Synthesis of ABA Triblock Copolymers via Acyclic Diene Metathesis Polymerization and Living Polymerization of α-Amino Acid−*N*-Carboxyanhydrides

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ABSTRACT: The synthesis of poly(γ-benzyl-L-glutamate)-*b*-polyoctenamer-*b*-poly(γ-benzyl-L-glutamate) (**13**) and poly(γ-benzyl-L-glutamate)-*b*-polyethylene-*b*-poly(γ-benzyl-L-glutamate) (**14**) triblock copolymers is described. α,ω-Bisamino-terminated polyoctenamer (**5**) was used to prepare a difunctional macroinitiator (**12**) used for the living polymerization of γ-benzyl-L-glutamic acid−*N*-carboxyanhydride (Glu−NCA) to form the triblock copolymers. **5** was synthesized by acyclic diene metathesis polymerization of 1,9-decadiene (**1**) in the presence of 11-phthalimido-1-undecene (**2**) and Grubbs' metathesis catalyst, $RuCl_2(=CHPh)(PCy_3)_2$ (**3**). Deprotection of the resulting phthalimide end-functionalized polymers (**4**) was performed, leading to difunctional **5** with number-average functionalities close to two. These methods allow the controlled preparation of polypeptide/(hydrocarbon polymer) block architectures with good control over the chain lengths of both domains and without formation of homopolypeptide contaminants.

Introduction

A variety of block copolymers containing one or more blocks of L-glutamic acid γ-ester residues combined with other non-peptide blocks, such as the AB diblock copolymer polybutadiene-*b*-poly(γ-benzyl-L-glutamate), have been prepared.[1] These copolymers are interesting from both structural and biological points of view. The structural interest arises from the existence of lamellar morphologies in the bulk material comprised of layers containing disordered hydrocarbon chains and layers filled with well-ordered polypeptide chains. In the example given above, the polybutadiene chains are amorphous random coils, whereas the polypeptide chains are in α-helical conformations and are hexagonally packed in the solid state. The potential to alter block copolymer morphology through the tunable conformational behavior of the polypeptide segments is an area that shows great promise. Biological interest in these materials arises from the possibility of model membrane preparation where the copolymer can act as an "amphipathic integral protein"[1b] mimic after transformation of the polypeptide domains into hydrophilic segments by deprotection of the side chain ester groups.[1b] Such simple mimics can be useful in studies of protein−lipid bilayer interactions.

Side reactions that occur during formation of the polypeptide segments have been a major limitation in the synthesis of block copolymers containing polypeptide domains. The presence of significant chain termination and transfer reactions in amine-initiated amino acid−NCA polymerizations yields block copolymers containing significant homopolypeptide and oligopeptide contamination.[2] Pure block copolymer can thus only be obtained after time-consuming fractionation and extraction steps that significantly decrease yields.[1c,3] These side reactions also make it difficult to accurately control block copolymer composition. To eliminate chain-breaking reactions in the NCA polymerizations, we utilized transition-metal initiators developed in our group.[4] We have shown that amido−amidate nickelacycles are the active intermediates in the controlled polymerization of NCAs and that these initiating centers can be placed on the ends of polymer chains bearing amino end groups.[4] Generation of these initiating species from zerovalent nickel precursors permits growth of polypeptides with defined molecular weights and narrow molecular weight distributions onto existing polymer segments to generate block copolymers.

Over the past several years there has been an increasing interest in the synthesis of polymers with low glass transition temperatures and reactive functional groups at both chain ends (e.g., telechelic polydienes). They have found use as agents capable of modifying the thermal and mechanical properties of condensation polymers, in the formation of polymeric networks, and as components in the synthesis of block copolymers.[1d,5] Telechelic polydienes can be synthesized via radical or anionic polymerization, with molecular weights and functionalities being controlled by the initiator and/or chain transfer agent.[5−10] However, the average number of functional groups per polymer chain (F_n) can be much less than two and depends strongly on experimental conditions, which are often demanding. Furthermore, varying amounts of 1,2-linkages are introduced during the polymerization of butadiene, limiting the elastomeric potential of the resulting polymers.[5]

Recent advances in acyclic diene metathesis (ADMET) polymerization,[11,12] ring-opening metathesis polymerization (ROMP),[5,13−17] and metathesis depolymerization[18−20] in the presence of a chain transfer agent have greatly simplified the preparation of telechelic polymers. For example, ROMP of 1,5-cyclooctadiene in the presence of a chain transfer agent provides a route for the preparation of telechelic polybutadienes with 100% 1,4-microstructure.[5,13] Preliminary results published by Wagener[12b] also show that there is potential for the modification of the unsaturated copolymers synthesized by ADMET chemistry. The olefinic groups can be cross-linked either thermally or photochemically. They can also be quantitatively modified by epoxidation followed

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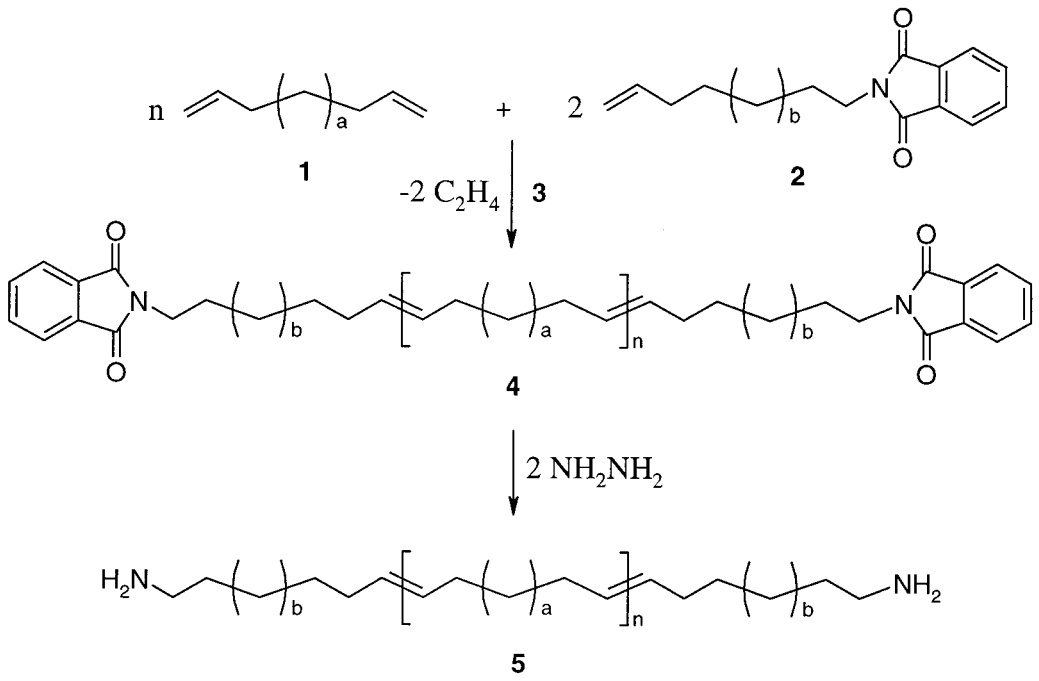
Scheme 1. Synthesis of Telechelic Polyoctenamer Oligomers Using ADMET Chemistry; *a* = 4, *b* = 5, 3 = $RuCl_2(=CHPh)(PCy_3)_2$



by subsequent conversion of the epoxides to chlorohydrin groups.[12b] Overall, a range of functionalized and telechelic and chemically modified polymers can be prepared by these methods.

This report describes the synthesis and characterization of new telechelic polyoctenamers prepared by ADMET polymerization using Grubbs' catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**3**).[21] These polymers were end-capped using a phthalimide functionalized chain transfer agent.[5] Deprotection of the resulting α,ω-phthalimide end-functionalized polymers leads to amino-terminated telechelic polyoctenamers (**5**) (Scheme 1). These telechelic polyoctenamers were subsequently converted for use as difunctional macroinitiators (**12**) for the living polymerization of Glu−NCA to form novel triblock copolymers (Scheme 2).[4] These unsaturated triblock copolymers (**13**) were fully hydrogenated using Wilkinson's catalyst[22] to yield triblock copolymers with perfectly linear polyethylene segments (**14**). The triblock architecture of the copolymers was confirmed by selective degradation of the polyoctenamer domains.

Experimental Section

Instrumentation. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer using NaCl plates. GPC data were obtained using an SSI Acuflow series II pump equipped with a SSI refractive index detector. HPLC-grade THF was used as mobile phase, and a column bank consisting of four Phenomenex columns (10^5, 10^4, 10^3, and 500 Å) was used as the stationary phase. A constant flow rate of 1 mL/min was maintained, and the instrument was calibrated using polystyrene standards. Tandem gel permeation chromatography/light scattering (GPC/LS) was performed on an SSI Acuflow series III liquid chromatography pump equipped with a Wyatt DAWN DSP light scattering detector and Wyatt Optilab DSP. Separations were effected by 10^5, 10^4, 10^3, and 500 Å Phenomenex 5μ columns using 0.1 M LiBr in DMF eluent at 60 °C. NMR spectra were measured on Bruker AVANCE 200 MHz spectrometer using chloroform-*d* as solvent, with 0.5% v/v TMS added as an internal reference. Differential scanning calorimetry (DSC) analyses were performed on a TA Instruments DSC 2920 differential scanning calorimeter. DSC samples were analyzed over the temperature range 0−140 °C with a scan rate of 10 °C/min. C, H, and N elemental analyses were performed by the Marine Science Institute Analytical Laboratory of the University of California, Santa Barbara, using a Control Equipment Corp. 440 elemental analyzer. The secondary structure of the PBLG domains in copolymer **13** was analyzed in THF using an Olis RSM spectrometer circular dichroism spectrometer.

Materials. Chemicals were obtained from commercial suppliers and used without purification unless otherwise stated. $RuCl_2(=CHPh)(PCy_3)_2$ (**3**) was obtained commercially (from Strem) and used without purification under dry nitrogen atmosphere. 1,9-Decadiene (**1**) (from Aldrich) was fractionally distilled from CaH_2, degassed under high vacuum by several freeze−thaw cycles, and vacuum-transferred successively into sodium-mirrored flasks until no reaction was observed. Alloc-L-amino acid amides[23] and Glu−NCA[24] were prepared according to literature procedures. Hexanes, THF, and THF-d_8 were purified by first purging with dry nitrogen, followed by passage through columns of activated alumina.[25] DMF, DMF-d_7, and chloroform (from Aldrich) were purified by drying over 4 Å molecular sieves and then degassed by three freeze−pump−thaw cycles before being transferred into the drybox. 11-Phthalimido-1-undecene (**2**) was synthesized according to a modified literature procedure.[26]

Synthesis of 11-Phthalimido-1-undecene (2).[26] Potassium phthalimide (15 g, 18 mmol) was added to a solution of 11-bromo-1-undecene (17.68 g, 75.8 mmol) in 100 mL of dimethylformamide. Stirring was continued for 24 h. After the addition of 120 mL of chloroform, the reaction mixture was poured into 300 mL of water. The aqueous phase was separated and extracted with two 30 mL portions of chloroform. The combined chloroform extracts were washed with 60 mL of 0.2 N sodium hydroxide (to remove unreacted phthalimide) and 60 mL of water. After drying over sodium sulfate the chloroform was removed to give the crude product (20 g, 88%); mp = 40−41.5 °C. Elemental analysis calculated for $C_{19}H_{25}NO_2$ (%): 76.22 C, 8.42 H, 4.68 N. Found: 75.97 C, 8.38 H, 4.69 N. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 7.89−7.70 (4H), 5.81 (CH_2=C*H*−, 1H), 4.94 (C*H*$_2$=CH−, 2H), 3.68 (−C*H*$_2$−N, 2H), 2.04 (2H), 1.32 (12H). ^{13}C NMR ($CDCl_3$): δ ppm 168.39 (−*C*=O), 139.15 (CH_2=*C*H−), 138.15, 133.78, 132.32, 123.15, 114.15 (*C*H$_2$=CH−), 38.09 (−*C*H$_2$−N), 33.86, 29.49, 29.45, 29.23, 29.14, 29.0, 28.66,

Scheme 2. Synthesis of 13 and 14; R′ = −$CH_2CH(CH_3)_2$, R = −$CH_2CH_2CO_2CH_2C_6H_5$, *a* = 4, *b* = 5, depe = 1,2-Bis(diethylphosphino)ethane, COD = 1,5-Cyclooctadiene, HOSu = *N*-Hydroxysuccinimide

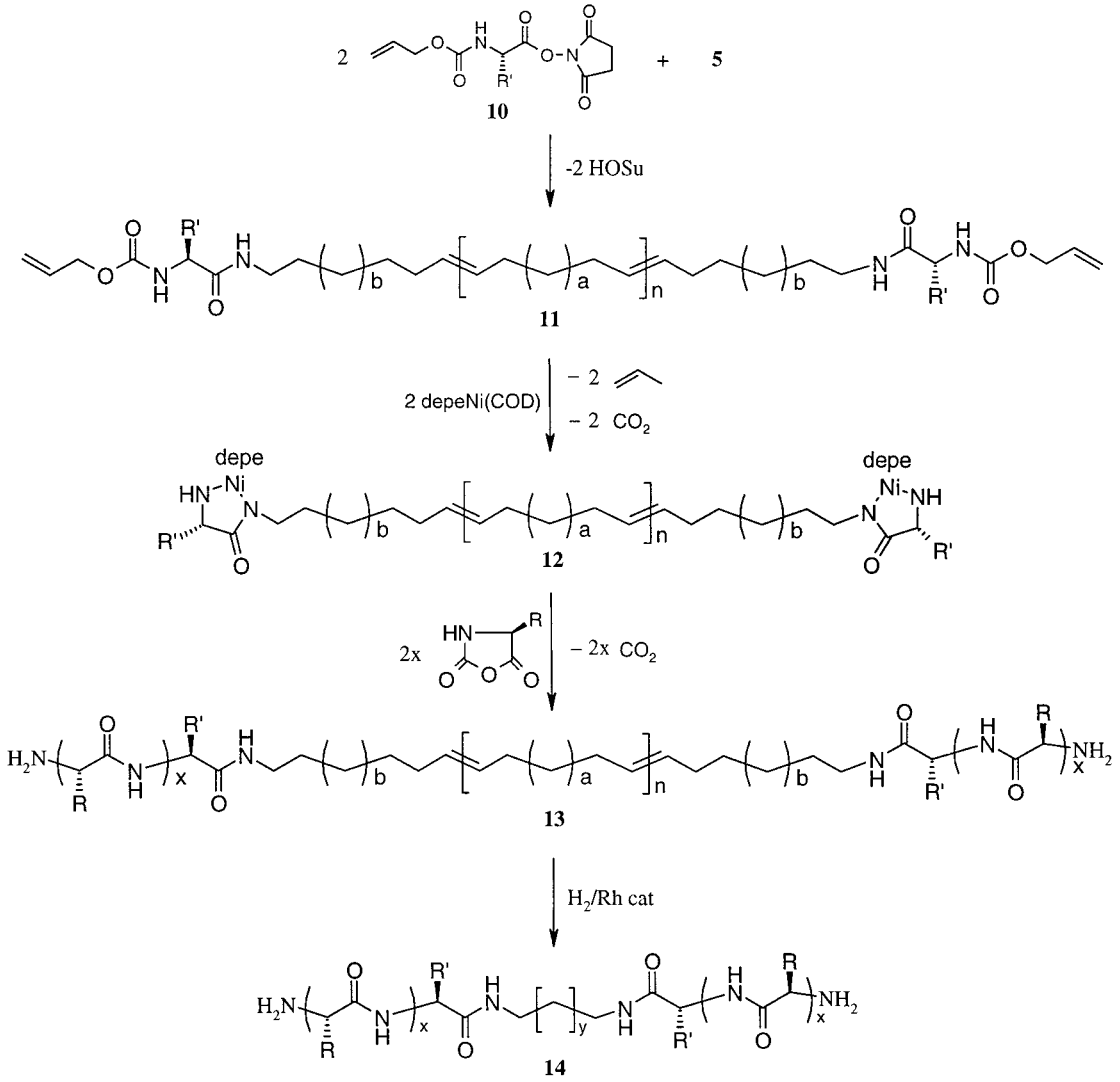


Table 1. Molecular Weights (M_n) of Polymers 4 and 5 Prepared by ADMET Polymerization

4					5				
M_n[a] (calcd)	M_n[b] (NMR)	M_n[c] (GPC)	M_w/M_n	conv (%)[d]	M_n[b] (NMR)	M_n[c] (GPC)	M_w/M_n	yield (%)[e]	F_n[f]
2100	2100	2500	2.0	97	1700	3300	2.0	85	2.05
2900	3200	3100	1.5	97	3100	3700	2.3	83	1.98
6600	7000	8100	1.9	97	10000	7600	2.0	86	2.01
11100	12500	18200	1.8	98	11800	18400	2.0	86	1.96

[a] Calculated from the initial ratio of monomer (**1**) to chain transfer agent (**2**) assuming $F_n = 2.0$. [b] Measured from ^{1}H NMR integrations assuming $F_n = 2.0$. [c] Measured by GPC (THF) calibrated using polystyrene standards. [d] Determined by ^{1}H NMR. [e] Total isolated yield. [f] Titration with HCl/THF standard solution.

27.02. IR (NaCl, THF, cm^{-1}): 3566.1, 2931.6, 2681.5, 2361.2, 1961.2, 1966.6, 1773.4, 1715.9, 1639.3, 1460.8, 1395.9, 1364.5, 1334.3, 1289.2, 1186.9, 1073.2, 908.9, 722.3, 657.3.

Metathesis of 2. In an nitrogen-purged drybox, a round-bottom flask (20 mL) equipped with a high-vacuum Teflon valve and magnetic stirring bar was charged with **2** (0.1 g, 0.33 mmol) and chloroform (2 mL) followed by addition of **3** (**2** to **3** ratio = 250:1). The reaction mixture was stirred at 43 °C and after 24 h was quenched by exposure to air. The product was stirred with silica and filtered to remove catalyst residue, and the solvent was removed under reduced pressure. Yield of metathesis was calculated to be ~85% from integration of the ^{1}H NMR spectrum of the reaction mixture. The integral ratio for signals at 5.4 ppm [−C*H*═C*H*−, 2H] [$I_{5.4}$] and at 4.9 ppm [CH_2═, 2H] [$I_{4.9}$] was found to be [$I_{5.4}$]:[$I_{4.9}$] = 70.4:1. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 7.89−7.30 (8H), 5.40 (−C*H*═C*H*−, 2H), 3.68 (4H) (−CH_2−N), 2.01 (4H), 1.67 (4H), 1.27 (24H). ^{13}C NMR ($CDCl_3$): δ ppm 168.43 (−*C*═O), 133.79, 132.32, 130.35 (−*C*H═*C*H−, trans), 129.88 (−*C*H═*C*H−, cis), 123.15, 38.09 (−*C*H_2−N), 33.86, 29.49, 29.45, 29.23, 29.14, 29.0, 28.66, 27.02. IR (NaCl, THF, cm^{-1}): 3502.0, 2931.7, 2681.5, 1943.1, 1772.9, 1714.0, 1653.6, 1447.5, 1396.0, 1365.2, 1289.6, 1187.3, 1067.2, 911.0, 722.3.

Synthesis of Bis(11-phthalimidoundecenyl) Polyoctenamer (4) (Table 1**).** 1,9-Decadiene (**1**) (3.0 g, 21.7 mmol) and **2** (0.91 g, 3.0 mmol) were transferred under nitrogen to a 50 mL round-bottom flask. **3** (0.06 g, 73 μmol) was then added, and after 2 h at room temperature, the reaction became viscous. After 24 h at 43 °C, the reaction was quenched by addition of ethyl vinyl ether. The product was dissolved in toluene and stirred with silica and filtered to remove catalyst residue. The

polymer was isolated by precipitation into methanol (2.9 g, 90%). The molecular weight of the product ($M_n \sim 2100$) was calculated from integration of resonances in the ^{1}H NMR spectrum of the polymer. The observed integral ratio for signals at 5.4 ppm (−C*H*=C*H*−, 2H) [$I_{5.4}$] and at 7.9−7.7 ppm (2 C_6H_4, 8H) [$I_{7.7-7.9}$] was found to be [$I_{5.4}$]:[$I_{7.7-7.9}$] = 4.65:1. These results compared well to the theoretical molecular weight ($M_n^{th} \sim 2100$, calculated from the ratio of **1** to **2**). From elemental analysis, the polymer was found to contain 1.38% nitrogen, giving $M_n \sim 2000$ by end group calculation. GPC (THF) gave $M_n = 2500$ and $M_w/M_n = 2.0$. MALDI-TOF MS: $M_n \sim 1500$. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 7.9−7.7 (8H), 5.40 (−C*H*=C*H*−, 2H), 3.68 (−CH_2−N, 4H), 1.98 (4H), 1.65 (8H), 1.3 (8H). ^{13}C NMR ($CDCl_3$): δ ppm 168.43 (−*C*=O), 133.8, 132.2, 130.3 (−*C*H=*C*H−, trans), 129.9 (−*C*H=*C*H−, cis), 123.1, 38.1 (−*C*H_2−N), 32.6, 32.2, 29.8, 29.6, 29.5, 29.2, 29.05, 28.77, 28.60, 27.2, 26.88. IR (NaCl, THF, cm^{-1}): 3566.1, 2955.8, 2855.6, 2677.8, 1966.7, 1772.7, 1716.7, 1653.6, 1461.1, 1361.1, 1288.9, 1183.3, 1066.7, 911.1, 655.6.

Deprotection of 4 Using Hydrazine. 4 (2.5 g, 1.2 mmol), 15 mL of THF, and 0.5 mL of methanol were introduced into a 50 mL three-neck flask connected to a reflux condenser and $CaCl_2$ drying tube. Anhydrous hydrazine (0.5 g, 16 mmol) was introduced into the flask under nitrogen. The reaction mixture was kept at 43 °C for 24 h. The polymer was precipitated into methanol (200 mL). The separated polymer was collected by filtration and washed with methanol (20 mL). After drying in vacuo, the amine functionalized polymer (**5**) was recovered (1.9 g, 85%, Table 1). The molecular weight of **5** ($M_n = 1700$) was calculated from integration of ^{1}H NMR resonances. The integral ratio for signals at 5.4 ppm (−CH=CH−, 2H) [$I_{5.4}$] and at 2.67 ppm (−CH_2−N, 4H) [$I_{2.67}$] was found to be [$I_{5.4}$]:[$I_{2.67}$] = 7.8:1. GPC (THF) gave $M_n = 3300$ and $M_w/M_n = 2.0$. From elemental analysis the polymer was found to contain 1.43% of nitrogen, giving $M_n = 2000$ by end group calculation. Titration of the amino end groups gave the functionality per chain: $F_n = 2.05$. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 5.40 (−C*H*=C*H*−, 2H), 2.67 (−CH_2−N, 4H), 1.96 (4H), 1.62 (8H), 1.28 (8H). The amino end group protons (−NH_2) were not observable since they were under the large signal for aliphatic protons at 1.28 ppm.[10] ^{13}C NMR ($CDCl_3$): δ ppm 130.35 (−*C*H=*C*H−, trans, ∼81%), 129.9 (−*C*H=*C*H−, cis, ∼19%), 42.14 (−*C*H_2−N), 32.61, 29.93, 29.76, 29.65, 29.5, 29.32, 29.19, 29.05, 28.85, 28.71, 27.23. IR (NaCl, THF, cm^{-1}): 3577.8, 2955.6, 2677.8, 2355.8, 1966.7, 1461.1, 1361.1, 1288.9, 1255.8, 1177.8, 1066.7, 966.7, 911.1, 811.1, 716.7, 655.6.

Amino End Group Titrations. A HCl standard solution in THF was first prepared and standardized as follows. 5 mL of concentrated aqueous HCl was mixed with 50 mL of THF. Allylamine (0.23 g, 4.0 mmol) was weighed, dissolved in 10 mL of THF, and then titrated using the HCl solution. A Corning pH meter model 320 was employed to record the pH vs volume titration curves. Three repeated titrations gave an average concentration of the HCl solution of 0.873 ± 0.001 M. The polymers were each dissolved in 10 mL of THF and titrated with the HCl standard solution. Duplicate titrations were carried out for each sample.

Synthesis of Alloc-L-leucine (8).[23] L-Leucine (**7**) (20 g, 150 mmol) was suspended in distilled water (100 mL) and then completely dissolved by addition of 4 N NaOH (38 mL, 150 mmol). The solution was cooled in an ice−water bath while allyl chloroformate (Alloc-Cl, **6**) (22.5 g, 167 mmol) was added to the vigorously stirred solution concurrently with additional 4 N NaOH (40 mL, 170 mmol) in five small portions to maintain the alkalinity of the reaction mixture at about pH = 9. **6** and NaOH were added over a period of 1 h. Some heat was evolved during the reaction and external cooling with ice−water was necessary to keep the temperature of the reaction mixture at about 25 °C. The reaction mixture was stored in the refrigerator overnight. The solution was then acidified to pH = 2−3 with concentrated hydrochloric acid. The product was extracted three times with ethyl acetate (100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the product (26 g, 80%). The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 6.0 (−N*H*, 1H), 5.90 (−C*H*=CH_2, 1H), 5.25 (−CH=CH_2, 2H), 4.57 (−O−CH_2−, 2H), 1.74 (2H), 0.95 [−(CH_3)$_2$, 6H]. ^{13}C NMR ($CDCl_3$): δ ppm 178.69 (−*C*=O), 156.68 (−*C*OOH), 133.04 (−*C*H=CH_2), 118.43 (−CH=*C*H_2), 77.56 (−*C*H_2−O), 52.87, 41.96, 25.29, 23.36, 22.19. IR (NaCl, THF, cm^{-1}): 3275.3 (ν NH), 2955.6, 1725.8 (ν, CO), 1650.0, 1538.0, 1455.96, 1366.9, 1327.8, 1259.1, 1056.7, 912.0, 778.8, 655.6.

Synthesis of Alloc-L-leucine−*N*-Hydroxysuccinimidyl Ester (10).[23] **8** (26 g, 120 mmol) was added to 25 mL of dry THF, and *N*-hydroxysuccinimide (**9**) (13.8 g, 120 mmol) was then added to the reaction mixture. The solution was cooled in an ice−water bath, and *N*,*N*′-dicyclohexylcarbodiimide (DCC) was added (24.7 g, 120 mmol as a solution in 20 mL of THF) to the vigorously stirred reaction mixture. A white precipitate was observed to form. The flask was stored in the refrigerater overnight. After filtration, the THF was distilled off on a rotary evaporator, and the product was three times extracted with ethyl acetate (150 mL), washed with $NaHCO_3$, H_2O, and NaCl/H_2O, and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to give the product (28.5 g, 94%). The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 6.0 (−N*H*−, 1H), 5.9 (−C*H*=CH_2, 1H), 5.25 (−CH=CH_2, 2H), 4.54 (−OCH_2−, 2H), 2.78 (4H), 1.77 (3H), 0.94 (−(CH_3)$_2$, 6H). ^{13}C NMR ($CDCl_3$): 168.31 (−*C*=O), 133.04 (−*C*H=CH_2), 118.47 (−CH=*C*H_2), 67.01 (−*C*H_2−O−), 52.88, 41.97, 25.98, 25.06, 23.18, 21.10 (−*C*H_3). IR (NaCl, THF, cm^{-1}): 3275.3 (ν NH), 2981.7, 2360.3, 1967.1, 1815.9, 1785.2, 1740.1 (ν CO), 1653.5, 1540.5, 1458.0, 1363.2, 1203.6, 1083.7, 912.9, 647.7.

Synthesis of Bisalloc-L-leucine-Terminated Polyoctenamer (11) (Scheme 2). 5 (0.80 g, 0.40 mmol) was added to a solution of **10** (0.25 g, 0.80 mol) in THF (2.5 mL). The reaction mixture was stirred for 1 h at room temperature, after which the resulting precipitate was removed by filtration and the solution was diluted with ethyl acetate (10 mL). This solution was sequentially washed with dilute aqueous HCl (3 mL), saturated $NaHCO_3$ (3 mL), and then saturated aqueous NaCl (3 mL) followed by drying over $MgSO_4$. The solvent was then evaporated under reduced pressure to give the product (0.74 g, 80%). The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 6.0 (−N*H*−, 1H), 5.90 (CH_2=C*H*−, 2H), 5.38 (−C*H*=C*H*−, POCT, 2H), 5.25 (CH_2=CH−, 4H), 4.54 (−CH_2−O−, 4H), 1.96 (4H), 1.29 (8H), 0.95 (−CH_3, 6H). ^{13}C NMR: δ ppm 168.3 (−*C*=O), 133.0 (CH_2=*C*H−), 130.33 (−*C*H=*C*H-, trans), 129.89 (−*C*H=*C*H-, cis), 118.11 (*C*H_2=CH−), 32.61, 29.65, 29.05, 27.24. IR (NaCl, THF, cm^{-1}): 3567.9, 3284.7 (ν NH), 2851.3, 2681.2, 1967.0, 1786.8, 1745.4, 1725.4 (ν, CO), 1459.1, 1364.2, 1289.0, 1182.2, 1070.0, 966.6, 911.6, 657.7.

Synthesis of (depe)NiNHCH(R′)C(O)N(CH_2)$_9$−[CH=CH(CH_2)$_6$]$_n$−(CH_2)$_9$NC(O)−CH(R′)NHNi(depe) (12) (Scheme 2); R′ = −$CH_2CH(CH_3)_2$. 1,2-Bis(diethylphosphino)ethane (depe) (17 μL, 0.073 mmol) in 0.5 mL of THF was added to a solution of Ni(COD)$_2$ (20 mg, 0.073 mmol) in THF (0.5 mL) and let stand at room temperature for 10 min, after which a solution of (depe)Ni(COD) had formed. **11** (87.4 mg, 36.5 μmol) in THF (1 mL) was then added to the yellow solution, which subsequently became orange-yellow. The solution was heated at 80 °C for 24 h to yield the product as an orange solution in THF. A ^{1}H NMR spectrum could not be obtained in THF-d_6, most likely because of paramagnetism of the metal centers (only broad lines for the polyoctenamer repeat were observed).[4]

Synthesis of Triblock Copolymers (13). In the drybox, γ-benzyl-L-glutamic acid−NCA (1.0 g, 3.4 mmol) was dissolved in DMF (22 mL) and placed in a 50 mL reaction tube which could be sealed with a Teflon stopcock. An aliquot of macroinitiator **12** (1.8 mL of a 36.5 mM solution in THF, 0.066 mmol) was added via a syringe to the flask, forming a cloudy suspension. A stir bar was added, and the flask was sealed, removed from a drybox, and stirred at 25 °C for 48 h. Precipitation was observed since the polyoctenamer component

Table 2. Synthesis of Copolymers 13 Using Macroinitiator 12 and Their Thermal Properties (T_m) As Examined by DSC

solvent	Glu−NCA:**12**	M_n[a] (calcd)	M_n[b] (GPC)	PDI (M_w/M_n)	yield (%)	T_m (°C)	ΔH (J/g)
DMF	21	4500	3500	1.9	86	52.1	7.07
THF	42	9100	46000	2.3	86	50.2	8.61
DMF	42	9100	7400	1.1	81	48.6	5.61
DMF	52	11200	11900, 12600[c]	1.1, 1.7	90	47.4	3.97

[a] Calculated from the initial ratio of Glu−NCA:**12** assuming $F_n = 2.0$. [b] Determined by GPC (0.1 M LiBr in DMF). [c] Determined by GPC (THF).

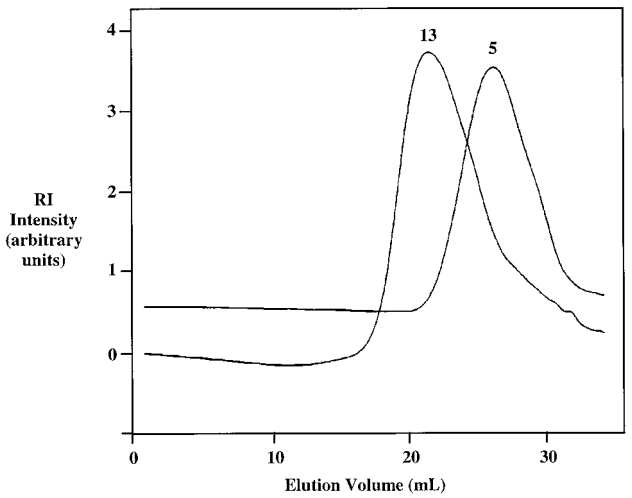


Figure 1. GPC chromatograms of **13** (M_n = 12 600 and PDI (M_w/M_n) = 1.7) and **5** (M_n = 3300 and PDI = 2.0).

of **12** is insoluble in DMF. After a few hours the reaction mixture clarified since the poly(γ-benzyl-L-glutamate) (PBLG) blocks that formed solublized the copolymer. Polymer was isolated by addition of the reaction mixture to methanol containing HCl (1 mM), causing precipitation. The polymer was then dissolved in DMF and passed through a 0.2 μm syringe filter to ensure complete removal of any unreacted insoluble **12**. The product was precipitated into methanol and dried under vacuum to give a white solid (0.804 g, 90%, Table 2). GPC (THF): M_n = 12 600 and M_w/M_n = 1.7. GPC (DMF): M_n = 11 900 and M_w/M_n = 1.12. DSC: T_m = 47.4 °C (ΔH = 3.97 J/g). The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ ppm 8.01 (−N*H*−, PBLG), 7.27 (−C_6H_5, PBLG), 5.055 (PBLG), 4.0 (PBLG), 1.99 (POCT), 1.29 (POCT). ^{13}C NMR ($CDCl_3$): δ ppm 175.40 (−C═O, PBLG), 136.06, 130.33 (−*C*H═*C*H−, trans, POCT), 129.89 (−*C*H═*C*H−, cis, POCT), 128.49 (C_6H_5, PBLG), 66.16 (−*C*H_2−NH−, POCT), 36.48, 32.60, 31.45, 29.64, 29.04, 27.21.

Degradation of the Polyoctenamer Block in 13. A sample of block copolymer **13** (0.6 g, M_n = 11 900 and M_w/M_n = 1.1) was transferred into a flask containing 50 mL of THF and 10 mL of H_2O_2 (35 wt % solution in water). An aliquot (1 mL) of a 3.0 mM osmium tetroxide solution in THF was then added, and the reaction mixture was heated under reflux for 8 h. After cooling to 25 °C, the solution was slowly poured into 300 mL of methanol while stirring. The resulting PBLG was filtered, washed with methanol, and dried at 40 °C in vacuo. GPC (DMF): M_n = 6600 and M_w/M_n = 1.2.

Hydrogenation of 13. A sample of **13** (0.15 g, M_n = 11 900 and M_w/M_n = 1.1) (Table 2) was combined with Wilkinson's reagent [$(Ph_3P)_3RhCl/Ph_3P$ (1/1 wt/wt, 16 mg)] and 8 mL of dry, degassed THF under N_2 in a pressure bomb.[22] The contents were exposed to 100 psi of H_2 at 100 °C with vigorous stirring. After 48 h, the reaction was quenched by release of pressure. A white solid polymer was obtained after precipitation into 2-propanol (0.12 g, 80%). GPC (THF): M_n = 17 000 and M_w/M_n = 1.7. DSC: T_m = 123.80 °C (ΔH = 13.50 J/g). The following spectral properties were observed: ^{1}H NMR (THF-d_8): δ ppm 8.01 (−N*H*−, PBLG), 7.24 (−C_6H_5, PBLG), 5.035 (PBLG), 4.0 (PBLG), 3.57, 2.51 (PBLG), 1.72 (−CH_2−, PE). ^{13}C NMR ($CDCl_3$): δ ppm 173.16 (−*C*═O, PBLG), 138.05, 128.49 (−C_6H_5, PBLG), 67.36, 26.77, 26.31, 26.08, 25.70, 25.28, 25.33, 24.48.

Results and Discussion

Synthesis of α,ω-Bisamino-Terminated Polyoctenamer (5). Since ADMET polymerization is an equilibrium step growth reaction,[27] monofunctional reagents can be used to cap reactive chain-end functional groups and, hence, limit the molecular weight.[11,12a] (Scheme 1). This property can be exploited to specifically place functionalized monoolefins at polyoctenamer chain ends, which results in the preparation of telechelic polyoctenamers with a functionality near two. Here we report the synthesis of α,ω-bisphthalimide-terminated telechelic polyoctenamer oligomers using catalyst **3** ($RuCl_2$-(═CHPh)$(PCy_3)_2$).[21] **3** was obtained commercially and used without purification under dry nitrogen atmosphere. 11-Phthalimido-1-undecene (**2**) was synthesized according to a modified literature procedure[26] and used as the chain transfer agent. The reactivity of this reagent was verified by observation that it dimerized readily under typical ADMET conditions in the presence of catalyst **3**.

Bis(11-phthalimidoundecenyl)-capped polyoctenamers (**4**) were thus prepared using agent **2** and monomer **1** and isolated in yields of 80−90% (Table 1). When the chain limiter was added to the reaction mixture, the molecular weight of **4** decreased proportionally with increasing ratios of **2** to **1**. The measured number-average molecular weights of the polyoctenamers were found equal to calculated values within the limits of experimental error. Some discrepancies between NMR and GPC determined molecular weights may be due to associations of the functional polymer chain ends during GPC or broadening of the end group resonances in the NMR experiments. Incorporation of phthalimide end groups into the polymer was demonstrated by the appearance of resonances from the phthalimide protons at 7.8−7.7 ppm in the ^{1}H NMR spectra of the oligomers. NMR spectroscopy showed these polymers to be at least 98% difunctionally capped with phthalimide, with the remaining 2% of chain ends bearing vinyl groups. The cis and trans internal olefinic carbons were easily distinguished by ^{13}C NMR spectroscopy since the trans olefinic carbons appear at 130.3 and cis appear at 129.9 ppm.[12,28] The telechelic oligomers were found to be of approximately ~80% trans stereochemistry.

The phthalimide groups on **4** (Table 1) were removed with excess hydrazine to give the corresponding α,ω-bisamino-functionalized oligomers **5** (Scheme 1). In the ^{1}H NMR spectra of the deprotonated polymers the signals of the phthalimide protons at 7.8−7.7 ppm were absent, and the protons on the methylene group adjacent to the phthalimide at 3.68 ppm were replaced by the −CH_2NH_2 protons at 2.68 ppm.[10] In the ^{13}C NMR spectra the signals of the phthalimide carbons at 168.43 (−*C*═O), 133.8, 132.2, 123.1, and 38.1 (−*C*H_2−N) were replaced by the −*C*H_2NH_2 signals at 42.14 ppm after

deprotection. The efficiency of deprotection as determined by ^{1}H NMR spectroscopy was >95%. A F_n near two for the lower molecular weight materials was supported by ^{1}H and ^{13}C NMR analysis as well as titration with an HCl/THF standard solution. A small decrease in number-average molecular weights after deprotection was also observed.

Synthesis of Triblock Copolymers 13. The most widely used method to prepare **A**−**B**−**A** type block copolymers containing polypeptide segments as the **A** domains and non-peptide polymers as the **B** domains is by polymerization of NCAs at the terminal amino ends of α,ω-bisamino-functionalized telechelic polymers.[2] In these systems, mixtures of copolymers and homopolymers were obtained, and removal of the homopolymers by extraction and fractionation was found to be necessary.[3] In general, NCA polymerizations employing amines as initiators are plagued by chain-breaking transfer and termination reactions that restrict control over molecular weight and chain architecture.[2] To eliminate these problems in polypeptide formation, our group has developed transition-metal initiators that allow the living polymerization of NCAs.[4] Here, we used this chemistry to grow polypeptide segments off of α,ω-bisamino-functionalized polyoctenamers to give triblock copolymers **13** and **14** (Scheme 2).

Molecular weight measurements confirmed the formation of the triblock copolymers. The number-average molecular weight (M_n) of macromonomer **5** was 3300 ($M_w/M_n = 2.0$). The number-average molecular weight (M_n) of a sample of **13** was determined by GPC to be 12 600 and $M_w/M_n = 1.7$. The GPC curves for these triblock polymers (Table 2) were unimodal, with no detectable residual polyoctenamer homopolymers. Since GPC and ^{1}H NMR spectroscopy do not allow discrimination between diblock and triblock copolymers of identical M_n, a characterization method based on the cleavage of the polyoctenamer segments was used to determine block architecture.[29] Selective polyoctenamer degradation of a sample of **13** ($M_n = 11\,200$ and $M_w/M_n = 1.12$) with OsO_4/H_2O_2 gave PBLG with $M_n = 6600$ and $M_w/M_n = 1.2$, as expected for a triblock sequence with two short PBLG segments as opposed to a single long PBLG segment in a diblock chain. No polyoctenamer was observed in the ^{1}H NMR spectra of these degraded samples, indicating that the degradation was complete.

The thermal properties of these new triblock copolymers were also analyzed using differential scanning calorimetry (DSC). The T_m of the polyoctenamer segments appeared at 48.6 °C, ($\Delta H = 5.61$ J/g). The melting points of these domains depend on the length of PBLG segments and decrease with increasing size of PBLG domains (Table 2). The conformations of the polypeptide domains of the triblock copolymers were analyzed using circular dichroism spectroscopy. The block copolymer **13** in THF gave a CD spectrum with minima at 210 and 222 nm, characteristic of the α-helical conformation for the PBLG segments.[1a]

Hydrogenation of 13 (Table 1). Perfectly linear polyethylene with no detectable branching has been prepared by the ADMET technique.[30] Hydrogenation raises the crystalline melting point of unsaturated polyoctenamer from about 67 to 134 °C for the resulting linear polyethylene.[31] After hydrogenation of **13** for 48 h at 100 °C, a polymer was isolated by filtration and precipitation into 2-propanol (Scheme 2). The white solid product (**14**) was very soluble in THF. GPC analysis of **14** gave $M_n = 17\,000$ and $M_w/M_n = 1.7$, and these values were similar to those obtained before hydrogenation ($M_n = 12\,600$ and $M_w/M_n = 1.7$). The thermal properties of **14** were analyzed using DSC. The T_m of the polyethylene segments appeared at 123.8 °C ($\Delta H = 13.5$ J/g). The ^{1}H and ^{13}C NMR spectra of the hydrogenated copolymers provided spectroscopic evidence that complete hydrogenation of unsaturated polyoctenamer was achieved. Multiple peaks at 5.4 ppm in the unsaturated precursor that correspond to the protons on the internal double bond were not observed in **14**, indicating complete removal of the unsaturation. The positions of PBLG resonances were unchanged during conversion of the **13** to **14**, and hydrogenation of PBLG segments was not observed, as expected.[32]

Conclusions

Our results demonstrate that amido−amidate nickelacycle end groups can be incorporated onto amine-terminated polymers, and the resulting complexes can be used as macroinitiators for addition of polypeptide segments. These methods allow the controlled preparation of polypeptide-*b*-(non-peptide polymer) block architectures with superior control over polypeptide chain length and without formation of homopolypeptide contaminants.

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