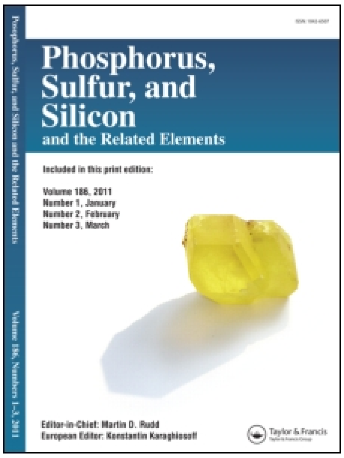

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Phosphorylation of Polyols with H_3PO_4: Towards Simple Synthesis of Poly(alkylene phosphate)s

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Phosphorylation of Polyols with H_3PO_4: Towards Simple Synthesis of Poly(alkylene phosphate)s

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Polycondensation of ethylene glycol and of glycerol with H_3PO_4 elaborated recently is summarized. Surprisingly, this apparently simple reaction, leading to a new class of synthetic polymers, has not previously been studied. In both reactions, soluble oligomers are formed, in spite of H_3PO_4, the class A3 component, being used. Dealkylation prevents the formation of high molar mass products, while also influencing the stability of the triesters in the case of ethylene glycol condensation. Polycondensation does not proceed directly with H_3PO_4. Independent kinetic experiments reveal that in the rate-controlling step, pyrophosphoric acid is formed. In polycondensation of glycerol, five- and six-membered rings are present in the main chain, indicating that the A3/B3 system has been converted into the A2/B2 system (at least partially). Both polymers have been shown to be efficient modulators of the $CaCO_3$ crystallization.

Keywords Phosphoric acid; polycondensation; polyols; polyphosphates

INTRODUCTION

It is still a challenge to find a simple and economically feasible method for larger scale synthesis of poly(alkylene phosphate)s—polymers resembling backbones of nucleic or teichoic acids. Since teichoic acids are known for their high specificity in interaction (binding) of Ca^{2+} and Mg^{2+} cations, this particular property could have important applications, not only in biomedicine.

We have prepared in the past the first high molar mass poly(alkylene phosphate)s by ring opening polymerization (Schemes 1 and 2).

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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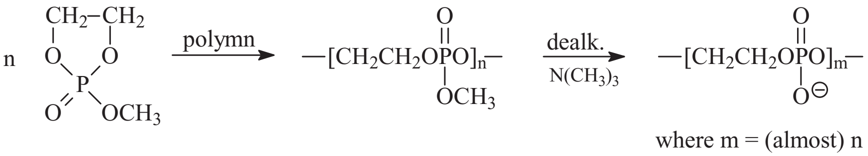
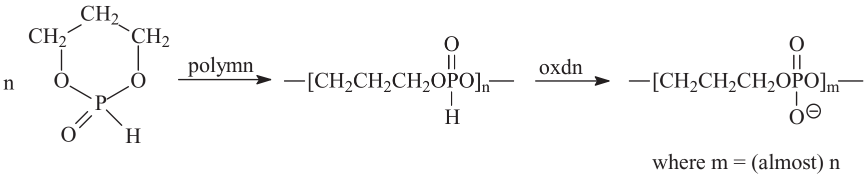


SCHEME 1

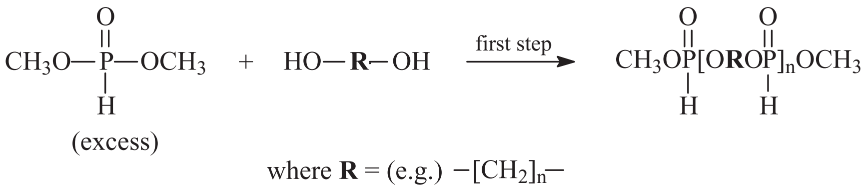


SCHEME 2

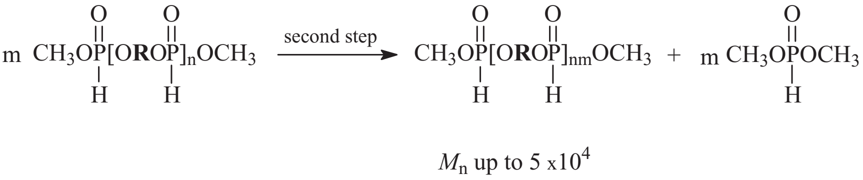
In the former method, poly(alkylene phosphate)s of M_n up to $8{\cdot}10^4$ were prepared,[1] whereas in the latter M_n up to 10^5 could be obtained.[2] Polymerization of the five-membered rings have been extended to the polymerization of the corresponding chiral monomers.[3] Since in the propagation step the center of chirality is not attacked (anionic or pseudoanionic polymerizations proceed by nucleophilic attack on the phosphorus atom), it was possible to obtain chiral substituted poly(ethylene phosphate)s closely resembling poly(1,2-glycerol phosphate)s—constituents of teichoic acids.[4]

Another successfully applied method has been based on the polycondensation–polytransesterification method.[5] Dialkyl-*H*-phosphonates (or corresponding diaryl derivatives) were reacted with respective glycols, leading to poly(alkylene-H-phosphonate)s with fairly high molar mass, which were converted by oxidation to the poly(alkylene phosphate)s (Schemes 3 and 4).

The two-step process was elaborated in order to avoid side reactions (dealkylations) at higher temperature when building up the high molar mass polymer.



SCHEME 3



$$m\ CH_3O\overset{O}{\underset{H}{P}}[O\mathbf{R}O\overset{O}{\underset{H}{P}}]_nOCH_3 \xrightarrow{\text{second step}} CH_3O\overset{O}{\underset{H}{P}}[O\mathbf{R}O\overset{O}{\underset{H}{P}}]_{nm}OCH_3 + m\ CH_3O\overset{O}{\underset{H}{P}}OCH_3$$

M_n up to 5 x10^4

SCHEME 4

Although these methods have been later applied in other laboratories in preparing biodegradable gene carriers,[6] nerve guides,[7] and in several other potential applications (e.g., drug carriers),[8,9] for some other, less sophisticated and/or larger scale applications these methods are not applicable because of the high cost and difficult-to-apply synthetic procedures. Therefore it has been attempted to apply the simplest reactions, namely polycondensation of polyols, mostly glycols and triols with H_3PO_4. Surprisingly, there were no reports in the literature describing success or failure of similar processes. The only article pertaining to this area was the work of Cherbuliez and Leber[10] on the equilibrium reaction of CH_3OH and H_3PO_4, found to be strongly shifted to the side of the starting compounds.

REACTION OF H_3PO_4 WITH GLYCOLS

This part of our work has been started with neopentyl glycol. This is the way the polymer chemist would select the starting glycol, since in neopentyl glycol (NG) there are no H-atoms in β position from the –OH group that could take place in dehydration. Nevertheless, the reaction of NG provided no ester formation and the only product formed (almost quantitatively) was 2-methyl-butyraldehyde: CH_3-$CH(CH_3)CH_2CHO$.[11]

Reaction with ethylene glycol (EG), in contrast to the reaction of neopentyl glycol, resulted in the formation of polyesters with almost no side products. Polycondensation has been conducted in a rather narrow range of temperatures. Indeed, below 100°C the reaction of H_3PO_4 and $HOCH_2CH_2OH$ is very slow, and above 180°C there is substantial formation of 1,4-dioxane.

The progress of the reaction was followed by ^1H, ^{13}C, and ^{31}P NMR spectroscopy. The composition of the resulting polymer was determined by MALDI-TOF-MS (MTMS). Samples taken from the reaction mixture were dissolved in H_2O, and the ^{31}P NMR spectrum was recorded at $pH = 12$. A typical course of reaction studied this way is shown in

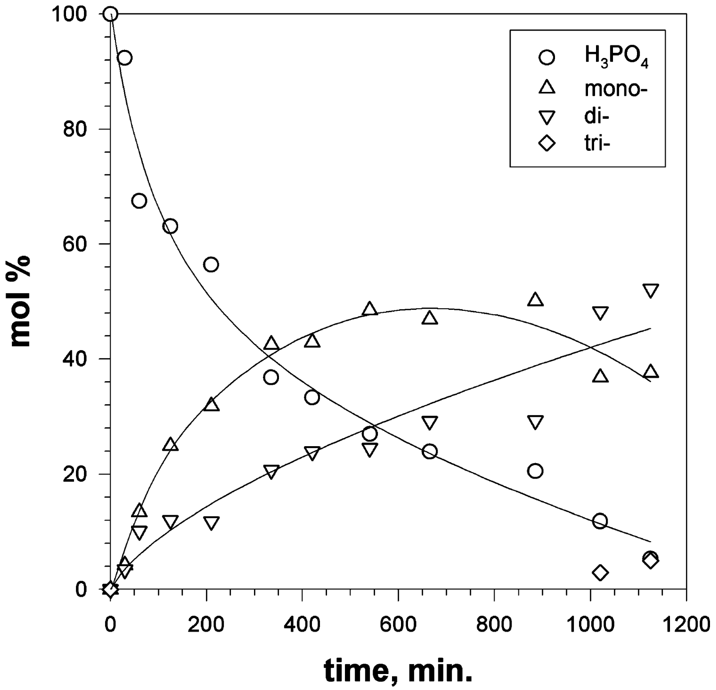


FIGURE 1 Kinetics of polycondensation carried out at 150°C, argon stream flow, $[EG]_0/[H_3PO_4]_0 = 1.58$, reaction in bulk. M – monoesters, D – diesters, T – triesters.[12]

Figure 1,[12] where proportions of H_3PO_4, monoesters (M), diesters (D), and triesters (T) are plotted as a function of time.

Proportions are expressed as mol % of phosphorus atoms present in the given compound (group) of the starting phosphorus atoms introduced with H_3PO_4. Thus, e.g., 20% of P in H_3PO_4after a certain time means that there is still 20% of unreacted H_3PO_4 in the system, and 10% of P in monoesters means that 10% of the originally introduced $H_3PO_4$is converted into 10% of monoesters.

Polycondensation was studied without any catalyst or in the presence of $Sc(OTf)_2$, known to be an efficient catalyst of esterification of carboxylic acids. Catalyzed polycondensation is a few times faster than the uncatalyzed process, with the final product being virtually the same.[11] Polycondensation was studied either in bulk or with added hydrocarbon solvents (heptane or toluene) to facilitate removal of water. It has been possible, after several hours of polycondensation, to reach ~2% of H_3PO_4 left in the system.

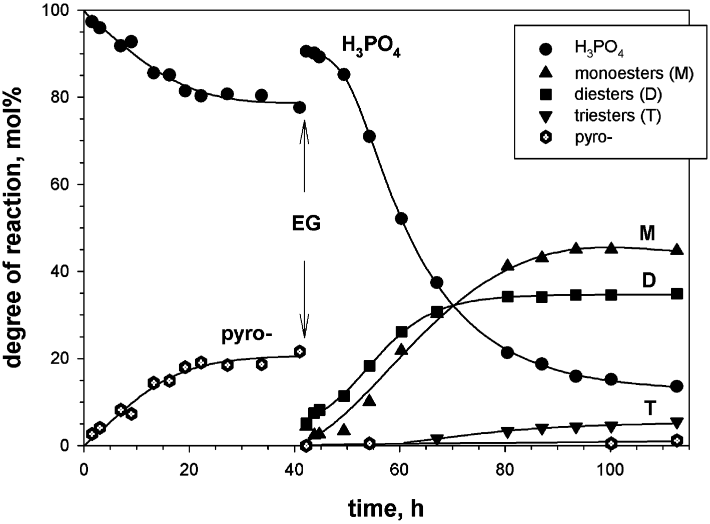
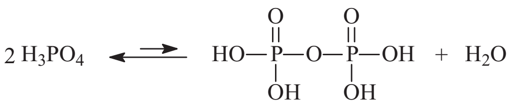


FIGURE 2 Kinetics of azeotropic (heptane, 98°C) polycondensation of H_3PO_4 with EG. EG added at time = 41 h when about 20% of P atoms were in pyrophosphoric structures. Note the fast addition of EG to the pyrophosphoric compound.[12]

It has been established that the rate-determining step in polycondensation is formation of the pyrophosphoric acid that is the actual phosphorylation agent. This was established on the basis of an experiment illustrated in Figure 2.

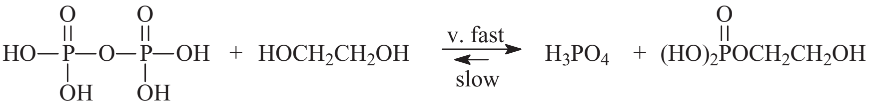
First, during almost 40 h, pyrophosphoric acid was formed from H_3PO_4, heated in the absence of a glycol. Then, when a certain concentration of pyrophosphoric acid had built up, EG was added at the same temperature. In a very short time (difficult to measure), the pyrophosphoric acid disappeared; half of the P atoms from it gave H_3PO_4 and the second half esters of EG. The sequence of reactions that took place is as follows (Schemes 5 and 6).

The pyrophosphoric acid is not observed during polycondensation, since apparently its steady state concentration is very low: it is slowly formed and very quickly consumed.



$$2\,H_3PO_4 \rightleftarrows HO-\underset{OH}{\overset{O}{\overset{\|}{\underset{|}{P}}}}-O-\underset{OH}{\overset{O}{\overset{\|}{\underset{|}{P}}}}-OH + H_2O$$

SCHEME 5



$$HO-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-O-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-OH + HOCH_2CH_2OH \underset{\text{slow}}{\overset{\text{v. fast}}{\rightleftarrows}} H_3PO_4 + (HO)_2\overset{\overset{O}{\|}}{P}OCH_2CH_2OH$$

SCHEME 6

Structures of the formed products have been established by MTMS. We noticed that the ratio of observed individual products depends on the mode in which the MTMS experiment is performed: either in cationic or anionic mode. Therefore for the MTMS analysis reaction products with fully methylated acidic groups were used. The result of one of such analysis is shown in Figure 3.[12]

All of the major populations differed only by the end groups X and Y, whereas the repeating units were of the same structure (Scheme 7).

X and Y end groups were as follows: X = $OP(O)(OCH_3)_2$ or (minor) OCH_2CH_2OH; Y = H or CH_2CH_2OH. The proportions of the given end group depend on the reaction conditions, although even when an excess of EG is used, population of polymers with two end groups of the structure of monoesters were observed. Thus before methylation, the prevailing structures of macromolecules were mostly as shown in Scheme 8.

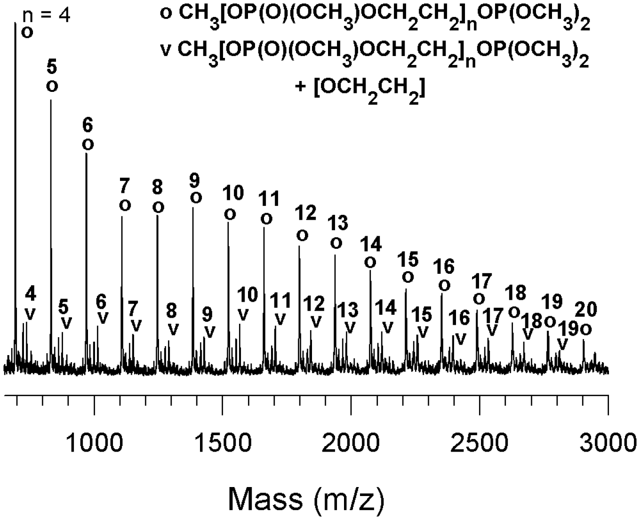
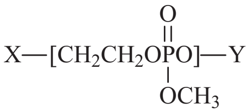
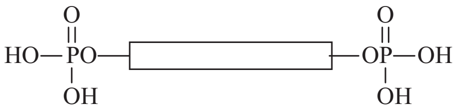


FIGURE 3 MTMS spectrum of the methylated polycondensation product, $[EG]_0/[H_3PO_4]_0 = 1.62$, catalyst $Sc(OTf)_3$ 0.15 wt %. Matrix THA/AC, positive ionization.[12]



$$X\text{—}[CH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}O]\text{—}Y$$ (X)

SCHEME 7

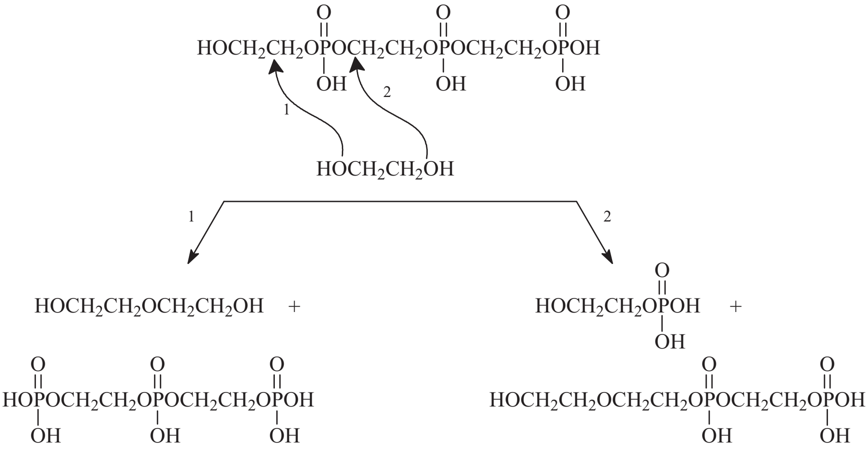


SCHEME 8

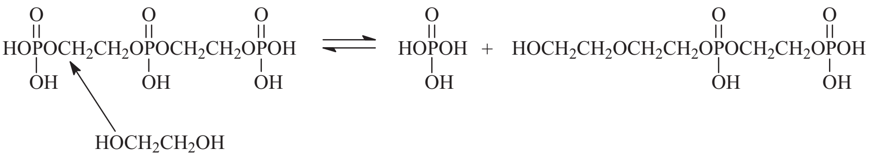
Another peculiarity of the observed structures was the presence of units built over diethylene glycol, either in the repeating units or at the end groups. These observations allowed formulation of the following side reaction, based on the dealkylation process (Scheme 9).

Further processes of dealkylation lead to liberation of H_3PO_4 from the already formed polymer. Therefore, at the finally equilibrated system there is always a certain amount of H_3PO_4 present. However, as mentioned above, its concentration could be rather low when the final equilibrium is reached, e.g., 2%. H_3PO_4 is formed by dealkylation in the reaction shown in Scheme 10.

Formation of the diethylene glycol (DEG) has been shown in independent experiments: DEG is present in the reaction mixture during



SCHEME 9



$$\mathrm{HO\overset{O}{\underset{OH}{P}}OCH_2CH_2O\overset{O}{\underset{OH}{P}}OCH_2CH_2O\overset{O}{\underset{OH}{P}}OH} \rightleftharpoons \mathrm{HO\overset{O}{\underset{OH}{P}}OH} + \mathrm{HOCH_2CH_2OCH_2CH_2O\overset{O}{\underset{OH}{P}}OCH_2CH_2O\overset{O}{\underset{OH}{P}}OH}$$

$$\mathrm{HOCH_2CH_2OH}$$

SCHEME 10

polycondensation; it is also shown to be present in the polymer after its hydrolysis.

PHOSPHORYLATION OF GLYCEROL (GL)

Direct reaction of glycerol with H_3PO_4 has not previously been studied and most probably proceeds in principle in a similar way as that described above for EG. However, the reaction is faster and some five- and six-membered rings are present in macromolecules. In Figure 4, the rates of phosphorylation of EG and GL are compared.

Tentative explanation of the faster rate observed for GL is based on the assumption that propagation involves the preliminary formation of cyclic phosphates (Scheme 11).

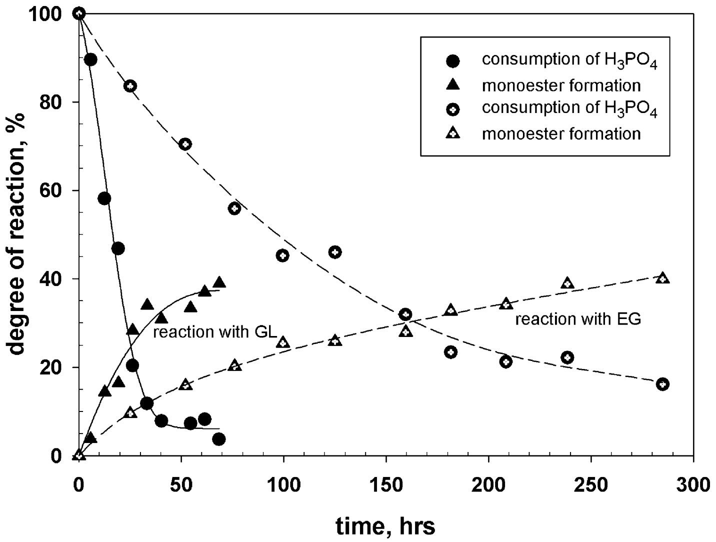
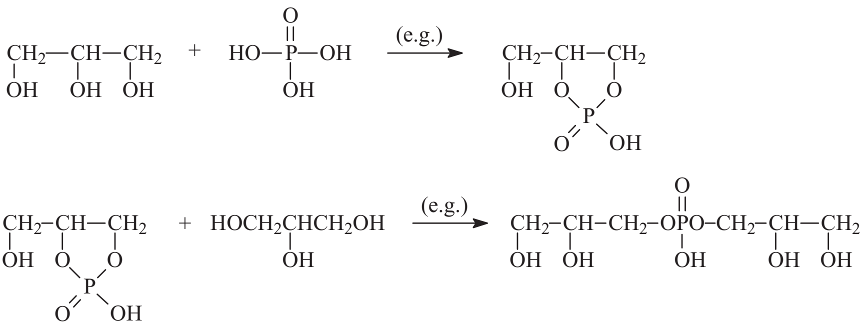


FIGURE 4 Comparison of the rates of reaction of H_3PO_4 with EG (dash lines) and GL (solid lines). Reaction conditions: $[H_3PO_4]_0/[EG]_0 = 1.54$, $[H_3PO_4]_0/[GL]_0 = 1.50$, 100°C.



SCHEME 11

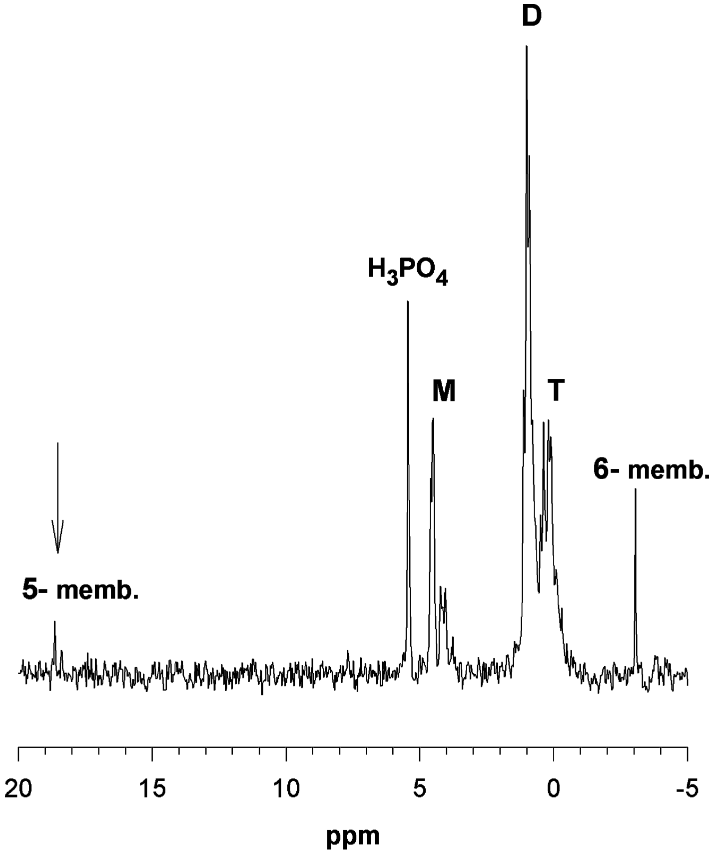


FIGURE 5 ^{31}P NMR spectrum (in D_2O, pH = 12) of the reaction mixture of GL with H_3PO_4. Reaction conditions: $[H_3PO_4]_0/[GL]_0 = 1.0$, heptane, 98°C.

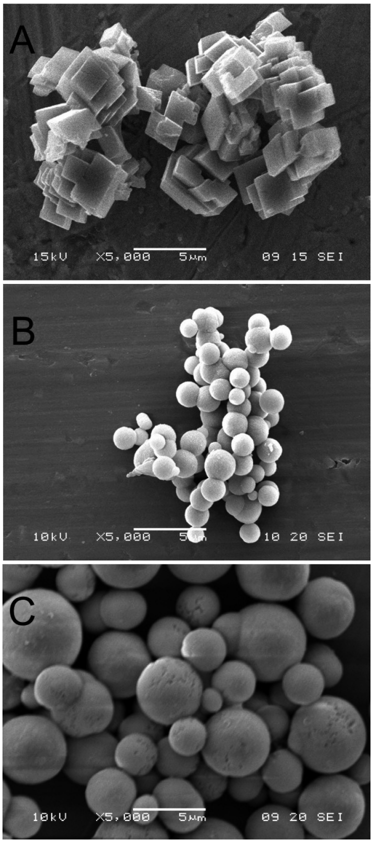


FIGURE 6 SEM images of $CaCO_3$ particles obtained in the absence of polymeric modifier (A), in the presence of poly(ethylene phosphate) (B), and phosphorylated glycerol (C). Magnification 5000 ×.

Their presence is clearly seen in the ^{31}P NMR spectrum of the polymer, shown in Figure 5.

Preliminary, independent experiments did not confirm this reaction path, however—benzyl alcohol does not react faster with H_3PO_4 in the presence of glycerol than in its absence (actually, polybenzyl is also formed).

INTERACTION OF POLY(ETHYLENE PHOSPHATE) AND OF POLY(GLYCEROL PHOSPHATE) WITH $CaCO_3$ CONTROLLED CRYSTALLIZATION

In our earlier work, controlled crystallization of $CaCO_3$ (from $CaCl_2$ and Na_2CO_3) has been studied in the presence of dihydrophilic block copolymers with ionic and nonionic blocks. It has been shown that the polyphosphate block is the most efficient when compared with ionic blocks based on derivatives of sulfuric or carboxylic acids.[13]

Surprisingly, both poly(ethylene phosphate) and phosphorylated glycerol efficiently mediate crystallization of $CaCO_3$, even if taken alone. In Figure 6, crystals formed in the absence and presence of the above-mentioned polymers are compared.

CONCLUSION

Simple polycondensation of H_3PO_4 with ethylene glycol or glycerol leads to oligomers, either mostly linear in the case of ethylene glycol (practically not containing triesters) or highly branched, but soluble in the case of glycerol, in spite of the reaction of two trifunctional components. It has been shown by kinetic experiments that actual polycondensation proceeds by preliminary formation of the pyrophosphoric acid. This acid is formed in a slow, rate-controlling step and is consumed very fast. Its stationary concentration is low, and thus it could not be detected during the polycondensation reactions. Both oligomers, with ethylene glycol as well as with glycerol, actively mediate crystallization of $CaCO_3$.

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