solvolyses of ANTI and NABA catalyzed by the imidazole–acrylic acid copolymer are most likely the result of ion pair formation between a substrate and a binding site in specific sequences. The enlarged selectivity of the imidazole–maleic acid copolymer, compared to the imidazole–acrylic acid copolymer, would be due to the increased electrostatic field potential around the polymer in solution.

The results obtained in this investigation suggest that this is the first example of synthetic, polymeric catalysts which presumably involve both long and short-range electrostatic interactions in their solvolytic reactions.

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Cooperative Effects Involved in Esterolytic Reactions Catalyzed by Imidazole–Carboxylic Acid Copolymers

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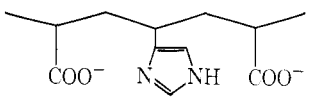
ABSTRACT: Studies of the esterolytic activities of copolymers of 4(5)-vinylimidazole and vinylsulfonic acid, in comparison with those of 4(5)-vinylimidazole and acrylic acid, were undertaken in order to elucidate the involvement of pendent carboxylate groups in the latter copolymers. It was found that the copolymers which were rich in vinylsulfonic acid were catalytically inactive. These results support the cooperative interaction of pendent imidazole and carboxylate functions in the imidazole–acrylic acid copolymer catalyzed reactions.

In the previous paper[2] it was reported that copolymers of 4(5)-vinylimidazole with acrylic acid had high selectivity toward the positively charged substrate, 3-acetoxy-N-trimethylanilinium iodide (ANTI), and that this high selectivity could be attributed to that of a specific monomeric sequence along the copolymer chain, *i.e.*, the sequence of carboxylate-neutral imidazole carboxylate (I).



I

It was previously reported from our group that basic pendent groups, such as neutral or anionic imidazole groups[3] and phenoxide groups,[4] could participate in the solvolytic reaction by interacting cooperatively with neutral, pendent imidazole groups in the solvolyses of esters. Since carboxylate anion has been known to catalyze hydrolyses of esters both intramolecularly[5,6] and intermolecularly,[5,6] it was anticipated that the pendent carboxylate groups in the imidazole–acrylic acid copolymers (such as in sequence I) might also participate in the catalytic action together with pendent imidazole groups. This possibility was previously suggested[2] in connection with the differences in the catalytic activities between the imidazole–acrylic acid copolymers and the imidazole homopolymer in the solvolysis of the neutral ester *p*-nitrophenyl acetate (PNPA). The former polymers, rich in the distribution of sequence I, were found to be significantly more active than the latter at the same degree of dissociation of the pendent imidazolium groups.

In order to elucidate the above possibility, copolymers of 4(5)-vinylimidazole with vinylsulfonic acid were prepared and their catalytic activities were compared with those of the imidazole–acrylic acid copolymers. The large difference in basicity and/or nucleophilicity between pendent carboxylate and pendent sulfonate groups in these copolymers were expected to reflect on the reactivity of the respective copolymers, if a pendent carboxylate group participates cooperatively with a pendent imidazole group in the solvolyses of esters.

Experimental Section

***n*-Butyl vinylsulfonate** was prepared by the procedure of Whitmore and Landan.[7]

Copolymerization of 4(5)-Vinylimidazole with *n*-Butyl Vinylsulfonate. 4(5)-Vinylimidazole, freshly distilled *n*-butyl vinylsulfonate (total amount of these monomers, 1.0 g) and azobisisobutyronitrile (0.02 g), was dissolved in 20 ml of reagent grade *n*-butyl alcohol in polymerization tubes. After removing oxygen by flushing with dry nitrogen, the

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TABLE I[a]
RESULTS OF THE PREPARATION OF COPOLYMERS OF 4(5)-VINYLIMIDAZOLE WITH VINYLSULFONIC ACID

Polymerization conditions		Results	
Feed composn, VIM mol %	Time, hr	Conversion, wt %	Copolymer composn,[b] VIM mol %
9.4	25.0	9.9	38.6
53.0	5.0	59.5	52.5
95.5	5.0	25.7	83.9

[a] In *n*-butyl alcohol, at 60°, AIBN as an initiator, with shaking during polymerization. [b] Based on both nitrogen and sulfur contents in the hydrolyzed copolymers.

tubes were sealed and then shaken in a constant-temperature bath at 60° for a proper period. The formed polymers precipitated during polymerization. The obtained dispersions were added to 500 ml of acetone and left overnight. The precipitated polymers were collected by filtration, washed with acetone, and dried in a vacuum oven overnight. The results are summarized in Table I.

Hydrolyses of the Copolymers of 4(5)-Vinylimidazole with *n*-Butyl Vinylsulfonate. The above mentioned copolymers were placed in a 100-ml round-bottom flask with 50 ml of deionized water. The copolymers of compositions 38.6 and 52.0 mol % in imidazole gradually dissolved in water but the other copolymer (83.9 mol % in imidazole) only swelled. After refluxing overnight, the first copolymer remained in solution, while the others partly formed thin films on the walls of the flasks. After evaporating the solutions to a few milliliters, the copolymers were recovered by freeze-drying. The infrared spectra (KBr pellet) of these polymers exhibited a rather broad absorption at 1140–1260 cm^{-1}, but no absorption was observed at 1340 and 1160 cm^{-1}. These copolymers were hygroscopic and the infrared spectra indicated the presence of some water in the sample although almost no weight loss was observed by drying to constant weight at 100° under vacuum.

Anal. Found: N, 21.72, 21.80; S, 4.29, 4.89 (83.9 mol % in imidazole); N, 11.78; S, 11.37, 12.55 (52.0 mol % in imidazole); N, 9.43, 9.19; S, 16.21, 17.82 (38.6 mol % in imidazole).

Potentiometric Titration of the Copolymers. The method of potentiometric titrations previously reported[2] was employed. No ranges of dissociation of pendent sulfonic acid groups were observed because of their low pK_a values. The ranges of dissociation of the pendent imidazolium groups were found to be broader than those estimated for the imidazole–acrylic acid copolymers.[2] This effect could be due to the formation of zwitterions between the pendent sulfonate and imidazolium ions.[8] The results of titrations are summarized in Table II.

Kinetic measurements were performed as previously described.[2,3]

Results

The rates of solvolyses catalyzed by the imidazole–sulfonic acid copolymers were found to be first order in the substrates at least up to one-half life. Dependencies of the rates on copolymer concentration were examined for the copolymer containing 83.9 mol % imidazole and also were found to be first order with respect to the copolymer (Figure 1).

The dependencies of the catalytic activities of the

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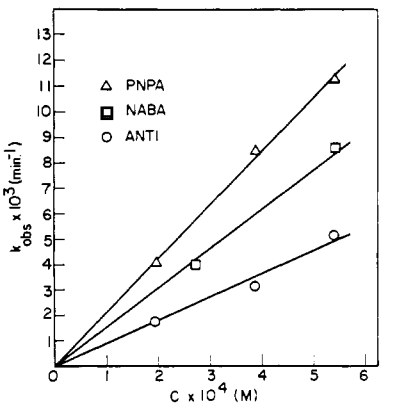

Figure 1. Plots of k_{obsd} *vs.* concentration of the imidazole–sulfonic acid copolymer (83.9 mol % imidazole) at 26°, in 28.5% ethanol–water, pH 9.0, ionic strength 0.02.

TABLE II[a]
RESULTS OF THE POTENTIOMETRIC TITRATIONS OF PENDENT IMIDAZOLIUM IONS IN THE COPOLYMERS OF 4(5)-VINYLIMIDAZOLE WITH VINYLSULFONIC ACID

Copolymer composn, VIM mol %	pK_i	n	Pptn range[b]
100[c]	5.78	2.42	*Ca.* 8.5∼
53.9	6.45	4.79	6.1 ∼ 7.9
52.0	7.90	3.19	3.0 ∼ 6.9
38.6	8.55	2.51	No ppt

[a] In 28.5% ethanol–water, at room temperature, ionic strength 0.015 ∼ 0.02, under nitrogen. [b] Range of pH where precipitation was observed. [c] Poly-4(5)-vinylimidazole.

TABLE III[a]
SECOND-ORDER CATALYTIC RATE CONSTANTS FOR 4(5)-VINYLIMIDAZOLE–VINYLSULFONIC ACID COPOLYMER CATALYZED SOLVOLYSES OF ANTI, PNPA, AND NABA

Substrate	Copolymer composn, VIM mol %	k_{cat}, l./mol min[b] pH 8.0	pH 8.4	pH 9.0	pH 9.9
ANTI	38.6	0.2	0.6 (2)	−1.6 (2)	−7.2 (3)
	52.0	0.0	0.3 (2)	−0.4	−1.1 (3)
	83.9		4.9 (2)	8.9 (3)	11.9 (3)
PNPA	38.6	0.3	0.0	−0.9	−0.4 (2)
	52.0	−0.1	0.2	0.5 (2)	6.8 (2)
	83.9		15.6	21.4 (3)	30.5 (2)
NABA	38.6		0.1	0.2	1.6
	52.0		0.2	−0.4	11.6
	83.9		13.9	15.5 (2)	17.9

[a] At 26°, in 28.5% ethanol–water, ionic strength 0.02. [b] Average value of the number of determinations shown in parentheses.

imidazole–sulfonic acid copolymers in the solvolyses of ANTI, PNPA, and NABA (3-nitro-4-acetoxybenzoic acid) on copolymer composition are listed in Table III. The effects of copolymer composition on the catalytic activities of the imidazole–sulfonic acid copolymers are entirely different from those of the imidazole–acrylic acid copolymers.[2] The latter copolymers exhibited different behavior characteristic to each substrate as previously discussed[2] while the former copolymers show roughly the same behavior for every substrate.

Special attention should be given to the large dif-

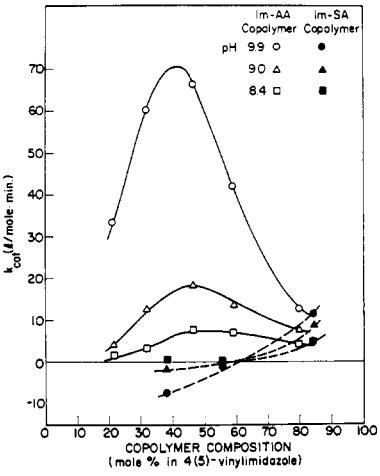

Figure 2. Effects of copolymer composition and pH on k_{cat} for the imidazole–acrylic acid copolymer catalyzed solvolyses of ANTI.

ferences in catalytic activities between the solvolyses of ANTI catalyzed by the imidazole–sulfonic acid copolymers and those catalyzed by the imidazole–acrylic acid copolymers, as shown in Figure 2. In the former solvolyses, no enhancement of the catalytic activities was detected at the copolymer compositions of 38.6 and 52.0 mol % in imidazole. Instead, catalytic activities decreasing with increasing pH were observed. The inhibitory effects of these copolymers in the solvolyses of ANTI can only be explained by assuming inertness of the pendent neutral imidazole groups in these copolymers, because the pendent sulfonate groups seem to have stronger binding ability toward cations than pendent carboxylate groups.[9] The fraction of free, pendent sulfonate groups increases with increase of pH, as caused by the destruction of the zwitterions. Consequently the capacity of these copolymers both for binding ANTI and for repelling hydroxide ions would increase with pH, resulting in the increased inhibitory effects with increasing pH. Retardation of the hydroxide ion-catalyzed solvolyses of positively charged substrate by a catalytically inactive polyanion has been reported.[10]

On the other hand, the catalytic activities of the imidazole–sulfonic acid copolymer are comparable to those of the imidazole–acrylic acid copolymer at the copolymer composition of *ca.* 80 mol % (Figure 2). This can be attributed to the contribution of the longer imidazole sequences in both systems.

Considering the high alternating tendency of 4(5)-vinylimidazole and vinylsulfonic acid along the copolymer chain, it can be concluded from the above results that at least the isolated neutral imidazole sequence in the imidazole–sulfonic acid copolymers is catalytically inactive. The difference in the catalytic activities between the isolated imidazole sequence in the imidazole–acrylic acid copolymers and that in the imidazole-sulfonic acid copolymers indicates that carboxylate groups on the copolymer chains are involved in the reaction in some manner which is strongly associated with the overall catalytic rate of the copolymer-catalyzed solvolyses.

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Discussion

The solvolytic rates of esters catalyzed by monomeric imidazoles can be generally expressed by[11]

$$\text{rate} = (\text{ester})[k_n(\text{IM}) + k'_{gb}(\text{IM}) + k_{gb}(\text{IM})^2 + k_a(\text{IM}^-)]$$

The first term, $k_n(\text{IM})$, is associated with nucleophilic imidazole catalysis and is predominant in the solvolyses of phenyl acetate derivatives having good leaving groups, such as phenyl, and *p*-chloro-, *p*-nitro, *m*-nitro, or 2,4-dinitrophenyl acetate, etc.[12–16] No significant deuterium solvent isotope effect was observed for these solvolyses.[17–19] In these imidazole catalyses, N-acetylimidazole was found to be an intermediate.[15] The monomeric imidazole-catalyzed solvolyses of ANTI and of NABA very likely proceed by this mechanism. The second term, $k'_{gb}(\text{IM})$, is associated with general base catalyses where neutral imidazole probably assists the attack of water on an electron-deficient carbonyl of ester. This type of imidazole catalysis was observed for N,O-diacetylserinamide,[19] ethyl esters of chloro-, dichloro-, or trifluoroacetic acid, *etc.*,[18,20] and 2,2-dichloro-, 2-chloro-, or 2-methoxyethyl acetate, etc.[21] The deuterium solvent isotope effects of *ca.* 2–3 (k_{H_2O}/k_{D_2O}) have been reported for these solvolyses. The third term, $k_{gb}(\text{IM})^2$, was observed in the solvolyses of phenyl acetate derivatives having poor leaving groups such as *p*-methoxy- or *p*-methylphenyl acetate.[12,22] In this case, the attack of imidazole on an ester carbonyl is assisted by another imidazole and a deuterium effect of 2.2 was obtained.[12] The last term, $k_a(\text{IM}^-)$, is associated with imidazole derivatives which possess low pK_2 values, *e.g.*, 4-nitroimidazole (pK_a 9.1)[13] and probably with the imidazole-catalyzed solvolyses of phenyl acetate or *p*-nitrophenyl toluate at high pH.[22]

For the solvolysis of PNPA catalyzed by poly-4(5)-vinylimidazole, bifunctional catalyses by the pendent imidazole groups have been proposed.[3] At high pH values, the contribution of bifunctional catalysis of a neutral imidazole group with an anionic[3a] or another neutral imidazole group[3c] becomes significant. As indicated above, for monomeric imidazole-catalyzed solvolyses, the bifunctional catalysis of the former type has never been reported, while that of the latter type has been observed, but only for phenyl esters having very poor leaving groups.[12,22] For the solvolysis of

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PNPA, neither type of bifunctional catalysis with monomeric imidazole has been observed.

If nucleophilic catalysis by pendent imidazole groups is the predominant catalytic reaction in copolymers containing both imidazole and another functional group, it can be assumed that replacing the latter functional groups with analogous but catalytically inactive groups on the polymer chain would not affect their catalytic activities to a large extent. It has, however, been found that the magnitudes of the catalytic activities of the copolymers of 4(5)-vinylimidazole with a monomer possessing an acidic group were drastically reduced by replacing the acidic comonomer with its catalytically inactive analog. The previously discussed differences between the imidazole–acrylic acid copolymers and the imidazole–sulfonic acid copolymers is one example of this effect. Other examples are the esterolytic catalyses by copolymers of 4(5)-vinylimidazole with *p*-hydroxystyrene and that with *p*-methoxystyrene. Although the former copolymer is a better catalyst than poly-4(5)-vinylimidazole for the solvolyses of PNPA at pH 9, the latter copolymer has been reported to possess no significant catalytic activity under the same conditions.[4] These results seem to indicate that nucleophilic imidazole catalysis is unlikely to be involved in the copolymer-catalyzed solvolysis of PNPA.

When the results of the previously reported poly-4(5)-vinylimidazole catalyzed solvolysis of PNPA are reconsidered from this viewpoint, other significant evidence seems to support the above possibility.

In the monomeric imidazole catalyzed solvolysis of PNPA, methyl substitution on the 1 position of imidazole has only a slight effect on its catalytic acitivity, *viz.*, N-methylimidazole is about 75% as active as imidazole.[15,23] On the other hand, poly-N-vinylimidazole is a much less active catalyst than poly-4(5)-vinylimidazole over a range of pH 7–9 (Table IV). It is believed that a major contribution to the rate of the catalyzed solvolysis of PNPA is nucleophilic imidazole catalysis for the former polymer and bifunctional imidazole catalysis for the latter polymer under these conditions.[3]

The preceding discussion indicates that the requirements for vinyl polymers containing 4(5)-vinylimidazole to have significant catalytic activities are the occurrence of bifunctional interactions between catalytically active, pendent, functional groups such as neutral imidazole with anionic[3a] or neutral imidazole groups,[3b,c] with phenoxide and hydroxyl functions[4] and with carboxylate groups.

The reason why there are distinctive differences in the catalytic behaviors of the copolymers of 4(5)-vinylimidazole with acrylic acid and those with sulfonic acid now becomes apparent. The inertness of the latter copolymers containing 52 mol % or less of imidazole can be rationalized by considering two factors. One is that the pendent sulfonate groups are too weakly basic to participate in the reaction, and the other is that there is a difficulty in interaction of two isolated, neutral pendent imidazole groups, because the electrostatic repulsion of the nearby sulfonate groups would not permit the imidazole functions to be in juxtaposition. Although the latter factor would be involved in the imidazole–carboxylic acid copolymers, significant catalytic effects would be noted if the pendent carboxylate groups participate in the catalysis. This was actually observed.

TABLE IV[a]
SECOND-ORDER CATALYTIC RATE CONSTANTS OF THE SOLVOLYSIS OF PNPA CATALYZED BY POLY-N-VINYLIMIDAZOLE AND BY POLY-4(5)-VINYLIMIDAZOLE

—Poly-N-vinylimidazole[b]—			—Poly-4(5)-vinylimidazole—		
pH	α_1	k_{cat}, l./mol min	pH	α_1	k_{cat}, l./mol min
7.2	0.99	3.0	7.3	0.80	16.3
8.0	1.00	3.5	8.0	0.90	24.3
9.2	1.00	3.5			

[a] At 26°, in 28.5% ethanol–water, ionic strength 0.02. [b] Taken from ref 2.

On the other hand, the high catalytic activities of the isolated, neutral imidazole sequence (I) in the imidazole–acrylic acid copolymer toward ANTI[2] might suggest that bifunctional catalysis by pendent imidazole and carboxylate groups could occur within this sequence. One of the carboxylates might act as a binding site for ANTI, and the other might cooperate with imidazole in the catalytic reaction.

Recently, Hartley and his coworkers reexamined the sequence around residue 102 in α-chymotrypsin and found it to be aspartic acid. Based on this discovery and stereochemical nature of the active site of this enzyme, they proposed a mechanism involving participation of a carboxylate group cooperatively with imidazole and hydroxyl groups in histidine and serine residues, respectively.[24] Our results also suggest feasibility of this cooperative effect.

Acknowledgments. The authors appreciate the helpful discussions of this work with Dr. I. Cho and Dr. J. C. Salamone. They also wish to acknowledge the financial support of the Research Laboratory, U. S. Army, Edgewood Arsenal, under Contract DAAA-15-67-C-0567, and the National Institutes of Health under Grant No. 2 RO1 GM 15256-02.

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