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Characterization of Hydrolytically Degradable Amino Acid Containing Poly(anhydride-*co*-imides)

Andrea Staubli, Edith Mathiowitz,[†] Melissa Lucarelli, and Robert Langer*

Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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ABSTRACT: The synthesis and characterization of poly(anhydride-*co*-imides) containing either naturally occurring amino acids or ω-amino acids linked via hydrolytically labile anhydride bonds are presented. The synthesis included initial condensation of the amino acids with trimellitic anhydride to form imide-containing diacids, followed by melt polycondensation via the corresponding mixed anhydride. The reaction conditions were optimized for both the homo- and copolymers with either sebacic acid (SA) or 1,6-bis(*p*-carboxyphenoxy)hexane (CPH) in defined ratios. Polymerizations performed at 180 °C gave, in general, maximal molecular weight after 1–2 h. High molecular weight was also obtained if the polymerizations were performed at lower reaction temperatures over longer periods of time. Higher molecular weight copolymers (>100 000) were generally obtained with an increasing content of flexible spacers. An increasing content of flexible spacers also resulted in low melting points (<100 °C) and good solubility in common organic solvents. Structural analysis and sequence distribution as a function of copolymer composition were determined by several spectroscopic methods. Analysis of the thermal behavior (by differential scanning calorimetry, DSC) revealed the classical melting point depression for these copolymers, according to the Flory–Huggins theory. The glass transition temperatures showed both negative and positive deviations from linearity, depending on the chemical nature and compatibility of the monomers. Both X-ray analysis and DSC showed that highly aromatic polymers were generally to a high degree amorphous. Increasing crystallinity was observed upon introduction of flexible spacers (either by copolymerization with sebacic acid or by incorporation of ω-amino acids containing long polymethylene chains) into the backbone. Analysis of the mechanical properties of selected poly(anhydride-*co*-imides) in the form of fibers showed that depending on the copolymer composition both high tensile strength values (as high as 3000 kg/cm^2) and high elongation at break (up to 340%) were obtained.

Introduction

Polymers, which are available in a wide variety of compositions and properties, constitute the broadest and most diverse class of biomaterials. The potential of these polymers in biomedical applications depends on a variety of physicomechanical and chemical properties as well as on their biocompatibility. Various synthetic poly(amino acids) have been used in structural, immunological, and enzymological studies as well as in biomaterials (e.g., sutures,[1] skin substitutes,[3,4] and drug delivery systems[5]). However, the potential of polypeptides in some applications (e.g., for medical purposes) is frequently limited due to undesirable chemical and physical properties, e.g., their chemical inertness (which leads to mainly enzyme-mediated and possibly irreproducible biodegradation[2]), and potential antigenicity. A possibility to overcome these limitations is the synthesis of nonpeptidic analogues based on side-chain and backbone modifications[6–8] as well as the polymerization of intact amino acids via their side-chain functionalities by nonpeptidic bonds.[9,10] On the other hand, previously reported polyanhydrides, which are used in various drug delivery applications, are known for their hydrolytic reactivity, which may be controlled by simple structural changes in the polymer backbone.[11] Recently, the synthesis of a new polymer class containing amino acids integrated into the polymer backbone via anhydride bonds has been reported, in an attempt to design poly(amino acids) displaying both enhanced degradability and structural integrity.[12] The amino acids (either naturally occurring amino acids or ω-amino acids with variable spacer length) were first converted into dicarboxylic acids by condensation with trimellitic anhydride and subsequently polymerized via the corresponding mixed anhydride by melt polycondensation to form poly(anhydride-*co*-imides) (Figures 1 and 2). These polymers displayed superior mechanical properties, compared to previously reported polyanhydrides, as a result of the imide bond.[12] On the other hand, as compared to other poly(imides) containing similar diacid structures,[13–21] both enhanced degradability (due to the existing anhydride bonds) and good solubility in organic solvents and low transition temperatures were observed.

In this report we present an in-depth analysis of the synthesis and properties of various poly(anhydride-*co*-imides), as a function of molecular structure, to establish some relevant structure–property relationships. The synthesis and analysis concentrated on polymers containing either ω-amino acids of various spacer length (**1a–g**) or naturally occurring amino acids with different side-chain groups (e.g., L-leucine, L-tyrosine, and *S*-benzylcysteine) (**2a–c**)), as illustrated in Figure 1. Furthermore, the effect of copolymerization with either an aliphatic spacer (SA) (**3a–g**) or a more hydrophobic monomer containing aromatic moieties (CPH) (**4a,b**) on the polymer properties was studied. Fourier transformed infrared spectroscopy (FTIR) was used to analyze and identify the molecular composition of these poly(anhydride-*co*-imides). An analysis of the thermal behavior (e.g., glass transition temperature (T_g), crystalline melting point (T_m), specific heat and enthalpy, and thermal degradation) and its dependence on molecular structure parameters was performed by differential scanning calorimetry (DSC). The degree of crystallinity of various homo- and copolymers was determined by X-ray analysis alone and in some cases in combination with the identified thermodynamic transitions of these polymers using DSC (which also reflected the degree of amorphous and crystalline regions in a given polymer). Furthermore, the mechanical properties (e.g.,

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* To whom correspondence should be addressed.

[†] New address: Brown University, Section of Artificial Organs, Department of Biology & Medicine, Providence, RI 02904.

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Table I
Copolymerization of TMA-gly, TMA-β-ala, or TMA-gaba with SA at Different Temperatures and with or without Various Catalysts

% TMA-AA	% SA	catalyst	polymerizn T, °C	polymerizn time, h	M_w[a]
		AA = gly			
20	80		100	3.5	18 040
20	80	1 mol % cadmium acetate	100	4.3	21 580
20	80		150	3.6	38 785
20	80	1 mol % barium oxide	150	2.5	55 545
20	80		180	0.75	30 420
20	80	1 mol % lead acetate	180	0.75	61 880
		AA = β-ala			
20	80		120	2	26 010
20	80		180	1.25	68 240
20	80	2 mol % titanium isopropoxide	100	3	11 700
20	80	2 mol % aluminum isopropoxide	120	3	25 110
16	84	2 mol % calcium carbonate	120	8	129 210
20	80	2 mol % lead acetate	120	16.8	77 375
20	80	2 mol % cadmium acetate	120	23.5	47 820
20	80	2 mol % cadmium acetate	150	4.5	86 045
		AA = gaba			
18	82		180	0.75	67 435
18	82	0.7 mol % lead acetate	180	1	72 380
18	82	0.7 mol % cadmium acetate	180	0.75	112 725

[a] Determined by GPC (see the Experimental Section).

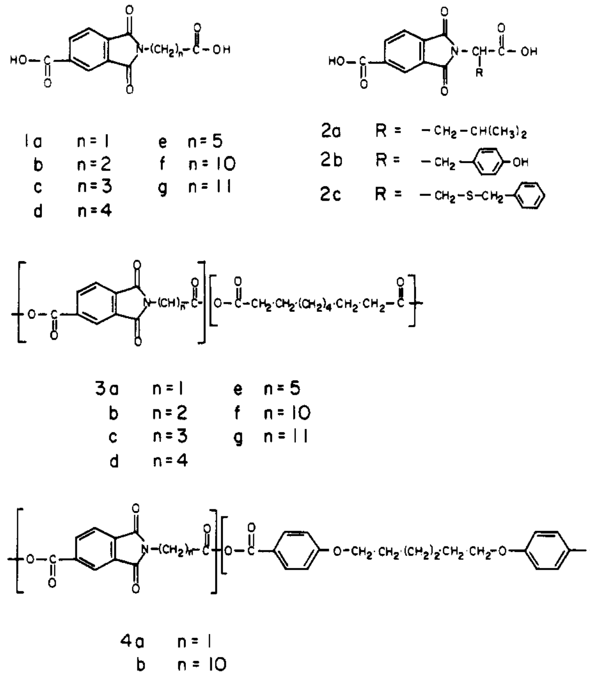

Figure 1. Monomer and polymer structures.

tensile strength and elongation) were determined as a function of molecular structure.

On the basis of these findings, synthesis of polymers with known chemical and morphological characteristics may be achieved, displaying a desired balance of physicochemical and mechanical properties on which the overall performance of the polymer depends.

Experimental Section

Materials. Trimellitic anhydride (TMA; Aldrich Chemical Co.) was recrystallized from a mixture of hot toluene and acetic anhydride. The amino acids used were glycine (Mallinckrodt), β-alanine, γ-aminobutyric acid, *S*-benzylcysteine (Sigma Chemical Co.), L-leucine (Fluka AG, Switzerland), L-tyrosine (Chemical Dynamics Corp.), 11-aminoundecanoic acid, and 12-aminododecanoic acid (Aldrich Chemical Co). Sebacic acid was obtained from Aldrich Chemical Co. Chloroform (gold label, Aldrich Chemical Co.) was purified by passing through basic aluminum oxide (ICN Biomedicals) and stored under inert atmosphere in brown bottles over molecular sieves. All other solvents (gold label, Aldrich Chemical Co.) were used without further purification, unless otherwise specified. 1,6-Bis(carboxyphenoxy)hexane (CPH) was obtained as described elsewhere.[22] The imide-containing diacids were prepared by condensation of equimolar amounts of amino acid and trimellitic anhydride.[11] All poly(anhydride-*co*-imides) were synthesized by melt polycondensation via their mixed anhydrides with acetic acid.[11] The solid catalysts (aluminum isopropoxide was obtained from Sigma Chemical Co., titanium isopropoxide and lead acetate from Aldrich Chemical Co., cadmium acetate dihydrate from Fluka AG (Switzerland), calcium carbonate from Mallinckrodt Inc. (Paris), and barium oxide from EM Science (Gibbstown, NJ)) were dried in a vacuum oven at 100 °C for 48 h and sieved manually to less than 50-μm particle size.

Methods. The melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations were measured by a SR6 polarimeter (Polyscience Corp.) at the sodium D line (589 nm) in a 200-mm measuring tube at 22 °C. Infrared spectroscopy was obtained on a FTIR spectrometer (Mattson Instruments). The samples were either film cast in chloroform onto an NaCl plate or pressed into KBr pellets. The molecular weights of all the polymer samples were determined on a Perkin-Elmer GPC system consisting of the Series 10 pump, the LKB 214 rapid spectral detector at 254-nm wavelength, and the PE 3600 data station. The samples dissolved in chloroform or a *N,N*-dimethylformamide/chloroform mixture were eluted through a PL gel column (Polymer Laboratories, PL-Gel, 30 cm × 7.5 mm, particles 5 μm, mixed bed) at a flow rate of 0.9 mL/min. The molecular weights of the polymers were determined relative to polystyrene standards (Polyscience). Elemental analysis was performed by Galbraith Laboratories (Knoxville, TN). ^1H and ^{13}C NMR spectra were obtained on Varian 250- or 300-MHz and Varian XL 400 spectrometers, respectively, using chloroform-d_1 or dimethyl-d_6 sulfoxide as a solvent and either tetramethylsilane (TMS) or external standards, respectively. Wide-angle X-ray powder diffraction (WAXD) of polymers in the form of pressed disks (ca. 1 mm thick) was recorded on a Rigaku RU 300 Philips X-ray diffractometer using a nickel-filtered Cu Kα source. Thermal analysis of the polymers was studied on the Series 7 thermal analysis system of Perkin-Elmer. An average sample weight of 5–10 mg was heated at heating rates ranging from 1 to 15 °C/min. Tensile properties of meltdrawn fibers were measured with an Instron (Model 4201) with a strain rate of 4 mm/min. The polymer fibers were drawn directly from the melt, and their

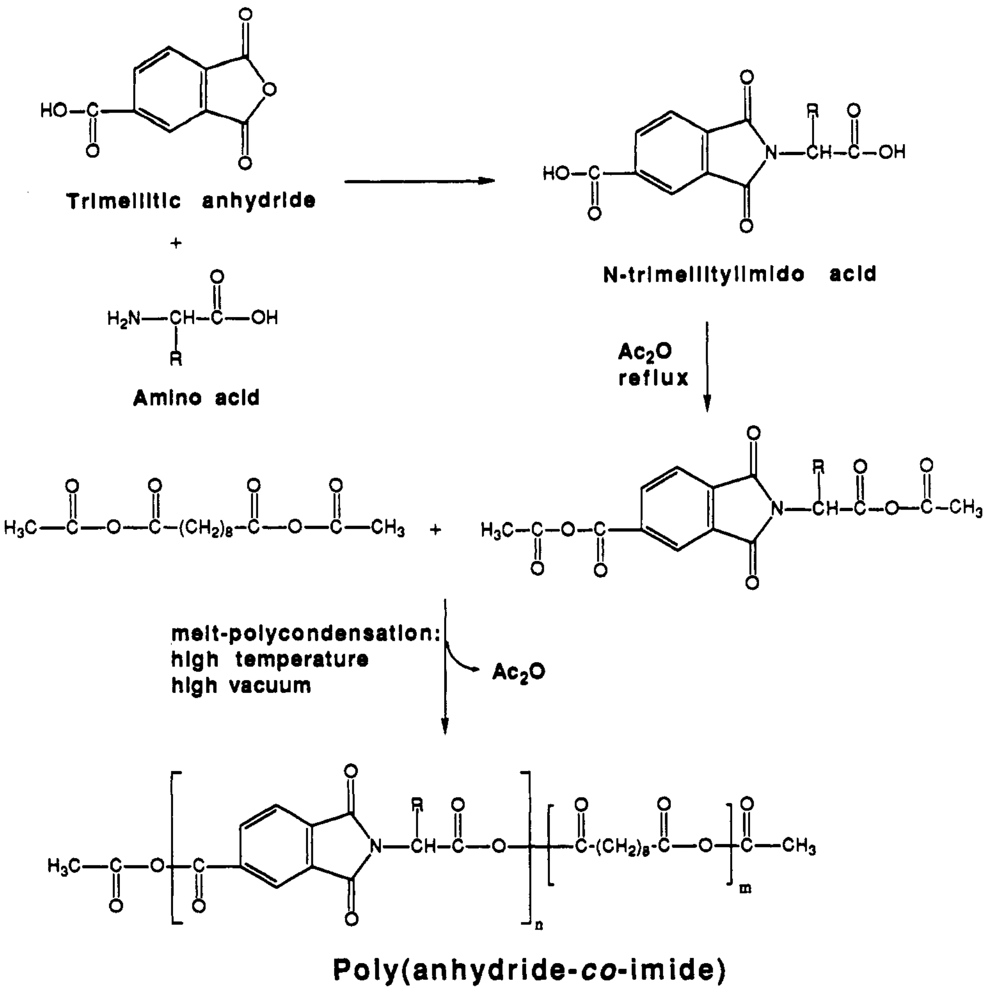

Figure 2. Reaction scheme.

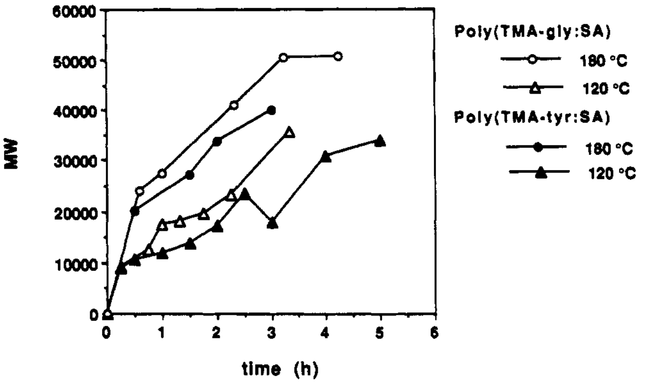

Figure 3. TMA-gly:SA (20:80) and TMA-tyr:SA (20:80), melt polymerized at 120 and 180 °C.

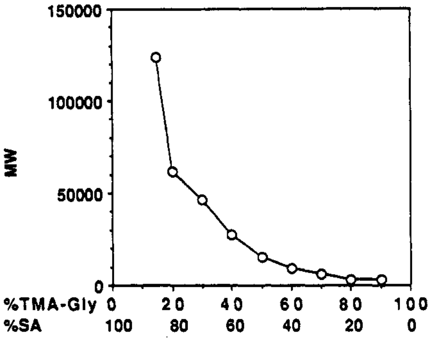

Figure 4. Poly(TMA-gly:SA) of various ratios, melt polymerized for 2 h at 180 °C.

dimensions were determined either by a micrometer and/or individually by SEM. The diameter of the fibers ranged from 0.01 to 0.7 mm; the lengths of the specimen varied between 1 and 2.5 cm.

Results and Discussion

Polymer Synthesis. The polymerizations were performed at reaction temperatures between 100 and 200 °C as illustrated in Figure 3. Maximal molecular weight over short periods of time (1–2 h) was generally observed at approximately 180 °C. Nevertheless, higher molecular weight polymers could also be obtained at lower temperatures after prolonged reaction times (up to 24 h) (Figure 3 and Table I). Dark-colored products were observed at reaction temperatures higher than 200 °C, probably as a result of decomposition or cross-linking reactions. In addition, several coordination catalysts were tested, assuming that complexation of the carbonyl oxygen would facilitate subsequent nucleophilic addition to the carbonyl carbon (as previously observed during polyanhydride synthesis,[11,12] in transesterification polymerizations and ring-opening polymerizations, which involve a metal–oxygen coordination mechanism[23,24]). As illustrated in Figure 5 and Table I, higher molecular weights in shorter times were generally obtained by addition of catalysts such as earth metal oxides and metal salts, whereas alkoxy metals caused a decrease in molecular weight (Table I).

The effect of the molecular structure of the polymer backbone on the molecular weights was determined by using selected homo- and copolymers melt polymerized (without catalyst) for 2 h at 180 °C. Highly aromatic homopolymers (1a–c) were in general rigid and brittle and of lower molecular weight (<10 000). Higher molecular

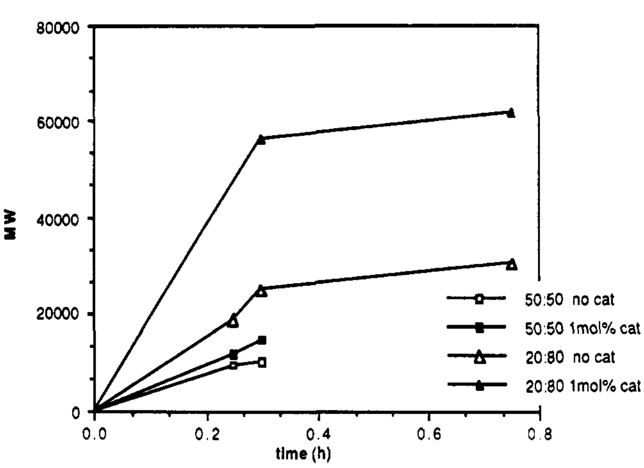

Figure 5. TMA-gly:SA (20:80) and (50:50), melt polymerized at 180 °C with or without 1 mol % Pb(ac)$_2$.

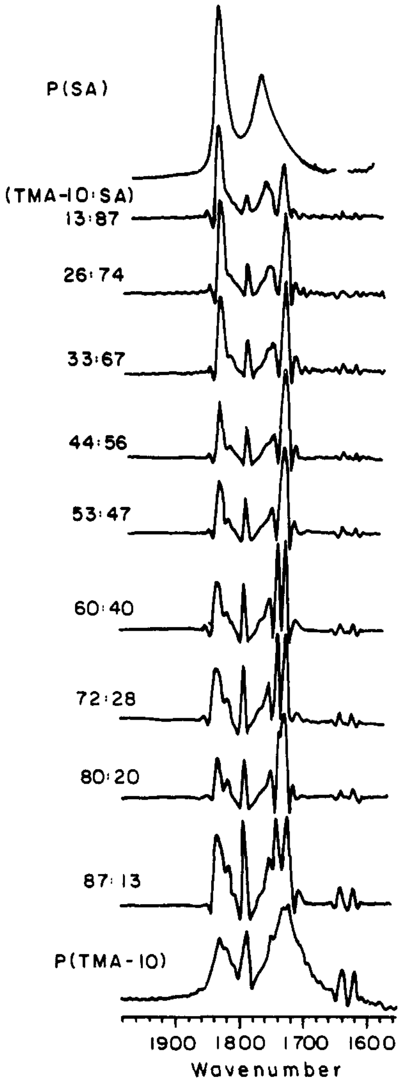

Figure 6. FTIR absorbances in the carbonyl region of TMA-10:SA copolymers in various ratios.

weights were obtained upon introduction of aliphatic carbon chains into the polymer backbone, e.g., by either copolymerization with SA (**3a–g**) or incorporation of ω-amino acids of increasing polymethylene chains (**1f,g**) (Figures 2 and 4).

As previously observed for pure polyanhydrides,[25] the solubility of these polymers in organic solvents was also a function of the molecular structure (and molecular weight). Poly(anhydride-*co*-imides) of high aromaticity were in general soluble in polar organic solvents only (e.g., *N,N*-dimethylformamide and dimethyl sulfoxide). On the other hand, the polymers with an increasing content of aliphatic chains were soluble in a wide range of common organic solvents including benzene, toluene, carbon tetrachloride, chloroform, methylene chloride, tetrahydrofuran, dioxane, and acetone (as well as *N,N*-dimethylformamide and dimethyl sulfoxide). None of these polymers were soluble in alkanes (e.g., hexane, heptane).

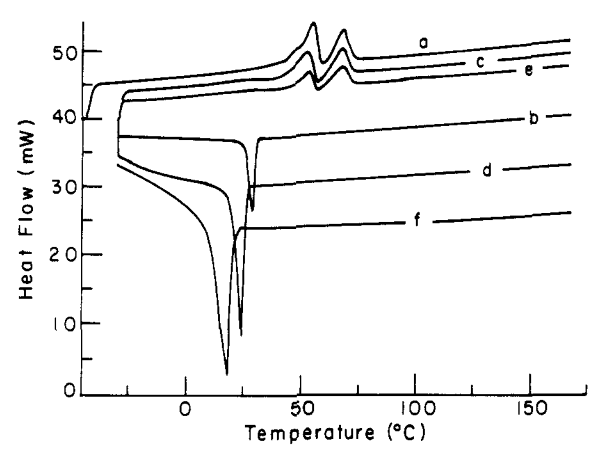

Figure 7. DSC scan of TMA-gly:SA (30:70): (a) 1st heating, (b) 1st cooling, (c) 2nd heating, (d) 2nd cooling, (e) 3rd heating, (f) 3rd cooling.

Table II
Transition Temperatures and Weight-Average Molecular Weights of Poly(TMA-*n*) Containing Polymethylene Chains of Various Length (*n*)

n	T_g, °C	MW
1	98	≤5000
2	102.7	≤5000
3	98.8	6500
4	81.5	6700
5	63.2	14800
10	21.4	11450
11	25.9	19250

Structure Analysis by FTIR Spectroscopy. The most instructive region in FTIR spectroscopy involves the carbonyl absorbances of the poly(anhydride-*co*-imides). The imide bonds usually display two absorbances near 1777 and 1718 cm^{-1}, which are attributed to the symmetric and asymmetric stretches of the carbonyl groups coupled through the five-membered ring.[26] Two additional characteristic bands for imide rings are located near 1400 and 720 cm^{-1} (the former generally being attributed to the C–N stretch and the latter to the deformation of the imide ring or to the imide carbonyl groups[26]). In the case of TMA-10:SA copolymers, theoretically four bands were expected for the anhydride linkages, two each for aliphatic and aromatic anhydride bonds, respectively. The lower frequencies were often observed as shoulders of low intensity only, due to overlapping interference with the absorbances of the imide linkages. Figure 6 illustrates the changes in the carbonyl region for TMA-10:SA copolymers of various ratios (**3f**). The frequencies for aliphatic anhydride bonds appeared near 1815 and 1745 cm^{-1}, as observed for poly(SA). As the TMA-10 monomer (which contains both an aromatic and an aliphatic end) was introduced, characteristic imide bands near 1720 and 1776 cm^{-1} and typical bands for aromatic anhydride linkages near 1800 and 1710 cm^{-1} appeared. The latter was initially overlapping with the imide absorbance near 1720 cm^{-1} and only visible at high enough concentrations of TMA-10 (>50%). In addition, the aliphatic anhydride band shifted from 1745

Table III
Transition Temperatures, Heats of Fusion, and Crystallinities of (TMA-gly:SA) Copolymers Melt Polymerized for 2 h at 180°C[a]

% TMA-gly	T_g, °C	T_{m1}, °C	T_{m2}, °C	T_{m3}, °C	ΔH, cal/g	crystallinity $W(c)$, %
0.00	50.0	86.0	NR	NR	36.60	66.0
0.10	43.9	76.3	NR	NR	17.54	42.0
0.21	7.3	64.9	NR	NR	11.81	34.0
0.31	12.0	62.7	73.0	110.5	9.09	25.0
0.40	13.9	58.1	72.1	117.0	7.15	20.0
0.45	17.2	51.5	NR	NR	3.99	20.0
0.50	29.3	NR	NR	NR	NR	23.0
0.63	54.7	NR	84.3	NR	NR	21.0
0.70	74.0	NR	NR	NR	NR	NR
0.80	91.4	NR	NR	NR	NR	NR
0.90	116.3	NR	NR	NR	NR	NR
1.00	98.0	NR	NR	NR	NR	NR

[a] NR means not reported; transition temperatures were not detectable under these conditions.

Table IV
Transition Temperatures, Heats of Fusion, and Crystallinities of (TMA-10:SA) Copolymers Melt Polymerized for 2 h at 180 °C[a]

					crystallinity	
% TMA-10	T_g, °C	T_{m1},[b] °C	T_{m2}, °C	ΔH, cal/g	$X(c)$, %	$W(c)$, %
0.0	50.0	86.0	NR	36.60	NR	66.0
13.3	31.5	71.6/76.2	NR	17.10	32.0	35.9
26.0	21.3	63.8/67.8	NR	13.32	26.0	27.3
33.3	0.6	58.6	NR	9.36	19.0	25.6
43.9	2.4	47.8	57.6	6.00	12.0	20.7
53.3	5.6	45.5/59.9	72.3	4.68	10.0	20.3
60.0	7.0	42.5	74.5	6.76	15.0	20.8
72.2	10.4	42.8	69.6	7.24	17.0	19.7
87.0	14.8	59.0	96.5	4.90	12.0	24.9
100.0	21.8	63.5	92.6	12.75	NR	32.5

[a] NR means not reported; transition temperatures were not detectable under these conditions. [b] Variation in melt temperature represents different crystallite structures.

Table V
Weight-Average Molecular Weights (Determined by GPC) and Glass Transition Temperatures (As Observed by DSC) of (TMA-gly:CPH) and (TMA-10:CPH) Copolymers of Various Ratios Melt Polymerized for 2 h at 180 °C

% TMA-gly	M_w	T_g, °C	% TMA-10	M_w	T_g, °C
0.00	12 525	31.4	0.00	12 525	31.4
0.09	13 305	42.5	0.18	12 940	30.5
0.34	11 445	70.8	0.28	18 615	32.5
0.35	16 610	73.9	0.33	20 635	38.2
0.53	7 345	84.5	0.51	28 610	35.7
0.70	8 205	96.9	0.53	30 010	33.9
1.00	≤5 000	98.0	0.69	16 220	32.4
			1.00	13 125	21.0

to 1735 cm^{-1}. However, in some cases exact peak assignment was complicated by a number of interfering bands originating from a combination of both anhydride and imide linkages.

Thermal Analysis. In the case of copolymers the thermal behavior and the crystallization mechanism depend on both the monomer ratio and the relative sizes and mutual affinities of the monomer units to each other. The compatibility of the monomers governs the formation of either block, random, or alternating copolymers, which may be determined by ^{1}H NMR spectroscopy.[27] Introducing a noncompatible monomer into a well-defined polymer system disrupts the packing of neighboring polymer chains, which has well-described effects on both melt and glass transition temperatures.[28]

In order to determine the effect of aliphatic spacers only on the thermal transition behavior (i.e., without the potential sequence distribution effects found in copolymers), selected homopolymers containing ω-amino acids of various chain length (**1a–g**) were investigated by DSC. As expected decreasing T_g's were observed in the case of the homopolymers with an increasing length of the polymethylene spacer (Table II). The observed low T_g of poly(TMA-gly) was probably due to its low molecular weight (the lower the molecular weight of a polymer, the more free chain ends are present, which are able to move around more easily, therefore lowering the T_g).[28] Only the ho-

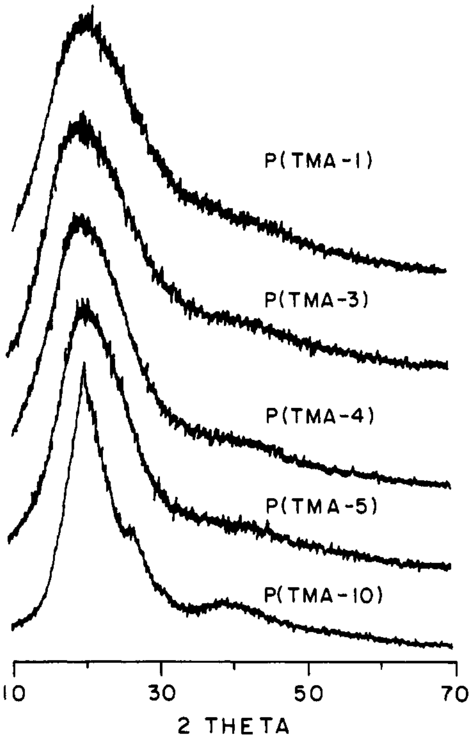

Figure 8. X-ray diffractions of homopolymers containing polymethylene spacers of various chain lengths.

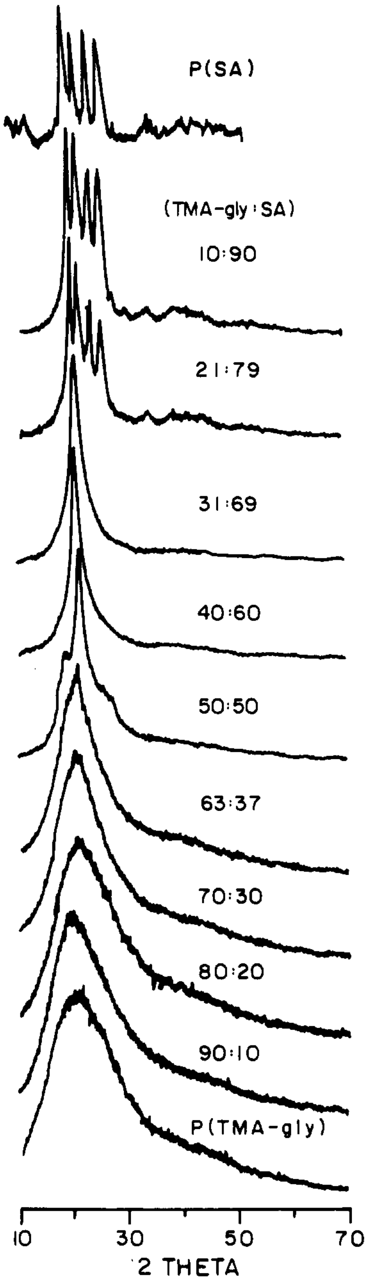

Figure 9. X-ray diffractions of TMA-gly:SA copolymers.

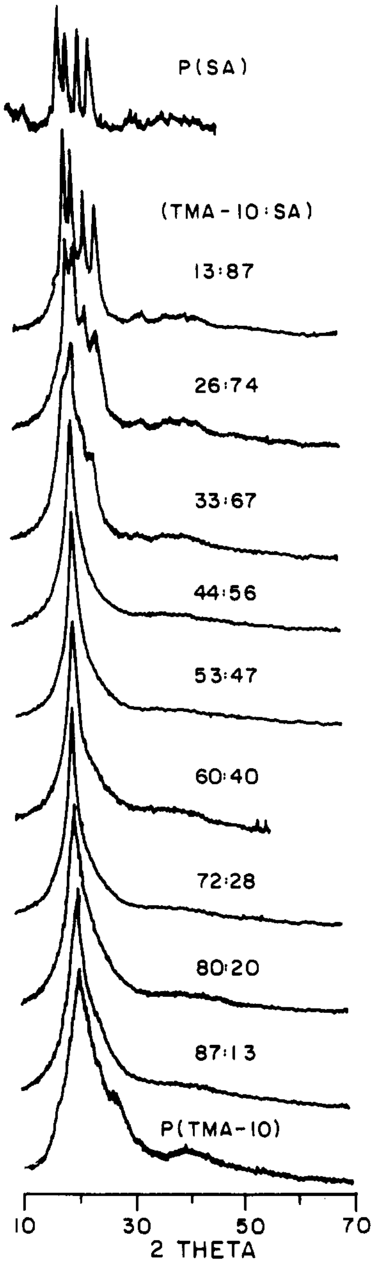

Figure 10. X-ray diffractions of TMA-10:SA copolymers.

mopolymers containing long polymethylene chains (n = 10 and 11) were able to align themselves in a higher order, such that both glass and melt transition temperatures were observed. In the case of poly(TMA-10), two transitions were detected at 63.5 and 92.6 °C (in addition to the T_g), whereas three transitions at 106.8, 127.6, and 137.1 °C were detected for poly(TMA-11). Various polymers of TMA-gly and TMA-10 copolymerized with either the aliphatic SA (**3a,f**) or the aromatic CPH (**4a,b**), respectively, were analyzed as a function of molecular structure. Tables III and IV summarize the transition temperatures (as determined by DSC and X-ray analysis) for the two copolymer systems containing either TMA-gly (**3a**) or TMA-10 (**3f**) copolymerized with SA in various ratios. In the case of TMA-gly-containing copolymers, a potential molecular weight dependence of the thermal transition temperatures had to be considered as a result of the low molecular weight copolymers obtained as the SA content decreased. Almost all TMA-gly-containing copolymers showed a T_g followed by at least one T_m (displaying the classical melting point depression as predicted by the Flory–Huggins theory[29]). In many cases, multiple neighboring peaks for melt tempeatures were observed, which tended to merge after repeated heating cycles, indicating differences in crystallite structures. Most of the copolymers also showed, analogous to their melt transitions, a negative deviation from linearity for their glass transition temperatures. An attempt to correlate the sequence distribution to the glass transition behavior is described elsewhere.[27] The copolymers containing 10–50% TMA-gly displayed both glass transition and melt temperatures. The copolymers containing 50–70% TMA-gly showed in general no melt transitions, unless they were annealed for 30 min to several hours at temperatures higher than their glass transition temperature. Melt transitions for the same (previously fully amorphous) materials were also observed after 1 year of storage at −20 °C under inert atmosphere, which was probably caused by aging processes.[30] The copolymers containing more than 70% TMA-gly were entirely amorphous according to DSC measurements (Table III). In addition, a second (generally smaller) endotherm was observed in the heating and/or cooling curves of the copolymers containing approximately 30–60% TMA-gly (Table III and Figure 7).

Table VI
Mechanical and Thermal Properties of Poly(imide-*co*-anhydride) Fibers Containing Imide Units of Various Spacer Length (n = 1-5, 10, and 11) Copolymerized with Either SA or CPH

compd	% TMA-n	% SA	M_w	elongation at break, %	tensile strength, kg/cm^2	T_g, °C
3a	30	70	≤5 000	13	98	12
	39	61	≤5 000	143	693	13.9
	50	50	≤5 000	44	205	29.3
3b	50	50	21 390	298	1872	26
3c	20	80	25 430	20	269	9.2
	40	60	28 090	42	1959	11.1
	50	50	18 060	339	3531	29.9
3d	100	0	14 600	54	1202	81
3e	100	0	12 350	21	1890	63
3f	53	47	17 760	37	1069	9.3
	72	28	15 970	15	341	10.4
	82	18	15 110	43	452	14.6
	87	13	7 740	15	51	14.8
	100	0	10 680	7	96	21.4
3g	100	0	19 250	23	71	25

compd	% TMA-n	% CPH	M_w	elongation at break, %	tensile strength, kg/cm^2	T_g, °C
4b	33	67	17 850	143	1731	38.8
	51	49	20 210	99	659	36
	69	31	14 850	226	897	32.4

As opposed to the glycine-containing monomer, the TMA-10 diacid (**1f**) contained a polymethylene spacer of 10 methylene groups, which acted in itself as a spacer lying between the rigid aromatic imide structures. In this case all copolymers had weight-average molecular weights higher than 15 000 (up to 100 000), such that a molecular weight independent behavior was assumed. All copolymers of this particular series displayed both glass transitions (with the exception of the copolymer containing 10% TMA-10 only, which was crystallizing very rapidly) and a sharp endotherm representing the melting process (T_{m1}) (Table IV). Copolymers containing equal to or more than 40% TMA-10 displayed a second smaller endotherm (T_{m2}), lying between 5 and 40 °C higher than the melt transition temperatures (not all of these endotherms displayed a corresponding exotherm in the cooling curves). The temperature difference between T_{m2} and T_{m1} tended to decrease with an increasing content of sebacic acid. In cases where broadened melt transitions were observed, a second small endotherm (lying very closely to the major endotherm) could occasionally be detected by reversing the cooling mode to the heating mode before the onset of crystallization.

Table V displays the thermal transition temperatures of TMA-gly and TMA-10, respectiively, copolymerized with the more hydrophobic CPH. These copolymers (containing aromatic substituents) displayed a completely different thermal behavior as compared to the copolymers containing aliphatic spacers (e.g., SA). No melt transitions were observed for any of the copolymers. In the case of the TMA-gly:CPH copolymers, a linear relationship was observed for the glass transition temperature as a function of molecular composition, which seemed to indicate some structural compatibility of these two fairly rigid, aromatic monomers. In the case of TMA-10:CPH copolymers, where a long polymethylene chain was introduced into the imide-containing monomer, a slight positive deviation from linearity was observed for the TMA-10:CPH copolymers.

X-ray Analysis. The degree of crystallinity of various homo- and copolymers was determined by X-ray diffraction alone and in some cases from the combination of both X-ray diffraction and DSC measurements.[31] Comparison showed the obtained results to be in good agreement (Table IV).

The effect of incorporating ω-amino acids containing polymethylene chains of increasing length (**1a**–**f**) is illustrated in Figure 8. The homopolymers containing short flexible spacers (**1a**–**d**) displayed an amorphous halo, which appeared to resolve into several single reflections as the chain length increased to n = 10. The increased tendency to crystallize (as observed for poly(TMA-10) as compared to poly(TMA-gly)) may be a result of increased mobility of the polymer chains, facilitating their alignment into an ordered structure.

In the case of copolymer systems, four different diffraction patterns may be observed theoretically by X-ray analysis: (1) the crystalline diffraction pattern of one of the homopolymers may remain distinct throughout the whole copolymer series, (2) the diffraction pattern of both homopolymers may be superimposed, (3) a new diffraction pattern may appear, or (4) the crystallinity may disappear.[32] Figure 9 displays the diffraction patterns of the copolymer series containing glycine as the amino acid component copolymerized with SA (**3a**). The sebacic acid homopolymer (poly(SA)) displayed a very distinct diffraction pattern, which slowly disappeared with decreasing sebacic acid content. The degree of crystallinity of poly(SA) was 67% as estimated from X-ray diffraction. On the other hand, amorphous halos were observed for poly(TMA-gly) and the copolymers containing a high ratio of TMA-gly (>70%), which corresponds to the DSC measurements reported above, where only T_g's were observed for these highly aromatic copolymers (Table III). This lack of crystallinity was probably caused by both the high rigidity of the imide-containing monomer unit (which sterically hindered chain alignment) and the rather low molecular weight obtained for the copolymers with decreasing SA content. A highly oriented structure is observed for the copolymers containing 30–50% TMA-gly. The observed sharp reflections at an angle θ of ca. 10.4° represent the lateral distance of the polymer chains.[17] On the other hand, both the homopolymers of TMA-gly and CPH and the various copolymers thereof (**4a**) displayed amorphous halos (as expected according to DSC measurements).

In the copolymer series containing TMA-10 (**3f**), the increased flexibility of the polymer backbone (caused by the incorporation of a long polymethylene chain into the imide monomer) resulted in a different type and degree of crystallinity of the copolymers (Table IV and Figure 10). As reported above, the distinct diffraction pattern of poly(SA) disappeared as the TMA-10 monomer was introduced into the polymer system. A highly oriented chain alignment is observed for the copolymers containing ca. 30–90% TMA-10, which display sharp reflections at an angle θ of ca. 10°, representing again the lateral distances between the layered polymer chains.[17]

Mechanical Properties. The mechanical properties (e.g., tensile strength, elongation, modulus, and processability) are known to depend primarily on the molecular weight and the molecular structure of the polymer. The amorphous state generally favors properties such as low elastic modulus and high elasticity, whereas increasing crystallinity lowers these viscoelastic properties and enhances mechanical strength.[33] Both tensile strength and percent elongation of selected poly(anhydride-*co*-imides) were analyzed as a function of molecular structure. The weight-average molecular weight of most copolymers was generally higher than 15 000 with the exception of the TMA-gly:SA copolymers. As expected, the incorporation of imide linkages into the polymer backbone generally resulted in an improvement of the mechanical properties (as compared to previously reported polyanhydrides[11]). Variations were observed as a function of the physicochemical properties of a given polymer. Best results were obtained with TMA-3:SA copolymers (**3c**), where tensile strength measurements higher than 3000 kg/cm^2 were obtained and the elongation at break reached values as high as 340% (Table VI). In-depth studies were performed on three different copolymer series containing either TMA-gly (**3a**), TMA-gaba (**3c**), or TMA-10 (**3f**) copolymerized with SA in various ratios. The results indicated that optimal mechanical properties were obtained at a specific ratio of flexible spacer to rigid imide-containing unit. At very high SA ratios the relative concentration of the reinforcing imide structure was probably too low to obtain strong fibers. On the other hand, at low SA content many copolymers tended to be too rigid and brittle to form flexible fibers. The monomer ratio associated with optimal tensile strength shifted to lower SA content as the number of methylene groups increased for the three copolymer series (from ca. 60% for TMA-gly copolymers to ca. 50% for TMA-3 copolymers to 20% for TMA-10 copolymers) (Table VI).

The elongation at break for many of these copolymers (e.g., the TMA-10 copolymers) was relatively low, although most of these copolymers were, to a high degree, amorphous and displayed T_g's near or below room temperature (Table VI). This may be explained by the already highly oriented and extended alignment of the polymer chains (as observed by X-ray analysis), limiting the elongation ratio of these copolymers.

The largely amorphous homopolymers poly(TMA-4) and poly(TMA-5) displayed high rigidity combined with significantly high tensile strength (which was indicative for their high T_g's). On the other hand, introducing longer polymethylene chains (**1f,g**) lowered the T_g to room temperature, resulting in an almost total loss of tensile strength (Table VI).

Selected polymer fibers (e.g., TMA-3:SA (40:60)) were also subjected to DSC studies to investigate the changes in crystallinity after exposure to strain. Both meltdrawn fibers and the polymer samples taken directly from the melt polymerization showed a similar degree of crystallinity and two closely lying melt transitions near 47 and 70 °C, indicating a certain degree of polymorphism. However, a higher degree of crystallinity was observed after subjecting the fiber to tensile strength measurements, and DSC measurements showed only one major endotherm near 60 °C (and a negligible minor peak near 41 °C), suggesting a more uniform structure of crystallites in their fully extended form.

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References and Notes

(1) Miyamae, T.; Mori, S.; Takeda, Y. U.S. Patent 3,371,069, Feb 27, 1968.
(2) (a) Dickinson, H. R.; Hiltner, A.; Gibbons, D. F.; Anderson, J. M. *J. Biomed. Mater. Res.* **1981**, *15*, 577. (b) Dickinson, H. R.; Hiltner, A. *J. Biomed. Mater. Res.* **1981**, *15*, 591.
(3) Aiba, S.; Minoura, N.; Fujiwara, Y. *J. Biomed. Mater. Res.* **1982**, *16*, 181.
(4) Aiba, S.; Minoura, N.; Fujiwara, Y.; Yamada, S.; Nakagawa, T. *Biomaterials* **1985**, *6*, 31.
(5) Kopecek, J. *Biomaterials* **1984**, *5*, 19.
(6) Spatola, A. F. In Peptide Backbone Modifications. *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*; Weinstein, B., Ed.; Marcel Deckker: New York, 1983; pp 268–357.
(7) Vlasov, G. P.; Rudkovskaya, G. D.; Ovsyannikova, L. A. *Makromol. Chem.* **1982**, *183*, 2635.
(8) Kumaki, T.; Sisido, M.; Imanishi, Y. *J. Biomed. Mater. Res.* **1985**, *9*, 785.
(9) Goodman, I.; Phys, J. A. *Polyesters*; American Elsevier: New York, 1965, Vol. 1.
(10) Kohn, J.; Langer, R. *J. Am. Chem. Soc.* **1987**, *109*, 817.
(11) Domb, A. J.; Langer, R. *J. Polym. Sci.* **1987**, *25*, 3373.
(12) Staubli, A.; Ron, E.; Langer, R. *J. Am. Chem. Soc.* **1990**, *112*, 4419.
(13) Lee, H.; Soffey, D.; Neville, K. *New Linear Polymers*; McGraw-Hill: New York, 1967, p 173.
(14) Koton, M. M. *Polym. Sci. USSR* **1973**, *A15*, 354.
(15) Kricheldorf, H. R.; Pakull, R. *J. Polym. Sci., Polym. Lett. Ed.* **1985**, *23*, 413.
(16) Kricheldorf, H. R.; Pakull, R. *Polymer* **1987**, *28*, 1772.
(17) Kricheldorf, H. R.; Pakull, R. *Macromolecules* **1988**, *21*, 551.
(18) Kricheldorf, H. R.; Pakull, R. *Macromolecules* **1988**, *21*, 1929.
(19) Kricheldorf, H. R.; Pakull, R.; Buchner, S. *J. Polym. Sci., Polym. Chem. Ed.* **1989**, *27*, 431.
(20) de Abajo, J.; Babe, S. G.; Fontan, J. *Angew. Makromol. Chem.* **1971**, *19*, 121.
(21) Gonzalez, J. I.; de Abajo, J.; Gonzalaz-Babe, S.; Fontan, J. *Angew. Markomol. Chem.* **1976**, *55*, 85.
(22) Conix, A. *Macromol. Synth.* **1966**, *2*, 95.
(23) Wilfong, R. E. *J. Polym. Sci.* **1961**, *54*, 385.
(24) Furukawa, J. F.; Saegusa, T. In *Polymerization of Aldehydes and Oxides*; Wiley-Interscience: New York, 1963; p 187.
(25) Mathiowitz, E.; Saltzman, W. M.; Domb, A.; Dor, Ph.; Langer, R. *J. Appl. Polym. Sci.* **1988**, *35*, 755.
(26) Pryde, C. A. *J. Polym. Sci., Polym. Chem. Ed.* **1989**, *27*, 711.
(27) Staubli, A.; Mathiowitz, E.; Langer, R. *Macromolecules*, in press.
(28) Eisenberg, A. In *Physical Properties of Polymers*; American Chemical Society: Washington, DC, 1984, p 55.
(29) Flory, J. P. *J. Chem. Phys.* **1947**, *15*, 397.
(30) Prest, W. M., Jr.; Roberts, F. J., Jr. In Structure and Mobility in Molecular and Atomic Glasses. *Annals of the New York Academy of Science*; O'Reilly, J. M., Goldstein, M., Eds.; 1981; Vol. 371, p 67.
(31) Mathiowitz, E.; Ron, E.; Mathiowitz, G.; Amato, C.; Langer, R. *Macromolecules* **1990**, *23*, 3212.
(32) Kakudo, M.; Kasai, N. *X-Ray Diffraction by Polymers*; Elsevier Publishing Co.: New York, 1972.
(33) Alfrey, T., Jr. *Mechanical Behavior of High Polymers*; Interscience Publishers: New York, 1948.

Registry No. (AA)(SA)(gly) (copolymer), 132492-71-8; (AA)(SA)(ala) (copolymer), 132492-72-9; (AA)(SA)(gaba) (copolymer), 132492-73-0; TMA-1 (copolymer), 78520-89-5; TMA-2 (copolymer), 132492-74-1; TMA-3 (copolymer), 132512-96-0; TMA-4 (copolymer), 132492-75-2; TMA-5 (copolymer), 132492-76-3; TMA-10 (copolymer), 132492-77-4; TMA-11 (copolymer), 132492-79-6; SA (homopolymer), 26776-29-4; SA (SRU), 26913-47-3; (SA)(TMA)(trp) (copolymer), 132492-80-9; CPH (homopolymer), 106680-96-0; CPH (SRU), 121265-91-6; (TMA)(gly)(CPH) (copolymer), 132492-81-0; (TMA-10)(CPH) (copolymer), 132492-82-1; cadmium acetate, 543-90-8; barium acetate, 1304-28-5; lead acetate, 301-04-2; titanium isopropoxide, 546-68-9; aluminum isopropoxide, 555-31-7; calcium carbonate, 15571-51-4.