Catalytic esterolysis of *p*-nitrophenyl esters by optically active polymeric oximes

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An optically active polymer containing oxime groups was prepared by partial quaternization of a copolymer of 4-vinyl pyridine and (+)(S)-4-methyl-1-hexen-3-one, with phenacyl bromide and subsequent reaction with hydroxylamine hydrochloride. This polymer was used as a catalyst for the esterolysis of esters of *p*-nitrophenol with aliphatic and aromatic carboxylic acids characterized by different steric and hydrophobic features. The detailed evaluation of kinetic parameters permitted identification of the main factors responsible for the catalytic behaviour.

INTRODUCTION

The relation between structure and catalytic properties of polymeric synthetic catalysts, with concern to the enzyme behaviour, was investigated by different authors[1-3].

A simple and effective way for obtaining a multi-functional macromolecular catalyst is to copolymerize vinyl monomers containing suitable functional groups. Particularly the use of a chiral system seemed to be helpful in providing conformational homogeneity and thus enabling us to get clearer information on the mechanism of the reaction involved[4].

With the aim of reaching a better knowledge in this field we prepared an optically active terpolymer containing oxime groups, by modifying a 4-vinyl pyridine/(+)(S)-4-methyl-1-hexen-3-one copolymer, by quaternization with phenacyl bromide and subsequent reaction with hydroxylamine hydrochloride.

The catalytic behaviour of this polymer P4VP-MPVKt-Ox19 was investigated with respect to the hydrolysis reaction of *p*-nitrophenol esters of acids of various length and with different steric hindrance around the ester carbonyl (*Table 1*) and was compared with the behaviour of the low molecular weight analogue.

The possibility of chiral discrimination was also tested in the reaction of the polymer with the two enantiomers of *p*-nitrophenyl-2-methylbutanoate.

EXPERIMENTAL

Materials

p-Nitrophenylacetate (PNPA) was obtained by the method of Chattaway[5]. The esters of *p*-nitrophenol (PNPesters):(S)-3-methylpentanoate (PNP3MP), racemic and (S)-2-methylbutanoate (PNP2MB), 2,2-dimethyl-propionate (PNPDMP), octanoate (PNPO), phenyl-acetate (PNPPA), 2-phenylbutanoate (PNP2PB), were prepared according to the method of Spassow[6] and purified by elution over silica gel (E. Merck No. 7734) using CHCl₃ as eluent.

4-Methyl-N-phenacyloximepyridinium bromide (4MeOx) was synthesized by reaction of 4-methyl-*N*-phenacylpyridinium bromide, prepared according to the method of Truitt[7], with hydroxylamine hydrochloride in 1:1 ethanol/pyridine.
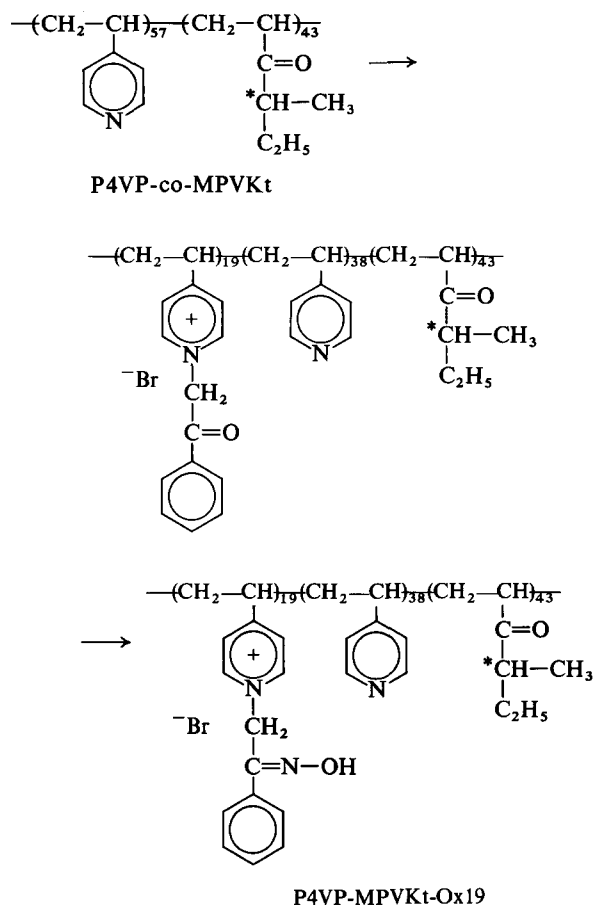

4MeOx
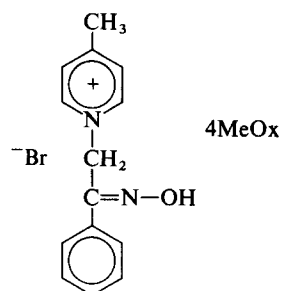
(+)(S)-4-methyl-1-hexen-3-one (o.p. = 66.3%) was prepared as reported by Lardicci *et al.*[8].

The copolymer of 4-vinyl pyridine (4VP) with the chiral vinylketone (MPVKt) (P4VP-*co*-MPVKt), obtained by AIBN initiated copolymerization of commercial 4VP, was partially (19% n.m.r.) alkylated with phenacyl bromide in absolute ethanol.

Finally, by reaction with hydroxylamine hydrochloride in 1:1 ethanol/pyridine at 60°C, we obtained the polymeric catalyst P4VP-MPVKt-Ox19, which was purified by dialysis toward water/ethanol mixtures.

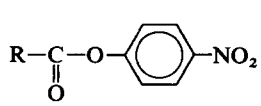The preparation of the polymeric catalyst is sketched as follows:

—(CH₂—CH)₅₇—(CH₂—CH)₄₃—

$$\underset{\text{P4VP-co-MPVKt}}{\begin{array}{c} \text{C=O} \\ \text{*CH—CH}_3 \\ \text{C}_2\text{H}_5 \end{array}} \longrightarrow$$

—(CH₂—CH)₁₉(CH₂—CH)₃₈(CH₂—CH)₄₃—

P4VP-MPVKt-Ox19

Kinetic measurements

The hydrolytic reaction of *p*-nitrophenol esters was followed with a VARIAN DMS 80 spectrophotometer by determining the absorption of *p*-nitrophenolate anion at 400 nm. The hydrolysis of PNPPA, characterized by a halflife much lower than one minute, was studied by the stopped flow technique using a DURRUM 110 spectrophotometer.

Kinetic measurements were performed in aqueous tris buffer (pH = 8.50) at 25°C. The concentration ranged from 10^{-5} M to 2×10^{-4} M for the esters, from 2×10^{-5} M to 2×10^{-4} M for the monomeric oxime and from 10^{-5} M to 2×10^{-5} M for P4VP-MPVKt-Ox19. An excess (4–5 to 1) of substrate was generally used in the hydrolysis reactions catalysed by the polymeric catalyst.

A series of kinetic experiments in tris and bicarbonate buffer allowed us to determine the catalytic contribution to the hydrolysis by OH⁻ species. Specific hydrolysis by the buffer components was found to be negligible[9]. Values of the second order catalytic constants by OH⁻, k_{OH}, are reported in *Table 2*.

The system of differential equations associated with the kinetic scheme considered, including the hydroxide anion catalytic path, was solved into the unknown acylation and deacylation constants, k_2 and k_3, by means of a numerical integration technique[10]. In this procedure zero approximation values of the kinetic constants allow a simulation of the experimental data thus providing a function of the deviations (experimental–calculated) which may be solved in the unknown parameters k_j through a least squares method. The resulting k_j values are then used as better estimates and the procedure is repeated until convergence.

The starting values of k_j parameters are determined using approximate solutions of the kinetic mechanism[11].

A few calculations in which the analytical concentration of the polymeric catalyst was also treated as an unknown, gave values in reasonable agreement with the measured quantities.

pH measurements

pH values were measured with a Metrohm E 388 pH meter.

RESULTS AND DISCUSSION

The esterolytic reaction catalysed by the terpolymer P4VP-MPVKt-Ox19 was carried out in alkaline medium with an excess of substrate (4–5:1). It exhibited a two steps behaviour: a first rapid evolution of the reaction product (PNP⁻ anion) was followed by a decrease of the reaction rate up to a stationary state, where the rate is constant (*Figure 1*). This behaviour can be explained by assuming that the first step corresponds to the nucleophylic attack of oxime anion on the substrate, while the second one corresponds to the hydrolysis of the O-acylated derivative of the polymeric oxime, giving regeneration of the catalytically active species.

Table 1 *p*-Nitrophenylesters used as substrates in the esterolysis experiments

General formula	R–	*p*-nitrophenyl-	
	CH₃–	acetate	PNPA
	CH₃CH₂—CH—CH₂— CH₃	3-methylpentanoate	PNP3MP
R—C—O—⬡—NO₂ ‖ O	CH₃—CH₃—CH— CH₃	2-methylbutanoate (racemic and +(S) enantiomer)	PNP2MB
	(CH₃)₃C–	2,2-dimethylpropionate	PNPDMP
	CH₃—(CH₂)₆—CH₂–	n-octanoate	PNPO
	C₆H₅—CH₂– C₆H₅—CH— C₂H₅	phenylacetate 2-phenylbutanoate	PNPPA PNP2PB

Table 2 Kinetic parameters for the hydrolysis of esters of p-nitrophenol in water at 25°C[a]

Ester	k_2[b] (1 mol⁻¹ s⁻¹)	$k_3 \cdot 10^4$ (s⁻¹)	k_{ox}[c] (1 mol⁻¹ s⁻¹)	k_{OH} (1 mol⁻¹ s⁻¹)	k_2/k_{ox}	$k_3/k_{OH} \cdot 10^5$ (mol l⁻¹)
PNPA	502±31	22±2	6.3	14.7±0.1	80	15
PNP3MP	553±21	3.2±0.2	1.1	3.83±0.03	500	8.4
(R,S)PNP2MB	234±8	2.2±0.2	0.59	2.98±0.04	400	7.4
(S)PNP2MB	247±13	1.8±0.3	–	–	–	–
PNPDMP	115±8	0.98±0.09	0.22	1.93±0.03	520	5.1
PNPO	7780±800	13.9±0.9	6.7	6.57±0.06	1160	2.1
PNPPA	10400±1500	127±10	13.7	55.0±1.2	760	2.3
PNP2PB	2460±180	5.0±0.2	2.1	8.54±0.12	1170	5.9

[a] pH = 8.50 (10⁻² M tris); Ionic strength = 0.01 M (NaCl); Concentrations: 1 × 10⁻⁵–2 × 10⁻⁴ M (esters); 1 × 10⁻⁵–2 × 10⁻⁵ M (polymeric catalyst P4VP-MPVKt-Ox19); 2 × 10⁻⁵–2 × 10⁻⁴ M (monomeric oxime 4MeOx); uncertainties on the kinetic parameters are given as standard deviations from the average

[b] This constant is normalized with respect to the concentration of the polymer expressed as moles of oxime groups per litre
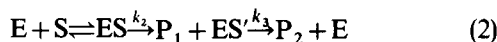
[c] The values reported are the average of 2–3 experiments. The uncertainty may be evaluated at 5–10%

The kinetic data were treated on the basis of mechanism[12] (1), which fairly fitted experimental data.

$$E \rightleftharpoons E^- + H^+ \tag{1}$$

$$E^- + S \xrightarrow{k_2} P_1^- + ES' \xrightarrow{k_3} P_2^- + E^- $$
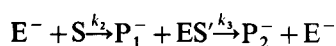
where: E = polymeric oxime residue; E⁻ = polymeric oxime monoanion; S = substrate; P_1^- = nitrophenolate anion; ES' = O-acylated derivative; P_2^- = carboxylate anion; k_2 = acylation constant; k_3 = deacylation constant.

The literature, for polymeric catalysts, also reported the following kinetic schemes[13] (for sake of simplicity charges have been omitted):

$$E + S \rightleftharpoons ES \xrightarrow{k_2} P_1 + ES' \xrightarrow{k_3} P_2 + E \tag{2}$$

$$E + S \rightleftharpoons ES \xrightarrow{k_2} P_1 + ES' \tag{3}$$

where ES is a catalyst–substrate complex.

Mechanism (3) was excluded on the basis of the experimental evidence that the PNP⁻ anion concentration increases, after the 'burst' step, with a slow rate, but higher, in any case, that in presence of OH⁻ hydrolysis alone.

The preequilibrium step with the ES species was also excluded, mainly on the basis of the analogy with other systems[14]. The low solubility of the reagents prevented an accurate kinetic investigation of this point. In any case the formation of the ES species was not detected spectrophotometrically in the time range of the stopped flow technique for the esterolysis of PNPPA and PNPO.

On these basis also scheme 2 was not taken into consideration.

For comparative purposes the second order kinetic constant, k_{ox}, for the reaction of each ester with the monomeric oxime 4MeOx was also determined.

Kinetic constants relative to each substrate, both for the polymeric and monomeric nucleophile, obtained as the average of several kinetic measurements conducted at different concentration of the reagents, are reported in *Table 2*.

It appears clearly that the polymer shows a higher activity than the monomeric analogue towards each substrate.

k_2 and k_{ox} reported are only apparent, pH-dependent constants; indeed, assuming that the catalytically active species is the oxime anion[15], the effective pH independent kinetic constants would differ from the observed constants according to:

$$k_{obs} = k_{eff} \frac{(K_a)^{1/n}}{(K_a)^{1/n} + (H^+)^{1/n}} \tag{4}$$

where K_a and n are the empirical parameters of Henderson's equation modified for polyelectrolytes[16], which become respectively the true ionization constant and unit in the case of the monomeric catalyst. The second factor of equation (4) takes into account the fact that at pH = 8.50 only a fraction of the total oxime groups are dissociated.*

Kinetic experiments on the hydrolysis of PNP3MP by 4MeOx run at different pH values, showed a little catalytic effect by the neutral oxime. This last effect was assumed to be unimportant in the polymeric catalyst, where at the experimental pH value the neutral oxime groups are even less.

Examination of the data of *Table 2* shows that k_{ox} regularly decreases with increasing steric hindrance in the
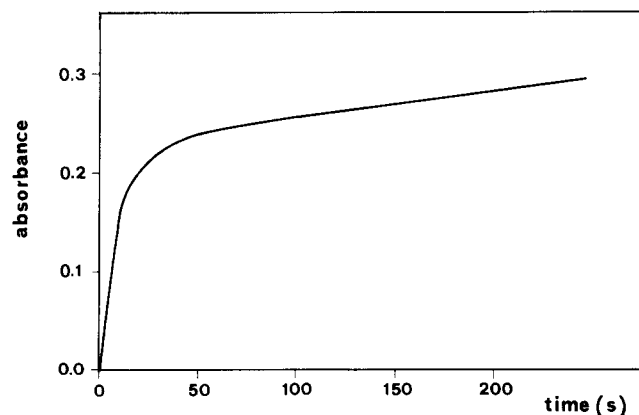
Figure 1 Esterolytic reaction of PNPO (1.7 × 10⁻⁵ M) in presence of P4VP-MPVKt-Ox19 as catalyst (1.4 × 10⁻⁴ M); pH = 8.50 (tris); ionic strength = 0.01 M; temperature 25°C; λ = 400 nm

* For 4MeOx a pK_a of 9.69 was found in this work. On the other side, Kabanov *et al.*[15] determined a pK_a = 8.50 for a poly-4-vinylpyridine quaternized with phenacylbromide oxime.

α position to the ester carbonyl according to the following order:

$$PNPDMP < PNP2MB < PNP3MP < PNPA$$

Concerning aromatic esters, we observe that k_{ox} is clearly larger compared with the above aliphatic substrates, owing to the strong inductive effect of the phenyl group. Again PNP2PB, with a side chain in α position to the ester group, exhibits a k_{ox} value which is markedly lower than for PNPPA.

A different trend may be observed if one refers to the values of ratio k_2/k_{ox}, where the polymer catalytic action is normalized with respect to the monomer, thus emphasizing the effect of the macromolecular structure. Indeed, the reactivity of PNPA, one of the fastest substrates in monomer catalysis thanks to the small steric hindrance of the acetyl group, results less enhanced by the polymer catalyst than that of the more hindered alkylesters (see *Tables 1* and *2*).

PNPDMP, PNP2MB and PNP3MP exhibit an analogous trend in the steric effect both in the polymer and monomer catalysis. However, the similar value of k_2/k_{ox} for these esters indicates that the steric hindrance plays the same role in the monomer and polymer structure. The determining factors for the acylation step acceleration seems to be only the hydrophobic interactions between polymeric catalyst and substrate. In fact PNPO and PNP2PB, which have the biggest hydrophobic groups, are the most reactive substrates. Moreover, the increase in hydrophobic surface, derived by the introduction of one ethyl group in α position to the carbonyl, when going from PNPPA to PNP2PB, yields an increase in reactivity which overwhelms the negative steric effect.

Finally, no difference is observed in the hydrolysis rate between racemic and (S) PNP2MB. This demonstrates that no chiral discrimination has occurred both in the acylation and deacylation step, as already observed for the terpolymer P4VP-Ox30-2MB20[4], acting with a similar mechanism.
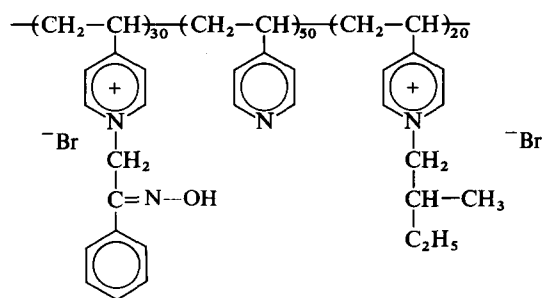
P4VP-Ox30-2MB20

A decrease of the deacylation constant k_3 is observed with increasing steric hindrance of the acyl chain, both for aliphatic and aromatic esters.

Assuming that the deacylation step catalysed by the solvent suffers a steric effect analogous to that reflected by k_{OH}, the values of the ratio k_3/k_{OH} would indicate an important role by the hydrophobic effect. Indeed a decrease of this ratio is observed as the aliphatic hydrocarbon surface of the ester is increased. Unfortunately some interfering effect seems to be present in the aromatic esters.

All these results emphasize once more the potentiality of suitably designed reactive polymers in modulated multifunctional catalysis.

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