Esterolytic Action of Synthetic Macromolecules

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The utilization of synthetic macromolecules to change the reactivities of low molecular weight species has recently received considerable attention,[2] particularly since these reactions can serve as models for the more complex enzymatic processes. Although these polymeric catalysts are considerably less efficient than enzymic catalysts, several analogies between the natural and synthetic macromolecular systems have been revealed. For example, synthetic polymeric species can be characterized by (a) higher reactivities than corresponding monomeric systems,[2] (b) specificity of substrate hydrolysis (particularly if the substrate is of a charge opposite to that of the charged groups on the polymer),[2-4] (c) competitive inhibition by substances similar to the reactive substrate,[5,6] (d) bifunctional catalysis involving the interactions of two pendent functional groups and substrate,[2,4,7-9] and (e) saturation (complexation) by high and low molecular weight reagents.[5,10-14]

In general, the behaviors of synthetic polymers toward low molecular weight compounds are of two different types. First, if two low molecular weight ionic species are the reactive reagents, a polymer with charged groups will tend to concentrate and/or repel one or both low molecular weight reagents in its vicinity and, consequently, will functon as either an inhibitor or an accelerator of the reaction. Secondly, if catalytically active functions are added to a polymer which contains charged groups, the polymer itself, and not its counterions, is able to react with either charged or neutral reagents. Several workers have investigated enhanced or inhibited catalytic actions of polyions that contain no catalytic functions (type 1) on the reactivities of similarly and/or oppositely charged, low molecular weight reagents.[11-13,15-18] This effect has been treated theoretically by considerations of the distribution of the electrostatic potential[11,13,15,17] and by investigation of the primary salt effect.[18] Reactions which involve polymers of the second type would apparently be more related to those of hydrolytic enzymes, since the charged groups can serve as electrostatic binding sites, thereby accumulating a substrate in a high local concentration of catalytically active substituents. This cooperative effect would lead to enhanced catalytic action.[2-5,19]

The work described here with the latter type of macromolecule will be chiefly concerned with esterolytic reactions catalyzed by synthetic, imidazole-containing polymers. These macromolecules were chosen for study because the imidazole moiety of histidine has been implicated in the active sites of several hydrolytic enzymes.[20-22]

It is well known that the efficiency of an enzymic reaction is in part dependent upon a cooperative, multifunctional interaction between catalyst groups comprising an active site and a reactive substrate. In esterolytic reactions catalyzed by imidazole- and benzimidazole-containing polymers, several types of cooperative interactions between the pendent groups have been observed. Such cooperative interactions have led to enhanced catalytic action of the polymers in comparison to their low molecular weight analogs. In this Account will be discussed the catalytic behaviors of synthetic vinyl polymers which contain pendent imidazole, benzimidazole, or triazole groups toward neutral and charged substrates. An attempt

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[1] This review is taken from the work of the following students and postdoctoral fellows: R. Corett, I. Cho, J. Lee, H. Maki, M. Morimoto, T. St. Pierre, J. C. Salamone, C. M. Shen, R. Sitaramiah, N. Vorchheimer, C. Yaroslavsky, S. Yaroslavsky, and P. S. Yuen.

[2] For a review see H. Morawetz, "High Polymers," Vol. XXI, Interscience Publishers, New York, N. Y., 1965, Chapter IX.

[3] R. L. Letsinger and T. J. Savereide, *J. Amer. Chem. Soc.*, **84**, 3122 (1962).

[4] C. G. Overberger, T. St. Pierre, N. Vorchheimer, J. Lee, and S. Yaroslavsky, *ibid.*, **87**, 296 (1965).

[5] R. L. Letsinger and I. Klaus, *ibid.*, **87**, 3380 (1965).

[6] C. G. Overberger, unpublished results.

[7] C. G. Overberger, T. St. Pierre, and S. Yaroslavsky, *J. Amer. Chem. Soc.*, **87**, 4310 (1965).

[8] C. G. Overberger, J. C. Salamone, and S. Yaroslavsky, *ibid.*, **89**, 6231 (1967).

[9] J. Hine, F. E. Rogers, and R. E. Notari, *ibid.*, **90**, 3279 (1968).

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[11] H. Morawetz and J. A. Shafer, *J. Phys. Chem.*, **67**, 1293 (1963).

[12] S. Yoshikawa and O.-K. Kim, *Bull. Chem. Soc. Jap.*, **39**, 1729 (1966).

[13] H. Morawetz and B. Vogel, *J. Amer. Chem. Soc.*, **91**, 563 (1969).

[14] C. G. Overberger, R. Corett, J. C. Salamone, and S. Yaroslavsky, *Macromolecules*, **1**, 331 (1968).

[15] H. Morawetz, *J. Polymer Sci.*, **42**, 125 (1960).

[16] C. L. Arcus, T. L. Howard, and D. S. South, *Chem. Ind.* (London), 1756 (1964).

[17] H. Morawetz, C. G. Overberger, J. C. Salamone, and S. Yaroslavsky, *J. Amer. Chem. Soc.*, **90**, 651 (1968).

[18] N. Ise and F. Matusi, *ibid.*, **90**, 4242 (1968).

[19] C. G. Overberger, R. Sitaramaiah, T. St. Pierre, and S. Yaroslavsky, *ibid.*, **87**, 3270 (1965).

[20] M. L. Bender and F. J. Kézdy, *ibid.*, **86**, 3704 (1964); H. Neurath, *Sci. Am.*, **211**, (6), 68 (1964).

[21] G. G. Hammes, *Accounts Chem. Res.*, **1**, 321 (1968), and the references cited therein.

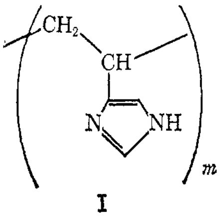
[22] C. H. W. Hirs, M. Halmann, and J. H. Kycia in "Biological Structure and Function," Vol. I, Academic Press, New York, N. Y., 1962, p 41; for a review see A. P. Mathias, A. Deavin, and B. R. Rabin in "Structure and Activity of Enzymes," T. W. Goodwin, J. I. Harris, and B. S. Hartley, Ed., Academic Press, New York, N. Y., 1964, pp 19–30.

has been made to describe pertinent data which illustrate the specific catalytic actions of synthetic macromolecules.

Neutral–Anionic Imidazole Interaction

Reactions of neutral substrates with polymers tend to be accelerated as the fraction of neutral, catalytically active groups on the polymer backbone increases. An example of this phenomenon was reported by Ladenheim and Morawetz for the partially ionized poly(methacrylic acid)-catalyzed displacement of bromide ion from α-bromoacetamide.[23] They observed that, as the degree of ionization of the polyacid increased, the catalytic power per carboxylate group decreased markedly. A similar behavior was noted by Letsinger and Savereide[3] in a study of the solvolysis of 2,4-dinitrophenyl acetate catalyzed by poly-4-vinylpyridine and its monomeric analog, 4-picoline. It was found that while the reaction rate constant for the monomeric reaction increased linearly with increasing fraction of neutral catalyst, the polymeric reaction was depressed and a plot of rate constant *vs.* fraction of neutral pyridine revealed an upward curvature as the fraction of neutral pyridine residues increased. The authors attributed the latter effect to an increase in the nucleophilicity of the pendent pyridine groups as the charge density of the polymer was decreased. More recently, Morawetz has considered this behavior to be caused by an exclusion of the substrate from the polyion as the charge density of the polyion is increased.[2] However, based on results which we have obtained with copolymers containing pendent imidazole and carboxylate groups (see Imidazole–Carboxylate Interaction), it appears that the varying charge density does not significantly alter the reactivity of a catalytically active polyion toward a neutral substrate.

We have also observed anomalous behavior of polymers toward a neutral substrate in the poly-4(5)-vinylimidazole (I) and the poly-5(6)-vinylbenzimidazole (II) catalyzed solvolyses of *p*-nitrophenyl acetate (PNPA) in 28.5% ethanol–water and 30% 1-propanol–water, respectively.[4] In Figure 1 are shown plots of the second-order catalytic rate constants, k_{cat},[4] *vs.* the fraction of neutral imidazole (α_1) for the solvolysis of PNPA catalyzed by imidazole and by poly-4(5)-vinylimidazole in 28.5% ethanol–water. The pH(α_1)–rate profiles reveal that the catalytic rate constants for the imidazole-catalyzed solvolysis of PNPA are linearly dependent upon the fraction of neutral imidazole present, *i.e.*, the protonated imidazole functions do not participate in the solvolytic reaction. The polymeric reaction does not display such linear dependence of α_1. Instead, an upward curvature is obtained which shows that the polymer is a less efficient catalyst than imidazole at α_1 values below 0.8, and more efficient than imidazole at α_1 values greater than 0.8.



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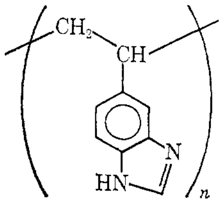

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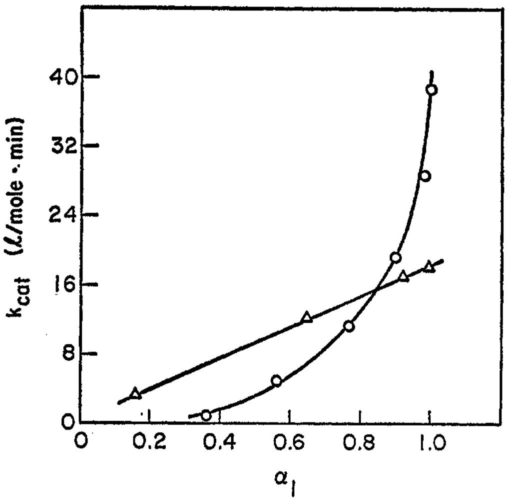
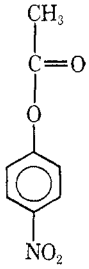
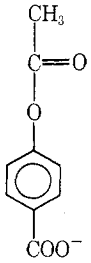


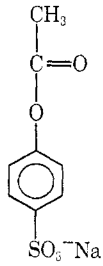
Figure 1. Solvolysis of PNPA catalyzed by poly-4(5)-vinylimidazole (○) and imidazole (△) (28.5% ethanol–water, ionic strength 0.02, 26°).



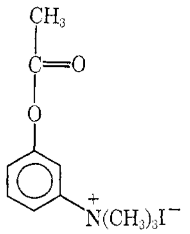
PNPA



NABA



NABS



ANTI

The enhanced activity of poly-4(5)-vinylimidazole at high pH values suggested the involvement of anionic imidazole functions (α_2) in the solvolytic process,[4] since the reaction rate did not appear to be dependent upon the fraction of neutral imidazole functions. If pendent, anionic functions were involved in such solvolytic reactions, it could be expected that a polymer with a lower pK_2 value than that of poly-4(5)-vinylimidazole (estimated to be > 14.5[24]) would be a more efficient catalyst than its monomeric analog, since the high local concentration of such groups on a polymer would increase the effectiveness of the polymeric reaction. Indeed, such a situation was observed in the poly-5(6)-vinylbenzimidazole-catalyzed solvolysis of PNPA where the reaction rate increased dramatically as the pH approached the apparent pK_2 (12.2[7]) of the pendent benzimidazoles. This dramatic enhancement was not noted for the benzimidazole-catalyzed reaction (pK_2 = 12.4[7]).[4]

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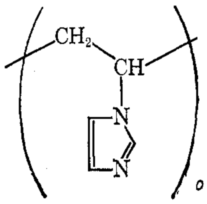
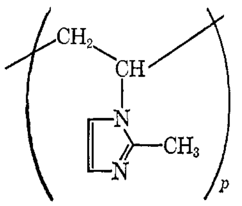
(23) H. Ladenheim and H. Morawetz, *J. Amer. Chem. Soc.*, **81**, 4860 (1959); H. Morawetz, Polytechnic Institute of Brooklyn, private communication, 1969.

(24) H. Walba and R. W. Isensee, *J. Org. Chem.*, **21**, 702 (1956); T. C. Bruice and J. L. Herz, *J. Amer. Chem. Soc.*, **86**, 4109 (1964).

To test the possible involvement of the pendent anionic functions, the solvolyses of PNPA catalyzed by poly-N-vinylimidazole (III) and poly-2-methyl-N-vinylimidazole (IV) were investigated because these polymers have no functional groups which can exist in the anionic form.[4] Although steric factors no doubt play a role in the solvolytic reactions catalyzed by the N-alkylated polymers, particularly for that of poly-2-methyl-N-vinylimidazole, the N-alkylated polymers could be expected to show activities slightly less than that of poly-4(5)-vinylimidazole if anionic pendent groups are not involved in their solvolytic process, *i.e.*, the reaction rate for each system is dependent upon the fraction of neutral functions. Such similar reactivities could be assumed owing to the fact that N-methylimidazole has been reported to be 75% as active as imidazole in the hydrolysis of PNPA.[25,26] However, when the reaction rates of poly-4(5)-vinylimidazole and the N-alkylated polymers are compared at α_1 values of *ca.* 1, it is found that the former system is dramatically more efficient than the latter. Such a phenomenon would appear to support the involvement of anionic residues in the poly-4(5)-vinylimidazole-catalyzed solvolyses of PNPA in 28.5% ethanol–water.



III



IV

The participation of anionic pendent groups has also been suggested by the poly-5(6)-vinylbenzimidazole-catalyzed solvolyses of the negatively charged esters 4-acetoxy-3-nitrobenzoic acid (NABA)[4] and sodium 4-acetoxy-3-nitrobenzenesulfonate (NABS).[7] To facilitate the solubility of the polymer, these reactions were performed in 30% propanol–water. In regard to the solvolysis of NABA, the reactivities of poly-5(6)-vinylbenzimidazole and its monomeric analog, benzimidazole, were nearly identical in the region of $\alpha_1 = 1$, *i.e.*, pH values up to 8. However, at pH 10 the catalytic activity of poly-5(6)-vinylbenzimidazole was *ca.* 50-fold greater than that of benzimidazole. At this pH value the enhanced polymeric reactivity cannot be correlated to an enhancement caused by the presence of cationic groups (see Neutral–Cationic Imidazole Interaction), since their concentration is zero. From a determination of the (apparent) pK_2 of benzimidazole and of the pendent benzimidazole groups in poly-5(6)-vinylbenzimidazole, it was concluded that the monomeric benzimidazole anions were unable to react with NABA or NABS. The noncatalytic behavior of benzimidazole anions with the negatively charged substrates was presumably due to an electrostatic repulsion. Consequently, the enhanced catalytic action of poly-5(6)-vinylbenzimidazole at high pH values was attributed to a bifunctional catalysis involving both neutral and anionic pendent benzimidazole groups.

In a study of the imidazole-catalyzed hydrolysis of *p*-methylphenyl acetate, Bruice and Benkovic[27] have shown that lowerings of enthalpy and entropy of activation were associated with the change in mechanism of nucleophilic imidazole catalysis to general base catalysis which involved two imidazole functions. The existence of multifunctional interactions in the poly-4(5)-vinylimidazole- and poly-5(6)-vinylbenzimidazole-catalyzed solvolysis of PNPA was further supported by a study of the activation parameters of these reactions and those of poly-N-vinylimidazole, imidazole, benzimidazole, and N-methylimidazole.[28] In contrast to the behavior of poly-N-vinylimidazole, solvolytic reactions of PNPA catalyzed by poly-4(5)-vinylimidazole and poly-5(6)-vinylbenzimidazole were found to have a marked decrease in enthalpy of activation relative to those of the corresponding monomeric analogs. A smaller decrease in the entropy factor was noted for the poly-4(5)-vinylimidazole and poly-5(6)-vinylbenzimidazole reactions. These results signified that a different mechanism is operative in reactions catalyzed by poly-4(5)-vinylimidazole and poly-5(6)-vinylbenzimidazole than in reactions catalyzed by their respective monomeric analogs. Since both polymeric and monomeric catalyses are over-all second-order processes, the high local concentration of catalytic groups on the polymers appears to facilitate the terfunctional interaction of two pendent imidazole or benzimidazole groups and the substrate.

Although the study of activation parameters appeared to substantiate the interaction of neutral and anionic imidazole functions for the poly-4(5)-vinylimidazole-catalyzed solvolysis of PNPA in 28.5% ethanol–water, recent evidence has suggested that the previously described data for this polymeric system can be interpreted by the existence of bifunctional neutral–neutral interactions,[29] as is observed for this reaction in 10% methanol–water at intermediate pH values (see Neutral–Neutral Imidazole Interaction).

Neutral–Cationic Imidazole Interaction

The phenomenon of enhanced catalytic action of a partially charged, catalytically active polymer toward an oppositely charged substrate has been reported by several workers.[3-5,7,19,30]

This electrostatic effect is illustrated in Figure 2 which describes the solvolyses of the negatively charged esters NABA and NABS catalyzed by imidazole and by poly-4(5)-vinylimidazole in 28.5% ethanol–water. For the reaction of imidazole with both NABA and

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[25] T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **79**, 1663 (1957).

[26] M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1656 (1957).

[27] T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).

[28] C. G. Overberger, T. St. Pierre, C. Yaroslavsky, and S. Yaroslavsky, *ibid.*, **88**, 1184 (1966).

[29] C. G. Overberger and P. S. Yuen, in preparation.

[30] H. Ladenheim, E. M. Loebl, and H. Morawetz, *J. Amer. Chem. Soc.*, **81**, 20 (1959).

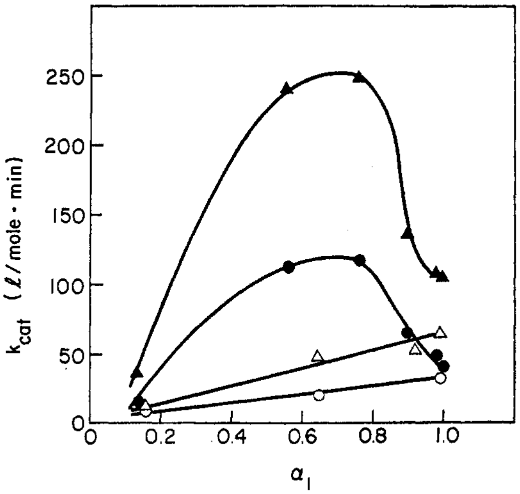


Figure 2. Solvolyses of NABA and NABS catalyzed by poly-4(5)-vinylimidazole (●, ▲) and imidazole (○, △), respectively (28.5% ethanol–water, ionic strength 0.02, 26°).

NABS, the catalytic rate constants are found to be linearly dependent upon the fraction of neutral imidazole present. In contradistinction, the plots of the polymeric reactions are quite different in that bell-shaped rate profiles are obtained with maxima at 75% of the neutral imidazole functions. At this point, the catalytic rate constants for the poly-4(5)-vinylimidazole-catalyzed reactions are each approximately fivefold greater than the values obtained for the monomeric reactions. The shapes of the polymeric reaction plots reveal that these reactions are principally dependent upon two factors,[31] *viz.*, a proper concentration of charged groups in the polyion to facilitate an electrostatic interaction with substrate and a proper concentration of neutral, pendent functions acting as catalytically active nucleophiles. The combination of these factors gives a rate maximum when three-quarters of the imidazole groups are in the neutral form.

Neutral–Neutral Imidazole Interaction

Bifunctional catalysis involving the interactions of two neutral imidazole or benzimidazole pendent groups with substrate has also been indicated in the poly-4(5)-vinylimidazole-catalyzed solvolysis of PNPA (10% methanol–water)[28] and in the poly-5(6)-vinylbenzimidazole-catalyzed solvolysis of NABS (30% propanol–water).[7] Both of these reactions occur near intermediate pH.

In Table I are presented the second-order catalytic rate constants and α_1 values for the solvolysis of PNPA catalyzed by imidazole and by poly-4(5)-vinylimidazole.[28] These reactions were performed in 10% methanol–water in order to increase the concentration of water in the solvent system. It is found that the catalytic rate constants for the solvolysis of PNPA catalyzed by poly-4(5)-vinylimidazole and by imidazole increased [in comparison to the reaction in 28.5% ethanol–water (Figure 1)] for this system, the former reaction to a larger extent. This fact indicates that, in a solvent of higher polarity, hydrophobic interactions between polymer and neutral substrate increase. From a determination of the (apparent) pK_1 values for imidazole and for the imidazole functions in poly-4(5)-vinylimidazole at half-neutralization, these results showed that polymeric imidazole was more catalytically active than imidazole even at pH values where the fraction of imidazole anions (α_2) was between 10^{-7} and 10^{-8}. This enhancement was, therefore, correlated to the interaction of two neutral imidazole functions with substrate.

Table I[a]

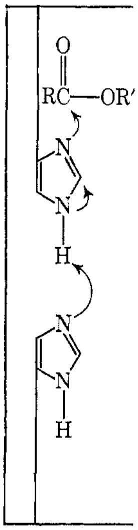
Catalytic Rate Constants for the Solvolysis of PNPA Catalyzed by Poly-4(5)-vinylimidazole and Imidazole

	Poly-4(5)-vinylimidazole		Imidazole	
pH	α_1	k_{cat}	α_1	k_{cat}
6.03	0.35	3.2	0.09	5.5
6.70	0.52	14.1	0.32	13.5
7.12	0.67	28.9	0.57	22.7
7.48	0.78	41.8	0.75	25.5

[a] In 10% methanol–water, ionic strength 0.02. k_{cat} in l./mol min.

Analogous results were obtained in the poly-5(6)-vinylbenzimidazole-catalyzed solvolysis of NABS where at intermediate pH the nucleophilic attack of neutral benzimidazole on substrate was catalyzed by another neutral benzimidazole function acting as a general base.

Three mechanisms have been presented which describe the interactions of two neutral pendent imidazole groups with a substrate (V–VII).[28] Mechanisms V and VI involve a general base catalysis of a nucleophilic imidazole attack, while mechanism VII entails a general acid catalyzed nucleophilic imidazole reaction.



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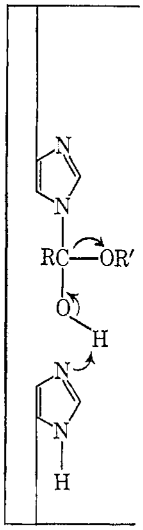

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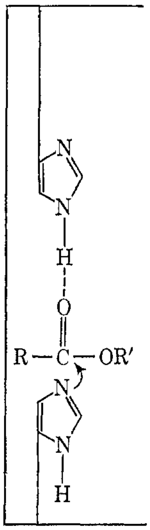

VII

The reduced action of poly-4(5)-vinylimidazole (in comparison to imidazole) in the solvolysis of PNPA at low α_1 values (Figure 1, Table I) can now be better understood. Since we have not observed that a polyion containing catalytically active groups can exclude a

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(31) See page 420 in ref 2.

neutral ester from its environment (see Imidazole–Carboxylate Interaction), this reduced activity can be attributed to at least two factors. First, an increasing protonation of imidazole residues can lead to a decrease in hydrophobic interactions of the neutral ester with the nonpolar regions of the polyion. This effect would tend to minimize the concentration of ester in an environment of catalytically active functions. Second, a lack of bifunctional (neutral–neutral) imidazole catalysis can occur because the polyion would be in a more extended conformation as the degree of protonation increases. This would render difficult the interactions of two imidazole functions, since the proportion of imidazole functions in juxtaposition would be less. The existence of general acid catalysis (VII) for the polyion with PNPA can be excluded because if protonation or polarization of the carbonyl oxygen of the ester is necessary for catalysis, an enhanced action of the polymer could be expected at low pH values. Obviously, this does not occur.

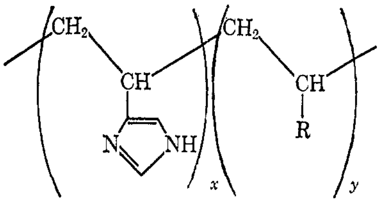
The total polymeric rate constant for the solvolysis of PNPA can, therefore, be represented by the following terms

$$k_{cat} = k_1\alpha_1 + k_2\alpha_1^2 + k_3\alpha_2 + k_4\alpha_1\alpha_2$$

where α_1 and α_2 are the fractions of imidazole residues in the neutral and the anionic form, respectively. The first two terms are operative at intermediate pH, and all four terms can contribute to the reaction rate at higher pH values.

Imidazole–Hydroxyl Interaction

The active sites of hydrolytic enzymes are normally comprised of several catalytic species. In order to ascertain if cooperative interactions between pendent imidazole and hydroxyl functions could occur in synthetic polymers, esterolytic reactions catalyzed by copolymers of 4(5)-vinylimidazole with vinyl alcohol (VIII, R = OH) and with *p*-vinylphenol (VIII, R = C_6H_4OH) were investigated.[8,32] A cooperative interaction of imidazole and hydroxyl groups underlies most of the mechanisms of α-chymotrypsin-catalyzed hydrolyses.[33] The phenol group of tyrosine has also been implicated.[34]



VIII

On the basis of potentiometrically determined α_1 values for two copolymers of 4(5)-vinylimidazole and vinyl alcohol (mole ratios 1:0.31 and 1:0.65 for imidazole and alcohol contents),[35] it found that these copolymers are slightly more active than poly-4(5)-vinylimidazole in esterolytic reactions. Furthermore, the shapes of the pH(α_1)–rate profiles for the imidazole–alcohol copolymers resemble those of the homopolymer for neutral and negatively charged esters.

Results obtained with a 1:1.95 copolymer of 4(5)-vinylimidazole and *p*-vinylphenol were, on the other hand, quite different from those of poly-4(5)-vinylimidazole. In Table II are listed the pH-dependent catalytic rate constants for the solvolysis of PNPA catalyzed by the 1:1.95 imidazole–phenol copolymer, by poly-4(5)-vinylimidazole, and by imidazole. The data were obtained in 80% methanol–water because of the limited solubility of the imidazole–phenol copolymer in alcoholic solvents containing a higher water concentration. It is seen that the reactivities of both poly-4(5)-vinylimidazole and imidazole are nearly identical in this solvent system for similar α_1 values. Furthermore, on comparison of these data with those obtained in 10% methanol–water (Table I), the reactivities of poly-4(5)-vinylimidazole and imidazole toward PNPA are strongly depressed in the solvent containing the higher alcohol content. In fact, in 80% methanol–water the reactivities of poly-4(5)-vinylimidazole and imidazole are nearly identical. This phenomenon is currently being investigated by considerations of hydrophobic interactions, the dielectric constant of the medium, and the conformation of the polymer. The conformation of the polymer would be expected to have a significant effect on multifunctional imidazole interactions.

Table II[a]

Catalytic Rate Constants for the Solvolysis of PNPA Catalyzed by 1:1.95 Imidazole–Phenol Copolymer, Poly-4(5)-vinylimidazole, and Imidazole

	Imidazole-phenol copolymer		Poly-4(5)-vinylimidazole		Imidazole	
pH	α_1	k_{cat}	α_1	k_{cat}	α_1	k_{cat}
7.38	0.87	1.2	0.87	0.84	0.91	1.1
8.22	0.97	2.0	0.92	1.20	0.95	1.0
9.12	0.99	11.4	0.97	1.26	0.98	1.1

[a] In 80% methanol-water, ionic strength 0.02. k_{cat} in l./mol min.

The second noteworthy factor in Table II is that the imidazole–phenol copolymer greatly enhanced the solvolytic rate of PNPA (relative to poly-4(5)-vinylimidazole and imidazole) as the pH of the solution

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(32) C. G. Overberger, J. C. Salamone, and S. Yaroslavsky, *Pure Appl. Chem.*, **15**, 453 (1967).

(33) M. L. Bender and F. J. Kézdy, *J. Amer. Chem. Soc.*, **86**, 3704 (1964).

(34) M. L. Bender, G. E. Clement, F. J. Kézdy, and B. Zerner, *ibid.*, **85**, 358 (1963).

(35) The apparent pK_1 values for the 1:0.31 and 1:0.65 imidazole–alcohol copolymers had been determined to be 5.45 and 5.55, respectively, by spectrophotometric titration at 250 mμ.[32] This determination has been found to be incorrect.[36] By differential potentiometric titration of the 1:0.31 and 1:0.65 imidazole–alcohol copolymer in 28.5% ethanol–water at an ionic strength of 0.02 the respective apparent pK_1 values are determined to be 5.41 and 5.39. Under similar conditions the apparent pK_1 of the imidazole groups in poly-4(5)-vinylimidazole is 5.78.[36]

(36) C. G. Overberger and H. Maki, in preparation.

was increased. It was also observed that neither phenol, nor poly-*p*-vinylphenol, nor a 1:0.48 copolymer of 4(5)-vinylimidazole and *p*-methoxystyrene (VIII, R = $C_6H_4OCH_3$) had any significant effect on the solvolysis of PNPA. The lack of activity of the imidazole–*p*-methoxystyrene copolymer is particularly significant, since this is a polymeric analog of the imidazole–phenol copolymer but possesses no phenoxide sites.

Consequently, the data in Table II strongly indicate that a contribution of bifunctional imidazole–phenolate catalysis exists in the pH region where the pendent phenol groups can dissociate.[37]

This cooperative interaction was further substantiated by the behavior of the imidazole–phenol copolymer toward the negatively charged esters NABA and NABS.[8] In Figure 3 the catalytic rate constants for the solvolysis of NABS in 80% methanol–water, catalyzed by the imidazole–phenol copolymer and by poly-4(5)-vinylimidazole, are plotted as a function of the neutral imidazole content. The catalytic rate constant for the imidazole-catalyzed reaction at $\alpha_1 = 1$ is approximately 10 l./mol min. Although both polymers display the characteristic electrostatic effect at intermediate pH values, the imidazole–phenol copolymer greatly enhances the reaction rate as the pH is increased, *i.e.*, in the region where the fraction of anionic phenol is increased. At α_1 values approaching 1, poly-4(5)-vinylimidazole is not a particularly effective catalyst in this solvent system. Since neither phenol nor the other polymeric catalysts have any significant catalytic effect toward NABS, the enhanced catalytic action of the imidazole–phenol copolymer can be correlated to the existence of a terfunctional interaction between neutral imidazole, anionic phenol, and substrate.

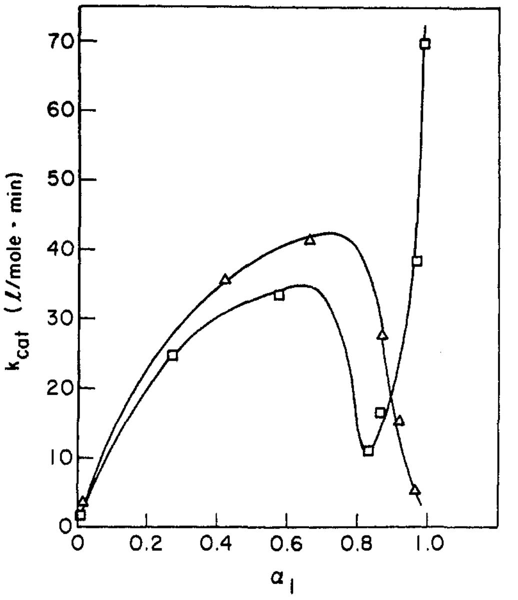

Figure 3. Solvolysis of NABS catalyzed by 1:1.95 imidazole–phenol copolymer (□) and poly-4(5)-vinylimidazole (△) (80% methanol–water, ionic strength 0.02, 26°).

Perhaps the most dramatic indication of the bifunctional imidazole–phenolate participation was noted in the solvolysis of the positively charged substrate 3-acetoxy-N-trimethylanilinium iodide (ANTI).[8,32] At high pH, neither phenol nor any of the polymeric analogs had any detectable effect on the solvolytic rate of ANTI. Although monomeric imidazole was found to have a catalytic rate constant of 2.3 l./mol min at $\alpha_1 = 1$, the imidazole–phenol copolymer had a rate constant of 151 l./mol min where all the neutral imidazole functions were in the neutral form and 10% of the phenol functions were in the anionic form. This enhanced reaction was considered to be caused by an electrostatic attraction of ANTI to the anionic sites of the polymer chain, thereby facilitating a solvolytic attack from either imidazole or anionic phenol, or from their combined action. From the reaction of ANTI with copolymers of 4(5)-vinylimidazole and vinylsulfonic acid (see Imidazole–Carboxylate Interaction), it can be concluded that, at the low concentrations of phenolate groups present, the possibility of monofunctional imidazole catalysis would not lead to a high rate of reaction. The lack of reactivity of partially ionized poly-*p*-vinylphenol excludes the possibility of phenolate ion catalysis when the substrate is attracted to the polymer. Bifunctional catalysis involving neutral imidazole and anionic phenol with a substrate attracted to the polymer chain by electrostatic forces, or a terfunctional reaction in which the frequency factor is enhanced due to the opposite charges of the reactants,[38] must account for the high rate.

We have attempted to ascertain if cooperative interactions between imidazole and phenol groups can occur in a dimeric model compound, 4(5)-[9(*p*-hydroxyphenyl)nonyl]imidazole. In 80% methanol–water this dimeric model revealed no enhanced catalytic effects toward either PNPA, NABS, or ANTI. This indicates that cooperative, catalytic interactions can occur to a significant extent only when a high local concentration of catalytically active groups is present, a circumstance which occurs on a polymer chain.

Although no cooperative effects were realized with this dimeric compound in 80% methanol–water, we have found strong evidence for hydrophobic interactions between catalyst and a neutral substrate. With *p*-nitrophenyl acetate, the imidazole–phenol dimer is approximately twice as reactive as imidazole. However, employing the ester *p*-nitrophenyl palmitate, a substrate with a long paraffinic chain, the imidazole–phenol dimer is approximately five times more reactive than imidazole. This effect is not caused by bifunctional imidazole–phenol catalysis because similar enhanced rates occur when the terminal phenol group is methylated.

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(37) A spectrophotometric titration of the phenol groups in the 1:1.95 imidazole–phenol copolymer showed that 10% of these groups were dissociated at pH 9.[8]

(38) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley & Sons, Inc., New York, N. Y., 1961, p 145.

Imidazole–Carboxylate Interaction

A cooperative electrostatic effect involving pendent imidazole and carboxylate groups was observed in the solvolysis of ANTI catalyzed by a polymer of 4(5)-vinylimidazole and acrylic acid (VIII, R = COOH).[19] Although this copolymer was a less effective catalyst than imidazole in solvolyzing PNPA and NABA, marked selectivity toward ANTI was realized at high pH values. The selectivity of the copolymer was rationalized by the electrostatic attraction of the positively charged ester to the anionic carboxylate groups on the polymer which accumulate the substrate in a high local concentration of imidazole nucleophiles. This type of cooperative effect is believed to be in part similar to that of the acetylcholinesterase-catalyzed hydrolysis of its positively charged substrate, acetylcholine.[39]

An illustration of the selectivity of polymers containing pendent imidazole and carboxyl groups toward ANTI is given in Figure 4. The catalytic rate constants are given as a function of the neutral imidazole content for an alternating copolymer of 4(5)-vinylimidazole and maleic acid, a copolymer of 4(5)-vinylimidazole and acrylic acid (46.3 mol % imidazole), a dimeric imidazole–carboxylic acid model, γ-4(5)-imidazoylbutyric acid, and imidazole. It is evident that both copolymers markedly enhance the solvolytic rate of ANTI, the former copolymer, containing more anionic sites, doing so to a greater extent.[36] These copolymers are found to be less reactive than imidazole in catalyzing the solvolyses of PNPA and NABA particularly for the negatively charged substrate. With regard to the neutral substrate, the imidazole–maleic acid copolymer and a series of imidazole–acrylic acid copolymers display almost identical reactivities for analogous contents of neutral imidazole. This behavior reveals that a neutral ester is not excluded from a catalytically active polyion as the negative charge density of the polyion is increased.

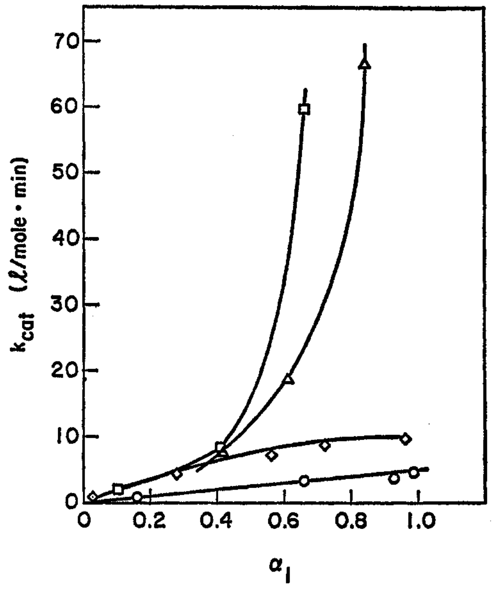

Figure 4. Solvolysis of ANTI catalyzed by an alternating copolymer of 4(5)-vinylimidazole and maleic acid (□), a copolymer of 4(5)-vinylimidazole and acrylic acid (46.3 mol % imidazole) (△), γ-4(5)-imidazoylbutyric acid (◇), and imidazole (○) (28.5% ethanol–water, ionic strength 0.02, 26°).

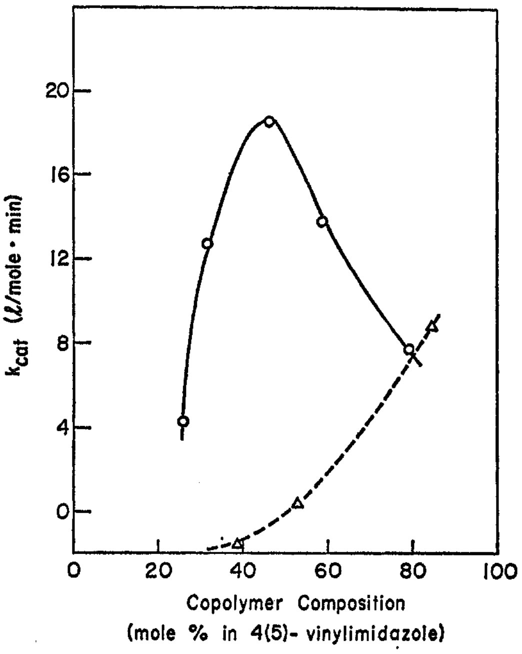

Figure 5. Solvolysis of ANTI catalyzed by copolymers of 4(5)-vinylimidazole with acrylic acid (○) and with vinylsulfonic acid (△) (pH 9.0, 28.5% ethanol–water, ionic strength 0.02, 26°).

In order to study in more detail the characteristics of the ANTI selective solvolysis, the effects of composition (mol per cent imidazole) and sequence distribution on the solvolytic rate of ANTI catalyzed by copolymers of 4(5)-vinylimidazole with acrylic acid and with vinylsulfonic acid (VIII, R = SO_3H) were investigated. It could be anticipated that if the carboxylate groups in the imidazole–carboxylic acid copolymers serve only to electrostatically attract the cationic ester to the polyion, then a copolymer of 4(5)-vinylimidazole and vinylsulfonic acid should reveal a similar catalytic activity. This behavior is not observed (Figure 5). At pH 9 the solvolytic rate of ANTI catalyzed by the imidazole–carboxylic acid copolymers reaches a maximum at approximately 47 mol % imidazole and decreases in the region of high and low imidazole contents. Apparently at a high imidazole content there are insufficient anionic sites to accumulate ANTI around the polymer. Conversely, at a low imidazole content the polymer begins to behave principally as a polyion. Through such an effect, the polyanion could accumulate the positively charged ester in its vicinity and repel the catalyzing hydroxide ions.[11,15] This would then lead to an inhibition of the solvolytic rate because of the decrease in collision frequency of the ionic reagents. Indeed, such an inhibitory effect occurs for the solvolysis of ANTI in the presence of anionic polyacrylic acid.

Inspection of the data for the 4(5)-vinylimidazole–

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[39] For a general review see N. Englehard, K. Prchal, and N. Nenner, *Angew. Chem. Intern. Ed. Engl.*, **6**, 615 (1967).

vinylsulfonic acid copolymer catalyzed solvolysis of ANTI reveals that a bell-shaped curve is absent. Instead, the reaction is apparently inhibited at imidazole contents less than 50 mol %. This suggests that the imidazole–sulfonic acid copolymer is behaving simply as a polyanion toward ANTI.

Therefore, it seems probable that, in the imidazole–acrylic acid copolymer catalyzed solvolysis of ANTI, some bifunctional catalysis between the neutral imidazole groups and carboxylate groups does exist. Besides functioning as binding sites for ANTI, the carboxylate groups can be involved in the solvolytic process in much the same fashion as the previously discussed pendent phenoxide groups.

Polymeric Triazole Catalysis

Polymeric catalysts containing pendent groups which are related in structure to imidazole are of interest for esterolytic action because they could be expected to display effects different from those previously described. Of particular interest in the five-membered nitrogen-containing heterocycles is 1,2,4-triazole. The pK_1 and pK_2 values of this compound are 4.4 units[40] less than those of the respective values of imidazole.[4,41] Consequently, it was thought that, at pH values in the region of pK_2, a strong catalytic effect by anionic triazole functions could occur in esterolytic reactions.

Preliminary studies of the solvolytic rates of PNPA, NABA, and NABS catalyzed by 1,2,4-triazole and poly-3-vinyl-1,2,4-triazole have been conducted in 28.5% ethanol–water.[29]

The pH–rate profiles for the solvolyses of PNPA, NABA, and NABS catalyzed by polymeric and monomeric triazole are presented in Figure 6. All these processes are over-all second-order reactions. It is found that 1,2,4-triazole is a catalyst superior to the polymer in the pH region investigated (6–9). Furthermore, there is a marked enhancement of the monomeric triazole catalyzed reaction with increasing pH, indicative of the participation of anionic triazole groups.

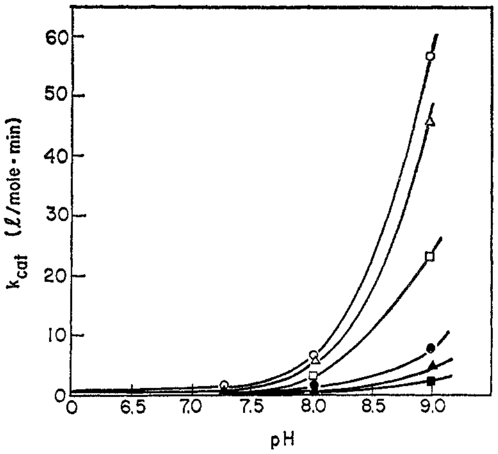

Figure 6. pH–rate profiles for the solvolyses of PNPA (○, ●), NABA (□, ■), and NABS (△, ▲) catalyzed by 1,2,4-triazole and poly-3-vinyl-1,2,4-triazole, respectively (28.5% ethanol–water, ionic strength 0.02, 26°).

Differential potentiometric titrations of 1,2,4-triazole and poly-3-vinyl-1,2,4-triazole in 28.5% ethanol–water gave pK_2 values of 10.1 and 11.0, respectively. The pK_1 for 1,2,4-triazole was determined to be 2.3. For the polymer, the apparent pK_1 appears to be lower than its monomeric analog. Therefore, at intermediate pH most of the triazole functions in the polymer and monomeric analog are in the neutral form. In this region both polymeric and monomeric catalyses appear to be equally inefficient. This fact signifies that the nucleophilic reaction of neutral triazole and substrate does not contribute significantly to the reaction rate. Inspection of the data at pH 9 indicates that the reaction rate is enhanced because of anionic triazole. Indeed, the participation of anionic functions in the monomeric and polymeric reactions is clearly revealed when the catalytic rate constants are plotted as a function of the fraction of anionic triazole. By this treatment the rate of reaction of (anionic) poly-3-vinyl-1,2,4-triazole is found to be as efficient as (anionic) 1,2,4-triazole in catalyzing the solvolysis of PNPA. However, the reaction of the polymer with the negatively charged esters is found to be considerably less efficient than that of its monomeric analog. This may indicate that the anionic sites which exist on the polymer can repel the anionic substrates. If this is true, it could be expected that poly-3-vinyl-1,2,4-triazole may show selective catalysis toward a positively charged substrate at high pH values.

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(40) E. Lieber, S. H. Patinkin, and H. H. Tao, *J. Amer. Chem. Soc.*, **73**, 1792 (1951).

(41) K. T. Potts, *Chem. Rev.*, **61**, 87 (1961).