Synthesis of Phosphorus-Containing Polymers with Aziridine Ring

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Synopsis. It has been established that phosphorus containing alkylammonium salts obtained by alkylation of primary amines with bis(2-chloroethyl) phosphonate or alkyl 2-chloroethyl phosphonate can be transformed into corresponding compounds with aziridine ring.

Physiologically active polymers replace successfully in recent years well known low-molecular therapeutic compounds. Advantages of such drug forms, lower toxicity, prolongated action, higher selectivity etc.[1,2] are due to the unique combination between the polymer character of the drug carrier and the physiological action of the low-molecular medicine.

This work is a continuation of our previous studies on the reaction of *N*-alkylation of compounds containing amino groups with esters of phosphorous acids.[3]

Polycations are effective anticancer agents. They create some level of selectivity regard to malignant cells, which possess greater negative charge and greater endocytic ability compared to normal cells.

The purpose of the present research is the synthesis of polymers with potential biological activity containing an ethyleneimine ring in its side chain.

Results and Discussion

It is well known[4,5] that ethyleneimine is obtained by treating 2-bromoethylamine with potassium hydroxide:

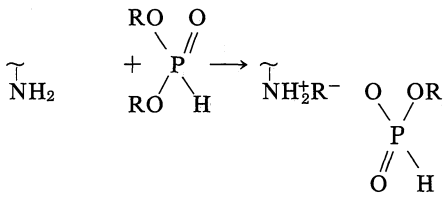
$$H_2N\text{-}CH_2CH_2Br + KOH \longrightarrow \underset{\diagdown\ \diagup}{\overset{}{CH_2\text{-}CH_2}} + KBr + H_2O \quad (NH)$$

This reaction is fundamental in our studies on the synthesis of phosphorus containing polymers with aziridine ring.

We used two polymers containing amino groups—a glucomacropeptide (GMP), and a vinylpyrrolidone—vinylamine copolymer (VP–VA). The fragments containing amino groups with reaction ability are different for them.

In the GMP the amino group is included in the amino acid lysine (ε-amino group) $-HN-\underset{\displaystyle (CH_2)_4}{\overset{\displaystyle NH_2}{CH}}-CO-$ while in the VP–VA copolymer this group is part of the following fragment $-CH_2-\underset{\displaystyle NH_2}{CH}-$.

As in the case of low-molecular amines the reaction of *N*-alkylation between polymers containing amino groups and dialkyl phosphonates will proceed according the scheme:



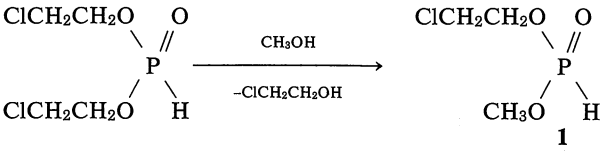
The *N*-alkylated polymers may be transformed into polymers containing aziridine ring only when as an alkylating agent bis(2-chloroethyl) phosphonate is used. In this case as a result of the alkylation reaction a quaternary nitrogen atom is obtained at which one of the replacers is the 2-chloroethyl group. It is this group that will take part at the second stage in the forming of the aziridine ring.

A. I. *N*-Alkylation of the VP-VA Copolymer with Bis(2-chloroethyl) Phosphonate. The ^1H NMR spectra (Table 1) of product **2** obtained from the interaction between the VP–VA copolymer and bis(2-chloroethyl) phosphonate in solution of methanol reveal one doublet for P–H protons at δ=6.6 and $^1J_{P-H}$=626 Hz and two triplets at δ=3.65 and δ=3.82 correspondingly for $\overset{+}{N}$–CH_2 and CH_2Cl protons. Together with these signals another doublet at δ=3.52 and J=12.6 Hz is observed. Its presence may be explained by the transesterification of bis(2-chloroethyl) phosphonate caused by the solvent methanol. It takes place according the scheme:

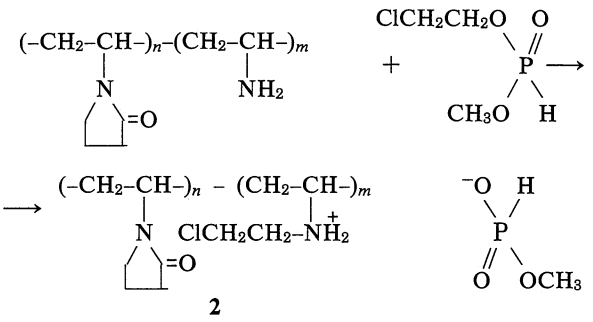
Table 1. ^1H NMR Spectral Data for Products **2**, **3**, **5**, **6**, and **7**

Compound	Solvent	^1H Chemical shifts δ/ppm						Coupling constants J/Hz			
		P–H	P–OCH_3	$\overset{+}{N}$–CH_2	CH_2Cl	$\overset{+}{N}H$ (△)	P–OCH_2	P–H	P–OCH_3	$\overset{+}{N}$–CH_2	CH_2Cl
2	$CDCl_3$	6.60(d)	3.52(d)	3.65(t)	3.82(t)	—	—	626.0	12.8	5.4	5.4
3	$CDCl_3$	6.60(d)	3.52(d)	—	—	a)	—	626.0	12.8	—	—
5	D_2O	6.67(d)	—	—	a)	2.72(s)	4.12(m)	634.9	—	—	—
6	D_2O	6.66(d)	3.54(d)	3.67(t)	3.84(t)	—	—	634.6	11.9	5.0	5.0
7	D_2O	6.66(d)	3.54(d)	—	—	2.71(s)	—	634.6	11.9	—	—

a) Overlaps with polymer signals.

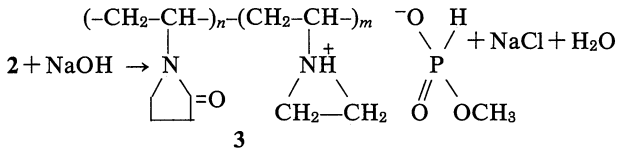


The reaction of transesterification at that temperature 50 °C, is possible as it takes place in a base environment which accelerates the reaction. The obtained methyl 2-chloroethyl phosphonate alkylates the copolymer following the scheme:



In the IR spectra of product **2** (Table 2) the bands for P=O and P–H groups are bathochromically shifted. This proves the ionic character of the bonds.[6]

A. II. Treating of Product 2 with NaOH. Further treatment of the reaction mixture by equimolar amount of 0.1 M NaOH leads to the final product **3** containing an aziridine ring.



The structure is proven by the disappearance of both triplets in the ^{1}H NMR spectra. The singlet at δ=2.71 for the aziridine ring can not be observed (Table 1) because of overlapping with the polymer signals.

B. Reaction of GMP with Bis(2-chloroethyl) Phosphonate. Dimethyl sulfoxide was used as a solvent in this case. The reaction takes place without the isolation of the intermediate product **4** and follows the equation:

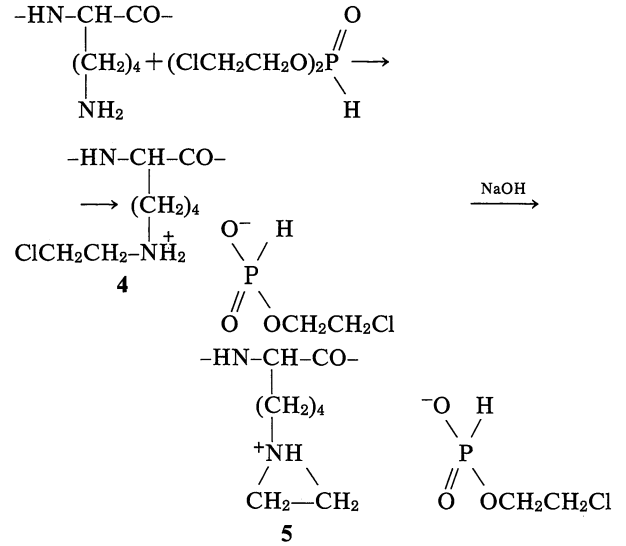


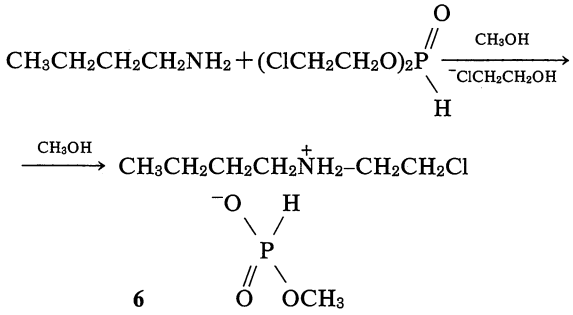
Table 2. IR Spectral Data for Products **2** and **5**

Compound	P=O/cm^{-1}		P–H/cm^{-1}	
	Starting ester	Product	Starting ester	Product
2	1268	1213	2444	2348
5	1268	1214	2444	2319

There is a singlet at δ=2.72 for the aziridine ring in the ^{1}H NMR spectrum of product **4**. The bathochromic shift of P–H and P=O group bands in the IR spectrum is a further proof for the ionic character of the bonds.

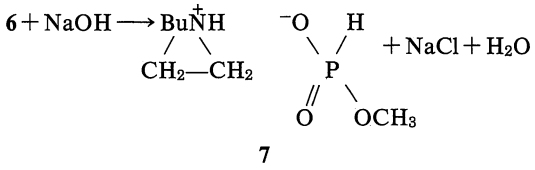
The structure of product **3** obtained from the reaction of the VP–VA copolymer with bis(2-chloroethyl) phosphonate is confirmed also by the model reaction between *n*-BuNH$_2$ and bis(2-chloroethyl) phosphonate. Methanol is used as a solvent.

In the first stage of the reaction a transesterification of the phosphonate takes place. It is followed by the *N*-alkylation of the amine by the methyl 2-chloroethyl phosphonate:

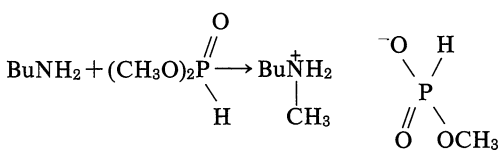


The process is followed by means of ^{1}H NMR spectroscopy. The characteristic doublets for P–H and P–OCH$_3$ protons at δ=6.66 and $^1J_{P-H}$=634.6 Hz, and δ=3.554 $^3J_{P-OCH}$=11.9 Hz, respectively are observed. At δ=3.67 and δ=3.84 two triplets appear for $\overset{+}{N}$–CH$_2$ and CH$_2$Cl protons.

In the second stage, after the treatment of product **6** with NaOH these triplets disappear while a singlet at δ=2.71 for the aziridine ring protons is observed.



Together with these signals the spectra of products **6** and **7** display another doublet at δ=6.78 with J=641.9 Hz and a singlet at δ=2.68 of very low intensity. It may be that under the conditions of the reaction part of bis(2-chloroethyl) phosphonate is transesterified to di methyl phosphonate which takes part further in the *N*-alkylation of butylamine:



The ratio between this component **8** and the main product **7** is 1 : 8.5 or 11.8% : 88.2% calculated from the integral intensity of the peaks.

These two signals are absent in the case of the reaction between the VP–VA copolymer and bis(2-chloroethyl) phosphonate in the presence of CH_3OH. It is probable that the ability for transesterification also of the *s*-alkoxyl group is a function of the basicity of the amines in use.

Experimental

Materials. We used two type of polymers:

A. Synthetic polymer—a copolymer of vinylpyrrolidone with vinylamine (VP–VA) was prepared according the literature[7] with molar ratio of 9:91 and molecular weight 80000±1000.

B. Natural polymer—a glucomacropeptide (GMP) isolated from milk[8] with molecular weight 6000. Galactose, galactosamine, neuraminic acid and 58 anino acids take part in its composition.

Bis(2-chloroethyl) phosphonate (Fluka product) purified by distillation under vacuum was used as an alkylating agent.

The solvents—methanol and dimethyl sulfoxide were purified and dried according the literature.[9]

Procedure. A. Reaction between the Copolymer VP-VA and Bis(2-chloroethyl) Phosphonate. The reaction is carried out in a flask equipped with a stirrer and a capillary for purging with argon. The copolymer is solved in methanol and the phosphonate is added. The temperature of the reaction is t=50 °C. After reaching pH=7 an equimolar amount of 0.1 M NaOH is added and the mixture is heated at 50 °C for 11 h. The product is isolated by precipitation in ether and is dried under vacuum. Elem. Anal. P=2.10%.

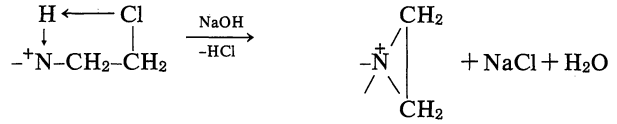
B. Reaction between GMP and Bis(2-chloroethyl) Phosphonate. The reaction is carried out in a flask equipped with a stirrer and a capillary for purging with argon. The GMP is solved in DMSO and the bis(2-chloroethyl) phosphonate is added. The mixture is stirred for 4 h at t=50 °C after which an equimolar amount of 0.1 M NaOH is added. After the reaction has taken place the polymer is precipitated in acetone (0 °C) and is dried under vacuum. Elem. Anal. P=3.14%.

C. Reaction between *n*-Butylamine with Bis(2-chloroethyl) Phosphonate. In a flask equipped with a stirrer and a capillary for purging with argon equimolar quantities of *n*-$BuNH_2$ and bis(2-chloroethyl) phosphonate are mixed. The mixture is heated at t=50 °C until reaching pH=7 after which 0.1 M NaOH is added. The reaction takes place at t=50 °C until once again pH=7 is reached. The final product is isolated by evaporating the methanol under vacuum.

The structure of the final products is proved by IR spectroscopy (PE 983) and ^{1}H NMR spectroscopy (BRUKER WP 250).

Conclusion

The presence of positive charge at the quaternary nitrogen atom probably will accelerate the reaction of forming an aziridine ring because the synthesis is accompanied by release of HCl. The positive charge at the nitrogen atom will provide for higher acidity of the proton associated with it and in this way will accelerate the acid-base reaction:



These results show that polymers containing amino groups *N*-alkylated by bis(2β-chloroethyl) phosphonate may be transformed into *N*-alkylated polymers with aziridine ring.

References

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