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CONTROLLED ACTIVITY POLYMERS. V. COPOLYMERS OF 2-(1-NAPHTHYLACETYL) ETHYL ACRYLATE WITH HYDROPHILIC COMONOMERS: RELEASE BEHAVIOR

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ABSTRACT

Release properties of the copolymers of 2-(1-naphthylacetyl)ethyl acrylate with hydrophilic comonomers of known molecular weight have been studied as a function of pH, composition, comonomer type, and copolymer microstructure. Fluorescence and solid-state ^{13}C-NMR studies have also been performed. Neighboring group effects for the hydrolysis were observed by the concentration of auxin released; the release mechanism differed with the comonomer type. In addition, the release behavior of the ionic copolymers is affected by the presence of intramolecular hydrophobic interactions.

INTRODUCTION

Our previous efforts have involved the controlled release study of herbicide-containing polymers [1-13]. We reported a series of polymers with metribuzin, an amine-functional herbicide, pendently attached to cellulose, chitin, starch, poly(vinyl alcohol), and copolymers of metribuzin-containing monomers. In a previous paper [14] we reported the synthesis and molecular characterization of the copolymers of 2-(1-naphthylacetyl)ethyl acrylate (NAEA) with hydrophilic comonomers; we now discuss the effect of copoly-

mer structure on the release of naphthylacetic acid (NAA), a plant growth regulator or auxin, from the copolymers.

EXPERIMENTAL

Materials

Copolymers of NAEA with hydrophilic comonomers were prepared by radical solution polymerization. Details of synthesis and characterization procedures were reported in a previous paper [14].

Analytical Methods

The copolymer compositions, molecular weights, and residual monomer content were determined (Table 1), and microstructures (Table 2) were calculated using statistical methods as described in a previous paper [14].

Sample preparation for release experiments was as follows: Polymer samples were ground and sieved to a particle size of 75-100 μm (No. 200 to No. 100 mesh U.S.A. Standard Testing Sieve). About 35 ± 0.01 mg of each polymer sample was placed in 10-cm long cellulose membrane dialysis tubing (cylinder diameter 6 mm, Spectrapor #2) obtained from Spectrum Medical Industries. After adding a known amount of the appropriate buffer solution (Table 3), the tubing was tied and placed in a screw-capped vial (10 × 2.5 cm diameter) having a Teflon-backed silicone rubber septum as cap liner.

The vial was filled with a measured quantity (about 40 mL) of the same buffer solution. The vial, wrapped with black vinyl tape to avoid any photolytic effects, was then rotated end-over-end at 30-60 rpm at ambient temperature. This rotation, combined with the fact that the dialysis tubing was distended with solution and long enough to prevent inversion in the vial, served to agitate the particles within the tubing very efficiently and prevent agglomeration. Periodically, 20 μL samples were withdrawn and analyzed by reversed-phase liquid chromatography (RPLC) to determine the amount of products released from the polymer.

All chromatography was conducted with a Waters Model 2000 A solvent delivery system having a Waters Model U6K injector. The detector was a Perkin-Elmer LC 75 variable-wavelength detector operating at 283.5 nm. All solvents were filtered and degassed using 0.45 μm membrane filters. The mobile phase of RPLC was 50 vol% acetonitrile and 50 vol% pH 7 aqueous buffer solution. The column was a Waters μ-Bondapak C-18 (3.9 mm i.d. × 30 cm). A precolumn filter (5 μm) and guard column packed with 30-50 μm

TABLE 1. Intrinsic Viscosity, Molecular Weight, and Residual Monomer Content of Auxin-Containing Copolymers

Copolymer[a]	$[\eta]$, dL/g	$\bar{M}_n \times 10^{-4}$	Residual NAEA, mol%[b]
NAEA(22.5)-AM	0.29	5.1	<0.1
NAEA(30.9)-AM	0.44	9.0	<0.1
NAEA(20.5)-MAA	0.53	14.0	<0.1
NAEA(21.5)-HEMA	1.02	–	0.3
NAEA(23.7)-AA	0.35	–	<0.1
NAEA(10.7)-VP	0.20	–	<0.1
NAEA(25.0)-VP	0.28	6.2	<0.1

[a]NAEA = 2-(1-naphthylacetyl)ethyl acrylate; AM = acrylamide; MAA = methacrylic acid; HEMA = 2-hydroxyethyl methacrylate; AA = acrylic acid; VP = *N*-vinyl-2-pyrrolidone.

[b]Mol% of totally incorporated NAEA.

TABLE 2. Structural Data for the Auxin Copolymers of Different Comonomer Combination (statistically calculated from reactivity ratios)

	Blockiness[a]		Alternation,[a]	Mean sequence length	
Copolymer	M_1-M_1	M_2-M_2	M_1-M_2	μ_{M_1}	μ_{M_2}
NAEA(22.5)-AM	4.20	64.08	31.72	1.27	5.04
NAEA(30.9)-AM	8.59	48.29	43.12	1.40	3.24
NAEA(20.5)-MAA	1.01	80.17	18.83	1.11	9.52
NAEA(21.5)-HEMA	3.82	58.99	37.18	1.21	4.17
NAEA(23.7)-AA	3.97	63.51	32.32	1.24	4.94
NAEA(10.7)-VP	2.19	8.08	89.73	1.05	1.18
NAEA(25.0)-VP	5.02	3.65	91.32	1.11	1.08

[a]Blockiness and alternation in mol%.

TABLE 3. Buffer Solution Composition

pH	Buffer salts, m*M*	Antibacterial agent (NaN_3), m*M*
6	50 KHPhth,[a] 6 NaOH	1.5
7	50 KH_2PO_4, 29 NaOH	1.5
8	50 KH_2PO_4, 47 NaOH	1.5
10	25 $NaHCO_3$, 11 NaOH	1.5

[a]Potassium hydrogen phthalate.

C-18 Corasil (Waters) were used to protect the analytical column. The flow rate was 1.2 mL/min.

Under these conditions, NAA eluted at 3.6 mL and 1-naphthylacetic ethylene glycol (NAA-EG) eluted at 5.3 mL (Fig. 1). Standard solutions in aqueous buffer solutions were prepared for calibration. Calibration curves (peak height vs concentration) were generated for each determination by using at least four external standard solutions in the appropriate concentration range. The percentage of the available NAA or NAA-EG released from each sample was calculated by multiplying the concentration by the volume of the aqueous solution in the vial and dividing by the molar amount of attached NAA in the sample.

Solid-state ^{13}C-NMR spectra were obtained at 50.32 MHz on a Bruker MSL 200 spectrometer using the CP/MAS technique.

Steady-state fluorescence spectra were recorded on a Perkin-Elmer Model 650-10S fluorescence spectrophotometer at room temperature. Nitrogen gas was bubbled through the samples for at least 10 min prior to the measurements. The concentration of the polymer and monomer samples was 10^{-4}-10^{-5} mol/L of the naphthyl moiety.

RESULTS AND DISCUSSION

Rates of hydrolysis of pendent bioactive agents from copolymers depend on a number of factors including the nature of the hydrolysis site and the accessability of the nucleophile (H_2O or OH^- in this case) to this site. In most cases the polymer backbone sterically limits approach of the nucleophile to the active site. In this study we first examine the monomer hydrolysis rate

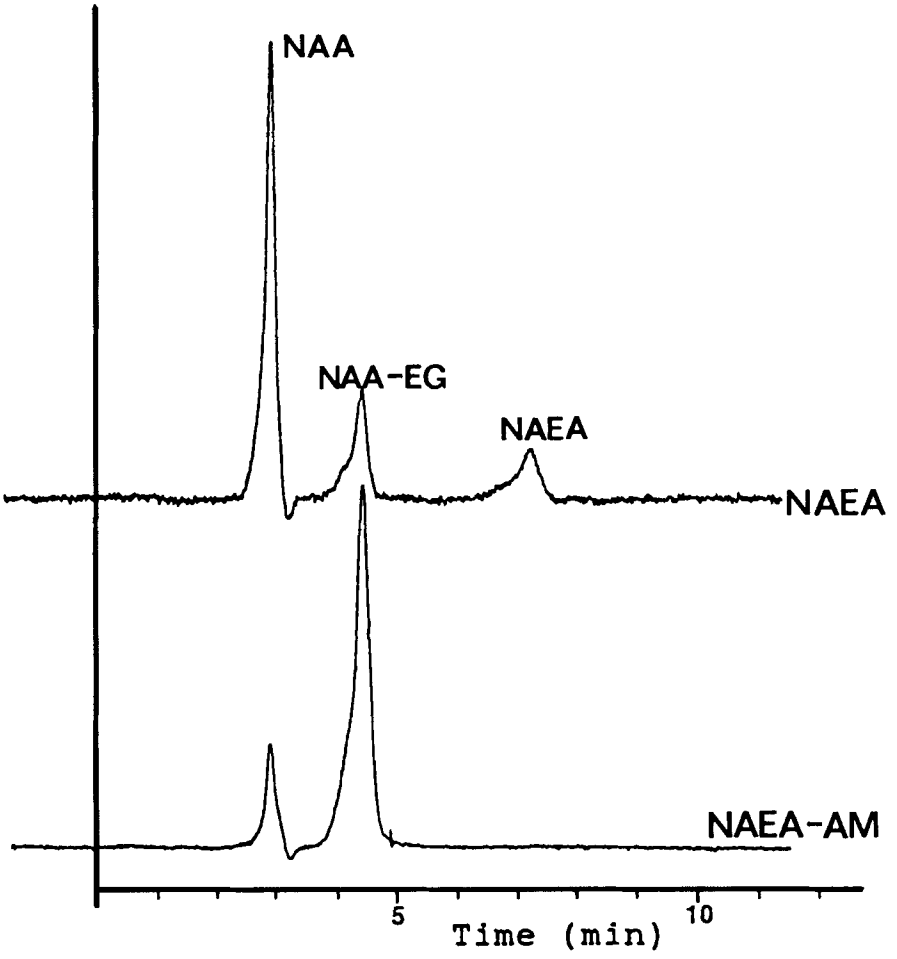

FIG. 1. RPLC chromatograms of hydrolysis products from NAEA monomer and poly(NAEA-*co*-AM).

behavior. Next, this rate behavior is compared with that of copolymers which are specifically tailored with hydrophilic moieties in the vicinity of the labile site and/or spacer units that allow greater accessibility to the active site.

Figure 2 shows simplified overall structures of the copolymers with two hydrolyzable sites, one near the backbone, the other farther removed by the

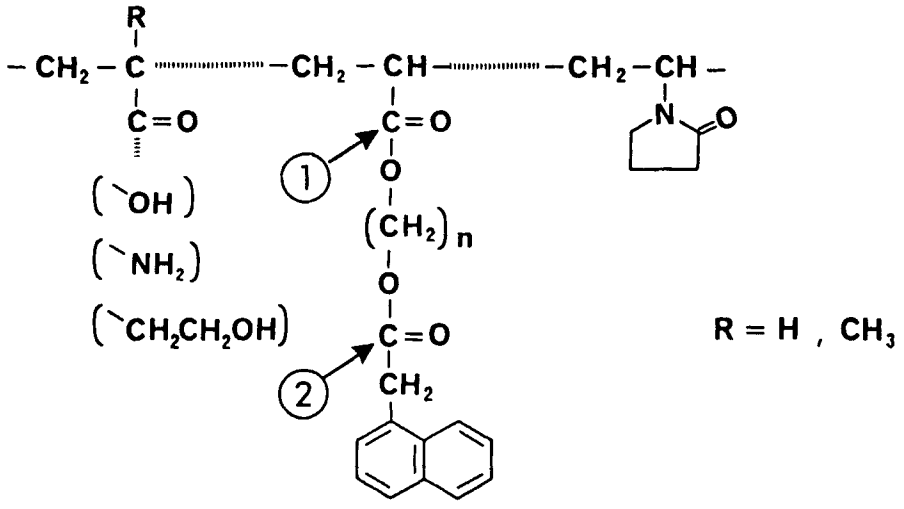

FIG. 2. Simplified overall copolymer structure and sites of release.

spacer. Hydrolysis at the first site yields NAA, and at the second site NAA-EG.

Monomer Hydrolysis Studies

Hydrolysis tests of NAEA monomer were performed at pH 8 and 10 with RPLC. Concentration during hydrolysis was 10 μmol/L since this auxin monomer is very hydrophobic and only sparingly soluble in water. Monomer hydrolysis data (Table 4) show two expected hydrolysis products and different hydrolysis rates at the two hydrolyzable sites. After 2 days at pH 8, the rate of hydrolysis of Site 2 (Fig. 2) is greater than that of Site 1, evidenced by NAA/NAA-EG ratios greater than unity. This effect is also exhibited at pH 10 (Table 4). After 4 d at pH 10, the NAA-EG concentration totally disappeared due to a sequential-step hydrolysis. The slower hydrolysis of Site 1 suggests it to be in a more hydrophobic environment than Site 2 provided by the different substituents (alkene vs naphthylmethyl).

Copolymer Hydrolysis Studies

A number of past studies have shown that hydrolysis near the polymer backbone is more difficult for steric and/or hydrophobic reasons. For ex-

TABLE 4. Hydrolysis Data for 2-(1-Naphthylacetic)-ethyl Acrylate, mol% NAA/mol% NAA-EG

Time, d	pH 8[a]	pH 10
0.2	t/t	19.6/15.7
1	t/t	51.9/19.1
2	2.5/1.3	63.6/5.7
4	5.5/2.8	73.5/–
9	11.7/9.1	86.5/–
40	30.7/8.0	100.0/–

[a]t = trace amount.

ample, it would be expected that hydrolysis at Site 2 (Fig. 2) would normally be favored, regardless of pH. However, we were interested in investigating the effects of polymer microstructure on rates of release. It has been previously shown that comonomers such as methacrylic acid (MAA) and acrylic acid (AA) aid in the hydrolysis of neighboring ester groups by an acid catalysis (termed anchimeric assistance) [15, 16]. Additionally, monomers such as acrylamide (AM) can hydrogen-bond with carbonyl groups of adjacent repeat units to aid in hydrolysis. Monomers such as AA, MAA, and 2-hydroxyethyl methacrylate (HEMA) would be expected to increase the hydrophilicity of Site 1, greatly facilitating Site 1 hydrolysis.

Table 5 shows release data as a function of time at two pH values for two NAEA-AM copolymers of different NAEA content. Greatly enhanced release rates are observed at pH 10 relative to pH 8. Greater concentrations of release products are observed for NAEA(22.5)-AM relative to NAEA(30.9)-AM. Increasing the NAEA content renders the copolymer more hydrophobic and, therefore, prevents the entry of H_2O or OH^- to the active sites, effectively decreasing the relative hydrolysis rates.

At pH 8, two release products are seen for both AM-containing copolymers, indicating that hydrolysis occurs at both active sites. Data at pH 8 indicate the rate of hydrolysis at Site 2 to be greater than that at Site 1 (Fig. 3 and Table 5). This behavior is totally opposite of that observed for the NAEA monomer in which Site 2 release predominated (Table 4). Therefore, neighboring AM assistance of Site 1 hydrolysis of the NAEA-AM copolymers is indicated. At pH 10, both copolymers show greater concentrations of NAA than

TABLE 5. Mole Ratio of Released Products from Auxin-Containing Copolymers[a]

Copolymer	pH	Release concentration ratio after t days				
		2	7	15	30	50
NAEA(22.5)-AM	8	0.3/1.9	0.6/6.2	1.2/12.8	4.1/23.4	
	10	40.5/19.4	85.2/3.3	90.0/0.1	99.2/–	
NAEA(30.9)-AM	8	0.2/1.8	0.3/3.4	0.8/5.2	1.8/6.5	3.3/8.2
	10	13.3/6.5	30.4/1.4	47.8/1.8	66.1/1.2	80.1/0.4
NAEA(20.5)-MAA	8	0.7/–	1.8/–	3.8/–	7.2/–	12.1/–
	10	2.9/–	8.7/–	13.8/–	32.6/–	45.5/–
NAEA(21.5)-HEMA	8	0.8/–	1.1/–	1.2/–	1.4/0.6	
	10	1.7/–	3.2/–	5.5/–	6.9/–	
NAEA(23.7)-AA	8	1.3/0.3	1.8/0.4	2.6/0.6	3.7/0.7	4.2/0.8
	10	2.5/0.2	5.7/–	10.5/–	18.6/–	25.5/–
NAEA(10.7)-VP	8	0.7/–	0.8/–	0.9/–	0.9/–	
	10	2.2/–	4.1/–	6.1/–	9.1/–	
NAEA(25.0)-VP	8	–/–	–/–	–/–	–/–	–/–
	10	–/–	t/–	t/–	t/–	

[a]mol% of available NAA released/mol% of available NAA-EG released; – not detected; t trace amount but not measurable.

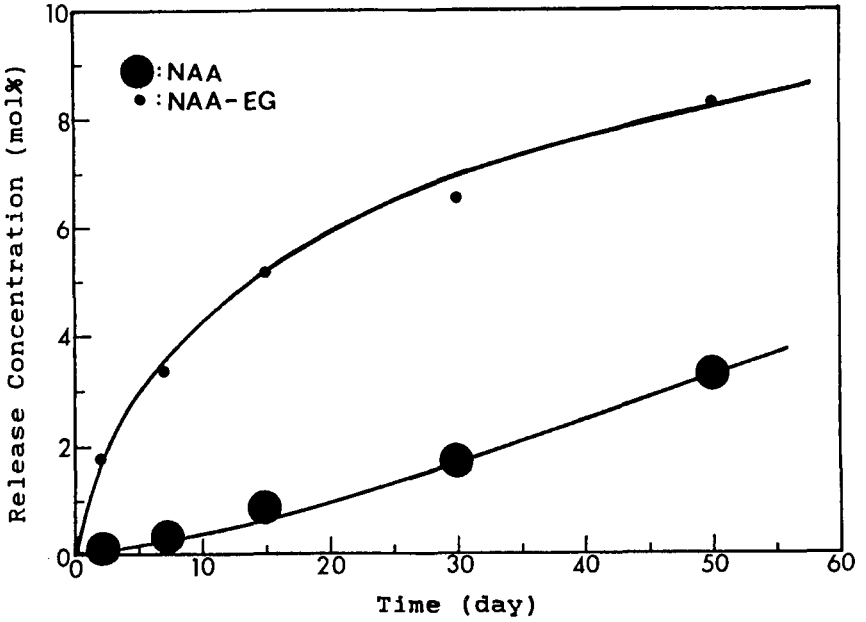

FIG. 3. Release concentration versus time of hydrolysis products from NAEA(30.9)-AM at pH 8.

of NAA-EG (Fig. 4 and Table 5). Several factors are probably responsible for this pH effect: specifically, Site 2 hydrolysis is expected to be enhanced by greater hydroxide concentration, and a sequential step hydrolysis of NAA-EG to NAA is likely also occurring as in the monomer hydrolysis behavior.

To get direct evidence of Site 1 hydrolysis, solid-state ^{13}C-NMR spectra were obtained with the NAEA(30.9)-AM sample. The copolymer, constrained by dialysis tubing, was hydrolyzed for 50 d at pH 10 and subsequently recovered by a freeze-drying technique. Figure 5 shows the solid-state ^{13}C-NMR spectrum of poly(NAEA-*co*-AM) before hydrolysis: δ27-48 (carbons at the polymer backbone), δ55-70 (–OCH_2CH_2O– of spacer linkage carbons), δ115-135 (naphthyl group carbons), and δ166-180 (–CO– of ester and amide). The solid-state ^{13}C-NMR spectrum of the same polymer after hydrolysis (Fig. 6) shows a reduction in the amount of spacer linkage carbon (δ = 63.3) compared to the main-chain carbons and a shifted carbonyl peak (δ = 170-186), which shows the presence of free acid. This evidence clearly indi-

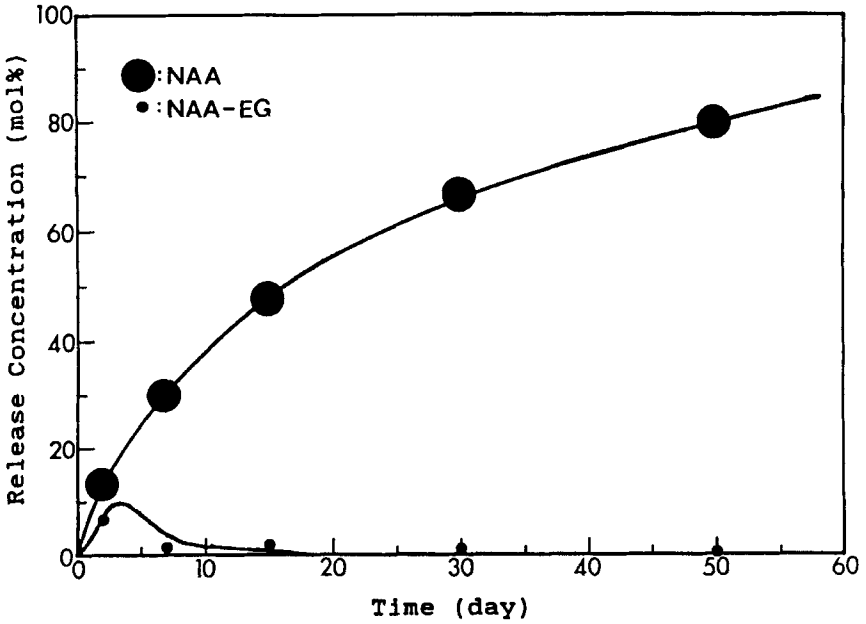

FIG. 4. Release concentration versus time of hydrolysis products from NAEA(30.9)-AM at pH 10.

cates Site 1 hydrolysis, likely due to neighboring assistance in poly(NAEA-*co*-AM).

The data in Table 5 for the NAEA-VP copolymers show substantial hydrophobic effects. An increase of the hydrophobic NAEA concentration in the copolymer to 25 mol% essentially stops the hydrolysis of the NAEA-VP. No Site 1 hydrolysis is observed for the NAEA-VP copolymers, in contrast to the NAEA-AM materials. Apparently the steric bulk of the pyrrolidone ring disallows any Site 1 hydrolysis. Microstructural effects are very important in this case and are discussed in a following section.

The hydrolysis behavior of copolymers of NAEA with MAA and AA would be expected to be affected by pH. At high pH the partially ionic nature of these polymers allows them to have extended conformations. Copolymers of MMA and AA with hydrophobic monomers are known to "hypercoil" under acidic conditions [18]. Such pH-dependent conformational behavior naturally affects the accessibility of the nucleophile to the hydrolysis site and should influence the hydrolysis rate.

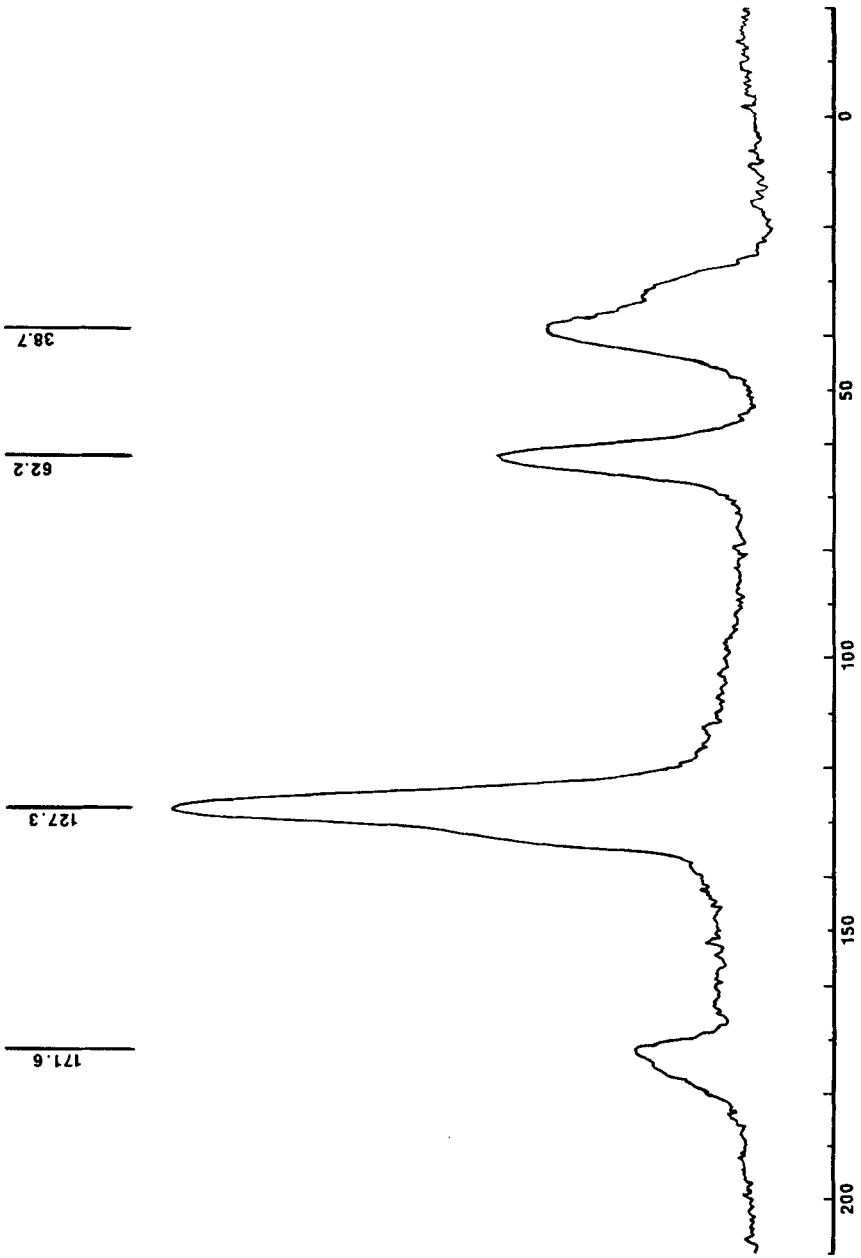

FIG. 5. Solid-state ^{13}C-NMR spectrum of NAEA(30.9)-AM before hydrolysis.

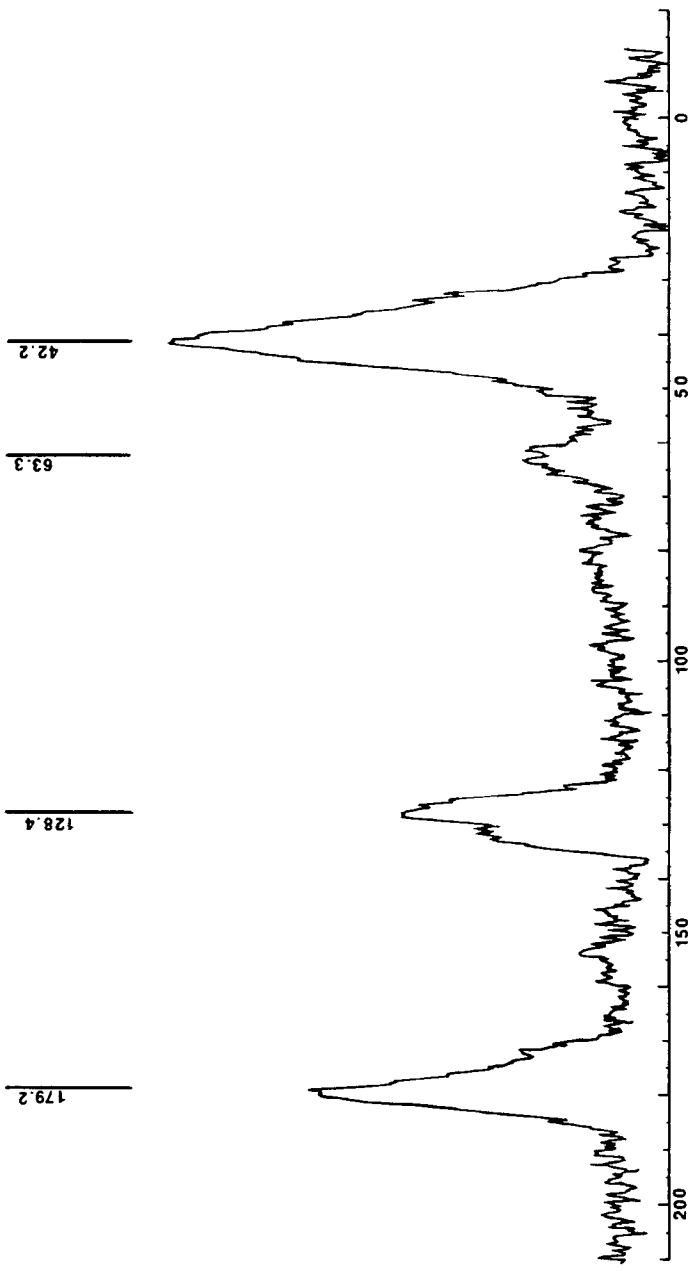

FIG. 6. Solid-state ^{13}C-NMR spectrum of NAEA(30.9)-AM after hydrolysis.

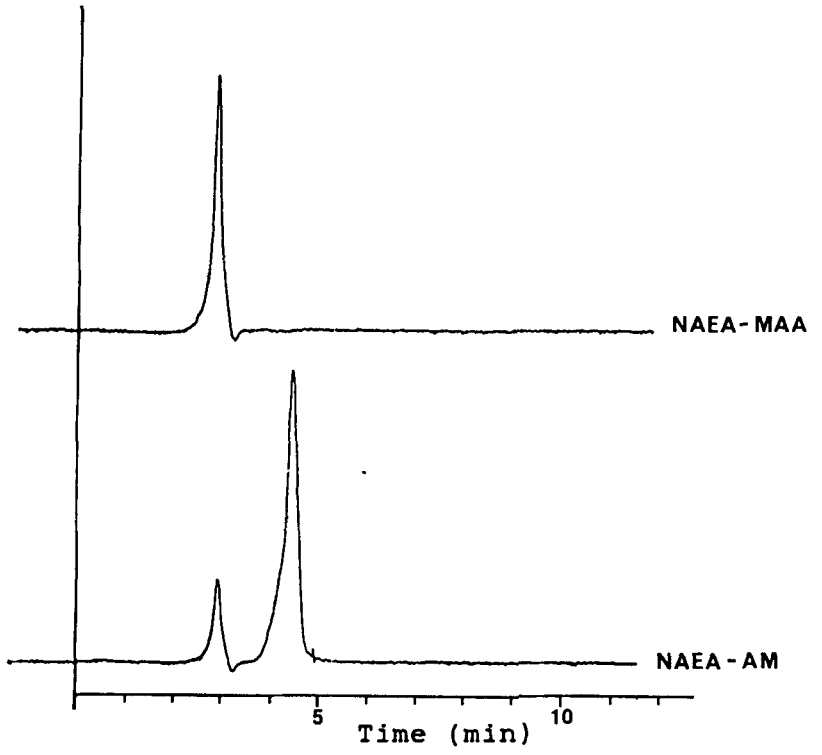

FIG. 7. RPLC chromatograms of hydrolysis products from poly(NAEA-*co*-AM) and poly(NAEA-*co*-MAA).

The two polymers containing pendent carboxylic acid moities, NAEA(20.5)-MAA and NAEA(23.7)-AA, would be in an expanded state at high pH. The NAEA(23.7)-AM copolymer release data at pH 8 show some Site 1 hydrolysis, but hydrolysis predominates at Site 2. At pH 10, some Site 1 product is observed initially (at 2 d) but disappears at longer times due to sequential-step hydrolysis. By contrast, NAEA(20.5)-MAA displays only Site 2 hydrolysis (Fig. 7). Steric effects of the methyl group along the polymer backbone may block approach of the nucleophile to Site 1.

The NAEA(21.5)-HEMA copolymer provides an example of a hydrophilic comonomer which is incapable of anchimeric assistance under the experimental conditions of this study. Release data (Table 5) at pH 8 for this copolymer

TABLE 6. Mole Ratio of Released Products from Auxin-Containing Copolymers at Different pH Values[a]

Copolymer	pH	Release concentration ratio after t days				
		2	7	15	30	50
NAEA(30.9)-AM	6	–/–	–/–	0.2/0.5	0.3/0.8	0.2/0.8
	7	0.1/0.4	0.1/0.8	0.3/1.5	0.3/1.9	0.3/2.5
	8	0.2/1.8	0.3/3.4	0.8/5.2	1.8/6.5	3.3/8.3
	10	13.3/6.5	30.4/1.4	47.8/1.8	66.1/1.2	80.1/0.5
NAEA(20.5)-MAA	6	0.6/–	0.6/–	0.7/–	1.0/–	
	7	0.8/–	1.7/–	2.9/–	3.6/–	
	8	0.7/–	1.8/–	3.8/–	7.2/–	12.1/–
	10	2.9/–	8.7/–	13.8/–	32.6/-	45.5/–

[a]mol% of available NAA released/mol% of available NAA-EG released; – not detected.

show no Site 1 hydrolysis until 30 d. The appearance of NAA-EG at this time suggests that hydrolysis of a portion of the HEMA moities to give MAA species may have occurred. Disappearance of NAA-EG at pH 10 (Table 5) parallels the copolymer behavior previously shown.

pH Effect and Fluorescence Studies

The pH effect on hydrolysis is evident for all copolymers (Table 5) prepared in this work. However, the copolymer with MAA is less sensitive to pH change than the AM copolymer (Table 6). To prove this, a fluorescence technique was used. It is well known that fluorescent molecules attached to a polymer chain can give information about the microenvironment and molecular interactions [17, 18]. Chromophores incorporated into polymer-pendent groups can form excimers easily, depending on the microstructure and configuration of polymer chains [17].

The extent of excimer formation as a function of pH was measured with poly(NAEA-*co*-AM) and poly(NAEA-*co*-MAA) (Fig. 8). The MAA copolymer shows a dramatic change in excimer concentration at pH 7 and plateaus before and after that point, but the AM copolymer shows little change with pH. Measurements were conducted at very low concentration (10-50 μmol/L), which is low enough to prevent excimer formation by the released chromophores to the polymer. An abnormally low value for poly(NAEA-*co*-AM) at pH 10 indicates hydrolysis during the experiment.

Our results are in line with the observation that polyelectrolytes, when copolymerized with hydrophobic monomer, undergo "hypercoiling" when dissolved in aqueous media [19, 20]. It is believed that, as the ionic strength increases, strong excimer emission occurs due to the formation of micelle-like structures of macromolecules; such structures make hydrolysis difficult.

The Effect of Copolymer Microstructure

In a previous paper [14] we reported ideal copolymerization behavior for the NAEA/AM comonomer pair and a perfectly alternating tendency for the NAEA/VP pair. A comparison of release behavior of the two copolymer systems shows the importance of polymer structure for hydrolysis behavior.

Table 7 gives microstructural and release data for some of the copolymers. The NAEA(25.0)-VP sample shows almost no release after 30 d even at pH 10, while NAEA(22.5)-AM with a similar auxin content shows nearly 100% release after 30 d at the same pH.

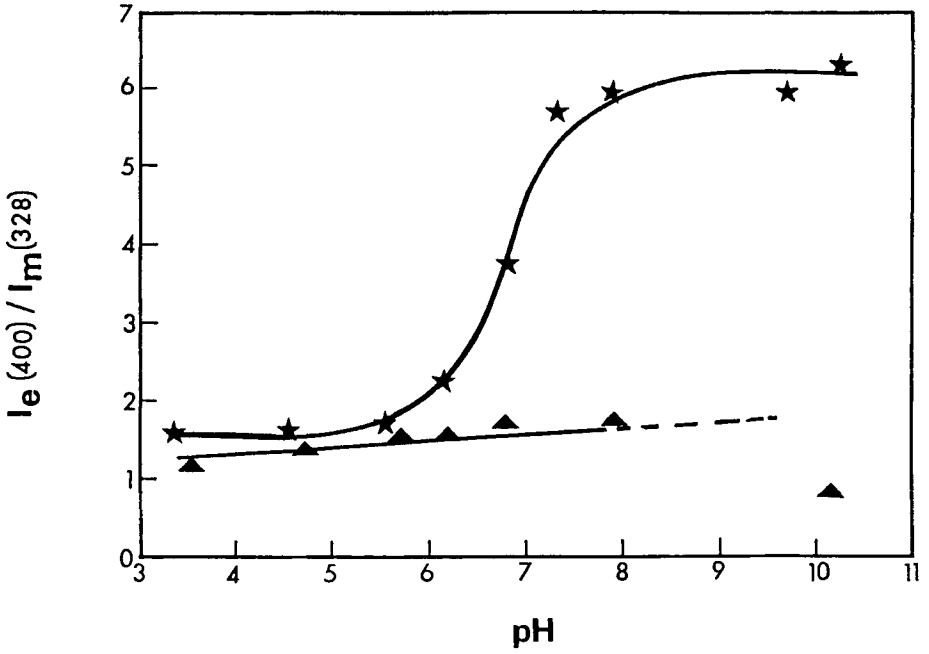

FIG. 8. Effect of pH on I_e/I_m of poly(NAEA-*co*-MAA) at 46.5 μmol/L (★) and poly(NAEA-*co*-AM) at 16.5 μmol/L (▲).

It is not easy to interpret the influence of copolymer microstructure on the release behavior independently of other effects. Structural effects of comonomers themselves, neighboring group assistance previously mentioned, incorporation ratio of comonomer, molecular weights, etc. affect the hydrolysis behavior of the labile linkage in the polymer structure. In this study, factors other than copolymer microstructure were kept as constant as possible. Comonomer ratios of NAEA in the copolymers were controlled at 23 ± 2 mol% and intrinsic viscosities, as measures of molecular weight, were from 0.20 to 0.53 (except 1.02 for NAEA(21.5)-HEMA copolymer). Polymers were purified so as to keep residual monomer contents below 0.1 mol% of the total amount of incorporated NAEA monomer.

Table 7 shows that NAEA(25.0)-VP with a μ_2/μ_1 value of 0.97 gives no release, NAEA(22.5)-AM with a μ_2/μ_1 value of 4.00 yields 4.1% released auxin, and NAEA(20.5)-MAA with a μ_2/μ_1 value of 7.15 gives 7.2% release.

TABLE 7. Microstructure and Release Data

Copolymer	Alternation,[a] M_1-M_2	Mean sequence length			Release concentration, mol%	
		μ_1	μ_2	μ_2/μ_1	15 d	30 d
NAEA(22.5)-AM	31.72	1.27	5.04	4.00	1.2	4.1
NAEA(20.5)-MAA	18.83	1.11	9.52	8.58	3.8	7.2
NAEA(21.5)-HEMA	37.18	1.21	4.17	3.45	1.2	1.4
NAEA(23.7)-AA	33.32	1.24	4.94	3.98	2.6	3.7
NAEA(25.0)-VP	91.52	1.11	1.08	0.97	–	–

[a]In mol%.

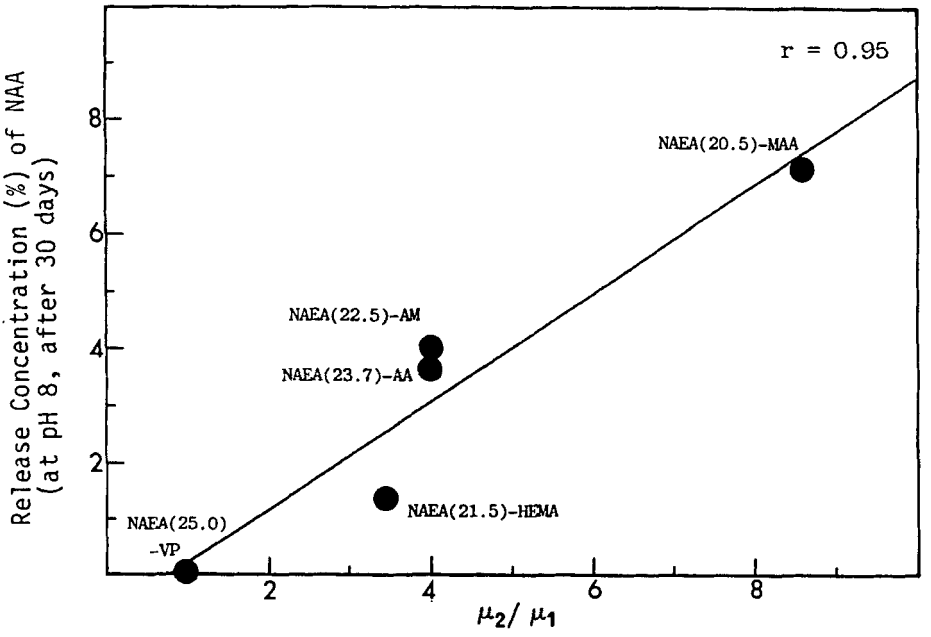

FIG. 9. Plot of mean sequence length ratio versus release concentration of NAA.

There is a clear trend (correlation coefficient (r) = 0.95) between microstructure and release behavior (Fig. 9).

CONCLUSIONS

The release behavior of NAEA copolymers with hydrophilic comonomers has been shown to be dependent upon the nature of the neighboring group, hydrophilicity, microstructure of the polymer backbone, and steric hindrance to the hydrolysis site. As a characteristic example, poly(NAEA-*co*-MAA) gives one hydrolysis product (that of Site 2); however, poly(NAEA-*co*-AM) gives two hydrolysis products, the latter indicating neighboring group assistance. Solid-state ^{13}C-NMR measurements are consistent with this suggestion.

Fluorescence studies have demonstrated the diverse pH sensitivities of hydrolysis of poly(NAEA-*co*-MAA) and poly(NAEA-*co*-AM). Polyelectrolytes

prepared by copolymerization of an ionizable monomer with a moderately high portion of hydrophobic comonomer are believed to form micelle-like structures by hydrophobic interactions, impeding hydrolysis. Similar effects may be present here.

Comparison of release behavior of these copolymer systems reveals the importance of polymer structure on hydrolysis behavior. As the microstructure approached a perfectly alternating configuration, the enhanced hydrophobicity of the copolymer retarded the approach of the nucleophile to the hydrolysis sites and therefore diminished release rates. Increasing the sequence length of the hydrophilic moiety, the distance of the labile site from the backbone, or the number of anchimerically assisting adjacent repeating units enhanced release rates.

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