Synthesis and catalytic activity of optically active polymers containing oxime groups

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Optically active polymers containing oxime groups have been prepared: (i) by partial quaternization of poly(4-vinyl pyridine) (P4VP) with phenacyloxime bromide and with (+)-(S)-1-bromo-2-methylbutane; and (ii) by reaction of the copolymer from 4VP and (+)-(S)-5-methyl-1-hepten-3-one with hydroxylamine. These polymers have been used as catalysts for the esterolysis of esters of *p*-nitrophenol with non-chiral and with chiral acids. The kinetic parameters of the catalytic process are markedly dependent on the structure of polymer and substrate. A moderate chiral discrimination of the antipodes of *p*-nitrophenyl 2-methylbutanoate is observed with the catalyst obtained from the copolymer of 4VP with (+)-(S)-5-methyl-1-hepten-3-one.

INTRODUCTION

Kabanov and coworkers[1] have shown that oxime groups attached to partly quaternized poly(4-vinyl pyridine) (P4VP) display interesting catalytic properties with respect to an analogous monomer oxime. These systems appear to be suitable for investigating multifunctional catalysis in polymers as an approach to the problem of 'enzyme analogues'[2].

The use of chiral systems is helpful both in providing conformational homogeneity and obtaining information on the mechanisms and stereochemistry of the reactions involved. To this end, we have prepared two types of optically active polymers containing oxime groups, either by alkylation of P4VP with optically active alkylhalides or by copolymerization of 4VP with optically active vinyl ketones; we have investigated behaviour towards esters of *p*-nitrophenol with chiral acids. For purposes of comparison, the same systems have been used for the esterolysis of *p*-nitrophenyl acetate.

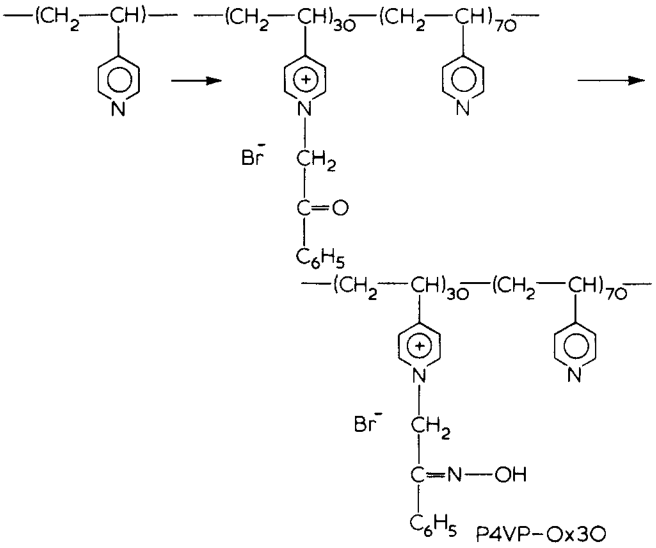
EXPERIMENTAL

Materials

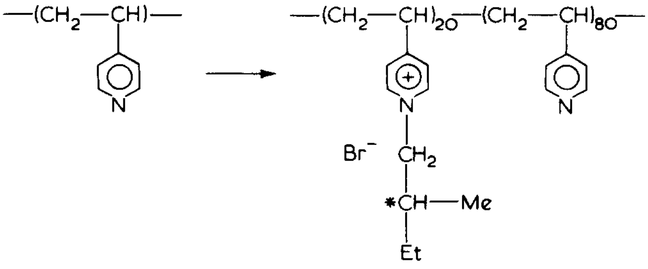
p-Nitrophenyl acetate (PNPA) was obtained by the method of Chattaway[3]. Racemic and (S)-*p*-nitrophenyl 2-methylbutanoate (PNP2MB), as well as the two antipodes of *p*-nitrophenyl 3-methylpentanoate (PNP3MP), were prepared according to the method of Overberger[4]. (+)-(S)-5-methyl-1-hepten-3-one was prepared as reported by Lardicci *et al.*[5].

The reaction of 4-methyl-*N*-phenacylpyridinium bromide prepared according to the method of Truitt[6] with hydroxylamine hydrochloride in 1/1 ethanol–pyridine gave 4-methyl-*N*-phenacyloxime pyridinium bromide.

Poly(4-vinyl pyridine) (P4VP) obtained by AIBN-initiated polymerization of commercial (Merck) 4VP was partly (30 mol %) alkylated with phenacyl bromide in absolute ethanol and successively reacted with hydroxylamine hydrochloride in 1/1 ethanol–pyridine at 60°C to give the polymeric catalyst P4VP–Ox30.



The catalyst P4VP–Ox30–2MB20 was obtained by partial alkylation (20 mol %) of P4VP with (S)-1-bromo-2-methylbutane at 70°C in 1/1 propylene carbonate–ethanol, followed by the same treatment as above to introduce the oxime group.



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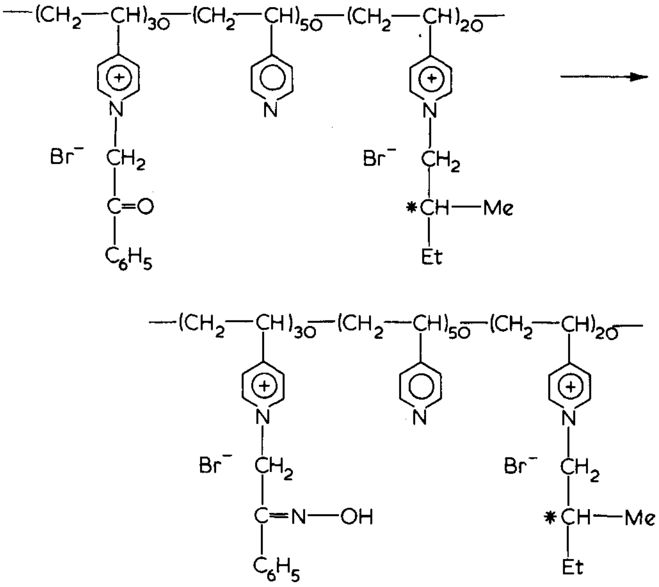
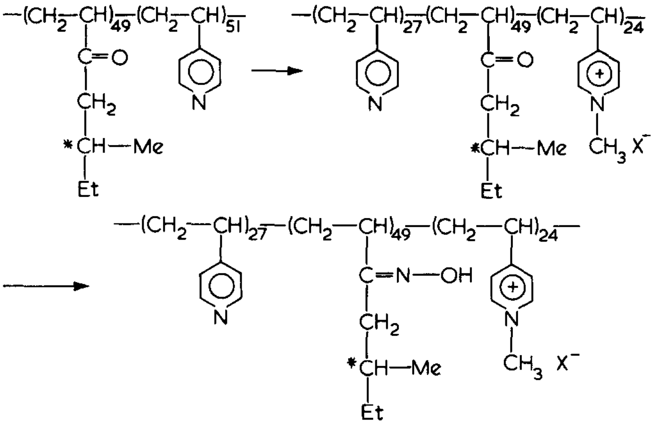


P4VP-Ox30-2MB20

The copolymer of 4VP with (+)-(S)-5-methyl-1-hepten-3-one (C4VP–MBVKt), also prepared by AIBN initiator, was partly alkylated (24%, n.m.r.) with dimethyl sulphate in absolute ethanol at 60°C and then reacted with an excess (3 to 1) of $NH_2OH \cdot HCl$ in 1/1 ethanol–pyridine at 60°C until disappearance of $>C{=}O$ i.r. band at 1710 cm^{-1}. The structure of the catalyst C4VP–MBVKtOx thus obtained is sketched as follows:



C4VP-MBVKtOx

All polymeric catalysts were purified by prolonged dialysis towards 1/1 water–ethanol mixtures.

Kinetic measurements

Kinetic measurements were performed in water at 26°C. P4VP–Ox30 and P4VP–Ox30–2MB20 were studied in a pH = 8.5 tris buffer with an excess (4 to 1) of substrate. C4VP– MBVKtOx was studied in a pH = 10.0 borax buffer with an excess (10 to 1) of catalyst (pseudo-first order kinetics). The hydrolytic reaction of *p*-nitrophenol esters was followed spectrophotometrically (Unicam SP 700A) by determining the absorbance of nitrophenolate anion at 401 nm. In experiments involving an excess of substrate the reference cell contained a solution of substrate and buffer at the same concentration as in the reaction cell, thus allowing direct determination of phenolate anion due to hydrolysis by the polymer catalyst. In the pseudo-first order kinetics experiments the first cell was filled only with buffer.

Approximate values of the kinetic constants relative to the first two catalysts were obtained by treating the data as if the substrate were in a large excess (burst kinetics). Kinetic curves were analysed through the equation:

$$P(t) = \frac{k'_2 S_0 E_0}{k'_2 S_0 + k_3}\left[k_3 t + \frac{k'_2 S_0}{k'_2 S_0 + k_3}\left(1 - \exp[-(k'_2 S_0 + k_3)t]\right)\right] \qquad (1)$$

where $P(t)$ is the molar concentration of the product (PNP^- anion) at the time t; S_0 and E_0 are the molar concentrations of the substrate and the catalyst, respectively; and

$$k'_2 = k_2 \cdot \left[\frac{(K_a)^{1/n}}{(K_a)^{1/n} + (H^+)^{1/n}}\right]$$

The latter term, containing the parameters K_a and n which describe the acid dissociation of the polymeric catalyst in the modified Henderson equation, accounts for the fact that the active sites in esterolysis are the oxime anions[10]. Equation (1) was obtained by introduction of the acid dissociation equilibrium into the scheme given by Bender[7].

The catalyst concentration E_0 was treated as an unknown parameter. Equation (1) was then solved in the unknown k'_2, k_3 and E_0, for the single kinetic curves, through a trial and error procedure which identifies which values of these parameters best reproduce the experimental curve. Kinetic constants were found to vary with the preparation of the polymer catalyst.

Values of E_0 were always found to be about half the stoichiometric concentration of oxime groups. This might indicate that the polymer structure is such as to allow only half of these groups to be active towards esterolysis. This should be confirmed at least by a complete kinetic study at different and proper E_0 and S_0 values. Since the catalysts under investigation did not give chiral discrimination, no further study was carried out with these polymers.

pH Measurements

pH values were measured with a Metrohm E 388 pH meter. Making use of the modified Henderson–Hasselbach equation[8], where the degree of dissociation is measured according to Parke and Davis[9], values of $pK_a = 11.4$ and $n = 2.2$ were found for C4VP–MBVKtOx.

RESULTS AND DISCUSSION

The copolymer P4VP–Ox30 and the terpolymer P4VP–Ox30–2MB20 were used as catalysts in the esterolysis of *p*-nitrophenyl acetate (PNPA) and of optically active and racemic *p*-nitrophenyl 2-methylbutanoate (PNP2MB). Both polymers show catalytic activity higher than the monomeric analogue (*Figure 1*) towards PNPA[10]; the optically active terpolymer displays lower activity towards PNP2MB than PNPA, while no difference in hydrolysis rate was observed between (R,S) and (S) PNP2MB (*Figure 2*), indicating that no chiral discrimination has occurred.

The reaction was carried out with an excess of substrate, exhibiting two-step behaviour. At first, a rapid evolution of the reaction product (PNP^- anion) is observed, followed by a decrease of reaction rate up to a stationary state where the reaction rate is constant.

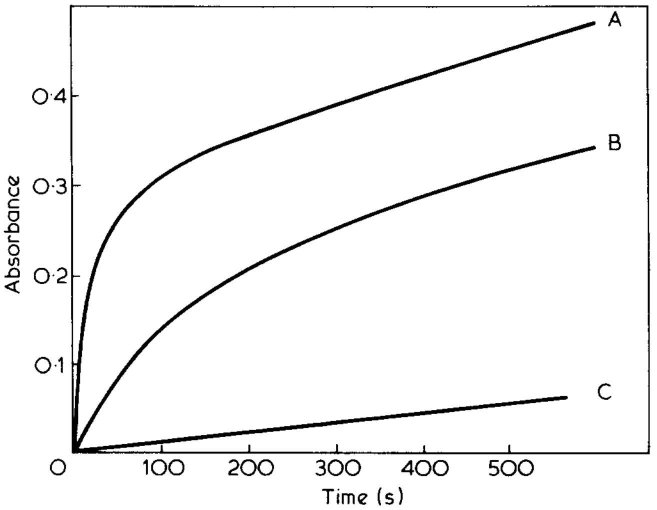


Figure 1 Esterolysis of PNPA catalysed by: (A) P4VP–Ox30; (B) P4VP–Ox30–2MB20; (C) 4-methyl-1-phenacyloximepyridineium bromide. Substrate, 10^{-4} M; catalyst, 2.52×10^{-5} M; tris buffer, pH 8.50; temperature, 26.0°C

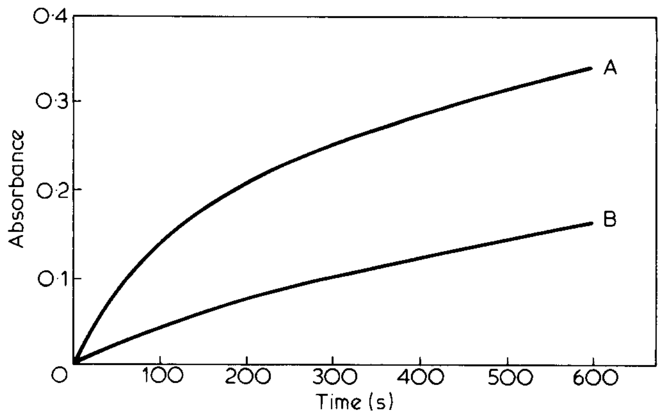


Figure 2 A, Esterolysis of PNPA; and (B) (R,S) or (S)PNP2MB catalysed by P4VP–Ox30–2MB20. Substrate, 10^{-4} M; Catalyst, 2.52×10^{-5} M; tris buffer, pH 8.50; temperature, 26.0°C

This behaviour can be explained assuming that the first step corresponds to the nucleophilic attack of oxime anion on the substrate while the second corresponds to the hydrolysis of the *N*-acylated derivative, giving regeneration of the catalytically active species[7]. Treatment of kinetic data can then be performed on the basis of the following mechanism*:

$$EH^+ \underset{}{\overset{k_a}{\rightleftharpoons}} E + H^+$$

$$E + S \xrightarrow{k_2} P_1 + ES' \qquad (2)$$

$$ES' \xrightarrow{k_3} P_2 + E \qquad (3)$$

where E is the catalyst, S the substrate and P_1 (PNP^- anion) and P_2 (carboxylate anion) the products.

Experimental evidence that the last step takes place has been found in the course of the present investigation. Indeed the PNP^- anion concentration surpasses the starting molar concentration of catalytically active groups (oxime groups) according to the oxime group deacylation[10,11]. Moreover, using a catalyst consisting of P4VP–Ox30 previously acylated with acetyl chloride in 10/1 DMSO–pyridine solution, the hydrolysis reaction exhibits a kinetic profile substantially similar to the stationary state observed in the preceding experiments.

Approximate values of the kinetic constants were calculated as described in the Experimental and their values are reported in *Table 1*. For step (2) the pseudo-acylation constant k'_2 is reported but, for relative comparisons, k'_2 may be regarded as true k_2 values owing to the predicted similar acid strength of the polymers.

The charged groups present in P4VP–Ox30–2MB20 to a larger extent than in P4VP–Ox30 should be statistically far from oxime groups both because of the high content of free pyridine units and of electrostatic repulsion. Moreover, the pK_a of poly(4-vinyl pyridine) partly alkylated with phenacyl bromide was found to be independent of the degree of quaternization[10]. Since the pK_a of P4VP–Ox30 was reported as 8.5[10], the values of k_2 would be twice the values of k'_2 reported here.

The lower catalytic activity observed in the esterolysis of PNP2MB with respect to PNPA with both catalysts (*Table 1*) can be in principle associated with both hydrophobic and steric effects. The higher value of the ratio k'_2 (PNPA)/k'_2 (PNP2MB) observed in the acylation step with the chiral catalyst (P4VP–Ox30–2MB20) having bulky side-chains suggests that the steric factor should be dominant.

The lack of chiral discrimination substantially agrees with the mechanistic picture of the reaction, in which the substrate interacts with oxime anion during the first reaction step (2) and in the second (3) probably interacts with 4VP groups, assisting deacylation. The optically active groups, carrying the same positive charge as the oxime-bound units, undergo electrostatic repulsion and are probably not involved in the acylation step. The low content of optically active groups (20 mol %), the heterotacticity of the macromolecules and the large distance of the side chain asymmetric carbon atoms from the backbone make small, if any, induced chirality in free 4VP units[12].

As a first consequence of these considerations the preparation of an optically active polymeric catalyst was based on a different approach using copolymers of 4VP with optically active vinyl ketones. 4VP was copolymerized by AIBN initiators with (S)-5-methyl-1-hepten-3-one to give several copolymers of different compositions. The reaction of ketonic side chains with $NH_2OH \cdot HCl$ allowed the oxime group to be directly bound to the same unit containing the asymmetric carbon atom. Complete water solubility of these copolymers was achieved by partial alkylation (24 mol %) of 4VP units with dimethyl sulphate.

Table 1 Values of pseudo-acylation and deacylation constant for the esterolytic reactions catalysed by P4VP–0 x 30 and P4VP–0 x 30–2MB20

Catalyst	Substrate	$k'_2 \times 10^{-3}$ ($l\,mol^{-1}\,min^{-1}$)	$k_3 \times 10^2$ (min^{-1})
P4VP–Ox30	PNPA	20	7.0
P4VP–Ox30	(R,S)PNP2MB	12	0.7
P4VP–Ox30–2MB20	PNPA	4.5	7.0
P4VP–Ox30–2MB20	(R,S)PNP2MB	1.5	4.8
P4VP–Ox30–2MB20	(S)PNP2MB	1.5	4.8

Temperature: 26° ± 0.1°C; buffer, tris (pH 8.50), 10^{-2} M; NaCl, 10^{-2} M. Substrate: 10^{-4} M; Catalyst, 2.52×10^{-5} M.
$k'_2 = k_2\ (K_a)^{1/n}/(K_a)^{1/n} + (H^+)^{1/n}$

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* For convenience of notation the dissociation of oxime groups is described as the acid dissociation of a hypothetical polyelectrolyte EH^+

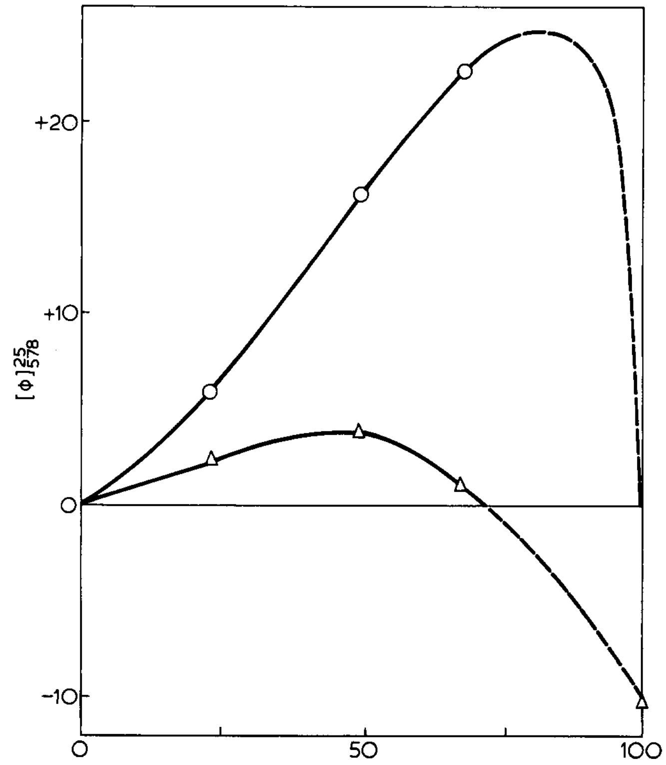

Figure 3 Molar optical rotation (per monomer residue) vs. composition of 4VP/2MBVKt copolymers obtained by radical initiation. —Δ—Δ—, copolymer; —○—○—, contribution of 4VP units

Table 2 Values of pseudo-first order constant for the esterolytic reactions catalysed by C4VP—MBVKtOx

Substrate	k_{obs} (min^{-1})	k_{cat} (min^{-1})
PNPA	0.539	0.4262
(R,S)PNP2MB	0.0953	0.0699 ± 0.0012
(S)PNP2MB	0.0996	0.0742 ± 0.0009
(R)PNP3MP	0.257	0.217 ± 0.005
(S)PNP3MP	0.255	0.215 ± 0.007

Temperature, 26° ± 0.1°C; borax buffer (pH 10.00), 10^{-2} M; substrate, 2.5×10^{-5} M; catalyst, 2.5×10^{-4} M; $k_{cat} = k_{obs} - k_{buffer}$, standard deviation =

$$\left[\frac{\Sigma(k_i - \bar{k})^2}{N(N-1)}\right]^{1/2}$$

owing to the small excess of catalyst, these numbers are not real uncertainties: they only reflect internal agreement and are meaningful for relative purposes

In these copolymers the macromolecules have a conformational arrangement with a predominant chirality. In fact their optical activity is opposite in sign to that of the poly-(S)-5-methyl-1-hepten-3-one suggesting that 4VP units in the copolymer have positive optical rotation which increases up to 75–80 mol % of the optically active comonomer (*Figure 3*)[13,14]. Preliminary c.d. investigations confirm this conclusion, showing that between 320 and 240 nm in addition to the typical dichroic band of >C=O at about 290 nm, a weaker band at 250 nm, related to electronic transitions of pyridine[15] is present.

These copolymers show a pK_a of 11.4 for the oxime groups. Therefore at the pH values necessary for appreciable oxime dissociation the buffer achieves an activity in the esterolysis comparable with the polymer catalyst and thus reliable data cannot be obtained. We investigated step (2) of the reaction under pseudo-first order conditions at pH 10.0 allowing for a buffer contribution about three times lower than that by the polymer. Under these conditions the terpolymer again shows much greater activity with respect to PNPA than to PNP2MB. Moreover, this catalyst shows a moderate chiral discrimination since the (S) antipode of PNP2MB is hydrolysed more quickly than the racemic mixture, even if only up to 6% (*Table 2*). The differences are too small to support a definite interpretation of reaction stereochemistry. However, they indicate the possibility of designing optically active polymeric catalysts with potential stereoselectivity. Considering the *p*-nitrophenol ester of 3-methylpentanoic acid, the esterolysis rate is intermediate between PNPA and PNP2MB while no appreciable difference is observed between the R (71% optical purity) and S antipode (98% optical purity). These results can be explained taking into account the lack of steric effects for this new substrate due to the larger distance, of the chiral centre from ester group with respect to PNP2MB (one methylene group).

Further studies on polymers combining the useful properties of the two catalytic systems will be reported in future papers (e.g. copolymers of optically active sec-butyl vinyl ketone with 4VP, where part of 4VP units are quaternized with phenacyloxime bromide).

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