POLYESTERS OF PHOSPHORIC ACID: SYNTHESIS AND KINETICS OF HYDROLYSIS

S.Penczek, J.Pretula, K.Kaluzynski

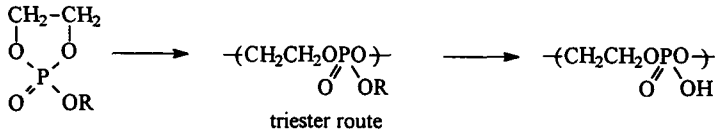
Polish Academy of Sciences, Center of Molecular and Macromolecular Studies, Department of Polymer Chemistry, 90-363 Lodz, Sienkiewicza 112, Poland

Abstract: Three major methods have been elaborated in our laboratory for preparation of polymers with poly(alkylene phosphates) backbones: ring-opening polymerization, poly-condensation and transesterification, and polyaddition.
The second method is based on the reaction of the commercially available compounds, namely dialkyl (or diaryl)-H-phosphonates and glycols. Reaction of the aliphatic H-phosphonates with aliphatic glycols is a reversible process, whereas polycondensation of diphenyl H-phosphonates with aliphatic and cycloaliphatic diols is practially irreversible. This latter method has recently been developed and is described in this paper.
Poly H-phosphonates with $\overline{M}_n$ up to $40 \cdot 10^3$ were prepared. Polymers are easily oxidized and quantitatively converted into the relatively stable poly(alkylene phosphates). Some physical properties of these polymers and kinetics of their hydrolysis is discussed.

Introduction

In the past we elaborated the ring-opening polymerization methods leading to polyesters of phosphoric acid. These methods have been based either on the polymerization of a cyclic triester with subsequent dealkylation of the former exocyclic group (the triester route) or on the polymerization of a cyclic H-phosphonates (or phosphoamidates) with conversion of the P-H or P-NR_2 bonds into the P-OH bonds (H-phosphonate routes):

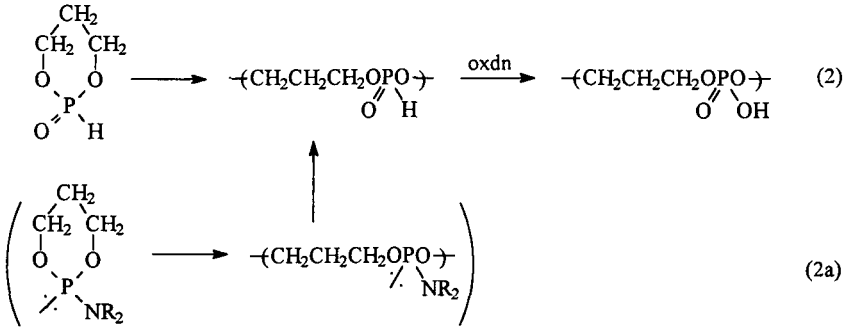
e.g.:



(1)

 CCC 1022-1360/98/$ 10.00

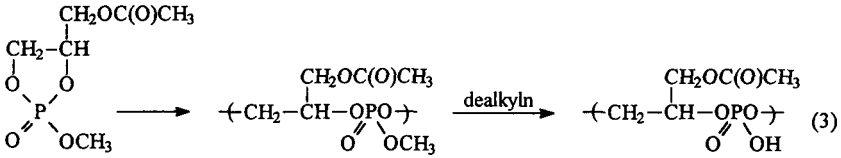
e.g.:



(2)

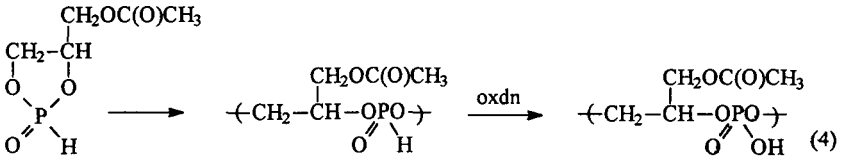
(2a)

Several high molecular weight polymers (in the range of $10^4 \div 10^5$) were prepared using these approaches. Some of these polymers were prepared either as models of related biomacromolecules, mostly teichoic acids, or as amphiphilic macromolecules, applied as liquid membranes. Models of teichoic acids (e.g. poly(glycerol-1,2-phosphate)) were prepared by polymerization of the corresponding cyclic compounds, yielding polymers with $\overline{M}_n$ above 10^4:



(3)

and



(4)

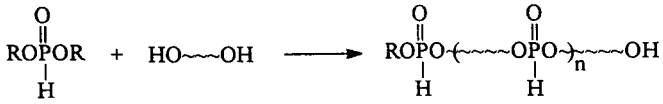
The ring-opening (R-O) polymerization has successfully been used in preparation of these and related polymers.

In the present paper we give a short account on the more recent method, based on polytransesterification of oligomeric dialkyl (diaryl) H-phosphonates prepared from the corresponding glycols. Results presented in this paper are mostly based on two recently submitted contributions (Ref. 1,2).

Synthesis of poly(alkylene phosphates) by polytransesterification and by polycondensation

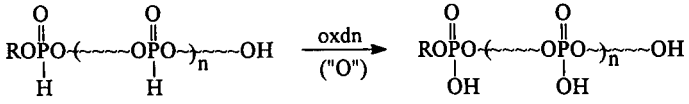
Synthesis of poly(alkylene phosphates) by polytransesterification

A few attempts have been made prior to our work to prepare poly-H-phosphonates by polycondensation of low molecular weight dialkyl H-phosphonates with glycols; further oxidation leads to poly(alkylene phosphates) (Ref. 3-6):



(5)

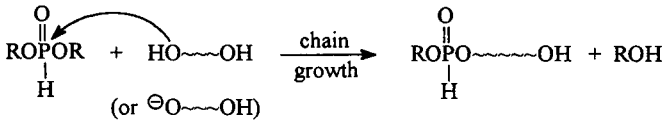
where HO~~OH is a glycol used; R are the alkyl groups, usually CH_3-



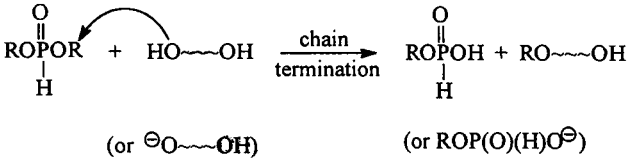
(6)

However, this direct reaction did not allow preparation of polymers with $\overline{M}_n > 10^3$. Several reasons have been proposed, mainly related to the departure from stoichiometry and side reactions.

These polycondensations proceed by base catalysed nucleophilic displacement at the P atom. It was assumed, that mostly alcoholate anions participate, although direct reaction with hydroxyl groups is also possible. This major reaction, leading to the chain growth, is accompanied with the chain breaking reaction, resulting from the nucleophilic attack on the carbon atom:

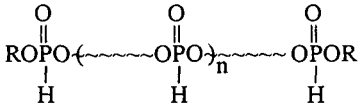


(7)



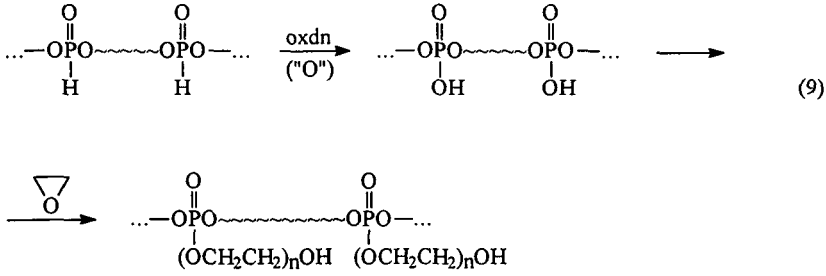
(8)

Formation of ROP(O)(H)OH (monomeric or polymeric) either in a direct reaction or with subsequent proton transfer to the originally formed salt, may catalyse further attack on carbon atom. The nonstoichiometry and the enhancement of side reactions due to the acid formation are eliminated, when transesterification is performed in place of polycondensation, according to our work (Ref. 7-10). Here, first, in the presence of sodium alcoholate as catalyst the low molecular weight oligomers are formed with hydroxyl groups substituted by esters of H-phosphonic acid. This substitution proceeds at the relatively low temperature, when selectivity of reaction is higher, and importance of attack on C-atom is relatively low. Once the α,ω-diester is formed:



(a low polymerization degree oligomer)

the excess of ROP(O)(H)OR is removed and further transesterification takes place at higher temperature. At this stage, hydroxyl groups are no more present, and even if the attack on the C atom still proceeds, the absence of the POH acidic protons eliminates the catalysis of side reactions. Thus, at these conditions high-molecular-weight (over 10^4) poly-H-phosphonates were prepared. In Table 1 (partially from Ref. 9) several examples of poly-H-phosphonates prepared this way are given. In $^{31}P\{^1H\}$ NMR spectra of these polymers there is only one peak, indicating high structural purity. In the same table information concerning the derived polymers are listed. $\bar{M}_n$ of the oxidized polymers and $\bar{M}_n$ of the oxyethylated polyacids confirm the correctness of measurements of the starting poly-H-phosphonates:



(9)

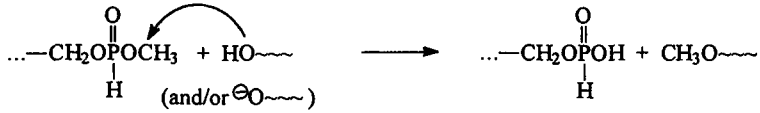
Table 1. $\overline{M}_n$ data on poly-H-phosphonates and their derivatives (Ref. 19, except [a]).

Diol	O=P-H	O=P-OH	O=P-OCH$_2$~
HO(CH$_2$)$_5$OH	6.300	7.800	8.200
HO(CH$_2$)$_8$OH	8.500	7.800	7.600
HO(CH$_2$)$_9$OH	9700	9.500	8.300
HO(CH$_2$)$_{10}$OH[a]	19.500	20.200	22.100
HO-⟨H⟩-OH	14000	15.000	16.200
HO(CH$_2$CH$_2$O)$_4$H[a]	32.800	-	38.200
HO(CH$_2$CH$_2$O)$_{45}$H[a]	34.700	27.000	25.500

[a] new data

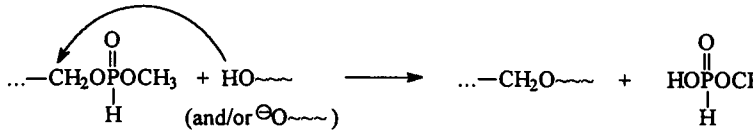
Polycondensation of glycols with diphenyl-H-phosphonate

In the previous section we described synthesis of poly-H-phosphonates with dialkyl-H-phosphonate as a starting compound. The major side reaction is the nucleophilic attack on the carbon atom and formation of the acidic monoester:



(10)

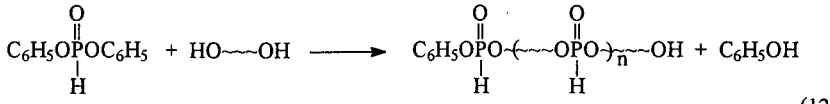
The same reaction can take place with the endo-carbon atom:



(11)

then, it results in chains coupling (doubling of $\overline{M}_n$) and formation of the monoester of phosphoric acid, which can be removed under the conditions of synthesis (high temperature and high vacuum), provided that it did not reacted before with components of the system. The first of the undesirable reactions creates, as it was stressed above, the unreactive end-groups. Therefore,

although dimethyl-H-phosphonate allowed preparation of polymers with $\overline{M}_n \sim 10^4$, one could expect, that elimination of the nucleophilic attack on the exo-carbon atom would still increase the molecular weight of polymers. This could be achieved with aromatic-H-phosphonate, for instance when diphenyl-H-phosphonate ($C_6H_5OP(O)(H)OC_6H_5$) is used. Besides, it is known, that diphenyl-H-phosphonate reacts with aliphatic alcohols almost irreversibly:



(12)

Our recent work (Ref. 2) has shown, that polycondensation can be performed even without removing of the C_6H_5OH formed. At these conditions poly-H-phosphonates with $\overline{M}_n$ up to $4.5 \cdot 10^4$ could be obtained. Like the polytransesterification with $CH_3OP(O)(H)OCH_3$, the course of reaction can be followed by $^{31}P\{^1H\}$ NMR, where the starting diphenyl-H-phosphonate, the end groups and the repeating units were observed independently and simultaneously. The $^{31}P\{^1H\}$ NMR spectra of the reacting mixture, taken at various times, is shown in Fig.1.

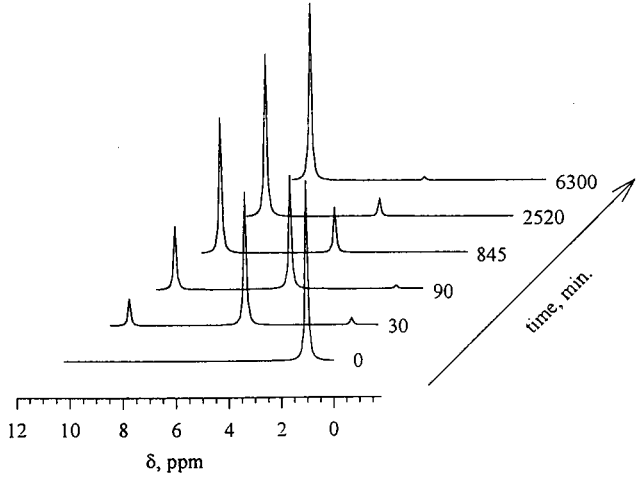


Fig.1. Development of the $^{31}P\{^1H\}$ NMR spectra during polycondensation of diphenyl H-phosphonate with 1,10-decanediol. Conditions: $[(PhO)_2P(O)H]_o = [HO(CH_2)_{10}OH]_o = 0.36$ mol/L, in boiling C_6H_6, without catalyst added. Chemical shifts of signals at $\delta = 1.18$, $\delta = 5.16$ and $\delta = 8.79$ ppm correspond to the P-atoms in $(PhO)_2P(O)H$, polymer end groups (PhOP(O)(H)O-...), and polymer repeating units (...-OP(O)(H)O$(CH_2)_{10}$-...), respectively.

In a typical experiment, well purified diol and diphenyl-H-phosphonate were placed in a one neck-round-bottom reaction flask into dry benzene solution and reaction was carried out until no more

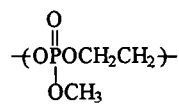
changes of concentration of the end-groups and starting diphenyl-H-phosphonate are observed. Higher $\overline{M}_n$ were observed at higher temperatures, and polymers with still higher $\overline{M}_n$ ($\sim 30 \cdot 10^3$) were obtained when C_6H_5OH was removed under vacuum and polycondensation was conducted in bulk. All of the processes are catalysed by ~0.1% of C_6H_5ONa. As in the polytransesterification process, the high purity of starting compounds is of utmost importance. ***If one fails to prepare the pure compounds, to analyse them correctly, in order to detect the impurities, and then to proceed the polytransesterification or the polycondensation in an anhydrous and (preferably) oxygen free atmosphere (to prevent oxidation of the P-H function), then the synthesis will not lead to a high polymer (in the range of $\overline{M}_n$ over 10^4).*** However, for several applications $\overline{M}_n$ of a few thousand is sufficient. Polymers of such a molecular weight are easily prepared without particular precautions, and several authors reported the use of the described above polycondensation with $CH_3OP(O)(H)OCH_3$ in preparation of poly-H-phosphonates.

Hydrolysis of poly(alkylene phosphates) (Ref. 11)

Oxidation of poly-H-phosphonates provides the corresponding poly(alkylene phosphates). These polymers are interesting for the following reasons:

- polymers can be made water soluble or insoluble, depending on the structure of the repeating unit and the extent of dissociation (in acidic or in salt form)
- the distance between the acidic groups ({OP(O)(OH)OR}) is given by the length of the hydrocarbon bridge (R): polymers from $\{CH_2\}_2$ to $\{CH_2\}_{12}$ and $\{CH_2CH_2O\}_{\sim 25}$ were prepared
- some of the polymers mimick the backbones of biomacromolecules - like nucleic acids and teichoic acids

It has been assumed that poly(alkylene phosphates) could be used in some biomedical applications, including the controlled drug delivery. In this connection it became important to understand their hydrolytical stability. The rate of hydrolysis of the esters of phosphoric acid is known to depend on pH, thus, the pertinent information is given in the form of the "pH kinetic profile". Besides, when poly(alkyl alkylene phosphates) are considered, e.g. poly(methyl ethylene phosphate):



then the relative rates of the "side chain"- methyl group and the main chain hydrolysis depend on pH. This is shown in Fig.2, taken from Ref. 11.

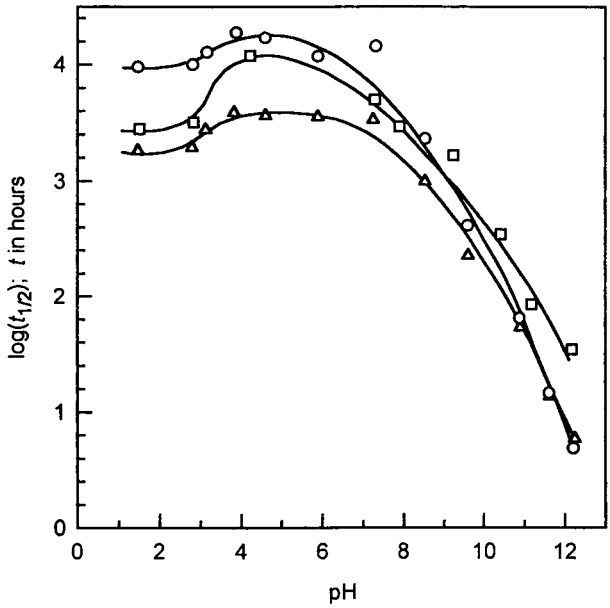
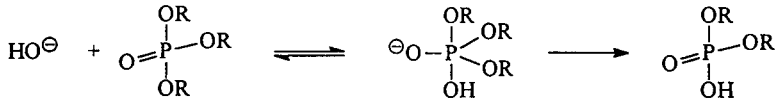


Fig.2. pH-Rate profiles for the hydrolysis of trimethyl phosphate (○: $t_{1/2}$) and poly(methyl ethylene phosphate) (△: $t_{s1/2}$; □ : $t_{m1/2}$) at 45°C; t_s - side methyl group, t_m = main chain; $t_{1/2}$ means the time required for hydrolysis of half of the ester bonds.

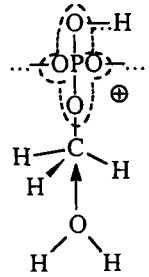
These differences are related to the different mechanisms of hydrolysis prevailing at the given pH. At basic conditions it is the phosphorus atom that is attacked by the strong nucleophile ($^{\ominus}$OH) and then the correspodning bond, after assuming the apical position, is broken.



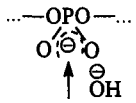
(13)

The rates of hydrolysis at the basic conditions are thus comparable for the methyl group and the main chain.

On the other hand, 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 ("umbrella") do not hamper the back-side attack:



Poly(alkylene phosphates) are much more stable toward hydrolysis particularly at pH > 7, than poly(alkyl alkylene phosphates). This is because at basic conditions the partial negative charge generated on the P atom hampers attack of the OH anion on this atom:



Rate constants of hydrolysis of poly(trimethylene phosphate) at 70°, as a function of pH, are given in Table 2 (taken from Ref. 11).

Table 2. Rate constants of hydrolysis of poly(trimethylene phosphate) at 70°C (Ref. 11).

pH	k_2 ($mol^{-1} \cdot L \cdot s^{-1}$)	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	-	$1.14 \cdot 10^{-8}$

On some properties and applications of polyesters of phosphoric acid

In the previous sections we reviewed methods applied mostly in this laboratory to the synthesis of the high-molecular poly(alkylene phosphates). These polymers were prepared by oxidation of poly(H-phosphonates), prepared by polycondensation of glycols with diphenyl-H-phosphonates or polytransesterification of the corresponding oligomers with methyl-H-phosphonate end-groups.

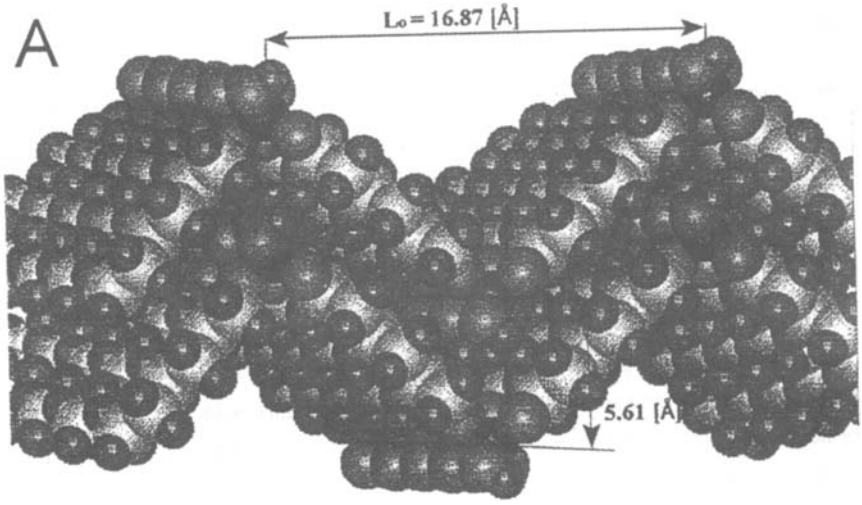
Some basic properties of polyphosphates are given in the Table 3.

Table 3. Some properties of poly(polymethylene phosphates) $\{(CH_2)_xOP(O)(OH)O\}_n$

X	$\bar{M}_n$	n	k (%)	T_m (°C)	T_g (°C)
6	17.400	97	21	68	-20
7	9.800	51	35	65	nd
8	8.500	41	43	83	-11
9	8.000	36	38	78	-35
10	10.200	43	30	93	-8
12	15.200	57	36	102	-17

k - degree of crystallinity (Hindeleh - Johnson method (Ref. 12))

More recently Wlochowicz a.o. studied the solid state properties of poly(alkylene phosphates) and determined the crystalline state of several polymers by X-rays. Below, in Fig.3 two of the thus determined structures are given (Ref. 13).



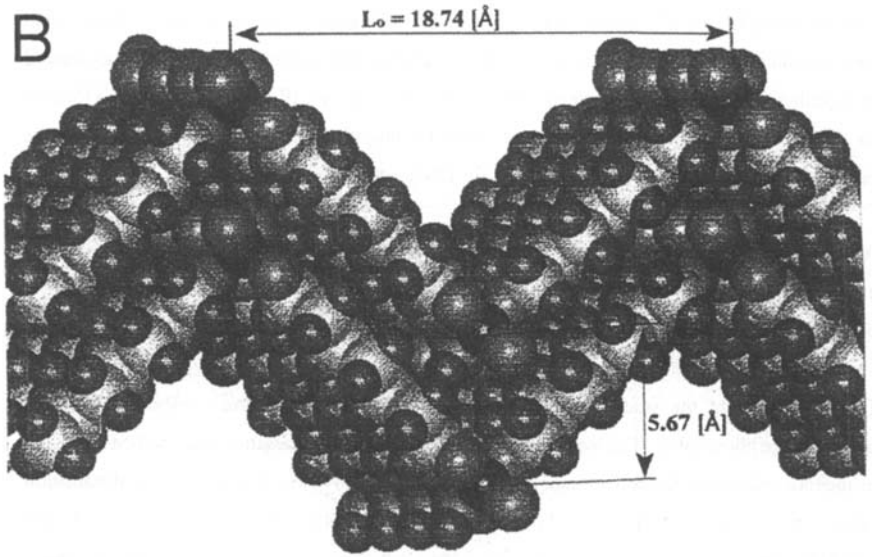


Fig.3.Crystalline structure of poly(alkylene phosphates), perspective view of "crystalline layers" composition in: (a) $[OP(O)(OH)O(CH_2)_6]_n$ and (b) $[OP(O)(OH)O(CH_2)_7]_n$; green: C atoms, red: O atoms, black: P atoms, violet: H atoms (Ref. 13).

Poly(alkylene phosphates) were studied in several research groups, mostly as models of biomacromolecules, in transporting metal cations and as conjugates of other polymers, containing matching reactive groups (e.g. amino groups).

In a series of papers from Torun University, poly(alkylene phosphate)s, prepared in our laboratory, were used as model polymers in order first to understand several features of the simple backbones, and then to use some of these polymers as synthetic membranes. Since it is known, that TA are active components of the cation transport in the biological membranes (particularly in the G-positive bacteria), it became of interest to understand the state of hydration of the phosphoryl groups and the binding of these groups to the mono- and divalent cations.

In poly(1,3-propylene phosphate), model of TA, in its pure hydrogen form, studied by the NMR pulsed field gradient technique, the immobile phase of water is formed by approx. one molecule per one functional group (Ref. 13). In the mixed hydrogen-magnesium (α=0.5) form the mean value of water molecules per one phosphate group is two in the phase of strongly restricted translational motion. Assuming, that the acid phosphate group in the mixed hydrogen-magnesium form hinders the motion of one water molecule, as in the pure HO-polymer, one can conclude, that three molecules of water per one Mg-polymer group form an immobile phase.

Simple poly(alkylene phosphate)s have been found to be well suited for studies of monovalent cation binding (Ref. 14). For instance, poly(1,3-propylene phosphate), which can be considered as a synthetic analogue of 1,3-glycerol TA, has been studied with IR spectroscopy in the form of its Na+ salt (Ref. 15). Further studies of cation binding by conductivity have shown, that the binding sequence is similar to that reported for DNA, namely

$$Ca^{+2} > Mg^{+2} > K+ > Na^{+}$$

Application of the ^{23}Na NMR to the studies of complexation of $Na^{\oplus}$ cations by poly(methyl ethylene phosphate) allowed the equilibrium constants of complexation to be determined; the numerical values are close to those known for poly(ethylene glycol) (Ref. 16).

Closely related to the studies of metal binding are the studies of the conformation of the poly(alkylene phosphate)s. The hypercoiled to extended coil state transition was studied (Ref. 17) in aqueous solution by the potentiometric method. A cooperative macroconformational transition takes place upon changing the fraction of dissociated phosphate groups from 0.3 to 0.4. The standard free energy ΔG_c for the transition from a hypothetical hypercoiled form to a loosely coiled form was estimated to be equal to 0.56 KJ mol^{-1}. This was calculated from the area between the experimental $pK_{(a)}$ curve and the extrapolated $pK_{(b)}$ curve as functions of the degree of dissociation:

$$\Delta G_c = 2.303\ RT \int_{\alpha=0}^{1} (pK_a - pK_b)\, d\alpha$$

where α is a degree of dissociation, and pK_a and pK_b are the apparent dissociation constants in the hypercoiled and loosely coiled states, respectively.

On the basis of these studies it was suggested, that in the native TA the presence of hydroxyl groups and the relatively low $\overline{DP}_n$ (lower than for some models studied) prevent the blocking of phosphate groups, making the transition into a hypercoiled state impossible. This conclusion is consistent with the observation of Doyle a.o. (Ref. 18) who found a rigid rod or extended conformation for wall TA of Bacillus substilis in salt-free solutions.

Transport phenomena

Another direction of research, using models described in this paper, is related to the transport phenomena. TA, as it has already been indicated, have been suspected to perform differently in transporting cations, depending on their chemical structure. Results available till now have shown, that indeed, the affinity of dialkyl phosphate groups in the chains for Mg^{+2} cations is strongly

dependent on the type of the phosphodiester unit. The shorter distance between phosphate groups, and a different conformation of the macromolecule for the poly(1,2-glycerol polyphosphate) diminishes the transport of Mg^{+2} ions and favors the Ca^{+2} ions. Thus, in view of this result it becomes understandable, that evolution has selected the 1,3-structures for TA, allowing them to transport mostly the Mg^{+2} ions, being of major importance in the biological functions.

These are merely a few examples of application of the simple poly(alkylene phosphate)s as models in studies of some basic phenomena of their native counterparts.

References

(1) J.Pretula, K.Kaluzynski, R.Szymanski, S.Penczek, *J.Polym.Sci.*, 1997, in press.

(2) J.Pretula, K.Kaluzynski, R.Szymanski, S.Penczek, *Macromolecules*, 1997, in press.

(3) K.A.Petrov, E.E.Nifanteev, R.G.Goltsova, *Vysokomol.Soedin.*, **6**,1545(1964).

(4) K.A.Petrov, E.E.Nifanteev, R.G.Goltsova, S.M.Korneev, *Vysokomol.Soedin., Geterotsepnye Vysokomol.Sodein.*, **68**,1964.

(5) W.Vogt, S.Balasubramanian, *Makromol.Chem.*, **163**,111(1973).

(6) G.Borisov, K.Troev, *Commun.Dep.Chem.Bulg.Acad.Sci.*, 1971 (vol.IV, No3), 369.

(7) J.Pretula, S.Penczek, *Makromol.Chem., Rapid Commun.*, **9**,731(1988).

(8) J.Pretula, S.Penczek, *Makromol.Chem., Rapid Commun.*, **191**,671(1990).

(9) J.Pretula, S.Penczek, *Macromolecules*, **26**,2228(1993).

(10) S.Penczek, P.Klosinski, *Biomimetic Polymers*, C.G.Gebelein Ed., Plenum Press, New York 1990, p.223-243.

(11) J.Baran, S.Penczek, *Macromolecules*, **28**,5167(1995).

(12) R.Kwiatkowski, A.Wlochowicz, *Journal de Physique IV, Colloque C8, supl*ément au Journal de Physique I, vol.**3**, 83(1993).

(13) R.Kwiatkowski, Ph.D.T., Bielsko-Biala, 1996.

(14) M.Litowska, *Colloid & Polymer Sci.*, **264**,352(1986).

(15) S.Penczek, P.Klosinski, A.Narebska, R.Wodzki, *Makromol.Chem., Macromol.Symp.*, **48/49**,1(1991).

(16) R.Wodzki, P.Klosinski, *Makromol.Chem.*, **191**,921(1990).

(17) R.Szymanski, S.Penczek, *Makromol.Chem.*, **194**,1645(1993).

(18) R.Wodzki, K.Kaluzynski, *Makromol.Chem.*, **190**,107(1989).

(19) R.I.Doyle, M.I.McDannel, J.R.Helman, U.N.Streips, *J.Bacteriol.*, **122**,152(1975).