Pure & Appl. Chem., Vol. 56, No. 10, pp 1309-1322, 1984.
Printed in Great Britain.

0033-4545/84 $3.00+0.00
Pergamon Press Ltd.

SYNTHETIC ANALOGUES OF PHOSPHORUS CONTAINING BIOPOLYMERS

S.Penczek*, G.Łapienis, and P.Kłosiński

Centre of Molecular and Macromolecular Studies,
Polish Academy of Sciences, 90-362 Łódź, Boczna 5, Poland

Abstract - Methods of preparing high molecular weight polymers with poly(dialkylphosphate) main chain as well as lower molecular weight telechelics with similar chains and controlled end-groups are described. These methods are mostly based on the ring-opening polymerization of the corresponding cyclic monomers. Polymers modelling nucleic acids, containing deoxyribose units, and polymers with nucleic acid bases, but without sugar moiety, have been prepared. Poly(dialkylphoshates) prepared this way are used as membrane models and are being tested as biologically active compounds.

INTRODUCTION

Polymer chemistry contributes in various ways in the present progress in biology, biochemistry and medicine, providing new methods for preparing and studying macromolecules as well as providing new, highly specified materials.One of these ways, we are particularly interested in, is the synthesis of new polymers structurally related to the natural biopolymers with phosphate main chains. We assume that for a number of applications it is not necessary to duplicate exactly the actual structure of natural biopolymers in order to provide the desired functions.

SYNTHESIS OF POLYPHOSPHATES: THE CONTRIBUTION OF POLYMER CHEMISTRY

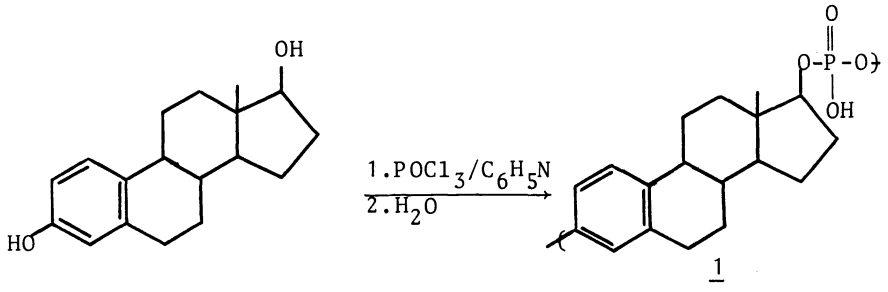
Biopolymers with polyphosphate backbones belong to the most intensively studied areas in chemistry, biochemistry and biology. The number of papers devoted to nucleic acids and their constituents and/or derivatives was in 1982 almost equal to the number of entries placed in the Synthetic High Polymers Section together with Synthetic Elastomers and Natural Rubber in Chemical Abstracts (∿5000 listings per year).
To the most important polymeric and oligomeric phosphates belong polynucleotides comprising DNA and several types of RNA. Polyphosphates of glycerol or ribitol and several other sugar containing polyphosphates of medium molecular weights (up to 25×10^3), namely teichoic acids (TA),are important constituents of the cell walls, particularly of some bacteria (Ref.1). Phospholipides, the lower molecular weight esters are also membrane constituents (Ref.2,3).
The common chemical feature of these products is the presence of the phosphodialkyl group, either in the repeating units (DNA, RNA, TA) or as one of the chemical groups (phospholipids).
Some research groups are using the already existing organic and polymer chemistry in attempts to formulate the supermolecular structures and entities of biological importance. We think, that this is a perfectly legitimate approach, but that on the other hand the activity at the borderline between polymer chemistry and biochemistry and biology requires that another gap is filled, namely between the structurally crude macromolecules,prepared till now by polymer chemists and much more structurally sophisticated biopolymers.
Thus, we have undertaken a program directed toward synthesis of polymeric dialkylphosphates related to nucleic acids (NA) and teichoic acids (TA). In this paper we summarize our recent and older work mostly on the synthesis and on some applications of these polymers.
The present and potential applications of polyphosphates, related to analogues of the natural products, can be divided into two groups, namely the biodegradable and non-biodegradable polyphosphates :

Biodegradable polyphosphates :
- biologically active polymers: polymers with biological activity originated from their inherent chemical and structural features
- drug carriers, allowing targeting, and then undergoing biodegradation
- components increasing pinocytosis, enhancement of the penetration of the carriers through the cell membranes

Non-biodegradable polyphosphates :
- components of synthetic membranes
- drug delivery systems
- models of enzyme functions and other biopolymeric systems
- chelating agents, including chelating of some metal ions, influencing in this way the antimicrobial activity.

EXAMPLES OF SOME EARLY APPLICATIONS

One of the early examples of successful application of polyphosphates as the drug components is the elaborated in Sweden poly(estradiol phosphate) (Estradurin ®) (1), prepared by a simple polycondensation of the diol with $POCl_3$ in the presence of pyridine :



(1)

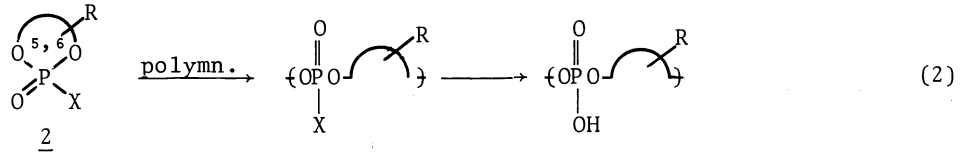
Over 850 papers have been devoted since 1958 to various aspects of the synthesis, application, and biological activity of Estradurin ® (Ref.4).
There are some conflicting information on the polymerization degree and the amount of branching, it is supposed that $\bar{M}_z=10^4$ and that the polymer contains at least 10% of the triester units (by titration). Estradurin ® (1) has originally been developed for the slow and controlled release of the diol, which shows strong antitumor ability.
Application of the components of NA, mostly lower molecular weight compounds, nucleotides and their constitutents as the biologically active compounds is better known and we shall refrain from discussing this area (Ref.5-7).

MODELLING OF NA ELEMENTS ON THE NON-PHOSPHATE CHAINS

Several authors elaborated methods of modelling DNA by using vinyl or ring-opening polymerization. These works started from polymerizing vinyl monomers derived from NA bases, like vinyl adenine, uracil, thymine, or imidazole. The latter one is not the NA base, but has been used to study the synthetic models of enzymatic action.
More recently Overberger (Ref.8), and Takemoto (Ref.9) used other chains, mostly polyamines or polypeptides, to impart hydrophilicity to the corresponding polymers. There are several comprehensive reviews published by Overberger (Ref.10-12), Takemoto (Ref.13, 14) and Ise (Ref.15) on the synthesis, properties, and applications of these polymers. Important progress has been made in matching the enzymatic activity of the natural enzymes with imidazole units (Ref.16).
The application of these and simpler polymers as the biologically active products, at least according to Pitha, has not yet given promising results (Ref.7). This is, in Pitha's judgment (Ref.7),mostly due to their electroneutral properties differing in this basic feature from the natural ones: the surface of the cells does not contain groups that could bind strongly enough polymer in question. The biomolecules that would have to interact are all located inside of the cells and thus isolated from the circulating polymer by membranes that these polymers cannot penetrate (Ref.7).
However, some polymers belonging to this group,like poly-1-vinylcytosine,are effective inducers of interferon in some human cells (Ref.5, 7).

POLYPHOSPHATE (POLY(DIALKYLPHOSPHATE)) CHAINS BY RING-OPENING POLYMERIZATION

In the previous sections we have shown that the major developments in synthetic polynucleotides and their models went two ways: in the biochemical field, as mostly the step-by-step synthesis, that led to the synthesis of the desired structures, identical to these of the natural biopolymers, and in the polymer chemistry, as mostly vinyl or some heterochain polymers, bearing bases or nucleosides in the side chain.
Thus missing in this development there were polyphosphates and poly(dialkylphosphates), modelling the backbone itself and eventually leading to the simpler models of polyphosphates. These contain bases or sugars alone, or all of the components of biopolymers attached to the poly(dialkylphosphate) polyanion, avoiding the discussed above drawbacks of the electroneutral polymers.
The program formulated this way has been started more than ten years ago and partially already reviewed. Mechanism of both anionic and cationic polymerization of the cyclic phosphates and related monomers has already been discussed by one of us (Ref.17), some preliminary data on the more advanced models of biopolymeric polyphosphates was also reviewed by us at the meeting on "Phosphorus Chemistry Towards Biology" (Ref.18) and at IUPAC Congress (Ref.36).
Application of the ring-opening polymerization requires some preliminary comments. The final chain is a polyanion, the required ring-opening polymerization is the ionic process, therefore, the corresponding monomer (2) in the form of a cyclic dialkylphosphate cannot be directly polymerized :



2 (2)

The substituents around the P atom in 2 (the exocyclic groups) should be chosen in such a way, that they would not hamper the ionic polymerization and would easily be convertible into the acidic groups, in the macromolecule, without altering the polymerization degree. Hopefully, cyclic compound containing the tetracoördinate penta-or tervalent and tricoordinated tervalent phosphorus atoms offer the ample possibilities to fulfil these requirements. Both 5- and 6-membered monomers were studied, remembering that although DNA have the 6-atom repeating units, some of the teichoic acids are based on the 5-atoms units.
Some additional limitations come from the polymerization thermodynamics. Below, in Fig.1, we compiled the ΔH_p and ΔS_p from our works (Ref.19-22). It is remarkable, that the enthalpy of polymerization of the six-membered cyclic phosphates, phosphites, and phosphoramidites is close to 0. The sign of ΔH_p may depend on the conditions of polymerization (whether in bulk or in the appropriate solvent).

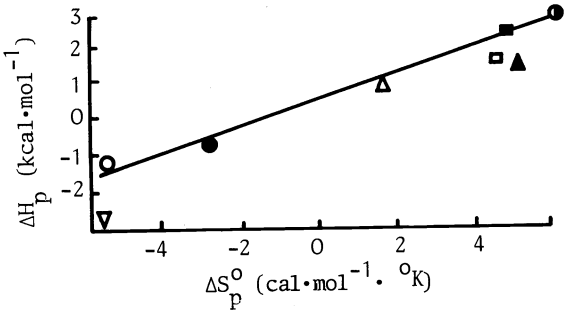
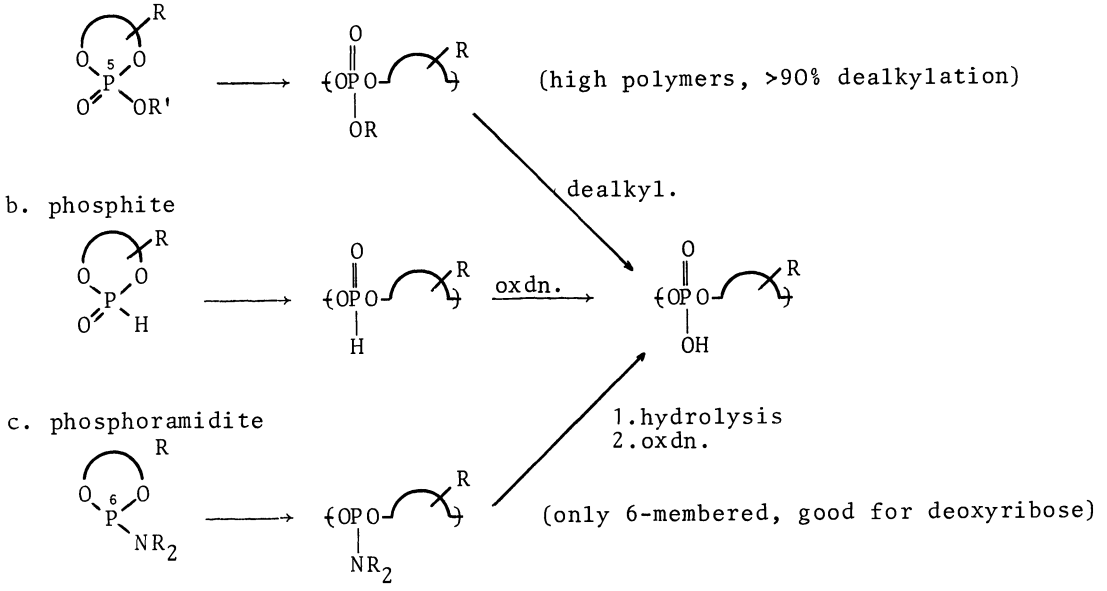


Fig.1. Isoequilibrium dependence for 2-oxo-1,3,2 λ^5-dioxaphosphorinanes (6-membered) substituted in a 2-position; substitutents: (○): methoxy (cationic), (●): methoxy (anionic), (Δ): ethoxy, (■): n-propoxy, (◑): trimethylsilyloxy, (□): hydrogen; and for comparison, (▲): 2-diethylamino-1,3,2-dioxaphosphorinane, (▽): 2-methoxy-2-oxo--1,3,2-dioxaphospholane (5-membered) (Ref.35).

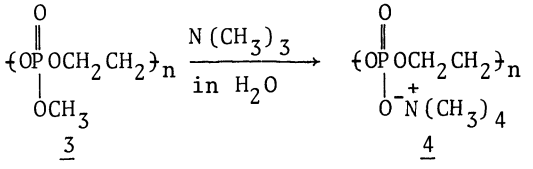
The significance of the compensation plot for the six-membered cyclic phosphates (we put on Fig.1 data on cyclic six-membered phosphite as well as the five-membered cyclic phosphate) was already discussed by us (Ref.17).Suffice

it to say, that the larger the exocyclic substitutent the lower the exothermicity of polymerization which is actually driven for larger substitutents by the positive change in entropy.
Three major synthetic routes were elaborated in our group, all based on the above described principle, these are :



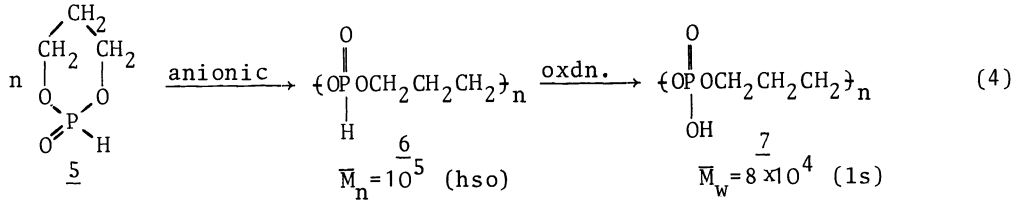
Scheme 1

The triester route can only be applied for the 5-membered rings. This is because of an extensive chain transfer in the much less strained 6-membered ones does not allow to prepare higher polymers (Ref.19, 20). More recently however Nakamura a.o. observed that monomer with the t-C_4H_9 exocyclic group leads to polymers with $\overline{M}_n$ up to 2.5×10^4 (Ref.23).
In our hands, application of the organometallic initiators in the polymerization of 1,3,2-dioxaphospholanes allowed the preparation of the linear polymers with $\overline{M}_n$ in the region 10^4-10^5.
The passage from the poly(trialkylphosphate) to poly(dialkylphosphate) requires dealkylation. This was elaborated for poly(2-methoxy-2-oxo-1,3,2-dioxaphospholane)(poly(methylethylenephosphate)) (3) and over 90% of dealkylation was obtained with less than 30% of decrease in the polymer $\overline{DP}_n$ (Ref.24) :



(3)

Further conversion of the polysalt (4) into polyacid is quantitative with applying the cation exchange resin (Ref.24).
Particularly successful has been the cyclic phosphite route. Polymerization of the six-membered 1,3-propylene phosphite (5) initiated anionically or with aluminium alkyls gives high linear polymers (6). Further oxidation yielded the first high molecular weight poly(dialkylphosphate) (7) with the sequence of atoms in the main chain identical to biopolymers, namely three carbon and two oxygen atoms and the phosphoryl group :

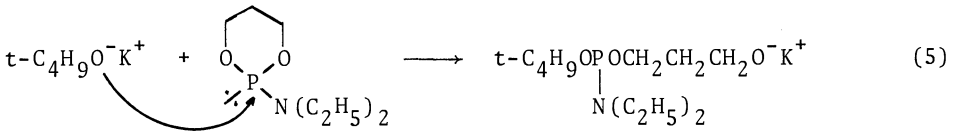


(4)

The high molecular weight poly(1,3-propylenephosphate) (7) is a solid rubbery product, soluble and stable in water solution. Sometimes it crystallizes during precipitation from solution and its water solubility decreases apparently due to the formation of the strong intermolecular hydrogen bonds.

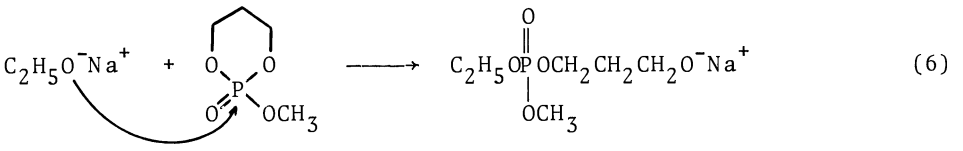
SOME ELEMENTS OF THE POLYMERIZATION MECHANISM

Cyclic phosphates and cyclic phosphites polymerize with anionic or "crypto--anionic" initiators (by crypto-anionic we mean the non-ionic initiators like trialkoxyaluminium, providing either anionic or coordinate anionic polymerization). Cationic polymerization is less favourable; monomers either cannot be polymerized at all or polymerize with some side reactions, decreasing the degree of polymerization of the resulting polymers.
Anionic initiators were shown to react with monomers by a direct nucleophilic attack on the phosphorus atom. This has been established by NMR, allowing to observe,the direct addition of the fragments of initiators to the first monomer molecule (Ref.22).
e.g.:



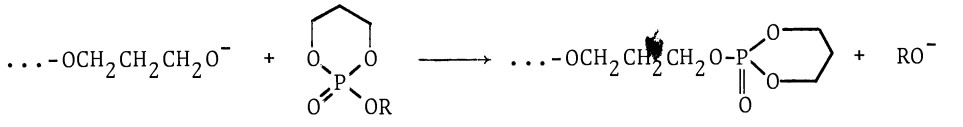
(5)

The presence of the t-C4H9O- group, attached directly to the P atom (and not, for instance, to the carbon atom of the CH_2 group), follows from the observed multiplicities (due to splitting by a nearby P atom) in ^1H- and ^{13}C-NMR.
Similarly, initiation with $C_2H_5O^-Na^+$ of the cyclic phosphate also generates alcoholate growing anion (Ref.19) :

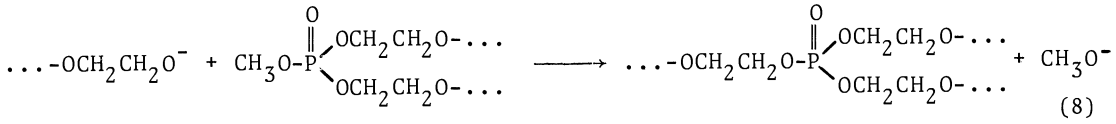


(6)

Chain propagation at these conditions is mostly governed by the behaviour of the alcoholate anions in the given media. Cations have to be used to ensure the breakdown of the nonreactive aggregates.
Several systems have been elaborated in this laboratory, leading to the living polymerization conditions. However, chain transfer was also observed to monomer and/or to the polymer chain (Ref.19, 17) :



(7)



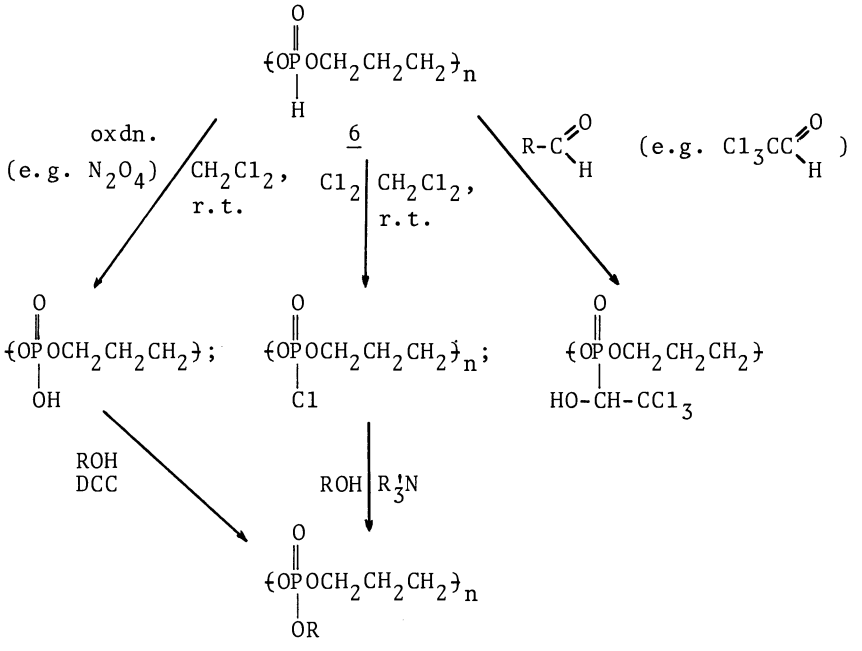
(8)

The former transfer is particularly active for monomers with low ring strain, when ring opening cannot compete sufficiently with breaking a bond to the exocyclic group.
Additional problems may arise in the polymerization of the unsymmetrically substituted rings since no efficient methods to the stereochemical control have been found yet.

REACTIONS IN THE MAIN CHAINS. DERIVATIZATION OF THE BASIC POLYMERS

Both poly(dialkyphosphite)(6) as well as the resulting poly(dialkylphosphate)

(7) can be used for preparing various derivatives and copolymers. Poly(dialkylphosphite) (6) is soluble in methylene chloride and some other polar solvents. The P-H bond is highly reactive in various addition reactions, particularly in the addition of the double bond, either olefinic or carbonyl. Another reaction is conversion of the P-H bond into the P-Cl, which gives access to the synthesis of polymeric amides, esters a.o. Finally, the poly(dialkylphosphate), formed first by oxidation of the corresponding polyphosphite, can also be converted into the polytriester in reaction with the corresponding alcohol and condensing agent (e.g. DCC).
These processes are illustrated in Scheme 2.



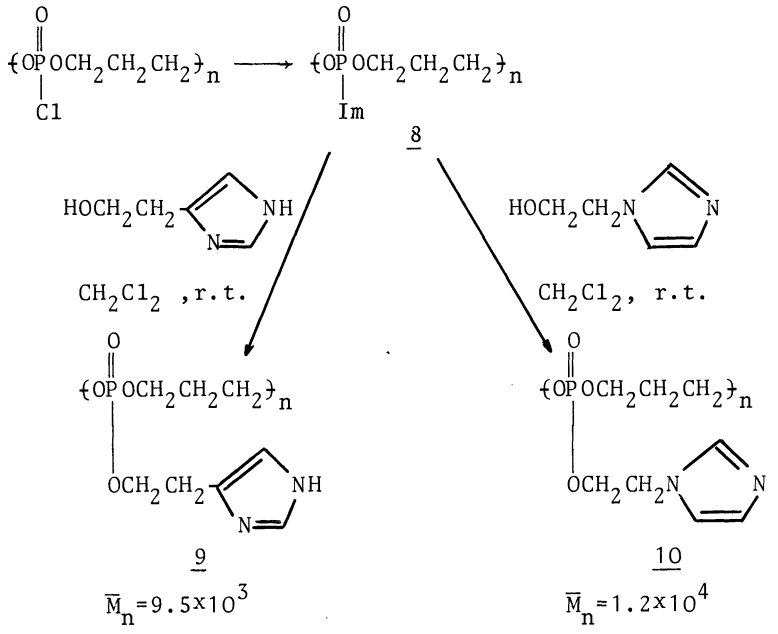
Scheme 2

Reactions shown in Scheme 2 proceed quantitatively. This is important in oxidation of the poly(dialkylphosphite) to poly(dialkylphosphate), because the former one is not hydrolytically stable whereas the poly(dialkylphosphate) did not show any sign of degradation when kept in water solution over six-month (determined by stability of the solution viscosity). However in some other products it is desirable to have in the same chain preserved dialkylphosphate units and the new ones, particularly when a hydrophobic unit is introduced but the water solubility is still desired. Examples of using transformation of various polyphosphites in the particular polymer syntheses will be given further in this paper.

POLYPHOSPHATES BEARING NITROGEN BASES IN THE SIDE CHAIN

N- and C-substituted imidazole

Polyphosphates containing imidazole groups can provide the appropriate balance of hydrophilic and hydrophobic interactions by changing the ratio of dialkyl (i.e. anionic) and trialkyl (i.e. neutral) units.
In order to avoid stereochemical ambiguity, we have been facing in modelling teichoic acids, we decided to use simple chains with symmetrical repeating units. The general scheme of reactions is shown below in Scheme 3.
The complete conversion into the trialkylphosphate is possible for the N-substituted polymer (10), whereas the C-substituted (9) contains in the best case up to 10% of the 1,3-propylenephosphate units, as evidenced from NMR.



Scheme 3

^{13}C-NMR spectrum of (10), containing 50% of 1,3-propylenephosphate units, is shown below in Fig.2, together with the corresponding assignements.

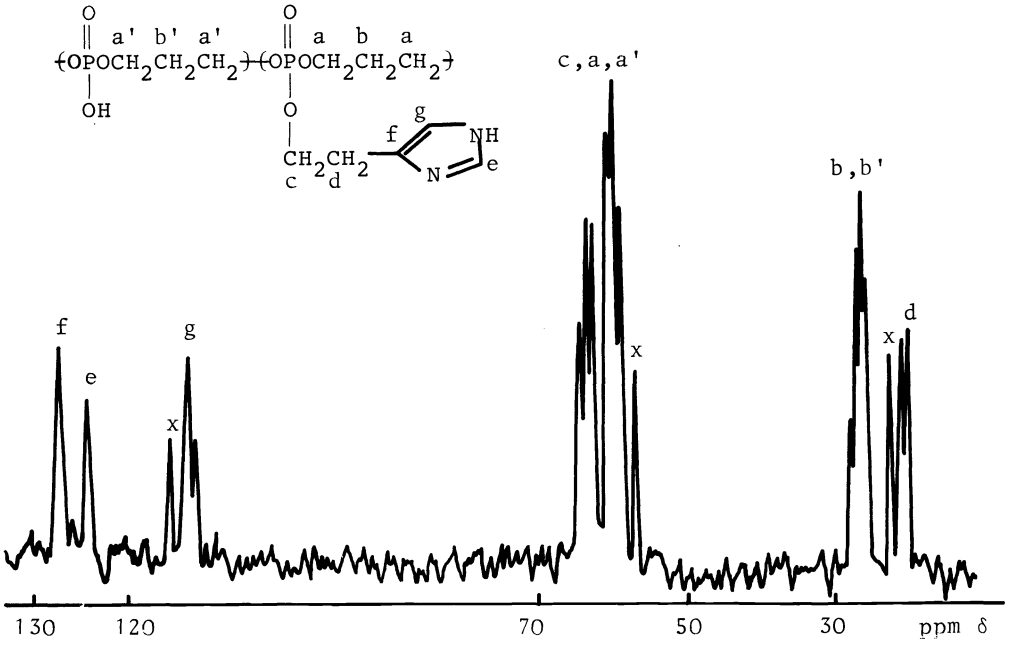


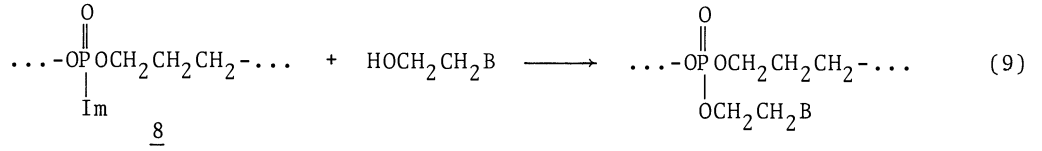
Fig.2. ^{13}C-NMR spectrum of polyphosphate with imidazole residue. (x-signals due to the presence of the alcohol residue). Recorded as ∿30% solution in D_2O at r.t. Jeol JNM-FX-60 (Ref.25).

The described above methods, and some of their ramifications (to be published shortly (Ref.25) and not covered in this paper), opened a way to prepare high molecular weight polyphosphates, with various degrees of hydrophilicity,

anionic charge and nucleic acids bases in the backbones.

NA Bases

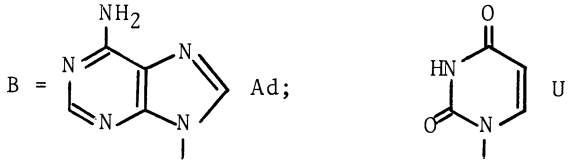
Similar method was applied for the synthesis of polymers containing nucleic acid bases. Thus, reaction 8 with NA bases (B), substituted with hydroxyethyl groups provide the desired polymers with NA bases :



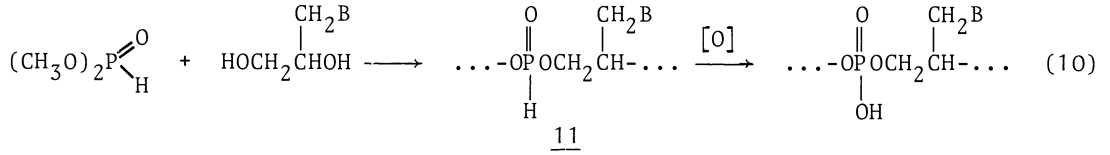
(9)

8

where



At the present stage however substitution is still only partial and no more than 70% of units containing B could be obtained. The remaining units are of dialkylphosphate structure.
Work is in progress in cooperation with V.A.Kropachev to increase the degree of substitution (Ref.26).
Polyphosphates containing B in the side chain but not bound to P atom were also obtained by polycondensation with dimethylphosphite or the corresponding amides.



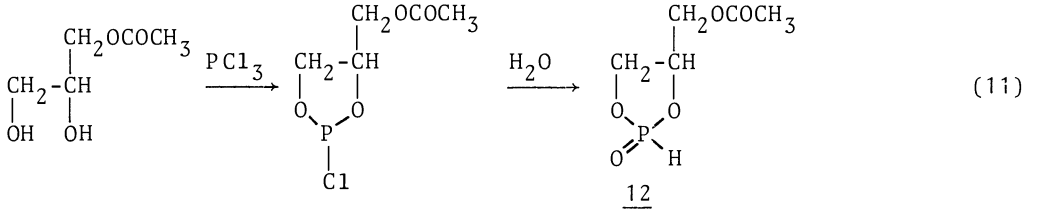
(10)

11

Condensation involving 1-(2',3'-dihydroxypropyl) imidazole leads to the polymer with $\overline{M}_n=5\times10^3$ (vpo) (Ref.27). Both head-to-head and head-to-tail structures are present. Oxidation of 11 gives the required polyacid with Im unit in the side chain. Similar direct methods led recently to the synthesis of oligomeric RNA (Ref.37).

SYNTHETIC GLYCEROL TEICHOIC ACID PREPARATION

Recently we have described the application of the phosphite route to the synthesis of poly(1,2-glycerolphosphate), the simplest analogue of the natural teichoic acid.
Starting monomer, 4-acetoxymethyl-2-hydro-2-oxo-1,3,2-dioxaphospholane (mixture of cis- and trans- isomers) was obtained in the following sequence of reactions (Ref.28) :

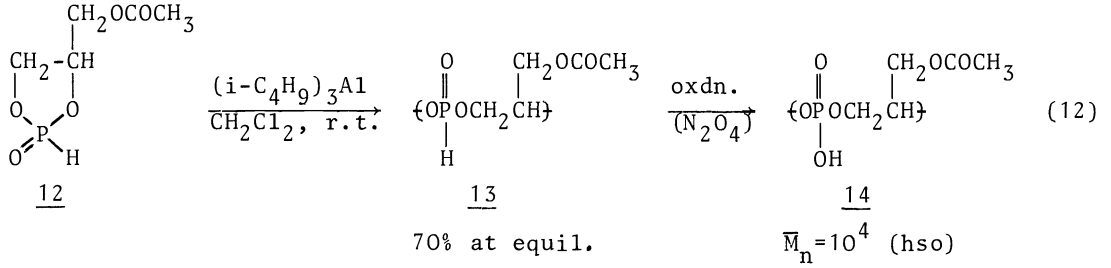


(11)

12

It is essential to keep the proper proportions of reactants in the hydrolysis step in order to avoid the spontaneous polymerization of the cyclic phosphite. The spontaneous equilibrium polymerization of the five-membered cyclic phosphites is a well known phenomenon (Ref.29).
Polymerization of 12 is the equilibrium process (70% of polymer at r.t.); and the resulting monomer-polymer mixture was directly oxidized without isolating of the polyphosphite polymer. Only at the stage of the poly(dialkylphosphate) polymer was isolated by precipitating from DMF to ethyl acetate; cyclic dialkylphosphate, which is no more in equilibrium with its polymer, is

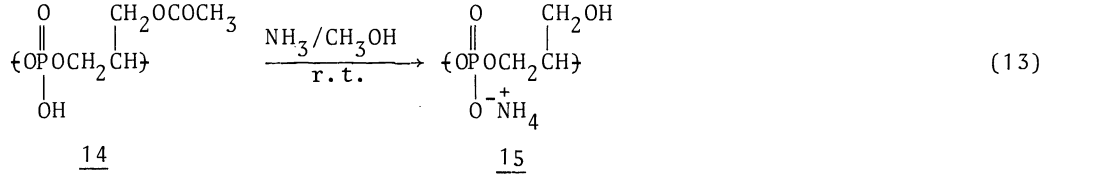
soluble in the resulting mixture :



12 13 14

70% at equil. $\bar{M}_n = 10^4$ (hso) (12)

The polyacid 14 is soluble in water but not stable, losing slowly the acetoxy groups, accompanied by some chain rupture. Its sodium salt however, prepared using Na_2CO_3 in DMF/H_2O solution becomes perfectly stable in water. $\bar{M}_w$ of the sodium salt of 14, determined by light scattering in NaCl solution reached 6.7×10^4.
The final conversion of 14 into the poly(1,2-glycerol phosphate ammonium salt) (15) proceeds in one step in methanolic ammonia solution (Ref.30) :



14 15 (13)

The microstructure of the thus prepared model of teichoic acid (15) was studied by NMR, and the ^1H, ^{13}C and ^{31}P-NMR spectra are shown in Fig.3.

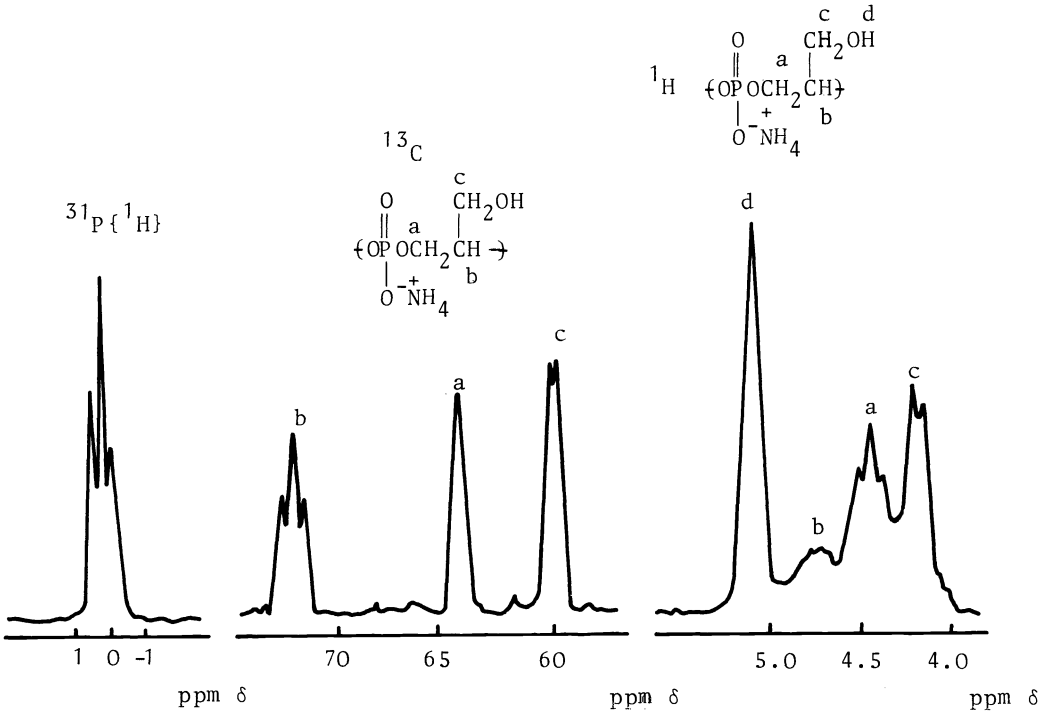


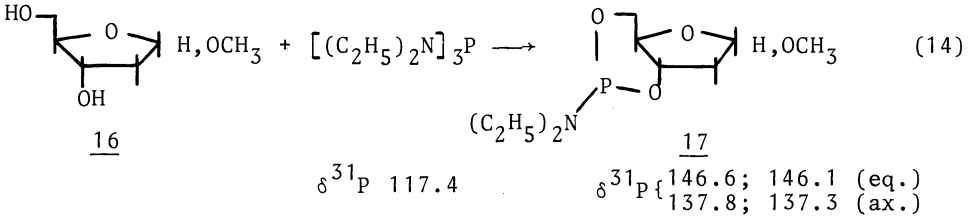
Fig.3. $^{31}P\{^1H\}$, ^{13}C and ^1H-NMR spectra of poly(1,2-glycerol phosphate ammonium salt) (15). Recorded as ∿30% solution in D_2O at r.t. Jeol JNM-FX-60 (Ref.30).

The multiplicities of the peaks are self-explaining, remembering the coupling both ^1H and ^{13}C nuclei to ^{31}P and superposition of some pairs of doublets into distorted three lines (a and b in ^{13}C and a in ^1H-NMR).
The $^{31}P\{^1H\}$-NMR spectrum shows three lines instead of the expected singlet. There are two possible sources of the appearance of three lines with the peak

area ratio close to 1:2:1; these are either caused by the differences in the placement of the neighbouring CH_2OH groups located on the chiral CH carbon atoms or are merely due to the presence of the head-to-head structures, due to the α- and β- ring opening in polymerization. The latter hypothesis seems at present to be substantiated by the model studies of the microstructure of the polymer of closely related structure (Ref.31).
The described above poly(dialkylphosphates) are being studied in several laboratories as models of membrane substitutents and biologically active polymers.

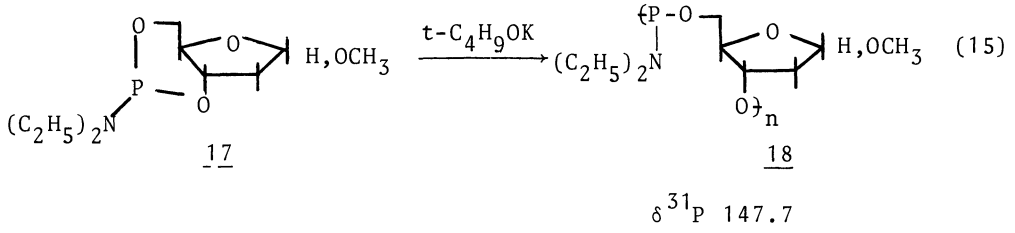
POLY(DIALKYLPHOSPHATES) BEARING DEOXYRIBOSE UNITS

Another analogue of NA, prepared by the ring-opening approach, is the poly-(dialkylphosphate) with deoxyribose units in the main chain. Thus, this is a structure of DNA devoid of base.
The complete scheme of preparation of this polymer, recently described in Ref. 32, includes first blocking of deoxyribose, then condensation with phosphorus hexaethyltriamide, affording bicyclic monomer -α(β)-methyl-2-deoxy-D-ribofuranoside cyclic diethylphosphoramidite accompanied by some polymer :



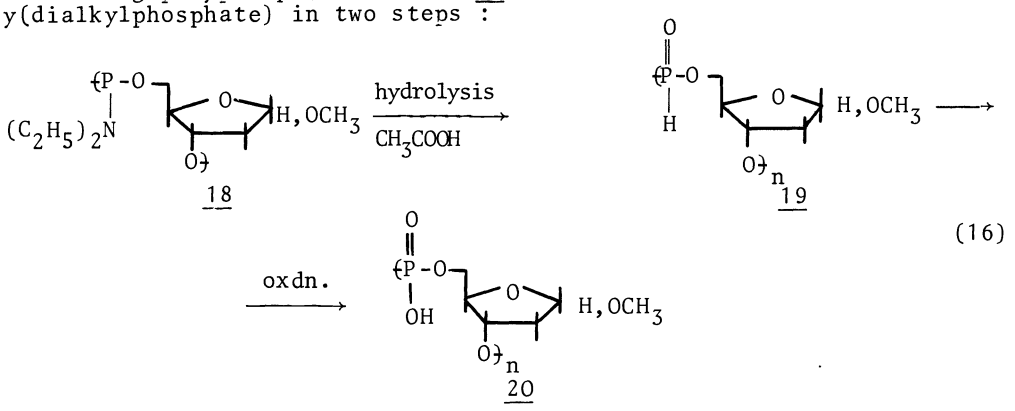
(14)

Monomer exists in four isomeric forms, depending on the position of the methyl group (α or β) in the sugar and Et_2N group at phosphorus atoms (equatorial or axial); the corresponding chemical shifts in ^{31}P-NMR are given above in eq. (14).
The bicyclic monomeric amide was isolated by distillation and was purified in this way before polymerization. Anionic polymerization with t-C_4H_9OK afforded the corresponding polymeric amide of trivalent P (18). Thus, this is the third route shown in Scheme 1 (Scheme 1 route C).



(15)

The resulting polyphosphoroamidite (18) was eventually converted into the poly(dialkylphosphate) in two steps :



(16)

$\overline{M}_n$ (determinated for 19) was equal to 9×10^3, analysis of the ^{31}P and ^{13}C-NMR spectra, shown below in Fig.4, agree well with structure of (20). The corresponding assignments are given directly in Fig.4.

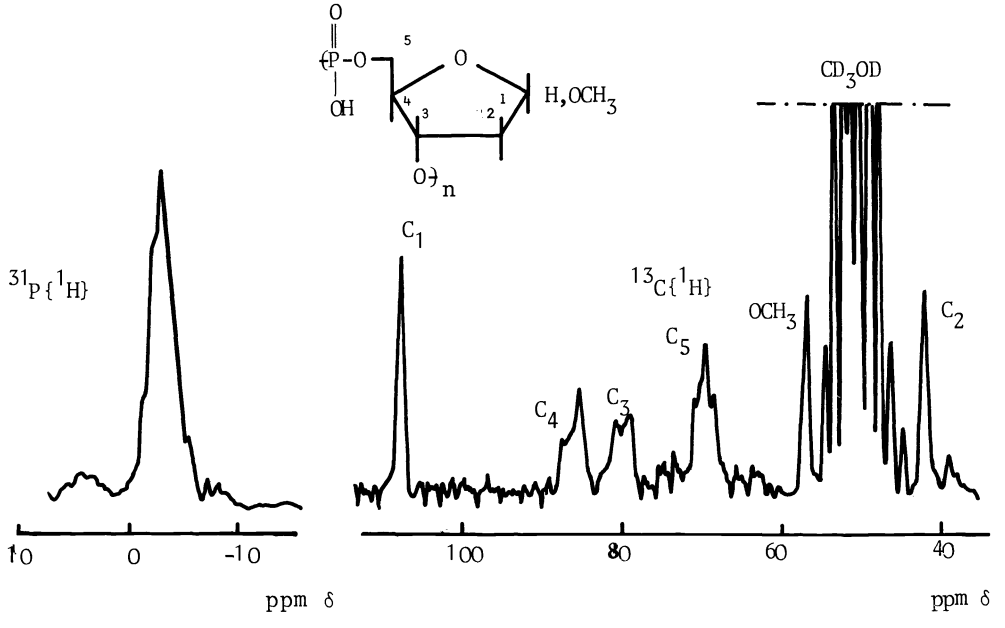
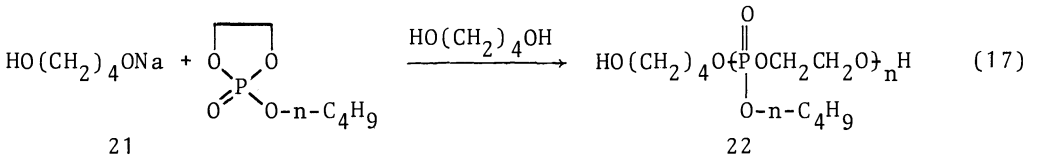


Fig.4. ^{31}P and ^{13}C-NMR spectra of poly(dialkylphosphate) (in acid form) of α(β)methyldeoxyribose (Ref.32).

Doublets or even multiplets observed for C_3, C_4 and C_5 carbon atoms are due to the splitting by ^{31}P atom, through four, three, and two bonds respectively. The peaks are however distorted, the isomerism of the chain (configuration of the rings) are not known at present with any certainty. C_1, and C_2 give single lines, somehow surprisingly, because isomerism (α,β) at C_1 could cause also some splitting. The polymer is optically active ($[\alpha]_D^{25} = +2.94^o$ in DMF measured for 19).
Thus, in the previous sections we described application of the ring-opening polymerization, namely the triester, phosphite, and phosphoramidite routes to obtain models of biopolymers with polyphosphate chains: simple poly(dialkylphosphates), teichoic acids, poly(dialkylphosphates) bearing bases and finally the poly(dialkylphosphate) with deoxyribose unit in the main chain.

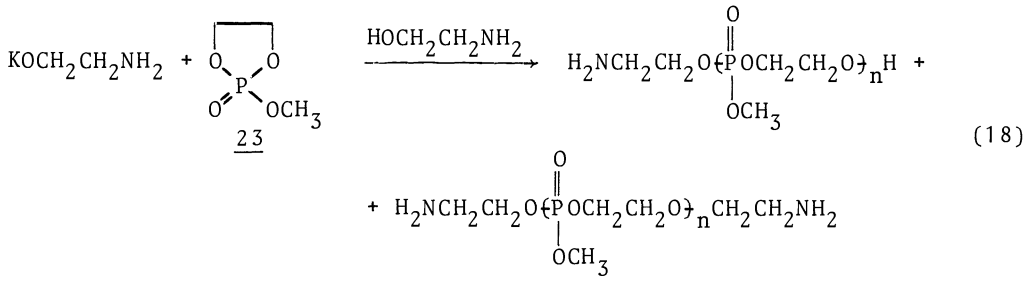
REACTIVE OLIGOMERS AND MACROMONOMERS

The living feature of the anionic polymerization of some 2-alkoxy-2-oxo-1,3,2-dioxaphospholanes has been used to synthesize oligomers having -OH or $-NH_2$ as the end-groups. Thus polymerization of 2-n-butoxy-2-oxo-1,3,2-dioxaphospholane (21) initiated with $NaO(CH_2)_4OH$ in the presence of $HO(CH_2)_4OH$ allowed to obtain the oligomeric polyphosphate glycols with $\overline{M}_n = 10^3 - 3 \times 10^3$ (22).



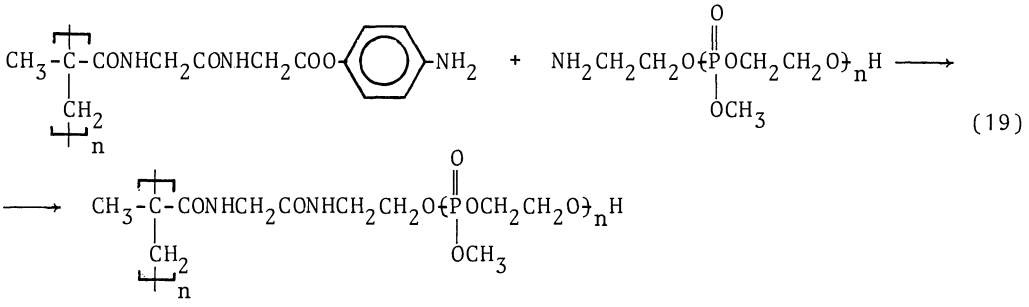
21 22

On the other hand, polymerization of 2-methoxy-2-oxo-1,3,2-dioxaphospholane (23) in the presence of $KOCH_2CH_2NH_2$ and $HOCH_2CH_2NH_2$ in dichloromethane or dimethyl formamide solvents gave oligomers fitted with NH_2 end-groups with $\bar{M}_n = 1.3 \times 10^3 - 8 \times 10^3$ (vpo). These values agreed well with the calculated ones. These oligomers contained ~ 85% of the expected $-NH_2$ end-groups according to the data obtained in the J.Kopeček's group (Ref. 33).



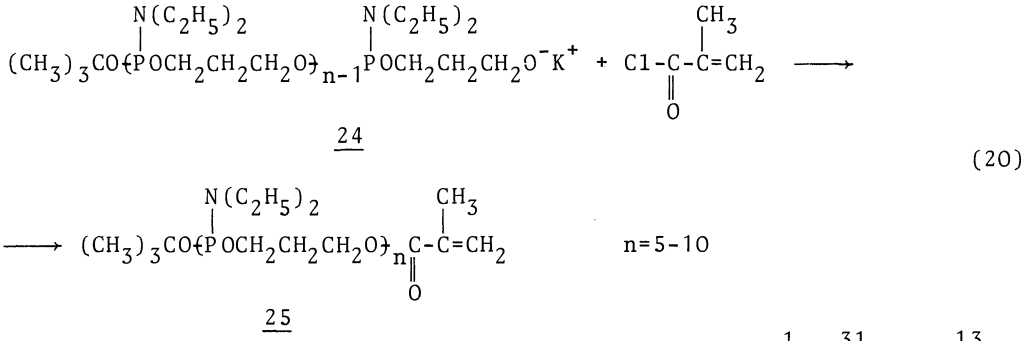
(18)

This oligomer was used by the same research group in the synthesis of the grafted copolymer



(19)

to be used for the biological tests.
The living feature of the anionic polymerization of cyclic compounds containing phosphorus atom in the ring has also been used in the synthesis of macromonomers. Thus, the anionic living poly(2-diethylamino-1,3,2-dioxaphosphorinan) (24) was terminated e.g. with methacryloyl chloride :

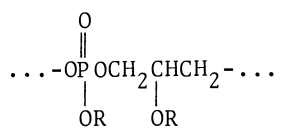


(20)

The structure of 25 was determined by the analysis of ^1H, ^{31}P and ^{13}C-NMR spectra. Thus prepared macromonomer was copolymerized with methyl methacrylate and with styrene giving copolymers with, however, lower content of P--containing mers than expected assuming that the macromonomer copolymerizes with the reactivity ratios close to these of similar methacrylates.

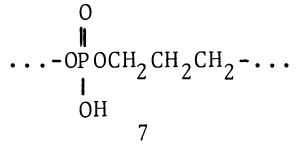
APPLICATION OF THE POLY(DIALKYLPHOSPHATES) IN STUDIES OF SOME MEMBRANE FUNCTIONS

Poly(dialkylphosphates) as models of the membrane constituents .(Ref. 34). Teichoic acids (TA) are known to occur in the cell walls, of the Gram-positive bacteria. Their content in cell membranes attains 50-60 wt %. Their major function is the active transport of ions (mainly Mg^{2+}) from an environment to the cell interior, followed by deposition of ions inside of the cell. The chain forming dialkylphosphate repeating :



where n=8-60, R=e.g. H or α-D-Glucose

is common to all the teichoic acids.
Studies of the transport phenomena have been undertaken by using poly(2-hydroxy-2-oxo-1,3,2-dioxaphosphorinan) (7)



7

where n=8-20

in order to establish the transport mechanism, binding of ions (Mg^{2+} and H^{+}) to 7 and the distribution of 7 in membranes.
The supported liquid membranes (SLM) were prepared either by mixing the preformed 7 and copolymer of acrylamide with N,N-methylenediacrylamide or by copolymerizing these monomers in the presence of 7. Studies of the membranes prepared in this way have proved that 7 is effective in the transport of Mg^{2+} from the Mg^{2+} rich to Mg^{2+} lean phase. The extent to which the active transport is taking place is being under investigation. The equilibrium state of Mg^{2+} distribution is attained stepwise in the oscillating manner. It has also been observed that the conductivity coefficient depends sharply on the 7 concentration and degree of polymerization. Apparently this is due to the strong interaction between the phosphoryl groups, particularly in the acidic form.

REFERENCES

1. J.Baddiley, Acc.Chem.Res.3, 98-105 (1970) and Essays Biochem. 8 35-77 (1972).
2. J.N.Hawthorne, and G.B.Ansell, Phospholipids, (New Comprehensive Biochemistry, Vol.4), Elsevier Biomedical Press, Amsterdam (1982).
3. M.H.Saier,Jr.,and Ch.D.Stiles, Molecular Dynamics in Biological Membranes, Springer-Verlag, New York (1975).
4. Reference list compiled by the producer of Estradurin: Aktiebolaget LEO, S-25109 Helsingborg, Norrbroplatsen 2, Sweden.
5. A.S .Jones, Int.J.Biol.Macromol. 1, 194- (1979).
6. E.De Clercq, First Cleveland Symposium on Macromolecules, 1976, p.217 Elsevier, Amsterdam (1977).
7. J.Pitha, Adv.Polym.Sci., 50, 1-16 (1983).
8. C.G.Overberger, and Y.Inaki, J.Polym.Sci.Polym.Chem.Ed. 17, 1739-1758 (1979)
9. K.Takemoto, H.Tahara, A.Yamada, Y.Inaki, and N.Ueda, Makromol.Chem., 169, 327-331 (1973).
10. C.G.Overberger, K.A.Brandt, S.Kikyotani,and A.G.Ludwick,Polym.Bull.5,481-488(1981)
11. A.G.Ludwick, and C.G.Overberger, J.Polym.Sci.Polym.Chem.Ed. 20, 2123-2138 (1982)
12. Ibidem , 20, 2139-2149 (1982)
13. K.Takemoto, J.Polym.Sci.Symp, 55, 105-125 (1976)
14. K.Takemoto, and Y.Inaki, Adv.Polym.Sci. 41,1-51 (1981).
15. T.Okube, and N.Ise, Adv.Polymer Sci. 25, 135-181 (1977).
16. J.A.Pavlisko, C.G.Overberger, in Biomedical and Dental Applications of Polymers Eds. Ch.G.Gebelein, and F.F.Koblitz, p.257-278, Plenum Press, New York (1981).
17. S.Penczek, J.Polym.Sci.Polymer Symp. 67, 149-168 (1980).
18. S.Penczek, in Phosphorus Chemistry Directed Towards Biology Ed. by W.J. Stec, p.133-143, Pergamon Press, Oxford (1980).
19. G.Łapienis, and S.Penczek, J.Polym.Sci.Polym.Chem.Ed. 15, 371-382 (1977).
20. G.Łapienis, and S.Penczek, Macromolecules, 10, 1301-1306 (1977).
21. K.Kałużynski, and S.Penczek, Makromol.Chem. 180, 2289-2293 (1979).
22. J.Pretula, K.Kałuzynski, and S.Penczek, J.Polym.Sci.Polym.Chem.Ed. (1984) in press.
23. H.Yasuda, M.Sumitani, and A.Nakamura, Macromolecules, 14, 458-460 (1981).
24. K.Kałuzynski, J.Libiszowski, and S.Penczek, Macromolecules, 9, 365-367 (1976).
25. J.Pretula, K.Kałużynski, and S.Penczek, in preparation.

26. Institute of Macromolecular Compounds, Leningrad, USSR,to be published.
27. In cooperation with A.Holy, Prague, Czechoslovakia, in preparation.
28. P.Kłosiński,and S.Penczek, Macromolecules, 16, 316-320 (1983).
29. G.Łapienis, and S.Penczek, in Ring-Opening Polymerization Vol.2,Eds. K.J.Ivin, and T.Saegusa, p.919, Applied Science Publishers (1984).
30. P.Kłosinski, and S.Penczek, to be published.
31. T.Biela, S.Słomkowski, and S.Penczek, to be published.
32. G.Łapienis, J.Pretula, and S.Penczek, Macromolecules, 16, 153-158 (1983).
33. Institute of Macromolecular Chemistry, Prague, Czechoslovakia,to be published.
34. Prepared in collaboration with Prof.A.Narębska, Dept.of Chemistry, University of Toruń, Poland
35. S.Sosnowski, J.Libiszowski, S.Słomkowski and S.Penczek, Makromol.Chem., Rapid Commun. 5, 239-244 (1984).
36. S.Penczek, G.Łapienis and P.Kłosiński, Main Lecture, IUPAC Congress, Bucharest, 1983,to be published.
37. T.Shimidzu, K.Yamana, N.Kanda, and S.Maikuma, Nucleic Acids Res. 12, 3257-3270 (1984).