Macromolecules **1980,** *13,* 1157-1162 **1157**

Kinetic Characteristics of Model Reactions Involving a Cross-Linked Polymer Reagent[1]

Shi-shyan Pan and Herbert Morawetz*

Polymer Research Institute, Polytechnic Institute of New York, Brooklyn, New York 11201.

Received March 4, 1980

ABSTRACT: When a fluorescing reagent is converted to a nonfluorescing reaction product, reflectance fluorescence yields precise kinetic data up to conversions exceeding 99%. This method was applied to a study of the acylation of aromatic amine residues in linear and cross-linked polymers by acetic and butyric anhydrides. It was found that cross-linking leads to a dispersion of the rate constant, which renders the final stages of the reaction extremely slow. This cannot be due to steric hindrance since it is only slightly dependent on cross-link density or the spacing of the reaction site from the chain backbone. Even the reaction of a linear aminostyrene copolymer entrapped in a cross-linked gel exhibits a similar kinetic behavior. A method is proposed for the characterization of the dispersion of the acylation rate constant and it is shown that this dispersion depends on the nature of the main monomer in the polymer gel. The quaternization of cross-linked poly[butyl methacrylate-*co*-4-(dimethylamino)styrene] by methyl fluorosulfonate in cyclohexane solution exhibited no deviation from first-order kinetics in the final stages of the process. It is proposed that the kinetic behavior of reactive groups attached to cross-linked polymers reflects the variation of the local polarity with an averaging by micro-Brownian motion impeded by the network structure. The difference in the behavior of the acylation and quaternization reactions is assigned to the different effect of the medium polarity on these two processes.

The use of a polymeric support in organic chemical synthesis was pioneered by Merrifield[2] for the preparation of polypeptides, and this technique has proved strikingly powerful for the preparation of long polypeptide chains with a predetermined amino acid sequence.[3] In recent years, polymeric reagents have been applied to a variety of problems and excellent reviews of the subject are available.[4] Although homogeneous solutions of polymeric reagents have also found some application in polypeptide synthesis,[5] most of the work in this area involves cross-linked polymers to which appropriate functional groups are attached, allowing easy separation of the polymer from an excess of the reagent in the solution phase and a simple isolation of the reaction product.

At this time, polypeptide synthesis on cross-linked polymeric supports may be considered the most important application of polymeric reagents. Yet, in spite of its many successes, the method suffers from a serious problem: since the intermediates during the buildup of the polypeptide chain are not isolated and purified, each reaction step must go to completion if the final product is not to be contaminated by polypeptides in which some of the amino acid residues are missing. This requirement is very exacting. For instance, in conventional organic synthesis a yield of 99% in a reaction would be considered eminently satisfactory, while in a synthesis of a polypeptide with 40 amino acid residues (requiring a deprotection and a coupling reaction for each residue[2]) a conversion of 99% in each step of the synthesis would lead to a product contaminated by 55% of polypeptides having the wrong amino acid sequence, with no hope for the removal of these undesirable impurities.

Past studies have shown[6] that chemically equivalent groups attached to a cross-linked polymer network are not equally reactive and this is undoubtedly the major cause of the difficulty attending "solid-state polypeptide synthesis". In this investigation we have aimed at pinpointing the factors which may cause such a dispersion of the rate constant characterizing a reactive group attached to a polymer gel. If the polymer-bound groups react with a large excess of a reagent dissolved in a solvent which swells the polymer network, then the deviation from first-order kinetics will define this dispersion of the rate constant. Since we are particularly interested in the final stages of the reaction, it will be necessary to use an analytical procedure allowing a continuous monitoring of the progress of the reaction with the signal proportional to the fraction of the polymer-bound reagent which has remained unreacted. To satisfy this requirement, we have chosen for study two model reactions in which a fluorescing reagent is converted to a nonfluorescing product and have used reflectance fluorescence to monitor these processes.

Experimental Section

Monomers. *p*-Aminostyrene (Polysciences Inc.) was distilled at 77 °C (1 torr). 4-(Dimethylamino)styrene (distilled at 0.1 torr) was obtained by a modification of the procedure described by Arcus and Hall.[7] Methyl acrylate [bp 50 °C (270 torr)], methyl methacrylate (bp 100 °C), and butyl methacrylate [bp 57 °C (11 torr)] were obtained from Rohm and Haas, ethylene dimethacrylate ([bp 76 °C (0.5 torr)], 1,6-hexamethylene diacrylate [bp 90 °C (1 torr)], and divinylbenzene [bp 57 °C (2 torr)] were purchased from Polysciences Inc., and *N,N*-dimethylacrylamide [bp 48 °C (0.5 torr)] was obtained from Kohjin Co. Ltd. *N*-Acrylylpyrrolidone was obtained as a gift from the late Professor R. Walter. All of the above monomers were distilled in the presence of 1% *tert*-butylcatechol polymerization inhibitor. *p*-Aminobenzyl methacrylate was prepared by reduction of *p*-nitrobenzyl methacrylate with dodecacarbonyltriiron, using Landesberg's method[8] for the reduction of nitroaryls.

Linear Polymers. Methyl acrylate and methyl methacrylate were each copolymerized in dioxane solution (for 1 h at 70 °C) with 4-aminostyrene (1.2 mol %), using 0.2 wt % AIBN initiator. The aminostyrene content of these copolymers (1.8 and 3.4 mol %, respectively) was obtained from the optical density in acetonitrile solution at 290 nm, using the extinction coefficient of *p*-toluidine (2090 $\mathrm{cm^{-1}\,M^{-1}}$) as a standard. A butyl methacrylate copolymer and butyl methacrylate–methyl methacrylate terpolymers were prepared at 60 °C from monomer mixtures containing 0.8 mol % of 4-aminostyrene; these were insoluble in dioxane, but, assuming a similar reactivity ratio for methyl and butyl methacrylates with aminostyrene, these polymers may be estimated to have contained 2.2 mol % aminostyrene residues. Butyl methacrylate was copolymerized with 0.57 mol % 4-(dimethylamino)styrene. Analysis by absorption at 298 nm in cyclohexane solution, using *N,N*-dimethylaniline (extinction coefficient 2100 $\mathrm{cm^{-1}\,M^{-1}}$) as a standard, yielded 1.8 mol % (dimethylamino)styrene residues.

Cross-Linked Polymers. Monomer mixtures containing divinyl derivatives and 0.6 wt % AIBN were polymerized at 70 °C for 6 h in a stainless steel mold covered with Teflon tape; a stainless steel O-ring was used to control the thickness of the film to 0.4 mm. Films containing 4-aminostyrene were extracted with acetonitrile to remove traces of unreacted monomers and were kept immersed in acetonitrile before use; the cross-linked butyl methacrylate copolymers with 4-(dimethylamino)styrene were

0024-9297/80/2213-1157$01.00/0 © 1980 American Chemical Society

Table I
Relative Reflectance Fluorescence Intensities of Mixtures of Aniline and Acetanilide in Acetonitrile[a]

f	I	I/f
1.0	60.0	60.0
0.8	46.9	58.6
0.6	35.1	58.5
0.5	29.0	58.0
0.4	23.7	59.3
0.2	12.2	61.0
0.1	6.2	62.0

[a] $c_{\mathrm{PhNH_2}} + c_{\mathrm{PhNHAc}} = 0.023$ M.

similarly treated with cyclohexane. A film was also prepared containing 6 wt % of the linear methyl acrylate–aminostyrene copolymer entrapped in a polymethacrylate cross-linked with 3 wt % of the ethylene dimethacrylate. This film was swollen to equilibrium with acetonitrile by exposing it to the vapor of this solvent in a desiccator.

Reaction Kinetics. The conversion of fluorescing reagents to nonfluorescing products was followed by intermittent reflectance fluorescence measurements,[9] using a Perkin-Elmer 204A spectrophotometer fitted with a thermostated cell compartment. With soluble samples, solutions were observed in a stoppered quartz cell; with cross-linked films, the sample was clamped between two steel frames fitted diagonally into a 1 cm × 1 cm quartz cell. After addition of the solution of the reagent, the cell was stoppered and shaken before it was placed into the thermostated compartment in the fluorimeter. An excitation wavelength was used at which the reagent and the reaction product have the same extinction coefficient. For *p*-toluidine and its acylated derivative the isosbestic point was at 275 nm with an extinction coefficient of 1100 $\mathrm{cm^{-1}\,M^{-1}}$; for dimethylaniline and trimethylanilinium the isosbestic point was at 250 nm with an extinction coefficient of 14000.

Results and Discussion

Use of Reflectance Fluorescence as an Analytical Tool for Studies of Reaction Kinetics. To maximize the sensitivity of reflectance fluorescence, it is advantageous to have all of the incident light absorbed by the sample. The fluorescence intensity will then be proportional to the fraction of unreacted reagent only if the reagent and the reaction product have the same extinction coefficient at the excitation wavelength, so that the volume of the sample in which the reagent is excited is independent of the progress of the reaction. To verify this principle and to assess the precision of our procedure, we irradiated mixtures of aniline and acetanilide with a fixed total concentration in acetonitrile solution at 275 nm, the isosbestic point of these two compounds. The results are listed in Table I, demonstrating a satisfactory proportionality between the observed fluorescence intensity and the fraction of aniline which is not acylated.

Collisional Quenching. A reagent may reduce the fluorescence intensity of a fluorescing species by collisional quenching before any reaction takes place. We found that such quenching of aniline fluorescence takes place in the presence of acetic anhydride. Its magnitude was evaluated by extrapolating the fluorescence intensity of an acetonitrile solution of aniline and various concentrations of acetic anhydride back to zero time and applying the relation $I/I_0 = 1 + K_{\mathrm{SV}}(Q)$, where I_0 and I are fluorescence intensities in the absence and the presence of a quencher with a concentration Q and K_{SV} is the Stern–Volmer constant. We found that $K_{\mathrm{SV}} = 13.5\ \mathrm{M^{-1}}$ for the collisional quenching of the aniline fluorescence by acetic anhydride at 30 °C. Thus, with an anhydride concentration of 0.14 M used in our studies of acylation kinetics, the initial fluorescence intensity of aniline in acetonitrile solution would be reduced by a factor of 2.9. Fluorescence quenching of aminostyrene residues in polymer gels would be expected to be smaller because of the reduced diffusion coefficient of the anhydride and the restricted mobility of the chromophore attached to the polymer network.

Table II
Acylation of 4.1×10^{-4} M *p*-Toluidine by 0.14 M Butyric Anhydride in Acetonitrile Solution at 40 °C

time, s	rel fluorescence	$72.4e^{-0.0027(t-90)}$	$t/t_{1/2}$
90	72.4	72.4	0.29
210	55.8	55.1	0.69
300	45.0	44.9	0.98
390	36.6	36.6	1.28
690	18.3	18.5	2.26
840	13.1	13.2	2.75
1020	8.5	8.8	3.34
1350	3.9	4.1	4.43
1890	1.1	1.2	6.20
2670	0.2	0.2	8.75

Acylation Kinetics of Aniline, *p*-Toluidine, Linear Copolymers of 4-Aminostyrene, and Cross-Linked Resins Containing 4-Aminostyrene Residues. Acylations of aniline and toluidine in acetonitrile solution by 0.14 M acid anhydrides could be followed to high conversion by the reflectance fluorescence technique. This is exemplified by data for the reaction of 4.1×10^{-4} M *p*-toluidine with butyric anhydride at 40 °C listed in Table II. It may be seen that the relative fluorescence intensities parallel closely those calculated with a rate constant of 0.00227 $\mathrm{s^{-1}}$ up to more than 7 half-lives. We know of no other technique which would allow the continuous monitoring of the final stages of a reaction with a comparable precision. The acylation of aniline and *p*-toluidine by acetic anhydride at 30 °C yielded first-order rate constants of 33×10^{-4} and 9.3×10^{-4}, respectively. The acetylation of solutions of poly(methyl acrylate-*co*-aminostyrene) and poly(methyl methacrylate-*co*-aminostyrene) at 30 °C followed also strictly first-order kinetics, showing that the aminostyrene residues in a given chain molecule were all equally reactive; the rate constants of 22.3×10^{-4} and 21.4×10^{-4} were intermediate between those of aniline and *p*-toluidine.

It should be noted that acetic acid is a catalyst for the acylation of aromatic amines by acid anhydrides,[10] and we have found that the acetylation of aniline is accelerated eightfold in the presence of 0.04 M acetic acid. However, the concentration of acetic acid produced in the acetylations under our experimental conditions is so low that no kinetic effect would be expected due to its formation.

By contrast with the behavior of the linear polymers in homogeneous solution, all the acylations of cross-linked aminostyrene copolymers in contact with 0.14 M acid anhydride solutions in acetonitrile deviated sharply from first-order kinetics in the final stages of the reaction. This difference in the kinetic behavior of the reactive residues attached to linear and cross-linked polymers is illustrated in Figure 1; while the plot of ln R, where R is the fraction of unreacted aminostyrene residues,[11] against time is linear up to a conversion of 99% for the polymer solution, this semilogarithmic plot for cross-linked gels deviates significantly from linearity at a conversion of about 80% and the final stages of the conversion are extremely slow. This deviation from first-order kinetics is remarkably insensitive to the cross-link density in the gel—as seen in Figure 1, it occurs at very similar conversion for methyl acrylate–aminostyrene copolymers containing 1 and 15 wt % of a cross-linking agent. It was found that the dispersion of the rate constant remained just as pronounced when the reaction site was moved further from the chain backbone

Table III
Mean First-Order Rate Constants of the Acetylation of Aminostyrene (AS) Residues in Cross-Linked Polymer Films by 0.14 M Ac_2O in Acetonitrile at 30 °C

main monomer	cross-linker[a]	wt % AS	swelling ratio[b]	$10^4\bar{k}$, s^{-1}
methyl acrylate	1 wt % EDM	0.64	3.2	11.0
methyl acrylate	3 wt % EDM	0.54	2.0	8.7
methyl acrylate	6 wt % EDM	0.38	1.4	9.3
methyl acrylate	15 wt % EDM	0.36	0.5	6.8
methyl acrylate	1 wt % HDA	0.40	3.2	14.7
methyl acrylate	2 wt % DVB	0.60	3.1	10.5
methyl methacrylate	1 wt % EDM	0.40	1.2	16.3
butyl methacrylate	1 wt % EDM	0.20	0.35	11.3
dimethylacrylamide	1 wt % MAA	0.34	2.9	22.5
N-acrylylpyrrolidine	1 wt % EAA	0.60	1.6	43
methyl methacrylate[c]	3 wt % EDM	0.11	2.0	15.7

[a] EDM = ethylene dimethacrylate; HDA = hexamethylene diacrylate; DVB = divinylbenzene; MAA = methylenebis(acrylamide); EAA = ethylene bis(acrylamide). [b] Grams of acetonitrile sorbed by 1 g of gel. [c] Cross-linked poly(methyl methacrylate) with entrapped poly(methyl acrylate-*co*-aminostyrene).

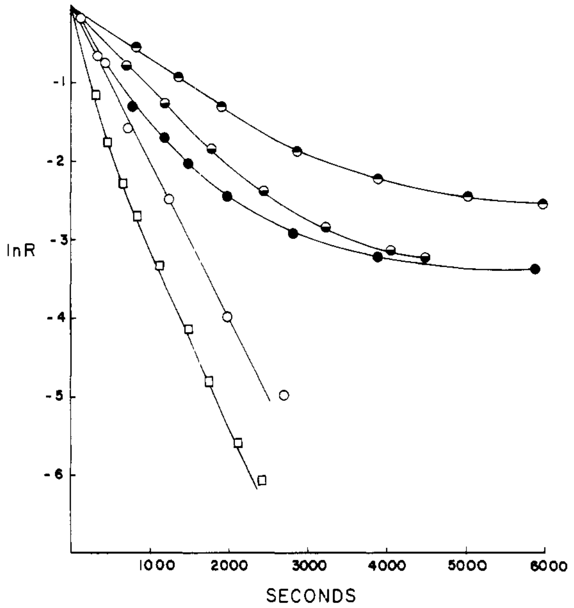

Figure 1. Course of acetylation of linear and cross-linked aminostyrene copolymers at 30 °C: (○) dilute solution of methyl methacrylate copolymer in acetonitrile; (□) linear poly(methyl methacrylate-*co*-butyl methacrylate) swollen with acetonitrile; (◒) methyl methacrylate copolymer cross-linked with 1 wt % ethylene dimethacrylate (EDM); (◓) methyl methacrylate copolymer cross-linked with 15% EDM; (●) poly(methyl acrylate) cross-linked with 3 wt % EDM containing entrapped linear poly(methyl acrylate-*co*-aminostyrene).

in a *p*-aminobenzyl methacrylate copolymer and it did not even require covalent bonding of the reactive residues to the cross-linked polymer network, being equally prominent when a linear methyl acrylate–aminostyrene copolymer was entrapped in the gel structure. Thus, this dispersion of the rate constant cannot be caused in our system by the relative inaccessibility of some of the reactive groups due to their proximity to a cross-link, as has sometimes been assumed.[12]

We considered the possibility that deviation from first-order kinetics may be inherent in a reaction taking place in a highly concentrated polymer system. To test this possibility, we prepared a linear terpolymer from a mixture of 30 mol % methyl methacrylate and 70 mol % butyl methacrylate to which 0.5 wt % aminostyrene had been added. This terpolymer sorbs 50 wt % of acetonitrile. The course of the acetylation of this polymer is also shown in Figure 1—there is a slight deviation from first-order kinetics which may be characterized by a rate constant of 3.7×10^{-4} s^{-1} for the first 70% of the reaction and a rate constant of 2.2×10^{-4} s^{-1} for its final stages up to a conversion of 99.5%, but this deviation from simple exponential decay is minor compared to that observed with the cross-linked gels.

Whenever a first-order rate constant of a reaction exhibits a dispersion, the fraction R of unreacted reagent at time t is given by

$$R = \int_0^\infty f(k)\exp(-kt)\,dk \qquad (1)$$

where $f(k)$ characterizes the probability distribution of the rate constant. It follows that the apparent initial rate constant is $\bar{k}$, the mean value of k, and Table III lists the $\bar{k}$ values observed with various cross-linked polymer films. It may be seen that $\bar{k}$ is rather insensitive to the cross-link density but increases rather strikingly when the poly(methyl acrylate) is replaced by the poly(*N*,*N*-dimethylacrylamide) or the poly(*N*-acrylylpyrrolidine) matrix. This effect is probably due to a more favorable distribution coefficient of the acetic anhydride between the gel and the solution phase.

Of greater interest is the dependence of the dispersion of the rate constant on the nature of the gel carrying the aminostyrene residues. It can be shown[13] that eq 1 may be converted to

$$R = \exp(-\bar{k}t)\left[1 + \sum_{r=2}^{\infty} (-1)^r \mu_r t^r / r!\right] \qquad (2)$$

where μ_r is the rth moment of the probability distribution $f(k)$. We have chosen to characterize the relative breadth of this distribution by

$$F \equiv [2/(\bar{k}t)^2]R\exp(\bar{k}t) \qquad (3)$$

which is, in terms of the moments of $f(k)$

$$F = \mu_2/\bar{k}^2 - \mu_3 t/3\bar{k}^2 + \mu_4 t^2/12\bar{k}^2 - \ldots \qquad (4)$$

Since the distribution of k is clearly negatively skewed (i.e., there are some groups with very low reactivity but no groups with $k \gg \bar{k}$), the μ_r with odd r will be negative, leading to an upward curvature of F as a function of a reduced time $t/t_{1/2}$.

Plots of F as a function of $t/t_{1/2}$ are shown in Figures 2–5. Figure 2 shows that for poly(methyl acrylate) cross-linked with ethylene dimethacrylate, deviations from first-order kinetics become significant at about $t/t_{1/2} = 3$. Although an increase in the cross-linker concentration from 1 to 3 wt % apparently reduced the dispersion of k, a further increase to 6 and 15 wt % EDM led to a significant increase in the fraction of groups with sharply reduced reactivity. In Figure 3 we compare poly(methyl acrylate) containing 1 wt % of different cross-linking agents. There

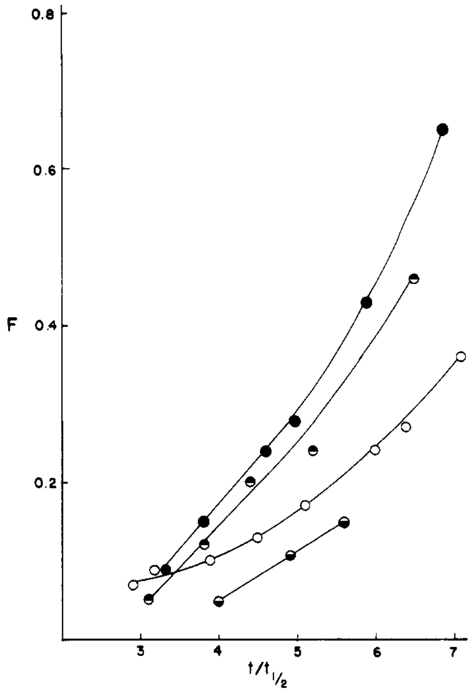

Figure 2. Characterization of the dispersion of the rate constant for the acetylation at 30 °C of poly(methyl acrylate-*co*-aminostyrene) containing varying cross-link densities: (○) 1 wt % EDM; (◒) 3 wt % EDM; (◓) 6 wt % EDM; (●) 15 wt % EDM.

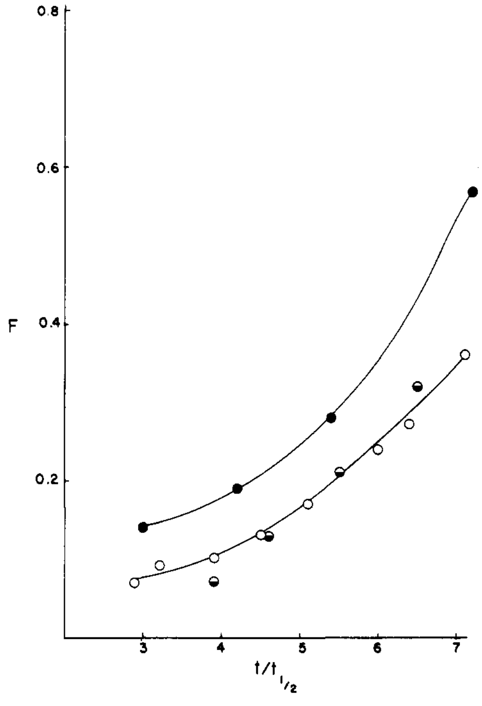

Figure 3. Characterization of the dispersion of the rate constant for the acetylation at 30 °C of poly(methyl acrylate-*co*-aminostyrene) cross-linked with 1 wt % of various divinyl compounds: (○) EDM; (◒) DVB; (●) HDA.

is no significant change in the dispersion of rate constants when ethylene dimethacrylate is replaced by divinylbenzene, in spite of the fact that DVB produces a tighter cross-linkage. On the other hand, the relative breadth of the distribution of reactivities is distinctly higher in the sample cross-linked by hexamethylene diacrylate, in spite of the looser cross-link structure. Figure 4 contains a plot characterizing the dispersion of rate constants for gels prepared from different monomers, all cross-linked with

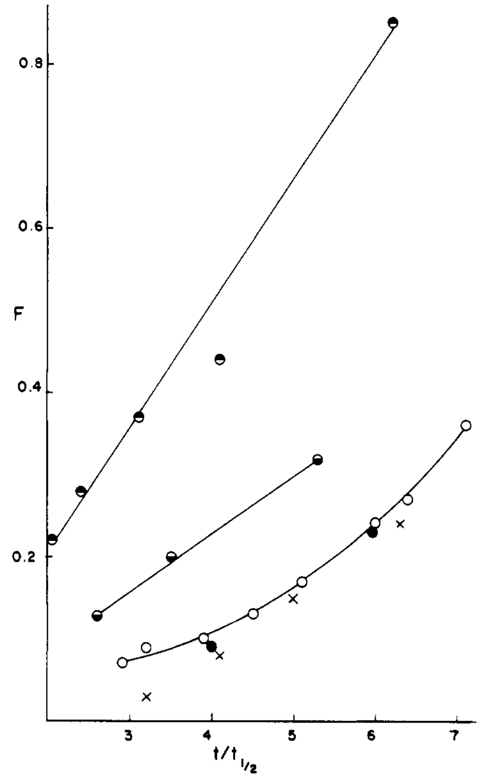

Figure 4. Characterization of the dispersion of the rate constant for the acetylation at 30 °C of various aminostyrene copolymers containing 1 wt % of cross-linking agent: (○) methyl acrylate copolymer cross-linked with EDM; (◒) methyl methacrylate copolymer cross-linked with EDM; (◓) butyl methacrylate copolymer cross-linked with EDM; (●) *N*,*N*-dimethylacrylamide copolymer cross-linked with MAA; (×) *N*-acrylylpyrrolidine copolymer cross-linked with EAA.

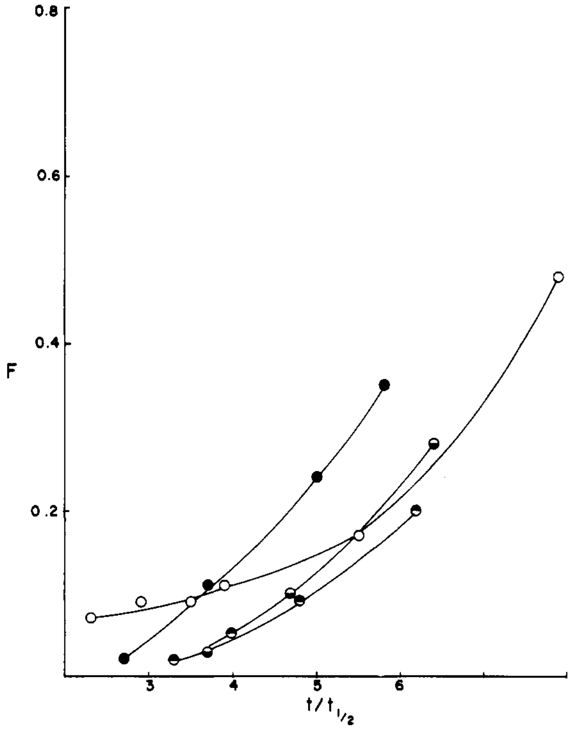

Figure 5. Characterization of the dispersion of the rate constant for acylations at 40 °C of poly(methyl acrylate-*co*-aminostyrene). Reaction with acetic anhydride: (○) copolymer cross-linked with 1 wt % EDM ($\bar{k} = 0.0018\ \mathrm{s}^{-1}$). Reactions with butyric anhydride: (◓) polymer cross-linked with 1 wt % EDM ($\bar{k} = 0.000\,57\ \mathrm{s}^{-1}$); (◒) polymer cross-linked with 3 wt % EDM ($\bar{k} = 0.000\,45\ \mathrm{s}^{-1}$); (●) polymer cross-linked with 6 wt % EDM ($\bar{k} = 0.000\,40\ \mathrm{s}^{-1}$).

1 wt % of a divinyl compound. The poly(methyl acrylate), poly(*N*,*N*-dimethylacrylamide), and poly(*N*-acrylylpyrrolidine) behave very similarly, but the dispersion of rate constants is distinctly higher in poly(methyl methacrylate) and it is very high in the poly(butyl methacrylate) gel. In Figure 5 we compare the acylation with acetic and butyric anhydrides, to assess if the dispersion of the rate constant is related to the bulk of the acylating reagent. It was found that for poly(methyl acrylate) cross-linked with 1 wt % of EDM the dispersion of *k* is actually less when butyric anhydride is the acylating reagent; at higher cross-link densities the curves characterizing the butyric anhydride reaction are almost superimposable on the curves in Figure 2 describing acetylation.

Quaternization of 4-(Dimethylamino)styrene Copolymers. The alkylation of *N*,*N*-dimethylaniline and its derivatives to the corresponding quaternary anilinium compounds leads to the quenching of the fluorescence of the reagent; therefore, this reaction also lends itself to a kinetic study of the reflectance fluorescence technique. However, alkylation reagents such as methyl iodide or dimethyl sulfate are inconveniently slow and we chose, therefore, as our alkylating agent methyl fluorosulfonate (MFS), which is known to lead to alkylation rates higher by about 4 orders of magnitude.[14] This reagent again was too fast for our analytical method in polar media and our studies had to be conducted with a rather dilute MFS solution in a nonpolar solvent, i.e., 0.008 M MFS in cyclohexane.

Although the methylation of 10^{-4} M *N*,*N*-dimethylaniline in cyclohexane leads eventually to a precipitation of the anilinium salt which makes it impossible to interpret reflectance fluorescence data, the initial stages of the reaction could be used to estimate a rate constant of 0.75 × 10^{-4} s^{-1} at 30 °C. When a copolymer of butyl methacrylate containing 1.8 mol % of 4-(dimethylamino)styrene was used as the reagent, the reaction product remained in solution and the progress of the transformation could be followed to conversions exceeding 99.5%. Figure 6 shows that the decay of the fluorescence followed strictly first-order kinetics with a rate constant of 19 × 10^{-4} s^{-1}, much higher than that of aniline. This large difference between the reactivity of a polymer substituent and its low molecular weight analogue is yet another example of a phenomenon noted previously,[15] i.e., that the difference between the polarity of the immediate vicinity of a polymer and the polarity of the solvent may lead to large changes in the reactivity of a functional group when it is appended to a polymer backbone.

When a 0.009 M MFS solution was allowed to interact with a butyl methacrylate copolymer containing 0.1 wt % (dimethylamino)styrene and cross-linked with 3 wt % of EDM (swelling with 76 wt % of cyclohexane at equilibrium), the apparent rate constant increased with time in the initial stages of the reaction, probably due to diffusion control. However, in the later stages, as seen on Figure 6, the reaction followed simple exponential decay up to a conversion in excess of 99%, in striking contrast to the behavior observed in the acylation of cross-linked aminostyrene copolymers.

Possible Causes for the Dispersion of the Rate Constant. As stated above, the pronounced dispersion of the rate constant characterizing the acylation of cross-linked polymers containing small concentrations of aminostyrene residues cannot be due to steric hindrance effects, since the magnitude of the dispersion is insensitive to the degree of cross-linking and remains just as pronounced when the reactive group is appended to a linear polymer entrapped in the gel rather than being covalently attached to the polymer network. We have also ruled out the high polymer concentration as being the cause of the dispersion, since the reaction of a partially swollen linear polymer deviates little from the behavior expected if all polymer-bound reactive groups were kinetically equivalent. Most surprising is the dramatic difference between the behavior of the acylation and quaternization reaction.

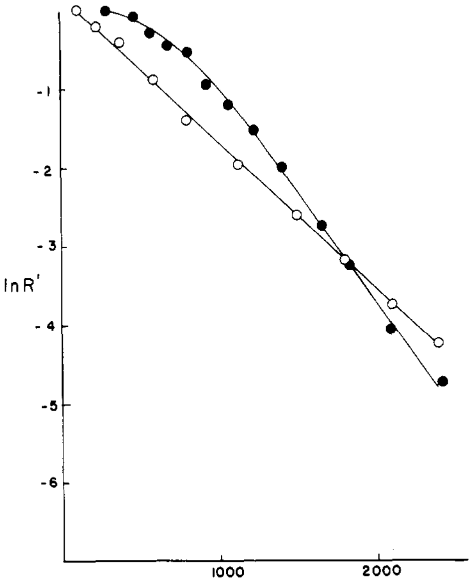

Figure 6. Quaternization of 4-(dimethylamino)styrene copolymers with butyl methacrylate by 0.009 M methyl fluorosulfonate in cyclohexane solution at 30 °C: (○) dilute solution of linear copolymer; (●) copolymer cross-linked with 3 wt % EDM swollen with 76 wt % cyclohexane. *R'* is the ratio of unreacted (dimethylamino)styrene residues at time *t* and at the time of the first reading of the fluorescence intensity.

In searching for a possible interpretation of this difference, we studied the dependence of the acylation of *p*-toluidine at 30 °C on the solvent medium. We found that in acetonitrile solution the acetic anhydride reaction was characterized by a second-order rate constant of 0.0233 M^{-1} s^{-1}, in dioxane or tetrahydrofuran it was 0.0203 and 0.0201 M^{-1} s^{-1}, respectively, but in cyclohexane it was sharply increased to 1.47 M^{-1} s^{-1}. This large increase of the acylation rate of aromatic amines in cyclohexane solution by almost 2 orders of magnitude has been observed previously by Oleinik,[10] who suggested a mechanistic interpretation for the phenomenon. It is in striking contrast to the solvent effect in the alkylation of amines; as Menschutkin reported in his classical study 90 years ago,[16] these reactions are strongly favored by an increase in the polarity of the medium, as would be expected for reactions in which uncharged reagents lead to ionic products.

We propose the following tentative hypothesis: As long as reactive groups are attached to linear polymer chains, micro-Brownian motion will lead to an averaging of the medium and chemically similar groups will react at similar rates (except for variations due to the stereoisomerism of the chain backbone which may be large if neighboring group activation is involved[17] but are minor if the stereoisomerism of the chain leads merely to a change in the effective local medium[18]). However, the introduction of cross-linkages will lead to a severe restriction to conformational mobility and under these conditions a spatial variation of the local polarity may result in a corresponding variation of the rate constant of a reaction which is sensitive to the properties of the medium. But the medium which is unfavorable for the acylation and leads to a very slow reaction for a small fraction of the aminostyrene residues will be precisely the medium favoring the quaternization of (dimethylamino)styrene residues, which would then be expected to have a fast initial phase. Unfortunately, this is not observable, since the reaction rate is governed by the diffusion rate of the quaternization reagent during the time when the most reactive polymer-bound groups would react. We concede that this interpretation of our results cannot be considered as proven and it is obvious that our attempt to deal with the important problem of the general principles governing the reactivity of cross-linked polymer networks should be considered only as a small contribution to its understanding. Whatever may be the explanation of the phenomena we have observed, they demonstrate that the presence or absence of a dispersion of the rate constant characterizing the reactivity of groups carried by a polymer network may depend on the nature of the reaction in which they take part.

It is uncertain whether the results of this investigation are pertinent to the problem of polypeptide synthesis on cross-linked polymer supports, the most important application to reactions of polymer networks. Atherton et al.[19] have demonstrated that results obtained in this synthesis may be very substantially improved by a judicious choice of the polymer. It would then be most desirable to apply our technique of kinetic analysis to amino acid deprotection and coupling and we hope to expand our studies in that direction.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research through Grant GM-05811. We acknowledge helpful advice received from Professor Y. Okamoto. Stimulation for this research was provided by a discussion with Professor R. B. Merrifield and we thank him for drawing our attention to this important problem.

References and Notes

(1) Abstracted from a doctoral dissertation submitted by S.-s. Pan to the Graduate School of the Polytechnic Institute of New York, June 1980.

(2) (a) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963); (b) *Adv. Enzymol.*, **52**, 221 (1969).

(3) B. W. Erickson and R. B. Merrifield in "The Proteins", Vol. 2, 3rd ed., H. Neurath and R. L. Hill, Eds., Academic Press, New York, 1976, p 257.

(4) (a) A. Patchornik and M. A. Kraus, *Pure Appl. Chem.*, **43**, 503 (1975); (b) G. Manecke and W. Storck, *Angew. Chem., Int. Ed. Engl.*, **17**, 657 (1978); (c) C. L. Leznoff, *Acc. Chem. Res.*, **11**, 327 (1978); (d) G. Manecke and P. Reuter, *Pure Appl. Chem.*, **51**, 2313 (1979).

(5) (a) E. Bayer, M. Mutter, R. Uhmann, J. Polster, and H. Mauser, *J. Am. Chem. Soc.*, **96**, 7333 (1974); (b) M. Mutter and E. Bayer, *Angew. Chem., Int. Ed. Engl.*, **13**, 88 (1974).

(6) (a) V. Gut and J. Rudinger, "Proceedings of the 9th European Peptide Symposium", E. Bricas, Ed., North-Holland, Amsterdam, 1968, p 185; (b) W. Geising and S. Hornle in "Proceedings of the 11th European Peptide Symposium", H. Nesvatba, Ed., North-Holland, Amsterdam, 1973, p 146, and the discussion of this work by Morawetz (H. Morawetz, *J. Macromol. Sci.—Chem.*, **A13**, 311 (1979)).

(7) C. L. Arcus and W. A. Hall, *J. Chem. Soc.*, 4199 (1963).

(8) J. M. Landesberg, L. Katz, and C. Olsen, *J. Org. Chem.*, **37**, 930 (1972).

(9) A number of solvents were found to react with aromatic amines under UV irradiation, and acetonitrile was chosen for the acylation study because of its relative inertness. Even with this solvent it was found desirable to expose the reactant to irradiation only for brief periods during which the fluorescence intensity was recorded.

(10) N. M. Oleinik, M. N. Sorokin, and L. M. Litvinenko, *Ukr. Khim. Zh.*, **38**, 343 (1972).

(11) We have here assumed that the first-order rate constant derived for the first few fluorescence readings also governed the progress of the reaction before the first reading was taken. This procedure may lead to a slight overestimation of the conversion, since it does not allow for the diffusion of the anhydride reagent into the gel. Since this diffusion leads to a sharp reduction of fluorescence intensity due to collisional quenching, the simple exponential decay of the fluorescence intensity throughout 2 half-lives may be taken as evidence that the diffusion-limited process was essentially completed before the first reading was taken.

(12) H. Morawetz in "Peptides: Chemistry, Structure and Biology", R. Walter and J. Meienhofer, Eds., Ann Arbor Science Publishers, 1975, p 385.

(13) S. L. Laiken and M. P. Printz, *Biochemistry*, **9**, 154 (1970).

(14) M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnot, and M. C. Whiting, *Chem. Commun.*, 1533 (1968).

(15) (a) P. H. Vandewijer and G. Smets, *J. Polym. Sci., Part C*, **22**, 251 (1968); (b) F. Mikeš, P. Štrop, and J. Kálal, *Makromol. Chem.*, **175**, 2375 (1974); (c) P. Štrop, F. Mikeš, and J. Kálal, *J. Phys. Chem.*, **80**, 694 (1976); (d) J. Su, I. S. Scarpa, and I. M. Klotz, *J. Am. Chem. Soc.*, **98**, 7060 (1976); (e) C.-P. Su and H. Morawetz, *J. Polym. Sci., Polym. Chem. Ed.*, **15**, 185 (1977); **16**, 1059 (1978).

(16) N. Menschutkin, *Z. Phys. Chem.*, **6**, 41 (1890).

(17) H. Morawetz, "Macromolecules in Solution", 2nd ed., Wiley-Interscience, New York, 1975, p 466–72.

(18) C.-P. Su and H. Morawetz, *J. Polym. Sci.*, **15**, 185 (1977).

(19) E. Atherton, D. L. J. Clive, and R. C. Sheppard, *J. Am. Chem. Soc.*, **97**, 6584 (1975).