

The Activation Parameters for Polymeric Imidazole Catalysis. The Efficiency of Multifunctional Catalysis on a Polymer Chain¹

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Abstract: The activation parameters for the catalyzed solvolyses of *p*-nitrophenyl acetate (PNPA) by poly-4(5)-vinylimidazole, poly-5(6)-vinylbenzimidazole, and poly-*N*-vinylimidazole were compared to those of imidazole, benzimidazole, and *N*-methylimidazole, respectively. In addition, the activation parameters for the poly-5(6)-vinylbenzimidazole- and benzimidazole-catalyzed solvolyses of 4-acetoxy-3-nitrobenzoic acid (NABA) also were determined. In contrast to the behavior of the *N*-alkylated polymer, reactions 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 monomers. A smaller decrease was noted for the entropy factor. As a consequence of this combination, the imine-free polymers show an over-all higher catalytic rate than the monomers. These results indicate that a different mechanism is operative in polymeric vs. monomeric catalysis. While both catalytic processes are over-all second-order reactions, polymeric catalysis most likely involves the terfunctional interaction of two imidazole or benzimidazole functions and the substrate. The high local concentration of pendent imidazole or benzimidazole groups on the polymer chain facilitates their action as multifunctional catalysts.

Catalysis by α -chymotrypsin involves in part enzyme complexation with substrate followed by the "intramolecular" solvolytic interaction between several component groups of the active site. The enzymatic activity of α -chymotrypsin has been attributed to the cooperative action of imidazole and serine,² imidazole, serine, and aspartic acid,³ and two imidazole functions and one hydroxyl moiety.⁴

The multicentered attack by the groups of the active site on the substrate is believed to lead to a lowering of the activation energy for the solvolytic reaction.⁵⁻⁷ In addition, enzyme-substrate complex formation may lead to a favorable entropy of activation which further increases the efficiency of enzymatic catalysis.⁸

In a study of imidazole-catalyzed hydrolyses of substituted phenyl acetates, Bruice and Benkovic have recently shown a lowering of ΔH^* and $T\Delta S^*$ accompanying the conversion of a second-order displacement reaction to a third-order catalytic process.⁶ The rate constants for the second- and third-order reactions were similar, that is, the unfavorable entropy factor for the third-order reaction was compensated for by a substantial decrease in activation energy for this order. A loss of *ca.* 4-6 kcal was associated per order in the $T\Delta S^*$ term.⁶

Reactions of polymeric or dimeric imidazoles may involve two imidazole functions in the catalytic step in an over-all second-order reaction.^{9,10} Such a case may

retain the favorable activation energy factor of the third-order reaction without a substantial entropy loss, the entropy approaching that of the second-order reaction.¹⁰ This should result in an improved terfunctional catalytic efficiency for the polymer relative to the third-order or second-order reaction of the monomer.

In several instances it has been verified that by a transfer of a second-order reaction into an intramolecular first-order reaction, the activation energy of the second-order reaction is retained while there is a positive gain in entropy (reflecting a smaller loss in translational entropy) which may boost the rate of the reaction by several orders of magnitude.^{8,11-13}

In attempting to further substantiate the multifunctional catalysis displayed by polymeric imidazoles and benzimidazoles,⁹ we have determined the activation parameters for poly-4(5)-vinylimidazole-, poly-5(6)-vinylbenzimidazole-, and poly-*N*-vinylimidazole-catalyzed solvolyses and compared these values to those of the respective monomers. Particular attention was given to the activation parameters obtained from the poly-*N*-vinylimidazole-catalyzed solvolysis of PNPA since it was believed that these imidazole groups could not participate in a multifunctional catalysis in the pH region investigated.

Experimental Section

The syntheses of the polymeric catalysts, as well as the preparation of the substrates, *p*-nitrophenyl acetate and 4-acetoxy-3-nitrobenzoic acid, were previously reported.^{9,14} For poly-4(5)-vinylimidazole, poly-*N*-vinylimidazole, and *N*-methylimidazole the kinetics of solvolysis were determined as before in 28.5% ethanol-water with 0.02 *M* tris(hydroxymethyl)aminomethane buffers with an

(1) This paper comprises a portion of the dissertations submitted by T. St. Pierre and by C. Yaroslavsky in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(2) For a review see J. A. Cohen, R. A. Oosterbaan, H. S. Jansz, and F. Berenda, *J. Cellular Comp. Physiol.*, **54**, 231 (1959); E. A. Barnard and W. D. Stein, *Advan. Enzymol.*, **20**, 51 (1958); M. L. Bender, *Chem. Rev.*, **60**, 105 (1960).

(3) J. E. Stewart, H. S. Lee, and J. E. Dodson, *J. Am. Chem. Soc.*, **85**, 1537 (1963).

(4) M. L. Bender and F. J. Kezdy, *ibid.*, **86**, 3704 (1964); H. Neurath, *Sci. Am.*, **211** (6), 68 (1964).

(5) M. L. Bender, F. J. Kezdy, and C. R. Gunter, *J. Am. Chem. Soc.*, **86**, 3714 (1964).

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

(7) Cf. C. Niemann, *Science*, **143**, 1287 (1964).

(8) T. C. Bruice, *Brookhaven Symp. Biol.*, **15**, 52 (1962).

(9) C. G. Overberger, T. St. Pierre, N. Vorchheimer, and S. Yaroslavsky, *J. Am. Chem. Soc.*, **85**, 3515 (1963); C. G. Overberger, T. St. Pierre, N. Vorchheimer, J. Lee, and S. Yaroslavsky, *ibid.*, **87**, 296 (1965).

(10) T. C. Bruice and R. G. Willis, *ibid.*, **87**, 531 (1965).

(11) P. E. Zimmerman, E. W. Westhead, and H. Morawetz, *Biochim. Biophys. Acta*, **25**, 376 (1957).

(12) M. L. Bender and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5388 (1958).

(13) T. C. Bruice and S. J. Benkovic, *ibid.*, **85**, 1 (1963).

(14) C. G. Overberger and N. Vorchheimer, *ibid.*, **85**, 95 (1963).

ionic strength adjusted to 0.02. For poly-5(6)-vinylbenzimidazole and benzimidazole the solvent was 30% propanol-water. Spectrophotometric measurements were made with a Beckman Model DU spectrophotometer having internal thermoregulated spacers. Potentiometric titrations were done in a double-walled thermoregulated beaker under an inert atmosphere using a Beckman expanded scale pH meter.

The catalytic rate constants for the poly-4(5)-vinylimidazole-catalyzed solvolysis of *p*-nitrophenyl acetate at pH 8 and at any temperature studied were corrected for the amount of neutral imidazole present by measuring the ultraviolet absorption of the polymer at 215 μ . The observed and corrected rate constants for 100% neutral imidazole concentrations are summarized in Table I.

Table I. Rate Constants for the Catalyzed Solvolysis of *p*-Nitrophenyl Acetate by Poly-4(5)-vinylimidazole

Temp, °C	$k_{\text{obsd}} \times 10^3$ min ⁻¹	α_{IM}	Cor $k_{\text{obsd}} \times 10^3$ min ⁻¹	k_{cat} , l./mol min
26	8.2	0.844	9.7	24.3
31	10.4	0.867	12.0	30.0
36	12.0	0.889	13.5	33.9
41	13.1	0.946	13.9	34.8
46	14.6	0.943	15.5	38.8

The pK_a of poly-N-vinylimidazole (4.4⁹) is much below the pH studied. Therefore, at pH 8 the ionization of the polymer is insensitive to pK_a variations with temperature. In the case of N-methylimidazole, the pK_a changes with temperature were determined potentiometrically and are reported in Table II. The observed catalytic rate constants for the solvolysis of *p*-nitrophenyl acetate by poly-N-vinylimidazole and the corrected constants for N-methylimidazole appear in Table III.

Table II. Variations of pK_a of N-Methylimidazole with Temperature in 28.5% EtOH ($\mu = 0.02$)

Temp, °C	pK_a
26	6.92
31	6.89
34	6.85
36	6.83
38	6.81
41	6.79
46	6.72

Table III. Rate Constants for the Catalyzed Solvolysis of *p*-Nitrophenyl Acetate by Poly-N-vinylimidazole and N-Methylimidazole

Temp, °C	k_{cat} , l./mole min	
	Poly-N-vinylimidazole	N-Methylimidazole
26	2.69	8.2
31	3.28	11.3
35	...	14.2
36	4.29	15.1
38	5.08	17.3
40	...	17.2
41	...	20.2
44	...	21.6
47	7.50	23.2

Poly-5(6)-vinylbenzimidazole also has a very low pK_1 (3.5⁹), and at pH 8.4 variations with temperature do not materially change the state of ionization of the polymer. A similar situation exists for monomeric benzimidazole ($pK_1 = 5.4$ ⁹). Because of the low solubility of poly-5(6)-vinylbenzimidazole at high pH values, the changes of its pK_2 with temperature could not be determined with

sufficient accuracy. Therefore, no corrections were made for the variations of benzimidazole anion concentration with temperature (see the Discussion). The data for the poly-5(6)-vinylbenzimidazole- and benzimidazole-catalyzed solvolyses of *p*-nitrophenyl acetate at pH 8.4 are given in Table IV, and for the negatively charged substrate, 4-acetoxy-3-nitrobenzoic acid, at pH 9.0 in Table V.

Table IV. Rate Constants for the Catalyzed Solvolysis of *p*-Nitrophenyl Acetate by Poly-5(6)-vinylbenzimidazole and Benzimidazole

Temp, °C	k_{cat} , l./mole min	
	Poly-5(6)-vinylbenzimidazole	Benzimidazole
16	0.92	0.14
21	1.03	0.18
26	1.17	0.31
31	1.37	0.22
36	1.89	0.41
41	1.87	...
46	2.35	0.65

Table V. Rate Constants for the Catalyzed Solvolysis of 4-Acetoxy-3-nitrobenzoic Acid by Poly-5(6)-vinylbenzimidazole and Benzimidazole

Temp, °C	k_{cat} , l./mole min	
	Poly-5(6)-vinylbenzimidazole	Benzimidazole
16	12.1	1.16
26	15.4	1.54
36	19.7	3.37
46	31.8	3.53

The activation parameters for the solvolytic reactions were calculated using the following equations: (1) the activation energy from the slope of a plot of $\log k_{\text{cat}}$ vs. $1/T$ as determined by the least-squares method (see the Discussion); (2) the enthalpy of activation from $\Delta H^* = \Delta E^* - RT$; (3) the free energy of activation from $\Delta F^* = 2.303RT \log (kT/hk_{\text{cat}})$; and (4) the entropy of activation from $\Delta S^* = (\Delta H^* - \Delta F^*)/T$.

Results and Discussion

The slope of the plot of $\log k_{\text{cat}}$ vs. $1/T$ may show a deviation from linearity if two competing reactions having different activation energies are involved in the catalysis.¹⁵ Polymeric imidazole catalysis could involve both mono- and difunctional imidazole interactions contributing to the solvolysis of substrate. Since difunctional imidazole interactions were not expected to occur with either poly-N-vinylimidazole or N-methylimidazole at pH 8,¹⁶ the slope of the plot of $\log k_{\text{cat}}$ vs. $1/T$ should be linear, and treatment of the data by the least-squares method can be considered correct (Figure 1). However, for poly-4(5)-vinylimidazole- and poly-5(6)-vinylbenzimidazole-catalyzed reactions, difunctional imidazole interactions have been indicated, and a least-squares treatment of these data may constitute only a general representation of the activation energies. The least-squares method also was utilized because of the limited accuracy obtainable in very dilute polymer solutions. The activation parameters obtained by this method should reveal the difference between polymeric and monomeric catalysis.

(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, p 25.

(16) C. G. Overberger, J. Lee, T. St. Pierre, and S. Yaroslavsky, in preparation.

Table VI.^a Activation Parameters for the Solvolysis of *p*-Nitrophenyl Acetate Catalyzed by Poly-N-vinylimidazole and N-Methylimidazole

Catalyst	ΔE^*	ΔH^*	ΔF^*	$T\Delta S^*$	ΔS^*	$\Delta\Delta H^*$	$\Delta T\Delta S^*$
Poly-N-vinylimidazole	9.6	9.0	19.4	-10.4	-34.8	-0.4	-1.1
N-Methylimidazole	10.0	9.4	18.7	-9.3	-31.1		

^a Studied at pH 8. All values are in kcal per mole except ΔS^* (eu).

Table VII.^a Activation Parameters for the Solvolysis of *p*-Nitrophenyl Acetate Catalyzed by Poly-4(5)-vinylimidazole and Imidazole

Catalyst	ΔE^*	ΔH^*	ΔF^*	$T\Delta S^*$	ΔS^*	$\Delta\Delta H^*$	$\Delta T\Delta S^*$
Poly-4(5)-vinylimidazole	4.3 ^b	3.7	17.3	-13.6	-45.5	-3.3	-2.9
Imidazole ^c	7.6	7.0	17.7	-10.7	-35.8		

^a Studied at pH 8. All values are in kcal per mole except ΔS^* (eu). ^b A similar result for ΔE^* was observed at pH 7.2. ^c Studied by Bruice and Benkovic (ref 6).

The activation parameters for the solvolysis of *p*-nitrophenyl acetate catalyzed by poly-N-vinylimidazole and N-methylimidazole are compared in Table VI. A small difference in the enthalpy of activation for the polymeric reaction relative to the monomeric reaction is noted. This may indicate that there is no difference in the solvolysis mechanism when the N-alkylated units are either in the monomeric or polymeric form. The larger reduction in the $T\Delta S^*$ term for the polymeric reaction may be rationalized by the presence of the bulky chain involved in the solvolysis.¹⁷

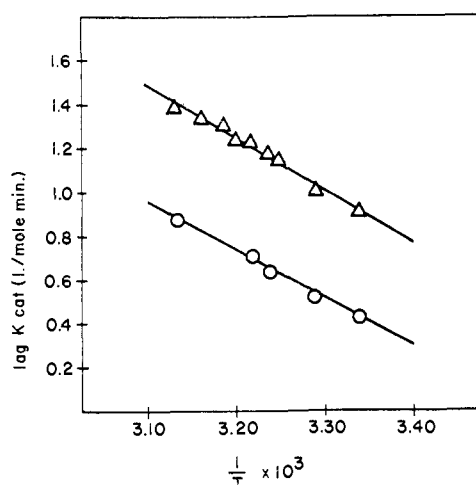


Figure 1. Plots of $\log k_{cat}$ vs. $1/T$ for the reactions of *p*-nitrophenyl acetate with poly-N-vinylimidazole (O) and N-methylimidazole (Δ).

In Table VII are listed the activation parameters for the solvolysis of *p*-nitrophenyl acetate catalyzed by poly-4(5)-vinylimidazole. These values are compared to those obtained by Bruice and Benkovic⁶ for imidazole. A strong reduction in the activation energy for the polymeric reaction relative to the monomeric reaction is seen (3.3 kcal), and a slightly smaller reduction in the entropy of activation for the polymer.

We have previously shown poly-4(5)-vinylimidazole and poly-5(6)-vinylbenzimidazole to be better catalysts than imidazole and benzimidazole, respectively, in the solvolysis of *p*-nitrophenyl acetate at high pH values.¹⁹ This was not observed with poly-N-vinylimidazole and

(17) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

N-methylimidazole. The enhanced catalytic efficiency of poly-4(5)-vinylimidazole and poly-5(6)-vinylbenzimidazole was believed to result from the terfunctional interaction between substrate and two imidazole or benzimidazole groups, one in the neutral form and the other in the anionic form in an over-all second-order reaction. The possibility of a similar interaction involving two neutral catalytic groups was mentioned and now appears to be realized in this investigation.

The catalytic rate constants obtained for the solvolysis of PNPA by poly-4(5)-vinylimidazole at pH 8 mainly reflect the contribution of the neutral imidazole species since the fraction of imidazole anions is less than 10^{-6} . From the pH-rate profile, the contribution of anionic species to the catalytic rate at pH 8 is estimated at less than 1 l./mole min. The large reduction in the activation energy found for the polymer-catalyzed reaction indicates a solvolytic mechanism different from that of monomeric imidazole. Therefore, in accordance with the findings of Bruice and Benkovic,⁶ catalysis by poly-4(5)-vinylimidazole at pH 8 most likely involves the terfunctional interactions of two neutral imidazoles and substrate in an over-all second-order reaction. Explicitly, this can be described as the nucleophilic attack on substrate by one imidazole unit being catalyzed by a neutral imidazole as a general base. The total polymeric rate constant is therefore a composite of the following terms

$$k_{cat} = k'_{neutral}\alpha_1 + k''_{neutral}\alpha_1^2 + k'_{anionic}\alpha_2 + k''_{anionic}\alpha_1\alpha_2 \quad (1)$$

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

Table VIII. Catalytic Rate Constants for Imidazole and Poly-4(5)-vinylimidazole with *p*-Nitrophenyl Acetate in 10% Methanolic Solutions

pH	k_{cat} , l./mole min.	
	Poly-4(5)-vinylimidazole	Imidazole
6.03	3.2	5.5
6.70	14.1	13.5
7.12	28.9	22.7
7.48	41.8	25.5

Table IX.^a Activation Parameters for the Solvolysis of *p*-Nitrophenyl Acetate Catalyzed by Poly-5(6)-vinylbenzimidazole and Benzimidazole

Catalyst	ΔE^*	ΔH^*	ΔF^*	$T\Delta S^*$	ΔS^*	$\Delta\Delta H^*$	$\Delta T\Delta S^*$
Poly-5(6)-vinylbenzimidazole	6.5	5.9	19.9	-14.0	-46.8	-2.8	-1.8
Benzimidazole	9.3	8.7	20.9	-12.2	-40.8		

^a Studied at pH 8.4. All values are in kcal per mole except ΔS^* (eu).

Further support for the interaction of two neutral imidazoles is the enhanced efficiency of poly-4(5)-vinylimidazole at intermediate pH when the proportion of water in the solvent system is increased. However, because of the limited solubility of the polymer in this pH region in 28.5% ethanol-water, 10% methanol-water solutions were used instead. It was found that the catalytic rate constants for the solvolysis of PNPA by both polymer and monomer increased with the larger proportion of water in the solvent, the former to a larger extent. These rate constants are summarized in Table VIII and are plotted against α_1 in Figure 2.¹⁸ The results indicate that polymeric imidazole is more active than imidazole even at pH values where the fraction of imidazole anions is between 10^{-7} and 10^{-8} . This is best explained by the contributions of the second term in eq 1, specifically, the interaction of two neutral imidazole functions. Furthermore, the nature of Figure 2 suggests a partial dependence of k_{cat} on α_1^2 .

In view of the fact that no third-order contributions were found for the solvolysis of PNPA by monomeric imidazole,^{6,19} poly-4(5)-vinylimidazole can then be considered as a concentrated agglomeration of imidazole functions which are more prone to act as multifunctional catalysts than is monomeric imidazole.

The activation parameters obtained for the solvolysis of PNPA by poly-5(6)-vinylbenzimidazole and benzimidazole at pH 8.4 appear in Table IX. These results also indicate a different mechanism of solvolysis for the polymer relative to the monomer. From pH-rate profiles studied earlier,⁹ it became evident that catalysis by polymeric and monomeric benzimidazole at pH 8.4 consists of contributions of neutral and anionic fractions. The activation energy, as calculated by the least-squares method, therefore represents the composite contributions of neutral and anionic benzimidazoles. No corrections were made for the variations of pK_2 with temperature because of the difficulties in their accurate assessment. In the case of benzimidazole, the rate equation is a composite of two terms, *i.e.*

$$k_{\text{cat}} = k_{\text{neutral}}\alpha_1 + k_{\text{anionic}}\alpha_2^{20} \quad (2)$$

For the polymer, contributions of all four terms in eq 1 may be involved in the solvolytic reaction. However, the over-all results (Table IX) still reveal a substantial decrease in the activation energy for polymeric benzimidazole relative to the monomer, with a smaller reduction in the $T\Delta S^*$ term. This situation could explain the faster rate for polymeric benzimidazole catalysis observed even below pH 7.

(18) The modified Henderson equation in 10% methanol-water solutions did not materially change from that earlier reported (ref 9) in 28.5% ethanol-water solutions.

(19) J. F. Kirsich and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 833 (1964).

(20) T. C. Bruice and G. E. Schmir, *ibid.*, **80**, 148 (1958).

The catalytic rate constants for the solvolysis of the negatively charged substrate 4-acetoxy-3-nitrobenzoic acid at pH 9 by poly-5(6)-vinylbenzimidazole and benzimidazole (Table V) involve fewer terms than for PNPA. From previously studied pH-rate profiles⁹ it became obvious that NABA does not interact with monomeric benzimidazole anions. The data collected at pH 9 represent only the second-order reaction of the neutral fraction (practically 1.0) of monomeric benzimidazole with this substrate. The reaction of the polymer is more complex and in the anionic region it

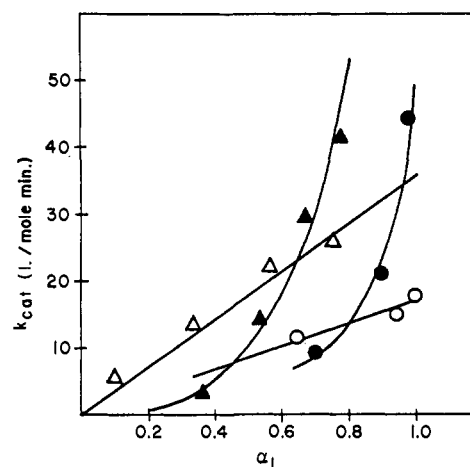


Figure 2. Solvolysis of *p*-nitrophenyl acetate (I) in 28.5% ethanolic solutions catalyzed by poly-4(5)-vinylimidazole (●) and imidazole (○); (2) in 10% methanolic solutions catalyzed by poly-4(5)-vinylimidazole (▲) and imidazole (△).

probably reflects terfunctional contributions which can be described as the nucleophilic reaction of benzimidazole being catalyzed by benzimidazole anion as a general base.⁹ If we assume that the pK_2 of the polymer decreases with increasing temperature, the activation energy observed for the polymer represents the higher limit for this value, which is still far below the value for the monomer. The smaller reduction in $\Delta T\Delta S^*$ relative to the reduction in $\Delta\Delta H^*$ (Table X) agrees with the anticipation that by transforming a terfunctional third-order reaction into a terfunctional second-order reaction, the ΔH^* of the third-order reaction may be retained with a $T\Delta S^*$ term which is very close to that of a second-order reaction.

Bifunctional imidazole catalysis can be described either as general base (such as I or II^{6,9,19}) or acid (such as III^{4,9,19,21}) catalysis of nucleophilic imidazole attack on the substrate. These processes could be concerted one-step reactions, or be composed of a two-step sequence. This is illustrated schematically by

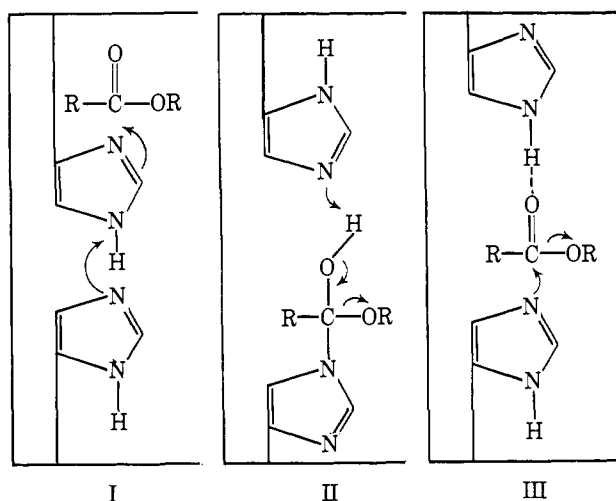
(21) Cf. M. A. Marini and G. P. Hess, *ibid.*, **82**, 5160 (1960).

Table X.^a Activation Parameters for the Solvolysis of 4-Acetoxy-3-nitrobenzoic Acid by Poly-5(6)-vinylbenzimidazole and Benzimidazole

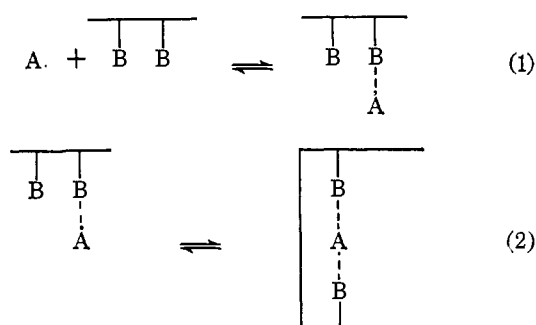
Catalyst	ΔE^*	ΔH^*	ΔF^*	$T\Delta S^*$	ΔS^*	$\Delta\Delta H^*$	$\Delta T\Delta S^*$
Poly-5(6)-vinylbenzimidazole	6.1	5.5	18.1	-12.6	-42.1	-1.9	-0.3
Benzimidazole	8.0	7.4	19.7	-12.3	-41.1		

^a All values in kcal per mole except ΔS^* (eu). Data collected at pH 9.

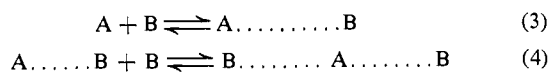
having a small molecule A interacting with two functional groups B which are independent of each other in the monomeric stage or attached to a macromolecular backbone in the polymeric stage. Let us compare the entropy of activation for the monomeric and polymeric stages. If, in each case, the formation of the transition



state is divided into two steps, we can write the following scheme for the polymer.



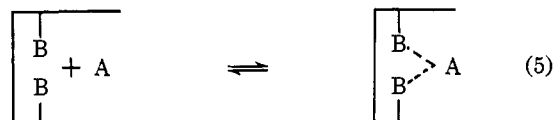
Similarly for the monomer



The entropy of activation in the first step (1 and 3) can be considered similar whether or not B is a part of a macromolecule. As for the ring closure process (2), the entropy change will depend on the concentration of the group B within the macromolecule and possible steric restraints to ring formation.

The results may be expressed in terms of "effective local concentration" of group B in the neighborhood of an arbitrary reference group, and we may state that ΔS^* will be less negative in the case of the polymeric reagent if this effective concentration is higher than 1 mole/l.^{22,23}

One-step concerted reactions may be statistically less favorable. However if the polymer contains both catalytic groups in an appropriate steric position such as to allow a simultaneous attack of both B groups on A (5), then ΔS^* for this process should be very close to that of a second-order monomeric reaction, *i.e.*, the ter-functional polymeric reaction would become more efficient than the third-order monomeric reaction. Furthermore, if ΔH^* for the polymeric reaction is lower (because of higher functionality) than a second-order monomeric reaction, the polymeric catalysis would be also faster than the second-order monomeric reaction, which was actually observed.



We can assume that specific steric requirements are accomplished on the ternary enzymatic structure by the complexation step. This may compound a gain in both ΔH^* and ΔS^* and make the catalytic action very efficient.⁸

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(22) H. Morawetz and E. Sammak, *J. Phys. Chem.*, **61**, 1357 (1957).

(23) H. Morawetz, *J. Polymer Sci.*, **23**, 247 (1957).