the reverse order at 100 °C.

$$2\ H_3PO_4 \quad \underset{k_{-PP}}{\overset{k_{PP}}{\rightleftharpoons}} \quad PP\ +\ H_2O \qquad (22)$$

$$\cdots\!-\!CH_2OP(O)(OH)_2\ +\ H_3PO_4 \quad \underset{k_{-MPP}}{\overset{k_{MPP}}{\rightleftharpoons}} \quad MPP\ +\ H_2O \qquad (23)$$

Side Reactions and Complete Scheme of Polycondensation

Small amounts of the side products (below 5%) were detected (besides some ethylene glycol) in water removed from the polycondensation systems. The ^1H NMR spectrum of these products, distilled from the reaction mixture (150 °C) is given in Figure 10. The presence of the following compounds was established:

$$(24)$$
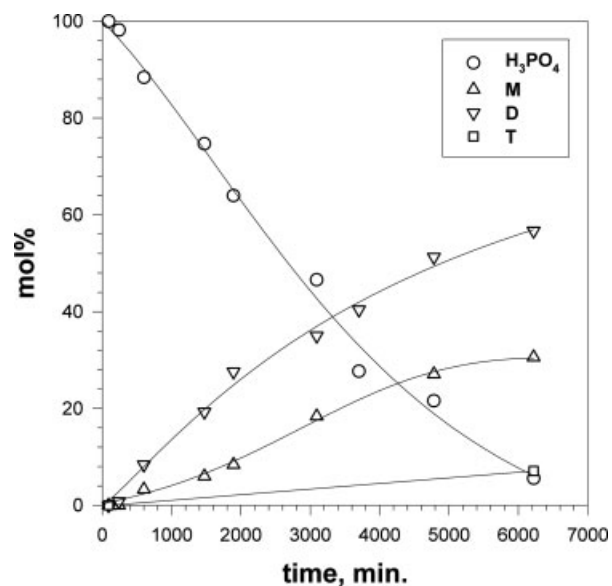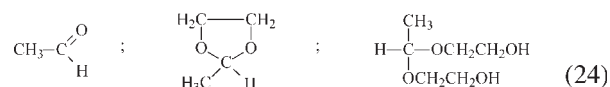
Figure 9. The dependence of the reaction mixture composition on time. Conditions: $[EG]_0/[H_3PO_4]_0 = 1.57$, 100 °C, reaction in bulk, argon stream flow, 0.15 wt % $Sc(OTf)_3$ used as catalyst.
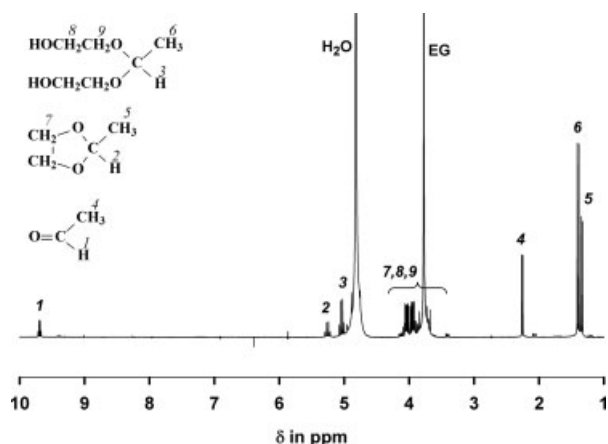
Figure 10. The ^{1}H NMR spectrum of the mixture of the volatile products collected during polycondensation EG with H_3PO_4 at 150 °C.
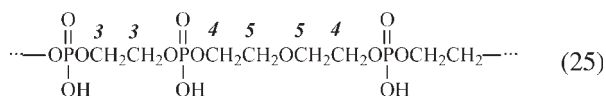
Formation of these compounds starts from acetaldehyde, which is a stable tautomeric form of the vinyl alcohol. It could be formed by dehydration of EG or by elimination process from the ester structures—monoesters and/or diesters (a small amount of oligomers with vinyl end group were detected in MTms in some experiments, cf. Fig. 6). Then, it reacts with EG, giving 2-methyl-1,3-dioxolane reacting further with the next molecule of EG and giving 2,2′-dihydroxy diethylene acetal. The amount of these products does not exceed 4.5% of the total amount of the volatile compounds.

The most important side products of polycondensation, with contribution varying in the range from a few to above 20% are oligomeric units in macromolecules derived from diethylene (DG) and triethylene glycols (TG). Not only these side products were detected in repeating units of oligomers (connecting two phosphoric groups or as the end groups) but also as free glycols in the reaction mixture.
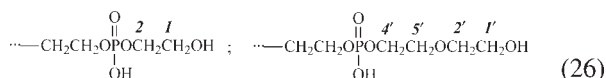
In Figure 11 an example of the ^{1}H NMR spectrum is shown. Description of signals is given in the figure. In the region close to 3.7 ppm signals corresponding to the $-CH_2C\underline{H}_2OC\underline{H}_2CH_2-$ groups are present.[29]

In Figure 12 the region from 60 to 75 ppm of the $^{13}C\{^1H\}$ NMR is given, and the major assignments are shown directly in this figure. The following supposed structures with EG and DG units have to be taken into account (first the backbone and then the end groups are shown).

The main chain:

$$\cdots-\underset{\underset{OH}{|}}{\overset{\overset{O}{\parallel}}{O}}POCH_2CH_2O\underset{\underset{OH}{|}}{\overset{\overset{O}{\parallel}}{P}}OCH_2CH_2OCH_2CH_2O\underset{\underset{OH}{|}}{\overset{\overset{O}{\parallel}}{P}}OCH_2CH_2-\cdots \quad (25)$$

The end groups:

$$\cdots-CH_2CH_2O\underset{\underset{OH}{|}}{\overset{\overset{O}{\parallel}}{P}}OCH_2CH_2OH \ ; \ \cdots-CH_2CH_2O\underset{\underset{OH}{|}}{\overset{\overset{O}{\parallel}}{P}}OCH_2CH_2OCH_2CH_2OH \quad (26)$$

It follows from the chemical shifts compared with the simulated spectra (using ACD/ChemSketch program, version: 4.55), that at $\sim$68 ppm there is a superposition of the chemical shifts belonging to C atoms from the end group (**2**) and from the DG repeating unit (**5**+**5′**) (small contribution from TG is indicated in the Fig. 12). Because at $\sim$61 ppm there is a chemical shift of the carbon atom at the end group adjacent to the $-OH$ group (**1**+**1′**), it is possible to estimate the
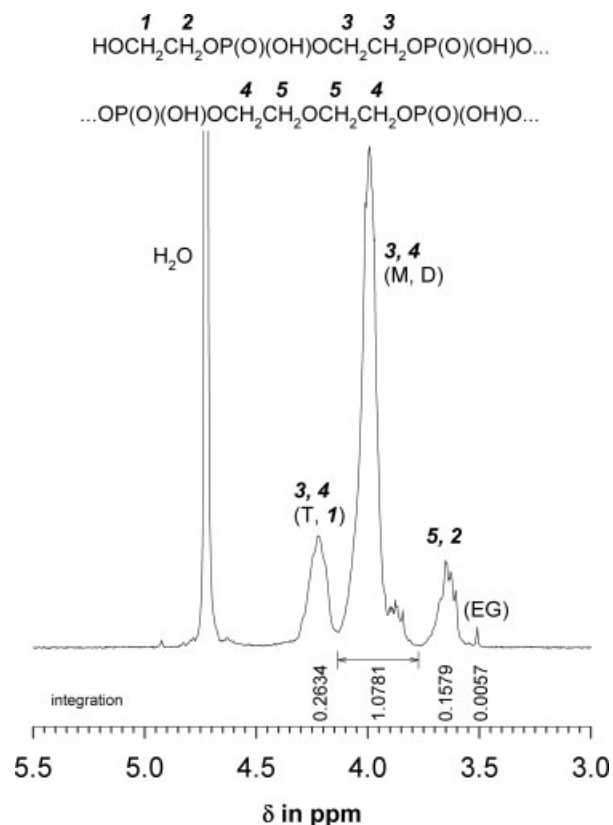
Figure 11. The ^{1}H NMR spectrum (in D_2O) of the polycondensation product, $[EG]_0/[H_3PO_4]_0 = 1.1$, reaction time 107 h, azeotropic removal of water (heptane, 98 °C), catalyst $Sc(OTf)_3$ 0.3 wt %, (H_3PO_4:monoester:diester:triester $= 2.8$:28.0:59.1:10.1); M, D, and T denote mono-, di-, and triester, respectively; other symbols explained in the figure.
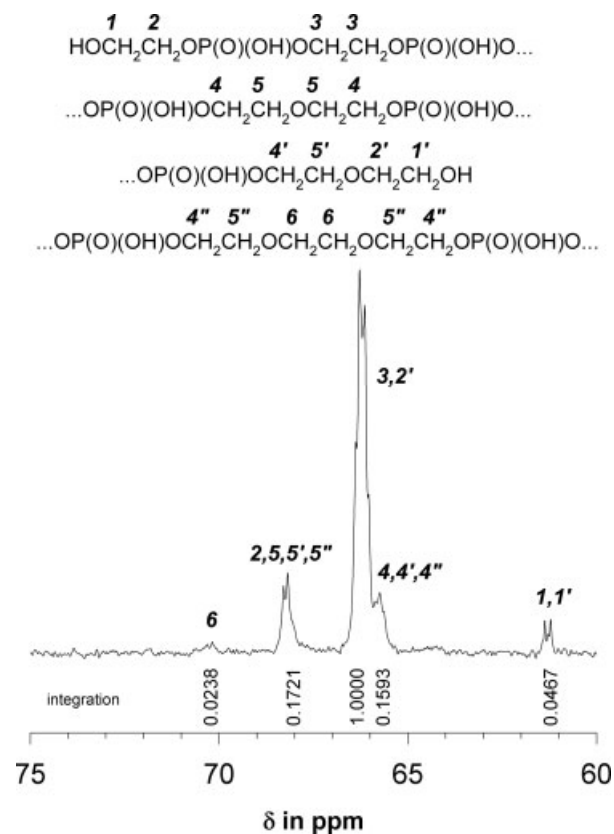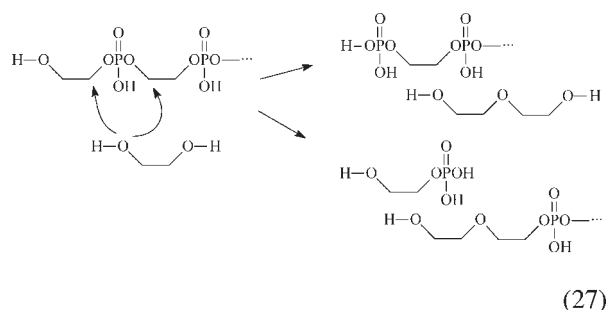
Figure 12. The $^{13}C\{^1H\}$ NMR spectrum (in D_2O) of the polycondensation product, $[EG]_0/[H_3PO_4]_0 = 1.62$, reaction time 209 h, azeotropic removal of water (heptane, 98 °C), catalyst $Sc(OTf)_3$ 0.15 wt %. (H_3PO_4:monoester:diester:triester = 12.1:44.6:38.9:4.4).

proportion of the DG units (comparing with integration for the EG units at ~66 ppm). This comparison is rather rough, especially because of neglecting the triethylene glycol (TG) units (small signal of the middle ethylene group of this unit is visible at ~70.2 ppm), and it gives ~10% of the DG units for the spectrum presented in Figure 12. The proportion of the DG units depends on the reaction conditions, the ratio of the starting components, temperature, time of reaction, and the catalyst used. No systematic studies have been undertaken in this area, although, for instance, in several experiments, particularly at lower temperature, the proportion of the DG (+TG) units was lower than 5%. To determine the presence of the TG units in the product the 2D NMR spectra were recorded. For the TG units there should be in the ^{31}P-^1H GRASP HMBC spectra, a region of the ^1H NMR spectra with no correlation with the $^{31}P\{^1H\}$ NMR. It follows from the cross peaks in Figure 13 that in the region from 3.50 to 4.00 ppm (^1H

NMR) there is the ^1H-^{31}P coupling, and that in the down field (below 3.50 ppm) such a coupling is absent. Thus, below 3.5 ppm ^1H NMR signals belong to the internal oxyethylene units of TG. Usually their proportion is low, and could be (after identification of signals from the 2D NMR spectra, as shown above) estimated from ^1H NMR spectra. These results have been confirmed by determination of EG, DG, and TG in the products of acidic hydrolysis of the product of polycondensation (in preparation).

DG and TG are formed by dealkylation reactions, shown below:

(27)

Figure 13. ^{31}P-^1H GRASP HMBC spectrum (in D_2O) of the polycondensation product, $[EG]_0/[H_3PO_4]_0 = 1.62$, reaction time 209 h, azeotropic removal of water (heptane, 98 °C), catalyst $Sc(OTf)_3$ 0.15 wt %. (H_3PO_4: monoester:diester:triester = 12.1:44.6:38.9:4.4). The ^1H NMR signals of the internal oxyethylene units of TG indicated by the arrow (see text).

Contribution of a direct dehydration of EG is also possible, although probably of less importance. Otherwise it would lead to high contribution of DG units at low conversions of polycondensation, which is not the case.

The dealkylation explains not only the presence of DG and TG but also explains why H_3PO_4 cannot be completely reacted, even at the prolonged reaction time and when excess of the EG was used. In dealkylation, at the corresponding end group H_3PO_4 is reformed. Dealkylation reaction is also responsible for higher proportion of oligomers with both acidic end groups, and the relatively low fraction of oligomers with alcohol end groups at both chain ends. The relevant processes are shown below (eq 28):

$$\text{(28)}$$
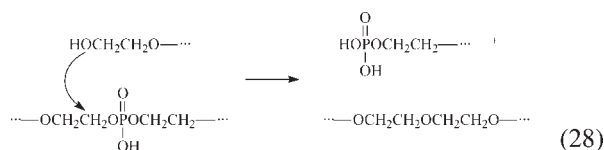
The relatively low-average polymerization degree of the products of polycondensation has the same origin.

In summary, the following major steps are taking place:

1. Reactions start by the relatively slow dimerization of H_3PO_4, forming pyrophosphoric acid (and higher polyphosphoric acids).

$$\text{(29)}$$
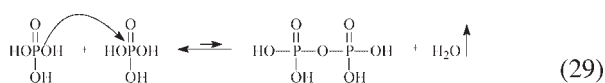
2. The first phosphorylation reaction, takes place by the reaction of pyrophosphoric acid with EG.

$$\text{(30)}$$
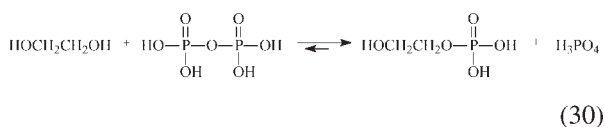
Whether H_3PO_4 takes part as such in phosphorylation is not clear.

3. Activation of the monophosphate esters (end groups) at any polymerization degree with H_3PO_4 proceeds via conversion of monoesters into pyrophosphoric acid esters, being the actual reactive acidic sites.

$$\text{(31)}$$
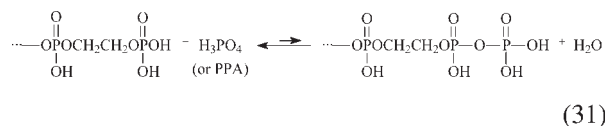
The steady-state concentration of pyro-compounds is determined by a slow reaction of their formation and fast reaction of their consumption—in reaction with water (the reversible reaction) and in the desired condensation with the alcohol groups. This concentration determines the rate of polycondensation.

4. This set of interconversions leads to over 95% conversion of H_3PO_4, complete conversion of EG, and formation of small number of the volatile side products (below 5%). The polycondensation product is mostly linear with a structure of poly(ethylene phosphate) as follows:

$$X-(CH_2CH_2O)\underset{\overline{n'}}{-}\left[\underset{OH}{\overset{O}{\overset{\|}{P}}}(OCH_2CH_2)\underset{\overline{n}}{-}\right]_m Y$$
$$\text{(32)}$$
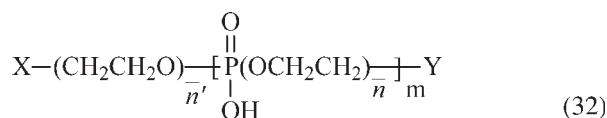
where $\overline{n}, \overline{n'} < 2$; $n, n' = 1, 2,$ or 3, mostly 1; X, Y are $-OP(O)(OH)_2$ and/or $-OH$ groups (with identical, acidic, or $-CH_2CH_2OH$ end groups, or with both types of end groups).

5. Some branch points (triester) are formed only at high temperature and prolonged polycondensation. The much lower reactivity of the third acidic function may be related to the intramolecular H-bonding. Addition of a catalyst (e.g. salts of triflic acid) is only slightly increasing the rate of polycondensation but allows preparation of the less colored products. The more detailed influence of various catalysts is not discussed in this article.

6. The dealkylation process with EG or any oligomer having an alcohol end group is the main side reaction responsible for the limited molar masses of the products and for the predominant presence of the acidic end groups. Dealkylation at the end group releases back H_3PO_4.

CONCLUSIONS

Polycondensation of H_3PO_4 with ethylene glycol at moderate temperature (100–150 °C) gives poly (ethylene phosphates), determined by MALDI-

TOF-ms P_n up to 21. Nevertheless, average P_n as determined from the end groups is significantly lower. Oligomeric macromolecules (oligomolecules) with two $-OP(O)(OH)_2$, two $-CH_2CH_2$ OH, or two different end groups are formed. Oligomers with two acidic end groups (monoesters of H_3PO_4) dominate. In this relatively simple and surprisingly not earlier described process, low-molecular mass macromolecules are formed because of the dealkylation reaction (ether bond formation) resulting from the nucleophilic attack of the $HOCH_2-$ groups on the carbon atom, instead of the attack on phosphorus atom, responsible for the desired polycondensation. Typical P_n determined by MTms is close to 5.0, whereas the largest individual macromolecules observed by MTms have degrees of polymerization close to 25. Dealkylation introduces repeating units of diethylene- and triethylene glycol and increasing proportion of acidic end groups.

REFERENCES AND NOTES

1. Pretula, J.; Kaluzynski, K.; Wisniewski, B.; Szymanski, R.; Loontjens, T.; Penczek, S. J Polym Sci Part A: Polym Chem 2006, 44, 2358.
2. Penczek, S. Pure Appl Chem 1976, 48, 363.
3. Kaluzynski, K.; Libiszowski, J.; Penczek, S. Makromol Chem 1977, 178, 2943.
4. Libiszowski, J.; Kaluzynski, K.; Penczek, S. J Polym Sci Polym Chem Ed 1978, 16, 1275.
5. Munoz, A.; Navech, J.; Vives, J. P. Bull Soc Chim Fr 1966, 2350.
6. Majoral, J. P.; Mathis, F.; Munoz, A.; Vives, J. P.; Navech, J. Bull Soc Chim Fr 1968, 4455.
7. Petrov, K. A.; Nifantiev, E. E.; Woblikow, W. F. Vysokomol Soedin 1962, 4, 246.
8. Penczek, S.; Libiszowski, J. Makromol Chem 1988, 189, 1765.
9. Pretula, J.; Penczek, S. Makromol Chem Rapid Commun 1988, 9, 731.
10. Pretula, J.; Penczek, S. Makromol Chem 1990, 191, 671.
11. Pretula, J.; Kaluzynski, K.; Szymanski, R.; Penczek, S. J Polym Sci Part A: Polym Chem 1999, 37, 1365.
12. Zhuo, R.; Wang, J. Eur Polym J 1999, 35, 491–497.
13. Myrex, R. D.; Farmer, B.; Gray, G. M.; Wright, Y.-J.; Dees, J.; Bharara, P. C.; Byrd, H.; Branham, K. E. Eur Polym J 2003, 39, 1105.
14. Branham, K. E.; Mays, J. W.; Gray, G. M.; Bharara, P. C.; Byrd, H.; Bittinger, R.; Farmer, B. Polymer 2000, 41, 3371.
15. Wang, J.; Sun, D. D. N.; Shin-ya, Y.; Leong, K. W. Macromolecules 2004, 37, 670.
16. Wen, J.; Kim, G. J. A.; Leong, K. W. J Controlled Release 2003, 92, 39.
17. Wang, J.; Zhang, P.-Ch.; Lu, H.-F.; Ma, N.; Wang, S.; Mao, H.-Q.; Leong, K. W. J Controlled Release 2002, 83, 157.
18. Physicochemical Kinetics and Transport at Biointerfaces; van Leeuwen, H. P.; Köster, W., Eds.; Wiley: Hoboken, NJ, 2004.
19. Narebska, A.; Wódzki, R.; Wyszynska, A. Makromol Chem 1989, 190, 1501.
20. Rudloff, J.; Antonietti, M.; Cölfen, H.; Pretula, J.; Kaluzynski, K.; Penczek, S. Macromol Chem Phys 2002, 203, 627.
21. Kałużyński, K.; Pretula, J.; Łapienis, G.; Baśko, M.; Bartczak, Z.; Dworak, A.; Penczek, S. J Polym Sci Part A: Polym Chem 2001, 39, 955.
22. Cölfen, H. Macromol Chem Rapid Commun 2001, 22, 219.
23. Cherbuliez, E.; Leber, J.-P. Helv Chim Acta 1952, 35, 644.
24. Kurosaki, T.; Wakatsuki, J.; Imamura, T.; Matsunaga, A.; Furugaki, H.; Sassa, Y. J Com Esp Deterg 1988, 19, 191.
25. Efremov, D. A.; Zavlin, P. M.; Tebby, J. C. In Phosphoric Anhydride: Structure, Chemistry and Applications; Wiley: Chichester, 1999; p 40.
26. Kirk-Othmer Encyclopedia of Chemical Technology Copyright © 2001; Wiley: New York.
27. Nyk, A.; Klosinski, P.; Penczek, S. Makromol Chem 1991, 192, 833.
28. Plutowski, U.; Richert, C. Angew Chem 2005, 117, 627 (Supporting information).
29. Abraham, R. J.; Warne, M. A.; Griffiths, L. J Chem Soc Perkin Trans 1998, 2, 1751.