NMR Characterization of Erodible Copolymers

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ABSTRACT: NMR spectroscopy analysis coupled with information from X-ray diffraction allowed understanding of the nature of the erosion phenomena for degradable polymers. The determination of copolymer composition and comonomer sequence distributions in anhydride copolymers of aliphatic and aromatic dicarboxylic acids is discussed. From high-field nuclear magnetic resonance spectroscopy data the copolymers' sequence was determined. In addition, the characterization of molecular weight distributions by intrinsic viscosity measurements and by gel permeation chromatography (GPC) using the universal calibration procedure was made.

Introduction

In development of erodible materials, the use of copolymers is attractive since, by employing different monomer ratios, widely varying erosion rates can be obtained, thus enabling different target times to be achieved with the same monomers.[1] Poly(lactic-*co*-glycolic) and polyanhydrides have been extensively explored as vehicles for drug delivery and are currently among the few degradable polymers being utilized clinically.[2] Very hydrophobic polyanhydrides display surface erosion in aqueous medium which makes them particularly desirable for controlled release of therapeutic substances.[3] The hydrolytic degradation rates can be altered several thousand-fold by simple changes in the polymer backbone.[3] Aliphatic polyanhydrides degrade in a few days while some aromatic polyanhydrides degrade over a few years; degradation rates of copolymers made of aliphatic and aromatic moieties vary between these extremes.[4]

Various techniques have previously been used to study and characterize these copolymers.[3,5] Yet, quantitative correlations between the polyanhydrides' physical properties and the analysis of ^{1}H NMR spectroscopy have not been reported. Such properties include (1) the degree of randomness that suggests whether the polyanhydride is either a copolymer or a mixture of homopolymers, (2) number-average sequences (L_n), and (3) frequency of occurrence of specific comonomer sequences.

This paper describes the determination of copolymer composition and comonomer sequence distributions in copolymers. As a model we used anhydride copolymers of aliphatic and aromatic dicarboxylic acids. The structure determination was made by high-field nuclear magnetic resonance spectroscopy data.

Previously we correlated, for the first time, the polyanhydrides' NMR spectroscopy data to the X-ray powder diffraction data.[6] Whereas NMR spectroscopy could identify statistical segments in the polymeric chain, X-ray powder diffraction combined with DSC was used to determine the degree of crystallinity and the type of polymer chains that form the crystalline region. The degree of crystallinity plays a major role in preventing water penetration into the polymer bulk, thus preventing bulk erosion. The structure determination by a careful integration of the NMR spectra coupled with the X-ray diffraction data of these copolymers yielded an improved understanding of the nature of the erosion phenomena.

Finally, we undertook the characterization of molecular weight distributions by intrinsic viscosity measurements and by gel permeation chromatography (GPC) using the universal calibration procedure.[7] The results were correlated to the data obtained by ^{1}H NMR spectroscopy.

Experimental Section

Instrumentation. Infrared spectroscopy was performed on a Perkin-Elmer 1430 spectrophotometer. Polymeric samples were film cast onto NaCl plates from a solution of the polymer in chloroform. Prepolymer samples were either pressed into KBr pellets or dispersed in Nujol onto NaCl plates. The melting points of prepolymers were determined on a Fisher-Johns melting point apparatus. Viscometry of the polymers in chloroform was measured in a Cannon-Ubbelohde 75 dilution viscometer. Afflux times were measured at four concentrations at 23 °C, and the data were analyzed by standard methods.[8] The molecular weight of the polymers was estimated on a Perkin-Elmer gel permeation chromatography (GPC) system consisting of the Series 10 pump and the 3600 data station with the LKB 214 rapid spectral detector at 254-nm wavelength. Samples were eluted in chloroform (alcohol free) through a PL gel 5-mm mixed column (Polymer Laboratories) at a flow rate of 0.9 mL/min at 23 °C. Molecular weights of polymers were determined relative to polystyrene standards (Polysciences: molecular weight between 500 and 160 000) using CHROM 2 and GPC 4 computer programs (Perkin-Elmer). Elemental analysis was performed by Galbraith Laboratories (Knoxville, TN). ^{1}H NMR spectra were obtained on a Varian 270-MHz spectrometer using chloroform-d_1 as a solvent and tetramethylsilane (TMS) as an internal reference (polyanhydride concentration 5–10% w/v). The recycle time ($5T_1$) between consecutive pulses was maintained at 1 s for all the polymers. Wide-angle X-ray powder diffraction of polymers in the form of pressed disks (1 mm thick) was recorded on a Philips X-ray diffractometer using a nickel-filtered Cu Kα source. The thermal properties of the polymers were determined on a Perkin-Elmer DSC-4 differential scanning calorimeter employing a heating rate of 20 °C/min.

Polymer Synthesis. Sebacic acid, 4-hydroxybenzoic acid, 1,3-dibromopropane, and 5-bromovaleric acid were all from Aldrich. The polyanhydrides were synthesized by melt polycondensation of mixed anhydrides of diacids and acetic acid.[9] Poly(sebacic anhydride) (poly(SA)), poly[1,3-bis(*p*-carboxyphenoxy)propane] (poly(CPP)), poly[1,3-bis(*p*-carboxyphenoxy)propane–sebacic acid] (poly(CPP–SA)), poly[1,3-bis(*p*-carboxyphenoxy)hexane] (poly(CPH)), poly[1,3-bis(*p*-carboxyphenoxy)hexane–sebacic acid] (poly(CPH–SA)), and poly[4-(*p*-carboxyphenoxy)valeric anhydride] (poly(CPV)) were prepared according to previous methods.[9,10] Different molecular weight polyanhydrides were obtained by modifying the reaction times.[9] Longer reaction times led to higher M_w polymers.

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Table I
Viscosity and GPC Data for Poly(CPP-SA) and Polystyrene

polymer	M_w	$[\eta]$
polystyrene	160 000	0.863
	120 000	0.665
	68 000	0.264
	22 000	0.208
	7 600	0.097
	3 750	0.049
poly(SA)	7 749	0.16
	7 179	0.20
poly(CPP-SA) 20:80	245 010	1.25
	199 060	1.18
	185 226	0.96
	141 600	0.90
	140 935	0.88
	116 800	0.92
	85 060	0.66
	81 937	0.61
	75 387	0.68
	63 247	0.64
	33 440	0.31
	29 340	0.41
	27 500	0.30
	27 469	0.20
	26 850	0.36
	23 678	0.26
	21 785	0.20
	14 369	0.22
poly(CPP-SA) 30:70	34 626	0.425
poly(CPP-SA) 50:50	51 781	0.55
	24 800	0.27
	23 335	0.24
	7 975	0.16
	2 842	0.13

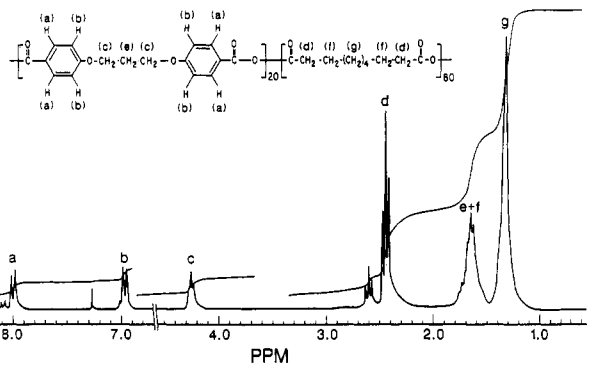

Figure 1. ^{1}H NMR spectra of poly(CPP-SA) 20:80 in chloroform-d_1.

Results and Discussion

Polyanhydrides were synthesized under various reaction times such that analysis by GPC revealed a weight-average molecular weight (M_w) between 2800 and 245 000 (Table I). IR spectra analysis of all the polymers revealed typical anhydride absorbencies at 1720 and 1780 cm^{-1}. Copolymer composition was verified by ^{1}H NMR by the integration ratio of the peaks at 1.3 ppm (8 protons of sebacic) and the peaks at 6.9–8.2 ppm (8 protons of either CPP or CPH) [the ^{1}H NMR of poly(CPP-SA) 20:80 is shown in Figure 1]. The copolymer composition in the polymer (by ^{1}H NMR) was identical with the comonomer ratio in the feed (weighted amounts). The relative degree of crystallinity of both the homopolymers and the copolymers was calculated from their X-ray powder diffractions and DSC.[6,11,12] X-ray crystallography revealed a high degree of crystallinity at high mole ratios of either aliphatic or aromatic diacids. The degrees of crystallinity as estimated from X-ray diffraction were 53% and 60% for poly(CPP) and poly(SA), respectively. All the polyanhydrides had an intrinsic viscosity (in chloroform) between 0.13 and 1.25 dL/g (Table I). Our studies also included viscometry and molecular weight distribution data for poly(CPP-SA). Table I summarizes the data. We also analyzed polystyrene samples of narrow molecular weight distribution (Polymer Laboratories) for their viscosities and retention volumes (Table I).

Table II
Comonomer Sequence Distribution of the Poly(CPP-SA) Series

mole ratio of SA–CPP in the polymer, p(SA)	probability of finding the diad SA–SA, p(SA–SA)	probability of finding the diad SA–CPP, p(SA–CPP)	av block length L(SA)	degree of randomness
0.96	0.86	0.14	12.3	0.3
0.87	0.76	0.22	7.8	0.4
0.82	0.67	0.30	5.4	0.6
0.82	0.67	0.30	5.5	0.6
0.78	0.61	0.34	4.6	0.7
0.63	0.45	0.36	3.5	0.7
0.67	0.45	0.44	3.1	0.9
0.68	0.44	0.50	2.8	1.0
0.59	0.36	0.47	2.5	0.9
0.49	0.24	0.49	2.0	1.0

From the viscosity data (Table I) we could calculate the Mark–Houwink relationship (eq 10) for poly(CPP-SA).

$$[\eta] = KM^{\alpha} \tag{1}$$

To obtain absolute values for poly(CPP-SA) molecular weight distributions, we used the universal calibration for gel permeation chromatography.[7] According to this method, the plot of the log of the molecular weight times the intrinsic viscosity $\{\ln (M[\eta])\}$ vs GPC retention volume (V) correlates for any polymer, regardless of composition. From the data presented in Table I we calculated the Mark–Houwink relationship for polystyrene in chloroform according to eq 1, $[\eta]^{25\,°C}_{CHCl_3} = 1.62 \times 10^{-4} M_w^{0.70}$ (lit.[7b] $[\eta]^{25\,°C}_{THF} = 1.10 \times 10^{-4} M_w^{0.725}$). To estimate the polyanhydride Mark–Houwink constants, we assumed approximate K and α values and then calculated M_w values for a few poly(CPP-SA) samples from the GPC profiles. We then correlated these M_w values with measured $[\eta]$ values and calculated new K and α values. After several cycles[7b] these constants converged to give

$$[\eta]^{23\,°C}_{CHCl_3} = 3.88 \times 10^{-7} M_w^{0.658} \tag{2}$$

From this Mark–Houwink relationship for both polyanhydrides and polystyrenes we obtained the universal calibration curve. All the experimental points lie on a single curve that fit the expression

$$\ln (M_w[\eta]) = 35.45 - 3.35V \quad (R = 0.96) \tag{3}$$

We were able to confirm that the universal calibration concept for GPC extends to poly(CPP-SA). It allows direct calculation of M_w without the need for intrinsic viscosity measurements. (By a suggestion of a reviewer, we analyzed polyanhydrides using GPC with a low-angle laser light scattering detector (KMX-6, Milton Roy). The absolute M_w obtained was the same within experimental error to the results presented within this paper.)

The weight-average M_w of the NMR-analyzed polyanhydrides was kept between 16 000 and 50 000 in order to solubilize them rapidly. We have shown that aliphatic polyanhydrides lose half of their initial M_w over 1 day in chloroform.[8] Therefore, the ^{1}H NMR spectra of the polyanhydrides was taken immediately after complete dissolution of the polymer. We set the recycle time ($5T_1$) in the Fourier transform NMR data acquisition procedure to be 1 s in order to bring the excited protons to full relaxation after each cycle. The longer relaxation time contributes

to quantitative interpretation of the spectra. In order to correlate the NMR spectra to the composition and the frequency of occurrence of specific comonomer sequences and to determine the degree of randomness and the number-average sequences (L_n), we modified mathematical models that were developed by Bovey[13] and Yamadera and Murano.[14] If the copolymer is not strictly alternating or blocklike, a randomly selected pair of comonomer units (diad) in the polymer chain may be represented as follows: SA–SA, SA–CPP (or CPP–SA), and CPP–CPP.

An examination of the ^{1}H NMR spectra of poly(CPP–SA) (Figure 1) revealed two doublets at 8.1 and 8.0 ppm (J = 8.7 Hz) and two triplets at 2.6 and 2.4 ppm (J = 7.4 Hz). The homopolymer poly(SA) has only one triplet at 2.4 ppm, and poly(CPP) has only one doublet at 8.1 ppm. These additional peaks in the copolymers' NMR spectra can be explained by long-range deshielding/shielding effects.[15] The protons close to electronegative groups, as the aromatic copolymers, experience a lower density of shielding electrons and absorb at lower frequency (deshielding). On the other hand, the protons distant from such groups, as next to aliphatic copolymers, absorb at a higher frequency (all expressed in relation to tetramethylsilane). These long-range effects affect the chemical shifts of the α-protons of the other comonomer. The downfield doublets at 8.1 and 8.0 ppm were the diads CPP–CPP and CPP–SA, respectively. Similarly, the upfield triplets at 2.6 and 2.4 ppm were the diads SA–CPP and SA–SA, respectively. As the molar ratio of the copolymers varied, the integration ratios of these peaks changed (Figure 2). By integration of the ^{1}H NMR spectra we calculated the following:

1. *Unconditional probability* [p(SA) and p(CPP)] of a randomly selected monomer unit in the polymeric chain to be either SA or CPP. It could be determined by the overall integration ratio of SA to CPP.

$$p(\mathrm{SA}) + p(\mathrm{CPP}) = 1 \tag{4}$$

2. *Probability* [p(SA–SA), p(SA–CPP), and p(CPP–CPP)] that a randomly selected diad was either SA–SA, SA–CPP, or CPP–CPP. This probability could be determined from the integration ratios of the diads: SA–SA/SA–CPP (peaks at 2.4 and 2.6 ppm, respectively) and CPP–CPP/CPP–SA (peaks at 8.1 and 8.0 ppm, respectively).

From these probabilities and the feed ratios we could calculate the following:

I. *Conditional probability* [p(SA–SA), p(SA–CPP), and p(CPP–CPP)] of a chain ending with SA (or CPP) to add SA (or CPP).

$$p(\mathrm{SA–CPP}) = p(\mathrm{SA–CPP})/p(\mathrm{SA}) \tag{5}$$

II. *Degree of randomness* (h) of the formed polymer.

$$h = p(\mathrm{CPP–SA})/p(\mathrm{SA})p(\mathrm{CPP}) \tag{6}$$

h = 0 means either a completely block copolymer or a mixture of homopolymers; h < 1 means block character of the copolymer; h = 1 means the polymer takes a random distribution; h > 1 means alternating tendency; and h = 2 means a completely alternating copolymer (e.g., ...–ABAB–...).

III. *Number-average sequence length of a monomer sequence* (L_n).

$$L_{\mathrm{SA}} = 1/p(\mathrm{SA–CPP}) \tag{7}$$

IV. *Reactivity ratio* (r_{SA}) of a chain ending with SA to add SA versus the addition of CPP

$$r_{\mathrm{SA}} = k_{\mathrm{SA–SA}}/k_{\mathrm{SA–CPP}} \tag{8}$$

and vice versa ($r_{\mathrm{CPP}} = k_{\mathrm{CPP–CPP}}/k_{\mathrm{CPP–SA}}$).

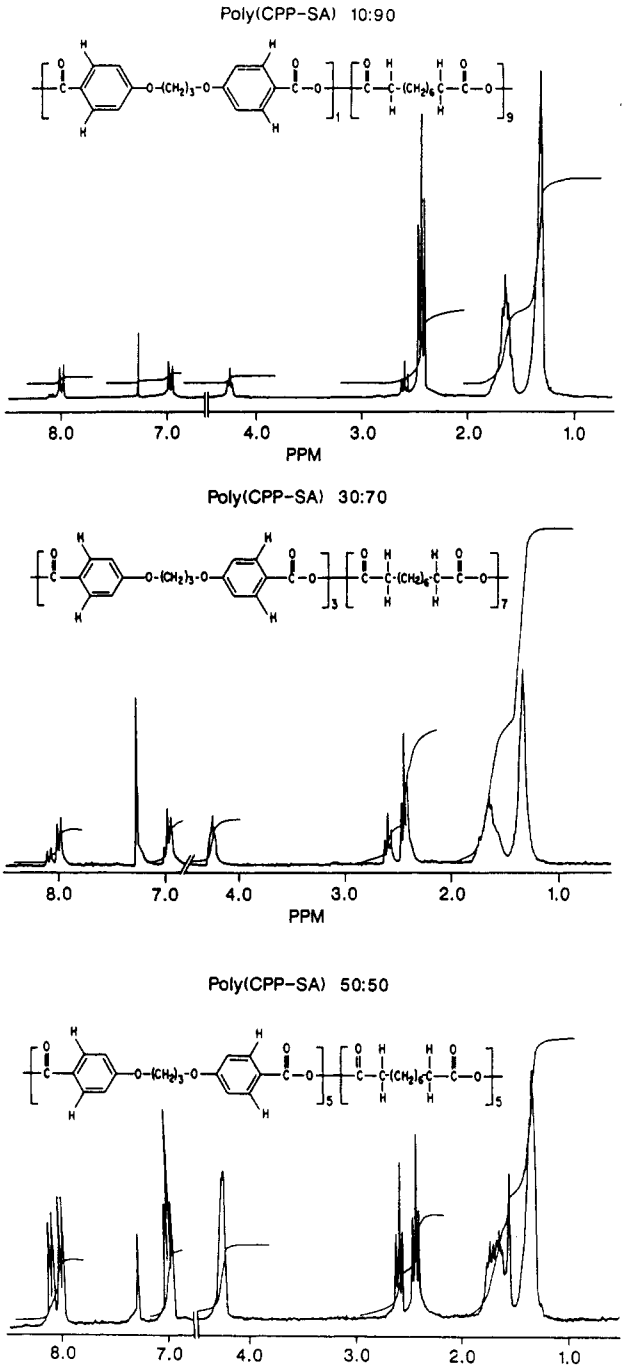

Figure 2. ^{1}H NMR spectra of poly(CPP–SA) 90:10, poly(CPP–SA) 30:70, and poly(CPP–SA) 50:50 in chloroform-d_1.

For the series poly(CPP–SA) with feed ratios from 5:95 to 50:50 the results are presented in Table II. We repeated these experiments for different reaction times, i.e., 20, 40, and 90 min. We also conducted melt polymerization reactions starting either from poly(SA) with CPP prepolymer or from poly(CPP) with SA prepolymer. As expected in this type of polycondensation, these reactions had a conversion of 100%, and the only differences were the weight-average molecular weights of the formed polyanhydrides. In addition, all the statistical results were similar within experimental error (±10%). Therefore, only the results from the 90-min experiments will be discussed. The conditional probability that a chain ending with SA would add either another SA or CPP was concentration dependent (e.g., a higher mole fraction of SA in the feed would lead to a higher probability of a chain ending with SA to add another SA comonomer). The degree of randomness (h) of the formed polyanhydride exhibited a block character up to a ratio of CPP–SA 25:75 wherefrom

Table III
Comonomer Sequence Distribution of the Poly(CPH-SA) Series

mole ratio of SA-CPH in the polymer, p(SA)	probability of finding the diad SA-SA, p(SA-SA)	probability of finding the diad SA-CPH, p(SA-CPH)	av block length L(SA)	av block length L(CPH)	degree of randomness
0.83	0.68	0.29	5.6	1.2	0.6
0.73	0.53	0.40	3.7	1.3	0.8
0.64	0.40	0.47	2.7	1.6	0.9
0.54	0.32	0.48	2.3	1.8	1.0
0.44	0.20	0.50	1.8	2.2	1.0
0.34	0.12	0.50	1.5	2.6	1.0
0.23	0.00	0.33	1.0	5.0	0.7
0.12	0.00	0.30	1.0	5.7	0.6

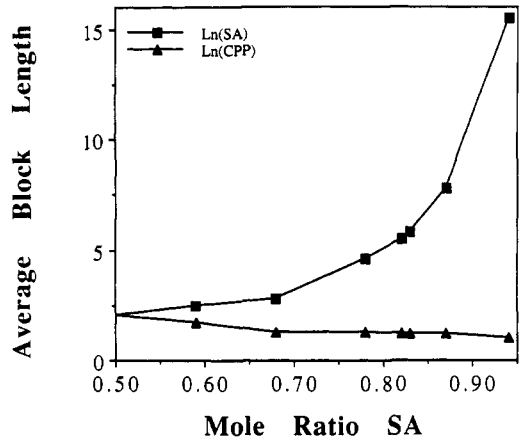

Figure 3. Average block length of both SA and CPP vs mole ratio of SA for poly(CPP-SA).

the formed polymers had a random copolymer distribution. The number-average sequence length (L_{SA}) of the sebacic acid decreased from 15 to 2 for the poly(CPP-SA) series from 5:95 to 50:50, respectively (Figure 3).

X-ray crystallography revealed a high degree of crystallinity at high mole ratios of either aliphatic or aromatic diacids (Figure 4). The degree of crystallinity as estimated from X-ray powder diffraction was 53% and 60% for poly(CPP) and for poly(SA), respectively. Both homopolymers displayed a well-defined diffraction pattern.[6] From the X-ray diffraction for polymers containing unequal amounts of monomers, the monomer in excess determines the type of crystallinities of the polyanhydride. As CPP was added the defined crystalline structure of poly(sebacic anhydride) disappeared and an amorphous structure emerged between the poly(CPP-SA) 25:75 and 75:25. Succeeding the amorphous stage, the crystalline structure of poly(CPP) emerged.[6]

It was recognized, both by ^{1}H NMR and by X-ray crystallography[6] that up to a ratio of 25:75 of either CPP-SA or SA-CPP the polymer had a blocklike arrangement. This phenomena was explained by the high feed concentration of SA (or CPP) that would lead to a block polymer. We compared the crystallinity to the average block length of SA (Figure 5). From this comparison both the crystallinity and the L_{SA} rose sharply over a feed ratio of 25% in SA-CPP copolymers. Yet, the degradation rate of these polyanhydrides with over 75% SA is faster than those polymers with less than 70% SA (vide infra). This phenomenon could be explained by a different morphology (i.e., porous structure) and hydrophilicity of the polyanhydrides.[6,16]

A complete series analysis was limited by the low solubility in common NMR solvents of the CPP-SA copolymers with mole ratios between 5:95 and 50:50. Therefore, the series poly(CPH-SA) with feed ratios from 10:90 to 90:10 was utilized. The results are presented in Table III. The conditional probability that a chain ending

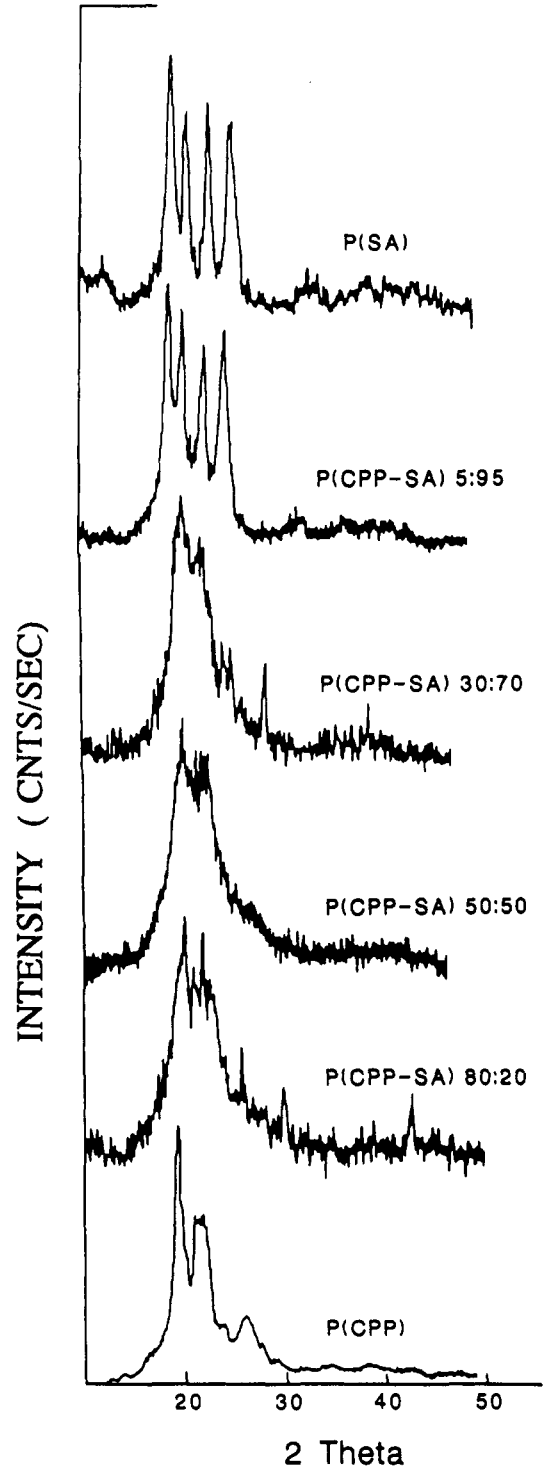

Figure 4. X-ray powder diffraction of poly(CPP-SA).

with SA would add either another SA or CHP was concentration dependent. Here, as for poly(CPP-SA), the degree of randomness ($h < 1$) suggested a tendency for clustering in blocks up to a ratio of CPH-SA 25:75, where-

Table IV
Comonomer Sequence Distribution of Poly(CPV), Poly(CPP-SA) 50:50, and Poly(CPH-SA) 50:50

polymer	mole ratio of SA in the polymer P(SA)	probability of finding the diad SA-SA p(SA-SA)	probability of finding the diad SA-Ar p(SA-Ar)	av block length L(SA)	degree of randomness
poly(CPP-SA) 50:50	0.49	0.24	0.49	2.0	1.0
poly(CPH-SA) 50:50	0.54	0.32	0.48	2.3	1.0
poly(CPV)	0.51	0.25	0.52	2.0	1.0

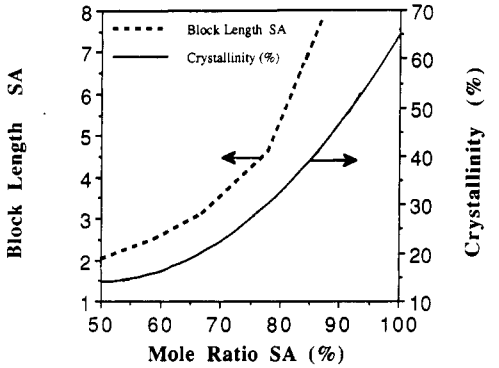

Figure 5. Crystallinity and the average block length of SA vs mole fraction of SA for poly(CPP-SA).

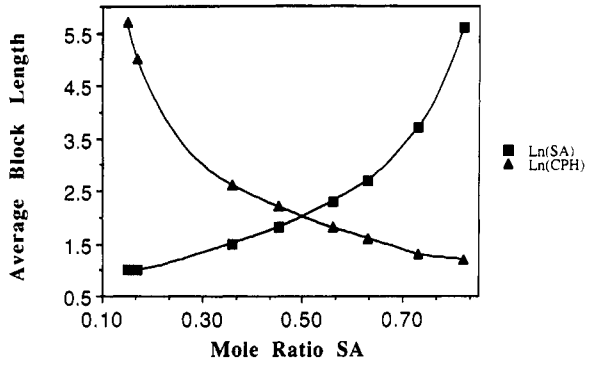

Figure 6. Average block length of both SA and CPH vs mole ratio of SA for poly(CPH-SA).

after the polymer took a random distribution ($h > 1$) up to a ratio of CPH-SA 75:25. The number-average sequence length (L_{SA}) of the sebacic acid decreased from 6 to 2 to 1 for the poly(CPH-SA) series from 10:90 to 50:50 to 90:10, respectively. Likewise, the number-average sequence length of CPH increased from 2 to 6 for poly(CPH-SA) from mole ratio 50:50 to 90:10, respectively (Figure 6).

Again, it was recognized, both by ^{1}H NMR spectroscopy and by X-ray crystallography,[6] that up to a ratio of 25:75 of either CPH-SA or SA-CPH the polymer had a block-like arrangement. This phenomenon was explained by the high feed concentration of either copolymer: SA or CPH. Thus, a high feed concentration of either comonomer would lead to a block polymer.

The three reactivity ratios of SA, CPP, and CPH were approximately 1. In a system where all the reactivity ratios equal 1 the final composition is always equal to the monomer feed composition and this remains true throughout the reaction. The polymerization starts with many low weight-average molecular weight oligomers that throughout the reaction combine to give higher weight-average molecular weight polymers.[17] This agrees with the observed similar statistical probabilities of different reaction times.

In order to illustrate our claims, we studied the aliphatic–aromatic homopolymer, poly(CPV). This polymer has an aromatic head and an aliphatic tail and forms a polymer where the maximum block length available is 2: head-to-head, tail-to-tail, and head-to-tail. This polymer exhibits probabilities of forming anhydride bonds between head-to-head, tail-to-tail, and head-to-tail similar to those of forming anhydride bonds between aromatic-to-aromatic, aliphatic-to-aliphatic, and aromatic-to-aliphatic within poly(CPP-SA) and poly(CPH-SA) 50:50. The results are presented in Table IV and confirm our hypothesis. The results agree with the assumption of head-to-head and tail-to-tail alternating units.

A good correlation between the NMR data and the X-ray powder diffraction was obtained.[6] We demonstrated that poly(CPP-SA) 5:95 displayed crystallinity with a diffraction pattern typical of SA (Figure 4). Judged by the ^{1}H NMR spectra, the L_{SA} for SA at this ratio of CPP-SA 5:95 was 8. Similarly, poly(CPP-SA) 50:50 had a low crystallinity (Figure 4), and indeed, as judged by the ^{1}H NMR spectra, there was a very low probability for the formation of blocks of either SA or CPP.

The above may suggest that NMR spectroscopy coupled with information from X-ray powder diffraction should provide improved insights for the design of new copolymers with degradation rates targeted for specific time periods.

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Registry No. SA (homopolymer), 26776-29-4; SA (SRU), 26913-47-3; CPP (homopolymer), 90409-77-1; CPP (SRU), 101017-51-0; (CPP)(SA) (copolymer), 90409-78-2; CPH (homopolymer), 132492-75-2; (CPH)(SA) (copolymer), 132492-68-3; CPV (homopolymer), 132492-70-7.