catalyst, as implied in prior studies. The pore dimensions and the distribution of these within the void network can control fragmentation and thereby the performance. To facilitate continued polymerization, the network should not become unduly congested by the polymeric product. Fragmentation of the catalyst depends on several interrelated aspects of the solid catalyst. These may include (but are not restricted to) the void fraction, the distribution of void dimensions, the nature of the connection between subparticles and the pore structure of the subparticles, the rate of polymer formation (and related heat generation), and the associated chemistry of the active polymerization sites as influenced by the preparation and pretreatment of the catalytic system.

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Pseudopoly(amino acids): A Study of the Synthesis and Characterization of Poly(*trans*-4-hydroxy-*N*-acyl-L-proline esters)

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ABSTRACT: The synthesis and characterization of polyesters derived from hydroxyproline (Hpr) were investigated. A series of new poly(*trans*-4-hydroxy-*N*-acyl-L-proline esters) were prepared in which the pendant acyl groups are ethanoyl (Ac), 2,2-dimethylpropanoyl (Piv), hexanoyl (Hex), decanoyl (Dec), tetradecanoyl (Myr), and hexadecanoyl (Pal). Weight average molecular weights (M_w) over 40 000 were obtained via ester interchange using 1 mol % titanium isopropoxide as a catalyst at 180 °C for 20–24 h. The different pendant groups on the monomers profoundly affect the polymerizability and the polymer properties. The molecular weight data obtained from gel permeation chromatography and vapor pressure osmometry suggest that these polymers assume a rodlet-like conformation in solution. When the length of the acyl group on the monomer increased, the molecular weight as well as the degree of polymerization increased. Differential scanning calorimetry analysis showed that poly(Ac-Hpr ester), poly(Piv-Hpr ester), poly(Hex-Hpr ester), and poly(Dec-Hpr ester) are amorphous, while poly(Myr-Hpr ester) and poly(Pal-Hpr ester) are semicrystalline. A declining trend in the glass transition temperatures of polymers was observed with increasing pendant chain length. However, it was reversed due to the side-chain crystallinity when the pendant chain length reached 14 carbons.

Introduction

In continuing efforts to develop improved biomaterials, an approach for synthesizing a new class of poly(amino acids) was recently proposed.[1] These polymers, named "pseudopoly(amino acids)", are different from conventional poly(amino acids) in that the polymer backbone is formed by utilizing the side-chain functional groups on the monomeric α-L-amino acids or dipeptides. Such an approach offers the opportunity to create polymers from naturally occurring metabolites but without some of the potential disadvantages of conventional poly(amino acids) resulting from the repeating amide bonds (e.g., poor mechanical strength and enzymatic degradation).

To date, the syntheses of only three subclasses of these polymers have been reported:[1,2] poly[(benzyloxycarbonyl)tyrosyltyrosine hexyl ester iminocarbonate], poly[*trans*-4-hydroxy-1-(1-oxohexadecyl)-L-proline ester], and poly[(benzyloxycarbonyl)glutamylphenylalanine anhydride]. In addition to the flexibility of designing polymers possessing various properties attributable to the polymer main-chain bonds, this approach also offers another advantage—the modification at the level of amino acid termini. In pseudopoly(amino acids), either the amino group or the carboxyl group or both can be chemically modified or used as sites for covalent attachment of drugs or bioactive molecules. It has been shown that pendant groups can significantly alter the physical properties of polymers.[3] The effect of pendant groups on the polymerizability of pseudopoly(amino acids) and on the properties of these polymers has not been examined.

In this paper we first report a study examining factors affecting the molecular weight of poly(Pal-Hpr ester); specifically, temperature, amount of catalyst, reaction time, and type of catalysts were varied. Second, we describe the syntheses of several new poly(*trans*-4-hydroxy-*N*-acyl-L-proline esters) where the acyl group is systematically al-

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Table I
Effect of Catalysts on the Polymerization of Pal-Hpr-Me

catalyst	time, h	polym^a M_w	M_n	M_w/M_n
none	24	690	590	1.17
p-toluenesulfonic acid	22	3920	2530	1.55
K *tert*-butoxide	20	4060	1650	2.46
$CaCO_3$	24	440	400	1.10
BaO	22	5120	3420	1.50
CaO	5	550	530	1.10
SbO	5	600	570	1.10
Bi_2O_3	18	1240	690	1.80
Cd acetate	24	10500	3230	3.25
Zn acetate	22	13800	5670	2.43
Pb acetate	24	13030	5630	2.31
diethylzinc:H_2O	22	13800	6480	2.12
ferric chloride	22	9900	3160	3.13
ferric acetylacetonate	24	8460	7350	2.51
Al *tert*-butoxide	26	11980	6150	1.95
Al isopropoxide	23	17260	5870	2.94
Ti *n*-butoxide	24	27880	9960	2.80
Ti isopropoxide	24	40600	9520	4.26

[a] Poly(Pal–Hpr ester) was melt polymerized at 180 °C by using 1 mol % catalyst. M_w and M_n were determined by GPC in chloroform relative to polystyrene standards.

tered. The physical properties of these polymers such as their solution conformation and thermal properties were also examined.

Results and Discussion

Polyesters based on hydroxyproline were chosen as model polymers because of their structural simplicity and potential biological relevance since hydroxyproline is a major constituent of collagen. The presence of both hydroxyl and carboxyl functional groups in the monomer makes it feasible for polyester formation via ester interchange.[1]

Initially, a study examining the various factors that might affect the molecular weight of poly(Pal-Hpr ester) was conducted. First, in addition to the five catalysts used previously[1] (*p*-toluenesulfonic acid, potassium *tert*-butoxide, cadmium acetate, zinc acetate, and aluminum isopropoxide), catalysts that are generally regarded to be effective for polyester formation, ring-opening polymerization via a metal–oxygen coordination mechanism, and high molecular weight polyanhydride formation were employed.[4–6] As shown in Table I, they include titanium *n*-butoxide, titanium isopropoxide, calcium carbonate, barium oxide, calcium oxide, stannous oxide, bismuth oxide, diethylzinc:H_2O, ferric chloride, ferric acetylacetonate, and lead acetate.

In the absence of catalyst, virtually no polymerization occurred. The polymerization with acidic and strongly basic catalysts such as *p*-toluenesulfonic acid and potassium *tert*-butoxide, respectively, resulted in relatively low molecular weights. On the other hand, the coordination catalysts, in general, were more effective. Among the coordination catalysts, such as zinc acetate, lead acetate, diethylzinc:H_2O, aluminum isopropoxide, and titanium alkoxides, titanium isopropoxide yielded the highest polymer molecular weights (greater than 40 000). The mechanism of action of these catalysts involves a coordination between the metal component and the carbonyl oxygen of the monomer followed by a facile nucleophilic attack on the carbonyl carbon.[5]

The optimal catalyst level was determined by polymerizing Pal-Hpr-Me at four different molar concentrations ranging from 0.5 to 3.0 mol % (Figure 1). The molecular weight was greater at 1.0 mol % than at the other three levels. No significant differences in molecular weights were observed among 0.5%, 2.0%, and 3.0% catalyst concentrations.

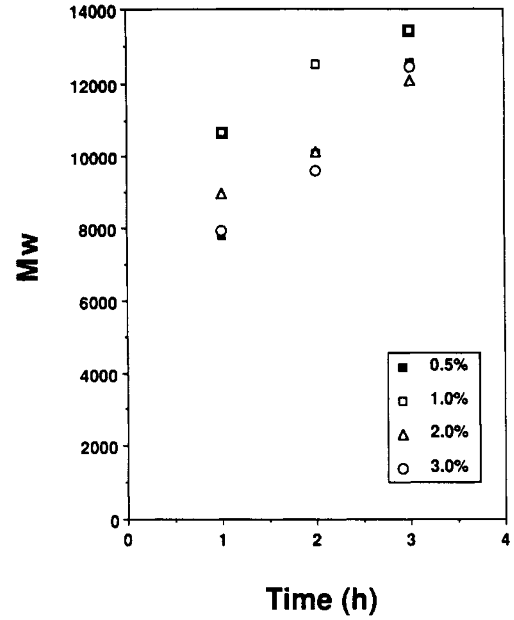

Figure 1. Effect of catalyst concentration on the preparation of poly(Pal-Hpr ester). N-Pal-Hpr-Me was polymerized at 180 °C by using titanium isopropoxide as a catalyst at 0.5, 1.0, 2.0, and 3.0 mol %.

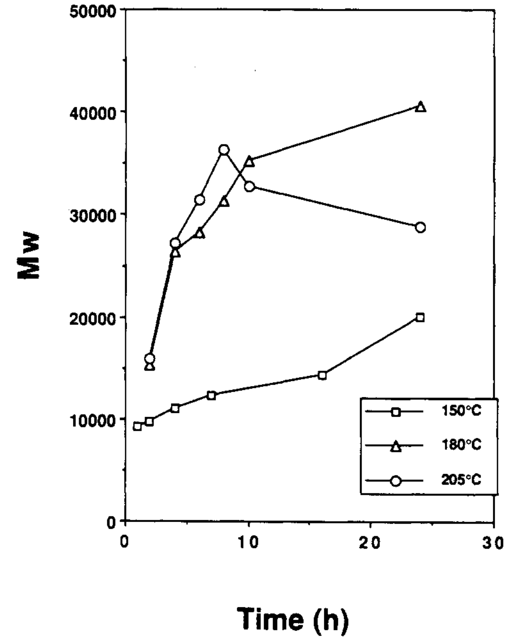

Figure 2. Effect of temperature on the preparation of poly(Pal-Hpr ester). N-Pal-Hpr-Me was polymerized at 150, 180, and 205 °C in the presence of 1 mol % titanium isopropoxide for 24 h.

To study the effect of reaction temperature, Pal-Hpr-Me was polymerized at three different temperatures: 150, 180, and 205 °C. The results are shown in Figure 2. The weight average molecular weight as a function of time is plotted for each of the three different temperatures. At 150 °C, the molecular weight slowly reached 20 000 after 24 h. At this temperature, the reaction mixture remained colorless throughout most of the reaction period and resulted in a slightly yellow product. When the polymerization was conducted at 205 °C, the molecular weight increased to over 35 000 in less than 10 h, but thereafter it gradually decreased with time. This temperature was too severe, as indicated by browning of the reaction mix-

Scheme I

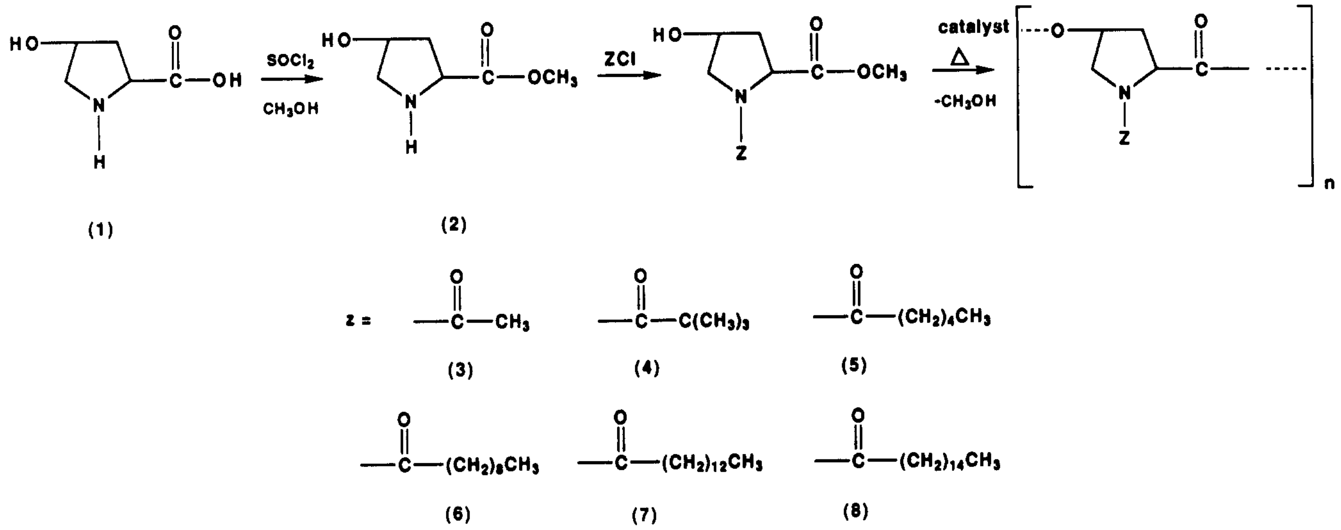

Table II
Molecular Weight Determination of Poly(Acyl-Hpr esters) by Gel Permeation Chromatography and Vapor Pressure Osmometry

polym[a]	M_w	M_n[b]	M_w/M_n	M_n[c]	DP[d]
poly(Ace-Hpr ester)	1980	1270	1.55	1370	9
poly(Piv-Hpr ester)	9820	5110	1.92	4840	25
poly(Hex-Hpr ester)	14400	4600	3.13	4760	23
poly(Dec-Hpr ester)	41500	11500	3.61	10010	38
poly(Myr-Hpr ester)	24570	9440	2.60	13400	41
poly(Pal-Hpr ester)	42390	11690	3.63	11760	33

[a] Acylhydroxyproline monomers were melt polymerized at 180 °C with titanium isopropoxide for 24 h. [b] Molecular weights were determined by GPC relative to polystyrene standards in chloroform. [c] Molecular weights were obtained by vapor pressure osmometry in chloroform. [d] Degrees of polymerization were obtained by dividing M_n from vapor pressure osmometry data by the molecular weight of the repeat unit.

Table III
Thermal Properties of Poly(Acyl-Hpr esters)[a]

polym	T_m, °C	T_g, °C
poly(Ace-Hpr ester)		118
poly(Piv-Hpr ester)		157
poly(Hex-Hpr ester)		83
poly(Dec-Hpr ester)		71
poly(Myr-Hpr ester)	111	96
poly(Pal-Hpr ester)	116	97

[a] The DSC analysis was conducted from 20 to 250 °C at a heating rate of 20 °C/min.

ture. At the end of 24 h, there was a reduction in the molecular weight. However, at 180 °C a steady increase in the molecular weight was observed reaching over 40 000 after 24 h.

On the basis of these findings, all the subsequent polymerization reactions were performed with 1 mol % titanium isopropoxide as the catalyst at 180 °C for 24 h. For this study, six hydroxyproline methyl esters having different N substituents were synthesized, and their structures were identified. The substituents were 1–oxoethyl (Ac), 1-oxo-2,2-dimethylpropyl (Piv), 1-oxohexyl (Hex), 1-oxodecyl (Dec), 1-oxotetradecyl (Myr), and 1-oxohexadecyl (Pal) groups (compounds 3–8) as shown in Scheme I. All but the 2,2-dimethylpropyl moiety are linear hydrocarbon chains. Piv-Hpr-Me was used to study the steric effect of the pendant group on the polymerization.

These monomers were then melt transesterified with a suitable catalyst at a high temperature, and methanol was liberated as a byproduct. The average molecular weight was determined by two methods: gel permeation chromatography (GPC) and vapor pressure osmometry (VPO) in chloroform. Since the molecular weight values obtained from gel permeation chromatography are representative of the molecular size of these polymers, the vapor pressure osmometry data were also obtained to determine the actual number average molecular weights of these polymers (Table II). On the basis of the results obtained from both methods, it is interesting to note that the number average molecular weight values from both measurements are in good agreement with each other. This suggests that poly(hydroxyproline esters) assume, in solution, a rodlet-like conformation. If they existed as random coils, then the size of the polymers would be proportional to the square root of the absolute polymer molecular weight.[7] However, such a relationship between the molecular size as determined by the GPC measurements and the molecular weight by the VPO measurements is not apparent in these data. The rodlet-like conformation results from the stiffness in the main chain imposed by a ring structure in the hydroxyproline repeat unit.

In regard to the polymerizability of these monomers, Ac-Hpr-Me resulted in the lowest M_w, 1920, and Piv-Hpr-Me gave a M_w of 9820. During the polymerization of each of these monomers, the reaction mixture became increasingly viscous in the first few hours, and stirring was very difficult to achieve. The initially molten mixture became very glassy and hard unless the temperature was raised well above 200 °C. Even at this temperature, the molecular weight did not increase to any appreciable extent. The M_w of poly(Hex-Hpr ester) was 14 400. With a further increase in the pendant chain length, as in Dec-Hpr-Me, Myr-Hpr-Me and Pal-Hpr-Me monomers, the polymerization was facilitated and the resulting molecular weights were markedly increased, reaching up to 40 000. The physical appearances of poly(Ac-Hpr ester), poly(Piv-Hpr ester), poly(Hex-Hpr ester), and poly(Dec-Hpr ester) were glassy, whereas poly(Myr-Hpr ester) and poly(Pal-Hpr ester) were waxlike, indicative of the developing crystallinity in the linear pendant chains.

The thermal properties of poly(*trans*-4-hydroxy-*N*-acyl-L-proline esters) were studied by differential scanning calorimetry (Table III and Figure 3). The second-order transitions appeared at 118, 157, 83, and 71 °C for poly(Ac-Hpr ester), poly(Piv-Hpr ester), poly(Hex-Hpr ester), and poly(Dec-Hpr ester), respectively. The observed Tg's are generally high mainly due to stiffness in the polymer

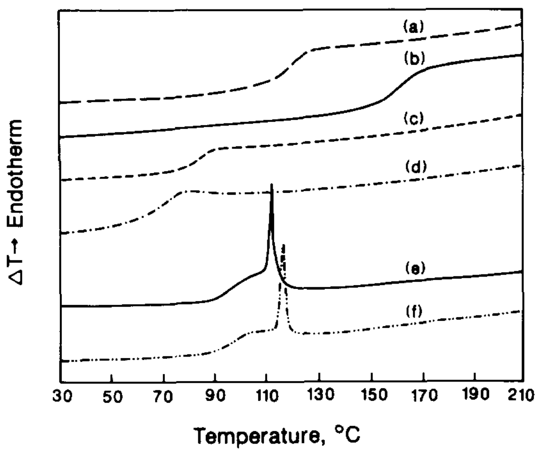

Figure 3. Differential scanning calorimetry scans of poly(N-Acyl-Hpr esters). The polymers were heated at a rate of 20 °C/min: (a) poly(Ac-Hpr ester); (b) poly(Piv-Hpr ester); (c) poly(Hex-Hpr ester); (d) poly(Dec-Hpr ester); (e) poly(Myr-Hpr ester); (f) poly(Pal-Hpr ester).

main chain imposed by its repeating ring structure and bulky side groups. The polymers with shorter pendant groups were completely amorphous as demonstrated by the absence of melting transitions up to 300 °C. On the other hand, the DSC thermograms of poly(Myr-Hpr ester) and poly(Pal-Hpr ester) showed two transition temperature peaks, a small broad peak followed immediately by a sharp, intense peak corresponding to a T_g of the polymer and T_m of the long side chain, respectively. In poly(Myr-Hpr ester), they appeared at 96 and 111 °C and in poly(Pal-Hpr ester) at 97 and 116 °C.

As the pendant group on the monomers became more flexible and longer, the T_g of the resulting polymers poly(Ac-Hpr ester), poly(Hex-Hpr ester), and poly(Dec-Hpr ester) declined (Figure 3). This is due to the fact that the side groups create an increased free volume between the polymer chains so that the polymer structure becomes looser. However, a further increase in the pendant chain length as in the tetradecanoyl and palmitoyl group containing monomers reverses this trend due to the developing crystallinity from the ordering and stacking of the side chains themselves. A similar trend was observed with *n*-alkyl acrylate and the methacrylate polymer series with increasing alkyl groups.[8] As summarized in Table III, T_g decreased with an increase in the acyl chain length up to 10 carbons in this study and started to increase with a further increase in the length.

The evidence from the DSC measurements can be used to elucidate the observed polymerization behavior of some hydroxyproline polyesters described above. One possible explanation for the lower molecular weight obtained for poly(Ac-Hpr ester) and poly(Piv-Hpr ester) may be that they were not polymerized at a reaction temperature sufficiently above the glass transition temperature to overcome the diffusional limitation. For example, poly(Piv-Hpr ester) solidified to a glass at 180 °C within a few hours and its T_g was 157 °C. To verify that this is truly the limiting factor, it may be useful to conduct the polymerization in the presence of external plasticizers to allow the viable functional group to be in close proximity to form ester linkages. However, if the molecular weight is not increased any further, then the limiting factor may be the loss of viable functional groups at high temperature conditions.

The solubility of poly(Hpr esters) in various organic solvents was also determined. In general these polymers dissolved in a wide range of organic solvents. Poly(Hex-Hpr ester) was soluble in benzene, toluene, chloroform, carbon tetrachloride, dichloromethane, tetrahydrofuran, acetone, dioxane, ethyl acetate, *N,N*-dimethylformamide, and isopropyl alcohol. It was slightly soluble in ether and methanol and insoluble in hexane. Poly(Dec-Hpr ester) was similar to poly(Hex-Hpr ester), except that it was soluble in ether and acetonitrile. Poly(Myr-Hpr ester) was partially soluble in acetone, ethyl acetate, and isopropyl alcohol and insoluble in hexane, methanol, and acetonitrile.

Experimental Section

Materials. *trans*-4-Hydroxy-L-proline, aluminum isopropoxide, *p*-toluenesulfonic acid, and *N*-nitroso-*N*-methylurea were purchased from Sigma Chemical Co., St. Louis, MO; *n*-hexanoyl chloride, *n*-hexadecanoyl chloride, *n*-decanoyl chloride, *n*-myristoyl chloride, trimethylacetyl chloride, titanium isopropoxide, titanium *tert*-butoxide, aluminum tri-*tert*-butoxide, dimethylaminopyridine, diethylzinc, ferric acetylacetonate, ferric chloride, lead acetate, antimony(III) oxide, bismuth(III) oxide, phosphomolybdic acid, deuterium oxide, deuterated chloroform (99.8 at. % D) containing 0.03% (v/v) tetramethylsilane (TMS), and potassium *tert*-butoxide were obtained from Aldrich Chemical Co., Milwaukee, WI; thionyl chloride and cadmium acetate dihydrate were obtained from Fluka AG (Switzerland); zinc acetate dihydrate, magnesium sulfate, calcium carbonate, and glacial acetic acid were purchased from Mallinckrodt Inc., Paris, KY; barium oxide and calcium oxide were purchased from EM Science, Gibbstown, NJ. Organic solvents were HPLC grade, and inorganic compounds were reagent grade or better. The catalysts were sieved to less than 50 μm.

Characterization. Melting point determinations were made on a Fisher-Johns melting point apparatus. The elemental analysis was performed by Galbraith Laboratories Inc., Knoxville, TN. Optical rotations were determined by an SR6 polarimeter (Polyscience Corp.) at the sodium D line (589 nm) with a 200-mm sample tube at 25 °C. Thin-layer chromatography plates were developed in an appropriate solvent chamber, dried, sprayed to saturation with a phosphomolybdic acid/ethanol solution (5% w/v), and detected by heating the plate on a hot plate. Infrared spectra were recorded with a Perkin-Elmer Series 1420 dispersive spectrophotometer. Samples were either film cast from chloroform onto NaCl plates or pressed into KBr pellets. Liquid samples were examined neat on NaCl plates. ^{1}H and ^{13}C NMR spectra were observed on Bruker WM 250 (250 MHz for ^{1}H) and Varian XL 400 (100 MHz for ^{13}C) spectrometers. The solvents were deuterated chloroform and deuterated water, and the internal reference was tetramethylsilane. Thermal analysis of the polymer was performed on a Perkin-Elmer system that consists of a DSC-2 differential scanning calorimeter, Series 4 thermal analysis microprocessor controller, and a Model 3600 thermal analysis data station microcomputer. The software used was a Perkin-Elmer thermal analysis data system (TADS) program. A graphics plotter was used to plot the thermograms. Sample weights were kept near 10.0 mg, and the samples were heated at a rate of 20 °C/min.

The weight and number average molecular weights (M_w and M_n, respectively) of polymer samples dissolved in chloroform were determined by a gel permeation chromatographic (GPC) system consisting of a Perkin-Elmer Series 10 liquid chromatograph pump, the LKB 2140 multiple-wavelength UV detector (235 nm), and the Perkin-Elmer 3600 data station microcomputer. A PL Gel, 5 μm, Mixed column (Polymer Laboratories) was used. The flow rate was 0.9 mL/min. The Perkin-Elmer CHROM 2 program was used to run the samples, and the GPC4 program was used to calculate the average molecular weight of the polymer relative to polystyrene standards (Polysciences, 580–160000 g/mol). The spectral data processed were printed on a Perkin-Elmer 660 printer. The number average molecular weight was also measured by a Knauer (Germany) vapor pressure osmometer (VPO, Model No. 11.00) equipped with a Model 06.00 digital meter.

Synthesis of Monomer. Palmitoyl hydroxyproline methyl ester (Pal-Hpr-Me, **8**) was synthesized from Hpr-Me·HCl (**2**).[9] All other monomers were prepared similarly. Scheme I illustrates the synthetic route for the monomers **3**–**8**. The yield of acetyl hydroxyproline methyl ester (Ac-Hpr-Me, **3**) was very low. Therefore, it was esterified from acetyl hydroxyproline (Ac-Hpr) by using an ether–diazomethane solution.[10] The yields obtained for the monomers ranged from 50 to 90%. All the monomers except Hex-Hpr-Me (5) were obtained as crystals. The monomers were characterized by elemental analysis, IR and NMR spectroscopy, and melting point determination. IR and NMR spectral analyses showed virtually the same spectra for all the monomers except for the progressive increase in the intensity of the peak that corresponds to the pendant chain.

***trans*-4-Hydroxy-1-(1-oxoethyl)-L-proline.** *trans*-4-Hydroxy-1-(1-oxoethyl)-L-proline was prepared by using *trans*-4-hydroxy-L-proline (1, 6.6 g, 50 mmol) in glacial acetic acid (100 mL) and acetic anhydride (6.8 mL, 72 mmol).[11] The mixture was stirred at room temperature for 3 h and filtered to remove any unreacted material. The filtrate was evaporated in vacuo to remove excess acetic anhydride and acetic acid. Cold anhydrous ether was added to the resulting viscous liquid and stored at 4 °C overnight. A white solid was recovered and washed well with ether. Yield 7.8 g (91%); ^{1}H NMR (D_2O) δ 4.44 (s, 1, H-4), 4.14 (s, 5, acetyl and H-5), 3.63 (t, 1, H-2), 3.20 (m, 2, H-3); ^{13}C NMR (D_2O) δ 157.13 (C-1, acetyl), 154.41 (C-1), 50.93 (C-4), 38.83 (C-2), 36.95 (C-5), 18.29 (C-3), 2.55 (C-2, acetyl); IR (KBr pellet, cm^{-1}) 3300–2600 (O–H), 2940 (C–H), 1730 (C=O, ester), 1610 (C=O, amide), 1430 (C–N), 1340 (C–H), 1230 (C–O), 1190 (O–C–C); TLC $R_f = 0.39$ acetone:glacial acetic acid (8:2); mp 132–134 °C (lit. mp 131–132 °C). Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.06; H, 6.70; N, 7.81.

***trans*-4-Hydroxy-1-(1-oxoethyl)-L-proline Methyl Ester (3).** *trans*-4-Hydroxy-1-(1-oxoethyl)-L-proline methyl ester (3) was prepared from *trans*-4-hydroxy-1-(1-oxoethyl)-L-proline (5.5 g, 32 mmol) in fresh dry dioxane (100 mL), as described by Neuberger[12] using a freshly prepared diazomethane ethereal solution (3.0 g, 70 mmol).[10] Yield 3.3 g (56%); ^{1}H NMR ($CDCl_3$) δ 4.56 (dd, 1, $J = 8, 8$ Hz, H-4), 3.78 (dd, 1, $J = 11, 4$ Hz, H-5), 3.74 (s, 3, methyl ester), 2.26 (m, 2, H-3), 2.09 (s, 3, acetyl); ^{13}C NMR ($CDCl_3$) δ 172.93 (C-1, acetyl), 170.83 (C-1), 69.86 (C-4), 57.51 (C-2), 55.89 (C-1, methyl), 52.26 (C-5), 37.86 (C-3), 22.19 (C-2, acetyl); IR (KBr pellet, cm^{-1}) 3360 (O–H), 2940 (C–H), 1745 (C=O, ester), 1640 (C=O, amide), 1440 (C–N), 1370 (C–H), 1240 (C–O), 1195 (CC(=O)–O), 1180 (O–C–C); TLC $R_f = 0.62$ acetone:glacial acetic acid (8:2); mp 80–82 °C (lit. mp 78 °C). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.10; N, 7.48. Found: C, 51.03; H, 7.13; N, 7.37.

***trans*-4-Hydroxy-1-(1-oxo-2,2-dimethylpropyl)-L-proline Methyl Ester (4).** Piv-Hpr-Me (4) was synthesized from Hpr-Me·HCl (14.8 g, 80 mmol) with trimethylacetyl chloride (10.6 g, 88 mmol) by using a procedure simliar to that described for Pal-Hpr-Me (8), with slight modifications. A colorless and clear liquid remained after evaporation of the solvent in vacuo. Petroleum ether (500 mL) was added, and the mixture was left at 4 °C overnight, filtered, and washed several times with petroleum ether. A white crystalline solid was obtained. Yield 7.5 g (41%); ^{1}H NMR ($CDCl_3$) δ 4.63 (dd, 1, $J = 8, 8$ Hz, H-4), 3.84 (dd, 1, $J = 11, 4$ Hz, H-5β), 3.73 (s, 1, H-5α), 2.24 (dd, 1, $J = 4, 4$ Hz, H-3β), 2.18 (s, 3, methyl ester), 2.03 (ddd, 1, H-3α), 1.27 (s, 10, *t*-Bu, H-2); ^{13}C NMR ($CDCl_3$) δ 177.49 (C-1, dimethylpropanoyl), 173.46 (C-1), 70.71 (C-4), 59.63 (C-2), 55.96 (C-1, methyl), 52.12 (C-5), 38.56 (C-2, dimethylpropanoyl), 36.08 (C-3), 27.15 (C-3-5, dimethylpropanoyl); IR (KBr pellet, cm^{-1}) 3400 (O–H), 2940 (C–H), 1745 (C=O, ester), 1600 (C=O, amide), 1410, 1080 (C-N), 1200 (CC(=O)–O), 1170 (O–C–C); TLC $R_f = 0.29$ chloroform:methanol (9:0.5); mp 71–73 °C; $[\alpha]^{25}_D$ –58.8° (*c* 2, chloroform). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.58; H, 8.26; N, 6.03.

***trans*-4-Hydroxy-1-(1-oxohexyl)-L-proline Methyl Ester (5).** A procedure similar to the above was followed with *n*-hexanoyl chloride (11.9 g, 88 mmol) with slight modifications. A clear, colorless liquid that did not crystallize was obtained. ^{13}C NMR ($CDCl_3$) δ 176.46 (C-1, hexanoyl), 173.27 (C-1), 69.84 (C-4), 57.56 (C-2), 55.10 (C-1, methyl), 52.13 (C-5), 37.55 (C-2, hexanoyl), 34.32 (C-3), 31.37 (C-4, hexanoyl), 24.17 (C-3, hexanoyl), 22.49 (C-5, hexanoyl), 13.86 (C-6, hexanoyl); IR (neat, cm^{-1}) 3400 (O–H), 2950, 2870 (C–H), 1745 (C=O, ester), 1630 (C=O, amide), 1435, 1085 (C–N), 1200 (CC(=O)–O), 1180 (O–C–C); TLC $R_f = 0.24$ ethyl acetate; $[\alpha]^{25}_D$ –74.3° (*c* 2, chloroform). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.92; H, 7.92; N, 5.79.

***trans*-4-Hydroxy-1-(1-oxodecyl)-L-proline Methyl Ester (6).** The procedure for Pal-Hpr-Me (8) was followed using *n*-decanoyl chloride (16.8 g, 88 mmol). After recrystallization from petroleum ether, white lustrous crystals formed. Yield 19.6 g (82%); ^{13}C NMR ($CDCl_3$) δ 173.23 (C-1, decanoyl), 172.66 (C-1), 70.07 (C-4), 57.56 (C-2), 55.11 (C-1, methyl), 52.20 (C-5), 37.69 (C-2, decanoyl), 34.48 (C-3), 31.84 (C-8, decanoyl), 29.43 (C-4, decanoyl), 29.38, 29.27, 29.19 (C-5-7, decanoyl), 24.61 (C-3, decanoyl), 22.64 (C-9, decanoyl), 14.05 (C-10, decanoyl); IR (KBr pellet, cm^{-1}) 3400 (O–H), 2920, 2850 (C–H), 1745 (C=O, ester), 1620 (C=O, amide), 1435, 1085 (C–N), 1200 (CC(=O)–C), 1175 (O–C–C); TLC $R_f = 0.29$ ethyl acetate; mp 41–42 °C; $[\alpha]^{25}_D$ –62.0° (*c* 2, chloroform). Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.19; H, 9.83; N, 4.66.

***trans*-4-Hydroxy-1-(1-oxotetradecyl)-L-proline Methyl Ester (7).** A procedure similar to the above was followed using *n*-myristoyl chloride (21.7 g, 88 mmol). After recrystallization from petroleum ether, white lustrous crystals were obtained. Yield 26 g (93%); ^{13}C NMR ($CDCl_3$) δ 173.11 (C-1, tetradecanoyl), 172.79 (C-1), 70.03 (C-4), 57.67 (C-2), 55.20 (C-1, methyl), 52.23 (C-5), 37.73 (C-2), 34.50 (C-3), 31.94 (C-12, tetradecanoyl), 29.67, 29.36 (C-4-11, tetradecanoyl), 24.66 (C-3, tetradecanoyl), 22.69 (C-13, tetradecanoyl), 14.13 (C-14, tetradecanoyl); IR (KBr pellet, cm^{-1}) 3450 (O–H), 2910, 2840 (C–H), 1740 (C=O, ester), 1610 (C=O, amide), 1465, 1085 (C–N), 1180 (O–C–C); TLC $R_f = 0.37$ ethyl acetate; mp 56–58 °C; $[\alpha]^{25}_D$ –55.7° (*c* 2, chloroform). Anal. Calcd for $C_{20}H_{37}NO_4$: C, 67.57; H, 10.49; N, 3.94. Found: C, 68.15; H, 10.73; N, 3.77.

***trans*-4-Hydroxy-1-(1-oxohexadecyl)-L-proline Methyl Ester (8).** Pal-Hpr-Me (8) was prepared as described in the literature.[1] Yield 28.2 g (92%); ^{13}C NMR ($CDCl_3$) δ 173.03 (C-1, hexadecanoyl), 172.65 (C-1), 70.13 (C-4), 57.54 (C-2), 55.12 (C-1, methyl), 52.24 (C-5), 37.71 (C-2, hexadecanoyl), 34.52 (C-3), 31.88 (C-14, hexadecanoyl), 29.66, 29.51 (C-4-13, hexadecanoyl), 24.59 (C-3, hexadecanoyl), 22.64 (C-15, hexadecanoyl), 14.07 (C-16, hexadecanoyl); IR (KBr pellet, cm^{-1}) 3350 (O–H), 2910–2860 (C–H), 1750 (C=O, ester), 1610 (C=O, amide), 1480, 1090 (C–N); TLC $R_f = 0.38$ (ethyl acetate); mp 61–63 °C (lit. mp 63–64 °C); $[\alpha]^{25}_D$ –48.8° (*c* 2, chloroform). Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.78; N, 3.65. Found: C, 69.48; H, 9.82; N, 3.60.

Synthesis of Polymer. In general, the polymerization was conducted in a Kimax tube equipped with a sidearm. The tube was charged with 2.0 g of the purified monomer and a 1 mol % catalyst and was then fitted with a dry ice/acetone trap. The reaction was carried out under a high vacuum (10^{-4} mmHg) at 180 °C. Initially the reaction mixture was agitated every 15 min during the first hour by flushing the system with nitrogen to enhance mixing and to remove moisture. The increase in molecular weight was followed at several intervals throughout the reaction period by removing small aliquots of the polymer melt and analyzing by gel permeation chromatography. For different polymers, different purification systems were necessary. The crude poly(Pal-Hpr ester) and poly(Myr-Hpr ester) were purified by dissolving in chloroform and precipitating into methanol with stirring. The nonsolvent for poly(Dec-Hpr ester) and poly(Hex-Hpr ester) was hexane. After purification, fine powder was obtained.

Poly[*trans*-4-hydroxy-1-(1-oxoethyl)-L-proline ester] (Poly(Ac-Hpr ester)). Ac-Hpr-Me (3, 1.0 g, 5 mmol) was heated with titanium isopropoxide (16 μL, 1 mol %) at 180 °C. Within 10 min, the reaction mixture became dark yellow and very viscous. At the end of 18 h, stirring was difficult, and the product appeared very glassy at 180 °C. The temperature was raised to 210–220 °C, and the reaction was prolonged for 3 h. A brown, glassy, and very brittle solid was obtained. GPC $M_w = 1920$, $M_n = 970$, $M_w/M_n = 1.97$; ^{1}H NMR ($CDCl_3$) δ 5.42 (br, 1, H-4), 4.50 (dd, 1, $J = 8, 8$ Hz, H-2), 3.81 (m, 2, H-5), 2.49 (br, m, 4, H-3), 2.11 (s, 3, CH_3, acetyl); ^{13}C NMR ($CDCl_3$) δ 171.43 (C-1, acetyl), 169.84 (C-1), 73.66 (C-4), 57.47 (C-2), 53.03 (C-5), 34.62 (C-3), 22.10 (C-2, acetyl); IR (film on NaCl, cm^{-1}) 2980–2920 (C–H), 1740 (C=O, ester), 1650 (C=O, amide), 1410, 1050 (C–N), 1180 (C–C(=O)–O). Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.02. Found: C, 52.19; H, 5.85; N, 8.52.

Poly[*trans*-4-hydroxy-1-(1-oxo-2,2-dimethylpropyl)-L-proline ester] (Poly(Piv-Hpr ester)). Piv-Hpr-Me (2.0 g, 8 mmol) was mixed with titanium isopropoxide (26 μL, 1 mol %) and polymerized at 180 °C. Within 30 min, the reaction mixture became very viscous and no coloration was observed. At the end of 2 h, the reaction mixture solidified. The temperature was raised to 210 °C to facilitate further polymerization. A glassy, white, and very brittle solid was obtained. GPC M_w = 9820, M_n = 5110, M_w/M_n = 1.92, DP = 25; ^{1}H NMR (CDCl$_3$) δ 5.39 (br, s, 1, H-4), 4.43 (dd, 1, J = 8, 8 Hz, H-2), 4.04 (d, 1, J = 11, H-5β), 3.86 (dd, 1, J = 12, 2 Hz, H-5α), 2.31 (dd, 1, J = 14, 8 Hz, H3-β), 1.99 (ddd, 1, J = 13, 8, 4 Hz, H-3α), 1.22 (s, 9, t-Bu); ^{13}C NMR (CDCl$_3$) δ 177.11 (C-1, dimethylpropanoyl), 171.77 (C-1), 74.39 (C-4), 59.78 (C-2), 53.10 (C-5), 38.51 (C-2, dimethylpropanoyl), 32.96 (C-3), 27.04 (C-3–5, dimethylpropanoyl); IR (film on NaCl, cm^{-1}) 3460 (O–H), 2970 (C–H), 1745 (C=O, ester), 1630 (C=O, amide), 1410, 1060 (C–N), 1175 (C–C(=O)–O). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 59.65; H, 7.54; N, 6.93.

Poly[*trans*-4-hydroxy-1-(1-oxohexyl)-L-proline ester] (Poly(Hex-Hpr ester)). Into a melt polymerization tube, Hex-Hpr-Me (**5**, 2.0 g, 8 mmol) was placed, and residual solvent in the monomer was removed under high vacuum for about 30 min. The reaction was initiated with titanium isopropoxide (120 μL, 1 mol %) at 180 °C; 1.5 g of a glassy and brittle solid was recovered. GPC M_w = 14 400, M_n = 4600, M_w/M_n = 3.13, DP = 23; ^{1}H NMR (CDCl$_3$) δ 5.41 (br, 1, H-4), 4.44 (dd, 1, J = 8, 8 Hz, H-2), 3.82 (m, 2, H-5), 2.34 (m, 4, H-3, CH$_2$), 1.62 (s, 2, CH$_2$, hexanoyl), 1.25 (s, 4, 2 CH$_2$, hexanoyl), 0.90 (t, 3, CH$_3$, hexanoyl); ^{13}C NMR (CDCl$_3$) δ 172.37 (C-1, hexanoyl), 171.80 (C-1), 73.71 (C-4), 57.55 (C-2), 52.34 (C-5), 34.26 (C-3; C-2, hexanoyl), 31.40 (C-4, hexanoyl), 24.11 (C-3, hexanoyl), 22.41 (C-5, hexanoyl), 13.92 (C-6, hexanoyl); IR (film on NaCl, cm^{-1}) 3450 (O–H), 2960, 2870 (C–H), 1750 (C=O, ester), 1655 (C=O, amide), 1420, 1065 (C–N), 1180 (C–C(=O)–O). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11; N, 6.63. Found: C, 61.71; H, 8.25; N, 6.48.

Poly[*trans*-4-hydroxy-1-(1-oxodecyl)-L-proline ester] (Poly(Dec-Hpr ester)). Dec-Hpr-Me (6.0 g, 20 mmol) was mixed with titanium isopropoxide (60 μL, 1 mol %) and polymerized at 180 °C. Initially, vigorous bubbling occurred, and the mixture became very viscous. A glassy and brittle material was obtained (4.7 g). GPC M_w = 41 500, M_n = 11 500, M_w/M_n = 3.61, DP = 38; ^{1}H NMR (CDCl$_3$) δ 5.39 (br, 1, H-4), 4.44 (dd, 1, J = 8, 8 Hz, H-2), 3.82 (m, 2, H-5), 2.31 (m, 4, H-3, CH$_2$), 1.61 (br, 2, CH$_2$, decanoyl), 1.25 (s, 12, 6 CH$_2$, decanoyl), 0.88 (t, 3, CH$_3$, decanoyl); ^{13}C NMR (CDCl$_3$) δ 172.39 (C-1, decanoyl), 172.06 (C-1), 73.71 (C-4), 57.52 (C-2), 52.31 (C-5), 34.35 (C-3; C-2 decanoyl), 31.85 (C-4, decanoyl), 29.48, 29.31 (C-5-8, decanoyl), 24.44 (C-3, decanoyl), 22.65 (C-9, decanoyl), 14.07 (C-10, decanoyl); IR (film on NaCl, cm^{-1}) 2850, 2920 (C–H), 1745 (C=O, ester), 1645 (C=O, amide), 1425, 1050 (C–N), 1180 (C–C(=O)–O). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43; N, 5.23. Found: C, 66.72; H, 8.78; N, 5.10.

Poly[*trans*-4-hydroxy-1-(1-oxotetradecyl)-L-proline ester] (Poly(Myr-Hpr ester)). A procedure similar to that described above was used. A waxlike, brittle material was obtained (4.6 g). GPC M_w = 24 570, M_n = 9440, M_w/M_n = 2.60, DP = 41; ^{1}H NMR (CDCl$_3$) δ 5.39 (br, 1, H-4), 4.44 (dd, 1, J = 8, 8 Hz, H-2), 3.82 (m, 2, H-5), 2.28 (m, 4, H-3; CH$_2$), 1.61 (s, 2, CH$_2$, tetradecanoyl), 1.25 (s, 20, 10 CH$_2$, tetradecanoyl), 0.88 (t, 3, CH$_3$, tetradecanoyl); ^{13}C NMR (CDCl$_3$) δ 172.40 (C-1, tetradecanoyl), 171.98 (C-1), 73.8 (C-4), 57.8 (C-2), 52.3 (C-5), 34.41 (C-3; C-2, tetradecanoyl), 31.92 (C-4), 29.70, 29.37 (C-5-14, tetradecanoyl), 24.47 (C-3, tetradecanoyl), 22.68 (C-15, tetradecanoyl), 14.12 (C-16, tetradecanoyl); IR (film on NaCl, cm^{-1}) 2917, 2850 (C–H), 1740 (C=O, ester), 1645 (C=O, amide), 1420, 1060 (C–N), 1180 (C–C(=O)–O). Anal. Calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.26; H, 9.96; N, 4.21.

Poly[*trans*-4-hydroxy-1-(1-oxohexadecyl)-L-proline ester] (Poly(Pal-Hpr ester)). The same procedure was used as above. A waxlike, semicrystalline material was obtained (4.6 g). GPC M_w = 42 390, M_n = 11 690, M_w/M_n = 3.62, DP = 33; ^{1}H NMR (CDCl$_3$) δ 5.41 (br, 1, H-4), 4.44 (dd, 1, J = 8, 8 Hz, H-2), 3.86 (m, 2, H-5), 2.31 (m, H-3; CH$_2$, hexadecanoyl), 1.61 (s, 2, CH$_2$, hexadecanoyl), 1.26 (s, 24, 12 CH$_2$, hexadecanoyl), 0.88 (t, 3, CH$_3$, hexadecanoyl); ^{13}C NMR (CDCl$_3$) δ 172.44 (C-1, hexadecanoyl), 172.37 (C-1), 73.4 (C-4), 57.47 (C-2), 52.2 (C-5), 34.40 (C-3; C-2, hexadecanoyl), 31.94 (C-4), 29.76, 29.39 (C-5–14, hexadecanoyl), 24.49 (C-3, hexadecanoyl), 22.70 (C-15, hexadecanoyl), 14.14 (C-16, hexadecanoyl); IR (film on NaCl, cm^{-1}) 2920, 2850 (C–H), 1750 (C=O, ester), 1650 (C=O, amide), 1440, 1060 (C–N), 1180 (C–C(=O)–O). Anal. Calcd for $C_{21}H_{37}NO_3$: C, 71.75; H, 10.61; N, 3.98. Found: C, 71.45; H, 10.95; N, 3.96.

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Registry No. 3, 67943-19-5; **3** (homopolymer), 120687-16-3; **3** (SRU), 120687-22-1; **4**, 99465-82-4; **4** (homopolymer), 120687-17-4; **4** (SRU), 120687-23-2; **5**, 120687-13-0; **5** (homopolymer), 120687-18-5; **5** (SRU), 120687-24-3; **6**, 120687-14-1; **6** (homopolymer), 120687-19-6; **6** (SRU), 120687-25-4; **7**, 120687-15-2; **7** (homopolymer), 120687-20-9; **7** (SRU), 120687-26-5; **8**, 106231-83-8; **8** (homopolymer), 120687-21-0; **8** (SRU), 120687-27-6; CaCO$_3$, 471-34-1; BaO, 1304-28-5; CaO, 1305-78-8; Sb$_2$O$_3$, 1309-64-4; Bi$_2$O$_3$, 1304-76-3; Fe$_2$Cl$_3$, 7705-08-0; FeAcAc, 14024-17-0; p-toluenesulfonic acid, 104-15-4; potassium *tert*-butoxide, 865-47-4; cadmium acetate, 543-90-8; zinc acetate, 557-34-6; lead acetate, 301-04-2; diethylzinc, 557-20-0; aluminum *tert*-butoxide, 556-91-2; aluminum isopropoxide, 555-31-7; titanium n-butoxide, 23355-24-0; titanium isopropoxide, 546-68-9; *trans*-4-hydroxy-1-(1-oxoethyl)-L-proline, 33996-33-7.

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