Polymer Bulletin 15, 93–100 (1986)

Polymer Bulletin

Biocide Polymers

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15. Esterification of Poly(Vinyl Alcohol) with Biologically Active N-Phosphorylated 3(5)-Methylpyrazoles

Manfred Hartmann, Hans-Jürgen Bauer, and Kurt Wermann**

Sektion Chemie der Friedrich-Schiller-Universität, DDR-6900 Jena, German Democratic Republic

SUMMARY

N-Phosphorylated 3(5)-methylpyrazoles, prepared from the antimicrobially active 3(5)-methylpyrazole by acylation with aryl phosphorodichloridates as well as with phosphoryl chloride, respectively, were reversibly linked to poly(vinyl alcohol). By changing the structure of the phosphorus-containing linkage between biocide and carrier, it is possible to regulate the hydrolytic release of the active agent. Comparative hydrolysis studies demonstrated that the release rates were essentially independent of the degree of substitution of the polymeric carrier.

INTRODUCTION

Polymers having covalently bound 3(5)-methylpyrazole as pendant groups are of particular interest as systems for the controlled release of this antimicrobially active agent. In our previous papers (1, 2) we have studied the synthesis of homopolymers and copolymers of the vinyl derivatives of 3(5)-methylpyrazole as well as the modification of poly(acrylic acid)s with 3(5)-methylpyrazole moieties. It was shown that the content of carboxyl groups in the copolymers and their change during the hydrolysis especially influence the hydrolytic cleavage of the polymer–biocide bond (3). In this paper we report on the reversible linking of 3(5)-methylpyrazole to poly(vinyl alcohol) via phosphorus-containing bonds designed for delivery of the active agent. Preliminary results of hydrolysis and the characterization of these copolymers are described and discussed.

EXPERIMENTAL

A. Materials

Commercial poly(vinyl alcohol) (PVAL, VEB Chemische Werke Buna, Schkopau, type 4205, 2 % acetate groups, M_n 29300) was used as received. The syntheses of phenyl phosphorodichloridate and 4-nitrophenyl phosphorodichloridate have been described (4).

* Part 14: M. Hartmann, H.-J. Bauer and K. Wermann, Angew. Makromol. Chem. 135, 1 (1985)

** To whom all communications should be addressed

Thiophosphoric acid dichloride ($PSCl_3$) was prepared from PCl_3 with powdery sulphur in the presence of $AlCl_3$ and purified by distillation (5). 3(5)-Methylpyrazole was distilled before use. Phosphoric acid isocyanate dichloride was prepared by the reaction of ethyl carbamate with PCl_5 (6).

B. Techniques

IR spectra in KBr pellets were recorded on a spectrometer UR 20 and the spectrometric determination of 3(5)-methylpyrazole was carried out on a Spekol equipped with EK 5 and the measuring amplifier (both Kombinat Carl Zeiss Jena). ^1H NMR and ^{31}P NMR spectra were recorded on a KRH-100 R (Academy of Sciences of the GDR) and on a WH 90 DS (Broker Physik AG), respectively, using $/^2H_6/$-DMSO solutions and hexamethyldisilane or phosphoric acid as internal standard. The determination of the phosphorus content of low molecular weight compounds and polymers was carried out according to the method described previously (7).

C. Procedures

1. Preparation of N-phosphorylated 3(5)-methylpyrazoles:

To a stirred solution of 8.2 g (0.1 mole) 3(5)-methylpyrazole (1) and 10.1 g (0.1 mole) triethylamine in 80 ml ether was added 26.1 g (0.1 mole) phenyl phosphorodichloridate (2a) and 25.6 g (0,1 mole) 4-nitrophenyl phosphorodichloridate (2b), respectively, in 50 ml ether at -15 °C. After 6 h of stirring at room temperature the precipitated triethylamine hydrochloride was filtered off, the ether evaporated and the residue distilled in vacuo.

O-Phenylphosphoric acid 1-(3-methyl)-pyrazolide chloride (3a): Yield 51 %, b.p. 204-207 °C / 0.53 kPa.

Anal. Calcd. for $C_{10}H_{10}ClN_2O_2P$ (256.6): C, 46.80 %; H, 3.93 %; Cl, 13.82 %; N, 10.92 %; P, 12.07 %. Found: C, 46.55 %; H, 4.08 %; Cl, 13.50 %; N, 10.79 %; P, 12.20 %.

O-4-Nitrophenylphosphoric acid 1-(3-methyl)-pyrazolide chloride (3b):
Yield 60 %, b. p. 220 - 223 °C / 0.53 kPa.

Anal. Calcd. for $C_{10}H_9ClN_3O_4P$ (301.6): C, 39.82 %; H, 3.01 %; Cl, 11.75 %; N, 13,93 %; P, 10.27 %. Found: C, 39.63 %; H, 3.07 %; Cl. 11.51 %; N, 13.71 %; P, 10.53 %.

Phosphoric acid bis/1-(3-methyl)-pyrazolide/ chloride (5):
16.4 g (0.2 mole) 3(5)-methylpyrazole and 20.2 g (0.2 mole) triethylamine were dissolved in 100 ml ether. The solution was cooled to -15 °C and 15.3 g (0.1 mole) $POCl_3$ in 50 ml ether was added with stirring. The mixture was stirred at room temperature for 6 h, the formed triethylamine hydrochloride was filtered off, the solvent removed by evaporation, and the residue washed with cold ether. Yield: 55 %, m.p. 25 - 27 °C; b.p. 212 - 216 °C / 0.27 kPa.

Anal. Calcd. for $C_8H_{10}ClN_4OP$ (244.6): C, 39.28 %; H, 4.12 %; Cl, 14.49 %; N, 22.91 % P, 12.66 %. Found: C, 39.21 %; H, 4.18 %; Cl, 14.71 %; N, 22.61 %; P, 12.79 %.

Thiophosphoric acid bis/1-(3-methyl)-pyrazolide/ chloride (6):

Pyrazole derivative 6 was prepared in an analogous manner to that described for compound 5 by using $PSCl_3$ as phosphorylating agent. After adding $PSCl_3$ at room temperature, the reaction mixture was refluxed for 6 h. Yield: 30 %, m. p. 42 - 43 °C.

Anal. Calcd. for $C_8H_{10}ClN_4PS$ (260.7): C, 36.85 %; H, 3.87 %; Cl, 13.60 %; N, 21.49 %; P, 11.88 %; S, 12.30 %. Found: C, 36.59 %; H, 3.91 %; Cl, 13.51 %; N, 21.31 %; P, 12.00 %; S, 12.47 %.

Phosphoric acid (1-carbonyl-3-methyl-pyrazolyl)amide dichloride (7):

A solution of 8.2 g (0,1 mole) 1 in 150 ml ether was treated with 16.0 g (0.1 mole) phosphoric acid isocyanate dichloride (4) at -15 °C and stirred at room temperature for 0.5 h. The compound 7 formed in this way was washed several times with ether. Yield: 90 %, m. p. 50 - 52 °C.

Anal. Calcd. for $C_5H_6Cl_2N_3O_2P$ (242.0): C, 24.81 %; H, 2.50 %; Cl, 29.30 %; N, 17.36 %; P, 12.80 %. Found: C, 24.61 %; H, 2.53 %; Cl, 29.51 %; N, 17.01 %; P, 12.53 %.

2. Esterification of poly(vinyl alcohol) with N-phosphorylated 3(5)-methylpyrazoles:

Reactions on PVAL have been carried out as described previously for the esterification reactions with N-phosphorylated 3-amino-1,2,4-triazoles (8). The yields and the characterization data of the obtained products are given in Table 2.

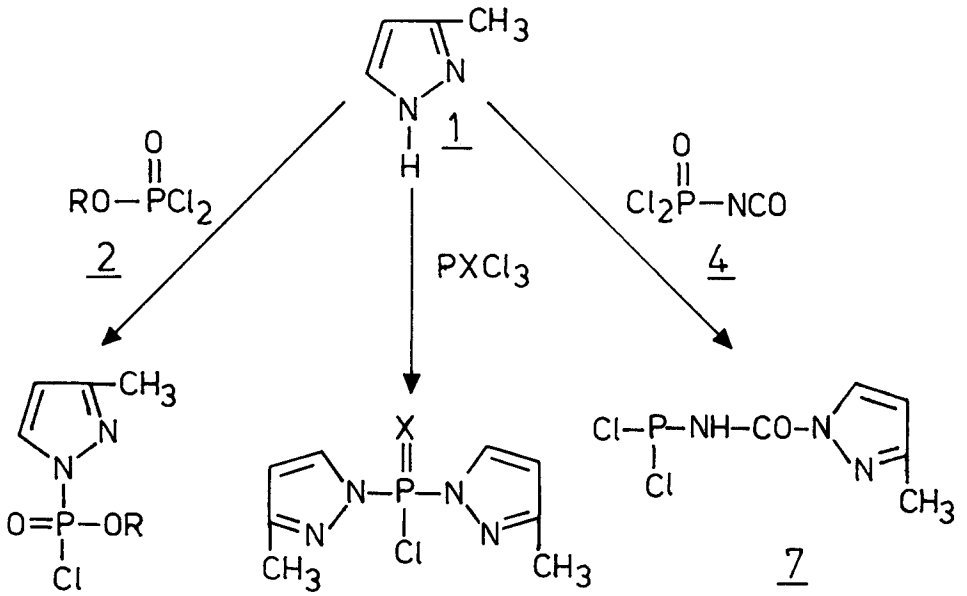
3. Hydrolysis of the biocide polymers:

The hydrolysis of the polymers 8 - 12 was carried out at 30 °C as described previously (2). The quantity of 3(5)-methylpyrazole released has been determined UV-VIS spectrometrically (9).

RESULTS AND DISCUSSION

In order to prepare N-phosphorylated 3(5)-methylpyrazoles suitable for the attachment to poly(vinyl alcohol), 3(5)-methylpyrazole (1) was converted to phosphoric amide ester chlorides by reaction with aryl phosphorodichloridates in the presence of triethylamine. The O-phenylphosphoric acid 3-methylpyrazolide chloride 3a and its O-4-nitrophenyl analogue 3b could be obtained in 60 % yield from an equimolar mixture of 1 and phenyl phosphorodichloridate (2a) and 4-nitrophenyl phosphorodichloridate (2b), respectively. By using 2:1 mole ratios of 1

and $POCl_3$ and $PSCl_3$, respectively, the disubstituted products 5 and 6, both with a higher content of the biocide agent, were formed. On the other hand, phosphoric acid isocyanate dichloride (4) reacted with equimolar amount of 1 and gave the urea derivative 7 in 90 % yield. In this reaction no phosphoric amide linkages were formed.



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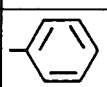
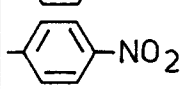
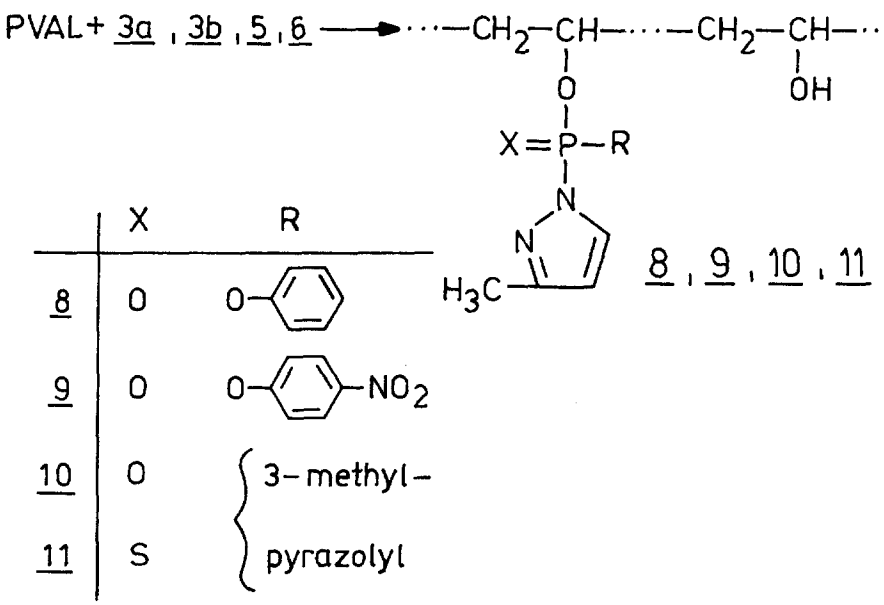
a	
b	

Table 1: Characteristic data of the IR, ^{1}H NMR and ^{31}P NMR spectra of N-phosphorylated 3(5)-methylpyrazoles

compound	IR data /cm^{-1}/		NMR data /ppm/	
	$\nu_{P=O}$	$\nu_{pyrazole\ ring}$	δ_{CH_3}	$\delta_{^{31}P}$
3a	1230	1560	2.35	-6.55
3b	1250	1560	2.35	-
5	1280	1560	2.47	-1.13
6	810[1)]	1560	2.47	-
7	1280[2)]	1560	2.35	-

1) $\nu_{P=S}$; 2) additional $\nu_{C=O}$ = 1710 cm^{-1}

As shown in Table 1, both the characteristic IR absorption data and the one chemical shift of CH_3-protons at the pyrazole ring in ^{1}H NMR spectra prove the phosphorylation at the N(1) of the pyrazole ring in the compounds 3a, 3b, 5, 6 and 7. In addition, the coupling constants of 3.1 Hz of the two doublets due to the CH-protons in the pyrazole ring are typical of 1-acyl-3-alkyl-pyrazoles (10). Furthermore, the peaks at -6.55 ppm for 3a and -1.13 ppm for 5 present in the ^{31}P NMR spectrum confirmed the purity of the compounds.



Esterification reactions of PVAL with the phosphorylated 3(5)-methylpyrazoles 3a, 3b, 5, 6 and 7 were carried out in toluene/pyridine (2:1) in the presence of 4-dimethylaminopyridine (11) and gave polymers containing up to 33.4 wt % of the agent 1. The apparent increase in the degree of substitution up to 40 % of the OH-groups at the polymer 9 is due to the more reactive 4-nitrophenyl derivative 3b compared to 3a. The results of these esterifications are summerized in Table 2.

Table 2: Esterification of PVAL with N-phosphorylated 3(5)-methylpyrazoles

Polymer	Elemental analyses N (%)	P (%)	Degree of substitution	Amount of bonded 1 (%)
8	3.30	3.59	0.07[1)]	9.6
	6.11	6.73	0.20[2)]	17.9
9	5.49	4.08	0.08[1)]	10.7
	11.31	8.34	0.40[2)]	22.1
10	5.43	2.98	0.05[1)]	15.9
	11.41	6.29	0.15[2)]	33.4
11	3.19	1.75	0.03[1)]	9.3
	5.80	3.20	0.06[2)]	16.9
12	7.96	5.80	0.14[2)]	15.5

[1)] equimolar amounts of PVAL and N-phosphorylated 1

[2)] molar ratios PVAL to N-phosphorylated 1 = 1:1.2

It is evident from the IR, ^{1}H NMR and ^{31}P NMR spectra of the modified PVAL 8 - 12, that the P-N and P-O bonds, respectively, of the low molecular compounds are present in the polymers. In the ^{31}P NMR spectra, e.g. of 10, only one signal appears at -1.13 ppm indicating the purity of this polymer. Contrary to the polymers 8 - 11 the polymer 12 is insoluble in DMSO and DMF, probably due to crosslinkings formed.

Results obtained in the heterogeneous hydrolysis of the polymers 8 - 12 in bidistilled water at 30 °C are shown in Figure 1 and Table 3. The data indicate that the release rates of the active compound 1 were essentially independent of degree of substitution of the PVAL-derivatives. However, introduction of an electron-withdrawing substituent into the paraposition of the phenyl ester component, e.g. a nitrogroup, favors hydrolytic cleavage of the phosphorus-pyrazolide linkage. This effect could be proved in the release behaviour of the polymer 9. On the other hand, the thiophosphorus bond in the polymer 11 may be responsible for the retarded release of 1 compared to that from 10. An incomplete hydrolysis was observed in the case of the cross-linked polymer 12.

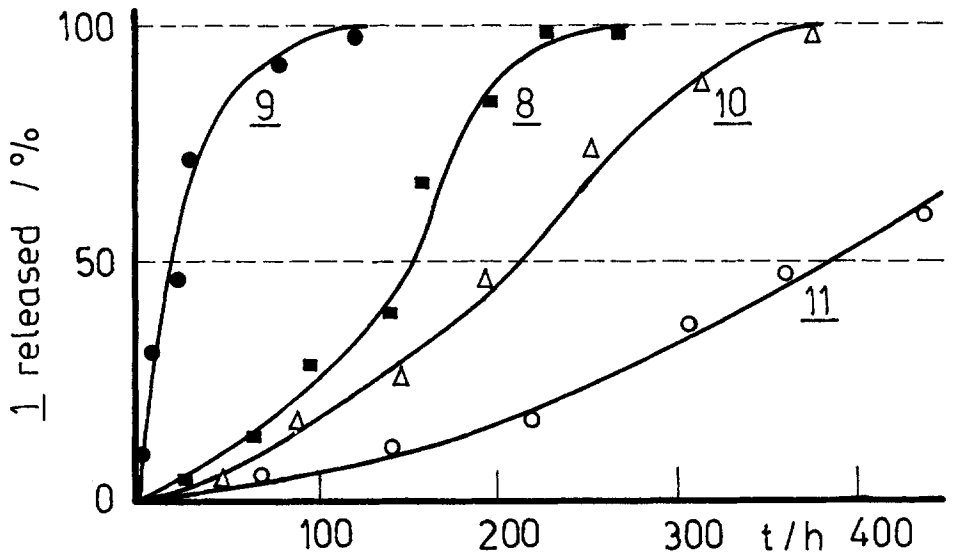


Figure 1: Hydrolytic release of 3(5)-methylpyrazole from modified poly(vinyl alcohol)s containing the agent moiety as pendant groups bound via phosphoric ester amide groups in bidist. water at 30 °C.

Table 3: Hydrolytic release of 3(5)-methylpyrazole from the polymers 8 - 12 at 30 °C in bidist. water

Polymer	Degree of substitution	Release of 1 (in h) t_{50}	t_{100}
8	0.07	145	252
	0.20	150	267
9	0.08	20	128
	0.40	23	137
10	0.05	215	338
	0.15	219	384
11	0.03	384	747
	0.06	384	747
12	0.14	240 (55 %)	-

Finally, the results presented in this study demonstrate that hydrolytic cleavage of phosphorus-pyrazolide linkages in PVAL derivatives proceeds more slowly than hydrolysis of analogous phosphorus-triazolide linking bonds (8). A similar

influence of different azolide bonds upon nucleophilic displacement reactions has been found for low molecular weight compounds by Staab et al. (12). From the findings of preliminary studies we conclude that the pyrazolide linkages in the polymers 8 - 12 are hydrolyzed faster than the ester bonds.

We thank Dr. B. Thomas, Sektion Chemie der Technischen Universität Dresden, for recording and evaluating the ^{31}P NMR spectra.

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Accepted February 5, 1986