

CATALYSIS OF ESTEROLYTIC REACTIONS BY WATER-SOLUBLE IMIDAZOLE CONTAINING POLYMERS

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Abstract: In a review article [*Accounts Chem. Res.*, 2, 217 (1969)] is a summation of our work up to 1968. In this review we summarized the activity of polyvinylimidazole and copolymers in esterolytic reactions. We explained the increased reactivity of these polymeric reactants in terms of cooperative effects and electrostatic factors. In 1967, we blundered into the extremely interesting discovery that long-chain esters provided us with enormous acceleration of rates at room temperature and we have attributed this in "general" terminology to apolar bonding as a third factor to understand the high reactivity of these synthetic macromolecules. Reference 1 describes our recent published work. We are heavily emphasizing the apolar bonding concept. Related work which conceptually can be regarded as similar to our own discovery was carried out by the group of Professor Irving M. Klotz at Northwestern(2), the group of Professor Kabanov at the University of Moscow(3), and the group of Professor Kunitake(4). This lecture will briefly review the background of the problem and discuss in detail the catalysis of esterolytic reactions by water-soluble copolymers of vinylimidazoles and vinylamines. Synthetic macromolecules containing pendant imidazole groups have been used as catalysts for the hydrolysis of esters. This report extends that study to copolymers of 4(5)-vinylimidazole and vinylamine. The latter component renders these polymers water soluble and, therefore, their catalytic activity could be studied in a totally aqueous environment. The precursor for the vinylamine monomer used for these copolymerizations was N-vinyl-t-butylcarbamate which, in turn, was prepared from vinylisocyanate. Extremely large rate enhancements were observed with these catalysts for hydrolyses of activated esters and these were attributed to cooperative, electrostatic and hydrophobic effects. The large cooperative effects were due to tight coiling of these copolymers in water, increasing the proximity of imidazole groups for interaction. The highly aqueous media in which these esterolysis could be carried out with these copolymers resulted in very large hydrophobic effects with long chain ester substrates. Less aqueous environments led to dramatic rate decreases. Esterolytic studies were also carried out under conditions of excess substrate which showed typical steady-state kinetics from which rates of deacylation of the catalyst could be determined. The fraction of imidazoles in these copolymers that were acylated under steady-state conditions were quite low.

INTRODUCTION

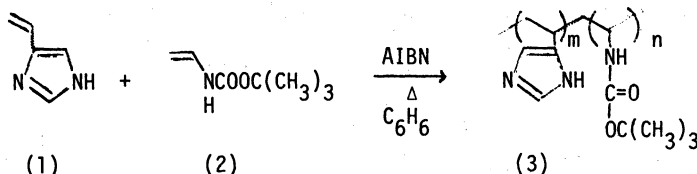
The utilization of synthetic macromolecules as catalysts for reactions has received considerable attention(6-9), especially because these reactions can serve as models for complex enzymatic processes. Though less efficient than enzymes, these polymeric catalysts have several analogous characteristics such as higher reactivities than the corresponding monomeric systems(6-9), specificity towards substrates(6-11), competitive inhibition(12-14), bifunctional catalysis(6-9,11,15-17) and saturation phenomena(12,18-24).

We have been interested in polymeric catalysts where the catalytically active site is a covalent part of the macromolecular species. One special interest has been concerned with esterolytic reactions in the presence of synthetic imidazole-containing macromolecules(7-9). Three factors have been attributed to the large rate increases generally observed with these catalysts: cooperative effects, electrostatic effects and hydrophobic effects. These rate enhancing factors have been demonstrated(25,1f) to be predominant in highly aqueous solvent systems, but due to the limitations on the solubility of poly[4(5)-vinylimidazole] in water, it was found necessary to synthesize copolymers of 4(5)-vinylimidazole which could be dissolved in solvents of high water content. This study was directed towards the synthesis and esterolytic activity of copolymers of 4(5)-vinylimidazole with vinylamine where the latter component would impart water solubility to the catalytic polymer.

RESULTS AND DISCUSSION

Monomer Synthesis: 4(5)-Vinylimidazole was synthesized by the method of Overberger(26). The monomer chosen for the vinylamine units in the copolymers was N-vinyl-t-butyl carbamate (NVBC). The t-butyl carbamate was chosen because Hart(27) has demonstrated that while it is difficult to hydrolyze the polymers of methyl or ethyl carbamates, the corresponding t-butyl carbamate can be easily hydrolyzed by acids to give polyvinylamine. Both 4(5)-vinylimidazole and N-vinyl-t-butyl carbamate were purified by sublimation.

Copolymerizations: The purified monomers were copolymerized in benzene solvent using 1 mole % of AIBN as a free-radical initiator. The polymers precipitated from the benzene solution and were purified by repeated precipitations from methanol into acetone. The composition of



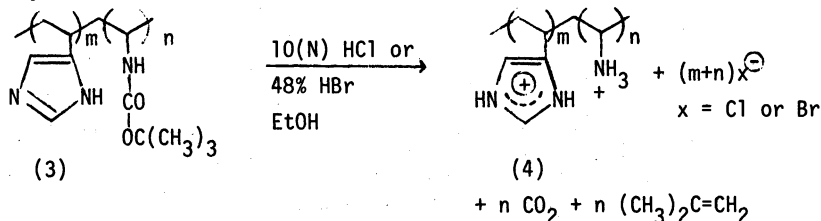
the copolymers could be determined from both the N-analysis of the copolymers and their NMR spectra. In the latter method, the ratio of proton signals for the imidazole and the t-butyl group in the copolymers were used to calculate the polymer composition. The agreement between the values obtained by the two methods was satisfactory. An examination of these copolymerization results (Table 1) show the low reactivity of N-vinyl-t-butyl carbamate to enter into copolymerization with 4(5)-vinylimidazole. Increased amounts of the carbamate monomer in the feed resulted in drastic reductions of copolymer yield and, even then, no more than 46% N-vinyl-t-butyl carbamate could be introduced into the copolymers.

TABLE 1. Copolymerization of 4(5)-VIm and NVBC^a

Sample	Mole Percent of NVBC in Feed	Time (hr)	Copolymer Yield %	Copolymer Composition Mole Percent of NVBC	
				NMR	N-Analysis
IC-1	9	24	39.0	24.7	23
IC-2	13	24	72.2		18
IC-3	32	24	54.1		33
IC-4	49	55	65.0	32	31
IC-5	50	32	50.5	28	32
IC-6	50	24	49.2		36.5
IC-7	72	30	24.7	35	34
IC-8	72	24	15.2		46

^a Polymerizations were carried out on 1.5 molar monomer solutions in benzene with 1 mole % AIBN at 65°C.

Hydrolyses of Copolymers: Two of the above copolymers (IC-1) and (IC-7) were chosen for hydrolyses of the carbamates to obtain the free amines. These hydrolyzed copolymers were used for the study of their catalytic action on esterolysis reactions. The hydrolyses were carried out with 10(N) hydrochloric acid(28,29) or 48% hydrobromic acid(30) in ethanol solution. The hydrolyzed copolymers were purified by repeated precipitations from methanol



solutions into acetone followed by drying at 60°C under a vacuum until constant weights were obtained. The compositions of these copolymers as determined from their NMR spectra and elemental analyses were consistent and agreed well with the compositions of the unhydrolyzed copolymers from which they were derived. Thus the polymer derived from IC-1 was found to contain 25% vinylamine units (IA-1) and that derived from IC-7 contained 33% vinylamine units (IA-7). The intrinsic viscosities of the hydrolyzed polymers were found to be 0.41 dl/g (IA-1) and 0.38 dl/g (IA-7) in 50 vol % methanol-water solutions at 25°C.

Potentiometric Titrations: The catalytically active imidazole group in the solvolyses of esters is known to be in the anionic and neutral forms(11) and since the protonated imidazoles and protonated amines in these copolymers would act as binding sites for negatively charged substrates, it was necessary to determine the fraction of pendent imidazole and amine groups that existed in the protonated forms at different pH values used for kinetic studies. Potentiometric titrations were carried out in water solutions at 25°C with an ionic strength of 0.02 (KCl). The titration of the imidazole and amine groups occurred over wide pH ranges, typical of polyelectrolytes, with considerable overlap. The polymers precipitated at pH~9. Modified Henderson-Hasselbach plots were constructed with pH against $\log(\alpha_1/1-\alpha_1)$ where α_1 is the fraction of the total imidazole and amine that is in the neutral form. From these curves and the known composition of the polymers, the pK's of the individual groups, imidazole and amine, were the pH values at which half of those individual groups had been neutralized. The pK values obtained by this method and those of polyvinylamine(31) and poly[4(5)-vinylimidazole](11,32) are given in Table 2.

TABLE 2. Titration of 4(5)-VIm-VAmine Copolymers^d

Sample	Mole % VAm	pK	
		Imidazole	Amine
IA-1	25	5.40	7.74
IA-7	33	5.11	7.35
PVIm	0	5.78-6.20 ^b	- -
PVAm	100	- -	7.50 ^c

^a Determined in 28.5% ethanol-water at room temperature and $\mu = 0.015-0.02$, Reference 32.

^b Determined in 28.5% ethanol-water at room temperature and $\mu = 0.02$, Reference 11.

^c Reference 31.

^d Determined in water at 25°C and $\mu = 0.02$.

The considerably lower pK values obtained for the imidazole residues in these copolymers as compared to those in poly[4(5)-VIm] may be ascribed to the polyelectrolyte effect from the strongly basic amine groups in the polymers. Similar dramatic decreases in pK have been previously observed in histidine graft copolymers of polyethylenimine(1n). The increased incorporation of the interacting amine units in IA-7 over IA-1 results in a lower pK value for the imidazole group in IA-7. The pK values of the amines obtained in these polymers (7.35-7.74) are quite similar to the pK value obtained for polyvinylamine by St. Pierre et al.(31)

Solvolysis of Esters: The kinetic studies of the hydrolysis of activated phenyl esters catalyzed by the copolymers of 4(5)-vinylimidazole and vinylamine, (IA-1) and (IA-7), were typically carried out in excess catalyst, ca. 5×10^{-4} M polymer and 5×10^{-5} M substrate. The slopes of the lines obtained by plotting $\ln(A_\infty - A_t)$ versus time gave the pseudo-first-order rate constants (k_{meas}) from which the first-order rate constants (k_{obs}) were calculated by subtracting the blank rate (k_{blank}).

$$k_{obs} = k_{meas} - k_{blank}$$

The second-order rate constant k_{cat} was then evaluated from the equation

$$k_{cat} = k_{obs} / [\text{catalyst}]$$

Where the plots of $\ln(A_\infty - A_t)$ against time deviated at higher conversions, the slopes of the initial linear portions were taken. The critical micelle concentrations for the substrate esters have previously been determined under these reaction conditions(1m) and the substrate concentrations were always maintained well below these values.

(a) **Cooperative Effects--the Hydrolysis of PNPA.** The interaction of imidazole groups pendent on a polymer backbone gives rise to what is known as cooperative effects (Figure 1). The existence of this effect is examined by monitoring the effect of pH on the rate of hydrolysis of p-nitrophenylacetate (PNPA). The catalytic activity of monomeric imidazole increases linearly with the fraction of neutral imidazole whereas for poly[4(5)-VIm], there is a rapid non-linear increase in the activity at high pH values(25). This increased effectiveness was explained in terms of neutral-neutral and neutral-anionic cooperative interactions between pendent imidazole groups(11). The mechanism of the participation was probably a general base catalysis of the attack of one pendent imidazole by another neutral or anionic imidazole moiety.

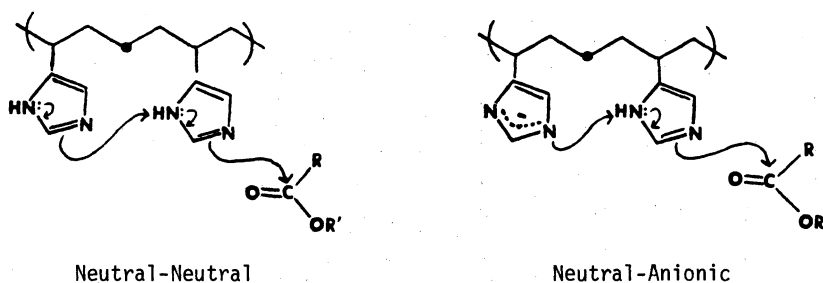


Fig. 1. Cooperative Interaction in Poly[4(5)-VIm].

The copoly[4(5)-VIm-VAmine] catalyzed hydrolysis of PNPA was studied over a pH range of 4-8 to examine these cooperative effects. The results are shown in Table 3 and Figure 2. It is

TABLE 3. Solvolysis of PNPA^a

Catalyst	$k_{\text{cat}} \text{ min}^{-1} \text{ M}^{-1} (\text{pH})$				
IA-1	22(4.69)	34(6.10)	47 (7.06)	84.3(8.06)	--
IA-7	21(4.65)	27(5.50)	51 (7.17)	54.3(e)	77 (8.09)
Imidazole ^b	--	4(5.76)	17.5(7.20)	27.5(8.06)	29(9.18)
Imidazole ^c	--	--	--	31.8(8.03)	--
Hist-PEI ^b	--	1(5.76)	3 (7.20)	5.5(8.06)	3(9.18)
Poly[4(5)-VIm] ^d	--	4(6.0)	7 (7.0)	20.5(8.0)	38(9.0)
Poly[4(5)-VIm] ^e	--	--	--	60.6(7.71)	--

^a [catalyst] = $5 \times 10^{-4} \text{M}$, [PNPA] = $5 \times 10^{-5} \text{M}$, solvent = 96.7% H₂O-3.3% CH₃CN, $\mu = 0.02$, 26°C.

^b Data taken from Reference 1n.

^c In 10% EtOH-H₂O system; taken from Reference 25.

^d In 28.5% EtOH-H₂O system; taken from Reference 25.

^e In 20% EtOH-H₂O system.

evident from this data, that the copolymers show a very strong cooperative effect in this aqueous medium and very large catalytic rate constants are obtained. Significant rate enhancements are known to occur for these reactions with increasing water contents of the solvent system(25) because of a greater amount of bifunctional catalysis in the polymer through shrinkage of the polymer coil in the highly aqueous medium. Viscosity studies(25) of poly[4(5)-VIm] corroborate this explanation. However, poly[4(5)-VIm] is insoluble in the 96.7% water systems we used for our study, and the only way of comparing our data with those obtained previously was by extrapolating the k_{cat} value from Overberger and Morimoto's data(25) to that at 96.7% water (Figure 3) and comparing this value to those obtained from our copolymers. Such an extrapolation gives $k_{\text{cat}} = 84 \text{ min}^{-1} \text{M}^{-1}$ at pH 8 and this compares favorably with the values of $k_{\text{cat}} = 84.3$ (IA-1) and 77.0 (IA-7) obtained with the copoly-[4(5)-VIm-VAmine]. This agreement suggests that the vinylamine units in the copolymer do not play any important intrinsic role in these cooperative interactions, other than imparting water solubility to the polymers. Indeed, St. Pierre et al.(31) have shown that in the solvolysis of PNPA in the presence of polyvinylamine, there was no evidence for amine catalyzed aminolysis and rate constants were less than that obtained for monomeric amines of comparable basicity.

That the cooperative effects were significantly increased in our system by the use of highly polar aqueous media was established by using the same copolymers and substrates in 20% ethanol-water systems when the catalytic rate constants were found to be greatly lowered (Table 3).

Another important observation in our studies with the copolymers was that at the lower pH values studied (pH 5.5-6.1) the copolymers were found to be extremely efficient catalysts compared to monomeric imidazole: $r = k_{\text{cat}}(\text{polymer})/k_{\text{cat}}(\text{imidazole}) = 6$ to 8. The value of "r" for poly[4(5)-VIm] in this pH range in 28.5% ethanol is <1(25), i.e., the polymer is less efficient than imidazole as a catalyst. This large difference between the homopolymer and the copolymer may be attributed to two causes. First, the imidazole units in the copolymer have lower pK values than those in the homopolymer and at this limiting pH range

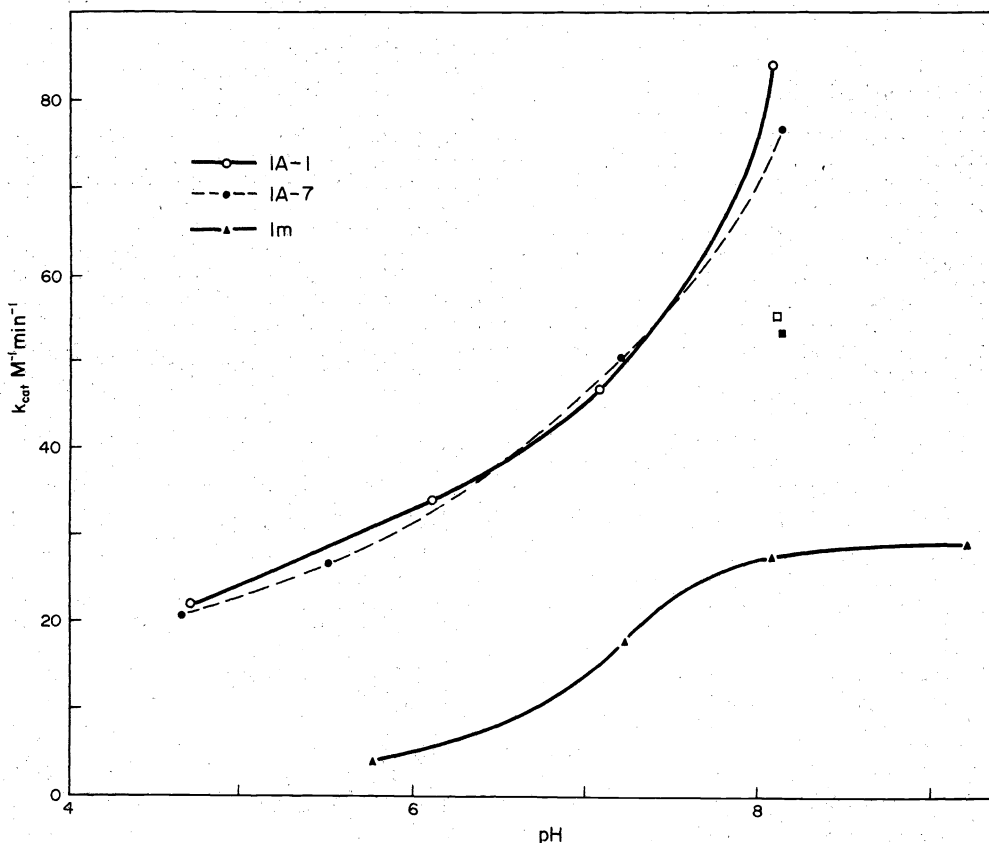


Fig. 2. Second-order rate constants for the hydrolysis of PNPA by the [4(5)-VIm-VAmine] copolymers and by imidazole(\blacktriangle) in 96.7% water-3.3% acetonitrile (o, \bullet) and in 20% ethanol-water (\square , \blacksquare), $\mu = 0.02$, 26°C.

(5.5-6.1), many more neutral imidazoles are available in the copolymers than in the homopolymers to participate in cooperative interactions. Second, in the much more polar aqueous systems at these lower pH regions, the protonated copolymers remain less extended than do the protonated homopolymer of [4(5)-VIm] in the less polar aqueous-ethanol systems. The more compact copolymers can therefore take part in bifunctional interactions which may not be possible in the extended case of the homopolymer.

The combination of these two factors, namely, the availability of more neutral imidazole residues and the shrinkage of the copolymers in the very polar aqueous solvent, could account for the large relative efficiency of the copolymer catalyst in the lower pH range.

(b) Electrostatic Effects--The Hydrolysis of NABA (S_2^-): Overberger and coworkers(22) have obtained rate enhancements of up to 50 times the rate exhibited by monomeric imidazole in the poly[4(5)-VIm] catalyzed hydrolysis of the negatively charged substrates 3-nitro-4-acetoxybenzoic acid (NABA, S_2^-) and 3-nitro-4-acetoxybenzene sulfonic acid (NABS). The large rate enhancements were attributed to electrostatic attraction between substrate and polymer. Bell-shaped pH-rate profiles were obtained in these cases with a maximum at around pH 7 where about 25% of the imidazoles remained protonated providing an attractive force for the negatively charged substrates.

When the copolymers (IA-1) and (IA-7) were used as catalysts for the hydrolysis of NABA in 96.7% water-3.3% acetonitrile over a pH range of 4 to 8, extremely high catalytic rate constants were obtained (Table 4). The rates were found to increase continuously with pH for these two copolymers and bell-shaped curves were not obtained (Figure 4). The absence of the bell-shaped pH-rate profiles can be rationalized by the fact that in the poly[4(5)-VIm-VAmine] copolymers, the imidazole groups can be completely deprotonated and yet the polymers can maintain a charged surface from the very much less acidic primary ammonium ions in the copolymer. The catalytic activity of all the imidazole groups are therefore restored in the high pH-range while the electrostatic attraction for the substrate is still maintained. Hence there is no drop in the reaction rates in this pH-range. Moreover, and probably more importantly, it is possible that the very large cooperative effects exhibited by these copolymers at high pH, may be the reason for the continued rate increases. The participation of the cooperative interactions in the high pH values could account for the

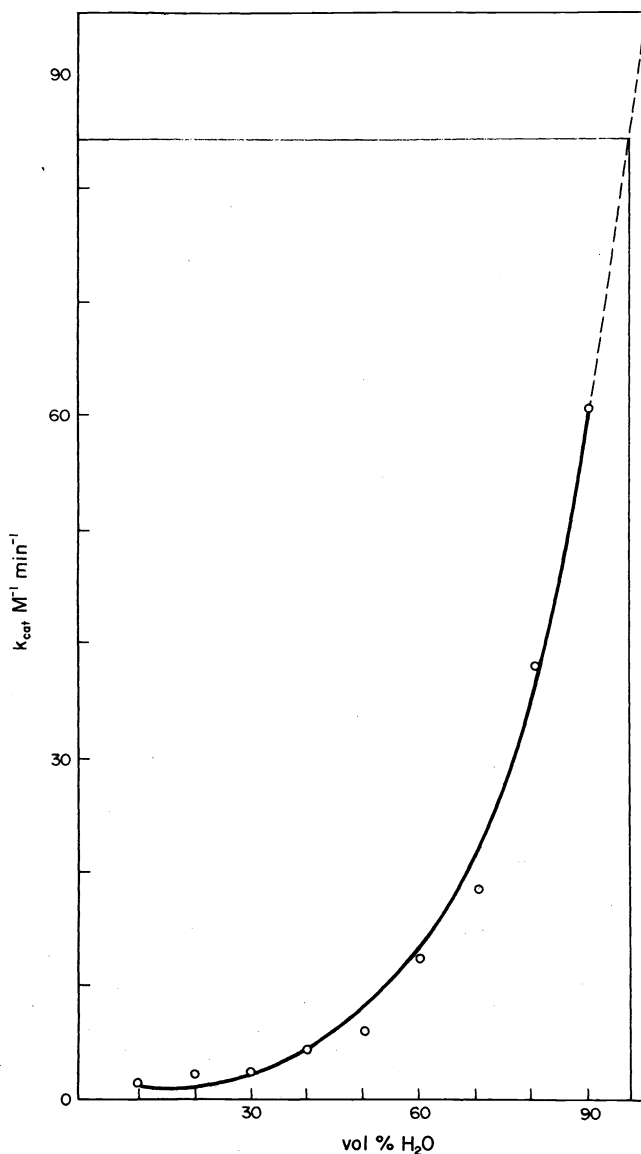


Fig. 3. Influence of water content of solvent on the rate of hydrolysis of PNPA by poly[4(5)-Vim] at pH=8; from Reference 25.

TABLE 4. Solvolysis of NABA^a

Catalyst	k_{cat} $M^{-1} min^{-1}$ (pH)				
Imidazole ^b	- -	- -	48(7.20)	70(8.06)	77(9.18)
IA-1	319(4.69)	360(5.35)	587(7.06)	1101(8.06)	- -
IA-7	320(4.65)	410(5.50)	663(7.17)	984(8.09)	- -

^a [catalyst] = $5 \times 10^{-4} M$; [NABA] = $5 \times 10^{-5} M$; solvent - 96.7% H_2O -3.3% CH_3CN , $\mu = 0.02$; 26°C.

^b Data taken from Reference 1n.

very high absolute rate constants obtained with IA-1 and IA-7. These large rate enhancements are largely due to the high aqueous content of the solvents used.

(c) Hydrophobic Effects--The Hydrolysis of the S_N^- Series. Hydrophobic or apolar effects have been shown to give rise to large rate enhancements for the poly[4(5)-Vim] catalyzed

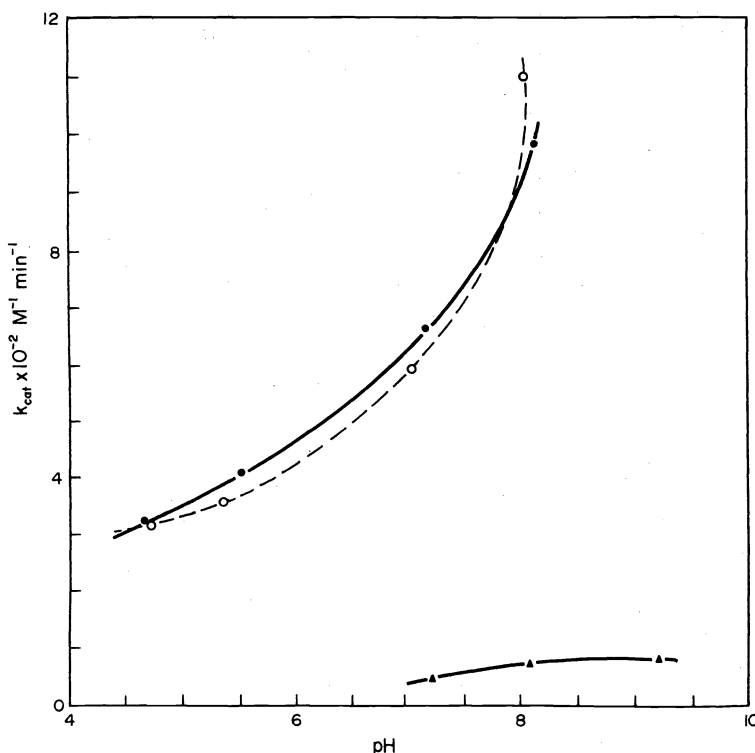


Fig. 4. Second-order rate constants for the hydrolysis of S_2^- catalyzed by [4(5)-VIm-VAmine] copolymers (o) IA-1, (●) IA-7 and by (▲) imidazole in 96.7% water-3.3% acetonitrile, $[S_2^-] = 5 \times 10^{-5} M$, $[catalyst] = 5 \times 10^{-4}$, $\mu = 0.02$, $26^\circ C$.

hydrolyses of long chain esters. Thus Overberger and coworkers(1f) observed that in the hydrolysis of a series of esters with increasing chain length, there was more than a 50-fold rate increase in going from an ester with a 2-carbon chain length to one with 12-carbons. The rate of monomeric imidazole catalyzed reactions, on the contrary, decreases with increase in chain length of substrate due to increased steric hindrance. This increased efficiency of polymeric catalysts has been ascribed to apolar or hydrophobic interactions. Overberger et al.(1f) have studied the effect of solvent composition on this hydrophobic effect and have observed that an increase in the water content of the medium dramatically increased the catalytic efficiency of the polymer, poly[4(5)-VIm], in the hydrolysis of 3-nitro-4-heptanoyloxybenzoic acid, S_7^- and 3-nitro-4-dodecanoyloxybenzoic acid, S_{12}^- .

The rates of hydrolyses of a series of esters, S_n^- ($n = 2, 4, 7$ and 12) were determined in 96.7% water-3.3% CH_3CN solutions at $pH = 8$ under conditions of ten-fold excess of catalyst over substrate. The catalytic rate constants were determined from the linear portions of the pseudo-first-order plots and are given in Table 5 and a plot of the rate constants against the length (n) of the side chain in the substrate is shown in Figure 5.

An examination of the data does indeed reveal the very large rate enhancements expected with long chain esters. The rate constants for the polymer catalysis increased almost ten-fold in going to longer chain esters. Thus, with S_{12}^- the copolymers were more than 300 times as efficient as imidazole in catalyzing the hydrolysis. As opposed to previous studies(1n,1m,1o), the catalytic rate constants increased in going from S_2^- to S_4^- with the copoly[4(5)-VIm-VAmine] indicating that hydrophobic interactions begin to play a dominant role with these copolymers even with S_4^- . This dominance is even more significant when we consider that steric factors should be large with these copolymers in aqueous systems where the polymer chains are expected to be more tightly coiled.

That hydrophobicity plays an important role starting from S_4^- is also evidenced from the fact that decelerative kinetics were observed for S_4^- , S_7^- and S_{12}^- . This deceleration is caused by partial precipitation of the acylated polymer which is highly hydrophobic. Such decelerative kinetics have previously been observed with other imidazole containing catalysts(1n,33).

Of the two copolymers we studied, IA-7 (with 33% VAmine units) was about 50% more reactive than IA-1 (with 25% VAmine units) for the substrate S_7^- . This is probably because IA-1, with less amine content, is more tightly coiled in solution, and steric effects decrease

TABLE 5. Solvolyses of the S_n - Series in Water^a

Catalyst		n			
		2	4	7	12
IA-1 ^f	$k_{cat}(M^{-1}min^{-1})$	1,101	1,788	3,228	10,706
	r^b	16.2	29.8	64.6	315
IA-7 ^f	$k_{cat}(M^{-1}min^{-1})$	984	1,451	4,670	11,409
	r^b	14.5	24.2	93.4	336
Poly[4(5)-VIm] ^c	$k_{cat}(M^{-1}min^{-1})$	338	- -	2,038	10,316
	r^d	5.8	- -	67.0	392
Imidazole ^e	$k_{cat}(M^{-1}min^{-1})$	68	60	50	34

^a Solvent 96.7% H₂O-3.3% CH₃CN; pH = 8.06; $\mu = 0.02$; [cat] = $5 \times 10^{-4}M$; $[S_n^-] = 5 \times 10^{-5}M$.

^b $r = k_{cat}(pol)/k_{cat}(imid)$ under conditions in (a).

^c Solvent 20% EtOH-80% H₂O; pH = 8.0; $\mu = 0.02$; [cat] = $5 \times 10^{-4}M$; $[S_n^-] = 5 \times 10^{-5}M$; reference 1f.

^d $r = k_{cat}(pol)/k_{cat}(imid)$ under conditions in (c).

^e Reference 1n.

^f Polymer solutions became turbid on standing.

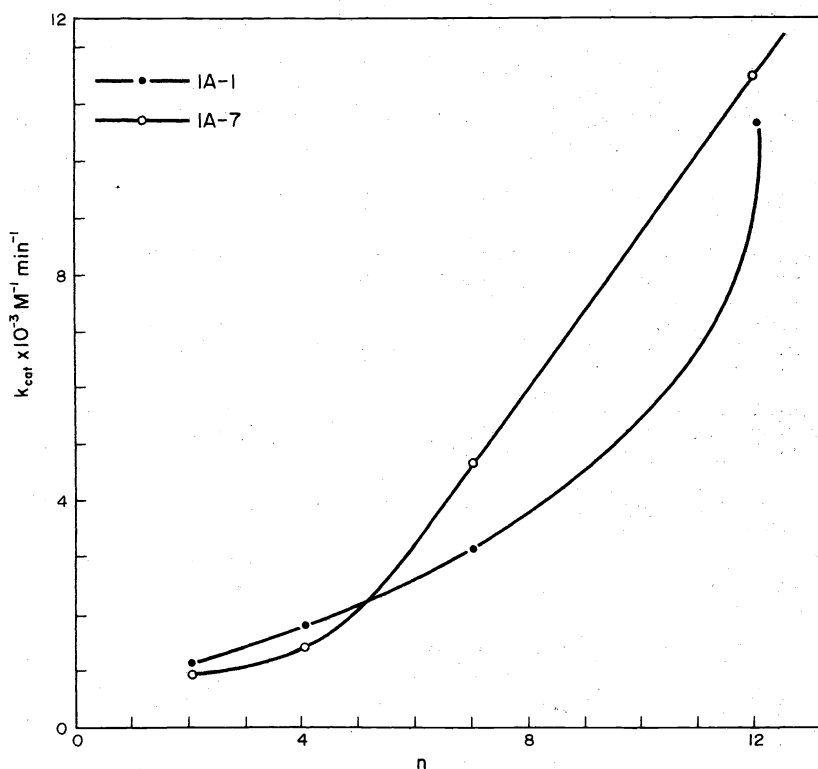


Fig. 5. Second-order rate constants for the hydrolysis of the S_n - series by the [4(5)-VIm-VAmine] copolymers (●) IA-1, (○) IA-7 in 96.7% water-3.3% acetonitrile, pH=8, $[S_n^-] = 5 \times 10^{-5}M$, [catalyst] = $5 \times 10^{-4}M$, $\mu = 0.02$, 26°C.

the accessibility of the bulky S_7^- to the active imidazole sites. With S_{12}^- , however, hydrophobic effects override all other factors and IA-7 is only about 7% more reactive than IA-1.

In order to establish that the very large rate constants observed in our system were greatly due to the high water content of the solution, hydrophobic interactions were studied with the same copolymers and substrates in 20% ethanol-water systems. The results are given in Table 6 and a plot of rate constants against the substrate chain length size, n , is shown in Figure 6. Comparison of these data with those obtained in water reveals the very large

TABLE 6. Solvolysis of the S_n^- Series in 20% EtOH-Water^a

Catalyst		n		
		2	7	12
IA-1	$k_{cat}(M^{-1}min^{-1})$	681	2125	4669
	r^b	11.8	69.9	177.5
IA-7	$k_{cat}(M^{-1}min^{-1})$	659	1618	5722
	r^b	11.4	53.2	217.6
Poly[4(5)VIm] ^c	$k_{cat}(M^{-1}min^{-1})$	338	2038	10,316
	r^b	5.8	67.0	392.2
Imidazole ^c	$k_{cat}(M^{-1}min^{-1})$	57.8	30.4	26.3

^a Solvent 20% EtOH-water; pH = 8, $\mu = 0.02$; $[cat] = 5 \times 10^{-4}M$; $[S_n^-] = 5 \times 10^{-5}M$.

^b $r = k_{cat}(pol)/k_{cat}(imid)$ under conditions in (a).

^c Reference 1f.

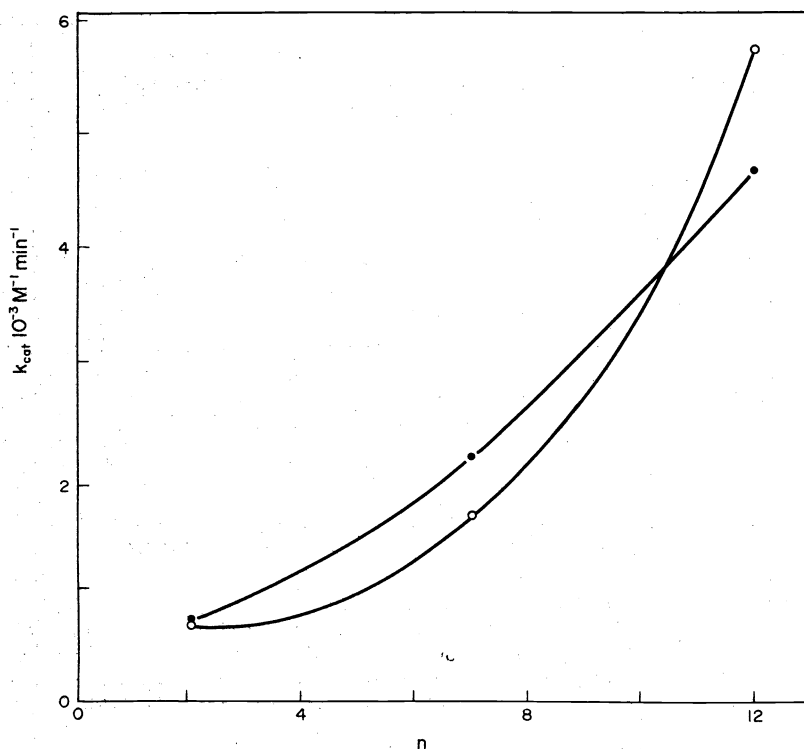
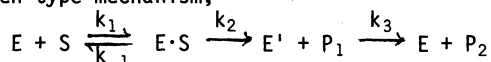


Fig. 6. Second-order rate constants for the hydrolyses of the S_n^- series by the [4(5)-VIm-VAmine] copolymers (●) IA-1, and (○) IA-7 in 20% ethanol-80% water, pH 8, $[S_n^-] = 5 \times 10^{-5}M$, $[catalyst] = 5 \times 10^{-4}M$, $\mu = 0.02$, 26°C.

effect of the water content of the solvent on the k_{cat} values for the copolymers. With S_2^- , the value for the copolymers is much lower in 20% ethanol largely due to the reduction in bifunctional catalysis in this system because of the more extended form of the polymer catalyst. With longer substrate chain lengths, the values of "r" change even more spectacularly until with S_{12}^- , they are about 55-60% of the values in water. This dramatic rate decrease in 20% ethanol-water solutions is accountable only by major reductions in hydrophobic interactions. On comparing the values of k_{cat} or "r" for the copolymers with those of poly[4(5)-VIm], it is apparent that hydrophobic effects are reduced by "dilution" with the vinylamine units, however, where apolar interactions are not predominant, e.g., with S_2^- , the more highly charged copolymer is a more effective catalyst than the homopolymer at the pH of kinetic studies, due to electrostatic effects.

(d) Solvolysis with Excess Substrate: In cases where acylated polymer intermediate accumulate during the reaction, the acylation-deacylation behavior of the polymer can be followed by studying the solvolysis in excess substrate. Such reactions show, typically, an initial burst region followed by a slow zero-order steady state deacylation region. Assuming a Michaelis-Menten type mechanism,



where E is the polymer, S is the substrate, E·S is the polymer-substrate complex, E' is the acylated polymer, P₁ is the liberated phenolate anion that is estimated spectrophotometrically and P₂ is the long-chain acid, a plot of the absorbance versus time can be described (34) by the equation

$$[P_1] = At + B(1 - e^{-bt})$$

where

$$A = k_{cat}[E]_0[S]_0/[S]_0 + Km(\text{apparent})$$

$$B = [E]_0(k_2/k_2 + k_3)^2/(1 + Km(\text{apparent})/[S]_0)^2$$

and

$$b = k_3 + k_2/1 + (K_s/[S]_0)$$

At time approaching infinity,

$$[P_1] = At + B.$$

We carried out the solvolysis of S_{12}^- in 96.7% water-3.3% acetonitrile with 4-10 times excess of the substrate over the catalyst. The absorbance versus time plots are shown in Figure 7. The slope of the zero order linear portion of the graph gives A, which is a measure of the steady state rate of release of phenolate anion, and the intercept for $t = 0$ obtained by extrapolation gives B, which measures the concentration of acylated residues at the steady state. Dividing A by B gives k_3 which is the rate constant for steady state deacylation. The values of A, B and k_3 as found from our study are tabulated in Table 7 along with the values for poly[4(5)-VIm] as found by previous workers. It is seen that the steady state concentration of acylated imidazoles is much less for the copolymers than for poly[4(5)-VIm] (in 28.5% ethanol-water). This suggests that the homopolymer is much more extended in the 28.5% ethanol-water system than the copolymer is in water.

The initial rates of these reactions, as measured from the initial slopes of the curves in the "burst" region are often indicative of the hydrophobic nature of the polymers(1m). Under the conditions of excess substrate, the value indicates the concentration of the polymer substrate complex [ES]. When the initial rates V_i are plotted against the substrate concentrations (Figure 8), complete saturation of the copolymers was not observed. Very high values of V_{in} were obtained, indicating efficient turnover in the copolymer system in water.

EXPERIMENTAL

A. Synthesis.

(1) 4(5)-Vinylimidazole. 4(5)-Vinylimidazole was prepared by the method of Overberger et al.(26).

(2) N-Vinyl-t-butyl Carbamate. N-Vinyl-t-butyl carbamate was prepared by the method of Hart(27).

(3) Copoly[4(5)-VIm-N-vinyl-t-butyl Carbamate]. The appropriate amounts of the two monomers (Table 1) were dissolved in benzene to give total concentrations of monomers of 1.5M; 1 mole % of AIBN was added and the solutions were sealed under vacuum in polymerization tubes. The samples were heated at 65°C for appropriate times (Table 1) and then precipitated into acetone or ethyl ether. The copolymers were purified by repeated precipitations from methanol solutions into acetone (for low NVBC polymers) or ethyl ether (high NVBC-containing polymers).

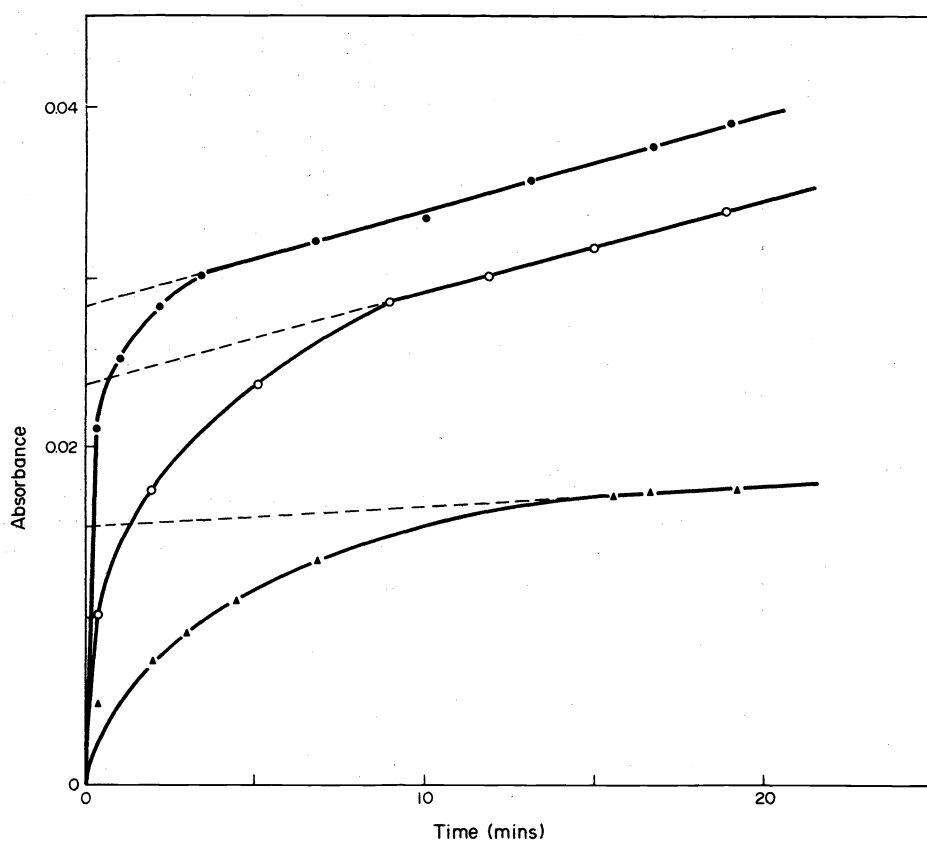


Fig. 7. Absorbance vs. time plot for the steady-state rate of release of phenolate anion from S_{12}^- by the [4(5)-Vim-VAmine] copolymer IA-7 in 96.7% water-3.3% acetonitrile, $[S_n^-]$ = (●) $2.5 \times 10^{-4}M$, (○) $1.5 \times 10^{-4}M$, (▲) $1.0 \times 10^{-4}M$.

TABLE 7. Steady State Rate of Release of Phenolate Anion from S_n^- by Imidazole-Containing Polymers under Conditions of Excess Substrate(a)

Catalyst	n	$[S_n^-]$	Rate of release of phenolate	Conc. of Acylated Residue(B)	k_3 (A/B)	V_{in}
		$M \times 10^4$	$M \text{ min}^{-1} \times 10^7$	$M \times 10^5$	$\text{min}^{-1} \times 10^3$	$M \text{ min}^{-1} \times 10^5$
IA-1	12	2.5	1.67	0.806(32%)	20.72	2.22
	12	1.5	1.58	0.667(27%)	23.69	0.96
	12	1.0	0.36	0.444(18%)	8.13	0.40
IA-7	12	2.5	1.67	0.778(31%)	21.47	2.33
	12	1.5	1.53	0.653(26%)	23.43	0.84
	12	1.0	0.36	0.417(17%)	8.66	0.36
Poly[4(5)VIm] ^b	12	2.6	6.98	1.65(66%)	42.3	--
Poly[4(5)VIm] ^c	7	2.5	2.11	1.75(70%)	12.1	--

^a pH = 7.11, μ = 0.02, solvent 96.7%-3.3% CH_3CN ; $[\text{cat}] = 2.5 \times 10^{-5}M$.

^b Solvent 28.5% ethanol-water, Reference 1o.

^c pH = 6.85; solvent 26.7% ethanol-3.3% CH_3CN -70% water, Reference 1m.

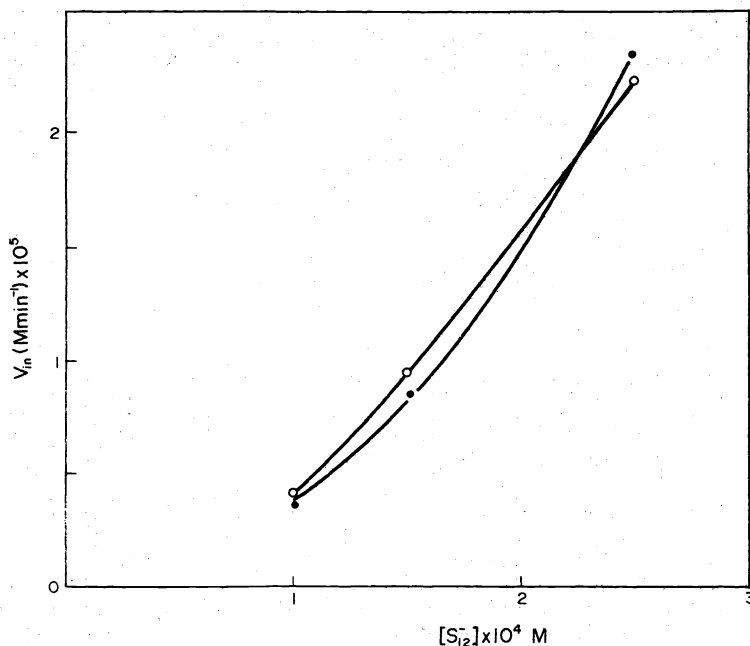


Fig. 8. Plot of V_{in} vs. concentration of S_{12}^- for the [4(5)-VIm-VAmine] copolymer (o) IA-1 and (●) IA-7 catalyzed solvolysis of S_{12}^- in 96.7% water-3.3% acetonitrile with [catalyst] = $2.5 \times 10^{-5}M$, pH = 7.11, $\mu = 0.02$, 26°C.

NMR (CDCl₃): δ 7.5 (s), 6.37 (s), 1.4 (s); IR ν_{max}^{KBr} (cm⁻¹): 3300, 1710, 1360. Elemental analysis: (IC-1): Calcd on the basis of (C₅H₆N₂)₇₇(C₇H₁₃NO₂)₂₃, C = 62.64; H = 7.02; N = 25.22. Found: C, 58.15; H = 6.81; N = 25.22.

(IC-7): Calcd on the basis of (C₅H₆N₂)₆₆(C₇H₁₃NO₂)₃₄, C = 61.59; H = 7.57; N = 21.00. Found: C = 58.74; H = 6.50; N = 21.00.

Preparation of Copoly{[4(5)-Vinylimidazole]-[Vinyl-Amine]} as Their Hydrochlorides or Hydrobromides. Two of the [4(5)-VIm-NVBC] copolymers, (IC-1) and (IC-7), were dissolved in ethanol (5-6% concentration w/v) and were treated with excess 48% hydrobromic acid and 10(N) hydrochloric acid, respectively. These solutions were heated under N₂ for 24 hr at 50°C and then the solutions were concentrated and precipitated into acetone. These precipitated copolymers were reprecipitated three more times each from methanol into acetone. These were then dried at 50°C under vacuum to constant weights.

NMR (MeOH-d₄): δ 8.77 (s); 7.40 (s); 2.1-2.3 (br); 1.6-1.8 (br). IR ν_{max}^{KBr} (cm⁻¹): 3000 (br), peaks due to *t*-butyl (1360 cm⁻¹) and carbamate (1710 cm⁻¹) completely absent. Elemental analysis, after neutralization and drying:

(IA-1): Calcd on the basis of (C₅H₆N₂)₇₅(C₂H₅N)₂₅, C = 61.80; H = 7.70; N = 30.50. Found: C = 61.35; H = 7.42; N = 29.97.

(IA-7): Calcd on the basis of (C₅H₆N₂)₆₇(C₂H₅N)₃₃, C = 61.16; H = 8.12; N = 30.72. Found: C = 60.58; H = 8.10; N = 30.52.

Intrinsic viscosity:

(IA-1): $[\eta]_{50\%}^{26^\circ}$ MeOH = 0.41 dl/g; (IA-7): $[\eta]_{50\%}^{26^\circ}$ MeOH = 0.38 dl/g.

B. Viscosity Measurements. The viscosity measurements were carried out at 26° ± 0.01°C with the most concentrated solutions used being 0.5 g/dl. A Cannon-Ubbelohde Semi-Micro dilution viscometer was used for these experiments.

C. Titrations. About 15 mg of the copolymer sample was placed in a thermostated cell at 26.0°C and it was dissolved in a mixture of 0.3 ml of 1.0M hydrochloric acid and 14.7 ml of water. The stirred solution was titrated incrementally with 1.0M sodium hydroxide solution from a micro-pipette (Manostat Digi-Pet). The ionic strength at the end point of the titration was 0.02. The pH was monitored by an Orion Model 601 Digital pH Meter. A blank curve was similarly obtained by titrating 0.30 ml of 1.0M hydrochloric acid diluted to 15.0 ml with water.

A differential titration curve was obtained by plotting pH vs. the difference in volumes of base at the same pH [$\Delta\mu$](35). Since sharp inflection points were not present in these curves, modified Henderson-Hasselbach plots were constructed by plotting pH against $\log(\alpha_1/1-\alpha_1)$, where α_1 is the fraction of neutral imidazoles.

E. Kinetic Measurements for Solvolysis of Esters.

(a) Slow Reactions in Excess Catalyst. To 2.9 ml of a buffered catalyst solution in a 1.00 cm quartz cell at 26°, was added 0.10 ml of an acetonitrile solution of the substrate. The final concentrations were [catalyst] = $5 \times 10^{-4}M$, [substrate] = $5 \times 10^{-5}M$, $\mu = 0.02$, [buffer] = 0.02M and 96.7% water-3.3% acetonitrile by volume. The buffer employed above pH 6 was tris(hydroxymethyl)aminomethane-HCl. For pH 6, and below, the systems were buffered with sodium acetate-acetic acid. For reactions in 20% ethanol, the substrates were prepared in ethanol and the catalysts were made in aqueous ethanol such that the final solutions were 20% in ethanol by volume.

All data obtained under conditions of [catalyst] >> [substrate] was treated as first-order kinetics by plotting $\ln(A_\infty - A_t)$ versus time. The absorbance measurements were made on Beckman DU and DU-2 Spectrophotometers. The slope of the first-order plot was taken as the pseudo-first-order rate constant (k_{meas}). Where significant, the blank rate constant (k_{blank}) was obtained from earlier work(36) (for 96.7% water), and Reference 37 (for 20% ethanol). When k_{blank} was subtracted from k_{meas} , we obtained k_{obs} .

$$k_{obs} = k_{obs}/[\text{catalyst}].$$

Infinity values were obtained after at least ten half-lives.

(b) Fast Reactions in Excess Catalyst. Fast reactions, i.e., those with half-lives less than about 2 min, were followed on a Durrum-Gibbs Stopped Flow Spectrophotometer. The data were obtained on an oscilloscope trace of %T versus time; this trace was photographed. The %T was obtained from the photographs at certain time intervals, then converted to absorbances.

The rates of the samples not giving first-order kinetics were obtained from the initial slope of the $\ln(A_\infty - A_t)$ vs. time plot, where the curve was still linear.

(c) Reactions in Excess Substrate. Essentially the same procedure was followed as described above except the catalyst concentration was held constant and the substrate concentration was varied. In all cases of excess substrate, the absorbance was plotted against time.

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