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Some Recent Studies of Polymer Reactivity

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Some Recent Studies of Polymer Reactivity

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ABSTRACT

The following aspects of polymer reactivity are discussed: (a) effects due to differences in the microenvironment of the polymer domain and the solvent; (b) effects due to spatial requirements of enzymatic attack on polymer side chains; (c) heterogeneous reactions of gel-bound functional groups with a reagent in a solution phase; and (d) the relation of the conformational mobility of a polymer and its low molecular weight analog.

In considering reaction rates of polymeric reagents, it is useful to use as a point of departure the assumption that the chemical behavior of a functional group should, in principle, be independent of the size of the molecule to which it is attached. The causes which may lead to pronounced deviations between the reactivity of polymeric reagents and their analogs are reasonably well understood, and I have summarized previously the literature up to 1975 [1]. Here I should merely like to discuss some recent developments in this area.

INFLUENCE OF THE NATURE OF THE CHAIN BACKBONE ON SIDE CHAIN REACTIVITY

The following factors [2] may lead to a significant difference between reaction rates of functional groups attached to polymer chains and analogous low molecular weight reagents.

(a) Energetic interactions between a polymer and a low molecular weight reagent may either concentrate or deplete the small molecules

in the polymer domain and this will affect their reaction rate with functional groups appended to the polymer.

(b) Since the polymer backbone makes a contribution to the effective solvent medium in its immediate neighborhood, this medium may be appreciably different from the pure solvent. If a reaction rate is sensitive to solvation effects, the polymeric reagent will then behave differently from the low molecular weight analog.

(c) If a group attached to a polymer is to react with a bulky reagent, easily accessible analogs do not properly simulate, the steric restraint due to the chain backbone.

Instructive data bearing on the role of the polymer backbone in determining the reactivity of side chains were obtained in a study of the aminolysis of p-nitrophenyl ester groups of copolymers of styrene, methyl acrylate or N,N-dimethylacrylamide with a small proportion of p-nitrophenyl acrylate [3]. Table 1 lists the ratio of the second-order rate constants k_2 observed for the polymer and the rate constant k_2^0 of its analog, the isobutyric acid ester, in dioxane solution. It may be seen that the active ester groups appended to polystyrene, poly(methyl acrylate) and to poly-N,N-dimethylacrylamide chains have relative reactivities, depending on the amine species, in the range from 1:9:130 to 1:13:230. The following points deserve special emphasis. The k_2/k_2^0 ratios are rather insensitive to the nature of the amine reagent. More importantly, such variations as are observed cannot be interpreted as resulting from variations in the solvent power of the amine. For instance, addition of ethanolamine to dioxane solutions increases the intrinsic viscosity of poly-N,N-dimethylacrylamide, while it decreases the intrinsic viscosities of polystyrene and poly(methyl acrylate). Thus, ethanolamine should be concentrated in the domain of the dimethylacrylamide copolymer but depleted in the neighborhood of the other two polymers. Yet, Table 1 shows that k_2/k_2^0 is smallest for the ethanolamine reaction with the dimethylacrylamide copolymer. This shows that energetic interactions between the polymer and the small reagent are not important in determining k_2/k_2^0. We must then assume that the reactivity of the polymers is governed by the "local medium" effect. Also, the active esters attached to the poly-N,N-dimethylacrylamide chains are substantially more reactive than their low molecular weight analogs. This is due to the fact that dimethylamide groups of the chain backbone can catalyze the aminolysis reaction.

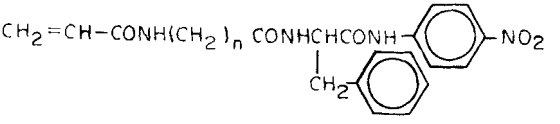
The importance of the local environment effect may be illustrated yet in another manner, i. e., if we study reactions of the polymeric reagent and its analog in different solvents. Since the polymer backbone contributes to the properties of the local medium, it would be expected to exercise a "buffering effect" on the reaction rate. It was found, in fact, that the aminolysis rate constants of polymeric reagents were much less affected by a change of the solvent than the reactions

TABLE 1. Ratio of the Second-Order Rate Constants for the Aminolysis of Nitrophenyl Acrylate Copolymers and Nitrophenyl Isobutyrate in Dioxane at 50°C

	k_2/k_2^0			
Comonomer	$n\text{-}C_4H_9NH_2$	$C_6H_5CH_2NH_2$	$n\text{-}C_{10}H_{21}NH_2$	$HOC_2H_5NH_2$
Styrene	0.0353	0.0204	0.0305	0.0223
Methyl acrylate	0.296	0.267	0.320	0.207
Dimethylacrylamide	5.68	4.67	4.92	2.93

of the analog [4]. For instance, the reaction of the dimethylacrylamide-p-nitrophenyl acrylate copolymer has almost the same rate in dioxane at 50°C as in water at 30°C, while the same change of the medium accelerates the p-nitrophenyl isobutyrate reaction by a factor of about 190.

The steric hindrance due to the polymer backbone becomes an important factor if a reaction of a group attached to the polymer is to be catalyzed by an enzyme. We have studied this effect on acrylamide copolymers with monomers having structures of type I carrying L-phenylalanine p-nitroanilide residues at varying distances from the chain backbone [5]. When the hydrolysis of the p-nitroanilide groups in these copolymers was catalyzed by chymotrypsin, the rate of the reaction was found to be comparable to that of the monomer only when the sensitive bond was spaced by eleven covalent bonds from the chain backbone. Shortening this distance to nine and



I (n = 1, 3, 5)

seven bonds led to a drastic reduction in the susceptibility of the polymer to enzymatic attack. This reflects the critical steric requirements of the active site of chymotrypsin. On the other hand, the length of the polymer chain is without effect on the rate of the enzyme-catalyzed reaction, so that groups attached to the polymer are not shielded from the enzyme by the macromolecular coil. This result is similar to other observations of reactions of two polymeric reagents involving substantial activation energies [6] but contrasts with diffusion-controlled processes which exhibit decreasing rate constants with an increasing length of the polymer [7, 8].

REACTIVITY OF GROUPS ATTACHED TO CROSSLINKED POLYMER NETWORKS

The use of crosslinked polymer beads as carriers for multistep syntheses as pioneered by Merrifield [9], has opened up new vistas in the synthesis of chain molecules with a predetermined sequence of monomer residues. The method has proved particularly valuable for the preparation of polypeptides with biological activity [10, 11].

There are, however, several serious problems with the application

of this technique. Merrifield selected crosslinked polystyrene as his carrier, a polymer which is still being used by most workers in this field. Yet, this substance was chosen because of its easy availability, not because it is particularly suitable for this specific application. It is a nonpolar polymer, and, as it gradually acquires a polypeptide side-chain, solvation of the beads changes drastically. This would be expected to affect the rates of reactions involving groups attached to the crosslinked network and it has, in fact, been demonstrated that crosslinked poly-N,N-dimethylacrylamide has more favorable characteristics as a polymeric support for polypeptide synthesis [10-12].

The second problem involves variations in the reactivity of chemically equivalent groups attached to a polymer network. Ideally, we should, of course, like to have a gel carrying groups which are all equally reactive. Then, with a large excess of a reagent in the continuous phase we would be certain that if a 90% conversion is obtained in time t, 99% will be obtained in 2t and 99.9% in 3t. This is important, since the utility of the solid-state polypeptide synthesis depends on our ability to obtain virtually quantitative yields in each reaction step. Unfortunately, chemically equivalent groups attached to a crosslinked polymer exhibit a pronounced dispersion of rate constants for a given reaction. For instance, Geising and Hornle [13] found for the addition of an isoleucine unit to a polypeptide chain a conversion of 90% in 10 min but conversions of only 93% and 95% after 1 and 2 hr. We have, therefore, tried to determine the factors responsible for this dispersion. For this we had to develop a technique for monitoring continuously the course of a reaction taking place in a gel phase. In particular, since we are most interested in the final stages of the reaction, we need a method which yields a signal proportional to the concentration of unreacted, rather than reacted groups.

We utilized in this study a model system consisting of a membrane of crosslinked poly(methyl acrylate) containing a small proportion of p-aminostyrene residues. We followed the acylation of these residues when the film was placed in contact with a solution containing a large excess of acetic anhydride by reflectance fluorescence which is completely quenched by the acylation [14]. The method is extremely sensitive, and when it is applied to a solution of linear polymer, it yields linear first-order plots which can be followed over seven half-lives. By contrast, data obtained on crosslinked films exhibit increasing deviations from first-order kinetics at conversions of somewhat above 80%. The results led to a most unexpected finding. It had been assumed that the dispersion of the rate constant is due to steric restraints of groups lying close to crosslinkage points and that this dispersion will become more pronounced with increasing crosslink density. No such effect was observed—in fact, the deviations from first-order kinetics were remarkably similar in films containing from 1 to 14.5 wt % bifunctional monomers (see Fig. 1). Even

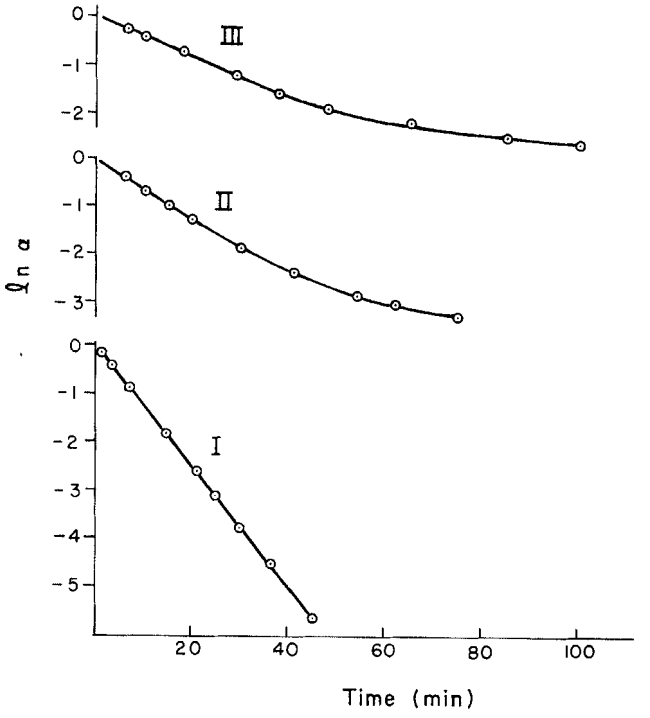


FIG. 1. Decay of the residual fluorescence α during the acylation of p-aminostyrene copolymers: (I) linear copolymer; (II) copolymer crosslinked with 1 wt % glycol dimethacrylate; (III) copolymer crosslinked with 14.5 wt % glycol dimethacrylate.

more surprising, when a linear copolymer carrying the aminostyrene residues was dissolved in methyl methacrylate containing some glycol dimethacrylate and the monomers were polymerized so that the linear chains were entangled in the crosslinked network, the kinetics were indistinguishable from those observed when the reactive groups were covalently linked to the gel.

It appears then that the dispersion of the rate constant reflects microscopic fluctuations in the gel structure. Other techniques have led to the conclusion that crosslinkages are not uniformly distributed in polymer networks, so that very dense regions are interspersed within regions in which the polymer presents very little resistance to the motion of low molecular weight species [15]. Our kinetic results may then be a consequence of this physical situation.

The above interpretation is supported by recent data on the

reactivity of aminostyrene residues attached to a linear polymer which swells to a limited extent in the acetic anhydride solution. First-order plots of the progress of the reaction were found to be linear up to high conversions, with the process followed through seven half-lives. This result suggests that it might be advantageous to use linear polymers swelling to a desirable degree in the reaction medium as a polymeric support for polypeptide and other similar syntheses, rather than polymers rendered insoluble by crosslinking.

RATES OF CONFORMATIONAL TRANSITIONS IN FLEXIBLE POLYMER CHAINS

It has long been assumed that conformational transitions in flexible polymer chains involve two hindered rotations taking place simultaneously, so that only a short segment of the chain has to move through the viscous medium. Although this suggestion was first advanced with respect to polymers in bulk [16], it has also been widely adopted in theoretical considerations of the behavior of polymer chains in dilute solutions [17-19] and in the interpretation of experimental data obtained in dilute systems [20-23]. However, if the two rotations were to be strictly simultaneous, the activation energy for this process would have to be twice as large as for the conformational transition in an analogous small molecule which requires only a single hindered rotation [16, 19]. It is, therefore, important to compare the rates of conformational transitions in polymers and their low molecular weight analogs so as to establish whether the behavior of chain molecules is consistent with the concept of crankshaftlike motions in dilute solutions.

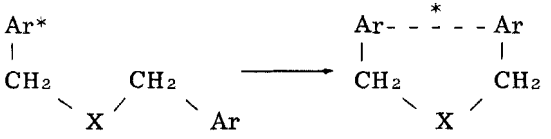
A number of techniques for the study of conformational mobility in polymer chains have been explored in recent years. However, methods which are sensitive to rotational diffusion cannot be used to compare polymers with their analogs. In large molecules, rotational diffusion of the molecule as a whole is negligible, and data obtained by measurements of dielectric dispersion, depolarization of fluorescence, NMR relaxation or the broadening of ESR spectra of spin labels have been interpreted in terms of the rates of local conformational transitions [24]. This is not possible for small molecules, since rotational diffusion of the molecules as a whole may be fast compared to the interconversion of the molecular conformations. We have, therefore, used in our studies spectroscopic techniques which yield information about hindered rotation around a specific bond and are unaffected by rotational diffusion of the molecule.

Early investigations which used an NMR technique to characterize the hindered rotation around amide bonds [25] or UV spectroscopy to follow the thermal cis-trans isomerization of azobenzene residues

built into a polymer backbone [26] revealed no difference between the behavior of polymers and their analogs. These studies suffered, however, from the fact that the hindered rotation which was being observed was characterized by a high energy barrier, while the polymer chain contained many much more flexible bonds. There was, therefore, a need to develop techniques by which very much faster processes could be observed.

We have now demonstrated two such methods. The first involves studies of the photochemical trans-cis isomerization of azobenzene residues in the backbone of polymers and in analogous small molecules [27]. It is known that the excited trans and the excited cis forms of azobenzene are separated by an energy barrier of 2-3 kcal/mole [28], similar to the energy barriers for conformational transitions of typical polymers. Thus, the relative quantum yield for this reaction in the polymers and the small molecules should tell us whether incorporation of a residue into the backbone of a polymer slows down its conformational transitions. In fact, no difference was found in dilute solutions between the quantum yields for the polymer and the analog.

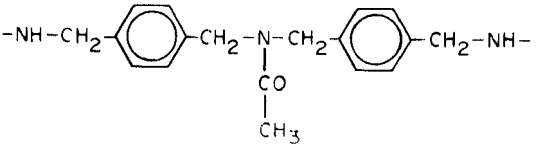
An even more convincing technique utilizes the formation of a sandwich complex between an excited aromatic chromophore, Ar, and a similar chromophore in the ground state, a so-called excimer. Such excimers are formed intramolecularly by a variety of compounds of the type $ArCH_2XCH_2Ar$ where X may be $-CH_2-$, $-O-$, $-NH_2^+-$, or $-NH(COR)-$ [29], and they have characteristic emission spectra distinct from those of the uncomplexed chromophore. Since the conformation required by the excimer would correspond to a prohibitive energy requirement for the unexcited molecule, excimer formation requires a conformational transition during the lifetime of the excited state of the chromophore, i. e., a process of the type:



Thus, the ratio of excimer and normal fluorescence intensity is a measure of the probability that this conformational transition takes place during the excited lifetime.

In applying excimer fluorescence to a comparison of the conformational mobilities of a polymer and its analog, a complication arises due to energy migration between chromophores attached to polymer chains, which tends to increase the excimer yield. We have overcome this difficulty by preparing polymers with a very low concentration of excimer-forming sites in the chain backbone. This was

accomplished by building a small proportion of units of type II into a polyamide chain. Emission spectra of this polyamide and of its low



II

molecular weight analog in formic acid solution over a range of temperatures indicated that the activation energy for the conformational transition required for excimer formation is essentially the same in the polymer and the analog [30]. This result seems to prove that crankshaftlike motions cannot be the mechanism for conformational transitions of polymers in dilute solutions.

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