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Hydrolysis of Polyesters of Phosphoric Acid. 1. Kinetics and the pH Profile

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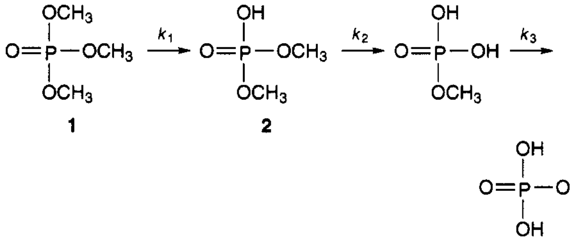
ABSTRACT: Kinetics of hydrolysis were studied for two polyesters of phosphoric acid, namely poly(methyl ethylene phosphate) and poly(trimethylene phosphate). The rate of hydrolysis was determined by direct titrimetric and NMR methods. The latter allowed establishment for poly(methyl ethylene phosphate) the rates of hydrolysis of the main chain (k_m) and the side methyl group (k_s). The rate constants determined for polymers have been found to be close to those measured for the corresponding low molecular weight models in the pH range from 1 to 12. In acidic conditions the methyl group hydrolyzes faster, whereas at basic conditions, both the methyl group and the main chain depart with approximately similar rates. This difference stems from different mechanisms of hydrolysis: in the acidic conditions the carbon atoms are attacked, whereas in the basic conditions the phosphorus atom is attacked. On the basis of kinetics of hydrolysis, the time required to break 1% of bonds in the macromolecule changes from ~150 h at pH ~2.0 to ~40 h at pH ~7.8 (both at 45 °C).

Introduction

Polyesters of phosphoric acid, like poly(methyl ethylene phosphate) (**3**), have ester functions in the main chain and in the side groups. Depending on structures and conditions of hydrolysis these ester functions may hydrolyze with different rates. This provides an interesting system, in which, for instance, side groups can be removed first and then the macromolecules will eventually hydrolyze with a lower rate.

Symmetrical trialkyl phosphates, like trimethyl phosphate, are known to hydrolyze with the rate constants differing very much, particularly in the alkaline solutions, for the hydrolysis of the first, second, and the third methyl groups (k_1, k_2, and k_3 are the corresponding rate constants).[1]

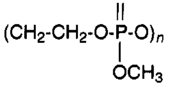


$$O{=}P(OCH_3)_3 \xrightarrow{k_1} O{=}P(OH)(OCH_3)_2 \xrightarrow{k_2} O{=}P(OH)_2(OCH_3) \xrightarrow{k_3} O{=}P(OH)_3 \quad (1)$$

1 **2**

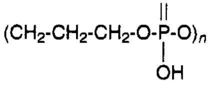
Depending on pH the $k_1/k_2/k_3$ ratios differ substantially, the ratio k_1/k_2 reaching a value as high as 10^5 at pH = 12.0 at 125 °C and only 10 in 0.2 M perchloric acid at 100 °C.[1,2]

In this paper, we studied the rates of hydrolysis of two polymeric poly(alkylene phosphates), namely poly(methyl ethylene phosphate) (**3**) and poly(trimethylene phosphate) (**4**):



$$(CH_2\text{-}CH_2\text{-}O\text{-}P(=O)(OCH_3)\text{-}O)_n$$

3



$$(CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}P(=O)(OH)\text{-}O)_n$$

4

in order to compare their rates of hydrolysis with those of the low molecular weight compounds and in order to determine the ratios of rates for various elements of the involved macromolecules.

Analysis of the mechanisms of hydrolysis of these esters on the level of the elementary reactions and based on the kinetics is difficult, because, depending on the pH of the reaction medium, the reacting ester can exist in several equilibrating forms. Thus, the diester, for instance, can simultaneously react as a monoanion and the conjugate acid. It has particularly been shown that dimethyl phosphate $(CH_3O)_2P(O)HO$ reacts with H_2O in both forms, with a simultaneous P−O and C−O bond rupture; altogether five coexisting mechanisms.[3]

The mechanistic aspects are simpler for triesters. Thus, the basic hydrolysis of trimethyl phosphate is believed to proceed as a simple bimolecular reaction (nucleophilic substitution at phosphorus) with hydroxide anion (^-OH) as the attacking nucleophile.[4,5] We refrain however in this work from any detailed mechanistic studies. We compare the pH profiles for the low- and high-molecular weights triesters, since this is the first work on hydrolysis of polymeric esters of phosphoric acid, and we compare for the triesters the relative rates of hydrolysis for the main chain and methyl substituent on phosphorus.

In our recent work we have shown that other groups can be attached to the chain having the "polydiester" structure. Thus the poly(alkylene phosphates) with amino acids attached to the main chain, may have the aminoacid or the peptide unit released before the main chain starts to hydrolyze.[6]

It is important to note that the polymer backbone can be formed from such elements as glycerol,[7] erythritol,[8] and deoxyribose[9] with a phosphoryl group in the repeating units and giving phosphoric acid and simple (e.g.) sugars upon complete hydrolysis or the corresponding low molecular weight phosphate esters.

Experimental Section

Materials. Trimethyl phosphate (**1**) was a commercial product (Merck), purified by distillation; its purity was better than 99% (GLC). Dimethyl phosphate **2** was prepared by oxidation with N_2O_4 of the commercially available dimethyl phosphite (Merck),[10] purified by distillation. Poly(methyl ethylene phosphate) (**3**) and poly(trimethylene phosphate) (**4**)

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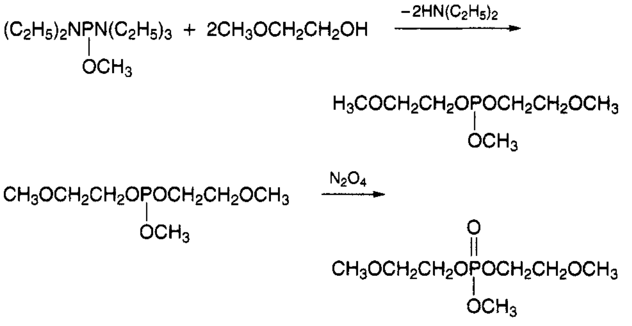
were prepared as previously described.[11-13] Bis(2-methoxyethyl) methyl phosphate (**5**) was obtained from a product of condensation of 2-methoxyethanol with bis(diethylamino)methoxyphosphine according to ref 14, followed by oxidation of the resulting phosphite to phosphate.



$$(C_2H_5)_2N\underset{OCH_3}{P}N(C_2H_5)_3 + 2CH_3OCH_2CH_2OH \xrightarrow{-2HN(C_2H_5)_2} H_3COCH_2CH_2O\underset{OCH_3}{P}OCH_2CH_2OCH_3$$

$$CH_3OCH_2CH_2O\underset{OCH_3}{P}OCH_2CH_2OCH_3 \xrightarrow{N_2O_4} CH_3OCH_2CH_2O\underset{OCH_3}{\overset{O}{\overset{\|}{P}}}OCH_2CH_2OCH_3$$

5

Hydrolysis. Hydrolysis of triesters **1** and **3** at basic conditions (pH from 7.30 to 12.30) were performed at constant pH. Thus, the thermostated and protected from air reaction flask was attached to the automatic titrimeter (SRB2c/ABU1b/TTA3, Radiometer Copenhagen, Denmark) with an automatic burette, containing 0.1 or 0.01 N NaOH (depending on the required pH of reaction). The burette was automatically adding the base, keeping pH at the chosen level. Hydrolysis at the basic conditions was treated as a second-order reaction. It is known to proceed by the P–O bond rupture:

$$HO^- + (RO)_3PO \xrightarrow{k_1} HOP(O)(OR)_2 + RO^- \qquad (2)$$

and

$$HO^- + (RO)_2P(O)O^- \xrightarrow{k_2} HOP(O)(OR)O^- + RO^- \qquad (3)$$

Thus, at least at lower stages of hydrolysis:

$$-\frac{d[A]}{dt} = k_1[A][B] \text{ (assuming } k_1 \gg k_2) \qquad (4)$$

(where [A] denotes the concentration of the ester, [B] denotes the concentration of ^-OH).

Since addition of the base solution, used to maintain constant pH during hydrolysis, leads to dilution, a correcting factor had to be introduced, taking into account not only the amount of the base consumed to neutralize the produced acid, but also to keep constant pH, because of dilution. Thus, the final equation, applied for the basic conditions was:

$$\ln \frac{[A]_0V_0}{[A]_t(V_0 + V_{ad})} = k_1[B]_0t = k'_1t \text{ (since } [B]_0 = \text{const)} \qquad (5)$$

where $V_0/(V_0 + V_{ad})$ is the correcting factor

$$[A]_t = \frac{[A]_0V_0 - V_{ad}(n_{NaOH} - [B]_0)}{V_0 + V_{ad}} \qquad (6)$$

where k'_1 = pseudo-first-order rate constant (in s^{-1}); k_1 = second-order rate constant (in mol^{-1} L s^{-1}); $[A]_0$ = starting concentrations of the triester (in mol L^{-1}); $[A]_t$ = starting concentrations of triester − concentration of triester hydrolyzed to diester; $[B]_0$ = starting and constant concentration of the base in solution (in mol L^{-1}); n_{NaOH} = concentration of the base added to the solution to keep constant pH (10^{-1} or 10^{-2} mol L^{-1}); V_{ad} = volume of the base added in time t (in mL); V_0 = starting volume of the reaction mixture (in mL); t = time (in s).

The experimental results were plotted according to eq 5; the least squares method gave the slope, allowing to compute $k'_1 = [B]_0\,k_1$.

Hydrolysis of diesters **2** and **4** at the basic conditions were performed in a different way than for **1** and **3**, because hydrolysis of diesters is so slow that CO_2 from atmosphere could influence the results of kinetic measurements. Thus, these hydrolyses were studied in the thermostated closed vessels without continuous addition of the basic solution. Conversions were kept low enough in order not to change pH more than by 1% of its original value. Thus, at these conditions only the early stages of hydrolysis were investigated (below 3%). The extent of hydrolysis was determined by back titration of the samples of the reaction mixture with an acid (0.01 N HCl). The second-order rate constants were calculated in each run from the following expression:

$$\ln \frac{[A]_0}{[B]_0}\frac{[B]_t}{[A]_t} = k_2([B]_0 - [A]_0)t \qquad (7)$$

where $[A]_0$, $[B]_0$, $[A]_t$, and $[B]_t$ denote starting and instantaneous concentrations of the diester and base respectively, k_2 = the second-order rate constant; t = time.

Hydrolysis at the neutral and acidic conditions (pH from 6.20 to 0.80) was studied in the same way for tri- and diesters. Samples with adjusted pH were kept sealed in ampoules in the thermostat and the extent of hydrolysis was determined by back titration to the required pH. In order to avoid complications, due to higher degrees of conversion, hydrolysis was stopped below 5% of conversion. In a typical experiment pH changed from e.g. 2.11 to 1.95 and hydrolysis could be treated as proceeding at the invariable pH. For all of these reactions the pseudo-first-order rate constants were calculated, assuming that hydrolysis involves the neutral ester and water in a bimolecular process:

$$k'_1 \text{ (or } k'_2) = \frac{1}{t}\ln\frac{[A]_0}{[A]_t} \qquad k'_1 \text{ (or } k'_2) = k_1 \text{ (or } k_2)[H_2O]_0 \qquad (8)$$

where, $[H_2O]_0$ is the concentration of "water in water" and equal to 55.56 mol L^{-1} (at 25 °C), k'_1 and k'_2 denote pseudo-first-order rate constants.

Kinetic Measurements of Hydrolysis Studied by ^1H and ^{13}C NMR Methods. ^1H and ^{13}C NMR (the inverted gate decoupling method) spectra were measured at 200 and 50 MHz, respectively, on a Brucker AC-200 instrument with D_2O as an internal standard. The spectra of the starting compounds and the changes through hydrolysis are discussed in the next section.

Hydrolyses of triesters **1**, **3**, and **5** at the strong basic conditions (pH = 13.0) were performed in the thermostated closed vessels (without addition of the basic solutions). Samples of the reaction mixture before taking the spectra were acidified with a concentrated HCl to the weakly acidic conditions (pH = 4–5) in order to slow down the hydrolysis. Then, the ^1H-NMR spectra were recorded. Hydrolysis of the triesters at less basic, neutral, and acidic conditions (pH = 10.0, 7.0, 2.0) were studied in the buffer solutions. Concentrations of starting triesters and products of hydrolysis (diesters) in the mixture were determined on the basis of integration of the appropriate signals. Using an excess of base in the strong alkaline hydrolysis and buffered solutions for the other hydrolysis conditions, we treated these reactions as hydrolysis occurring at constant pH. Therefore, the pseudo-first-order rate constants for hydrolysis of **3** and **5** (hydrolysis of the side group and of the main chain, k_s and k_m, respectively) were determined from the following expressions (where $[M]_t$ and $[D]_t$ denote concentration of methanol, the product of hydrolysis of the side group, and concentration of the product of hydrolysis of the main chain, respectively):

$$[M]_t = \frac{k_s}{2k_m}[D]_t \qquad (9)$$

$2k_m$ stems from the statistical factor, cf. scheme (12). Thus,

$$\ln \frac{[A]_0}{[A]_t} = (k_s + 2k_m)[B]_0 t = k'_1 t \qquad (10)$$

in the base, and

$$\ln \frac{[A]_0}{[A]_t} = (k_s + 2k_m)[H_2O]_0 t = k'_1 t \qquad (11)$$

in the neutral and acidic conditions.

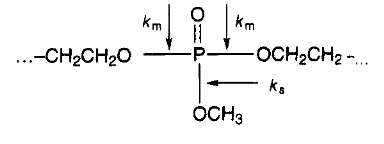
Values of all rate constants were calculated by the least square method from the experimental data, plotted according to eqs 9 and 10. With expressions ($k_s + 2k_m$) and k_s/k_m known, k_s and k_m were finally calculated.

Results and Discussion

First we describe results obtained by NMR measurements, and then we compare the obtained data with results of the direct titrimetric studies.

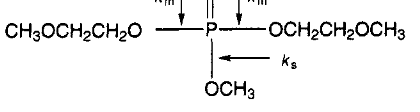
The Site of Hydrolysis. The ^{1}H NMR gave quantitative information on the rate constants of hydrolysis of the main chain and the side group. As far as the model reaction is concerned (hydrolysis of trimethyl phosphate (**1**), in which all three bonds are equivalent) the rate constants determined by chemical method and ^{1}H NMR are close to each other; thus at pH = 12.8 and 45 °C we found $k_1 = 2.02 \cdot 10^{-4}$ (chemical) and $k_1 = 1.87 \cdot 10^{-4}$ (^{1}H NMR) (both in mol^{-1} L s^{-1}).

In **3** and **5** one substituent at phosphorus is a methyl group, two others are ethylene groups, joined to the phosphoryl units:



$$\ldots\text{–}CH_2CH_2O \overset{k_m\downarrow}{\text{—}} \underset{\overset{\uparrow k_s}{OCH_3}}{\overset{O}{\overset{\|}{P}}} \overset{\downarrow k_m}{\text{—}} OCH_2CH_2\text{–}\ldots$$

3 (polymer)



$$CH_3OCH_2CH_2O \overset{k_m\downarrow}{\text{—}} \underset{\overset{\uparrow k_s}{OCH_3}}{\overset{O}{\overset{\|}{P}}} \overset{\downarrow k_m}{\text{—}} OCH_2CH_2OCH_3 \qquad (12)$$

5 (polymer model)

The rate constants of hydrolysis of the main chain versus the side chain (OCH_3) were measured by ^{1}H NMR.

The ^{1}H NMR spectrum of **3** has already been described in ref 15. In order to better see changes in the spectrum during hydrolysis, spectra of the starting polymer and of the polymer after a certain extent of hydrolysis at pH = 12.8 are given, respectively (Figures 1a and 1b).

Thus, the starting spectrum of **3** consists of a doublet centered at 3.88 δ ppm and three lines at 4.38 δ ppm. There are two major absorptions due to $CH_3OP(O)$ and $-(O)POCH_2CH_2OP(O)(OCH_3)-$ protons, respectively, coupled to two phosphorus atoms (a doublet split into two doublets, giving three lines). Besides, there is also a small doublet at 3.85 δ ppm (a few percent of the major doublet for the studied sample) which may come from the chain imperfections (structural errors).

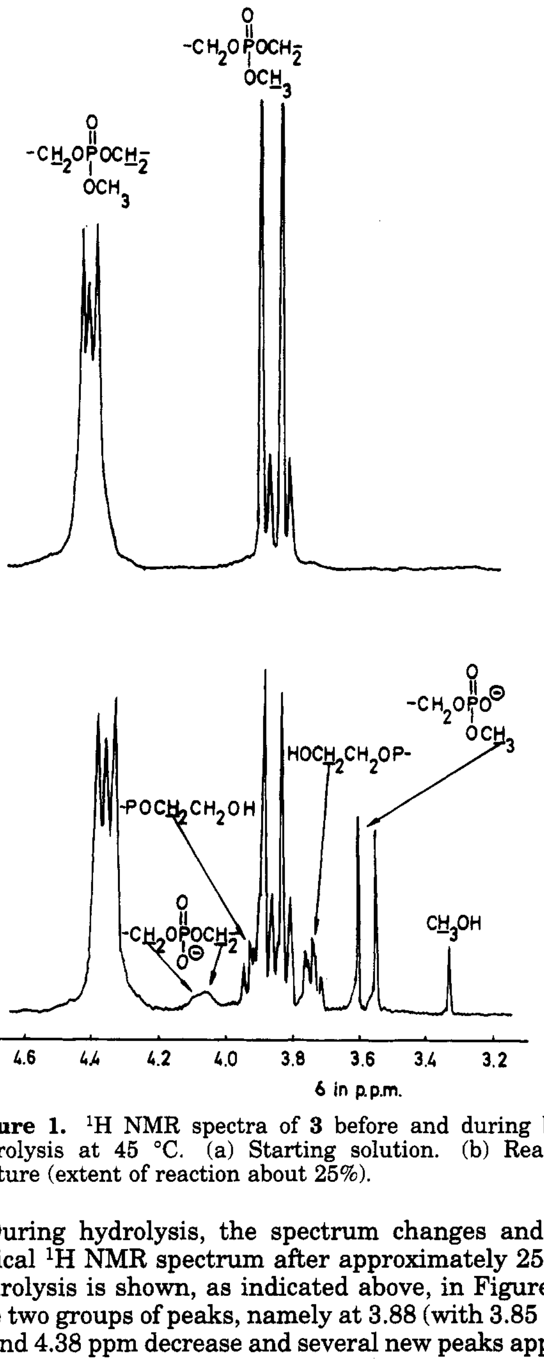
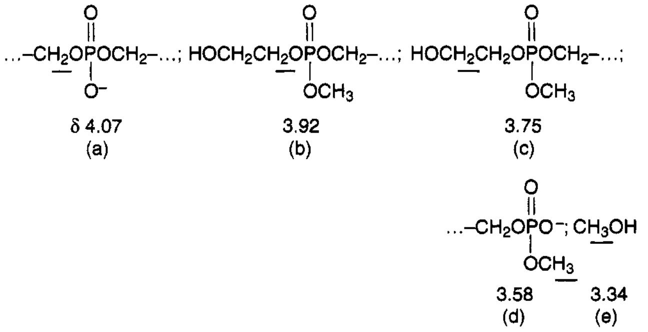


Figure 1. ^{1}H NMR spectra of **3** before and during basic hydrolysis at 45 °C. (a) Starting solution. (b) Reaction mixture (extent of reaction about 25%).

During hydrolysis, the spectrum changes and the typical ^{1}H NMR spectrum after approximately 25% of hydrolysis is shown, as indicated above, in Figure 1b. The two groups of peaks, namely at 3.88 (with 3.85 ppm δ) and 4.38 ppm decrease and several new peaks appear. These new chemical entities, responsible for the new absorptions, can be assigned as follows:



$$\ldots\text{–}\underline{CH_2}O\underset{O^-}{\overset{O}{\overset{\|}{P}}}OCH_2\text{–}\ldots;\ HOCH_2\underline{CH_2}O\underset{OCH_3}{\overset{O}{\overset{\|}{P}}}OCH_2\text{–}\ldots;\ HO\underline{CH_2}CH_2O\underset{OCH_3}{\overset{O}{\overset{\|}{P}}}OCH_2\text{–}\ldots;$$

δ 4.07 (a); 3.92 (b); 3.75 (c)

$$\ldots\text{–}CH_2O\underset{O\underline{CH_3}}{\overset{O}{\overset{\|}{P}}}O^-;\ \underline{CH_3}OH$$

3.58 (d); 3.34 (e)

Thus, for every molecule of CH_3OH released (e) there should be one structure (a) formed; by the same token, for every chain rupture, giving structure d, there should be another end formed, giving chemical shifts b and c.

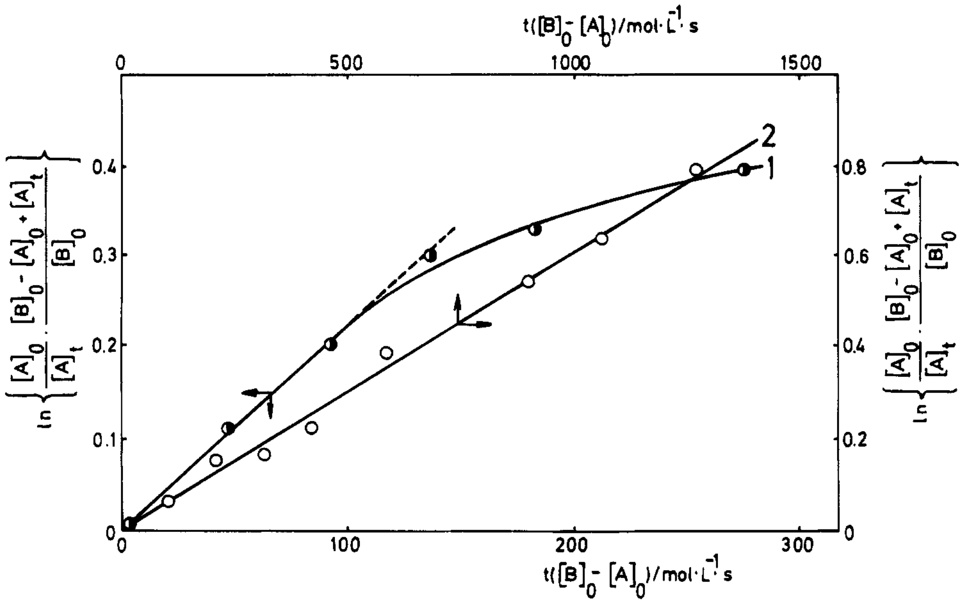
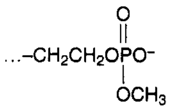


Figure 2. Kinetic plot of hydrolysis of **3** (line 1) and **5** (line 2) in basic conditions (pH = 12.8) at 45 °C.

There are also some other new chemical shifts, related to the longer range interactions, like, e.g.



$$\ldots\text{-}CH_2CH_2O\overset{\overset{O}{\|}}{\underset{\underset{OCH_3}{|}}{P}}O^-$$

(three and four bonds) but these were not clearly seen and therefore not taken into account. The simplest, unambiguous assignment, allowing determination of the relative rates of the side-to-main chain hydrolysis, are based on the CH_3OH formation (3.34 ppm) and the doublet at 3.58 ppm, due to the d structure. In the spectrum given in Figure 1, the ratio of the corresponding sum of integrations of CH_3 protons (ΣCH_3) to the total of CH_2 protons (ΣCH_2) is equal to 0.73 (calcd 3:4 = 0.75), and the ratio of structure d to the sum of b and c (calcd 3:4 = 0.75) was determined as equal to 0.7. With conversion, when some of the signals are becoming too weak and some other signals broaden, due to the long range interactions, these ratios are becoming less close to the calculated ones. Therefore calculations based on the NMR spectra were performed at less than 50% of hydrolysis.

In Figure 2 kinetic plot for hydrolysis studied by ^1H NMR (pH 12.8), presented according to eq 13, is given. The first points, as far as up to about 50% of hydrolysis, give the linear plot; further curvature seems to indicate the decrease of the apparent (observed) rate constant. This may be due to the influence of the already hydrolyzed groups, bearing a negative charge (for basic hydrolysis) on the rate of hydrolysis of the still unhydrolyzed groups. The kinetics of hydrolysis at high conversion will be described elsewhere and compared with results of poly(methyl methacrylate) hydrolysis.[16]

The points given in Figure 2 have been calculated from the ^1H NMR spectra on the basis of two integrals being compared: this of all of the protons (ΣI), and integral of methyl groups in the triester units ΣI_T (at 3.85 and 3.88 ppm). If the starting concentration of the polymer units equals to $[A]_0$, then the instantaneous concentration of the triester units (not yet hydrolyzed) equals to $[A]_t = [A]_0\{(\Sigma I_T)/3\}/\{(\Sigma I)/7\}$. Since the instantaneous concentration of base $[B]_t = [B]_0 - \{[A]_0 - [A]_t\}$, then the sum of the rate constants of hydrolysis of the main chain (k_m) (P–OCH_2) and the side group (P–OCH_3) (k_s) is given by the following dependence

$$\ln\frac{[A]_0}{[A]_t}\frac{[B]_0 - [A]_0 + [A]_t}{[B]_0} = (k_s + 2k_m)([B]_0 - [A]_0)t = k_1([B]_0 - [A]_0)t \quad (13)$$

From the linear part of line 1 in Figure 2 the sum $k_s + 2k_m$ was determined to be equal to $2.0 \cdot 10^{-3}$ mol^{-1} L s^{-1} for pH = 12.8 and 45 °C (with a correlation coefficient equal to 0.996).

Moreover, in Figure 2 line 2 represents the kinetic plot of hydrolysis at pH = 13 of the model compound **5**. Apparently, the small changes of the reaction conditions can be neglected, since all of the experimental points fit the straight line.

In a similar way the sum of the rate constants of hydrolysis for pH = 10.0, 7.0, and 2.0 were measured. The corresponding kinetic plots, presented according to eq 10 (pseudo-first-order reaction), are given in Figure 3.

In the next step the ratio k_s/k_m has been determined.

If it is assumed that the mechanism of hydrolysis is the same for both the main and the side chain for a given pH, then we can determine the corresponding ratios of k_m/k_s directly from the observed rates. Thus:

$$-\frac{d[A]}{dt} = (k_s + 2k_m)[A]; \quad \frac{d[M]}{dt} = k_s[A]; \quad \text{and } \frac{d[D]}{dt} = 2k_m[A]$$

$$\frac{d[M]}{d[D]} = \frac{k_s}{2k_m}; \text{ since } [M]_0 = 0, \text{ and } [D]_0 = 0; \quad \frac{[M]_t}{[D]_t} = \frac{k_s}{2k_m}$$

where [D] and [M] are concentrations of the diester formed due to hydrolysis of the main chain and of methyl alcohol formed, respectively. According to the

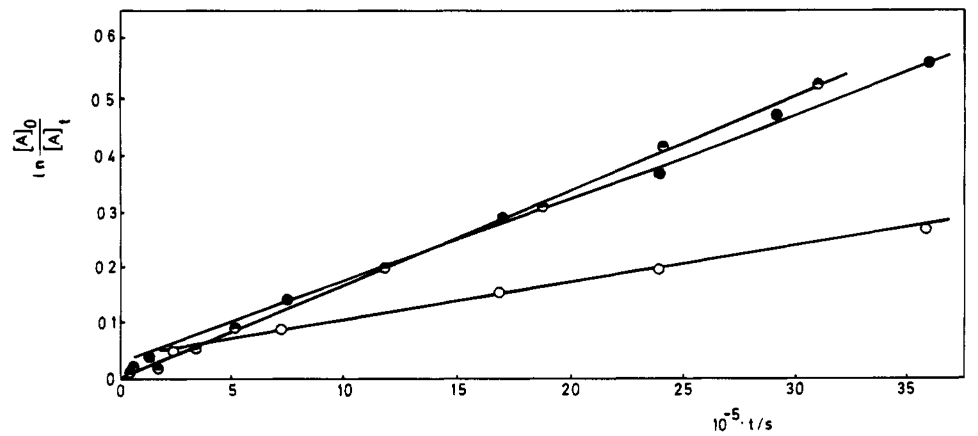


Figure 3. Kinetic plots of hydrolysis of **3** in different conditions: (○) pH = 2.0; (●) pH = 7.0; (◓) pH = 10.0.

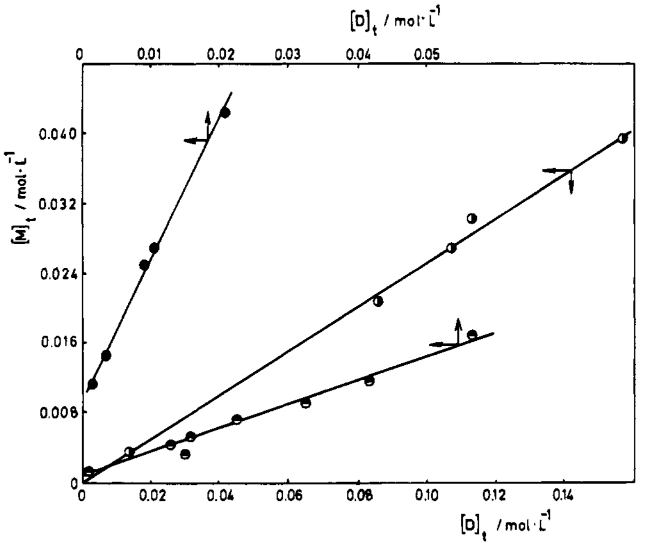


Figure 4. Plots of the $[M]_t = f([D]_t)$ of hydrolysis of **3** in different condition at 45 °C: (●) pH = 7.0; (◓) pH = 10.0; (◑) pH = 12.8.

previous analysis:

$$\frac{[M]_t}{[D]_t} = \frac{I_M}{I_D} \tag{14}$$

$$[M]_t = \frac{(I_M)/3}{(\Sigma I)/7}[A]_0$$

$$[D]_t = \frac{(I_D)/3}{(\Sigma I)/7}[A]_0$$

where I_M and I_D are integrations of the methyl group in methanol and of diester, respectively.

In Figure 4 the $[M]_t = f([D]_t)$ plots for several experiments of hydrolysis are given and the k_s/k_m ratios are calculated for various pH.

Thus, for pH = 12.8 the $k_s/km = 0.5$ while for pH = 7.0 the $k_s/k_m = 3.1$.

These findings have been confirmed, at least qualitatively, by the studies of the ^{13}C NMR spectra during hydrolysis. Figure 5, parts a and b, present the ^{13}C NMR spectra of the starting and partially hydrolyzed **3**.

Below, the assignments for the new chemical shifts, appearing during hydrolysis are given, starting from the higher and finishing at the lower field:

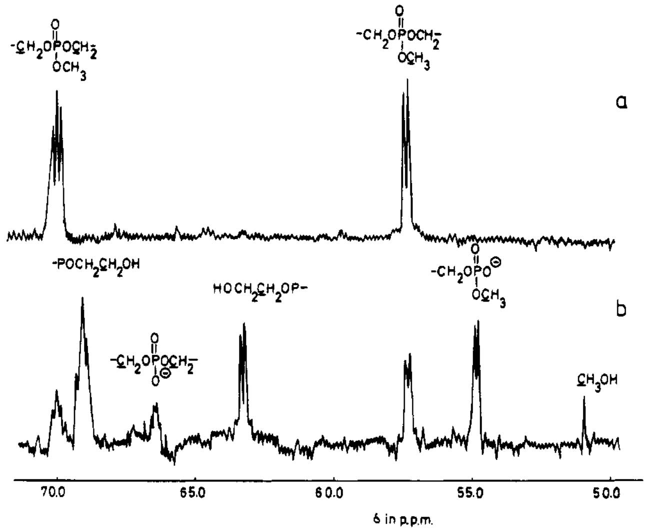
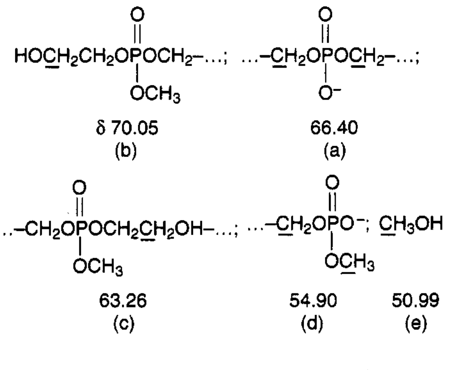


Figure 5. ^{13}C NMR spectra of **3** before and during basic hydrolysis at 45 °C: (a) Starting reaction mixture. (b) Reaction mixture (extent of reaction above 50%).



$$HO\underline{C}H_2CH_2O\overset{\overset{O}{\|}}{\underset{\underset{OCH_3}{|}}{P}}OCH_2\text{–}\ldots;\quad \ldots\text{–}\underline{C}H_2O\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}O\underline{C}H_2\text{–}\ldots;$$

δ 70.05 (b)   66.40 (a)

$$\ldots\text{–}CH_2O\overset{\overset{O}{\|}}{\underset{\underset{OCH_3}{|}}{P}}OCH_2\underline{C}H_2OH\text{–}\ldots;\quad \ldots\text{–}\underline{C}H_2O\overset{\overset{O}{\|}}{\underset{\underset{O\underline{C}H_3}{|}}{P}}O^-;\quad \underline{C}H_3OH$$

63.26 (c)   54.90 (d)   50.99 (e)

The chemical shifts are assigned on the basis of the model compound **5** and according to refs 17, 18; the letters correspond to structures given in the analysis of the ^1H NMR spectrum.

The carbon atoms in methylene groups are coupled to two phosphorus atoms ($J^2{}_{P-C}$ and $J^3{}_{P-C}$), and the methyl groups are coupled to one phosphorus atom ($J^2{}_{P-C}$), the next one being seven bonds apart.

Although the quantitative analysis of the ^{13}C NMR spectrum has not been undertaken, but qualitative analysis shows that the same groups can be recognized as observed by ^1H NMR. The spectrum given in Figure 5a is self-explanatory.

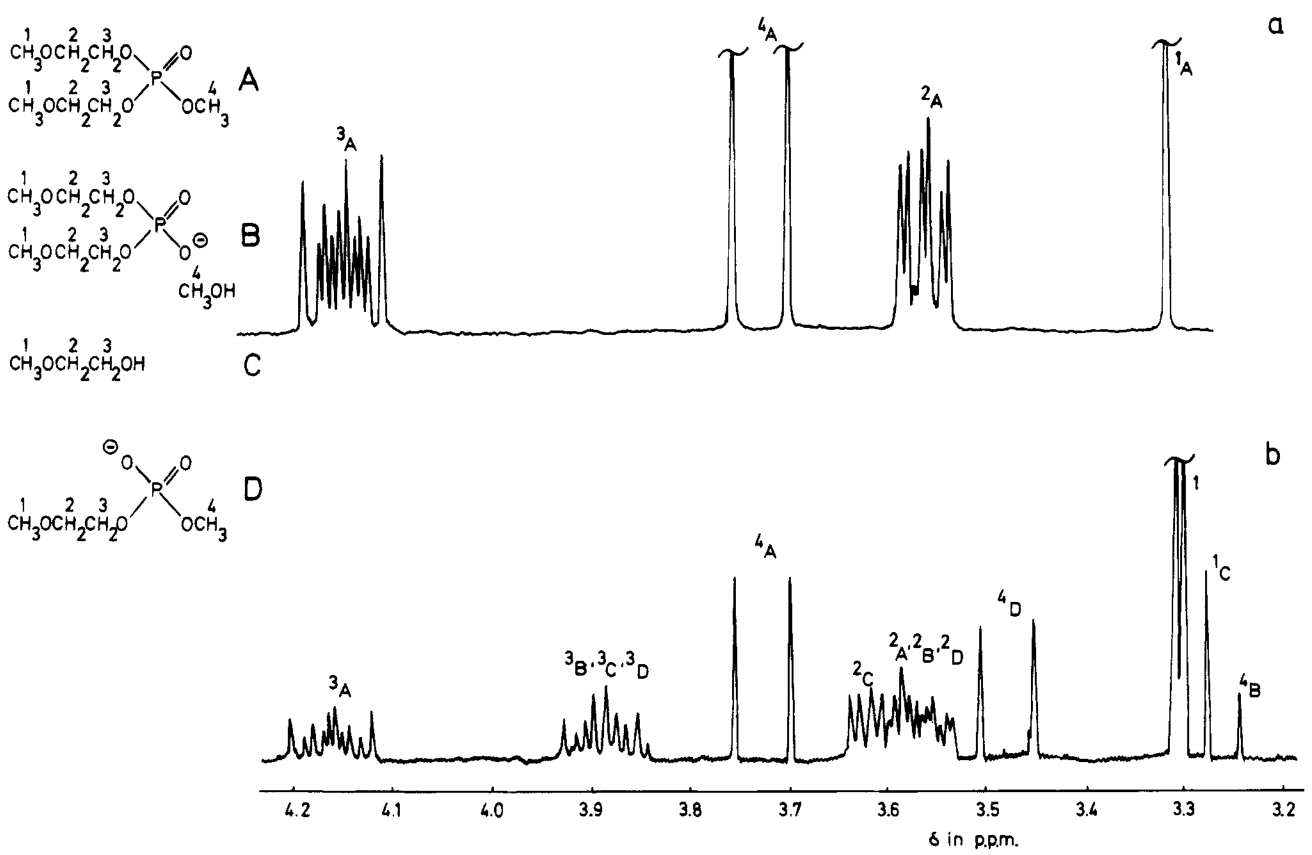


Figure 6. ^{1}H NMR spectra of **5** before and during basic hydrolysis (pH = 13.0) at 45 °C: (a) Starting solution. (b) Reaction mixture (extent of reaction approximately 30%).

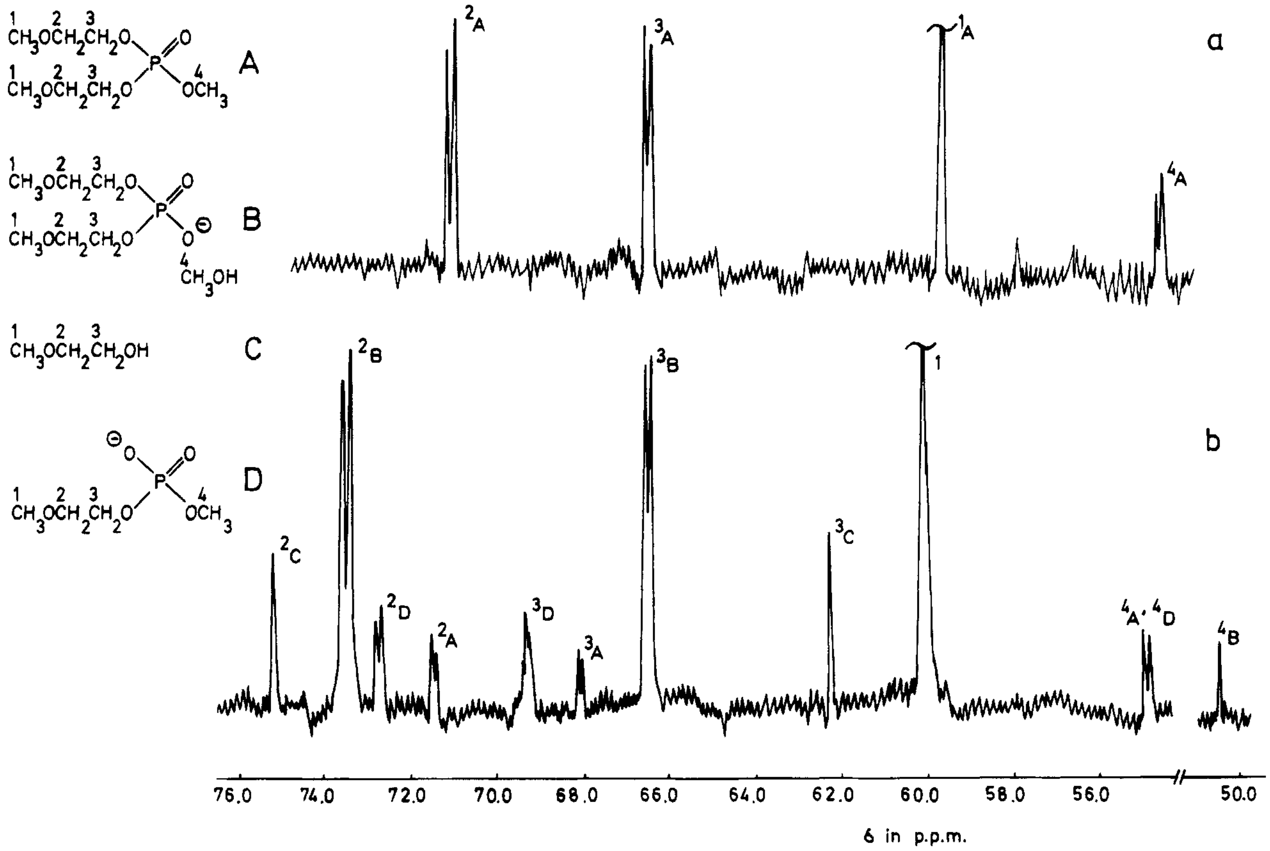


Figure 7. ^{13}C NMR spectra of **5** before and during its hydrolysis at 45 °C: (a) Starting compound. (b) Reaction mixture (extent of reaction approximately 50%).

In the same way the hydrolysis of the low molecular model, bis(2-methoxyethyl) methyl phosphate (**5**) was investigated. In Figures 6 and 7, ^{1}H and ^{13}C NMR spectra for starting **5** and its reaction mixture are shown.

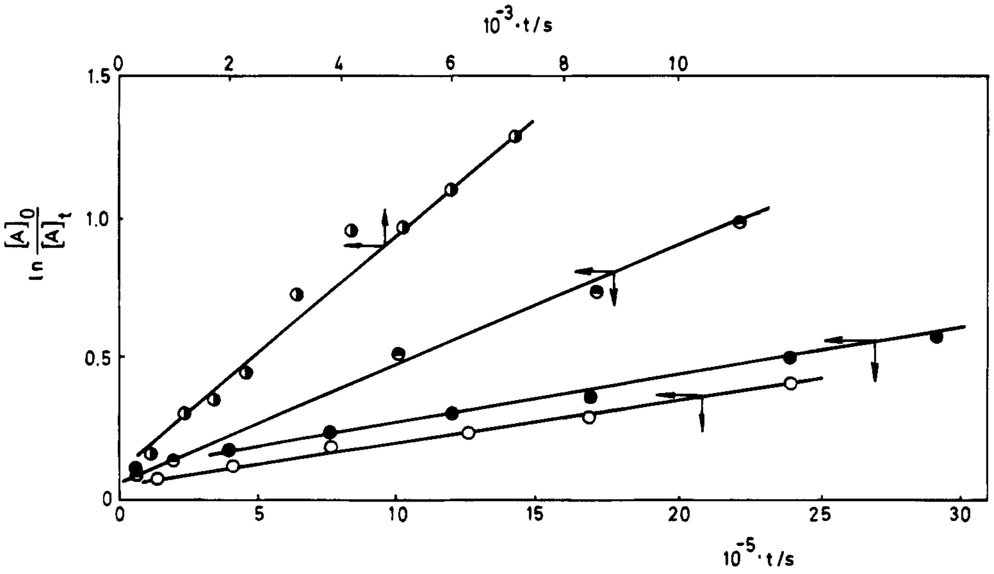


Figure 8. Kinetics plots of hydrolysis of **5** at different conditions: (○) pH = 2.0; (●) pH = 7.0; (◒) pH = 10.0; (◑) pH = 13.0.

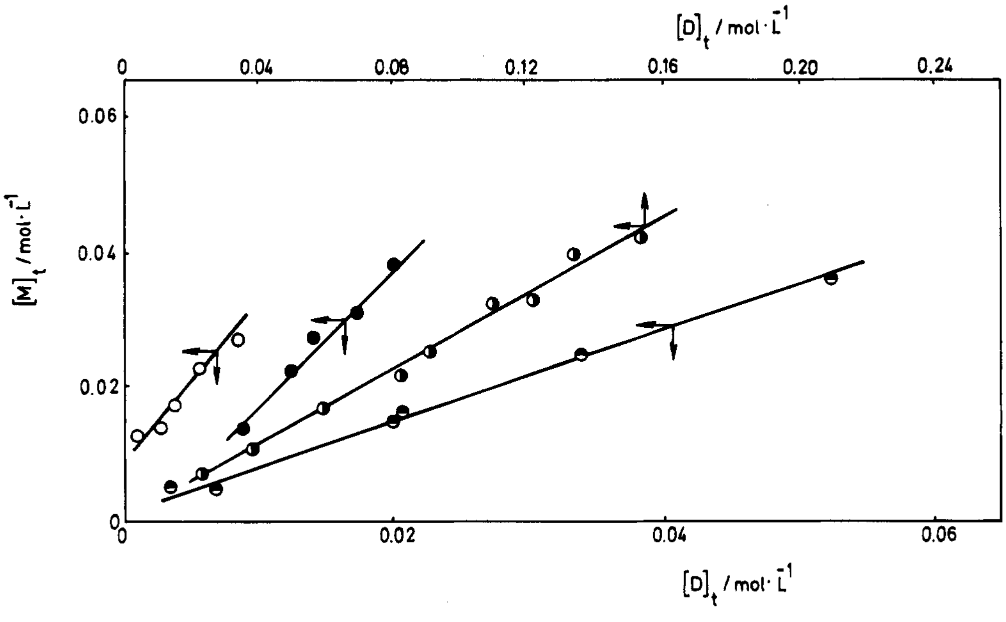


Figure 9. Plots of $[M]_t = f([D]_t)$ for hydrolysis of **5** at various conditions: (○) pH = 2.0, (●) pH = 7.0, (◒) pH = 10.0, (◑) pH = 13.0.

The integration of signals of methoxy groups in different structures was used to calculate the instantaneous concentrations of the triester **5** and the hydrolysis products (the signals of methylene groups are too complicated to be taken into account in calculations). Thus:

$$[A]_t = \frac{(I_T)/3}{(\Sigma I)/17}[A]_0 \tag{15}$$

where I_T is the integral of a doublet at 3.48 ppm and ΣI is the whole integral

$$\frac{[M]_t}{[D]_t} = \frac{I_M}{I_D} = \frac{k_s}{2k_m} \tag{16}$$

$$[M]_t = \frac{(I_M)/3}{(\Sigma I)/17}[A]_0$$

$$[D]_t = \frac{(I_D)/3}{(\Sigma I)/17}[A]_0$$

where I_M and I_D are integrations of methyl groups in methanol and of diester after hydrolysis of 2-methoxyethyl group, like in eq 14.

In Figures 8 and 9 the corresponding kinetic plots are given, similarly to Figures 3 and 4.

The determined ratios of the rate constants for polymer **3** and the model **5** are given below (Table 1) for four different pH, namely 2.0, 7.0, 10.0, and ~13.0. The statistical factor (1:2) has been taken into account.

Low Degrees of Hydrolysis of 3. The Direct Titrimetric Analysis. Before studying the hydrolysis of the polymer **3**, we first checked our kinetic treatment by measuring k'_1 and k_1 for **1** (trimethyl phosphate) at several pH, and then we compared the obtained values with these published previously. In Table 2 we give this comparison. Thus, the agreement is reasonable.

Then we measured k'_1 for **3**, using the same equipment and the same method as for determining k'_1 for

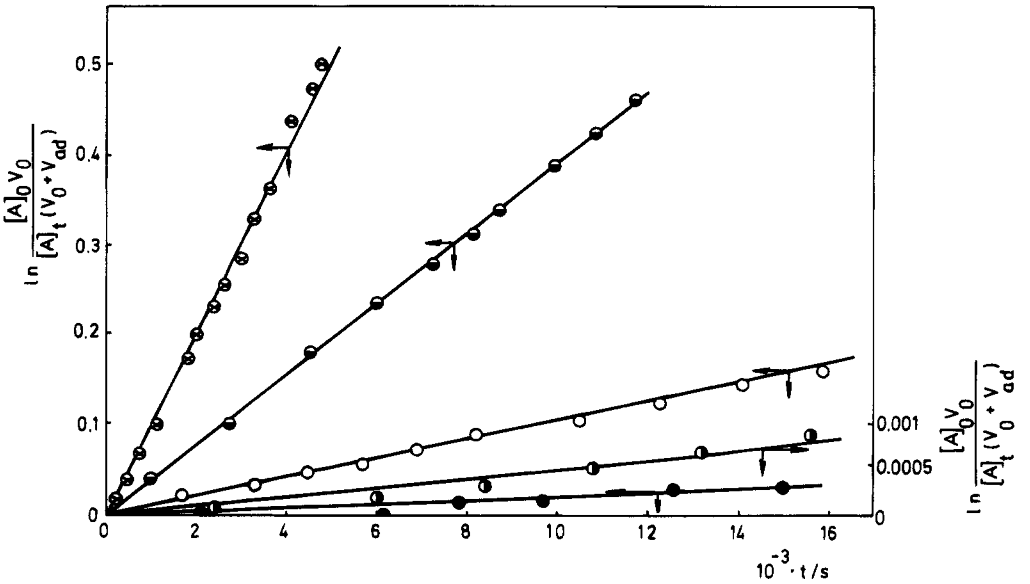


Figure 10. Typical kinetic plots of hydrolysis of poly(methyl ethylene phosphate) (**3**) in basic solutions at 45 °C: (⊗) pH = 12.3; (⊖) pH = 11.7; (○) pH = 10.9; (●) pH = 9.6; (◑) pH = 7.3.

Table 1. The Ratio of the Rate Constants of Hydrolysis of the Methyl Side Group and the Main Chain (k_s/k_m) of Poly(methyl ethylene phosphate) (3) Compared with Bis(2-methoxyethyl) Methyl Phosphate 5 as a Function of pH at 45 °C

3	pH	12.8	10.0	7.0	2.0
	k_s/k_m	0.50	0.54	3.20	5.00
5	pH	13.0	10.0	7.0	2.0
	k_s/k_m[a]	0.76	1.28	4.60	5.50

[a] Here k_s and k_m refer to methyl and methoxyethyl groups, respectively.

1. A few of the corresponding kinetic plots (experimental points from hydrolysis in basic conditions) are shown in Figure 10.

These plots are linear; k'_1 determined for the same temperatures, but at different pH, have different values. In Table 3, values of the rate constant k'_1 for **1** (whole pH range) and **3** are collected. The k'_1 rate constant for **3** encompass hydrolysis of the side group (k'_s) and the main chain (k'_m). Knowing from the NMR experiments the k_s/k_m ratios we give in Table 3 separately k'_s and k'_m calculated with these ratios.

In Figure 11, according to Table 1, the k_s/k_m ratio, determined for **3** (●) and **5** (○) are plotted as a function of pH. Points are very much dispersed, but they clearly show the general trend: at lower pH the k_s/k_m increased; however, in the range of pH from 2 to 10 this ratio changes approximately from 5.50 to 1.28.

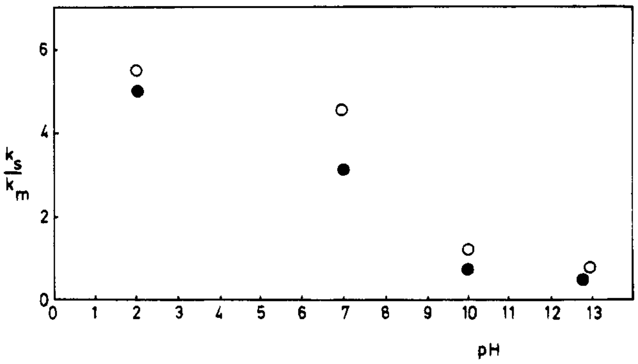


Figure 11. The ratio k_s/k_m for **3** (●) and **5** (○) as a function of pH.

Assuming that at nearly neutral conditions hydrolysis proceeds as the bimolecular reaction involving exclusively water molecules and uncharged polymer repeating units, the second-order rate constants could be calculated by dividing the pseudo-first-order constants k'_1 by the concentration of "water in water" (~55.5 mol L^{-1} at 25 °C). On the other hand, in the strongly basic conditions the second-order rate constants k_1 could be calculated by dividing the experimental first-order rate constants k'_1 by the concentration of OH^-, related to the pH of the reaction medium. At these conditions the assumption has to be made that hydrolysis proceeds exclusively by the nucleophilic attack of the OH^- anion on the phosphorus atom.

It follows that at low degrees of hydrolysis the rate constant k'_1 for **1** as well as and k'_s, and k'_m for **3**, although not identical, are sufficiently close to each other at the same pH. This means, that at the used concentration of **3** the conformational changes of the macromolecule, due to changing pH, do not influence substantially the rate of hydrolysis.

Table 2. Rate Constants of Hydrolysis of Trimethyl Phosphate 1 at Various Conditions. Comparison of the Literature Data with Results from This Work

T (°C)	[**3**] (mol L^{-1})	[OH^-] (mol L^{-1})	[H^+] (mol L^{-1})	pH	k_1 (mol^{-1} L s^{-1})	k'_1 (s^{-1})
35.0	0.0619	0.0770	–	12.7	$1.12 \cdot 10^{-4}$ [a]	–
35.0	0.0460	0.0525	–	12.4	$1.47 \cdot 10^{-4}$ [b]	–
44.7	0.2480	0.3460	–	13.2	$2.49 \cdot 10^{-4}$ [a]	–
45.0	0.0612	0.0105	–	11.7	$2.46 \cdot 10^{-4}$ [b]	–
44.7	–	–	–	~7.0	–	$5.30 \cdot 10^{-8}$ [a]
45.0	0.0884	–	–	7.22	–	$5.53 \cdot 10^{-8}$ [b]
45.0	0.0610	–	0.0282	1.55	–	$6.30 \cdot 10^{-8}$ [b]

[a] Calculated according to ref 1 (the authors did not provide the pH of solution and the concentration of trimethyl phosphate in neutral conditions; pH's were calculated from starting concentrations of the base). [b] This work.

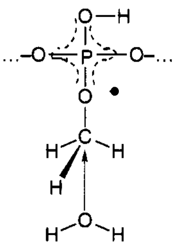
Table 3. Rate Constants of Hydrolysis of Trimethyl Phosphate 1 and Poly(methyl ethylene phosphate) (3) at Different pH at 45 °C

1		3			
pH	k'_1 (s^{-1})	pH	k_s/k_m	k'_s (s^{-1})	k'_m (s^{-1})
12.18	$5.33 \cdot 10^{-6}$	12.30	0.80	$3.18 \cdot 10^{-5}$	$3.96 \cdot 10^{-5}$
11.16	$2.36 \cdot 10^{-6}$	11.70	1.06	$1.40 \cdot 10^{-5}$	$1.32 \cdot 10^{-5}$
10.42	$5.70 \cdot 10^{-7}$	10.90	1.40	$3.72 \cdot 10^{-6}$	$2.66 \cdot 10^{-6}$
9.20	$1.79 \cdot 10^{-7}$	9.60	1.96	$8.81 \cdot 10^{-7}$	$4.49 \cdot 10^{-7}$
7.86	$6.17 \cdot 10^{-8}$	8.60	2.39	$1.87 \cdot 10^{-7}$	$7.84 \cdot 10^{-8}$
7.22	$5.50 \cdot 10^{-8}$	7.30	2.95	$3.76 \cdot 10^{-8}$	$1.27 \cdot 10^{-8}$
–	–	5.90	3.55	$5.29 \cdot 10^{-8}$	$1.49 \cdot 10^{-8}$
4.13	$1.38 \cdot 10^{-8}$	4.60	4.11	$5.27 \cdot 10^{-8}$	$1.28 \cdot 10^{-8}$
–	–	3.78	4.46	$5.10 \cdot 10^{-8}$	$1.14 \cdot 10^{-8}$
–	–	3.15	4.74	$6.93 \cdot 10^{-8}$	$1.46 \cdot 10^{-8}$
2.78	$6.00 \cdot 10^{-8}$	2.80	4.89	$9.08 \cdot 10^{-8}$	$1.86 \cdot 10^{-8}$
1.55	$6.93 \cdot 10^{-8}$	1.50	5.45	$1.10 \cdot 10^{-7}$	$2.01 \cdot 10^{-8}$

Data from Table 3 allowed determination of the times needed to break half of the ester bonds at the specified conditions. These data are gathered in Table 4, separately for the side groups ($t_{s\,1/2}$) and the main chain ($t_{m\,1/2}$) for polymer **3** of the polymerization degree $\overline{DP}_n$ equal to 100. Also we gave in Table 4 the times required to break one ester bond. Then, in Figure 12, these $t_{1/2}$, values are given as a function of pH.

The Hydrolytic Stability of the Main Chain and the Side Group. It follows from Table 3, that at strongly acidic conditions hydrolysis of the methyl group proceeds faster, whereas in the strongly basic and neutral solutions both main chain and side groups (taking into account the statistical factor) hydrolyzed with similar rates. This difference is related to the different mechanisms of hydrolysis prevailing at given pH. At basic conditions it is the phosphorus atom that is attacked by the strong nucleophile ($^-$OH) and then the corresponding bond, after assuming the apical position, is broken. Apparently, the probability of the chain units and side groups to occupy this position (apicophilicity) is comparable.

In the acidic conditions it is the carbon atom that is attacked by a nucleophile. Attack of the carbon atom in the methyl group proceeds faster; three hydrogen atoms do not hamper the back-side attack:



(acidic conditions)

whereas the presence of the polymer chain makes the attack on the α-carbon atom in the main chain more difficult.

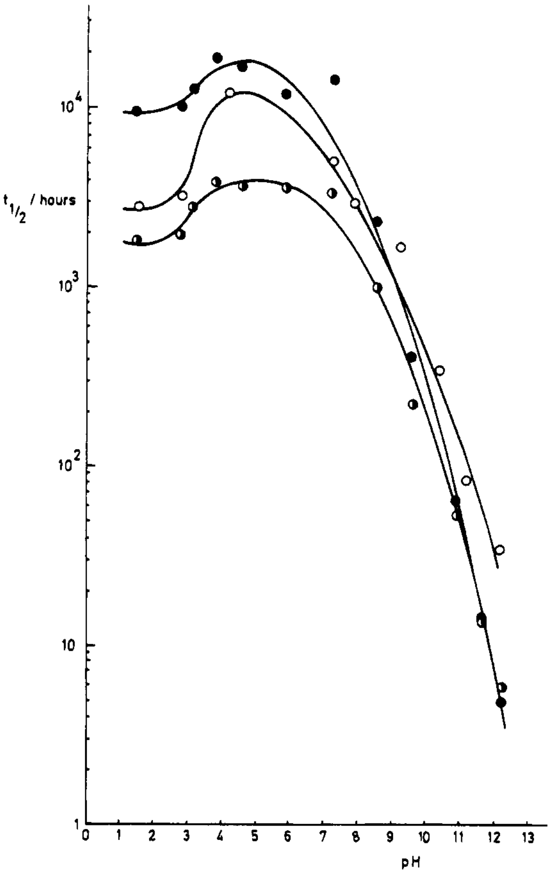
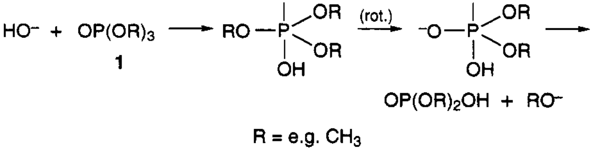


Figure 12. pH−Rate profiles for the hydrolysis of trimethyl phosphate (**1**) (○:$t_{1/2}$) and poly(methyl ethylene phosphate) (**3**) (◑, $t_{s\,1/2}$; ●, $t_{m\,1/2}$) at 45 °C.

Table 4. Times Needed for Hydrolysis of Half of the Ester Bonds in Poly(methyl ethylene phosphate) (3) (side group-$t_{s\,1/2}$ and main chain-$t_{m\,1/2}$, respectively), and Time Required to Hydrolyze 1% of Bonds. Time in Hours, 45 °C

3			
pH	$t_{s\,1/2}$	$t_{m\,1/2}$	$t_{m\,1\,\%}$
12.30	6.0	5.0	0.1
11.70	14.0	15.0	0.2
10.90	52.0	72.0	1.0
9.60	219.0	429.0	6.0
8.60	1030.0	2456.0	36.0
7.30	5121.0	15161.0	220.0
5.90	3640.0	12922.0	187.0
4.60	3654.0	15042.0	218.0
3.78	3775.0	16890.0	245.0
3.15	2778.0	13188.0	191.0
2.80	2121.0	10352.0	150.0
1.50	1750.0	9579.0	139.0

Hydrolysis of the triesters of phosphoric acid in basic conditions is considered to proceed by nucleophilic attack of the OH$^-$ on the phosphorus atom, located in the center of the trigonal pyramid. Hydrolysis may proceed by a number of steps: the attack takes place at the apical position and the leaving group departs from the same direction. To fulfill this requirement there should be an exchange of positions of the substituents, if in the attacked molecule the phosphoryl oxygen atom happens to be located at the apical position and the alkyl groups at the equatorial positions. This exchange proceeds by a process called pseudorotation (rot.).[5] Thus:



(17)

The rate of hydrolysis was expressed as $-d[\mathbf{1}]/dt = k_1[\mathbf{1}][^-OH]$, where k_1 stands for the second-order rate constant of hydrolysis of the first ester group in the triester. It is known,[1] as we have already indicated in

Table 5. Rate Constants of Hydrolysis of Dimethyl Phosphate (2) at 70 °C

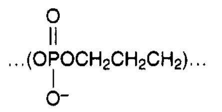
pH	k_2 (mol^{-1} L s^{-1})	k'_2 (s^{-1})
10.80	$1.29 \cdot 10^{-6}$	–
9.30	$6.50 \cdot 10^{-8}$	–
6.20	–	$1.50 \cdot 10^{-9}$ [a]
4.55	–	$1.08 \cdot 10^{-9}$
2.80	–	$5.80 \cdot 10^{-9}$
1.00	–	$6.25 \cdot 10^{-8}$
1.24	–	$8.00 \cdot 10^{-8}$ [b]

[a] Estimated from direct measurements to be equal to $\sim 8.0 \cdot 10^{-11}$ s^{-1} at 45 °C. [b] Calculated from data from ref 19.

Introduction, that in the hydrolysis of the low molecular weight triesters the first group departs so much faster than the second one (and then the third one), that these next steps do not have to be taken into account in the kinetic analysis, when the hydrolysis of the first one is concerned.

Hydrolysis of Poly(trimethylene phosphate) (4). The major aim of this work is to obtain information on the stability of the poly(alkylene phosphates) in water solutions at various pH and the comparative study with the rates of hydrolysis of the side methoxy group in **3**. Therefore, we refrain also in this section from discussing the mechanistic features of the diester hydrolysis as we have already stated in the Introduction. Actually, diester can be present in solution as a neutral molecule, conjugate acid, or conjugate base, the proportions of these species depending on the pH of solution.

Poly(trimethylene phosphate) (**4**) is a diester, thus devoid of side groups. Thus, studies of its hydrolysis

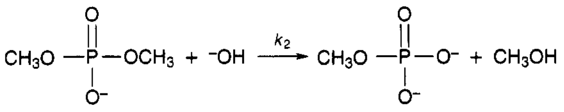


$$\ldots(\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^-}{|}}{O P}}OCH_2CH_2CH_2)\ldots$$

4

provide information not only on the rate of hydrolysis itself, but also of the rate of hydrolysis of **3**, within the unit from which the side group has already been removed.

As in our comparative studies of **1** and **3**, we first compared hydrolysis of dimethyl phosphate **2** and then polymer **4**. These studies have been conducted exclusively by the titrimetric method (cf. Experimental Section):



$$CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}-OCH_3 + {}^-OH \xrightarrow{k_2} CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}-O^- + CH_3OH \qquad (18)$$

2

(the subscript 2 in k_2 indicates that the rate constant refers to the hydrolysis of the second group k_2 refers second-order rate constant and k'_2 pseudo-second-order).

Table 6. Rate Constants of Hydrolysis of Poly(trimethylene phosphate) (4) at 70 °C

pH	k_2 (mol^{-1} L s^{-1})	k'_2 (s^{-1})
11.70	$5.94 \cdot 10^{-6}$	–
10.56	$8.45 \cdot 10^{-6}$	–
7.32	–	$4.60 \cdot 10^{-9}$
4.75	–	$5.80 \cdot 10^{-9}$
1.82	–	$1.14 \cdot 10^{-8}$

For **2** we obtained results comparable with these available in the literature for this compound (Table 5).

Our measurements of k_2 for the polymer **4** are shown in Table 6.

The following conclusion can be drawn from data of Tables 5 and 6: there is a good agreement between the determined values and the literature data (ref 18); rate constants of hydrolysis for poly(trimethylene phosphate) are comparable to these of the low molecular weight model; the rate constant of hydrolysis strongly depends on pH, increasing approximately 10^2 times, between the almost neutral (pH = 6.2) and acidic (pH = 1.0) conditions.

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