Theoretically there is considerable question as to the validity of using the factor of 2 in this conversion.[13] We are unable to decide this question and pending a definitive theoretical interpretation have included it in the calculation. This factor in no way impairs the qualitative or quantitative conclusions reached in this study. In passing it may be noted that the bimolecular rate constant can be predicted by the Smoluchowski theory of diffusion rates by substituting the Stokes–Einstein relationship for the diffusion coefficient.[14] For DTBN the predicted rate is 8.3×10^9 l./mole sec which compares with the experimental value in Table I of 7.5×10^9 l./mole sec (which includes the factor of 2). Considering the crudeness of the Stokes–Einstein relation, the agreement is surprisingly good, but may be fortuitous and cannot be advanced as an argument in favor of the calculation.

The approximately 80% variation of the spin–spin rate constants of the mononegative species is of little significance. Errors of 20–30% are introduced in these rate constants from the concentration and line-width determinations owing to both the intrinsic lack of precision in area measurements and the changing line shapes at these concentrations. The important point we wish to make is that it appears that the spin–spin rates of a wide variety of organic radicals are purely diffusional controlled (at least over a moderately dilute concentration range, *ca.* 5×10^{-4} to 5×10^{-3} *M*). However, the electron-transfer rates for these same compounds vary by over an order of magnitude.

In the spin–spin case there must exist considerable overlap of the wave functions of the unpaired electrons. For the electron-transfer reaction there must be overlap of the wave functions of the unpaired electron and the acceptor molecule. From the similarity of the spin–spin rates it is seen that the frequency of occurrence of such overlaps is approximately the same for all molecules in question. Thus, it would appear that retardation of the electron-transfer rates by steric, solvent, and substituent effects is not due to any alteration in the probability of collisions which have wave function overlap. Instead, the retardation is caused by the reorganization energy associated with charge transfer in the electron-transfer process. This intuitive argument seems to be substantiated by the experimental data.

Acknowledgments. The support of this work by the Atomic Energy Commission through Contract AT-(11-1)1686-41 and by the Kansas Heart Association through an undergraduate research grant to the author (T. A. M.) is gratefully acknowledged. We wish to acknowledge valuable discussions of the quantitative nature of the spin–spin interaction with Dr. A. D. McLachlan and Dr. M. T. Jones.

---

[13] M. T. Jones, private communication.

[14] E. F. Caldin, "Fast Reactions In Solution," Blackwell Scientific Publication, New York, N. Y., 1964.

The Interaction of Chain Molecules Carrying Reactive and Catalytic Chain Substituents[1]

H. Morawetz and W. R. Song

Contribution from the Polymer Research Institute, Polytechnic Institute of Brooklyn, Brooklyn, New York. *Received May 20, 1966*

Abstract. The hydrolysis of acrylamide (A) and dimethylacrylamide (D) copolymers with *p*-nitrophenyl acrylate (NA) and *p*-nitrophenyl N-acrylyl-6-aminocaproate (NAC) was studied in the presence of catalytic copolymers of 4-vinylimidazole (VI) or N-acrylylhistamine (AH). Copolymers of VI did not catalyze the solvolysis of copolymers of NA, presumably because steric hindrance is prohibitive when both interacting groups are close to the chain backbone. Copolymer A–AH did not catalyze the solvolysis of copolymer A–NA in water but was catalytically active in 40% aqueous methanol, a relatively poor solvent medium. The reaction of A–NAC catalyzed by A–AH followed first-order kinetics in water solution and the rate was independent of the molecular weight of the A–AH used. This suggests that shielding of the reactive groups by the macromolecular coil is negligible under the conditions employed. In water–methanol solution the reaction exhibited slight but significant deviation from first-order kinetics. In experiments involving D–NAC with A–AH and D–AH, the expected specificity in favor of interaction of reactive groups attached to similar polymer backbones was not observed.

In the selection of methods for the study of polymer solutions, little use has been made, so far, of the possibilities inherent in studies of the chemical reactivity of dissolved chain molecules. Yet, a recent survey of this field[2] leads to the conclusion that such methods may supplement the more usual physicochemical techniques to yield information which may not be attainable by other means.

Consider a system represented schematically in Figure 1 in which a solution contains two types of chain molecules. The backbones of these chain

---

[1] Abstracted from the Ph.D. thesis submitted by W. R. Song to the Graduate School of the Polytechnic Institute of Brooklyn in June 1965. Financial support of this work by Grant GM-05811 of the National Institutes of Health is gratefully acknowledged.

[2] H. Morawetz, "Macromolecules in Solution," Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1965, Chapter IX.

molecules are identical, but one type carries a small number of reactive side chains A while the other type carries a small number of substituents with a catalytically active group B. In a dilute polymer solution the coiled chain molecules do not easily interpenetrate one another, and the attachment of groups A and B to the polymer backbone would then be expected to shield those groups which find themselves at any given time in the interior of the molecular coil from encounters with groups attached to another chain molecule. As a result, the solution of the mixed polymers would be expected to react at a substantially lower rate than a solution containing a similar concentration of groups A and B in compounds of low molecular weight. If the conformation of the chain molecules in solution were fixed, a comparison of the kinetic patterns observed in systems containing the mixed polymers and their low molecular weight analogs, respectively, would be interpretable in terms of the extent of the mutual interpenetration of the molecular chains. It would also indicate the extent to which groups attached to the center of the polymer backbone, and therefore somewhat more likely to find themselves in the center of the molecular coil, are more effectively shielded from the second polymeric reagent than groups attached close to the end of a chain molecular. Since, however, the polymer chain molecules undergo conformational transitions on a time scale which is very fast compared with the rate of the chemical reactions investigated in the present study, every chain substituent will find itself at some time close to the surface of the molecular coil and will then be accessible to a second polymeric reagent even if chain interpenetration is relatively small. The superposition of effects caused by mutual interpenetration and by conformational transitions of the chain molecules introduces some ambiguity into the interpretation of the experimental results. Nevertheless, the technique is believed to be valuable in supplementing other physicochemical methods for the study of polymer solutions, and we have attempted, in the present study, to survey its possibilities in systems containing polymers carrying phenolic ester groups and polymers carrying imidazole residues, which are known to catalyze the solvolysis of phenolic esters.[3]

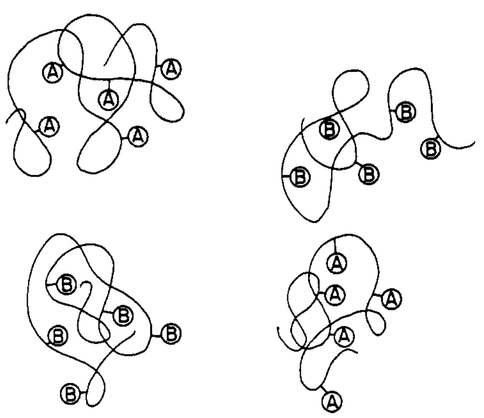


Figure 1. Schematic representation of a system containing two types of flexible chain molecules carrying reactive groups A and catalytically active groups B, respectively.

Experimental Section

Monomers. Acrylamide (Eastman Kodak) was recrystallized from chloroform. N,N-Dimethylacrylamide (Borden Chemical Co.) was distilled using the fraction boiling at 63–65° (5 mm.). 4-Vinylimidazole (VI)[4] was obtained from Dr. S. Yaroslovsky. *p*-Nitrophenyl acrylate (NA) was prepared as previously described.[5]

N-Acrylylhistamine (AH). Histamine hydrochloride (8.4 g) was dissolved in 15 ml of 4 *N* NaOH, 20 ml of 10% sodium carbonate, and 28 ml of dioxane. To the solution cooled in an ice–salt mixture, acrylyl chloride (5.3 g) and 4 *N* sodium hydroxide (30 ml) were added dropwise simultaneously with stirring, continuing until the odor of acrylyl chloride disappeared. The solution was neutralized with HCl to pH 5 and was concentrated. The residue was dissolved in absolute ethanol, filtered, and concentrated again. At this stage both the amino group and the imidazole residue were acylated. The material was dissolved in 60 ml of methanol and treated for 1 hr with 6 ml of 1 *N* sodium hydroxide at room temperature to hydrolyze the acylimidazole group. The solution was then neutralized to pH 7, concentrated under vacuum, taken up in absolute ethanol, and chromatographed on activated alumina (neutral) with absolute ethanol as eluent. The first fraction running through was collected, evaporated, and recrystallized from ethanol–chloroform (mp 142–144°).

Anal. Calcd for $C_8H_{11}N_3O$: C, 58.18; H, 6.67; N, 25.45. Found: C, 57.95; H, 6.64; N, 25.23.

***p*-Nitrophenyl N-Acrylyl-6-aminocaproate** (NAC). Bis(*p*-nitrophenyl) sulfite was prepared as previously described.[6] 6-Aminocaproic acid was acylated with acrylyl chloride under Schotten–Baumann conditions. The N-acrylyl-6-aminocaproic acid (mp 96–98°) was then esterified by bis(*p*-nitrophenyl) sulfite using the procedure of Iselin, *et al.*[6] The product was recrystallized from acetone–ether (mp 113–115°).

Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.88; N, 9.15. Found: C, 58.64; H, 5.98; N, 9.05.

Preparation and Characterization of Copolymers. Copolymerization of acrylamide was carried out in deaerated solutions containing 20 ml of 0.06 *M* sodium dihydrogen phosphate with methanol varying from 4 to 15 ml and 10–20% of the mixed monomers at a temperature of 50°. Under these conditions no appreciable ester hydrolysis occurred during the polymerization and the polymer remained in solution throughout the reaction. In the copolymerization of N,N-Dimethylacrylamide, dioxane solutions containing 25% of mixed monomers were employed. The reactions were initiated by 1–10 mg of azobisisobutyronitrile, and, since the comonomers had generally similar reactivities, the copolymerizations were carried to high conversion. The compositions of copolymers containing ester groups were determined by ultraviolet absorption measurements after complete hydrolysis. Molar extinction coefficients used were 9.8×10^3 at 320 mμ for un-ionized *p*-nitrophenol and 1.84×10^4 for the *p*-nitrophenolate ion. The composition of copolymers with catalytically active VI or AH residues was estimated assuming that in aqueous buffers the catalytic efficiency of the imidazole groups is identical in the monomeric AH, and in the copolymers when they act on an ester of low molecular weight (*e.g.*, NAC). The kinetic data obtained in solutions containing NAC and AH in water and in 40% aqueous methanol are plotted in Figure 2. They correspond to second-order rate constants for imidazole catalysis k_{Im} of 0.051 and 0.018 l. mole^{-1} sec^{-1}, respectively. The ratio of the catalytic efficiency of the A–AH-1 copolymer in these two solvent media was slightly higher, *i.e.*, 3.4. The chain length of some of the copolymers was characterized by the intrinsic viscosity in 1% NaCl solution at 25°. These intrinsic viscosities may be interpreted approximately in terms of the molecular weight, using for acrylamide[7] $[\eta] = 6.8 \times 10^{-4}M_n^{0.66}$ and for dimethylacrylamide[8] $[\eta] = 2.32 \times 10^{-5}M^{0.81}$ obtained in water solutions. Data on the copolymers employed in this study are listed in Table I.

---

(3) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1952 (1957); **80**, 148, 1173 (1958); T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).

(4) C. G. Overberger and N. Vorchheimer, *ibid.*, **85**, 951 (1963).

(5) E. Gaetjens and H. Morawetz, *ibid.*, **83**, 1738 (1961).

(6) B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, *Helv. Chim. Acta*, **40**, 375 (1957).

(7) E. Collinson, F. S. Dainton, and D. S. McNaughton, *Trans. Faraday Soc.*, **53**, 489 (1957).

(8) L. Trossarelli and M. Meirone, *J. Polymer Sci.*, **57**, 445 (1962).

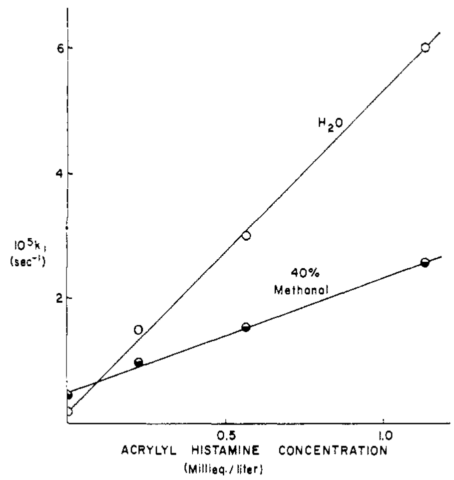


Figure 2. Solvolysis of NAC catalyzed by AH: ester concentration 0.02 g/l., pH 6.75, 25°.

Buffers. Sodium phosphate buffers with an ionic strength of 0.06 were used. Measurements of pH were carried out with a Cambridge Research Model pH meter.

Table I. Copolymers Employed in This Investigation

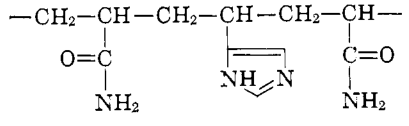
Designation[a]	Wt % comonomer in copolymer	[η], dl g^{-1}
A-VI	1.2	5.5
A-AH-1	4.5	6.2
A-AH-2	4.4	4.1
A-AH-3	4.3	1.0
A-NA	1.4	2.2
A-NAC	0.9	3.0
D-AH	4.5	1.1
D-NAC	0.8	1.2

[a] The first letter designates the main component, A = acrylamide, D = dimethylacrylamide. The comonomer designations following the hyphen are the same as in the section describing monomer preparation. The numbers at the end of the A-AH designations refer to the three preparations of varying molecular weight.

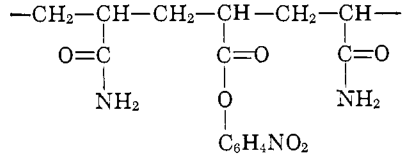
Kinetic Studies. Stock solutions of low molecular weight esters were prepared in dioxane. In studies of ester copolymers, solutions in ice-cooled buffers were obtained immediately before use. The reaction was initiated by adding 0.5 ml of the ester solution in dioxane to a thermostated solution of the catalyst in 100 ml of the appropriate buffer or by mixing cold buffer solutions of the ester copolymer and the catalytic copolymer and warming them to the reaction temperatures. The progress of ester hydrolysis was followed by optical density readings in a Beckman DU spectrophotometer at the wavelengths specified in the section on the characterization of the copolymers. "Infinity" readings were taken on aliquots heated to 80° until the optical density attained a constant value. In most cases, first-order kinetics were observed; wherever this was not the case, the reaction was characterized by an apparent first-order constant k_{app} corresponding to the time required for hydrolysis of half of the ester groups.

Results

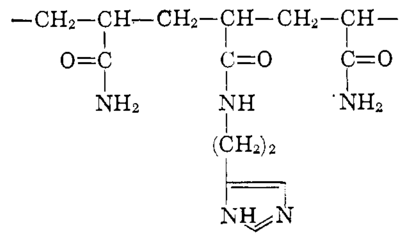
Hydrolysis of Acrylamide–Ester Copolymers in the Presence of Catalytic Copolymers of Acrylamide. The ability of polymers carrying imidazole residues to catalyze the hydrolysis of ester groups attached to polymer chains was found to depend critically on the distance of the interacting functional groups from the backbone of the polymer. This distance is very short in copolymers A-VI and A-NA, while in A-AH and in A-NAC the imidazole and ester functions are well separated from the chain backbone.



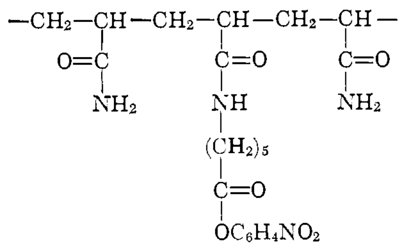
A-VI



A-NA



A-AH



A-NAC

The copolymer of acrylamide with 4-vinylimidazole at a concentration of 4 g/l. (corresponding to 5.2 × 10^{-4} *M* imidazole residues) was found to be without effect on the ester hydrolysis rate of the copolymer A-NA (1.4 g/l.) in aqueous buffers of pH 6.3–7.1 and in the temperature range of 20–50°, although polyvinylimidazole is known to attack efficiently such low molecular weight esters as *p*-nitrophenyl acetate.[9] This result was ascribed to the relative proximity of both interacting functional groups to the backbones of the chain molecules to which they are attached. With the A-AH copolymer, the catalytically active imidazole residue is more easily accessible, and it was then of interest to see whether this copolymer would be able to attack ester groups attached to chain molecules. It was found that A-AH was without effect on the hydrolytic rate of A-NA in an aqueous medium but did catalyze the ester hydrolysis in 40% methanol. The reaction rate was first order with respect to both ester and imidazole residues. The second-order rate constant for their interaction was k_{Im} = 0.005 l. mole^{-1} sec^{-1}, smaller by less than a factor of 4 as compared to the rate of the reaction of the two low molecular weight species, AH and NAC, under comparable conditions.

An extensive study was undertaken of reaction rates in solutions containing A-AH and A-NAC, *i.e.*,

---

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

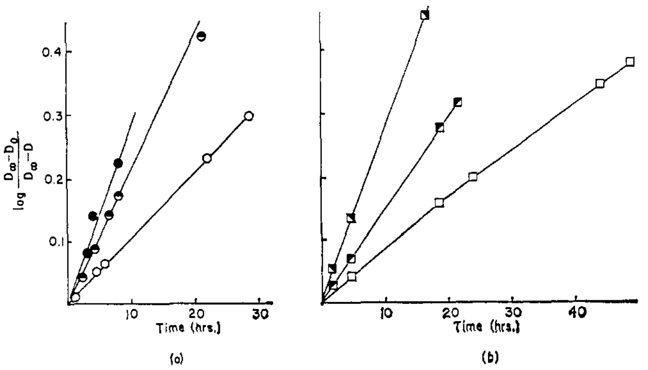


Figure 3. Kinetics of ester hydrolysis in copolymer A–NAC (concentration 2 g/l.) catalyzed by copolymer A–AH-1, pH 6.75, 25°: (a) water solution, A–AH-1 concentration (g/l.), ○ 2, ◒ 4.5, ● 6; (b) 40% methanol, A–AH-1 concentration (g/l.), □ 1.2, ◩ 3, ◪ 6.

copolymers in which both the catalytically active imidazole residue and the susceptible ester group are well separated from the backbone of the chain molecule. The concentration of A–AH was varied from 1 to 6 g/l. and that of A–NAC in the range of 1 to 3 g/l.; the pH was held at 6.75 and the temperature at 25°. Observed effects may be summarized as follows.

(a) Since the system was rather dilute (most of the kinetic runs were carried out at a total polymer concentration of 4 g/l.) the polymer coils would be expected to occupy separate regions in space, and the initial rate of ester hydrolysis should be proportional to the stoichiometric concentration of ester and imidazole residues. This relationship was strictly followed in all cases. At high polymer concentrations, where the chains interpenetrate extensively, some deviation from this simple relation might be expected, but the high viscosity of the system prevented us from exploring this problem.

(b) In aqueous solution the ester hydrolysis followed strictly first-order kinetics. This suggests that ester groups attached to various portions of the A–NAC copolymer were exposed equally to attack by imidazole residues of the A–AH copolymer. In a poor solvent medium (40% methanol) the reaction exhibited a slight deviation from first-order kinetics at low concentrations of the catalytic copolymer. This small but probably significant difference between the kinetic pattern in the two solvent media is shown in Figure 3.

(c) First-order rate constants in aqueous solution and k_{app} values in 40% methanol obtained with 2 g/l. of copolymer A–NAC and varying concentrations of A–AH are plotted in Figure 4. The reaction rate is seen to be proportional to the concentration of the catalytic polymer with k_{Im} identical, within experimental error, in the two solvent media (0.0100 and 0.0090 l. mole^{-1} sec^{-1}), respectively. However, since the corresponding rate constants of A–NAC hydrolysis catalyzed by the monomeric AH (Figure 2) are 0.0051 and 0.018 l. mole^{-1} sec^{-1}, respectively, the relative catalytic efficiency of the AH residues in the A–AH copolymers is seen to increase in passing from the good to the poor solvent medium from 0.20 to 0.50.

(d) The data plotted in Figure 4 show that the efficiency with which the imidazole residues of the A–AH copolymers attack the ester groups in copolymer

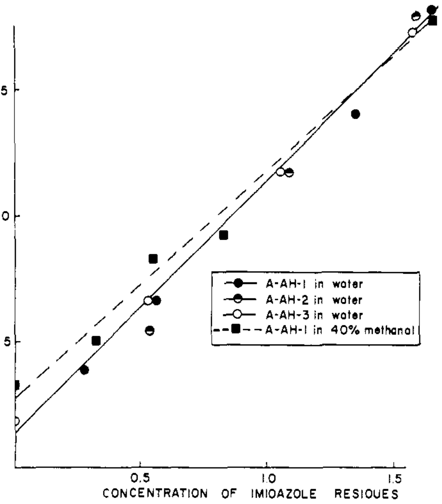


Figure 4. Rate constants for the solvolysis of A–NAC (concentration 2 g/l.) catalyzed by A–AH of varying chain length, pH 6.75, 25°.

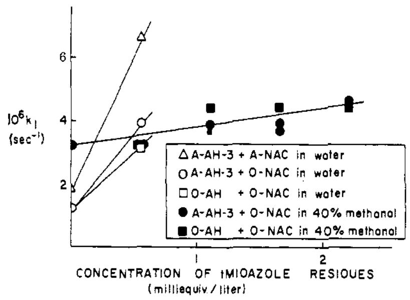


Figure 5. Dependence of the reaction rate on the chain backbone carrying interacting groups: ester copolymer concentration 2 g/l., pH 6.75, 25°.

A–NAC are independent of the length of the chains carrying the catalytic groups.

Dependence of the Reaction Rate on the Nature of the Polymer Chain Carrying the Interacting Reactive Groups. The question arose to what extent the interaction of ester and imidazole residues depends on the type of chain molecule to which they are attached. To explore this problem, reaction rates were measured in systems in which either of these groups was attached to a copolymer containing predominantly acrylamide or N,N-dimethylacrylamide residues. The results are plotted in Figure 5. In water solution, the catalytic efficiency of the imidazole groups in systems containing A–AH-3 with A–NAC, A–AH-3 with D–NAC and D–AH with D–NAC was characterized by k_{Im} values of 0.0087, 0.0049, and 0.0036 l. mole^{-1} sec^{-1}, respectively. In 40% methanol, both catalytic polymers had low reactivities, which led only to a small change from the hydroxyl-ion catalyzed reaction rate.

Discussion

Insight into the extent of mutual interpenetration of flexible chain molecules may be gained from the excluded volumes calculated from the concentration dependence of the osmotic pressure and of light scattering characterizing polymer solutions.[10] Such data

---

[10] (a) P. J. Flory, "Principles of Polymer Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 519; (b) H. Morawetz, "Macromolecules in Solution," Interscience Publishers, Inc., New York, N. Y., 1965, pp 169–172.

lead to the conclusion that relatively little interpenetration occurs when the molecular coils are placed in good solvent media. If the conformation of the macromolecules were fixed, reactive groups which are deeply buried within the molecular coil would be virtually inaccessible to reactive groups attached to a different molecular chain, while groups close to the surface of the molecular coil would be characterized by a much higher reactivity. Since the polymer coils are subject to rapid conformational transitions, all pendant groups will be exposed at the surface of the coil at some time, but it was nevertheless expected that groups attached to the center of the chain would be exposed somewhat less frequently than those attached close to the chain end.[11] It was one of the objectives of this study to measure this variation in shielding experienced by groups attached at different points to the chain backbone, an effect which would not be easily subjected to quantitative theoretical analysis. The fact that we have observed no deviation from first-order kinetics in aqueous solutions containing the copolymers A–AH and A–NAC, in spite of the high precision of the experimental method, shows that all the groups attached to the polymer chain must, in fact, be exposed almost equally to other polymer reagents. This finding is surprising. Moreover, the shielding of reactive groups by the molecular coils seems to be negligible, under the conditions of these experiments, since the imidazole residues carried by A–AH-1, A–AH-2, and A–AH-3 (with estimated molecular weights of 10^6, 5.3×10^5, and 6.3×10^4) have been found to be equally efficient in catalyzing ester hydrolysis in copolymer A–NAC (with an estimated molecular weight of 3.3×10^5). It is hard to see how this result can be reconciled with the rare occurrence of chain entanglements when polymers are dissolved at low concentration in a good solvent medium. This would lead to the expectation that the fraction of pendant groups exposed to attack of the surface of the molecular coils should decrease as the coils increase in size.

In the much more poorly solvating water–methanol mixture, the relative reactivity of the imidazole residues in the A–AH copolymer (referred to the reactivity of monomeric AH) is higher than in water solution. This effect was expected since the attraction of the polymers for one another is increased by a reduction in the solvent power of the medium. It was also found that the solvolysis of A–NAC catalyzed by copolymer A–AH shows now a slight deviation from first-order kinetics. (The initial slope of the first-order plot is 20% larger than the slope observed when half of the esters have reacted.) This seems to imply that some conformations, corresponding to extensive contacts between chain segments, are significantly favored in poor solvent media and that reactive groups which find themselves well below the surface of the coil in these conformations are correspondingly less likely to react.

Finally, let us consider the effect of the nature of the chain backbone on the reaction rate of solutions of mixed polymers. When the chains carrying the reactive and the catalytic polymers mix with an evolution of heat, molecular association of the polymers will be highly favored and the reaction rate will be strongly increased. This effect was studied by Letsinger and Klaus[12] on a system containing an acrylic acid–ester copolymer and poly(N-vinylimidazole). An entirely different situation is to be expected if mixing of the two polymers is endothermic, as would be generally expected wherever no acid–base interaction is involved. It is well known that chain molecules are very resistant to mixing under these conditions, so much so that even dilute solutions of two different polymers in the same solvent will not mix with one another.[13] It would then be expected that reactive and catalytic groups attached to dissimilar polymers, mixing with an absorption of heat, should react with each other more slowly than if the interacting groups were attached to similar polymer chains. This principle implies the possibility of observing a new type of specificity in the catalysis of an organic reaction, with each polymeric catalyst specific for "homologous" polymeric substrates.

The experiments in which reaction rates were measured in systems in which ester groups and catalytic groups were attached to chains composed predominantly of acrylamide and N,N-dimethylacrylamide residues were to test the principle outlined above. The results did not conform to our expectation. In water solution, the system containing the heterologous copolymers A–AH and D–NAC was characterized by a rate constant intermediate between that found for the two homologous pairs A–AH + A–NAC and D–AH + D–NAC. It is possible that the mixing of polyacrylamide with poly(N,N-dimethylacrylamide) is nearly thermoneutral, which would account for the absence of a specificity effect. In aqueous methanol, the susceptibility of NAC residues to attack by the catalytic copolymers was found to be highly sensitive to the nature of the chain molecule to which the ester groups are attached. A comparison of Figure 4 and Figure 5 shows that the interaction of the homologous copolymers was much larger in the A–AH + A–NAC system than in solutions containing D–AH + D–NAC. This contrast reflects the poor solvation of the polyacrylamide chain in the aqueous methanol solution.

---

[11] The probability distribution function for the location of specific chain segments of random flight chains (A. Isihara, *J. Phys. Soc. Japan*, **5**, 201 (1950); P. Debye and F. Bueche, *J. Chem. Phys.*, **20**, 1337 (1952)) may be used to show that the average distance of the terminal segment from the center of gravity of the chain is twice as large as the corresponding distance for the central chain segment.

[12] R. L. Letsinger and I. Klaus, *J. Am. Chem. Soc.*, **86**, 3884 (1964).

[13] For a discussion and review of this phenomenon, see ref 10b, pp 85–86.