Articles

Hydrophilic Aliphatic Polyesters: Design, Synthesis, and Ring-Opening Polymerization of Functional Cyclic Esters

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ABSTRACT: The synthesis and homo- and copolymerization of new cyclic esters containing protected functional groups (hydroxyl, bishydroxyl, amino, and carboxyl) are described. Each of the ϵ-caprolactone derivatives was generated by the Baeyer−Villiger oxidation of the corresponding cyclohexanone derivative. Monoprotection of 1,4-cyclohexanediol by benzylation or esterification was accomplished in moderate yields by reaction of benzyl bromide or 2,2′-bis(phenyldioxymethyl)propionyl chloride. Each could be oxidized with pyridinium chlorochromate to yield the respective protected hydroxyl and bis(hydroxyl) functional cyclohexanones. The benzyl ether and benzyl ester protecting groups are readily removed by catalytic hydrogenolysis using Pd/C. Alternatively, ethyl-4-ketocyclohexylcarboxylate was hydrolyzed, and the free carboxylic acid was reesterified to the benzyl or *tert*-butyl 4-ketocyclohexylcarboxylate by esterification with either benzyl bromide or *tert*-butyl alcohol. These protecting groups were chosen because they are readily cleaved to the respective carboxylic acids under mild conditions. The aza-cyclohexanone derivative was produced from the commercially available ethylene ketal of 4-piperidone by acetylation with trifluoroacetic anhydride followed by transketalization using *p*-toluenesulfonic acid in excess acetone. The trifluoroacetyl protecting group is easily removed by $NaBH_4$ reduction. Polymerization of the new monomers was accomplished either in bulk (110 °C) initiated from benzyl 2,2′-bis(hydroxymethyl)-propionate in the presence of stanneous 2-ethyl hexanoate ($Sn(Oct)_2$) or from $Al(O^iPr)_3$ in toluene (0 °C), yielding polymers close to their targeted molecular weights (5000−15 000) with modestly narrow polydispersities (1.20−1.35). Removal of the protecting groups on the aliphatic polyesters yielded the functionalized polymers.

Introduction

The past two decades have seen increasing attention paid to synthetic polyesters for biomedical applications including surgery and medicine.[1] Many of these polymers are readily hydrolyzed to their constituent α-hydroxy acids which are eliminated by general metabolic pathways.[2] However, the biodegradation rates of these polyesters are difficult to control due to their hydrophobicity and semicrystalline morphology.[3] The impetus for research in this area has focused on the need for functional polyesters. Toward this end, advances in the living ring-opening polymerization (ROP), particularly using aluminum alkoxide catalysts, have enabled the preparation of homopolymers with defined molecular weights, narrow polydispersities, functionalized end groups as well as random, block, and graft copolymers, and star structures with extremely complex molecular architectures.[4,5] Nonetheless, further advances in the field will require new functional monomers/polymers which permit subsequent transformations to allow desirable solubility/property enhancements. The availability of functional pendant groups along the polymer backbone would be a highly efficient means of tailoring the properties of polyesters including features such as hydrophilicity, biodegradation rates, bioadhesion, drug attachment, etc. More importantly, the combination of biodegradability and water solubility would significantly expand the possible applications for polymers in biomedical applications.

There are numerous reports of functional polyesters prepared from protected monomers by both condensation and ring-opening polymerization techniques.[6] In one example, Jérôme et al.[6k] used 5-ethylenedioxycaprolactone as a comonomer in the synthesis of aliphatic polyesters and subsequent deketalization and reduction of the generated ketone functionality produced a multihydroxyl functional polyester. These hydrophilic polymers can be used for applications that utilize this developed functionality including the preparation of amphiphilic block copolymers and nanoparticles. Kimura et al.[6f,i] reported the synthesis of pendant carboxyl functional polyesters through the ROP of 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione with lactide in the presence of stannous 2-ethylhexanoate ($Sn(Oct)_2$). The benzyl protecting groups were readily removed by catalytic hydrogenolysis to give the highly functionalized bioresorbable polyester. Extensive work, by Höcker et al.[7] and more recently Vandenburg et al.,[8] on functionalized polycarbonates is also noteworthy, particularly the preparation of hydroxyl functional biopolymers. Langer et al.[6j] have reported the synthesis

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of poly(lactic acid-*co*-lysine) copolymers from the protected functional monomer, 3-*N*-(benzoxycarbonyl-L-lysyl)-6-L-methyl-2,5-morpholinedione, and attached a peptide onto the pendant lysine amino group for tissue engineering applications. Recently, Russell et al.[6l] described one of the most exquisite routes to functional polyesters from divinyl adipate and various triols utilizing the intrinsic chemospecificity of an enzyme. Controlled generation of pendant hydroxyl functionality was demonstrated.

An alternative way to introduce additional functionality into polyesters and related materials is through the manipulation of the polymer architecture. For instance, graft, block, hyperbranched, dendrimeric, starburst, and dendri-graft are just a few examples of polymer architectures that lead to large numbers of chain ends.[9−11] Noteworthy examples of both hyperbranched and dendrimeric aliphatic polyesters have been reported by Hult and co-workers utilizing the self-polymerization of 2,2′-bis(hydroxymethyl)propionic acid (bis-MPA).[10g,j] The hyperbranched polyesters were prepared in the melt via an acid-catalyzed polyesterification reaction, while the dendrimers were prepared by coupling different generation dendrons to a polyfunctional core. Furthermore, the end group functionality in these materials has been shown to be accessible for subsequent polymer analogous transformations.[11] Other examples of hyperbranched and dendritic polyesters have used either poly(ϵ-caprolactone) or poly(lactides) as polymeric building blocks to high molecular weight, highly functional materials which provide properties intermediate between linear and branched macromolecules.[5]

Our interest in the synthesis of functional aliphatic polyesters has focused on two goals. First, we[12a] and others[12b] have shown that cyclic esters containing additional nucleophilic functionality, such as hydroxyl groups, will self-polymerize to form hyperbranched polyesters by living ROP in a one-step process. Second, carefully designed functional lactones allow us to impart amphiphilic character to dendrimer-like star polymers to produce biocompatible/biodegradable micelles and reverse micelles.[5] In this paper, we describe our initial results on the (i) synthesis of protected functional monomers (hydroxyl-, bishydroxyl-, amino-, and carboxyl-substituted), (ii) their subsequent polymerization using either Al(O^iPr)$_3$ or benzyl 2,2′-bis(hydroxymethyl)-propionate in the presence of Sn(Oct)$_2$ (a model initiator for the dendrimer-like star polymers), and (iii) their deprotection to yield the functional polyesters.

Experimental Section

Materials. 1,4-Cyclohexanediol, ethyl-4-hydroxycyclohexanecarboxylate, pyridinium chlorochromate (PCC), *m*-chloroperoxybenzoic acid (m-CPBA), benzyl bromide, trimethylsilyl iodide, Pd/C (10 wt %), aluminum triisopropoxide (sublimed and dissolved in dry toluene), and ϵ-caprolactone (distilled from CaH_2) were obtained from Aldrich Chemical Co. The stannous(II) 2-ethylhexanoate (Sn(Oct)$_2$ was used as obtained from Sigma. 2,2′-Bis(phenyldioxymethyl)propionic acid was synthesized by a method previously described.[5f] Polymerizations were accomplished according to literature procedures.[5]

Measurements. Size-exclusion chromatography (SEC) was carried out on a Waters chromatograph connected to a Waters 410 differential refractometer. Four 5 μm Waters columns (300 × 7.7 mm) connected in series in order of increasing pore size (100, 1000, 10^5, 10^6 Å) were used with THF as the eluant. The SEC results were calibrated with linear polystyrene standards. The thermophysical properties were recorded on a Perkin-Elmer DSC-7. ^{1}H NMR spectra were recorded in solution using a Bruker AM 250 (250 MHz) spectrometer. ^{13}C NMR spectra were recorded at 62.9 MHz on a Bruker AM 250 spectrometer with the solvent carbon signal as an internal standard. GPC analyses were performed with a Hewlett-Packard 5890 Series II gas chromatograph.

Synthesis. **4-Benzyloxycyclohexanol (2).** A suspension of NaH (20.2 g, 0.55 mol) and DMF (70 mL) was slowly added to a solution of 1,4-cyclohexanediol (58.0 g, 0.50 mol) in DMF (400 mL). The solution was stirred for 1 h and then heated to 50 °C. After 2 h the reaction mixture was cooled, and benzyl bromide (64.3 g, 37.5 mmol) was slowly added. The mixture was then refluxed for an additional 16 h before the reaction was quenched with HCl (1 M) and poured into diethyl ether in order to precipitate NaBr, which was removed by filtration. The THF and DMF were then evaporated and distilled, respectively. The remaining solid was dissolved in CH_2Cl_2 and washed with water and brine, dried, and concentrated in vacuo. The monoprotected alcohol was isolated by flash chromatography (silica gel, using a gradient elution with EtOAc/hexane). The yield was 26.0 g (33.6%) of a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.86−1.41 (m, 2H, −CH_2CH(OR)CH_2−), 1.51−1.73 (m, 4H, −CH_2CH(OR)CH_2− and −CH_2CH(OH)CH_2−), 1.86−2.02 (m, 2H, −CH_2CH(OH)CH_2−), 3.34−3.51 (m, 1H, −CH(OH)−), 3.62−3.73 (m, 1H, −CH(OR)−), 4.50 (s, 2H, −OCH_2Ph), 7.21−7.39 (m, 5H, −Ph). ^{13}C NMR ($CDCl_3$) δ 27.3, 29.3, 30.2, 32.3, 69.1, 69.3, 69.9, 73.4, 76.1, 127.0, 127.1, 127.2, 128.0, 128.1, 138.5, 138.7.

4-Benzyloxycyclohexanone (3). Pyridinium chlorochromate, PCC (12.6 g, 58.3 mmol), was added to a solution of **2** (10.0 g, 48.5 mmol) in CH_2Cl_2 (200 mL). After 3 h, the solution was diluted with Et_2O (300 mL) and filtered through silica and concentrated in vacuo. The ketone was isolated as a slightly yellow oil by flash chromatography (15% EtOAc/hexanes). Yield: 7.0 g (71%). ^{1}H NMR ($CDCl_3$) δ 1.86−2.01 (m, 2H, −CH_2CH(OR)CH_2−), 2.06−2.29 (m, 4H, −CH_2CH(OR)-CH_2− and −CH_2COCH_2−), 2.53−2.66 (m, 2H, −CH_2COCH_2−), 3.79 (m, 1H, −CH(OR)−), 4.58 (s, 2H −OCH_2Ph), 7.22−7.35 (m, 5H, −Ph). ^{13}C NMR ($CDCl_3$) δ 30.3, 37.0, 69.9, 71.9, 127.0, 127.2, 128.0, 138.2, 210.5.

γ-Benzyloxy-ϵ-caprolactone (4). A solution of **3** (11.0 g, 53.8 mmol) in $CHCl_3$ (100 mL) was added to a stirred solution of 80% *m*-chloroperoxybenzoic acid (11.2 g, 65.0 mmol) in $CHCl_3$ (75 mL). After 3 h the solution was filtered through Celite, washed twice with saturated $NaHCO_3$ and once with brine, dried with $MgSO_4$, and concentrated in vacuo. The monomer, a slightly yellow oil, was isolated by flash chromatography (silica gel, using an ethyl acetate/hexane elution gradient). The yield was 10.9 g (92%) of a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 1.82−2.09 (m, 4H, −CH_2CH(OR)CH_2−), 2.36, 2.45 (ddd, 1H, −CH_2COOC−), 2.94−3.06 (ddd, 1H, −CH_2-COOC−), 3.76 (m, 1H, −CH(OR)−), 3.99−4.08 (ddd, 1H, −COOCH_2), 4.45−4.59 (ddd, 1H, −COOCH_2−), 4.50 (s, 2H, −OCH_2Ph), 7.23−7.41 (m, 5H, −Ph). ^{13}C NMR ($CDCl_3$) δ 2.87, 29.7, 32.7, 60.2, 61.2, 71.1, 74.6, 127.6, 127.7, 128.3, 129.6, 138.2, 177.5. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79. Found: C, 70.40; H, 7.32.

4-Hydroxycyclohexyl 2,2-Bis(phenyldioxymethyl)propionate (5). The 2,2′-bis(phenyldioxymethyl)propionyl chloride (10.0 g, 42.0 mmol) was added to a THF solution of 1,4-cyclohexanediol (5.70 g, 0.049 mol) and triethylamine (7.42 g, 0.07 mol). After 24 h, CH_2Cl_2 (1000 mL) was added, and the solution was washed with 1 M HCl (3×) and water (2×), dried ($MgSO_4$), and concentrated. The product was purified by column chromatography (silica gel using hexane/ethyl acetate gradient as eluant). Yield (40%). ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 3H, −CH_3), 1.57−1.61 (m, 4H, CHCH_2−), 1.95−2.02 (m, 4H, −CHCH_2−), 3.66 (m, 3H, −CCH_2OR− and −CHOH), 4.62 (d, ABq, 2H, −CCH_2OR−), 4.99 (m, 1H, −CHPh), 7.22−7.38 (m, 5H, Ar).

4-Ketocyclohexyl 2,2-Bis(phenyldioxymethyl)propionate (6). Pyridinium chlorochromate (PCC) (4.95 g, 0.022 mol) was added to a solution of **5** (5.40 g, 0.019 mol) in CH_2Cl_2. After 24 h, diethyl ether was added (300 mL), and the mixture filtered through silica gel. The product was then purified by column chromatography (silica gel using ethyl acetate/hexane

as the eluant): yield 64%. ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 3H, $-CH_3$), 2.01−2.07 (m, 2H, $-COCH_2-$), 2.12−2.39 (m, 4H, $-CHCH_2-$), 2.50−2.65 (m, 2H, $-COCH_2-$), 3.64 (d, ABq, 2H, $-CCH_2OR-$, J = 12 Hz), 4.64 (d, ABq, 2H, $-CCH_2OR-$, J = 12 Hz), 5.25 (m, 1H, $-CHOR$), 5.46 (s, 1H, $-CHPh$), 7.31−7.47 (m, 5H, Ar).

***γ*-(ϵ-Caprolactone) 2,2-Bis(phenyldioxymethyl)propionate (7). 6** (2.55 g, 0.0096 mol) was dissolved in 30 mL of $CHCl_3$ and added dropwise to a solution of 3-chloroperoxybenzoic acid (60%) (3.16 g, 0.018 mol) in $CHCl_3$ (300 mL). The mixture was stirred for 24 h and then filtered through Celite. The yellow solution was washed with 2 M $NaHCO_3$ (2×) and NaCl solution (2×) and concentrated. The extracted product was purified by column chromatography (silica gel using hexane/ethyl acetate as the eluant) followed by crystallization from ethanol to give a white crystalline powder in 51% yield. ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3H, $-CH_3$), 1.85−2.18 (m, 4H, $-CHCH_2-$), 2.39−2.49 (m, 1H, $-CH_2COO-$), 2.89−3.00 (m, 1H, $-CH_2COO-$), 3.66 (d, ABq, 2H, $-CCH_2OR-$, J = 12 Hz), 4.11 (m, 1H, $-COOCH_2-$), 4.40−4.50 (m, 1H, $-COOCH_2-$), 4.62 (d, ABq, 2H, $-CCH_2OR-$, J = 12 Hz), 5.21 (m, 1H, $-CHOR$), 5.45 (s, 1H, $-CHPh$), 7.31−7.47 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ 174.9, 173.0, 138.0, 129.0, 128.2, 125.8, 101.6, 73.9, 73.7, 73.6, 73.6, 70.4, 63.5, 42.7, 33.7, 28.3, 27.4, 17.6. Anal. Calcd: C, 64.66; H, 6.63. Found: C, 64.54; H, 6.73.

Ethyl 4-Ketocyclohexanecarboxylate (9). To a vigorously stirred suspension of pyridinium chlorochromate (80 g, 0.37 mol) in CH_2Cl_2 (550 mL) at 5 °C was added a solution of ethyl 4-hydroxycyclohexanecarboxylate (**8**) (53 g, 0.31 mol) dissolved in CH_2Cl_2 (50 mL). This mixture was stirred at room temperature for 2 h and then at 45 °C for 5 h. The reaction was determined to be complete when no starting alcohol was detected by GLC; the mixture was cooled, the solvent was carefully decanted, and the residue was rinsed with ether (4 × 200 mL). The combined organic fractions were filtered through silica gel, and the crude product was distilled using a Kugelrohr apparatus at 55 °C (0.02 mTorr). Pure product was distilled at 70 °C (0.02 mTorr) to give a colorless oil (51 g, 97% yield): ^{1}H NMR ($CHCl_3$) δ 4.14 (q, 2H, J = 7.2 Hz), 2.7−2.6 (m, 1H), 2.4−2.2 (m, 4 H), 2.2−2.0 (m, 2H), 1.97−1.88 (m, 2H), 1.2 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 210.0, 174.0, 60.6, 40.6, 39.6, 28.4, 14.1.

4-Ketocyclohexanecarboxylic Acid (10). A solution of ethyl 4-ketocyclohexanecarboxylate (**9**) (12 g, 70 mmol) in 2% H_2SO_4 was heated to 115 °C for 4 h. The cooled solution was extracted with ethyl ether, and the organic layer was separated and dried over magnesium sulfate. The solvent was evaporated, and the product was distilled at 180 °C (0.02 mTorr) to give a colorless solid 6.8 g (68% yield); mp 72−73 °C. ^{1}H NMR ($CHCl_3$) δ 2.8−2.7 (m, 1H), 2.5−2.35 (m, 4H), 2.34−2.19 (m, 2H), 2.09−1.97 (m, 2H). ^{13}C NMR ($CHCl_3$) δ 210.5, 180.2, 40.4, 39.5, 28.2.

Benzyl 4-Ketocyclohexanecarboxylate (11). A suspension containing 4-ketocyclohexanecarboxylic acid (**10**) (8.4 g, 59 mmol) and potassium carbonate (32.6 g, 0.24 mol) in 250 mL of acetone was stirred vigorously as benzyl bromide (12 g, 71 mmol) was added dropwise at room temperature. The mixture was stirred at 60 °C for 3 h, then cooled, and filtered, and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel using 30% ethyl acetate in hexanes as the eluant afforded 12 g (87% yield) of colorless oil: ^{1}H NMR ($CHCl_3$) δ 7.4−7.3 (m, 5H), 5.14 (s, 2H), 2.84−2.73 (m, 1H), 2.47−2.35 (m, 4H), 2.29−2.15 (m, 2H), 2.07−1.97 (m, 2H). ^{13}C NMR ($CHCl_3$) δ 210.0, 173.9, 128.6, 128.4, 128.2, 66.5, 40.7, 39.7, 28.5.

Benzyl *γ*-(ϵ-Caprolactone)carboxylate (12). A solution of benzyl 4-ketocyclohexanecarboxylate (**11**) (12.1 g, 52.0 mmol) in $CHCl_3$ (50 mL) was added to a mixture of 57−86% *m*-chloroperoxybenzoic acid (15 g) in 100 mL of $CHCl_3$, with vigorous stirring. After the mixture was heated to 65 °C for 2 h, it was cooled, filtered through Celite, and extracted with dilute $NaHCO_3$. The organic layer was separated and dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel using 50% ethyl acetate in hexanes as the eluant followed by Kugelrohr distillation at 160 °C (0.02 mTorr) gave a colorless oil (11.3 g, 87% yield): ^{1}H NMR ($CHCl_3$) δ 7.34−7.27 (m, 5H), 5.07 (s, 2H), 4.32−4.23 (m, 1H), 4.14−4.05 (m, 1H), 2.73−2.64 (m, 2H), 2.57−2.47 (m, 1H), 2.16−1.82 (m, 4H). ^{13}C NMR ($CHCl_3$) δ 175.0, 173.3, 135.6, 128.7, 128.5, 128.2, 66.7, 66.6, 44.1, 32.1, 31.4, 24.8. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.49; Found: C, 67.44; H, 6.46.

***tert*-Butyl 4-Ketocyclohexanecarboxylate (13).** Oxalyl chloride (1.80 g, 14.0 mmol) was slowly added to a cooled solution of 4-ketocyclohexanecarboxylic acid (1.00 g, 7.00 mmol) and DMF (62 mg, 0.84 mmol) in CH_2Cl_2 (15 mL) under N_2. After stirring at room temperature for 14 h, excess oxalyl dichloride and solvent were removed under reduced pressure. The residue was redissolved in CH_2Cl_2, followed by addition of *tert*-butyl alcohol (1.00 g, 14.00 mmol) and triethylamine (1.40 g, 14.0 mmol). This mixture was stirred at room temperature for 1.5 h before being poured into water. Extraction with CH_2Cl_2 followed by column chromatography on silica gel using 20% ethyl acetate in hexanes as the eluant gave a colorless oil. Pure product was obtained by Kugelrohr distillation at 65 °C (0.02 mTorr) to provide 0.8 g of colorless solid (56% yield); mp 46−47 °C. ^{1}H NMR ($CHCl_3$) δ 2.64−2.54 (m, 1H), 2.44−2.24 (m, 4H), 2.15−2.06 (m, 2H), 2.0−1.9 (m, 2H), 1.41 (s, 9H). ^{13}C NMR ($CHCl_3$) δ 210.5, 173.4, 80.7, 41.5, 39.7, 28.6, 28.0.

***tert*-Butyl *γ*-(ϵ-Caprolactone)carboxylate (14).** Oxidation of *tert*-butyl 4-ketocyclohexanecarboxylate with m-CPBA was performed as described above. Purification by column chromatography over silica gel using 30% ethyl acetate in hexanes followed by Kugelrohr distillation at 90 °C (0.03 mTorr) afforded a colorless solid in 90% yield; mp 57−58 °C. ^{1}H NMR ($CHCl_3$) δ 4.36−4.27 (m, 1H), 4.17−4.08 (m,1H), 2.77−2.49 (m, 3H), 2.09−1.87 (m, 4H), 1.39 (s, 9H). ^{13}C NMR ($CHCl_3$) δ 175.2, 172.9, 81.1, 66.7, 44.9, 32.1, 31.4, 28.0, 24.9. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.46. Found: C, 60.54; H, 8.35.

7-Trifluoroacetyl-7-aza-1,4-dioxaspiro[4,5]decane (16). 1,4-Dioxa-7-azaspiro[4,5]decane (30.0 g, 209.9 mmol) was added dropwise into trifluoroacetic anhydride (87.8 g, 418.0 mmol) at 0 °C. The reaction was maintained at 60 °C for 3 h and then added to 200 mL of a water/ice mixture, stirred for 15 min, extracted with CH_2Cl_2 (3×), dried with $MgSO_4$, and concentrated. Yield: 100 g (50.7%). ^{1}H NMR ($CDCl_3$) δ 1.73 (t, 4H, $-CH_2N-$), 3.6−3.75 (2t, 4H, CH_2N-), 3.95 (t, 4H, $-CH_2O-$). ^{13}C NMR ($CDCl_3$) δ 35.02, 42.69, 112.1 (q, J_{C-F} = Hz), 155 ppm.

1-Trifluoroacetyl-4-ketopiperidine (17). To an acetone solution (700 mL) of **16** (50.0 g, 209.0 mmol) were added *p*-TSA (4.37 g) and water (100 mL) and heated to 80 °C for 48 h. The solution was concentrated, diluted with 1 L of CH_2Cl_2, extracted with $NaHCO_3$ (3×) and water (1×), dried with $MgSO_4$, and concentrated. The product was purified by recrystallization from an ethyl acetate hexane mixture yielding a white crystalline solid; yield 25.0 g (61%). ^{1}H NMR ($CDCl_3$) δ 2.53 (m, 4H, $-CH_2CO-$), 3.85 (m, 4H, CH_2N-). ^{13}C NMR ($CDCl_3$) δ 40.55, 43.30, 112.1, 155.54, and 204.59 ppm.

4-Trifluoroacetyl-7-oxo-1,4-oxazaperhydroepine (18). *m*-Chloroperoxybenzoic acid (40.5 g, 0.137 mmol) was added dropwise to a solution of **17** (25.0 g, 125.0 mmol) in CH_2Cl_2 (250 mL) at 0 °C. The reaction was continued for 14 h at room temperature. The crude reaction was extracted with $NaHCO_3$ solution (3×) and water (1×), dried with $MgSO_4$, and concentrated. The crude product was purified by recrystallization (3×) from a hexane/ethyl acetate solution to yield a white solid; yield 15.0 g (60%). ^{1}H NMR ($CDCl_3$) δ 2.85 (m, 2H, $-CH_2CO-$), 3.75−3.95 (3m, 4H, $-CH_2N-$) and 4.30 (t, 2H, $-CH_2OCO-$). ^{13}C NMR ($CDCl_3$) δ 36.60, 41.65, 48.40, 68.19, 112.1, (q, J_{C-F} = 289 Hz), 155.54, and 172.20 ppm. Because of restricted rotation of the amide bond, the ^{13}C NMR signals of compounds **16**, **17**, and **18** spectra appear as doublets that collapse when the spectra was taken in DMSO-d_5 at 105 °C.

General Procedure for Lactone Polymerization Initiated with Sn(Oct)$_2$. The initiator benzyl 2,2′-bis(hydroxymethyl)propionate, prepared according to literature procedures,[5a] was distilled and stored in a glovebox until used. The initiator

and monomer were charged into a flamed flask and dissolved in 2 mL of toluene. The temperature was increased to 110 °C, and $Sn(Oct)_2$ was added. The polymerization was continued for 24 h. The viscous solution was diluted with THF and precipitated in cold methanol. The polymer, **20**, was isolated in nearly quantitative yield: ^{1}H NMR ($CDCl_3$) δ 7.23−7.31 (m, 5H, −Ph), 4.6 (s, 2H, $-OCH_2Ph$), 4.14 (m, 2H, $-CO_2CH_2-$), 3.51−3.55 (m, 1H, CH−O), 2.23−2.27 (m, 2H, $-CH_2CO_2-$), 1.78−1.96 (m, 4H, $-CH_2CHCH_2-$).

General Procedure for Lactone Polymerization Initiated with Al(O^{i}Pr)$_3$. Polymerization of **18** and copolymerization of **18** with ϵ-caprolactone were accomplished using $Al(O^iPr)_3$ in THF. The monomer/monomers dried by repeated toluene azeotropic distillation (toluene, 3×), solvent, and initiator (0.3 M solution in toluene) were added successively through a rubber septum with either a syringe or stainless steel capillary at 0 °C. The polymerization was continued for 24 h. Upon completion of polymerization, an excess of 1 N HCl was added, and the polymer was recovered by precipitation in methanol.

General Procedure for Deprotection of the Trifluoroacetamido Polymers. The deprotection of the trifluoroacetamido protecting groups of copolymers **23b**−**d** and homopolymers **23a** was accomplished with $NaBH_4$. For example, copolymer **23a** (0.30 g, containing 0.39 mmol of trifluoroacetamido units) was dissolved in CH_2Cl_2 (5 mL) followed by the addition of $NaBH_4$ (15.0 mg, 0.39 mmol) at 0 °C. The reaction was quenched after 15 min by precipitation into hexane, and the polymer was filtered and dried (yield = 0.25 g, 85%).

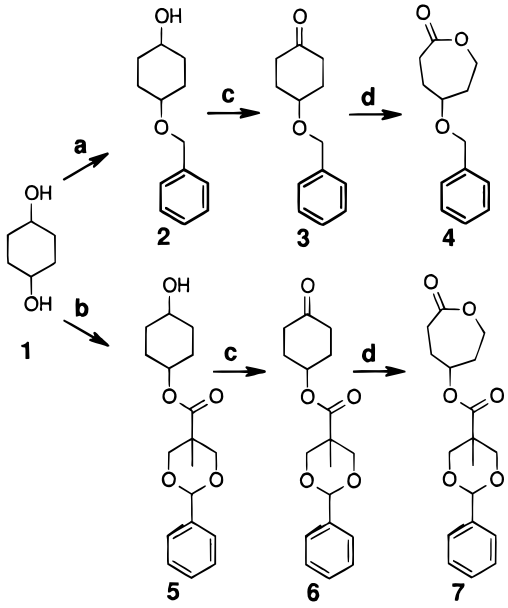
General Procedure for the Removal of the Benzyl Protecting Groups. To a solution of polymer **20** (1.00 g) in a 80/20 mixture of EtOAc/THF (70 mL) was added Pd/C (0.15 g). The Parr pressure apparatus was evacuated and filled with H_2(g). The reaction mixture was shaken for 24 h, and the Pd/C was removed by filtration. The filtrate containing the polymer was precipitated into cold methanol. The polymer was isolated as a white powder, 0.50 g (50% yield). ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3H, $-CH_3$), 1.96−1.99 (m, 4H, $-CH_2CH-CH_2-$), 2.25−2.35 (m, 2H, $-CH_2COO-$), 3.45−3.65 (m, 4H, $-CCH_2OR$), 4.01 (s, 2H, $-CH_2O-$), 4.9 (m, 1H, −CCHOR).

Results and Discussion

The general synthetic strategies for the preparation of the functionalized caprolactone monomers (**4**, **7**, **12**, **14**, and **18**) are shown in Schemes 1−3. In each case, the caprolactone derivatives were generated by the Bayer−Villiger oxidation of the corresponding cyclohexanone derivative. Suitable protecting groups were employed where necessary to permit clean oxidation without side products or rearrangements. For example, Pitt et al.[14] have shown that γ-hydroxy-ϵ-caprolactone is unstable and undergoes a facile intramolecular transesterification to yield ϵ-hydroxyethyl-γ-butyrolactone, and hence the liberation of the free hydroxy functionality prior to ring-opening polymerization must be avoided.

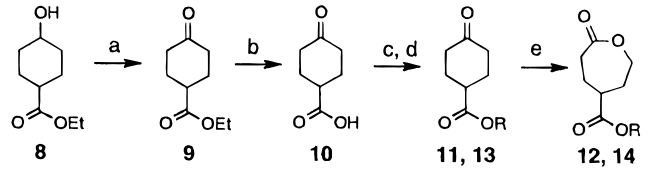
1,4-Dihydroxycyclohexane (**1**) is commercially available as a mixture of isomers. Monoprotection can be accomplished in moderate yields, and purification from unreacted starting material and diprotected byproduct is easily accomplished by flash column chromatography over silica gel. In this fashion, the monoprotected derivatives **2** and **5** were prepared. Each could be oxidized with PCC to yield the respective functionalized cyclohexanones **3** and **6** in good yields. Commercially available ethyl-4-hydroxycyclohexyl carboxylate (**8**) could be similarly oxidized to ethyl-4-ketocyclohexylcarboxylate (**9**) without difficulties and the free acid **10** produced by hydrolysis in dilute (2%) sulfuric acid. The carboxylic acid **10** was reesterified to the benzyl ester **11** by alkylation with benzyl bromide under basic conditions. The corresponding *tert*-butyl ester **13** was prepared by

Scheme 1[a]



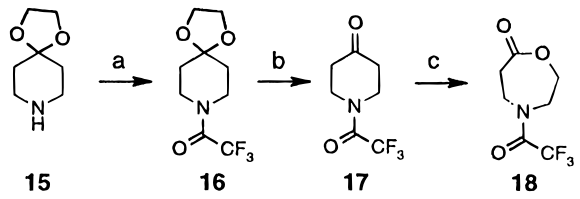
[a] Reaction conditions: (a) NaH, benzyl bromide, 25 °C, 16 h; (b) 2,2′-bis(phenyldioxymethyl)propionyl chloride, Et3N, 25 °C, 24 h; (c) PCC, 24 h; (d) m-CPBA (60%), 24 h.

Scheme 2[a]



[a] Reaction conditions: (a) PCC, 45 °C, 7 h; (b) H_2SO_4 (2%), 115 °C, 4 h; (c) K_2CO_3, benzyl bromide, 60 °C, 3 h; (d) (1) oxalyl chloride, DMF, 24 h (2) t-BuOH, methylamide, 25 °C, 1.5 h; (e) m-CPBA (60%), 65 °C, 2 h.

Scheme 3[a]



[a] Reaction conditions: (a) trifluoroacetic anhydride, 60 °C, 3 h; (b) p-TSA, 80 °C, 48 h; (c) m-CPBA (60%), 25 °C, 14 h.

esterification with *tert*-butyl alcohol in the presence of oxalyl chloride and dimethylformamide (DMF). Benzyl and *tert*-butyl protecting groups were selected because they are easily cleaved to the respective carboxylic acids under mild conditions: hydrogenolysis for the benzyl esters and nonaqueous acid for the *tert*-butyl ester. Mild deprotection procedures are needed to ensure the integrity of the respective poly(caprolactones) produced by ROP procedures (vide infra). The aza-cyclohexanone derivative **16** was generated from the commercially available ethyleneketal of 4-piperidone (**15**) by acetylation with trifluoroacetic anhydride followed by transketalization to **17** using *p*-TSA in an excess of acetone. The trifluoroacetyl protecting group was selected because it is easily removed using either K_2CO_3 in methanol or $NaBH_4$ reduction. The desired caprolactone

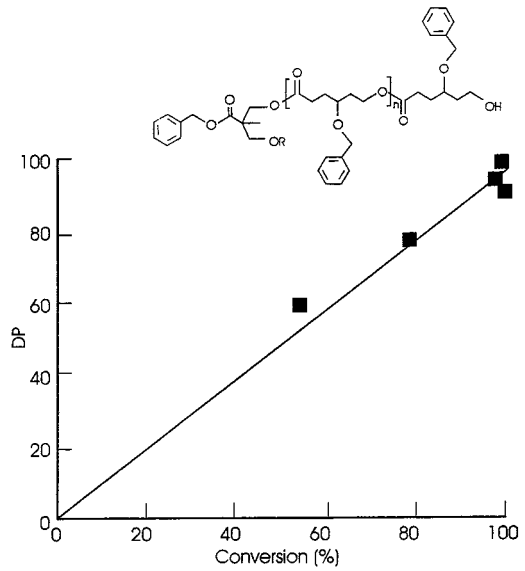
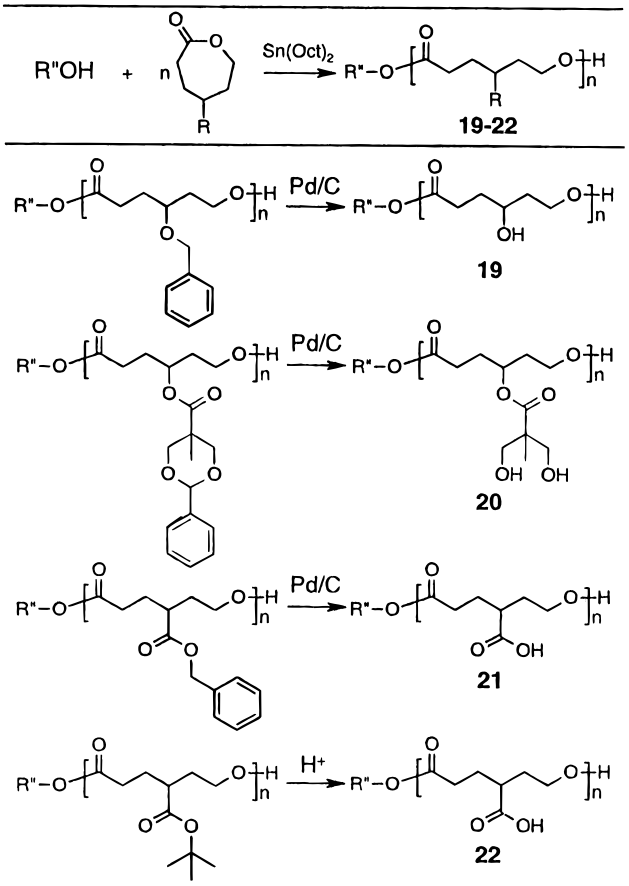


Figure 1. Molecular weight as a function of conversion for polymer **19**.

Scheme 4



derivatives **4**, **7**, **12**, **14**, and **18** were prepared from the corresponding substituted cyclohexanones using *m*-chloroperoxybenzoic acid in methylene chloride. The functionalized caprolactone derivatives were isolated in good yields and were purified by distillation, recrystallization, or column chromatography.

Polymerization of the new monomers was accomplished either in bulk or with ~5% toluene diluant added to mediate the viscosity using the benzyl ester of bis MPA as an initiator in the presence of $Sn(Oct)_2$

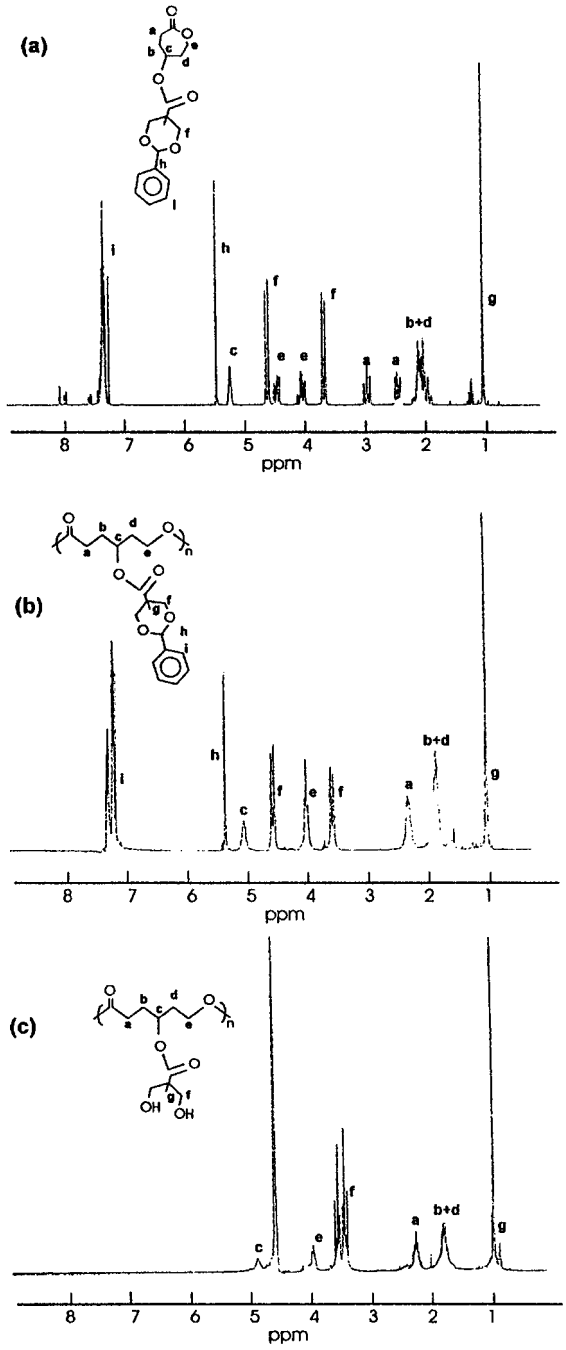


Figure 2. ^{1}H NMR spectra of (a) **4**, (b) polymer **20a**, and (c) deprotected polymer **20a**.

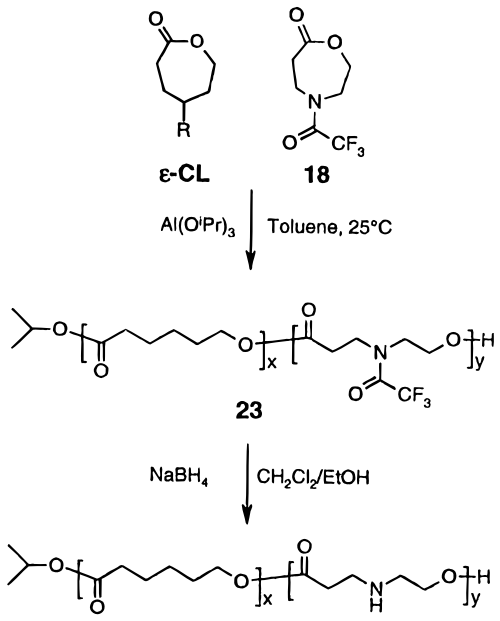
(Scheme 4). In each case, homogeneous solutions of the monomer and initiator were realized either with or without the addition of toluene. Polymerization temperatures were maintained at 110 °C to minimize possible transesterification side reactions. The molar ratio of initiating alcohol to $Sn(Oct)_2$ ([M]/[CAT]) was kept as high as possible to minimize possible transesterification reactions. Nearly quantitative conversion of monomer to polymer was realized after 48 h reaction time. The extended polymerization times somewhat compromised the polydispersities, presumably due to transesterification reactions. We have recently reported that substituted lactones polymerized in this manner generally react slower than ϵ-caprolactone.[13] Quantitative monitoring of the polymerization of γ-benzyloxy-ϵ-caprolactone (**4**) shows that nearly quantitative conversion of momomer to polymer was not observed in less

Table 1. Characteristics of Substituted Poly(ϵ-caprolactones)

sample entry	substituent	$\langle M_n \rangle$, g/mol theor	$\langle M_n \rangle$, g/mol ^{1}H NMR	$\langle M_n \rangle$, g/mol SEC	$\langle M_w \rangle / \langle M_n \rangle$
19a	benzyloxy	20 000	22 000	15 400	1.23
19b	benzyloxy	30 000	33 000	22 000	1.3
20a	phenyldioxymethyl	10 000	9 000	5 000	1.2
20b	phenyldioxymethyl	20 000	19 000	12 400	1.39
21a	*tert*-butyl ester	8 000	1 400	2 000	1.42
21b	*tert*-butyl ester/ϵ-CL (20/80)	20 000	18 500	12 999	1.39
22a	benzyl ester	4 000	2 000	1 000	1.36
22b	benzyl ester	10 000	4 000	2 200	1.18
23a[a]	trifluoroacetamide	5 000	5 000	15 000	1.35
23b[a]	trifluoroacetamide/ϵ-CL (80/20)	5 000	5 000	14 500	1.2
23c[a]	trifluoroacetamide/ϵ-CL (90/10)	14 000	13 500	25 000	1.24
23d[b]	trifluoroacetamide/ϵ-CL (90/10)	13 000	12 000	23 000	1.5

[a] Initiated with $Al(O^iPr)_3$ at 45 °C [b] Initiated with $Sn(Oct)_2$ at 80 °C

Scheme 5



than 48 h reaction time. A plot of molecular weight (degree of polymerization (DP) determined by ^{1}H NMR) of **19** as a function of conversion (Figure 1) shows a linear relationship, consistent with a "living" or controlled polymerization. The ^{1}H NMR spectrum (Figure 2) of polymer **20** shows the major peaks associated with the poly(lactone) together with the protected functional group. This general procedure was used to polymerize the monomers, and the characteristics of the polymers are shown in Table 1. Molecular weights ranging between 5000 and 30 000 g/mol were obtained with polydispersities between 1.2 and 1.53. The polydispersities (Table 1) are somewhat broader than reported for previous examples, a feature which presumably stems from the extended reaction times. The molecular weights were targeted to modest values to facilitate characterization by ^{1}H NMR end-group analysis.[5] The polymerization of **18** using the benzyl ester of bis-MPA in the presence of $Sn(Oct)_2$ required milder temperatures (80 °C) to prevent the premature deprotection of the amino group (polymer **23d**, Table 1). In this case, the use of aluminum isopropoxide at 0 °C (Scheme 5) was found to be more a more efficient initiator (polymers **23a**−**c**, Table 1). The ^{1}H NMR spectrum of polymer **23** shown in Figure 3 shows only the major peaks of the polylactone and the end groups, with no evidence of transesterification side reactions.

Interestingly, monomers **12** and **14** were particularly slow to homopolymerize with only modest monomer conversion to polymer observed after 48 h, and lower than expected molecular weights were obtained. ^{1}H NMR analyses showed no signs of adverse transesterification reactions. Copolymerization of monomer **14** with ϵ-caprolactone, however, led to near quantitative monomer conversion and produced polymers with controlled molecular weights and modest polydispersities. Shown in Figure 4 is the ^{1}H NMR spectrum of copolymer **21b**, and the resonances associated with each monomer type are clearly observed with no evidence of side reactions or transesterification. The copolymerization of **12** with ϵ-caprolactone was not as successful with only modest monomer conversions (60−70%) producing lower than expected molecular weights (Table 1).

The benzyl protecting groups of polymers **19**, **20**, and **22** were removed by catalytic hydrogenolysis. Analysis of the deprotected polymer **19** by ^{1}H NMR was difficult, presumably due to contributions from hydrogen bonding. However, ^{13}C NMR spectroscopy in combination with SEC measurements showed clear signs of polymer degradation, including a significant decrease in molecular weight. Likewise, other deprotection schemes including trimethylsilyl iodide produced analogous results.[15] These data are consistent with reports from Pitt et al.[14] In contrast, removal of the benzilidine protecting group from polymers **20a** and **20b** by catalytic hydrogenolysis was more successful, and the molecular weight measured by ^{1}H NMR did not change after deprotection; however, the elution volume of the SEC chromatogram changed somewhat as expected. Nevertheless, the chromatogram was symmetrical with no evidence of degradation or transesterification. The ^{1}H NMR of the deprotected sample was obtained in D_2O, and the hydrogenolysis reaction causes the dissappearance of the aromatic (7.31 ppm) and benzylic (5.07 ppm) proton signals assigned to the protecting group (Figure 2c). The resulting polymers were viscous, low-T_g liquids showing no evidence of crystallization. The polymers were water-soluble at low solids content. Likewise, the removal of the benzyl ester protecting group on polymers **22a** and **22b** was accomplished by catalytic hydrogenolysis using Pd/C, and ^{1}H NMR analyses showed the disappearance of the aromatic protons (7.3 ppm) and the benzylic protons (5.10 ppm) assigned to the protecting groups.

The *tert*-butyl ester protecting groups on polymers **21a** and **21b** were removed with trifluoromethanesulfonic acid. Prior protection of the hydroxyl chain end was required to prevent cross-linking of the polymer concurrent with the deprotection of the acid functional-

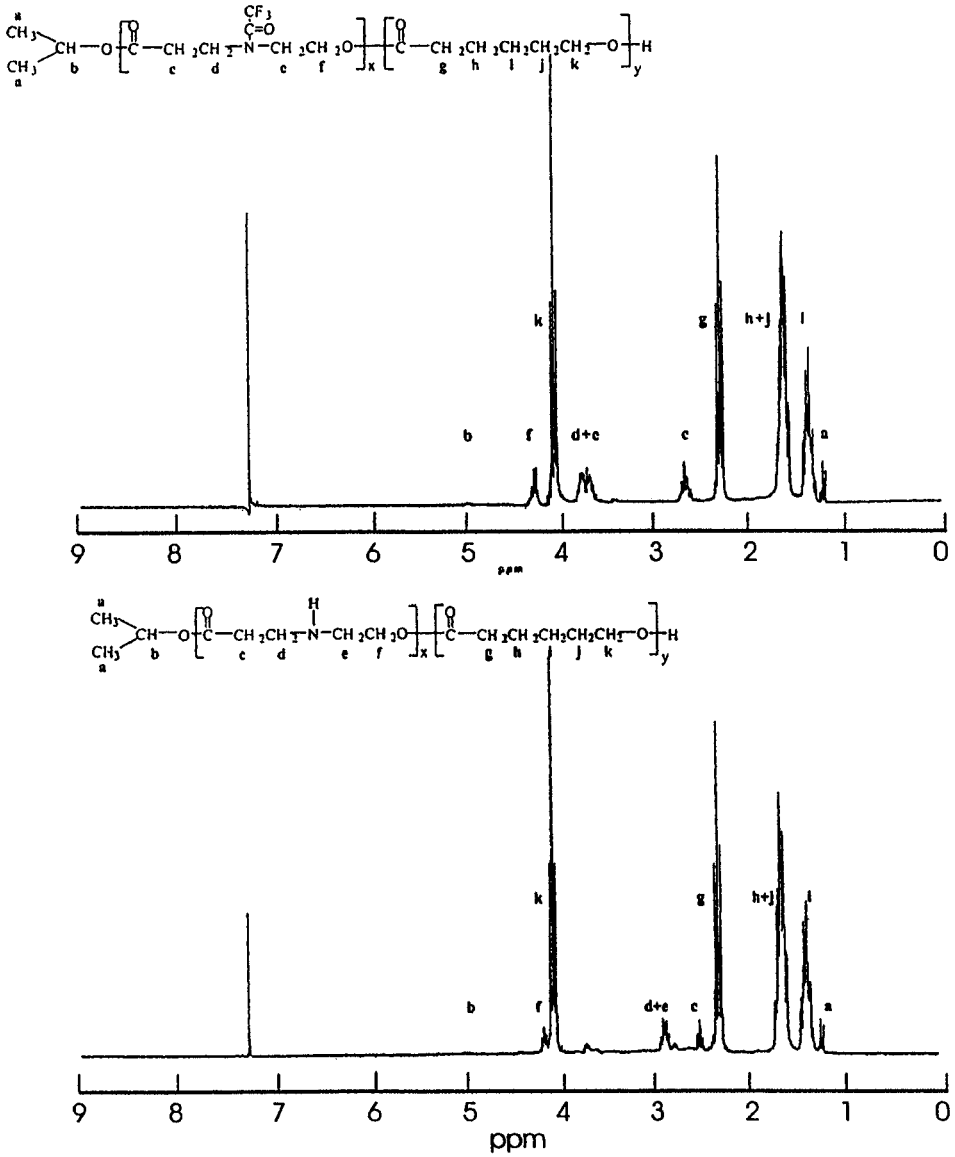


Figure 3. ^{1}H NMR spectra of (top) polymer **23** and (bottom) polymer **23** deprotected.

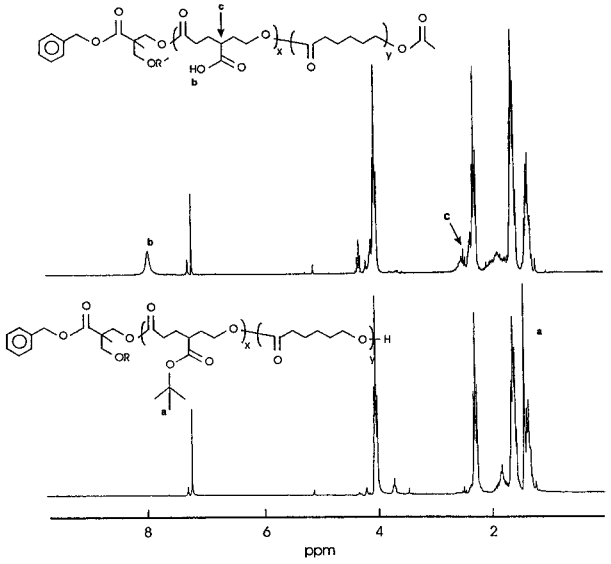


Figure 4. ^{1}H NMR spectra of (bottom) **21a** and (top) **21a** deprotected.

ity. This was accomplished by the reaction of **21** with acetyl chloride in the presence of triethylamine. ^{1}H NMR analysis shows a quantitative shift in the methylene protons assigned to the chain ends from 3.66 to 4.35 ppm after derivatization. In these cases, the deprotection transformation was quantitative with no evidence of residual protecting groups. ^{1}H NMR analysis of deprotected polymers **21a** and **21b** shows the disappearance of the resonance associated with the *tert*-butyl protons (1.42 ppm) of polymer **21b** (Figure 4), along with the appearance of a peak assigned to the acid. This polymer analogous transformation was slow, requiring ~50 h to effect quantitative deprotection, presumably due to collapse of the hydrophilic chains hindering further deprotection. This transformation was, however, accomplished with minimal decrease in molecular weight, as determined by ^{1}H NMR (Figure 4). Consistent with these data, the IR spectra of polymer **21a** after deprotection (Figure 5) shows the formation of a broad peak around 3200 cm^{-1} characteristic of the carboxylic acid. The SEC chromatograms (Figure 6) of the deprotected material show monomodal peaks with retention volumes comparable to those of the protected copolymers. In each case, the polymers were viscous, low-T_g liquids which showed no evidence of crystallization.

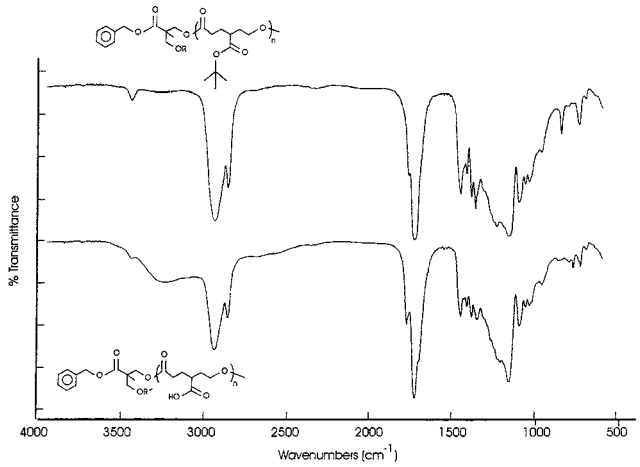


Figure 5. IR spectra of polymer **21** (a) before and (b) after deprotection.

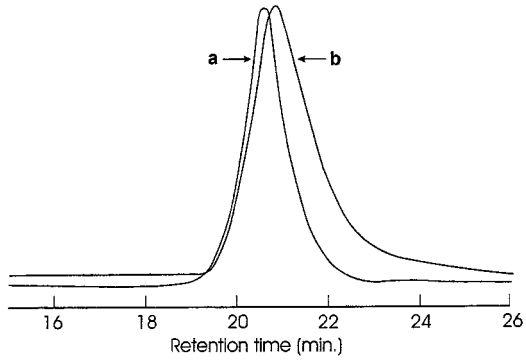


Figure 6. SEC chromatograms of polymer **21a** (a) before and (b) after deprotection.

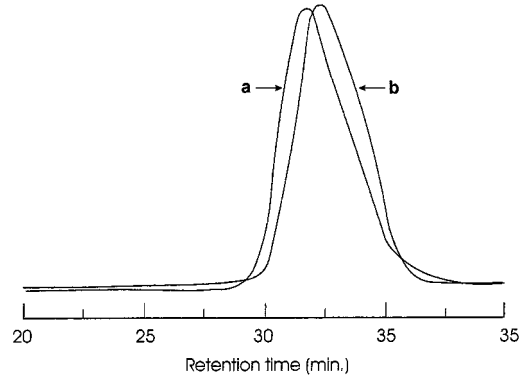


Figure 7. SEC chromatograms of polymer **23a** (a) before and (b) after deprotection.

Finding conditions for the selective deprotection of the amino functionality of polymers **23a**−**d** was complicated by the sensitivity of the polyester backbone. The most effective deprotection reagent surveyed was $NaBH_4$, and mild conditions and short reaction times were required to minimize polymer degradation. Figure 7 shows the SEC chromatograms of **23** before and after deprotection. After 15 min reaction, the transformation is complete and polymer degradation is minimal. In this case, the polydispersity broadens from 1.18 to 1.32 with a slight shift in the number-average molecular weight. Shown in Figure 3 are the ^{1}H NMR spectra before and after deprotection. Significant shifts in the resonances associated with the protons adjacent to the functional groups, denoted as **d** and **e**, and no evidence of degradation was observed.

Summary

The synthesis and polymerization of new cyclic esters containing protected functional groups (hydroxyl-, bis(hydroxyl)-, amino-, and carboxyl-substituted) have been described. Three general synthetic strategies were designed and implemented as general routes to these substituted cyclic esters. Polymerization of the new monomers was accomplished either in bulk initiated from the benzyl ester of bis-MPA in the presence of $Sn(Oct)_2$ or in toluene initiated from $Al(O^i\,Pr)_3$. Accurate control of molecular weight and narrow polydispersities were obtained for most of the monomers surveyed, and a plot of molecular weight versus conversion for representative examples showed a linear relationship with near quantitative conversion. These combined data suggest that polymerization from these initiators is living. Conversely, the cyclic esters (**12**, **14**) containing the protected carboxylic acid functionality did not appreciably homopolymerize after 50 h; however, copolymerization was possible. Through the judicious choice of the protecting group, mild deprotection procedures were enabled, preserving the integrity of the respective functional poly(ϵ-caprolactones). The transformations were judged to be quantitative with minimal degradation of the polyester backbone by ^{1}H NMR and ^{13}C NMR, IR, and SEC measurements. Future studies will extend the use of the functional monomers to the dendrimer-like star molecular architecture to prepare amphiphilic block polymers for unimolecular micelles, nanoreactors, and drug delivery systems.

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