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THE HYDROLYSIS OF p-NITROPHENYL ACETATE BY POLYMER CATALYSTS CONTAINING HYDROXAMATE AND IMIDAZOLE FUNCTIONS

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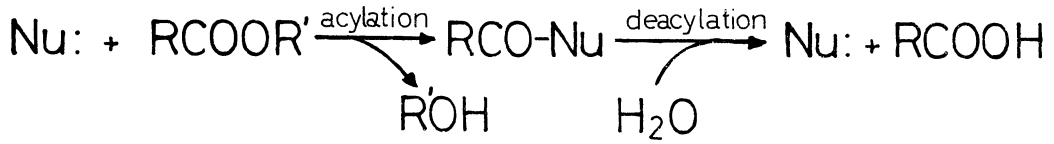
The hydrolysis of p-nitrophenyl acetate by a polymer catalyst containing the hydroxamate and imidazole functions includes the formation of acetyl hydroxamate and its subsequent decomposition assisted by the intramolecular imidazole group. The overall catalytic efficiency is enhanced by the presence of these complementary nucleophilic functions.

The nucleophilic catalysis of ester hydrolysis by simple nucleophiles and by some esterases proceeds via the formation and subsequent decomposition of acyl intermediates.[1] Therefore, the high overall efficiency is attained only when both



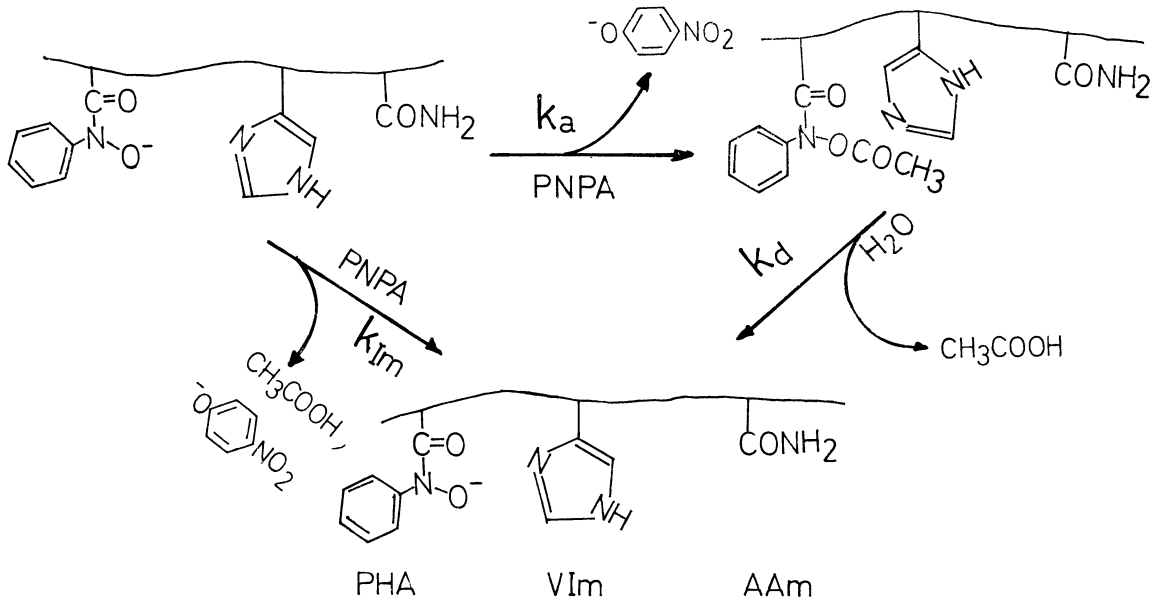
of the acylation and deacylation steps are fast. We have been making attempts to synthesize efficient hydrolytic catalysts by combinations of complementary functional groups in polymeric and small-molecule systems.[2] In this communication is described the hydrolysis of p-nitrophenyl acetate(PNPA) by polymer catalysts containing hydroxamate and imidazole functions. These functions act as nucleophilic catalysts of a complementary nature : the acylation step being faster for hydroxamate and deacylation faster for imidazole. A small-molecule catalyst of similar nature has been reported by Bender and coworkers.[3]

Polymer catalysts (PHA-VIm-AAm) were prepared by radical copolymerization of acetyl N-phenylacrylohydroxamate,[4] 4(5)-vinylimidazole[5] and acrylamide in benzene at 80°C with AIBN initiator. The polymer was washed with ether, dried and treated with NH_2NH_2 in aqueous solutions for 24 hr. The deacylated polymer was reprecipitated from water and acetone. Other binary copolymers (PHA-AAm, VIm-AAm) were prepared by similar procedures.

The hydrolysis of PNPA was followed by the increase in the absorption at 401 nm due to the p-nitrophenolate anion formed. When PHA-VIm-AAm-1 copolymer was used as catalyst for the hydrolysis of PNPA in the commonly-employed concentration

range, ([PNPA] = 1.16 × 10^{-4}M, [PHA] = 5.81 × 10^{-5}baseM), the pseudo-first-order plot was linear up to 90% reaction, with a rate constant of 19.5 × $10^{-5}$$sec^{-1}$ at pH 8.74. This value is much greater than that of the VIm-AAm copolymer under similar conditions. This result suggests that the hydroxamate site is used as catalyst repeatedly, since the substrate concentration is greater than the concentration of the PHA unit : major site of acylation.

In the reaction of a PHA-AAm copolymer with PNPA under similar conditions, the deacylation process is very sluggish compared with acylation, and the acetyl hydroxamate is accumulated.[4] However, the present kinetic result clearly indicates that there is no accumulation of the acetyl intermediate because of faster deacylation. Thus, the rate-determining step of the catalytic hydrolysis is changed from deacylation to acylation by the introduction of the imidazole unit under the reaction condition employed.



In contrast, when the catalytic hydrolysis was carried out with large excesses of PNPA ([PNPA] = 0.01 - 0.02 M, [PHA] = 5.80 × 10^{-4}baseM), typical burst kinetics were observed : the rapid release of p-nitrophenol followed by slower, steady release. An example of the time course is given in Fig. 1. The k_a and k_d values can be in principle determined from analyses of the initial burst and the subsequent linear portion, according to the method of Bender et al.[6] However a modification is necessary in the present system, because both hydroxamate and imidazole

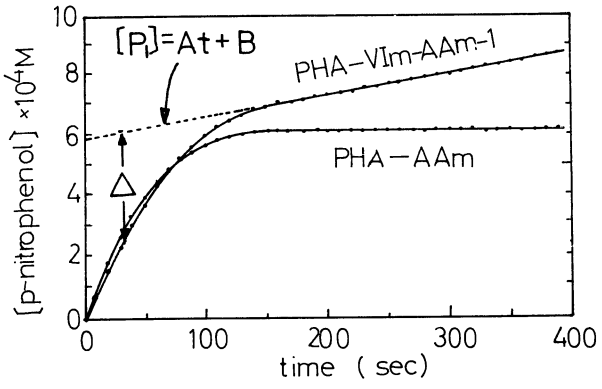


Fig.1 Hydrolysis of PNPA by Polymer Catalysts

functions contribute to the hydrolysis. The initial p-nitrophenol release due to the imidazole group in the terpolymer can be assumed to proceed linearly with time, as confirmed in the hydrolysis of PNPA by a VIm-AAm copolymer. Therefore, the overall burst kinetics are composed of the two terms : one is a typical burst-type reaction taking place at the PHA site and the other a linear increase of p-nitrophenol(P_1) due to the VIm function alone.

The linear portion of the burst kinetics is expressed by $[P_1] = At + B$. This is extrapolated to zero time, and the difference between this line and the burst curve is designated as Δ. Then, the following linear relation holds : $\ln \Delta = \ln B - bt$. The b and B values are determined from the slope and intercept, respectively, and the rate constants are calculated from these values.

$$k_a = \frac{b}{[PNPA]_0}\sqrt{\frac{B}{[PHA]}} \qquad k_d = b - k_a[PNPA]_0$$

$$k_{Im} = \frac{1}{[PNPA]_0[VIm]}\left(A - \frac{k_a \cdot k_d \cdot [PHA][PNPA]_0}{b}\right)$$

Table 1 Apparent Rate Constants of Acylation and Deacylation[a]

Polymer (composition,mol%)[b]	pH	$k_{a,obs}$ $M^{-1}sec^{-1}$	$k_{Im,obs}$ $M^{-1}sec^{-1}$	$10^2 k_{d,obs}$ sec^{-1}
PHA-VIm-AAm-1[c]	8.04	0.79	0.03	0.96
(5 : 35 : 60)	8.55	1.70	0.05	1.50
	9.01	2.59	0.08	2.64
PHA-VIm-AAm-2[d]	8.07	0.28	0.01	0.26
(3 : 7 : 90)	8.55	0.82	—	0.55
	9.00	2.20	—	0.89
PHA-AAm[e] (10 : 90)	9.00	3.25	—	0.0024
VIm-AAm	8.55	—	0.065	—
(10 : 90)	8.77	—	0.081	—

a. 28.9 v/v% EtOH-H_2O, 30°C, 0.1 M KCl, 0.15 M Barbital buffer The rate constants were calculated for the total catalyst concentration.

b. Determined by potentiometric titration and NMR spectroscopy.

c. pK_a(PHA unit) = 9.0 d. pK_a(PHA unit) = 9.1 e. pK_a(PHA unit) = 9.12

The validity of this analysis is supported by agreements of the kinetic constants which are given in Table 1. The k_a values of the PHA-VIm-AAm polymers are close to the corresponding value of the PHA-AAm polymer, and the $k_{Im,obs}$ values for the terpolymer show good correspondence to those observed for the VIm-AAm co-

polymer. These results further suggest that the acylation of the hydroxamate and imidazole groups occur fairly independently of each other. Since the k_a values of the hydroxamate group are much greater than k_{Im}, the initial acylation must occur predominantly at the hydroxamate site of the terpolymer catalyst. This must be true also under the pseudo-first-order conditions.

The rate constant of deacylation of acetyl hydroxamate, $k_{d,obs}$, for the terpolymer is enhanced remarkably relative to that of the PHA-AAm copolymer. The rate enhancement amounts to 1000 folds at pH 9.0 ($2.64 \times 10^{-2} sec^{-1}$ compared with $2.41 \times 10^{-5} sec^{-1}$). The $k_{d,obs}$ values for PHA-VIm-AAm-1(VIm content, 35 mol%) were greater than those of PHA-VIm-AAm-2(VIm content, 7 mol%) by a factor of 3-4 over the pH range studied. This difference reflects the efficiency of intramolecular imidazole catalysis.

The $k_{d,obs}$ value increases from pH 8 to 9. Since the imidazole unit is considerably dissociated in this pH region, the $k_{d,obs}$ variation cannot be attributed simply to the availability of the neutral imidazole species. Two interesting possibilities for this phenomenon are as follows. (1) The conformation of the polymer chain changes with the pH increase so as to render the assistance of deacylation by imidazole more effective at higher pH's. (2) If the deacylation process involves the rapid, reversible acyl transfer to imidazole, the decomposition of the acetylimidazole intermediate can be the slow step of deacylation which might be accelerated by the general-basic catalysis of the hydroxamate and/or imidazole functions at pH 8 to 9.

In conclusion it is now clear that the rate-determining step of the nucleophilic catalysis can be changed from deacylation to acylation even for a powerful nucleophile like hydroxamate anions. The use of complementary catalytic functions is useful in providing highly efficient catalytic systems.

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