Synthesis and Characterization of Degradable Poly(anhydride-*co*-imides)

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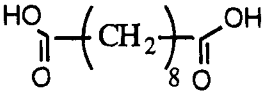
ABSTRACT: A series of poly(anhydride-*co*-imides) based on trimellitylimidoglycine (TMA-gly), pyromellitylimidoalanine (PMA-ala), sebacic acid (SA), or 1,6-bis(carboxyphenoxy)hexane (CPH) were synthesized by condensation polymerization. Monomers and polymers were characterized by NMR and IR spectroscopy, elemental and thermogravimetric analyses, and thermal transition temperatures. Contact angle, intrinsic viscosity, and compressive strength measurements were also performed on the polymers. For all polymer systems, the molecular weights decreased as the amount of imide in the backbone increased. Polymers containing CPH are more hydrophobic, have higher compressive strengths, have higher glass transition and decomposition temperatures relative to polymers containing SA, and exhibit no melting transitions. The mechanical and thermal stability of the materials are increased by the incorporation of imide groups in the polymer backbone. The selection of imide monomers, TMA-gly vs PMA-ala, can significantly affect the resulting polymer characteristics. Both imide monomers affect the hydrophobicity of the resulting polymers in similar ways, with the materials becoming more hydrophilic as the imide content is increased. However, polymers containing PMA-ala have thermal transition temperatures that are higher than the corresponding polymers with TMA-gly.

Introduction

Major research efforts have been directed toward the development of biodegradable polymers for medical applications.[1] The most commonly used biodegradable polymers for medical devices are polyesters. Temporary surgical implants have focused on hydrophilic polyesters, such as poly(lactic acid) and poly(glycolic acid). However, recent clinical evidence has shown that there is a foreign body inflammatory response in 7–48% of the cases, even though fracture healing occurred.[2] Presumably, bulk degradation of the device generates large amounts of acid degradation products at the end stage of the degradation. Alternately, poly(ortho esters) may degrade more slowly and release more pH neutral degradation products over longer time periods. However, initial mechanical properties and dynamic loading studies indicate that it is an inadequate material for load-bearing applications, such as orthopedic devices[3] which require compressive strengths similar to bone (~50 MPa).

The goal of this study is to develop a biocompatible, high-strength polymer that upon degradation will not generate toxic byproducts. In this study, polyanhydrides provide the basis for the development of such polymers. Polyanhydrides are biocompatible,[4] have well-defined degradation characteristics, and have been successfully utilized clinically as drug delivery systems.[5] These polymers have hydrophobic backbones with hydrolytically labile anhydride linkages formed via the exchange of acetyl anhydrides. Hydrolytic degradation rates of poly(anhydrides) can be altered by simple changes in the polymer backbone by choosing the appropriate monomers, such as sebacic acid (SA) (**1**) to increase its hydrophilicity or 1,3-bis(*p*-carboxyphenoxy)hexane (CPH) (**2**) to increase its hydrophobicity. Despite the desired degradation characteristics of the poly(anhydrides), these materials have limited mechanical properties that restrict their usefulness in load-bearing applications. For example, the homopolymer of CPH has a Young's modulus of 1.3 MPa,[5] which is well below the modulus of human bone (40–60 MPa).[6]



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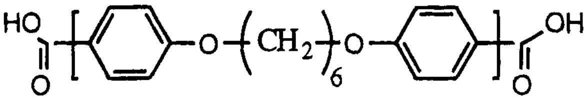

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The mechanical strength of biodegradable polymers may be increased by the incorporation of rigid units, such as imides. Polyimides are often used in the microelectronics industry because of their high thermal and mechanical stabilities. The combination of polyimides, such as Kapton, with the readily biodegradable poly(anhydrides) should yield copolymers with mechanical strengths higher than that of the anhydride homopolymers. In this paper, we attempted to synthesize biocompatible polymers with high mechanical strength, by incorporating imide groups in the backbone of biodegradable polyanhydrides. This idea is strengthened by a study[7] in which several commercially available aromatic polyimides were evaluated and reported to be biocompatible.

Some poly(anhydride-*co*-imides) have been previously synthesized and shown to have high thermal stabilities.[8] Thermal gravimetric analyses of the polymers indicated no thermal breakdown before 350 °C. However, the polymers synthesized require polar solvents, such as dimethylformamide and *m*-cresol, for dissolution.[8]

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In this paper, we had three objectives. First, we synthesized and characterized a series of poly(anhydride-*co*-imides) containing pyromellitic acid derivatives for potential use as degradable, high compressive strength materials. Polyimides based on pyromellitic acid are frequently used in the microelectronics industry because of their high thermal and mechanical stabilities but have not been used in degradable polymers. Second, we wished to improve upon the poly(anhydride-*co*-imide) systems initially prepared by Staubli et al.[9] in this laboratory, which have trimellitic acid derivatives incorporated into the polymer backbone, to investigate the influence of trimellitylimidoglycine on the polymer properties. However, the properties (e.g. molecular weight and tensile strength) of the polymers synthesized by Staubli varied from batch-to-batch.[10] By carefully purifying the monomers, we have improved the reproducibility of the properties of the TMA-containing polymers. In addition, elemental analysis, thermal decomposition, contact angle and intrinsic viscosity measurements are presented here for the TMA-containing polymers for the first time. Third, we wished to better understand the role of the imide and anhydride repeat units in the properties of the poly(anhydride-*co*-imides), such as thermal transition temperatures, hydrophobicity, and mechanical strengths. Therefore, a series of copolymers were synthesized in which not only the ratio of imide monomer to anhydride monomer was varied but also the type of imide monomer (PMA-ala vs TMA-gly) and anhydride monomer (CPH vs SA).

Results and Discussion

We have synthesized a series of poly(anhydride-*co*-imides) in which the ratio of imide monomers, based on trimellitylimidoglycine (TMA-gly) or pyromellitylimidoalanine (PMA-ala), and anhydride monomers, based on **1** or **2**, were varied. This report will focus primarily on the influence of imide and anhydride comonomers on polymer properties.

An outline of the monomer and polymer synthesis is shown in Scheme 1.

Glycine is inserted into trimellitic anhydride (**3**) to give trimellitylimidoglycine, **4**. The diacid (**4**) is activated with acetic anhydride to give the imide–anhydride monomer, **4a**. The imide–anhydride monomer (**4a**) is polymerized in the presence of an anhydride monomer, such as the acetylated sebacic acid (**1a**) shown here. The poly(anhydride-*co*-imides) are prepared by melt condensation at 180 °C for 90–120 min under vacuum (0.05 mmHg).

In previous studies in this lab, the molecular weights of poly(trimellitylimidoglycine-*co*-sebacic acid) (TMA-gly:SA) and poly[trimellitylimidoglycine-*co*-bis(carboxyphenoxy)hexane] (TMA-gly:CPH) varied from batch-to-batch for each polymer composition (from M_w of <5000 to 35 000).[10] By careful purification and storage of the monomers, we found that variations in polymer properties, e.g. molecular weight, for defined comonomer ratios could be kept to a minimum. Before use, the monomers were checked for hydrolysis by infrared spectroscopy and reacetylated if necessary. In addition, caution was taken to ensure that the polymerization vessels were dry.

Poly(trimellitylimidoglycine-*co*-sebacic acid) (TMA-gly:SA). Copolymers consisting of TMA-gly and SA were synthesized, and the polymer properties are shown in Table 1. Copolymer composition will be denoted as 10:90, for example, where 10 refers to the mole percent of imide monomer used in the feed composition. The molecular weights, as determined by gel permeation chromatography (GPC), decrease as the percentage of imide groups increases. The weight-average molecular weights range from 39 000 for the copolymers containing 10 mol % imide, to 5000 for copolymers containing 50 mol % imide. There is essentially no change in the polydispersity index (PDI) as the ratio of imide to anhydride groups changes. Polymers that contain over 50 mol % trimellitylimidoglycine were insoluble in common organic solvents, such as chloroform and tetrahydrofuran and soluble in high-boiling, polar solvents, such as dimethylformamide (DMF) and dimethylacetamide (DMAc). Inherent viscosities of the chloroform-insoluble polymers were determined on 1 wt % solutions in DMAc at 23 °C and indicate that these chloroform-insoluble polymers are oligomeric (Experimental Section).

Table 1. Characteristics of Poly(TMA-gly:SA) Synthesized at 180 °C for 90 min under Vacuum

% TMA-gly (feed)	M_w	PDI	T_g (°C)	T_m (°C)	T_d (°C)	% TMA-gly (^{1}H NMR)
0	39 100	1.81	<−50	78, 84	314	0
10	36 100	2.93	−24	65, 71	320	7
30	10 500	2.84	9.8	56, 61	321	22
50	5 400	2.84	33	45	321	40
70	*a*	*a*	32	*b*	329	64
90	*a*	*a*	87	*b*	368	88
100	*a*	*a*	86	*b*	372	100

[a] Not available. [b] Not found.

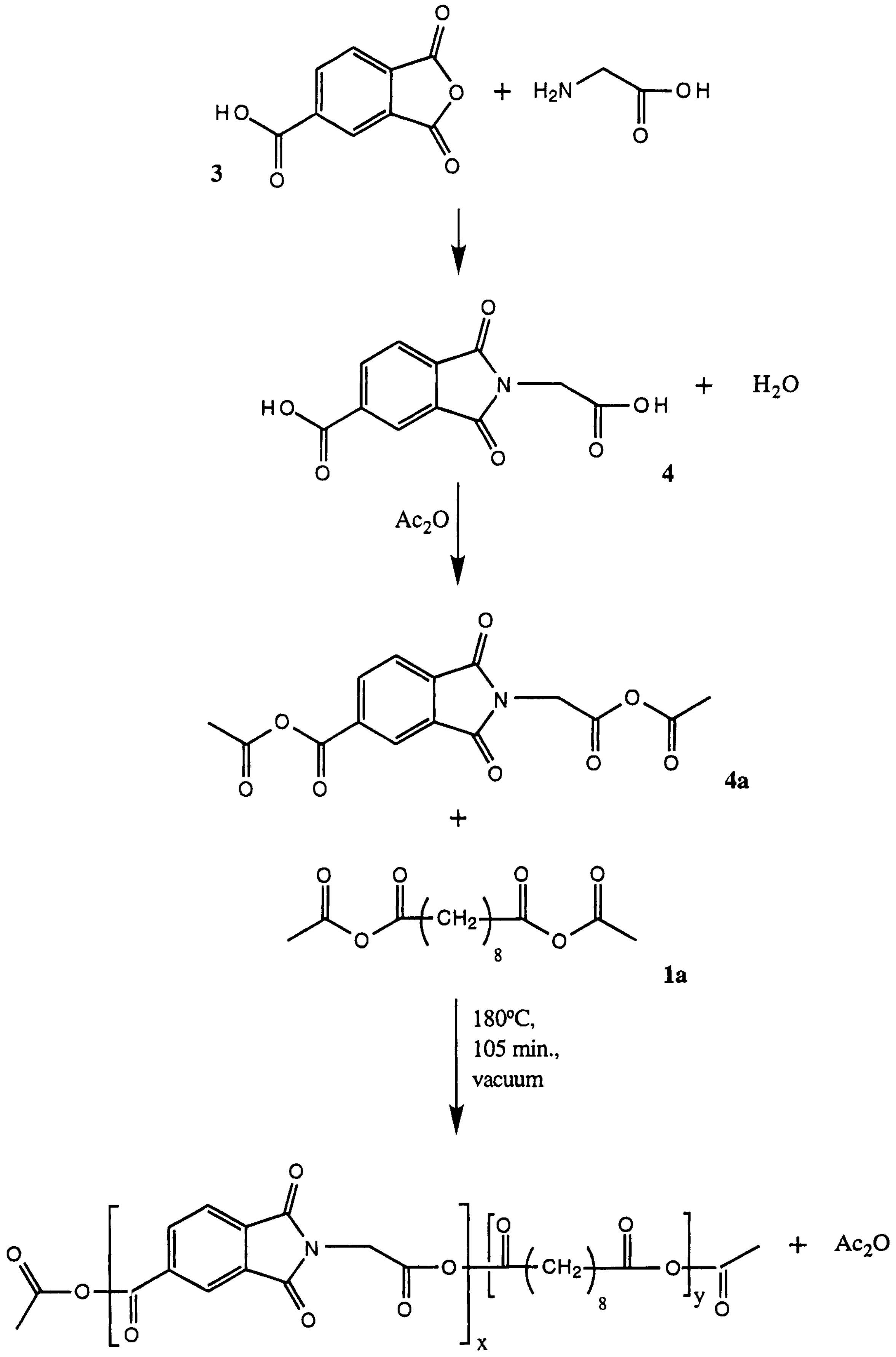
The glass transition (T_g) and melting (T_m) temperatures were determined by differential scanning calorimetry (DSC). Glass transition temperatures generally increase from <−50 to +87 °C with increasing imide content. No T_g is observed for the sebacic acid homopolymer down to −50 °C. Melting temperatures decrease with imide content for the soluble polymers relative to the homopolymer of sebacic acid, and no melting transitions are observed for the chloroform-insoluble polymers. Thus, the melting transitions reflect portions of the polymer chains containing several sebacic acid repeat units. The appearance of several T_m's, corresponding to sebacic acid-rich regions, has been previously observed in poly(anhydrides) containing sebacic acid.[11] With less than 30 mol % of sebacic acid in the polymers, the melting transitions are not observed. The decomposition temperature (T_d) of the polymers as measured by thermal gravimetric analysis (TGA) are not dramatically affected by the change in polymer composition up to 70 mol % imide. At higher imide content (90%) the decomposition temperature is raised by 40 °C (Table 1).

The T_g and T_d of the homopolymer derived from monomer **4** closely correlate with those of the 90:10 copolymer of TMA-gly:SA. However, elemental analysis indicates that the 90:10 copolymer is not identical to the homopolymer of TMA-gly (Experimental Section).

For elemental analyses of these polymers, carbon and hydrogen contents roughly correlate with the theoretical values, although the nitrogen content is lower than the calculated value by 0.1 to 0.7%. The ^{1}H NMR spectra show that the amount of imide monomer incorporated into the polymer corresponds to the monomer feed ratio, although the values are lower than the monomer feed ratio by 2 to 10% (Table 1).

Poly[trimellitylimidoglycine-*co*-bis(carboxyphenoxy)hexane] (TMA-gly:CPH). Domb[11] had shown

Scheme 1



that the hydrolytic stability of polyanhydrides could be increased by the incorporation of more hydrophobic units into the polymer backbone. Based on this, the corresponding series of poly(anhydride-*co*-imides) using the acetylated aromatic acid, CPH (**2a**), was synthesized. Results are shown in Table 2.

Table 2. Characteristics of Poly(TMA-gly:CPH) Synthesized at 180 °C for 90 min under Vacuum

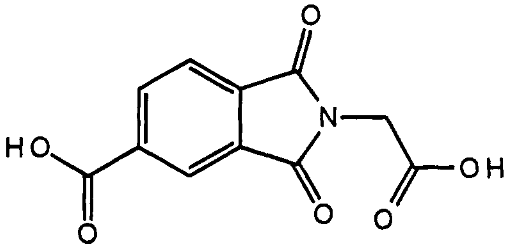
% TMA-gly (feed)	M_w	PDI	T_g (°C)	T_d (°C)	% TMA-gly (^{1}H NMR)
0	20 900	2.30	39^a	398	0
10	21 700	2.51	46	467	8.5
30	11 900	2.77	68	428	23
50	6 300	2.70	80	398	43
70	b	b	64	338	80
90	b	b	90	350	91

^{a} T_m = 144 °C. ^{b} Not available.

Similar to the polymers containing sebacic acid, the molecular weights of the polymers decrease as the mount of trimellitylimidoglycine in the polymer was increased and the ranges of weight-average molecular weights are analogous, ranging from 21 000 to 6000. Polymers that contained over 50 mol % trimellitylimidoglycine were insoluble in chloroform. For the chloroform-insoluble polymers, inherent viscosity measurements indicate that these insoluble polymers are oligomeric (Experimental Section).

There is an increase in glass transition temperatures from 39 to 90 °C with increasing imide content. No melting transitions are observed for the copolymers, although the homopolymer of CPH has a T_m of 144 °C. With increasing imide content, decomposition temperatures decrease from 467 to a minimum of 338 °C before increasing slightly to 350 °C. Elemental analyses indicate that the nitrogen content of the TMA-gly:CPH polymers closely correlates to the theoretical values. The ^{1}H NMR spectra show that the amount of imide monomer incorporated into the polymer corresponds to the monomer feed ratio, although the values are lower than the monomer feed ratio by 1–10% (Table 2). The NMR spectra are similar to those previously reported.[12]

Polymers Based on Pyromellitylimidoglycine. In addition to evaluating the effect of the anhydride monomer (SA vs CPH) on the polymer properties, the influence of the imide monomer on polymer properties was also investigated. Glycine derivatives of pyromellitic anhydride (PMA) (**5**) were used in place of the trimellitic anhydride derivative, **4**. The inflexibility of the pyromellitic group, as well as the additional imide bonds, should increase the mechanical strength of the polymers by increasing the stiffness of the polymer backbone. As the number of imide bonds in the pyromellitic acid derivative will be twice that of the trimellitic acid derivative, this should have a significant effect on the mechanical properties of the polymers.



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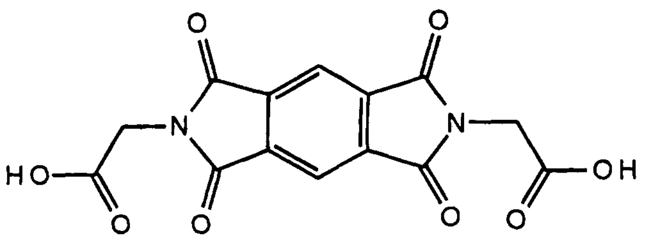

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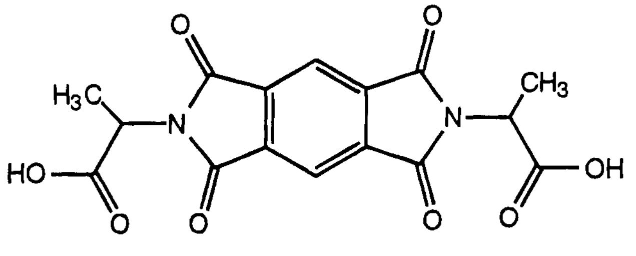
Table 3. Characteristics of Poly(PMA-ala:SA) Synthesized at 180 °C for 90 min under Vacuum

% PMA-ala (feed)	M_w	PDI	T_g (°C)	T_m (°C)	T_d (°C)	% PMA-ala (^{1}H NMR)
10	31 700	1.56	69	80	324	8.8
30	9 300	2.83	48	60	319	23
50	2 700	1.67	34	58	333	40
70	a	a	56	b	362	67
90	a	a	102	b	384	90
100	a	a	207	b	393	100

^{a} Not available. ^{b} Not found.

Monomeric pyromellitylimidoglycine (PMA-gly) (**5a**) was prepared using methods similar to those described for the synthesis of trimellitylimidoglycine. Under the melt condensation conditions used previously (180 °C, 90–120 min, 0.05 mmHg), copolymers of PMA-gly:SA or PMA-gly:CPH are completely insoluble in organic solvents, even polar, high-boiling solvents. Polymerizations performed in high-boiling solvents, such as diphenyl ether or *m*-cresol, also yielded insoluble polymers.

Poly(pyromellitylimidoalanine-*co*-sebacic acid) (PMA-ala:SA). To increase the solubility of the polymers derived from pyromellitic acid, the branching of the polymer backbone was modified by the incorporation of racemic alanine to give pyromellitylimidoalanine (**6**).



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In contrast to the acetylated pyromellitylimidoglycine (**5a**), the T_m of the acetylated pyromellitylimidoalanine (**6a**) is below the polymerization temperature of 180 °C. The use of PMA-ala gave soluble polymers, similar to those obtained with the TMA-gly monomer.

Results for the polymerization of PMA-ala with SA are shown in Table 3. The molecular weights follow the same trend as previously observed; i.e. increasing imide content yields lower molecular weight polymers. Copolymers of PMA-ala:SA have molecular weights similar to the previously described polymers, ranging from 31 700 for low imide ratios to 2700 for higher imide ratios. At greater than 40 mol % imide content, the polymers are insoluble in chloroform, yet soluble in high-boiling, polar solvents. Inherent viscosity measurements indicate that the chloroform-insoluble polymers are oligomeric (Experimental Section).

In Figure 1 is shown the ^{1}H NMR spectrum of PMA-ala:SA in a molar ratio of 50:50. The molar fractions of PMA-ala incorporated into the polymer backbone were determined from the corresponding relative intensities of the aromatic protons to the methylene protons of the sebacic acid unit (**1**). Due to the symmetry of the monomer units, only three dyad sequences should be

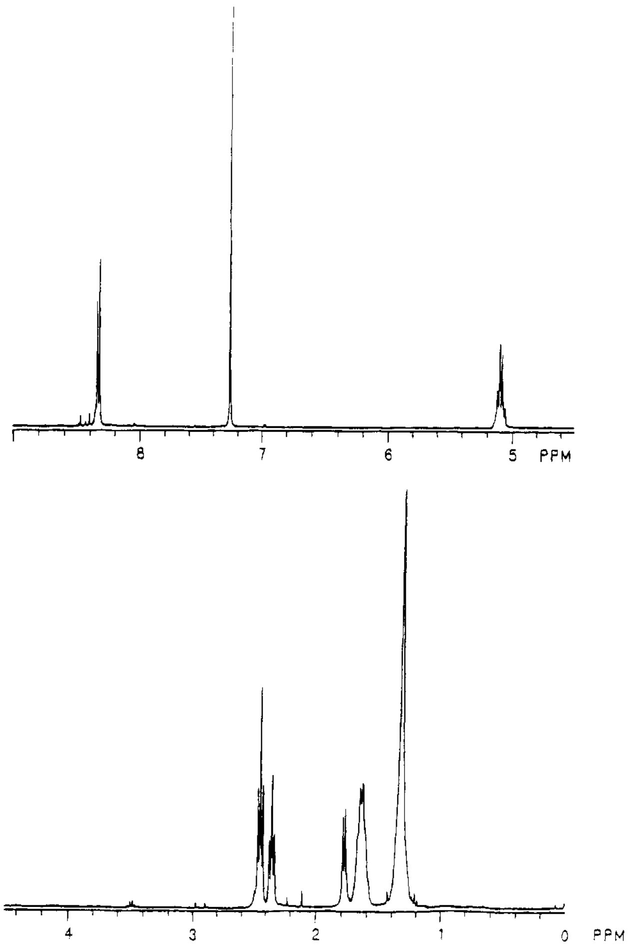
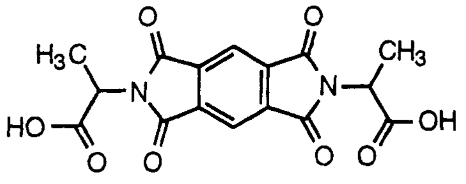
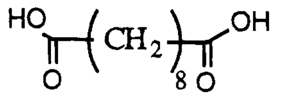


Figure 1. ^{1}H NMR spectra of PMA-ala:SA (50:50).

Table 4. Signal Assignment in ^{1}H NMR Spectra of PMA-ala:SA



PMA-ala = A



$\mathrm{HO{-}CO{-}(CH_2)_8{-}CO{-}OH}$

SA = B

dyad	ppm	assgnt
A-A	8.32	s, Ar H
A-B	8.26, 8.34	s, Ar H
A-A, A-B, B-B	5.09–5.10	q, CH
B-B	2.44	t, α-CH_2
A-B	2.35	t, α-CH_2
A-A, A-B, B-B	1.79	d, CH_3
A-A, A-B, B-B	1.70	m, β-CH_2
A-A, A-B, B-B	1.55, 1.32	br, γ-CH_2

present (A-A, A-B, and B-B). These dyads were identified by ^{1}H NMR spectroscopy; proton signal assignments are given in Table 4. The aromatic protons of PMA-ala resonate near 8.3 ppm. PMA-ala/PMA-ala dyads resonate at 8.32 ppm, and PMA-ala/SA dyads at 8.26 and 8.34 ppm. At 5.10 ppm, the quartet for the methine protons of PMA-ala is observed. Triplet signals for α-methylene protons of SA resonate at 2.44 ppm for SA/SA dyads and at 2.35 ppm for SA/PMA-ala dyads. At 1.79 ppm, a doublet for the methyl protons of PMA-ala is observed. Broad signals for the remaining methylene protons of SA resonate near 1.7 and 1.3 ppm. Integration of the ^{1}H NMR spectra indicates that the amount of imide monomer incorporated into the polymer is slightly less than the monomer feed ratio (Table 3).

Table 5. Characteristics of Poly(PMA-ala:CPH) Synthesized at 180 °C for 90 min under Vacuum

% PMA-ala (feed)	M_w	PDI	T_g (°C)	T_d (°C)	% PMA-ala (^{1}H NMR)
10	25 000	1.64	56	408	11
30	13 800	1.60	82	393	30
50	5 000	1.9	97	376	48
70	*a*	*a*	118	372	70
90	*a*	*a*	141	378	92

[a] Not available.

Glass transition temperatures decrease from 69 to 34 °C as the imide content increases for the chloroform-soluble polymers yet increase from 56 to 207 °C for the chloroform-insoluble polymers. Melting transitions decrease with increasing PMA-ala content for the chloroform-soluble polymers, from 80 to 58 °C. No melting transitions are observed for the chloroform-insoluble polymers. Correspondingly, no melting transition is observed for the homopolymer of PMA-ala. Decomposition temperatures generally increase from 320 to 393 °C with increasing imide content, as observed with the TMA-gly:SA copolymers (Table 3). The PMA-ala homopolymer has the highest decomposition and glass transition temperatures.

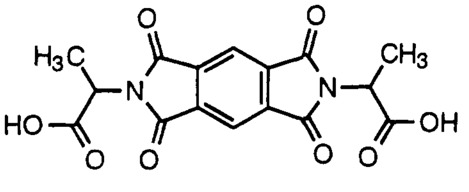
Elemental analysis shows that the carbon content is lower and that of hydrogen is higher by 0.2–1.0% than the theoretical values and the nitrogen content is lower by 0.1–0.2% than the calculated values (Experimental Section).

Poly[pyromellitylimidoalanine-*co*-bis(carboxyphenoxy)hexane] (PMA-ala:CPH). Properties of the PMA-ala:CPH copolymers are shown in Table 5. The weight-average molecular weights are similar to those of the TMA-gly:CPH polymers, ranging from 25 000 to 5000 at higher imide content. There are no observed melting transitions for the PMA-ala:CPH copolymers. Glass transition temperatures increase from 56 to 141 °C with increasing imide content. Decomposition temperatures decrease with increasing imide content for the chloroform-soluble polymers from 408 to 376 °C and increase slightly to 378 °C for the insoluble polymers. Inherent viscosity measurements indicate that the chloroform-insoluble polymers are oligomeric (Experimental Section).

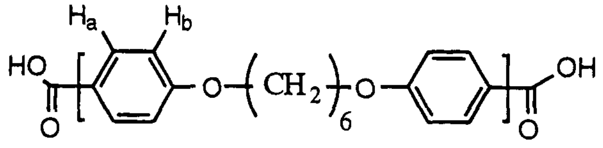
The carbon content is higher by 0.3–2.5%, and that of hydrogen is lower by 0.2–0.4% than the theoretical values. The nitrogen content is higher than the calculated values by 0.1–0.7% (Experimental Section).

The ^{1}H NMR spectrum for a 50:50 molar composition of PMA-ala:CPH is shown in Figure 2 and is more complex than the spectrum shown in Figure 1. The molar fractions of PMA-ala incorporated into the polymer backbone were determined from the corresponding relative intensities of the methine protons to the methylene protons of the CPH unit (**2**). Due to the symmetry of the monomer units, only three dyad sequences should be present (A-A, A-B, and B-B). These dyads were identified by ^{1}H NMR spectroscopy; proton signal assignments are given in Table 6. Aromatic

Table 6. Signal Assignment in ^{1}H NMR Spectra of PMA-ala:CPH



PMA-ala = A



CPH = B

dyad	ppm	assgnt
A-A	8.32	s, Ar H of **A**
A-B	8.26, 8.34	s, Ar H of **A**
B-B	8.07	d, Ar H_a of **B**
A-B	7.98, 7.90	d, Ar H_a of **B**
B-B	7.01–6.82	d, Ar H_b of **B**
A-B	6.85	d, Ar H_b of **B**
A-B	5.28	q, CH
A-A	5.07	q, CH
A-A, A-B, B-B	4.06	m, α-CH_2
A-A, A-B, B-B	1.87	br, β-CH_2
A-A, A-B, B-B	1.77	d, CH_3
A-A, A-B, B-B	1.58	br, γ-CH_2

protons in PMA-ala resonate near 8.3 ppm. Similar to the data for PMA-ala:SA copolymers, PMA-ala/PMA-ala dyads resonate at 8.32 ppm and PMA-ala/SA dyads at 8.34 and 8.26 ppm. For aromatic protons of CPH, doublets resonate at 8.1 and 6.9 ppm for the CPH/CPH dyads. Dyads of PMA-ala/CPH resonate downfield as doublets at 8.0 and 7.9 ppm and as indistinguishable sets of doublets near 6.85 ppm. The methine protons of PMA-ala are observed at 5.3 ppm for PMA-ala/CPH dyads, and at 5.1 ppm for PMA-ala/PMA-ala dyads. Broad signals for the methylene protons of CPH are observed near 4.1, 1.9, 1.8, and 1.6 ppm. The doublet signal for the methyl proton of PMA-ala should resonate at 1.7 ppm but is hidden under the methylene proton signals for the CPH. The ^{1}H NMR spectra for all polymer compositions indicate that the amount of imide monomer incorporated into the polymer backbone is nearly identical to the monomer feed ratio (Table 5). This is an indication of good miscibility and compatibility of the PMA-ala and CPH monomers.

Polymers prepared by melt condensation are generally considered to have random structural units along the polymer chain, due to the almost equal reactivities of the monomers and the random anhydride exchange reaction during the polycondensation process. The appearance of dyad sequences in the ^{1}H NMR spectra indicates that the copolymers presented in this report have random structures (Figures 1 and 2). In addition, random structures are substantiated by the presence of only one glass transition temperature per polymer composition (Tables 1–3 and 5). A comparison of glass transition temperatures for the polymers are shown in Figure 3. As the T_g's of the copolymers fall within the transition temperatures of the imide and anhydride homopolymers and only one transition is observed for each composition, the data also indicate that the polymers have random sequences.

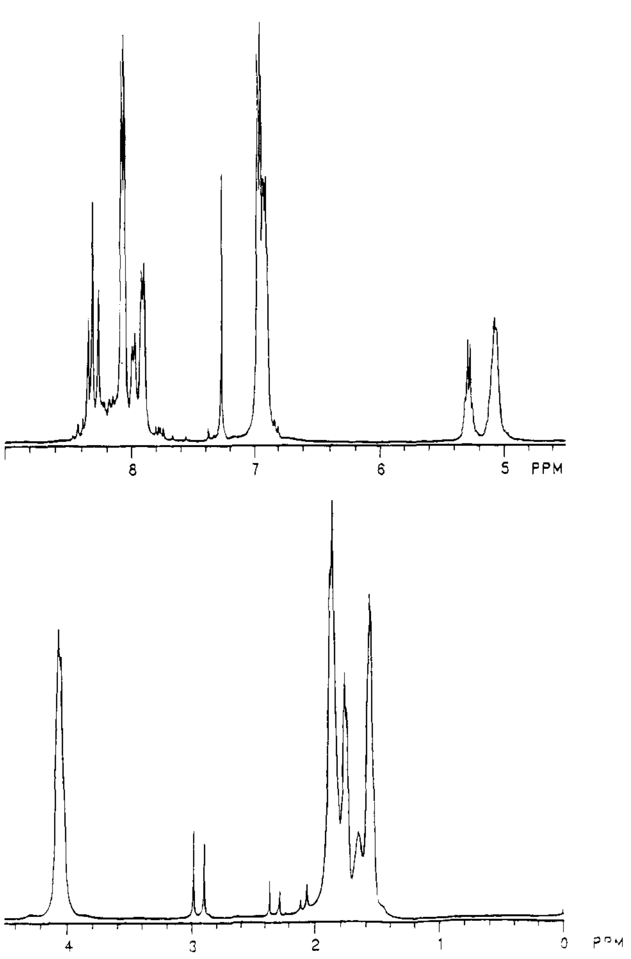


Figure 2. ^{1}H NMR spectra of PMA-ala:CPH (50:50).

Polymer Hydrophobicity. Sessile drop contact angle experiments, which measure the contact angle of liquids (in this case, water) on a planar surface, were performed on all polymers. The lower the contact angle, the higher the tendency of the water to spread over the surface.[13] Thus, hydrophilic materials are expected to have lower contact angles than hydrophobic materials. Data for these materials are presented in the Experimental Section and are plotted in Figure 4. Generally, polymers containing the aromatic acid, CPH, are more hydrophobic than polymers with the aliphatic acid, SA. Increasing the imide content in the polymer backbone tends to increase hydrophilicity, especially in polymers containing the hydrophilic monomer, SA. Hydrophobicity of PMA-ala:CPH copolymers does not change significantly with increasing imide content, indicating that the PMA-ala monomer is not as hydrophilic as the TMA-gly monomer (Figure 4).

Hydrophobicity, as determined by contact angle measurements, can be correlated to the degradation rates of the various copolymers—increasing the polymer hydrophilicity will increase the degradation rate. Degradation experiments on compressed polymer disks (1 mm × 14 mm) of the TMA-gly and PMA-ala copolymers will be reported elsewhere.[14] Depending on the imide content, disks of SA-containing polymers degrade completely from 30 to 200 h. Alternately, disks of CPH-containing polymers do not completely dissolve, but begin to disintegrate from 200 to 1400 h.

Mechanical Properties. Uniaxial, mechanical compression was performed on polymer cylinders (with a 2:1 aspect ratio) to simulate orthopedic devices, e.g. bone nails. Copolymers with molar compositions of 10:90, 30:

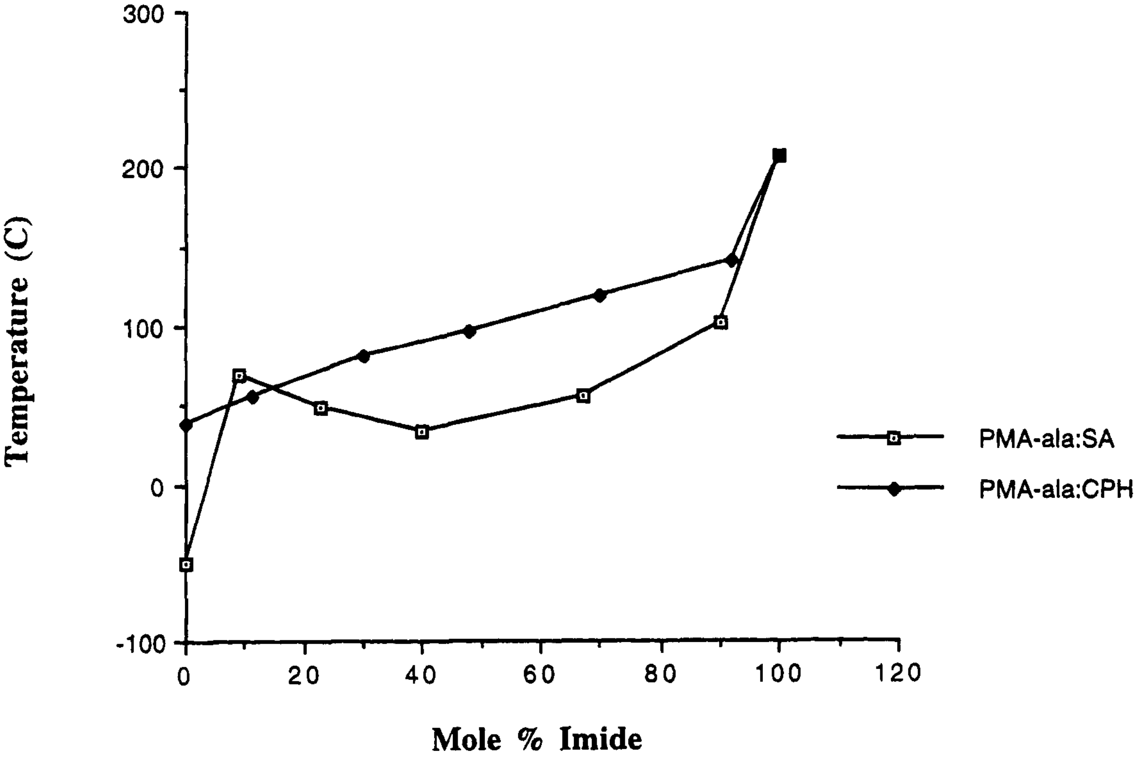


Figure 3. Effect of imide concentration on glass transition temperatures.

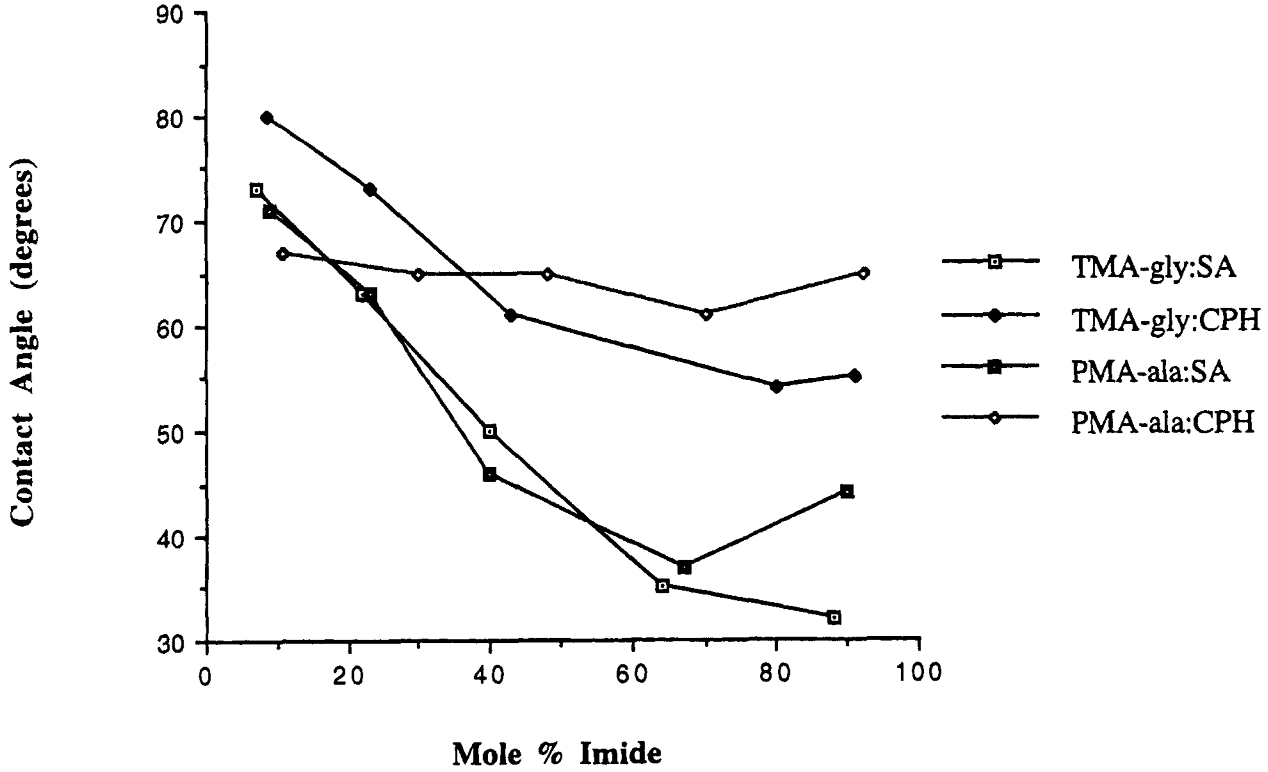


Figure 4. Sessile drop contact angle measurements.

70, and 50:50 were examined. Upon yielding, the polymer cylinders did not disintegrate. Instead, crack formation primarily occurred in the direction of loading, while the device maintained its original shape and form.

Polymers containing the aromatic monomer, CPH, have higher yield strengths than copolymers containing the aliphatic monomer, SA. The difference in compressive strengths of the 50:50 compositions of TMA-gly:CPH and PMA-ala:CPH may be attributed to the hydrophilicity of TMA-gly:CPH. The contact angle data indicate that the TMA-gly:CPH polymer is more hydrophilic, leading to increased water absorption relative to the PMA-ala:CPH polymer, which may affect the mechanical properties. Polymers of PMA-ala:CPH may be the most promising materials, as they have the highest, initial compressive strengths (36–56 MPa) in addition to long degradation times.[14] The copolymer of 50:50 PMA-ala:CPH has surprisingly good mechanical properties, considering the low molecular weight relative to the 10:90 and 30:70 compositions. In general, increas-

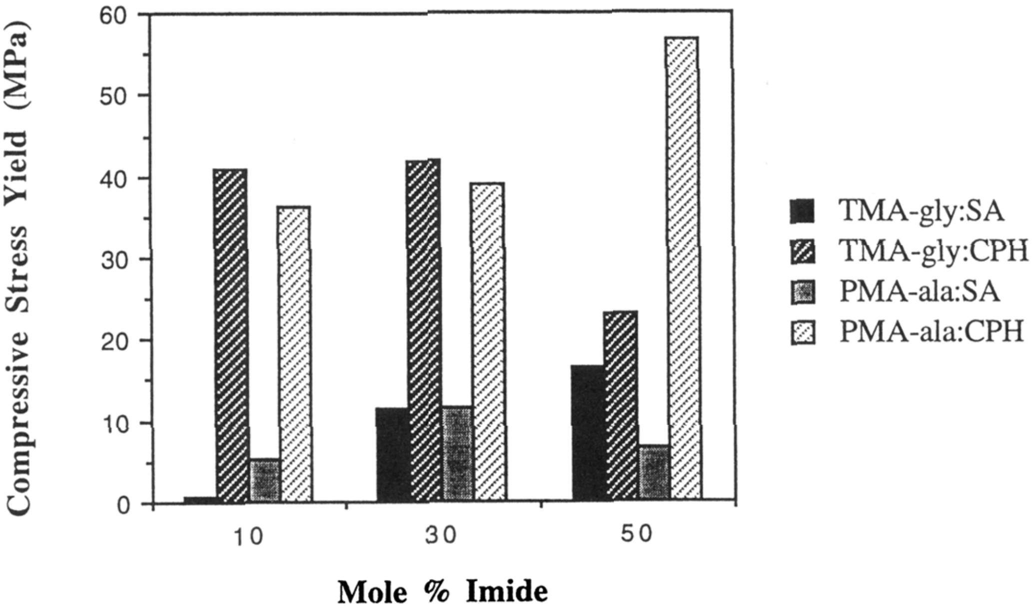


Figure 5. Compressive strengths of poly(anhydride-*co*-imides).

ing the molecular weight gives a corresponding increase in mechanical properties.[15] Therefore, the mechanical strengths of this polymer may be related to the rigidity of the aromatic imide group.

Our studies have shown that the compressive strengths of the poly(anhydride-*co*-imides) are similar to that of the currently used resorbable sutures of poly(lactic acid), which have initial compression yield stresses of 50–60 MPa.[16] However, poly(lactic acid) loses its stiffness within a time interval too short to guarantee bone healing.[17] For orthopedic applications, the reduction in implant strength as the polymer cylinders degrade should closely match the increase in strength of human bone, which has an average compressive strength of 5 MPa.[6]

The ability to synthesize polymers that degrade over a specified time period by simply altering monomer ratios is a major advantage of the poly(anhydride-*co*-imide) systems, similar to the poly(anhydrides) which degrade anywhere from days to years.[5] It is anticipated that the poly(anhydride-*co*-imides) presented here can, with further study, offer a biocompatible, degradable polymer alternative to the currently used poly(lactic acids). Thus, future work will measure changes in mechanical properties as a function of degradation time of the PMA-ala:CPH copolymers.

Conclusion

Poly(anhydride-*co*-imides) were synthesized by melt condensation polymerization. For all polymers systems, the molecular weights decreased as the amount of imide in the backbone increased. We believe this is due to the decreased flexibility (and increased viscosity) of the polymers that contained high amounts of imide groups. This limited polymer mobility may decrease polymer chain interaction, and limit the anhydride exchange that leads to higher molecular weight polymers. We are investigating this phenomenon further by incorporating monomers that should enhance flexibility, or mobility. Generally, the molecular weights of the polymers remained approximately the same as the type of imide or anhydride monomer was altered.

When comparing the thermal and mechanical properties of these polymers, one must consider that the molecular weights of the materials may dramatically affect the results. However, even at low molecular weights, the polymers have thermal and mechanical properties compatible with the needs of orthopedic devices.

The choice of anhydride monomer has a prominent effect on the polymer properties. Polymers containing CPH are more hydrophobic, have higher compressive strengths, have higher glass transition and decomposition temperatures, and exhibit no melting transitions relative to polymers containing SA. In addition, properties of the polymers containing SA are less reproducible due to the rapid degradation of these materials upon exposure to air.

As anticipated, the mechanical and thermal stability of the materials are increased by the incorporation of imide groups in the polymer backbone. The selection of TMA-gly vs PMA-ala can significantly affect the resulting polymer characteristics. Both imide monomers affect the hydrophobicity of the resulting polymers in similar ways, with the materials becoming more hydrophilic as the imide content is increased. However, polymers containing PMA-ala have thermal transition temperatures that are higher than the corresponding polymers with TMA-gly.

Experimental Section

Materials. Trimellitic anhydride, pyromellitic anhydride, glycine, DL-alanine, sebacic acid, acetic anhydride, dimethylformamide, *m*-cresol, and diphenyl ether were obtained from Aldrich and used as received. Methylene chloride and diethyl ether were obtained from Fisher and used as received. 1,3-Bis(*p*-carboxyphenoxy)hexane,[18] trimellitylimidoglycine,[8] and pyromellitylimidoglycine[8b] were prepared as previously reported.

Methods. All glassware was dried in a 120 °C oven overnight (12 h) and then cooled under argon.

Infrared spectroscopy was obtained on a Nicolet Magna 550 FTIR spectrometer and Nicolet data station with OMNIC 1.20 software. Samples were either film cast in chloroform onto NaCl plates or pressed into KBr pellets.

The molecular weights were determined on a Perkin-Elmer system consisting of the isocratic LC pump 250 and LC-30 RI detector. Turbochem3 software was used on a DECpc 433 data station. Samples dissolved in chloroform were eluted through two columns in series (Polymer Laboratories, PL-Gel, linear and 100 Å). Molecular weights of the polymers were determined relative to narrow molecular weight polystyrene standards (Polysciences).

Thermal analysis was determined on a Perkin-Elmer system consisting of TGA7 and DSC7 analyzers, with TAC7/7 instrument controllers. UNIX software was used on a DECpc 433 data station. For DSC, an average sample weight of 5–10 mg was heated at either 10 or 20 °C/min under a flow of N_2 (30 psi). For TGA, an average sample weight of 10 mg was heated at 20 °C/min under a flow of N_2 (8 psi).

Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN).

^{1}H and ^{13}C NMR spectra were obtained on a Nicolet 360 MHz spectrometer on solutions in $CDCl_3$, with the solvent used as the internal reference.

Inherent viscosities were measured with a Cannon 75 Ubelholde viscometer in 1 wt % solutions in DMAc at 23 °C.

Sessile drop contact angle measurements were obtained with a NRL Goniometer (Ramé-hart, Inc.). The measurements were performed on polymer disks (average weight of 0.15 g, average size of 1 × 13 mm) compressed at room temperature for 10 min at 7000 psi with a Carver press. An average of five measurements were taken with no more than 7% deviation from the mean (~5 deg).

Cylinders with a 2:1 aspect ratio were prepared by compression molding the isolated polymer (1.00 g) with an 8 mm diameter die. Samples were tested in uniaxial compression on an Instron machine (Model 4505) at a constant crosshead rate of 0.5 mm/min with a 1000 lb. load cell. An average of six samples at each composition were tested with no more than 17% deviation from the mean.

Preparation of Imide–Acids. Derivatives of trimellitic and pyromellitic anhydride were synthesized by a method similar to that reported by González et al.[8b] In brief, the reaction mixture of anhydride and amino acid in *m*-cresol (or dimethylformamide) were heated to near reflux temperatures for 4 h. Upon cooling, a precipitate is formed that is isolated by filtration, washed with diethyl ether and toluene, dried, and recrystallized from water.

Trimellitylimidoglycine, 4. Yield: 84%. T_m = 269 °C (lit = 268 °C),[8] T_d = 344 °C.

Pyromellitylimidoglycine, 5. Yield: 44%. ^{1}H NMR (CD_3OD): ∂ 4.44 (s, 4H, CH_2), 8.32 (s, 2H, ArH). ^{13}C (CD_3OD): ∂ 40.1 (CH_2), 120.1 (Ar CH), 132.2 (Ar C), 164.5, 178.0 (C=O). IR (KBr, cm^{-1}) 3500 (O—H), 1789 (C=O, imide), 1729 (C=O, acid), 1413 (C—N), 1124 (C—O). Anal. Calc: C, 50.60; H, 2.41; N, 8.43. Found: C, 50.46; H, 2.20; N, 8.34. T_m = 263 °C, T_d = 300 °C.

Pyromellitylimidoalanine, 6. Yield: 48%. ^{1}H NMR (CD_3OD): ∂ 1.69 (d, J = 7.4 Hz, 6H, CH_3), 5.00 (q, J = 7.4 Hz, 2H, CH), 8.27 (s, 2H, ArH). ^{13}C (CD_3OD): ∂ 15.3 (CH_3), 48.5 (CH), 118.9 (Ar *C*H), 138.5 (Ar *C*), 167.0, 172.8 (C=O). IR (KBr, cm^{-1}): 3200 (O—H), 1782 (C=O, imide), 1713 (C=O, acid), 1468 (C—N), 1087 (C—O). Anal. Calc: C, 53.33; H, 3.33; N, 7.78. Found: C, 53.20; H, 3.22; N, 7.81. T_m = 252 °C, T_d = 292 °C.

Preparation of Acetylated Monomers. The derivatives of trimellitic and pyromellitic anhydride were acetylated in a method similar to that reported by Staubli et al.[9] Briefly, the imide–acids were treated with a large excess of acetic anhydride and heated at reflux temperature until the starting material has dissolved (1 h). The reaction mixture was cooled and evaporated to dryness. Upon addition of excess diethyl ether, a white precipitate formed. The precipitate was filtered, crushed, stirred in an excess of diethyl ether, filtered again, and dried.

Acetylated Trimellitylimidoglycine, 4a. Yield: 67%. T_d = 197 °C.

Acetylated Pyromellitylimidoglycine, 5a. Yield: 88%. ^{1}H NMR ($CDCl_3$): ∂ 2.31 (s, 6H, CH_3), 4.62 (s, 4H, CH_2), 8.40 (s, 2H, ArH). ^{13}C NMR ($CDCl_3$): ∂ 22.2 (CH_3), 39.9 (CH_2), 119.3 (Ar CH), 137.2 (Ar C), 162.5 (*C*OCH$_3$), 164.5, 164.7 (C=O). IR (KBr, cm^{-1}): 1841, 1808 (C=O, anhydride), 1755 (C=O, imide), 1413 (C—N), 1117 (C—O). Anal. Calc: C, 51.92; H, 2.88; N, 6.73. Found: C, 51.24; H, 2.76; N, 6.80. T_d = 176 °C.

Acetylated Pyromellitylimidoalanine, 6a. Yield: 56%. ^{1}H NMR ($CDCl_3$): ∂ 1.77 (d, J = 7.4 Hz, 6H, *C*H$_3$CH), 2.89 (s, 6H, CH$_3$CO), 5.11 (q, J = 7.4 Hz, 2H, CH), 8.36 (s, 2H, ArH). ^{13}C NMR ($CDCl_3$): ∂ 14.9 (*C*H$_3$CH), 22.3 (*C*H$_3$CO), 48.4 (CH), 119.1 (Ar *C*H), 137.0 (Ar *C*), 162.3 (*C*OCH$_3$), 164.7, 164.9 (C=O). IR (neat, cm^{-1}): 1841 (C=O, anhydride), 1736, 1722 (C=O), 1394 (C—N), 1078 (C—O). Anal. Calc: C, 54.06; H, 3.63; N, 6.30. Found: C, 53.66; H, 3.52; N, 6.23. T_m = 159 °C, T_d = 362 °C.

Acetylated Sebacic Acid, 1a. T_d = 298 °C.

Acetylated 1,6-Bis(carboxyphenoxy)hexane, 2a. T_d = 225 °C.

Melt Polymerization. The method as described by Domb[11] was used. In brief, the reaction mixture was heated to 180 °C for 90–120 min under high vacuum (0.05 mmHg). During the polymerization, a strong Ar sweep was performed for 30 s every 15 min. The polymer was purified by precipitation from methylene chloride into diethyl ether.

TMA-gly:SA (10:90). Yield: 100%. Anal. Calc: C, 64.23; H, 7.90; N, 0.74. Found: C, 64.16; H, 8.25; N, <0.5. Contact angle: 73 ± 1°. Compressive yield stress: 0.70 ± 0.1 MPa.

TMA-gly:SA (30:70). Yield: 99%. Anal. Calc: C, 62.42; H, 6.41; N, 2.12. Found: C, 62.48; H, 6.98; N, 1.55. Contact angle: 63 ± 4°. Compressive yield stress: 11.6 ± 0.5 MPa.

TMA-gly:SA (50:50). Yield: 97%. Anal. Calc: C, 60.72; H, 5.06; N, 3.37. Found: C, 60.59; H, 5.80; N, 2.76. Contact angle: 50 ± 2°. Compressive yield stress: 16.4 ± 2.4 MPa.

TMA-gly:SA (70:30). Yield: 88%. Anal. Calc: C, 59.20; H, 3.83; N, 4.52. Found: C, 58.20; H, 4.44; N, 3.90. $[\mu]$ = 0.061 dL/g. Contact angle: 35 ± 5°.

TMA-gly:SA (90:10). Yield: 83%. Anal. Calc: C, 57.80; H, 2.70; N, 5.57. Found: C, 56.30; H, 3.20; N, 5.19. $[\mu]$ = 0.065 dL/g. Contact angle: 32 ± 3°.

^{1}H NMR ($CDCl_3$) for the TMA-gly:SA copolymers are as follows: ∂ 8.65–8.40 (m, Ar $H_{2',6'}$), 8.15–7.95 (m, Ar $H_{5'}$), 4.82–4.54 (s, CH_2 of TMA-gly), 2.67–2.36 (t, α-CH_2 of SA), 1.76–1.65 (t, β-CH_2 of SA), 1.50, 1.32 (br s, CH_2 of SA). IR (KBr, cm^{-1}): 2940, 2860 (C—H), 1820 (C=O anhydride), 1750 (C=O imide), 1060 (C—O).

TMA-gly:CPH (10:90). Yield: 77%. Anal. Calc: C, 69.64; H, 5.62; N, 0.43. Found: C, 68.42; H, 5.99; N, <0.5. Contact angle: 80 ± 1°. Compressive yield stress: 40.9 ± 1.6 MPa.

TMA-gly:CPH (30:70). Yield: 80%. Anal. Calc: C, 67.56; H, 5.04; N, 1.37. Found: C, 66.52; H, 5.48; N, 1.22. Contact angle: 73 ± 2°. Compressive yield stress: 41.8 ± 7.4 MPa.

TMA-gly:CPH (50:50). Yield: 77%. Anal. Calc: C, 65.15; H, 4.39; N, 2.45. Found: C, 64.23; H, 4.98; N, 2.32. Contact angle: 61 ± 3°. Compressive yield stress: 23.1 ± 2.8 MPa.

TMA-gly:CPH (70:30). Yield: 85%. Anal. Calc: C, 62.34; H, 3.60; N, 3.72. Found: C, 58.24; H, 4.38; N, 3.20. $[\mu]$ = 0.025 dL/g. Contact angle: 54 ± 2°.

TMA-gly:CPH (90:10). Yield: 84%. Anal. Calc: C, 59.03; H, 2.69; N, 5.21. Found: C, 55.58; H, 3.86; N, 5.90. $[\mu]$ = 0.016 dL/g. Contact angle: 55 ± 2°.

^{1}H NMR ($CDCl_3$) for the TMA-gly:CPH copolymers are as follows: ∂ 8.69–8.57 (m, Ar $H_{2',6'}$), 8.21–7.88 (m, Ar $H_{5'}$ and H_a), 7.10–6.82 (d, Ar H_b), 4.78–4.45 (s, CH_2 of TMA-gly), 4.06 (t, α-CH_2 of CPH), 1.88 (br, β-CH_2 of CPH), 1.59 (br, γ-CH_2 of CPH). IR (KBr, cm^{-1}): 2940 (C—H), 1790 (C=O anhydride), 1730 (C=O imide), 1050 (C—O).

PMA-ala:SA (10:90). Yield: 91%. Anal. Calc: C, 63.66; H, 7.71; N, 1.40. Found: C, 62.35; H, 8.33; N, 0.78. Contact angle: 71 ± 4°. Compressive yield stress: 5.21 ± 1.6 MPa.

PMA-ala:SA (30:70). Yield: 65%. Anal. Calc: C, 61.22; H, 6.14; N, 3.63. Found: C, 59.43; H, 7.11; N, 2.41. Contact angle: 63 ± 6°. Compressive yield stress: 11.6 ± 4.0 MPa.

PMA-ala:SA (50:50). Yield: 50%. Anal. Calc: C, 59.32; H, 4.94; N, 5.32. Found: C, 56.72; H, 5.86; N, 4.22. Contact angle: 46 ± 5°. Compressive yield stress: 6.69 ± 0.5 MPa.

PMA-ala:SA (70:30). Yield: 45%. Anal. Calc: C, 57.84; H, 4.01; N, 6.65. Found: C, 55.06; H, 4.03; N, 6.56. $[\mu]$ = 0.10 dL/g. Contact angle: 37 ± 2°.

PMA-ala:SA (90:10). Yield: 45%. Anal. Calc: C, 56.65; H, 3.25; N, 7.73. Found: C, 54.36; H, 3.48; N, 7.74. $[\mu]$ = 0.084 dL/g. Contact angle: 44 ± 5°.

^{1}H NMR ($CDCl_3$) for the PMA-ala:SA copolymers are as follows: ∂ 8.34, 8.32, 8.26 (s, Ar H), 5.09–5.10 (q, J = 7.4 Hz, CH), 2.44, 2.35 (t, J = 7.4 Hz, α-CH_2 of SA), 1.79 (d, J = 7.4

Hz, CH_3), 1.70, (m, β-CH_2 of SA), 1.55, 1.32 (br s, CH_2 of SA). IR (KBr, cm^{-1}): 2940, 2860 (C—H), 1830 (C=O anhydride), 1750 (C=O imide), 1090 (C—O).

PMA-ala:CPH (10:90). Yield: 79%. Anal. Calc: C, 69.14; H, 5.58; N, 0.82. Found: C, 68.02; H, 5.73; N, 0.87. Contact angle: 67 ± 3°. Compressive yield stress: 36.3 ± 2.6 MPa.

PMA-ala:CPH (30:70). Yield: 81%. Anal. Calc: C, 66.26; H, 4.99; N, 2.47. Found: C, 65.48; H, 5.18; N, 2.25. Contact angle: 65 ± 4°. Compressive yield stress: 38.8 ± 4.6 MPa.

PMA-ala:CPH (50:50). Yield: 74%. Anal. Calc: C, 62.34; H, 4.40; N, 4.11. Found: C, 62.66; H, 4.72; N, 3.80. Contact angle: 65 ± 6°. Compressive yield stress: 56.8 ± 2.3 MPa.

PMA-ala:CPH (70:30). Yield: 72%. Anal. Calc: C, 60.46; H, 3.81; N, 5.74. Found: C, 58.38; H, 4.20; N, 5.08. $[\mu]$ = 0.061 dL/g. Contact angle: 61 ± 4°.

PMA-ala:CPH (90:10). Yield: 56%. Anal. Calc: C, 57.58; H, 3.22; N, 7.37. Found: C, 55.08; H, 3.54; N, 7.09. $[\mu]$ = 0.061 dL/g. Contact angle: 65 ± 3°.

^1H NMR ($CDCl_3$) for the PMA-ala:CPH copolymers are as follows: ∂ 8.34, 8.32. 8.26 (s, Ar H), 8.07, 7.98, 7.90 (d, J = 7.6 Hz, Ar H_a), 7.01−6.82 (dd, J = 8.6 and 2.5 Hz, Ar H_b), 5.28, 5.07 (q, J = 7.3 Hz, CH), 4.06 (m, α-CH_2 of CPH), 1.87 (br, β-CH_2 of CPH), 1.77 (d, CH_3), 1.58 (br, γ-CH_2 of CPH). IR (KBr, cm^{-1}): 2950, 2870 (C—H), 1790 (C=O anhydride), 1730 (C=O imide), 1040 (C—O).

P(SA). Yield: 100%. Anal. Calc: C, 65.22; H, 8.70. Found: C, 63.94; H, 8.85.

P(CPH). Yield: 100%. Anal. Calc: C, 70.59; H, 5.88. Found: C, 67.76; H, 5.90.

P(TMA-gly). Yield: 79%. ^1H NMR ($CDCl_3$): ∂ 8.50 (d, Ar $H_{2'}$), 8.38 (s, Ar $H_{6'}$), 8.10 (d, $H_{5'}$), 4.48 (CH_2). Anal. Calc: C, 57.14; H, 2.16; N, 6.06. Found: C, 53.12; H, 3.44; N, 6.28. $[\mu]$ = 0.067 dL/g. IR (KBr, cm^{-1}): 2960 (C—H), 1790 (C=O anhydride), 1740 (C=O imide).

P(PMA-ala). Yield: 86%. ^1H NMR ($CDCl_3$): ∂ 8.32 (s, ArH), 5.09 (q, J = 7.3 Hz, CH), 1.70 (d, J = 7.3 Hz, CH_3). Anal. Calc: C, 56.14; H, 2.92; N, 8.19. Found: C, 54.12; H, 3.23; N, 7.79. $[\mu]$ = 0.031 dL/g. IR (KBr, cm^{-1}): 2930 (C—H), 1850 (C=O anhydride), 1780, 1740 (C=O imide).

Solution Polymerization. The method as described by González[8] was used. Briefly, the monomers were slurried in diphenyl ether and heated to high temperatures (180−245 °C) for 17 h. On cooling, a precipitate forms that was filtered out, washed with diethyl ether, and dried.

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