Synthesis of Polyamides Containing Dipeptide Linkages

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A synthetic approach to polyamides containing the tyrosine–leucine linkage is presented. The DPPA coupling technique was utilized to synthesize the monomers. A chloroform solution of tyrosylleucyliminohexamethyleneiminoleucyltyrosine, monomer **I**, and triethylamine was reacted with chloroform solutions of adipoyl and sebacoyl chlorides, to give polymers with molecular weight, M_w/M_n of 14200/7200 and 20800/8100, respectively. Interfacial polymerization of monomer **I** yielded a fibrous cross-linked material. This was found to be a poly(amide ester) as indicated by IR analysis. In another reaction, the monomer, β-alanyltyrosylleucyl-β-alanine (monomer **II**) in DMF was polymerized using DPPA and triethylamine to give a polyamide with M_w/M_n of 16500/5700.

Introduction

The incorporation of enzyme targeted cleavage points in polymers has great potential in that materials for specific applications can be synthesized. This is particularly important in the biomedical field where highly specialized systems are required.[1] Some of these biomedical applications include dialysis membranes, artificial skin substitutes, degradable sutures and drug delivery systems. A wide range of homopolymers and copolymers containing α-amino acids have been synthesized and their application in the biomedical field investigated.[2,3] Pseudopoly(amino acids), which are structural analogs of conventional poly(amino acids), have also been synthesized by utilizing the reactive side chains of the α-amino acids.[4] Most of the structural modifications are aimed at obtaining biocompatible materials with superior qualities for specific applications.

Numerous synthetic approaches to polymers containing amino acids have been investigated. For example, the glycine containing nylons such as nylon 26, nylon 266, and nylon 2626 have been synthesized by using solution and/or interfacial polymerization methods.[5-7] In the solution method, relatively low molecular weight polymers were obtained. Furthermore, in the active ester method usually applied,[8] there is the possibility of racemization where chiral molecules are concerned. However, the azide activation technique utilizing diphenyl phosphoryl azide (DPPA) has been applied with considerable success in both the coupling and polymerization of amino acids to give racemization-free peptides and polypeptides, respectively.[8-12] It has also been used with amino acids with side-chain functional groups without any repercussions.[8] Recently, DPPA has been utilized to make polyamides, polyureas, and polyurethanes from their respective monomers.[12-14]

In this paper, a synthetic approach utilizing DPPA to incorporate the dipeptide tyrosine-leucine (Tyr-Leu) in polyamides is outlined. The tyrosine–leucine bond is known to be susceptible to specific enzyme attack,[15] and it is anticipated that polyamides derived from the dipeptide will be biodegradable.

Experimental Section

Materials. The amino acid derivatives were obtained from Advanced ChemTech Inc. Louisville, KY, and were used without further purification. DPPA was obtained from Aldrich Chemical Co. and was purified by distilling under reduced pressure. Adipoyl and sebacoyl chlorides were distilled under reduced pressure while hexamethylenediamine was purified by vacuum sublimation. Triethylamine was dried over calcium hydride and distilled at atmospheric pressure. Anhydrous dimethylformamide (DMF) was obtained by drying over BaO and distilling it under reduced pressure.

Characterization. Elemental analysis was done at Galbraith Laboratories Inc., Knoxville, TN. The intrinsic viscosities of the polymers were measured in 0.5 g/dL solutions of 90% formic acid at 25 °C using an Ubbelohde viscometer. The infrared spectra of the samples (KBr pellet or film cast from $CHCl_3$) were recorded on a Nicolet 60SX FTIR spectrometer. ^1H NMR spectra were obtained on an IBM AF-270 NMR spectrometer (270 MHz), with CF_3COOD or $CDCl_3$ as the solvent. Molecular weights of the monomers were determined using the fast atom bombardment (FAB) technique on a Kratos MS50RF high-resolution magnetic sector mass spectrometer. Thermal analyses of the polymers/oligomers were performed using a Perkin-Elmer DSC-7 in N_2 at a heating rate of 10 °C/min. GPC analysis was conducted in *m*-cresol with a Waters 150-C ALC/GPC equipped with μ-styragel

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HT column of 10^5, 10^5, 10^3, and 10^3 Å pore sizes at 130 °C and a flow rate of 1 mL/min. Polystyrene narrow molecular weight standards were used for calibration. Solubilities were tested with 10-mg polymer samples in 1 mL of solvent.

Synthesis of Monomers. *Tyrosylleucyliminohexamethyleneiminoleucyltyrosine (Tyr-Leu-$(CH_2)_6$-Leu-Tyr).* To a stirred mixture of BOC-Tyr (5.63 g, 20 mmol) and Leu-OMe·HCl (4.0 g, 22 mmole) in DMF (80 mL), DPPA (6.05 g, 22 mmol) in DMF (10 mL) was added with cooling in ice. This was followed by the addition of triethylamine (TEA, 5.85 g, 42 mmol) in DMF (10 mL). The mixture was stirred with cooling in ice for 4 h and then left overnight at room temperature. To the reaction mixture was added ethyl acetate–benzene (4:1, 800 mL) and the mixture was washed with 5% HCl (2 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), saturated NaCl (2 × 100 mL), and water (2 × 100 mL). The resulting organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The solid obtained was dried in vacuum to give 6.70 g (82.1%) of the dipeptide BOC-Tyr-Leu-OMe. The peptide was used without further purification.

NMR ($CDCl_3$) δ (ppm) 0.85 (d, 6H, $(CH_3)_2$, Leu), 1.50–1.52 (m, 12H, $CHCH_2$, Leu, $(CH_3)_3$, BOC), 3.24 (d, 2H, CH_2, Tyr), 3.72 (s, OCH_3) 4.50–4.60 (t, 2H, CH-N Tyr, leu), 6.84–7.12 (d, 4H, aromatic H, Tyr). IR (KBr pellet) 3500–3200 cm^{-1} (O–H stretching), 3300 cm^{-1} (N–H stretching), 3050 cm^{-1} (C-H stretching, aromatic), 2930 and 2858 cm^{-1} (C–H stretching aliphatic), 1652 cm^{-1} (amide I), 1521 cm^{-1} (amide II).

The dipeptide (6.70 g, 16.4 mmol) was dissolved in acetone (20 mL) and reacted with NaOH (1.6 g, 40 mmol) in 20 mL water. The acetone was removed under reduced pressure and the aqueous phase was extracted twice with diethyl ether. It was then acidified with 1 N HCl to pH 3. The resulting white precipitate was immediately extracted with ethyl acetate (2 × 100 mL). The ethyl acetate phase was washed with water several times and then dried over anhydrous Na_2SO_4. The solvent was evaporated off under reduced pressure and the white solid obtained was dried in vacuum to give 6.07 g (77.0%) of the deblocked dipeptide, Boc-Tyr-Leu-OH. The ^1H NMR spectrum of the sample showed no methoxy peak at around 3.72 ppm.

BOC-Tyr-Leu-OH (6.07 g, 15.4 mmol) and hexamethylenediamine (0.897 g, 7.7 mmol) in DMF (60 mL) were coupled using 4.40 g of DPPA (16 mmol) and 3.62 g of TEA (36 mmol) as explained above. After the workup, 6.1 g (91.3%) of the dry crude product was obtained. This sample was reacted with 20 mL of TFA for 1 h at room temperature. After evaporating off the TFA, the remaining sample was triturated in ether several times. It was then recrystallized from methanol–ether. The white crystalline sample obtained was dried in vacuum to give 4.13 g (65.6%) of the TFA salt of monomer **I**, Tyr-leu-$(NH(CH_2)_6NH$-leu-Tyr, mp, 160 °C. The MS (FAB) gave a peak at 670, (m + 2H), for the protonated monomer without TFA anion.

Elemental Anal. Found: C, 51.89; H, 6.76; N, 8.75. Calcd for $C_{40}H_{58}N_6O_{10}F_6 \cdot H_2O$; C, 52.51; H, 6.61; N, 9.19.[14,18]

NMR (CF_3COOD) δ (ppm) 0.81 (m, 12H, $(CH_3)_2$, Leu), 1.35–1.58 (m, 14H, $CHCH_2$, Leu, CH_2, diamine), 3.1–3.2 (m, 8H, CH_2-NH, diamine, CH_2, Tyr), 4.5–4.6 (t, 4H, CH–N Tyr, Leu), 6.8–7.0 (d, 8H, aromatic H, Tyr). IR (KBr pellet) 3500–3200 cm^{-1} (O–H stretching), 3298 cm^{-1} (N–H stretching), 3080 cm^{-1} (C–H stretching, aromatic), 2930 and 2858 cm^{-1} (C–H stretching, aliphatic), 1652 cm^{-1} (amide I), 1521 cm^{-1} (amide II).

Synthesis of β-Alanyltyrosylleucyl-β-alanine (β-Ala-Tyr-Leu-β-Ala). *(a) (tert-Butyloxycarbonyl)-β-alanyltyrosine (BOC-β-Ala-Tyr-OH).* To a stirred mixture of BOC-β-Ala (3.78 g, 20 mmol) and Tyr–OMe·HCl (5.10 g, 22 mmol) in DMF (80 mL) at 0 °C was added DPPA (6.05 g, 22 mmol) in DMF (10 mL) followed by TEA (5.85 g, 42 mmol) in DMF (10 mL). The mixture was allowed to react and worked-up as explained above to afford 6.20 g (84.7%) of the dipeptide, BOC-β-Ala-Tyr-OMe.

NMR ($CDCl_3$) δ (ppm) 1.44 (s, 9H, $(CH_3)_3$, BOC), 2.37 (t, 2H, CH_2CO, β-Ala), 3.05 (t, 2H, CH_2NH, β-Ala), 3.72 (s, OCH_3), 4.83 (t, 1H, CH–N Tyr), 5.16 (br s, 1H, NH), 6.17 (d 1H, NH), 6.73–6.94 (d, 4H, aromatic H, Tyr). IR (KBr pellet) 3500–3200 cm^{-1} (O–H stretching), 3300 cm^{-1} (N–H stretching), 3080 cm^{-1} (C–H stretching, aromatic), 2950 and 2860 cm^{-1} (C–H stretching, aliphatic), 1652 cm^{-1} (amide I), 1520 cm^{-1} (amide II).

The methyl ester protecting group was deblocked using aqueous NaOH (1.6 g, 40 mmol) in the usual way to afford 5.19 g (73.5%) of BOC-β-Ala-Tyr-OH. ^1H NMR of the compound done in $CDCl_3$ showed no methoxy peak at around 3.72 pmm. The dipeptide was used in segment coupling without further purification.

(b) (tert-Butyloxycarbonyl)leucyl-β-alanine (BOC-Leu-β-Ala-OH). To an ice-cooled stirred mixture of BOC-Leu-OH (5.0 g 20 mmol) and β-Ala-OMe·HCl (3.07 g, 22 mmol) in DMF (80 mL) was added DPPA (6.05 g, 22 mmol) in DMF (10 mL), followed by TEA (5.85 g, 42 mmol). The mixture was treated the same way as that of BOC-β-Ala-Tyr-OMe, and 5.52 g (87.3%) of an oily colorless product was obtained.

NMR ($CDCl_3$) δ (ppm) 0.93 (m, 6H, $(CH_3)_2$, Leu), 1.44 (s, 9H $(CH_3)_3$, BOC), 1.64 (m, 3H, $CHCH_2$, Leu), 2.55 (t, 2H, CH_2CO, β-Ala), 3.53 (t, 2H, CH_2-N, β-Ala), 3.72 (s, OCH_3), 4.06 (m, 1H, CH–N), 4.98 (d 1H, NH), 6.70 (br s, 1H, NH). IR (film): 3300 cm^{-1} (N–H stretching), 2950 and 2860 cm^{-1} (C–H stretching, aliphatic), 1650 cm^{-1} (amide I), 1520 cm^{-1} (amide II).

The BOC protecting group in BOC-Leu-β-Ala-OMe was removed by reacting the sample (5.52 g, 17.5 mmol), with TFA (20 mL) for 1 h at room temperature. Excess TFA was removed *in vacuo*. Diethyl ether (30 mL) was then introduced to the residual sample and trituration was done several times. A TFA salt of the dipeptide, Leu-β-Ala-OMe, 4.55 g (67%), was obtained. ^1H NMR of the compound in CF_3COOD did not give the BOC peak at around 1.5 ppm. The sample was used in segment condensation.

(c) 2+2 Segment Condensation. BOC-β-Ala-Tyr-Leu-β-Ala-OMe. To an ice-cooled mixture of BOC-β-Ala-Tyr-OH (5.19 g, 14.7 mmol) and H-Leu-β-Ala OMe (4.55 g, 13.4 mmol) in DMF (60 mL) was added DPPA (4.13 g, 15 mmol) in DMF (10 mL) followed by TEA (3.04 g, 30 mmol) in DMF (10 mL). The mixture was maintaind at 0 °C for 4 h and was then left overnight at room temperature. It was diluted with ethyl acetate–benzene (4.1, 600 mL) and washed with 2 × 50 mL portions of 5% HCl, saturated $NaHCO_3$, saturated NaCl and water. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give 7.64 g of the crude protected tetramer. The sample was placed in a column packed with 120 g of silica gel 60 and eluted with ethyl acetate–heptane (80:20). The fractions containing the tetramer were pooled together, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a white product. This was dried in vacuum to give 4.42 g (60%) of the tetrapeptide BOC-β-Ala-Tyr-Leu-β-Ala-OMe, mp 145 °C, MS (FAB), 551 (m + H).

Elemental Anal. Found: C, 59.00; H, 7.72; N, 9.96. Calcd for $C_{27}H_{42}O_8N_4$: C, 58.9; H, 7.64; N, 10.2.

NMR (CF_3COOD) δ (ppm) 0.81 (d, 6H, $(CH_3)_2$, Leu), 1.20–1.53 (m, 12H, CH_2CH, Leu, $(CH_3)_3$, BOC), 2.70 (t, 2H, CH_2CO, β-Ala), 2.98 (d, 2H CH_2, Tyr), 3.60 (t, 2H, CH_2-N, β-Ala), 3.76 (s, 3H, OMe), 4.51–4.75 (t, 2H, CH-N, Tyr, Leu), 6.8–7.0 (d, 4H, aromatic H, Tyr).

(d) Deblocking of the Tetrapeptide. A sample of the tetrapeptide (1.5 g, 2.73 mmol) was placed in 5 mL of acetone. To the mixture was added 0.22 g (5.5 mmol) NaOH followed by 5 mL of water. The solution was stirred at room temperature for 30 min. The acetone was removed under vacuum, and the aqueous phase was extracted with ether. It was then acidified using 1 N HCl to pH 3. The white precipitate formed was extracted using ethyl acetate. The extract was washed with water and then dried over anhydrous Na_2SO_4. It was concentrated under vacuum, and the solid obtained was dried in a vacuum oven. This solid was then treated with 5 mL of TFA for 1 h to deblock the BOC protecting group. The sample was purified as in the case of the dipeptide and again dried in a vacuum oven to give 1.22 g (68.9%) of trifluoroacetic acid salt of the tetrapeptide, β-Ala-Tyr-Leu-β-Ala (monomer **II**), which was used in the DPPA polymerization.

NMR (CF_3COOD) δ (ppm) 0.81 (d, 6H, $(CH_3)_2$, Leu), 1.20–1.53 (m, 12H, CH_2CH, Leu, $(CH_3)_3$, BOC), 2.70 (t, 2H, CH_2CO, β-Ala), 2.98 (d, 2H CH_2, Tyr), 3.60 (t, 2H, CH_2–N, β-Ala), 4.51–4.75 (t, 2H, CH–N, Tyr, Leu), 6.81–7.02 (d, 4H, aromatic H, Tyr).

Polymerization. Poly(tyrosylleucyliminohexamethyleneiminoleucyltyrosyladipoyl) (PTLA). The peptide Tyr-Leu-$NH(CH_2)_6$NH-Leu-Tyr (1.0 g, 1.28 mmol, monomer **I**) and 0.8 mL of freshly distilled triethylamine was dissolved in 5 mL of dry chloroform. To this mixture was added a solution of 0.23 g (0.19 mL, 1.28 mmol) of adipoyl chloride in 5 mL of chloroform while stirring. The mixture became viscous immediately and a white solid appeared. After 5 min the product was

poured into hexane with stirring. The resulting precipitate was filtered and washed thoroughly with water, methanol, and acetone. The sample was then dried in vacuum at 60 °C. A white solid (0.52 g, yield, 52.2%) with an intrinsic viscosity, [η], of 0.14 dL/g in 90% formic acid was obtained, (M_w/M_n, 14200/7200, DP ~ 10).

Elemental Anal. Found: C, 61.87; H, 8.27; N, 10.06. Calcd for $C_{42}H_{62}N_6O_8 \cdot 2H_2O$: C, 61.89; H, 8.16; N, 10.31.[14,18]

NMR (CF_3COOD) δ(ppm) 0.83 (d, 12H, $(CH_3)_2$, Leu), 1.3–1.5 (m, 18H, $CHCH_2$, Leu CH_2, diamine, adipoyl), 2.3 (m, 4H, CH_2-CO, adipoyl), 2.96–3.3 (m, 8H, CH_2, Tyr, CH_2–N, diamine), 4.6–4.8 (m, 4H, CH–N, Tyr, Leu), 6.8–7.0 (d, 8H, aromatic, Tyr). IR (KBr pellet) 3500–3200 cm^{-1} (O–H, stretching) 3317 cm^{-1} (N–H, stretching) 3084 cm^{-1} (C–H stretching, aromatic), 2933 and 2853 cm^{-1} (C–H stretching, aliphatic), 1653 cm^{-1} (amide I), 1518 cm^{-1} (amide II).

Poly(tyrosylleucyliminohexamethyleneimino-leucyltyrosylsebacoyl) (PTLS). To a solution of monomer **I** (0.9 g, 1.0 mmol) and 0.6 mL of triethylamine in dry chloroform (15 mL) was added 0.196 g (0.82 mmol) of sebacoyl chloride dissolved in 15 mL of dry chloroform. The mixture was polymerized as in the case of adipoyl chloride. A total of 0.25 g (yield, 37%) of the polymer was obtained, having an intrinsic viscosity, [η], of 0.13 dL/g in 90% formic acid (M_w/M_n, 20800/8100, DP ~ 10).

Elemental Anal. Found: C, 63.22; H, 8.48; N, 8.71. Calcd for $C_{46}H_{70}N_6O_8 \cdot 2H_2O$; C, 63.42; H, 8.56; N, 9.65.[14,18]

NMR (CF_3COOD) δ (ppm) 0.82 (d, 12H $(CH_3)_2$, Leu), 1.2–1.5 (m, 26H, $CHCH_2$, Leu, CH_2, diamine, sebacoyl), 2.4 (m, 4H, CH_2-CO, sebacoyl), 3.0–3.3 (m, 8H, CH_2 Tyr, CH_2–N diamine) 4.6–4.8 (m, 4H, CH–N, Tyr, Leu), 6.8–7.0 (d, 8H, aromatic H, Tyr). IR (KBr pellet) 3500–3200 cm^{-1} (O–H stretching), 3298 cm^{-1} (N–H stretching), 3080 cm^{-1} (C–H stretching, aromatic), 2929 and 2858 cm^{-1} (C–H stretching, aliphatic), 1653 cm^{-1} (amide I), 1522 cm^{-1} (amide II).

Interfacial Polymerization. (*a*) *Cross-Linked Polyamide Ester.* A solution of monomer **I** was made by mixing 0.46 g (0.51 mmol) of the monomer with 0.082 g (2.04 mmol) NaOH in 5 mL of water. This aqueous solution was added to a solution of adipoyl chloride (0.094 g, 0.51 mmol), in chloroform (2 mL). The mixture was stirred vigorously for 5 min. The white fibrous material obtained was washed thoroughly with water, water–methanol (1:1), and methanol. It was then dried at 60 °C in a vacuum oven to give 0.18 g (yield, 45.3%) of the product. The polymer was found to be insoluble in most organic solvents including trifluoroacetic acid as well as formic acid among others.

IR (KBr pellet) 3292 cm^{-1} (N–H stretching), 3061 cm^{-1} (C–H stretching, aromatic), 2923 and 2846 cm^{-1} (C–H stretching, aliphatic), 1754 cm^{-1} (C=O stretching, ester), 1650 cm^{-1} (amide I), 1523 cm^{-1} (amide II). The same procedure as described for adipoyl chloride polymerization was followed with sebacoyl chloride and similar results were obtained.

(*b*) *Peptide Polyester.* A solution of amino protected monomer **I** was made by mixing 0.80 g (0.92 mmol) of the sample with 0.074 g (1.85 mmol) NaOH in 10 mL of water. This aqueous solution was added to a solution of adipoyl chloride (0.168 g, 0.92 mmol), in chloroform (3 mL). The mixture was allowed to react and was worked up as described above. A polymer (0.40 g, yield, 44.4%) with an intrinsic viscosity, [η], of 0.18 dL/g in 90% formic acid was obtained (M_w/M_n, 3500/2500, DP ~ 2.5).

Elemental Anal. Found: C, 62.74; H, 7.95; N, 8.33. Calcd for $C_{52}H_{78}N_6O_{12} \cdot H_2O$: C, 62.65; H, 8.03; N, 8.43.[14,18]

NMR (CF_3COOD) δ (ppm) 0.83 (d, 12H, $(CH_3)_2$, Leu), 1.32–1.63 (m, 36H, $(CH_3)_3$, BOC, $CHCH_2$, Leu, CH_2, diamine, adipoyl), 2.66 (m, 4H, CH_2CO, adipoyl), 3.09–3.34 (m, 8H, CH_2, Tyr, CH_2N, diamine), 4.50–4.59 (m, 4H, CH–N, Tyr, Leu), 6.97–7.23 (d, 8H, aromatic, Tyr). IR (KBr pellet) 3500–3200 cm^{-1} (O–H, stretching) 3317 cm^{-1} (N–H, stretching) 3084 cm^{-1} (C–H stretching, aromatic), 2933 and 2853 cm^{-1} (C–H stretching, aliphatic), 1754 cm^{-1} (C=O stretching, ester), 1653 cm^{-1} (amide I), 1518 cm^{-1} (amide II).

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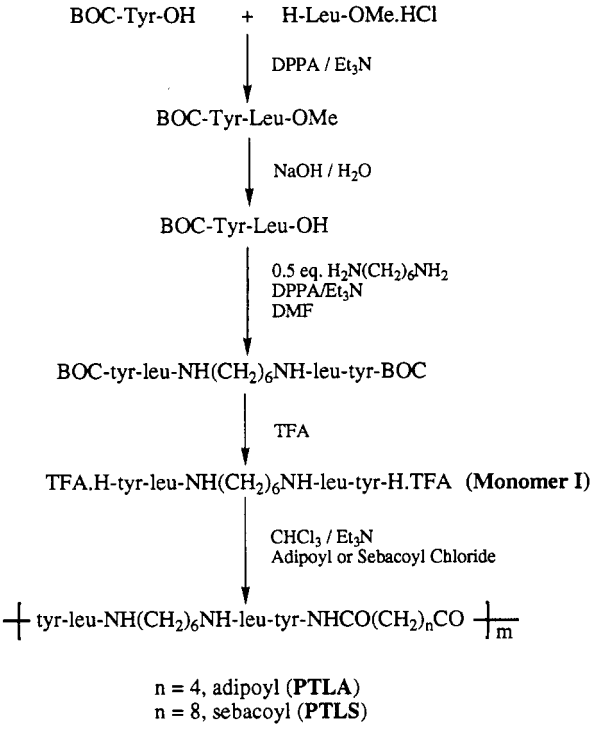
Scheme I. Synthesis of Tyr-Leu-NH$(CH_2)_6$NH-Leu-Tyr Polymers



β-Alanyltyrosylleucyl-β-alanine Polymer (PATL). To a stirred solution of monomer **II**, β-Ala-Tyr-Leu-β-Ala (1.15 g, 2.07 mmol) in DMF (2 mL) was added DPPA (0.741 g, 2.69 mmol) and 0.482 g (4.76 mmol) of triethylamine. The mixture was stirred at 5–8 °C for 1 h. A viscous mass was observed after 1 h. This was left at room temperature for 2 days. It was then precipitated by adding water and centrifuged. The resulting solid was washed three times with each of the following solvents: water, methanol, and ether. The polymer was then dried in vacuum. An off-white solid (0.5 g, yield 55.4%) was obtained and had an intrinsic viscosity, [η], of 0.07 dL/g in 90% formic acid (M_w/M_n, 5300/2900, DP ~ 5).

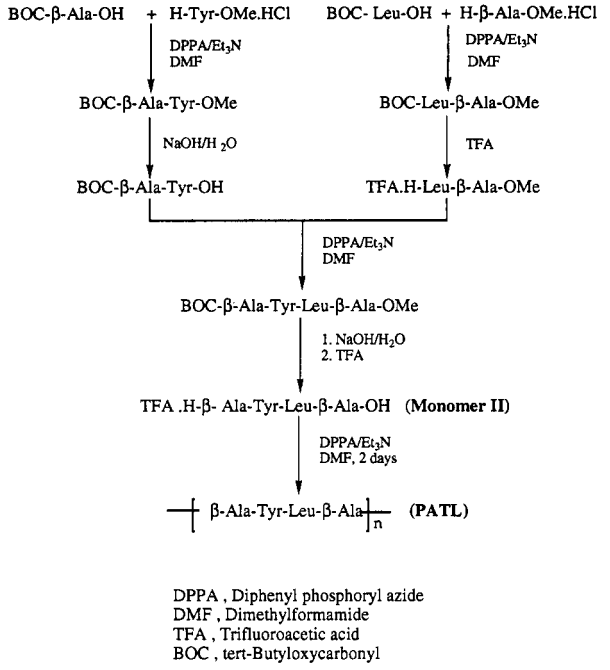
Elemental Anal. Found: C, 57.8; H, 7.24; N, 12.3. Calcd for $C_{21}H_{30}N_4O_5 \cdot H_2O$; C, 57.8; H, 7.34; N, 12.8.[14,18]

NMR (CF_3COOD) δ (ppm) 0.81 (6H, $(CH_3)_2$, Leu), 1.5 (3H, CH_2–CH, Leu), 2.7 (4H, CH_2–CO, β-Ala), 2.97 (2H, CH_2, Tyr), 3.56 (4H, CH_2–N, β-Ala), 4.5–4.75 (2H CH–N, Leu, Tyr), 6.8–7.0 (4H, aromatic H, Tyr). IR (KBr pellet) 3500–3200 cm^{-1} (O–H stretching), 3298 cm^{-1} (N–H stretching), 3082 cm^{-1} (C–H stretching, aromatic), 2955 and 2858 cm^{-1} (C–H stretching, aliphatic), 1670 cm^{-1} (amide I), 1516 cm^{-1} (amide II).

Results and Discussion

Scheme I gives the general outline of synthesizing adipoyl or sebacoyl polymers containing the Tyr-Leu-$(CH_2)_6$-Leu-Tyr unit. (*tert*-Butyloxycarbonyl)-L-tyrosine (BOC-Tyr-OH) was coupled with L-leucine methyl ester·HCl (Leu-OMe·HCl) using DPPA and triethylamine in DMF.[8,9] The methyl ester protecting group was deblocked using aqueous NaOH. Incorporation of the hexamethylenediamine unit was achieved by reacting 1 equiv of the amino protected dipeptide, BOC-Tyr-Leu-OH with 0.5 equiv of the amine using DPPA. The resulting peptide, BOC-Tyr-Leu-NH$(CH_2)_6$NH-Leu-Tyr-BOC was reacted with anhydrous trifluoroacetic acid (TFA) at room temperature to give monomer **I**. In the process of synthesizing the monomer, the intermediate compounds were used without elaborate purification, however, the success of each reaction step was confirmed by ^{1}H NMR and IR spectroscopic methods.

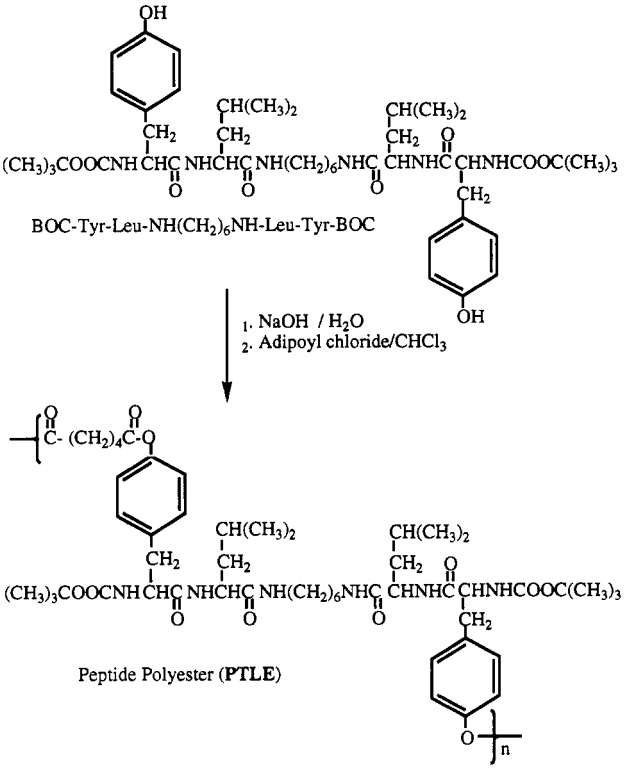
Scheme II. Synthesis of β-Ala-Tyr-Leu-β-Ala Polymer



Solution polymerization of monomer **I** was achieved by reacting a chloroform solution of the monomer and triethylamine with chloroform solutions of either adipoyl or sebacoyl chlorides to give the corresponding polymers.[16] The adipoyl polymer (PTLA, 0.52 g, yield, 52.2%) had an intrinsic viscosity, [η], of 0.14 dL/g while that of sebacoyl (PTLS, 0.25 g, yield, 37%) had an intrinsic viscosity of 0.13 dL/g in 90% formic acid.

The interfacial polymerization of monomer **I** was carried out by reacting the sodium hydroxide solution of the monomer with chloroform solutions of either adipoyl or sebacoyl chloride.[7] A cross-linked poly(amide ester) was obtained in each case. This was due to the reaction of both the amino and hydroxyl groups in the tyrosine unit with acid chloride in alkaline medium. To confirm the reaction due to the hydroxyl group in the tyrosine unit, interfacial polymerization of an alkaline solution of amino protected monomer **I** and a chloroform solution of adipoyl chloride was carried out, (Scheme III). An oligomer, PTLE (M_w/M_n, 3500/2500), was obtained. It had an intrinsic viscosity of 0.18 dL/g in 90% formic acid. The IR spectrum of this peptide polyester (PTLE), was compared with that of cross-linked poly(amide ester). The two spectra had peaks at 1765 cm^{-1} (ester), 1656 cm^{-1} (amide I), and 1517 cm^{-1} (amide II).[12,17] The amide peaks in the ester can be attributed to the peptide bonds originally present in the monomer. The IR spectrum of the polymer, PTLA, made by solution polymerization of monomer **I** did not show the ester peak at 1765 cm^{-1} (Figure 1). This result indicates that the hydroxyl group in tyrosine only reacts in a highly alkaline medium. Hence solution polymerization of monomer **I** can be carried in tertiary amine bases without the hydroxyl group protection, and this forms the basis of selective polymerization. All the polymers showed IR features typical of polypeptides.[12] However, the cross-linked poly(amide-ester) had a broad peak between 1600 and 1700 cm^{-1}. This broadness could be attributed to the presence of both amide I and acid carbonyl peak from the carboxyl end group.

Scheme III. Synthesis of Peptide Polyester



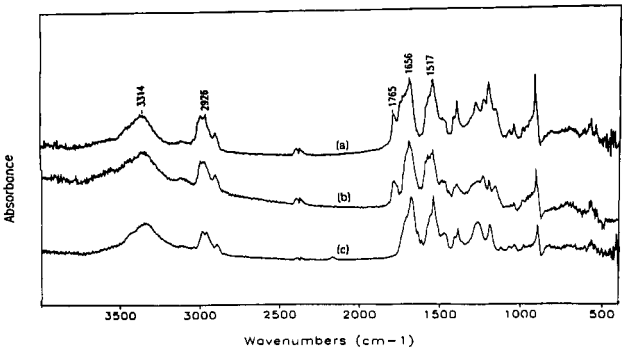


Figure 1. Infrared spectra of the polymers: (a) poly(amide ester), cross-linked, (b) peptide polyester, PTLE, (c) polyamide, PTLA.

The synthesis of poly(β-alanyltyrosylleucyl-β-alanine), PATL, is outlined in Scheme II. The synthetic approach leading to monomer **I** was followed to make monomer **II**. Here shorter carbon chains (β-alanine) were introduced on either side of the tyrosine-leucine dipeptidete to give a tetrapeptide, β-Ala-Tyr-Leu-β-Ala, monomer **II**. Poly-(β-Ala-Tyr-Leu-β-Ala) was obtained by dissolving monomer **II** in DMF and reacting it with DPPA in the presence of triethylamine for 2 days.[10] The polymer, (PATL), 0.50 g, yield 55.4%) had an intrinsic viscosity, [η], of 0.07 dL/g in 90% formic acid.

The physical properties of the polymers are given in Table I. The yields obtained were moderate and comparable to those of other polymers synthesized by similar techniques.[12,16,21] The molecular weights were determined by GPC in *m*-cresol at 130 °C with a flow rate of 1 mL/min and calibrated with narrow molecular weight polystyrene standards. They range from low in case of PTLA and PTLS to oligomers for PTLE and PATL. The molecular

(21) Gonsalves, K. E.; Chen, X. *J. Polym. Sci., Polym. Chem. Ed.* **1993**, *31*, 701.

Table I. Yields, T_m, and GPC Data of the Polymers/Oligomers

	sample				
	PTLA	PTLS	PTLE	PATL	PATL-II
yield, %	52.2	37	44.4	55.4	55.3
M_w	14200	20800	3500	5300	16500
M_n	7200	8100	2500	2900	5700
M_w/M_n	1.97	2.57	1.40	1.83	2.89
T_m, °C	230	160	131	*a*	138

[a] Not determined.

weights of the former are comparable to that of nylon 266 made by the interfacial method.[21] The two polymers, PTLA and PTLS, were synthesized by the solution method, using chloroform in presence of TEA. The polymers precipitated out of the solution rather quickly, which could be one of the reasons for the observed low molecular weights. The bulky pendant groups in the monomer can also introduce steric hindrance to polymerization. This effect may be the most important factor responsible for the very low molecular weight observed in the case of PTLE, prepared by the interfacial method to investigate the reactivity of the hydroxyl group of the tyrosine in an alkaline medium. In this case the amino terminal was protected with the bulky *tert*-butyloxycarbonyl group. Although only an oligomer was obtained, the reaction is important because it can be exploited to synthesize pseudopoly(amino acids) which are potential biomaterials.[4]

The DPPA solution polymerization technique was used to synthesize PATL. According to the method of Nishi,[12] and the yield and the molecular weight of the polymer are comparable. Here, besides the steric effect, inefficient mixing might have contributed a great deal to low molecular weight because the reaction mixture became too viscous after only a few minutes. To correct this effect, repolymerization of the oligomer was done after 2 days according to the method of Skrull et al.[18] More DMF was added to the reaction mixture followed by 1.3 and 2.3 equiv of DPPA and triethylamine, respectively. The reaction was continued for 2 more days. The molecular weight improved from M_w/M_n, 5300/2900 to 16500/5700 according to GPC analysis, but the polymer was slightly off white. Another interesting feature observed in the GPC analysis of the PATL II was a possible bimodal molecular weight distribution which could also account for the broad polydispersity. This observation is indicative of a two-step polymerization.

The thermal analyses of the polymers gave lower values of the T_m as compared to similar type of polymers made from linear monomers without bulky pendant side groups.[21] The large pendant groups decrease molecular symmetry and thereby prevent the effective packing of the molecules. This leads to decreased intermolecular secondary forces and hence the low T_m.[22,23]

All the polymers were found to be soluble in formic acid, acetic acid, and *m*-cresol at room temperature but insoluble in common solvents such as acetone, chloroform, benzene, chlorobenzene, and dioxane among others. This behavior is typical of polymers containing the amide bond. Table II gives some of the solubility data. Polymer films obtained by solvent casting from formic acid solutions were found to be transparent and brittle.

Table II. Solubility of the Polymers/Oligomers[a]

	solvent					
sample	*m*-cresol	NMP	DMAc	DMF	DMSO	MeOH
PTLA	+	±	±	±	±	–
PTLS	+	±	±	±	±	–
PTLE	+	+	+	+	+	±
PATL	+	±	±	±	±	–

[a] (+) soluble at room temperature, (±) soluble after heating, (–) insoluble. Note: solubility determined using 10-mg sample in 1 mL of solvent.

To improve on the molecular weights of the polymers, optimization of the reaction conditions is desirable. Methods being investigated include, the effect of solvents and the matrix-controlled solid-state synthesis according to the method of Goodman.[19,20] Another technique being investigated is that of copolymerizing acid chlorides with molar ratios of the tetrafunctional monomer **I** and other diamines. This method has been applied to make copolymers of nylon 266 and nylon 66, and the results have shown improvements in molecular weight and mechanical properties.[21]

Conclusions

The above studies indicate that the DPPA technique has been successful in synthesizing peptide monomers containing the tyrosine–leucine linkage, a potential target for enzymatic degradation. It has also been demonstrated that it is possible to vary the carbon chain of the peptide monomers in satisfactory yields. The peptides monomers can be utilized to synthesize sequential polymers in both solution and interfacial polymerization methods (Schemes I and III). Direct polymerization is also possible using DPPA (Scheme II). The formation of peptide polyester, albeit as an oligomer, has demonstrated that it is possible to control the polymerization of the tetrafunctional monomer **I** by varying the reaction conditions. Thus we are exploring the potential of using this monomer to synthesize functionalized polymers, e.g., polyamides containing pendant hydroxyl groups or conversely polyesters containing pendant amino groups and branched polymers.

Acknowledgment. We acknowledge discussions with Dr. Tommy K. Wong of National Medical Care, Rockleigh, NJ.

(22) Billmeyer, F. W. *Textbook of Polymer Science*, 3rd ed.; Wiley-Interscience: New York, 1984; p 335.
(23) Sperling, L. H. *Introduction to Physical Polymer Science*; Wiley-Interscience: New York, 1986; pp 207–208.