Consequences of the Excluded Volume Effect on the Rate of Reactions Involving Two Randomly Coiled Polymer Chains. II. Hydrolysis of Phenyl Ester Groups in Side Chains of Acrylamide Copolymers in the Presence of Acrylamide Copolymers Carrying Pyridine Residues[1]

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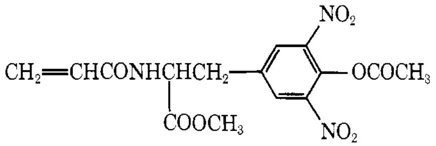
ABSTRACT: Copolymers of acrylamide with small concentrations of *N*-acrylyl-*O*-acetyl-3,5-dinitrotyrosine methyl ester or with *N*-acrylyl-4-aminomethylpyridine were prepared. The second-order rate constant k_2 for the solvolysis of the phenyl ester groups catalyzed by the pyridine residues in solutions containing the two copolymers was compared with the rate constant k_2^0 observed in solutions containing the reactive and catalytic monomer. In aqueous solution, k_2/k_2^0 was found to exceed unity with a catalytic copolymer of low molecular weight and it fell off only slowly with an increasing chain length of this copolymer. In ethylene glycol, lower values of k_2/k_2^0 were observed and they were more sensitive to the chain length of the catalytic copolymer. The results were contrary to theoretical expectation since (a) kinetic curves showed no evidence of the predicted dispersion of the solvolysis rate constant, (b) the k_2/k_2^0 were much higher than expected and were lower in glycol, a poorer solvent medium, than in water. The reaction of the two copolymers with each other was slowed down by addition of polyacrylamide. This effect levels off at polyacrylamide concentrations of about 20 g/l. and is independent of the molecular weight of the added polymer.

In a preceding paper[2] two approaches were outlined for estimating the extent to which the excluded volume effect impedes the chemical interaction of two groups attached to a randomly coiled chain molecule. In the first model, the polymers were represented by spherical clouds containing uniform concentrations of chain segments with the reaction taking place within the jointly occupied volume of two overlapping spheres. This led to the prediction that k_2/k_2^0, the ratio of the second-order rate constant of interacting groups attached to chain molecules to the rate constant characterizing their low molecular weight analogs, should be a rapidly decreasing function of $Z = (v_2^2/v_1v_e)(\frac{1}{2} - \chi)$. Here v_2 and v_1 are molecular volumes of the polymer and the solvent, respectively, v_e is the volume of the spherical cloud representing the extension of the randomly coiled chain and χ is the Flory-Huggins polymer-solvent interaction parameter. The second approach involved the generation, on a diamond lattice, of chains representing the reagents and the transition state complex, in which two reagent chains are linked to each other. The ratio k_2/k_2^0 was then taken as equal to $f_{AB}(2n)/f_A(n)f_B(n)$, where $f_A(n)$ and $f_B(n)$ is the fraction of nonintersecting chains of type A and B with n atoms in the chain backbone, while $f_{AB}(2n)$ is the corresponding quantity for the transition state formed during their reaction. This model provided some insight concerning the importance of the placement of the interacting groups along the length of the chain and the spacing of these groups from the chain backbone. However, the Monte Carlo computation required for the estimation of $f_A(n)$, $f_B(n)$, and $f_{AB}(2n)$ did not take account of the bulk of side chains attached to the polymer and of the effect of solute-solvent interaction, so that the results would not be readily comparable with experimental data.

In designing an experiment for the evaluation of the "kinetic excluded volume effect" it is important that the two interacting polymer chains should be virtually identical. The chemical process to be studied has to satisfy two conditions. (1) The interaction of the groups carried by the two polymer chains must not lead to the formation of a bond which would link the two chains to each other for a time which is significant compared to the time scale of the process which is being followed. (2) It must be possible to follow the progress of the reaction at extreme dilution, *i.e.*, under conditions which do not correspond to extensive interpenetration of the chain molecules. These conditions impose severe restrictions on the choice of suitable reactions. We chose the pyridine-catalyzed solvolysis of phenyl esters as a process satisfying the above criteria and used acrylamide copolymers with very small concentrations of comonomers I and II, respectively. It is known



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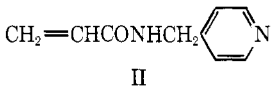

II

that the pyridine-catalyzed solvolysis of phenyl esters involves the formation of an acylpyridinium intermediate;[3] by attaching the phenyl rather than the acyl residue to the chain backbone we made sure that the two chains would not be linked even for the lifetime of this rather labile reaction intermediate. The k_2/k_2^0 ratio was studied as a function of the chainlength of the catalytic copolymer, the total polymer concentration and the solvent.

Experimental Section

Monomers. 3,5-Dinitro-L-tyrosine (mp 230-231°) obtained by the method of Chalmers *et al.*[4] was converted in Na_2CO_3 solution by acrylyl chloride to *N*-acrylyl-3,5-dinitro-L-tyrosine (mp 118–

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(1) Abstracted from a Ph.D. thesis to be submitted by J.-R. C. to the Graduate School of the Polytechnic Institute of Brooklyn, June, 1973. A portion of the data was presented at the Detroit meeting of the American Chemical Society, May 1973.

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120°). This was treated in methanol solution with anhydrous HCl to yield the methyl ester hydrochloride (mp 142-143°) and converted to *N*-acrylyl-*O*-acetyl-3,5-dinitro-L-tyrosine methyl ester (monomer I) (mp 106-108°) by acylation in tetrahydrofuran solution at −5° with acetyl chloride in the presence of *N*-methylmorpholine. *N*-Acrylyl-4-aminomethylpyridine (mp 71-72°) (monomer II) was obtained by treating 4-aminopyridine with acrylic anhydride in ether solution. Acrylamide was recrystallized from ethyl acetate.

Polymers. Copolymerization of acrylamide with the catalytic comonomer II was carried out to low conversion in aqueous solution using the sodium metabisulfite-potassium persulfate redox initiator system at 0° or room temperature. The composition of the copolymer was estimated from the difference in the optical density at 260 nm at pH 2 and 10, using a value of 2.1×10^3 l. mol^{-1} cm^{-1} for the excess molar extinction coefficient in the acid solution.[5] The viscosity average molecular weights were estimated from the intrinsic viscosity in 1% aqueous NaCl solution at 25°, using the relation obtained by Scholtan for polyacrylamide.[6] The mole fractions of monomer II and the molecular weights for the three copolymers prepared were 0.025 and 1.32×10^5(C1), 0.013 and 5.01×10^5(C2), and 0.010 and 15.5×10^5(C3).

Copolymerization of acrylamide with monomer I could not be carried out in aqueous solution because of significant hydrolysis of I. The reaction was, therefore, carried out in dioxane solution at 60° using azobis(isobutyronitrile) polymerization initiator. The copolymer composition was determined spectroscopically at pH 12 after complete hydrolysis of the ester groups using a molar extinction coefficient of 6.80×10^3 for the 3,5-dinitrotyrosinate residues at 445 nm. The copolymer (R) contained a mole fraction 0.021 of I and had a molecular weight of 1.24×10^5. Attempts to prepare copolymers of I with a higher molecular weight were unsuccessful.

Kinetic Measurements. The solvolysis of the phenyl ester groups of monomer I or of its copolymer was studied at 25°. Aqueous solutions were buffered at pH 6; ethylene glycol solutions were used without a buffer. The progress of the hydrolysis was followed by uv absorption measurements at 445 nm. Observed reaction rates in aqueous solutions containing monomers I and II or their copolymers were corrected for the spontaneous hydrolysis rate; in ethylene glycol solution the spontaneous solvolysis was negligible (6.5×10^{-6} min^{-1} for copolymer R). Additions up to 3 wt % of water to an ethylene glycol solution of monomers I and II had no significant effect on the reaction rate.

Results and Discussion

The spontaneous solvolysis rate of the ester group in copolymer R was 1.84×10^{-3} min^{-1}, significantly higher than the rate of 1.31×10^{-3} min^{-1} observed for monomer I. This effect is believed to be due to nucleophilic attack by the conjugate base of the amide residues of the polymer. Previous studies in this laboratory[7] have shown that appropriately placed amide groups may be very effective acyl acceptors and although the steric conditions are not favorable in copolymer R for such an intramolecular process, the high concentration of amide groups within the molecular coil could well be responsible for the observed effect.

The ester solvolysis in solutions containing reactive and catalytic copolymers followed in all cases first-order kinetics. The k_2/k_2^0 ratios obtained, reflecting the reaction of ester and pyridine residues in water and in ethylene glycol, are listed in Table I. In water solution, the reaction with the catalytic polymer of lowest molecular weight has k_2/k_2^0 actually higher than unity and k_2/k_2^0 decreases slowly with an increase in the chain length of the catalytic copolymer. In ethylene glycol, all the k_2/k_2^0 values are less than unity and the decrease in this ratio with an increase in the chain length of the catalytic polymer is much more pronounced.

A value of $k_2/k_2^0 > 1$ can only be understood as reflecting a difference in the properties of the solvent medium in the immediate vicinity of the polymer chain and the bulk properties of the solvent. We tried to simulate this effect by studying the interaction of monomers I and II in mixtures of water and acrylamide. However we found that the rate constants in solutions containing 28.8, 64.6, and 107.7 g of acrylamide per l. were 13, 27, and 47% *lower* than the rate constant observed in pure water. It is possible that the effect of the polymer on the structure of water in its vicinity is responsible for the anomalous rate of the reaction; such an interpretation has been suggested to explain why isotopic hydrogen exchange with poly(vinylacetamide)[8] and poly(*N*-isopropylacrylamide)[9] in aqueous solution takes place at substantially different rates than those characterizing their low molecular weight analogs.

Table I
Relative Reaction Rates in Solutions Containing Reactive and Catalytic Copolymers and in Solutions Containing Monomers I and II

Medium	Copolymer R (g/l.)	Catalytic Copolymer Species	Catalytic Copolymer g/l.	k_2/k_2^0	q
Water	2.73	C1	1.27	1.20[a]	0.123
		C2	1.39	0.79[a]	0.210
		C3	1.54	0.79[a]	0.427
Glycol	2.00	C1	2.68	0.40[b]	0.145
		C2	1.58	0.29[b]	0.205
		C3	2.12	0.18[b]	0.539

[a] $k_2^0 = 72.0$ l. mol^{-1} min^{-1}. [b] $k_2^0 = 9.88$ l. mol^{-1} min^{-1}.

In a preceding paper[2] we developed a theory of the "kinetic excluded volume effect" in which we used a model representing the polymer coils by spherical clouds with a uniform density of chain segments. The k_2/k_2^0 ratio was then given by

$$k_2/k_2^0 = 12\int_0^1 (y^5 - 3y^3 + 2y^2)\ \exp[-Z(y^3 - 3y + 2)]\mathrm{d}y$$

$$Z = (0.025Mv_{\mathrm{sp}}^2/V_1[\eta])(\tfrac{1}{2} - \chi) \qquad (1)$$

where M is the molecular weight and v_{sp} the specific volume of the polymer, $[\eta]$ is its intrinsic viscosity in dl-g^{-1}, V_1 is the molar volume of the solvent and χ is the Flory-Huggins interaction parameter. To compare our results with the predictions of this theory, we have to estimate χ. We obtained this quantity for the polyacrylamide-water system by applying to Scholtan's intrinsic viscosity data[6] the Stockmayer-Fixman relation[10]

$$[\eta]/M^{1/2} = K_\theta + 0.51\Phi(v_{\mathrm{sp}}^2/V_1N)(1 - 2\chi)M^{1/2}$$

where $\Phi = 2.6 \times 10^{21}$ is the universal constant of the Flory theory of intrinsic viscosity[11] and N is Avogadro's number. Using $v_{\mathrm{sp}} = 0.699$ cm^{3}g^{-1},[12] the Stockmayer-Fixman treatment yielded $\chi = 0.470$. We may then evaluate Z for the case of the reaction involving polymer R with polymer C1 (with similar intrinsic viscosities of 0.75 and 0.79 dl-g^{-1}, respectively) as $Z = 3.4$ and eq 1 leads to a

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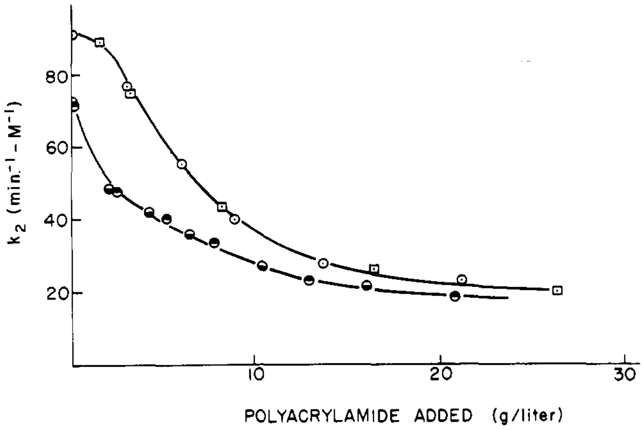

Figure 1. Effect of added polyacrylamide on the reaction rate of copolymer R in the presence of catalytic copolymers. (Polyacrylamide with $[\eta] = 2.00$ and copolymers C1 (○), C2 (◐), and C3 (●); polyacrylamide with $[\eta] = 0.61$ and copolymer C1 (□); concentration of copolymer R 2.73 g/l., concentration of catalytic copolymers 1.56 g/l.

predicted value of $k_2/k_2^0 = 0.22$. This is, in fact, a much lower value than that observed in water solution with any of the catalytic copolymers.

Our results disagree in two other important respects with predictions based on theoretical analyses. (a) In considering the reaction rate of two polymeric reagents from the point of view of transition state theory, we showed[2] that the magnitude of the "kinetic excluded volume effect" should depend on the location of the interacting groups along the length of the macromolecule. For a reaction involving two copolymers carrying reactive and catalytic chain substituents, respectively, we should then expect a dispersion of the apparent rate constant, with groups attached close to the chain ends reacting most rapidly. The fact that all reactions obeyed strictly first-order kinetics is in striking contrast to this expectation. (b) Ethylene glycol was found to be a poorer solvent medium for polyacrylamide than water, since a polymer sample which had $[\eta]_{25} = 2.00$ dl-g^{-1} in water has only $[\eta]_{25} = 1.60$ dl-g^{-1} in ethylene glycol solution. Yet, k_2/k_2^0 values were lower in glycol solution with the use of all three catalytic copolymers and they also fell off more rapidly as their chain length was increased from C1 to C2 and C3. This feature of our result is particularly disturbing, since the reduced reaction rate reflecting the resistance of the polymer coils to mutual interpenetration, and the chain expansion beyond its unperturbed dimensions should reflect the same excluded volume effect.

The possibility was considered that the discrepancy between the theoretical expectation and the experimental results could be due to insufficient dilution of the solutions studied. Assuming that we may treat the hydrodynamic behavior of the polymer coils as that of rigid spheres, we obtain for the ratio of the volume occupied by these coils to the total volume of the system $q = (2/5) \times \Sigma_i c_i[\eta]_i$, where $c_i[\eta]_i$ are the products of the concentrations and the intrinsic viscosities of the dissolved polymers in consistent units. The last column of Table I lists the q values corresponding to the various kinetic runs. We may note that $q = \pi/3(2)^{1/2} \approx 0.74$ corresponds to hexagonal close packing of monodisperse spheres. The q values are certainly not as small as might be desired and it was suspected that this may have been the cause for the unexpectedly small magnitude of the "kinetic excluded volume effect."

To test this interpretation, we studied the effect of an addition of polyacrylamide on the reaction rate between the acrylamide copolymers carrying reactive and catalytic substituents. If the unexpectedly high interaction rate of the reactive and catalytic copolymers was due to the forced chain entanglement resulting from insufficient dilution, then addition of the inert homopolymer should lead to an acceleration of the process. However, the results illustrated in Figure 1 show that, on the contrary, polyacrylamide addition led to a pronounced *decrease* in the reaction rate. This decrease could clearly not be accounted for as a consequence of a change in the reaction medium, since the effect produced by an addition of acrylamide was very much smaller than that produced by the polymer. For instance, whereas the addition of 9 g of polyacrylamide/l. reduced the reaction of polymers R and Cl by 57%, 26.8 g of acrylamide/l. produced only a rate reduction by 17%. Two other features of the results seem to be significant. (1) The reaction rate appears to reach a limiting value at polyacrylamide concentrations of about 20 g/l. (2) For solutions containing polymers R and Cl, the effect on the reaction rate did not depend on the molecular weight of the added polyacrylamide. It should be noted that the solution concentration of the polyacrylamide with the higher molecular weight was carried up to values *corresponding to* $q = 1.6$, *i.e., a concentration* leading to a very extensive interpenetration of the molecular coils.

In view of these results it appears unlikely that the small magnitude of the "kinetic excluded volume effect" observed in this investigation was a result of insufficient dilution of the system. It is unfortunate that polymers rich in acrylamide residues have a very limited range of solvents and that the reaction under study could be followed only in two media, both rather close to the Θ condition. Undoubtedly, if reactions involving two polymers could be studied in media of widely varying solvent power, new insights could be obtained. Because of the restrictions on processes suitable for a study of this type, outlined earlier in this paper, this objective is not easily realized. It is possible that it might be attained by utilizing polyions with a small density of reactive and catalytic substituents. The excluded volume of polyelectrolytes may be varied within wide limits by adjustment of the concentration of added salt[13] and it would then be most instructive to compare k_2/k_2^0 with the excluded volume determined from thermodynamic data. It is probable that the large excluded volume effect found by Wetmur and Davidson[14] in their study of the rate of renaturation of DNA was a consequence of the high charge density of the interacting polymer chains. Wetmur[15] claimed that he could account quantitatively for the magnitude of the effect, but in fitting the data to his theoretical analysis he used for the excluded volume of the chain segment a cylinder with an effective diameter of 10 Å, which seems too small for a highly charged polyion. There is no indication in his discussion that this quantity must be sensitive to the ionic strength.

We are unable, at the present time, to offer a convincing explanation for the various characteristics of the inhibitory effect produced by the addition of an inert polymer on the reaction of two chemically interacting polymeric reagents. While this effect seems to be related to the forced entanglement of the polymeric chains, it is difficult to see why it should approach a limit at rather low

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polymer concentrations and why the effect should be independent of the chain length of the added polymer. At this stage, more is to be gained by a candid expression of our lack of understanding than by the proposal of an interpretation which may fit only part of the data.

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Theory of Copolymer Crystallization

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ABSTRACT: A theory of the crystallization of copolymers of A and B reveals that they do not achieve an equilibrium composition. Rather, the fraction of B is determined by kinetic considerations. The kinetic theory employed is that of Lauritzen, DiMarzio, and Passaglia. Specific attention is devoted to the case where B is in low concentration, and there are positive free-energy terms associated with the incorporation of B into the lattice. Qualitatively one finds that as conditions and parameters are varied, the faster the crystal growth, relative to the equilibration processes, the greater is the inclusion of excess B. A few numerical results have been worked out with results which vary from a fewfold to manyfold excess of B concentration over equilibrium predictions.

I. Introduction

The nature of polymer crystals can be profoundly affected by rather small amounts of coconstituents (in the form of comonomers, stereoisomers, branches, chain ends, etc.). In this paper we shall consider copolymer crystals, and demonstrate that their composition is kinetically controlled. The role of kinetics in determining the properties of polymer crystals is amply attested to by previous experimental and theoretical studies. Furthermore, we now have faith in the ability of a fairly simple mathematical model to simulate the observed behavior.[2a,b]

By "kinetic control" of properties we mean that various states of the crystal are not found in equilibrium concentration. Rather, they are present in proportions which reflect the rates at which these states are added to the crystal, detach from the crystal, and eventually are trapped in the crystal. Specifically, consider a sequential growth process; *i.e.*, growth of a sequence by addition and detachment of elements only at the end of the line. An example is the case of interest: lamellar crystal growth by addition onto a substrate of a portion of a polymer chain, followed by a fold, addition of another portion, etc. These portions of polymer chains added to the crystal are called stems. The developing sequence of stems forms a strip of crystal which we call the growth strip. Eventually this strip will serve as a substrate for deposition of the next strip of stems, and thus is built up the lamellar polymer crystal.

Consider that each growth element (the stem) can be in one of several states (here, the comonomer content of the stem). When a stem is added, the initial probability distribution function for its states will be a reflection of the forward rate constants. The faster the rate constant for addition of a stem in a given state, the more likely that state is to appear. Now a process begins which brings the population toward equilibrium. The stem just added may dissociate, and the states which dissociate most rapidly have a decreased representation in the distribution. The gist of the law of detailed balance is that the ratio of forward to backward rate constants must be such as to ensure that infinite repetition of the addition–dissociation process leads to an equilibrium probability distribution. If, however, the process is interrupted, equilibrium concentrations will not be achieved. In the present case of sequential growth this interruption will occur if the stem in the end position, upon which we have been focusing attention, is covered. Maybe the cover will detach and allow the equilibration to proceed, but eventually the cover will be covered, and so on. Then the distribution of states for this stem is fixed, short of equilibrium. Thus the role of forward and reverse rate constants, as well as time available for equilibration (as reflected in growth rates), is clarified.

A quantitative theory of kinetically controlled, sequential processes was devised by Lauritzen, DiMarzio, and Passaglia (LDP).[2b] Their technique, outlined in section III, is general enough to handle the features which appear necessary in a description of copolymer crystallization. An innovation is that we treat the equations in a self-consistent, rather than explicit, manner, in order to account, in what we believe to be good approximation, for the effect of the substrate's state on the growth rate.

To apply the LDP theory, rate constants for the crystal growth and dissolution processes must be provided. The physics of the crystal growth model is translated into these rate constants in section IV.

For the present study we envision the process of copolymer crystal growth as follows. The basic model is the familiar one employed in the homopolymer theory. Stems, *i.e.*, portions of chains, each n monomer units long, are added sequentially onto a substrate to build up a lamella. After each stem of n units is completed, the macromolecule folds back and attaches another stem of n. The fold free energy, Q_f, includes contributions dependent on the energy of making the fold, the distribution of loop sizes, and the composition. Its determination is a problem separate from that being considered here.

To treat the A–B copolymer problem, within the context of the present model, we must specify the number of B units in each stem. (A more complete and accurate theory can be constructed if one specifies the location of each B in the stem, but such a theory is numerically intrac-

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† The order of the authors was settled in a poker game.

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