Novel Bioerodible Poly(hydroxyalkylene carbonates)s: A Versatile Class of Polymers for Medical and Pharmaceutical Applications

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ABSTRACT: Starting with properly protected sugar alcohols, bioerodible polycarbonates having pendant hydroxy substituents at the main polymer chain (poly(hydroxyalkylene carbonate)s, (PHAC's)) have been synthesized for the first time. The PHAC's are the first examples of water-soluble polycarbonates. Due to water solubility, these polyols may replace PEG's in some applications. On derivatization of the hydroxy groups as a carboxylic or carbonic acid ester or as an ortho ester, additional bioerodible polycarbonates having quite different solubility and degradation properties were available.

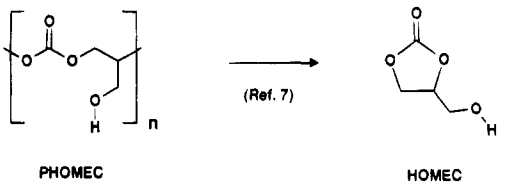
Introduction

Polycarbonates were known as rather stable materials for a long time and have found many commercial applications. The first polycarbonate reported to be biodegradable was poly(ethylene carbonate) (PEC),[1,2] which undergoes rapid, enzyme-mediated in-vivo bioabsorption within 2−3 weeks in rats.[3] PEC is not degradable in vitro in phosphate-buffered saline at pH 7.4. The in-vivo degradability of the next homologue, poly(trimethylene carbonate) (PTMC), was already strongly suppressed, and only 21% weight loss of an implant was found after an implantation time of 6 months in rats.[4] Introduction of a methyl substituent into PEC, i.e., poly(1,2-propylene carbonate), completely suppressed the biodegradability in vivo and in vitro.[3] Functional groups, e.g., hydroxy groups, are supposed to enhance the degradability of polycarbonates. Recently, copolyesters having pendant hydroxy substituents have been reported.[5,6] The first polycarbonate with pendant hydroxy groups, poly[(hydroxymethyl)ethylene carbonate] (PHOMEC), was reported to be labile, undergoing rapid autodegradation into the five-membered ring monomer (hydroxymethyl)ethylene carbonate (HOMEC)[7] (Scheme 1). The autodegradation was shown to proceed by the nucleophilic attack of the pendant hydroxy group at a carbonate function. On the other hand, poly[2-ethyl-2-(hydroxymethyl)trimethylene carbonate], synthesized by Kuehling et al.,[8] was proved to be stable and was fully characterized by the authors. The product of autodegradation in this case would be a six-membered ring carbonate, which is kinetically less favored than the five-membered ring. No biodegradation data were given for the product.

Bioerodible polymers having pendant functional groups are of particular interest, since they are capable of covalent prodrug formation and other functionalizations. On derivatization of the pendant functional groups, variations in hydrophilicity, physical properties, and biodegradation times of the products can be achieved. Polyesters with pendant functional groups, such as poly(malic acid)[9−12] and poly(L-serine ester),[13,14] are already known, having pendant carboxyl and amino groups, respectively. Recently, polydepsipeptides with pendant carboxyl or amino or thiol groups have been reported.[15]

Water-soluble poly(hydroxyalkylene carbonate)s (PHAC's) having pendant hydroxy substituents on the main-chain carbon atoms have now been synthesized for the first time. Their syntheses, as well as physical, chemical, and some of their degradation properties, will be discussed. The hydroxy substituents have been partly or completely derivatized to give potentially bioerodible terpolymers. By choosing the proper derivatives and controlling the extent of derivatizations, variations in hydrophilicity/hydrophobicity, physical properties, and degradation times of the products could be achieved.

Scheme 1



Experimental Part

General Methods and Abbreviations. Molecular weights (M_w = weight-average molecular weight; M_n = number-average molecular weight) were determined by gel permeation chromatography on a Waters 840 system with a Waters 410 refraction index detector and a Waters 490 UV detector. Columns: polystyrene−divinylbenzene crosslinked gels, Polymer Laboratories, combination of columns with pores of 10^3, 10^4, and 500 Å, at 35 °C. Calibration was with standard polystyrenes, Polymer Laboratories, for a molecular weight range of 1.75×10^6−580. Glass transition temperatures (T_g) and melting points (T_m) were measured on a Perkin-Elmer DSC 7 instrument with a data station and intracooler at a scanning rate of 10 °C/min of heating. The sample was heated in a first run above the glass transition temperature followed by fast cooling to −30 °C and in a second run to give the T_g value. Inherent viscosities (η_{inh}) were measured at 20 °C on an AVS 350 instrument with a Micro−Ubbelohde capillary. Optical rotations $[\alpha]_D$ were measured on a Perkin-Elmer 241 polarimeter. IR spectra were obtained on a Bruker IFF 66 spectrometer. NMR spectra were recorded on a Bruker AM 360 spectrometer using tetramethylsilane as internal standard. The chemical shift δ is given in ppm. Solvents and reagents (puriss p.a. or Merck z.A., Fluka, Switzerland) were used as purchased without purification: DCC, *N,N'*-dicyclohexylcarbodiimide; DMAP, 4-(dimethylamino)pyridine; THF, tetrahydrofuran; DMF, dimethylformamide. Di-*n*-butyltin oxide (dibutyltin oxide) was purchased from Swedstab (26488, Sweden).

Polymer Degradation in Vitro. The polymers were pressed into disks of 5 mm diameter and 25 mg of weight. Three disks for each time point and polymer were incubated

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in 40 mL of sterile phosphate-buffered saline (0.15 M ionic strength, pH 7.4) at 37 °C. The buffer of all samples was replaced weekly. Samples were taken at selected time points and dried in vacuo over phosphorus pentoxide to constant weight. The mass loss was determined gravimetrically. Changes of the molecular weight were measured by GPC.

Polymer Degradation in Vivo. Male Wistar Rats of 240–260 g of body weight, kept under optimal conditions, were anaesthesized by an inhalation narcotic, and one polymer disk was implanted in each rat under laminar flow conditions in a subcutaneous skin pouch. Two rats were used for each time point and polymer. At selected time points, the rats were killed by an overdose of the inhalation narcotic. The polymer residues were taken out, freed from adhering tissue, dried, and analyzed as described above for the in-vitro experiments.

Synthesis of Bis(ethoxycarbonyl)-2,3-*O*-isopropylidene-D-threityl (D-2). A total of 1.62 g (10 mmol) of D-(−)-threitol was stirred with 2.1 mL (22 mmol) of ethyl chloroformate and 1.8 mL (22 mmol) of pyridine in 30 mL of tetrahydrofuran for 3 h at room temperature. After the usual workup, the product was purified by chromatography on silica gel with ethyl acetate/hexane as eluent to give 2.5 g (8.16 mmol, 82%) of D-**2** as a colorless oil. IR (film, cm^{-1}): 2987 (aliphatic CH), 1750, 1258 (O−C(O)−O), 1092 (CO). ^1H NMR ($CDCl_3$): δ 1.32 (t, J = 7 Hz, 6 H, CH_3), 1.43 (s, 6 H, geminal CH_3), 4.11 (m, 2 H, CH), 4.21 (q, J = 7 Hz, 4 H, CH_2), 4.22 (dm, $^2J_{AB}$ = 11 Hz, 2 H_B of CH_2), 4.34 (dm, $^2J_{AB}$ = 11 Hz, 2 H_A of CH_2). ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 27.0 (geminal CH_3), 64.5 (CH_2), 67.0 (CH_2), 75.6 (CH), 110.5 (tertiary C), 155.0 (O−C(O)−O). Anal. Calcd for $C_{13}H_{22}O_8$: C, 51.0; H, 7.2. Found: C, 50.6; H, 7.3.

General Procedure for the Synthesis of Poly[[(oxycarbonyl)oxy]-2,3-*O*-isopropylidenethreityl] (3). In a typical procedure, 79.06 g of 2,3-*O*-isopropylidene-DL-threitol (DL-**1**; 488 mmol) (a 1:1 mixture of D-**1** and L-**1** was placed in a dry, round-bottomed flask, as a part of a distillation apparatus. A total of 370 mL (3050 mmol) of diethyl carbonate and 1.6 g of dibutyltin oxide were added under a slight stream of argon. The mixture was stirred 16 h at room temperature and for an additional 20 h at 120 °C, during which time ethanol was distilled. The distillate was removed under an argon stream, and the pressure was reduced to 50 mbar. The temperature was increased stepwise to 100 °C during 3 h to distill excess diethyl carbonate. When the distillation was completed, the pressure was set to atmospheric pressure with argon and the distillate was removed under an argon stream. Then, the pressure was reduced to 8 mbar, and the temperature was increased stepwise to 120 °C during 1 h. The reaction mixture was stirred for 20 h at 120 °C (8 mbar) and for 20 h at 140 °C (0.5 mbar). The product mixture was then cooled down to 40 °C and dissolved in 600 mL of dichloromethane. The solution was treated with 6 g of Hyflo Cel, stirred for 1 h at room temperature, and filtered. The solvent was evaporated to a final volume of ca. 250 mL under reduced pressure, and the product was precipitated by dropwise addition of the solution to 4000 mL of methanol. The brownish–beige precipitate was dissolved in 1500 mL of acetone, and 2.2 mL of 30% hydrogen peroxide in water was added slowly to the stirred solution. After 4 h of stirring at room temperature, 8 g of Florisil was added and stirring was continued for an additional 18 h. The suspension was then treated with 6 g of Hyflo Cel, stirred for another 1 h, and filtered. The solvent was evaporated at reduced pressure to a final volume of ca. 250 mL, and the product was precipitated by dropwise addition of the dichloromethane solution to 4000 mL of methanol. Drying of the precipitate in vacuo at 40 °C for 48 h gave 71 g (77%) of polycarbonate DL-**3** as an almost colorless solid. The mother liquor was evaporated and the residue was dissolved in 20 mL of dichloromethane and precipitated from 1000 mL of methanol to give, after drying in vacuo, an additional 4.6 g (5%) of DL-**3**. For selected physical properties, see Table 1. IR (KBr, cm^{-1}): 2990 (m), 2940 (m), 2907 (m), 1757 (s, br), 1576 (w), 1457 (m), 1385 (s), 1233 (s, br), 1169 (m), 1092 (s), 993 (m), 963 (m), 845 (m), 786 (m), 737 (w), 607 (w), 513 (m). ^1H NMR ($CDCl_3$): δ 1.42 (s, 6 H, 2 CH_3), 4.10 (m, 2 H, 2 CH), 4.24 (dm, $^2J_{AB}$ = ca. 11.5 Hz, 2 H, 2 H_B of 2 CH_2), 4.357 (dd, $^2J_{AB}$ = ca. 11.5 Hz and J = ca. 3.5 Hz, 2 H, 2 H_A of 2 CH_2). ^{13}C NMR ($CDCl_3$): δ 154.61 (O−C(O)−O), 110.57 (OCO), 75.34 (CH), 67.20 (CH_2), 26.86 (CH_3). Anal. Calcd for $(C_8H_{12}O_5)_n$: C, 51.08; H 6.38. Found: C, 50.60; H, 6.30.

Table 1. Selected Physical Properties of the Polycarbonates 3, 4, and 7

product	M_w ($\times 10^{-3}$)	M_n ($\times 10^{-3}$)	M_w/M_n	T_g (°C)	$[\alpha]_D$[a]	η (dL/g)
L-**3**	11.35	8.25	1.38	51.3	−34.0°	0.11[b]
D-3	14.70	9.95	1.48	52.2	+33.5°	0.14[b]
DL-3	16.55	10.30	1.61	47.5		0.14[b]
L-**4**				31.4		0.08[c]
D-4				32.3		0.07[c]
DL-**4**				39.6		0.10[c]
L-**7**	10.95	7.75	1.41	56.2	−31.0°	0.11[b]
D-**7**	11.25	7.30	1.54	58.6	+30.0°	0.10[b]
DL-**7**	13.80	9.05	1.52	57.8		0.14[b]

[a] In $CHCl_3$ (c = 1 g/dL) at 20 °C. [b] Inherent viscosity in $CHCl_3$, 20 °C, 10 mg/mL. [c] Inherent viscosity in H_2O at 20 °C, 10 mg/mL.

The enantiomerically pure polycarbonates L-**3** and D-**3** were prepared by procedures similar to that described above for the synthesis of DL-**3**.

L-**3**: Almost colorless solid. For physical properties, see Table 1. IR (KBr, cm^{-1}): 2992 (m), 2942 (w), 2908 (w), 1757 (s), 1460 (m), 1386 (s), 1235 (s, br), 1169 (m), 1092 (s), 992 (m), 964 (m), 845 (m), 786 (m), 607 (w), 514 (m). ^1H NMR ($CDCl_3$): δ 1.42 (s, 6 H, 2 CH_3), 4.096 (m, 2 H, 2 CH), 4.245 (dm, $^2J_{AB}$ = 11.5 Hz, 2 H_B of 2 CH_2), 4.357 (dd, $^2J_{AB}$ = ca. 11.5 Hz and J = ca. 3.3 Hz, 2 H_A of 2 CH_2). ^{13}C NMR ($CDCl_3$): δ 154.60 (O−C(O)−O), 110.55 (OCO), 75.35 (CH), 67.20 (CH_2), 26.85 (CH_3). Anal. Calcd for $(C_8H_{12}O_5)_n$: C, 51.08; H, 6.38. Found: C, 50.90; H, 6.50.

D-**3**: Almost colorless solid. See also Table 1. IR and NMR spectra of D-**3** were identical to the spectra of L-**3**. Anal. Calcd for $(C_8H_{12}O_5)_n$: C, 51.08; H, 6.38. Found: C, 50.80; H, 6.50.

General Procedure for the Synthesis of Poly[[(oxycarbonyl)oxy]-1,4-threityl] (4). In a typical procedure, 85 mL of water and 470 mL of trifluoroacetic acid were added to a stirred solution of 58.68 g (312 mmol) of DL-**3** in 470 mL of dichloromethane. The reaction mixture was stirred rigorously for 20 min at room temperature. The product was then precipitated by dropwise addition of the solution to 5000 mL of diethyl ether. The suspension was stirred for an additional 10 min at room temperature, and the precipitate was isolated under an argon stream and washed twice with diethyl ether. Drying in vacuo for 48 h gave 44.97 g (97%) of DL-**4** as a hygroscopic, white powder, which was kept under argon. For physical properties of DL-**4**, see Table 1. IR (KBr, cm^{-1}): 3468 (s, br), 2968 (w), 2917 (w), 1751 (s, br), 1458 (m), 1409 (m), 1284, 1259 (s, br), 1132 (m), 1075 (m), 959 (m), 895 (w), 787 (m). ^1H NMR (DMSO-d_6): δ 3.696 (m, 2 H, 2 CH), 4.044 (dd, $^2J_{AB}$ = ca. 10.7 Hz and J = ca. 7 Hz, 2 H, 2 H_B of 2 CH_2), 4.125 (dd, $^2J_{AB}$ = ca. 10.7 Hz and J = ca. 4 Hz, 2 H, 2 H_A of 2 CH_2), ca. 4.91 (br s, 2 H, 2 OH). ^{13}C NMR (DMSO-d_6): δ 154.55 (O−C(O)−O), 68.58 (CH_2), 68.32 (CH). Anal. Calcd for $(C_5H_8O_5)_n$: C, 40.56; H, 5.40. Found: C, 40.90; H, 5.60.

The enantiomerically pure PHAC's L-**4** and D-**4** were obtained from the hydrolysis of L-**3** and D-**3**, respectively, according to the procedure described above.

L-**4**: White, hygroscopic powder. For physical properties, see Table 1. IR (KBr, cm^{-1}): 3447 (s, br), 2967 (w), 2917 (w), 1750 (s, br), 1460 (m), 1408 (m), 1282 and 1262 (s, br), 1134 (m), 1077 (m), 960 (m), 895 (w), 788 (m). ^1H NMR (DMSO-d_6): δ 3.697 (m, 2H, 2 CH), 4.044 (dd, $^2J_{AB}$ = ca. 10.7 Hz and J = ca. 7 Hz, 2 H, 2 H_B of 2 CH_2), 4.125 (dd, $^2J_{AB}$ = ca. 10.7 Hz and J = ca. 4 Hz, 2 H, 2 H_A of 2 CH_2), ca. 4.76 (br s, 2 H, 2 OH). ^{13}C NMR (DMSO-d_6): δ 154.59 (O−C(O)−O), 68.62 (CH_2), 68.37 (CH). Anal. Calcd for $(C_5H_8O_5)_n$: C, 40.56; H, 5.40. Found: C, 39.90; H, 5.60.

D-**4**: White, hygroscopic powder. See also Table 1. IR and NMR spectra of D-**4** were identical to those of L-**4**. Anal. Calcd for $(C_5H_8O_5)_n$: C, 40.56; H, 5.40. Found: C, 39.20; H, 5.50.

Synthesis of Poly[[(oxycarbonyl)oxy]-2,4:3,5-di-*O*-isopropylidene-1,6-D-mannityl] (D-5). 2,4:3,5-di-*O*-isopropylidene-D-mannitol[19] (5.25 g, 20 mmol) was reacted with

diethyl carbonate according to the procedure described for the synthesis of DL-**3** to yield 3.28 g (57%) of D-**5**. η_{inh} (dL/g) = 0.19 in $CHCl_3$. GPC: M_w = 16 000, M_n = 11 700, M_w/M_n = 1.37. DSC: T_g = 105.6 °C. $[\alpha]_D$ = +14.3° (c = 1 in $CHCl_3$, 20 °C). IR (KBr, cm^{-1}): 1756, 1384, 1266, 1219, 1173. ^1H NMR ($CDCl_3$): δ 1.32 (s, 6 H, 2 CH_3), 1.39 (s, 6 H, 2 CH_3), 3.80–3.96 (m, 4 H, 4 CH), 4.22 (dd, $^2J_{AB}$ = ca. 11.5 Hz and J = 6.2 Hz, 2 H_B of 2 CH_2), 4.28 (dd, $^2J_{AB}$ = ca. 11.5 Hz and J = 2.7 Hz, 2 H_A of 2 CH_2). ^{13}C NMR ($CDCl_3$): δ 155.02 (O–C(O)–O), 101.14 (OCO), 67.88, 67.76 (CH), 67.54 (CH_2), 27.55, 23.64 (CH_3). Anal. Calcd for $(C_{13}H_{20}O_7)_n$: C, 54.19; H, 6.94. Found: C, 54.00; H, 7.10.

Synthesis of Poly[[(oxycarbonyl)oxy]-1,6-D-mannityl] (D-6). A total of 5.0 g (17.3 mmol) of D-**5** (having M_w = 6650 and M_n = 5270) was hydrolyzed with 46 mL of trifluoroacetic acid and 7 mL of water in 46 mL of dichloromethane, according to the procedure described for the preparation of DL-**4**. Yield 3.54 g (99%) of D-**6**. η_{inh} (dL/g) = 0.07 in H_2O. DSC: T_g = 47.2 and 58.9 °C (from the 1st run). IR (KBr, cm^{-1}): 3408, 1741, 1282, 1074. ^1H NMR (DMSO-d_6): δ 3.59 (d, J = 9 Hz, 2 H, 2 CH), 3.68 (m, 2 H, 2 CH), 4.07 (m, 2H, 2 H_B of 2 CH_2), 4.33 (d, J = 10.5 Hz, 2 H, 2 H_A of 2 CH_2), 2.8–4.8 (br m, 4 H, 4 OH). ^{13}C NMR (DMSO-d_6): δ 155.16 (O–C(O)–O), 70.36 (CH_2), 68.72 (CH), 68.10 (CH). Anal. Calcd for $(C_7H_{12}O_7)_n$: C, 40.39; H, 5.81. Found: C, 39.60; H, 6.00.

Synthesis of the Acetate Ester Derivatives 7. In a typical procedure, 6.07 g (41 mmol) of DL-**4** was suspended in 90 mL of dry tetrahydrofuran. A total of 1.7 mL of pyridine and 97 mL of acetic anhydride were added to the suspension under an argon stream. The mixture was stirred for 18 h at room temperature, and then the solvent was evaporated under reduced pressure and the residue was dissolved in 30 mL of dichloromethane. The product was precipitated by dropwise addition of this solution into 750 mL of *tert*-butyl methyl ether. The precipitate was washed with 300 mL of water, redissolved in 30 mL of dichloromethane, and reprecipitated from 750 mL of *tert*-butyl methyl ether. The precipitate was dried in vacuo at 50 °C to give 6.9 g (73%) of DL-**7** as a fine, white powder. For physical properties, see Table 1. IR (KBr, cm^{-1}): 2977 (w), 1750 (s, br), 1449 (w), 1411 (w), 1376 (m), 1279 (sh), 1216 (s, br), 1057 (m), 1015 (w), 951 (w), 847 (w), 787 (m), 631 (w), 603 (w). ^1H NMR ($CDCl_3$): δ 2.12 (s, 6H, 2 CH_3), 4.17 (m, 2 H, 2 H_B of 2 CH_2), 4.38 (dm, $^2J_{AB}$ = ca. 12.1 Hz, 2 H, 2 H_A of 2 CH_2), 5.328 (m, 2 H, 2 CH). ^{13}C NMR ($CDCl_3$): δ 169.79 (–C(O)–O), 154.21 (O–C(O)–O), 68.70 (CH), 65.66 (CH_2), 20.66 (CH_3). Anal. Calcd for $(C_9H_{12}O_7)_n$: C, 46.57; H, 5.17. Found: C, 46.70; H, 5.40.

L-**7**: White, fine powder. See also Table 1. IR (KBr, cm^{-1}): 2978 (w), 1751 (s, br), 1456 (w), 1410 (w), 1376 (m), 1279 (sh), 1217 s, br), 1057 (m), 1015 (w), 951 (w), 847 (w), 787 (m), 632 (w), 603 (w). ^1H NMR ($CDCl_3$): δ 2.12 (s, 6 H, 2 CH_3), 4.165 (dd, $^2J_{AB}$ = ca. 11.8 Hz and J = ca. 5.6 Hz, 2 H, 2 H_B of 2 CH_2), 4.385 (dd, $^2J_{AB}$ = ca. 11.8 Hz and J = ca. 3.3 Hz, 2 H, 2 H_A of 2 CH_2), 5.339 (m, 2 H, 2 CH). ^{13}C NMR ($CDCl_3$): δ 169.82 (–C(O)–O), 154.22 (O–C(O)–O), 68.68 (CH), 65.67 (CH_2), 20.66 (CH_3). Anal. Calcd for $(C_9H_{12}O_7)_n$: C, 46.57; H, 5.17. Found: C, 46.30; H, 5.40.

D-**7**: White, fine powder. See also Table 1. IR and NMR spectra of D-**7** were identical to those of L-**7**.

Caproate Ester Derivative L-8: Viscous oil. For preparation and physical properties, see Tables 3 and 4. IR (KBr, cm^{-1}): strong absorptions at 1750, 1246, and 1164. ^1H NMR ($CDCl_3$): δ 0.899 (t, J = 7 Hz, CH_3 of caproate side chain), 1.317 (m, 2 CH_2 of caproate side chain), 1.55–1.70 (m, CH_2 of caproate side chain), 2.26–2.44 (m, CH_2 of caproate side chain), 4.02–4.56 (m, 2 CH_2 of diunits, 2 CH_2 of monounits, 1 CH of monounits and OH of monounits), 5.205 (m, 1 CH of monounits), 5.353 (m, 2 CH of monounits). ^{13}C NMR ($CDCl_3$): δ 172.9, 172.6 (–C(O)–O), ca. 154.5 (multiple signal, O–C(O)–O), ca. 70.1 (multiple signal, CH), ca. 68.6 (multiple signal, CH), ca. 65.8 (multiple signal, CH_2), 33.97 (CH_2 of caproate side chain), 31.17 (CH_2 of caproate side chain), 24.46 (CH_2 of caproate side chain), 22.26 (CH_2 of caproate side chain), 13.87 (CH_3).

Stearate Ester Derivative DL-9: White, powdery solid. See also Tables 3 and 4. The ^1H-NMR spectrum of the product is mainly attributed to the major diunits. Most of the signals of the minor monounits either were overlapping with the signals of the diunits or were too small to obtain. IR (KBr, cm^{-1}): strong absorptions at 2918, 2850, 1751, and 1254. ^1H NMR ($CDCl_3$): δ 0.88 (t, J = ca. 7 Hz, CH_3), 1.00–1.35 (m, CH_2), 1.61 (m, CH_2), 2.34 (m, CH_2), 4.14 (m, 2 H, 2 H_B of 2 CH_2–O of diunits), 4.363 (m, 2 H, 2 H_A of 2 CH_2–O of diunits), 4.0–4.5 (m, CH–O and CH_2–O of monounits), 5.20 (m, 1 CH of monounits), 5.34 (m, 2 CH of diunits).

Ethyloxalate Ester Derivative DL-10: White, fine powder. See also Tables 3 and 4. IR (KBr, cm^{-1}): strong absorptions at 1779, 1749, 1313, 1249, 1181, and 1151. ^1H NMR ($CDCl_3$): δ 1.364 (t, ^3J = ca. 7 Hz, 6 H, 2 CH_3), 4.346 (q, ^3J = ca. 7 Hz, 4 H, 2 side chain CH_2), 4.295–4.410 (m, 2 H, 2 H_B of 2 CH_2), 4.475–4.575 (m, 2 H, 2 H_A of 2 CH_2), 5.522 (m, 2 H, 2 CH). ^{13}C NMR ($CDCl_3$): δ 156.69 (–C(O)–O), 156.59 (–C(O)–O), 153.88 (O–C(O)–O), 71.09 (CH), 65.01 (CH_2), 63.48 (CH_2), 13.84 (CH_3). Anal. Calcd for $(C_{13}H_{16}O_{11})_n$: C, 44.85; H, 4.60. Found: C, 44.70; H, 4.80.

Synthesis of the Formate Ester Derivative DL-11. A total of 7.4 g (50 mmol) of DL-**4** was formylated with in-situ generated formic–acetic anhydride.[20] The product was precipitated from diethyl ether, dissolved in acetone or methyl acetate, and reprecipitated from diethyl ether. The product was dried in vacuo to give 5.5 g (54%) of DL-**11** as a fine, white powder. For physical properties, see Table 4. IR (KBr, cm^{-1}): strong absorbtions at 1758, 1727, 1251, and 1154. ^1H NMR (DMSO-d_6): δ 4.275 (dd, $^2J_{AB}$ = ca. 12 Hz and J = ca. 6 Hz, 2 H, 2 H_B of 2 CH_2), 4.34 (d, $^2J_{AB}$ = ca. 12 Hz, 2 H, 2 H_A of 2 CH_2), 5.40 (m, 2 H, 2 CH), 8.30 (s, 2 H, 2 H–C(O)–O). ^{13}C NMR (DMSO-d_6): δ 65.58 (CH_2), 68.11 (CH), 153.54 (O–C(O)–O), 161.06 (H–C(O)–O). Anal. Calcd for $(C_7H_8O_7)_n$: C, 41.20; H, 3.92. Found: C, 41.30; H, 4.00.

Synthesis of the Ethoxycarbonyl Derivative DL-12. A total of 5.18 g (35 mmol) of DL-**4** was ethoxycarbonylated with 57.22 g (353 mmol) of diethyl pyrocarbonate and 6.958 g (88 mmol) of pyridine in tetrahydrofuran during 3 h at room temperature. After the usual workup, the product was precipitated from *n*-hexane. The precipitate was dissolved in dichloromethane and reprecipitated from diethyl ether–hexane (2:1). The product was dried in vacuo for 48 h to give 8.31 g (81%) of DL-**12**. IR (KBr, cm^{-1}): strong absorbtions at 1752 and 1245. ^1H NMR ($CDCl_3$): δ 1.315 (t, J = ca. 7 Hz, 6 H, 2 CH_3), 4.222 (q, J = ca. 7 Hz, 4 H, 2 CH_2), 4.16–4.32 (m, 2 H, 2 H_B of 2 chain CH_2), 4.42–4.52 (m, 2 H, 2 H_A of 2 chain CH_2), 5.175 (m, 2 H, 2 CH). ^{13}C NMR ($CDCl_3$): δ 154.13 (O–C(O)–O), 72.43, 72.38 (CH), 65.47 (CH_2), 64.81 (CH_2), 14.11 (CH_3). Anal. Calcd for $(C_9H_{12}O_7)_n$: C, 45.21; H, 5.52. Found: C, 45.50; H, 5.60.

Ethoxycarbonyl Derivative DL-13: White powder. See also Tables 3 and 4. IR (KBr, cm^{-1}): 3508 (OH absorption) and strong absorptions at 1757, 1234, 1005, and 786. ^1H NMR ($CDCl_3$): δ 1.312 (t, ^3J = ca. 7.2 Hz, 2 CH_3 of diunits and 1 CH_3 of monounits), 2.75–3.35 (m, 1 OH of monounits), 4.22 (q, ^3J = ca. 7.2 Hz, 2 CH_2 of diunits and 1 CH_2 of monounits), 4.08–4.40 (m, 2 H of diunits and 4 H of monounits), 4.40–4.54 (m, 2 H of diunits and 1 H of monounits), 5.02 (m, 1 CH of monounits), 5.18 (m, 2 CH of diunits).

(Cholesteryloxy)carbonyl Derivative DL-14: White powder. See also Tables 3 and 4. IR (KBr, cm^{-1}): strong absorptions at 2951, 1758, and 1249. ^1H NMR ($CDCl_3$): δ 0.684 (s, 6 H, 2 CH_3), 0.869 (dd, ^3J = ca. 6.5 Hz, 12 H, 4 CH_3), 0.921 (d, ^3J = ca. 6.2 Hz, 6 H, 2 CH_3), 1.083 (s, 6 H, 2 CH_3), 0.75–2.10 (m, 52 H, various CH_2 and CH), 2.28–2.47 (m, 4 H, 2 CH_2), 4.241 (m, 2 H, 2 H_B of 2 chain CH_2), 4.40–4.55 (m, 4 H, 2 H_A of 2 chain CH_2 and 2 CH of cholesteryl residue), 5.153 (m, 2 H, 2 chain CH), 5.396 (m, 2 H, 2 olefin H). Anal. Calcd for $(C_{61}H_{96}O_9)_n$: C, 75.32; H, 9.87. Found: C, 75.10; H, 9.60.

***p*-(Methoxycarbonyl)phenylcarbonate Derivative DL-15**: White, powdery solid. See also Tables 3 and 4. IR (KBr, cm^{-1}): strong absorptions at 1772, 1723, 1282, 1235, 1211, and 1112. ^1H NMR ($CDCl_3$): δ ca. 3.86 (br s, 6 H, 2 CH_3), 4.28–4.45 (m, 2 H, 2 H_B of 2 CH_2), 4.64 (m, 2 H, 2 H_A of 2 CH_2), 5.319 (m, 2 H, 2 CH), 7.18–7.30 (m, 4 H, 4 aromatic H), 7.95–8.09 (m, 4 H, 4 aromatic H). ^{13}C NMR ($CDCl_3$): δ 165.85 (–C(O)–O), 154.23 (aromatic C), 154.04 (O–C(O)–O), 152.19

(O–C(O)–O), 131.22 (aromatic CH), 128.20 (aromatic C), 120.73 (aromatic CH), 73.50 (CHO), 65.32 (CH_2O), 52.19 (CH_3). Anal. Calcd for $(C_{23}H_{20}O_{13})_n$: C, 54.78; H, 3.97. Found: C, 54.20; H, 3.90.

Phenylcarbamate Derivative DL-16: White powder. See also Tables 3 and 4. IR (KBr, cm^{-1}): strong absorptions at 1744, 1602, 1530, 1446, and 1211. ^1H NMR (DMSO-d_6): δ 3.85–4.50 (m, 1 CH and 2 CH_2 of monounits and 2 CH_2 of diunits), 5.04 (1 CH of monounits), 5.30 (m, 2 CH of diunits), 5.63 (m, OH of monounits), 6.96 (m, 2 aromatic H), 7.23 (m, 4 aromatic H), ca. 9.80 (m, 2 NH). ^{13}C NMR (DMSO-d_6): δ ca. 154.0 (multiple signal, O–C(O)–O, 152.5 (O–C(O)–NH), 138.6 (aromatic C), 128.6 (aromatic CH), 122.7 (aromatic CH), 118.5 (aromatic CH), ca. 69.5 (br, CH), ca. 66.5 (br, CH_2). Some additional weak signals of the minor monocarbamoylated units were also present.

Boc-L-Phenylalanyl Ester Derivative 17: White powder. See also Tables 3 and 4. IR (KBr, cm^{-1}): 3399, 2979 and strong absorptions at 1760, 1717, 1499, 1251, and 1166. ^1H NMR (DMSO-d_6): δ 1.18 (m, 18 H, 6 CH_3), 2.78–2.94 (m, 2 H, benzyl CH_2), 2.94–3.07 (m, 2 H, benzyl CH_2), 4.04–4.30 (m, 6 H, 2 chain CH_2 and 2 side chain CH), 5.24–5.40 (m, 2 H, 2 chain CH), 7.12–7.38 (m, 12 H, 2 NH and 10 aromatic H). ^{13}C NMR (DMSO-d_6): δ 171.5, 171.0 (–C(O)–O), 155.3, 155.2 (O–C(O)–O), 153.6 (NH–C(O)–O), 137.2 (aromatic C), 128.9, 128.0, 126.3 (aromatic CH), 78.4, 78.3 (side chain C), 69.1 (chain CH), 65.4 (chain CH_2), 55.0 (side chain CH), 36.2, 35.9 (benzyl CH_2), 28.0, 27.7 (CH_3). Anal. Calcd for $(C_{33}H_{42}N_2O_{11})_n$: 61.67; H, 6.59; N, 4.36. Found: C, 61.40; H, 6.40; N, 4.30.

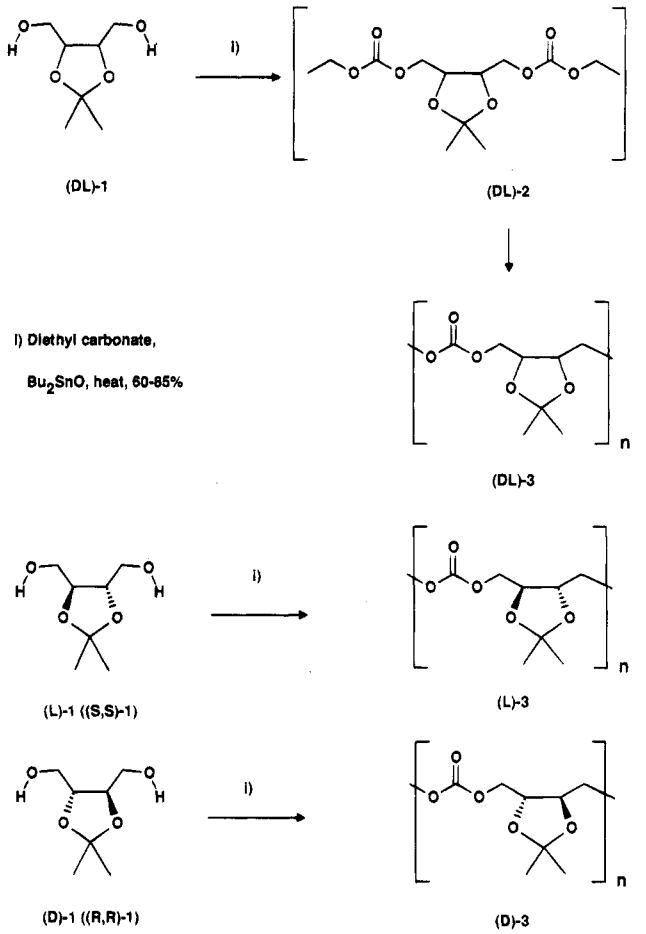
(Z)-L-Leucyl Ester Derivative 18: White powder. See also Tables 3 and 4. IR (KBr, cm^{-1}): strong absorptions at 3370, 2962, 1762, 1723, 1528, 1262, 1162, and 1048. ^1H NMR (DMSO-d_6): δ 0.70–0.97 (m, 12 H, 2 CH_3), 1.34–1.70 (m, 6 H, 2 side chain CH_2 and 2 side chain CH), 4.00–4.35 (m, 6 H, 2 chain CH_2 and 2 side chain CH), 5.00 (m, 4 H, 2 benzyl CH_2), 5.32 (m, 2 H, 2 chain CH), 7.18–7.42 (m, 10 H, 10 aromatic CH), 7.70 (m, 2 H, 2 NH). ^{13}C NMR (DMSO-d_6): δ 172.2, 171.7 (–C(O)–O), 156.0, (O–C(O)–O), 153.5 (NH–C(O)–O), 136.6 (aromatic C), 128.2, 127.6 (aromatic CH), 69.2 (chain CH), 65.5 (chain CH_2), 52.3 (side chain CH), 24.1 (side chain CH), 22.7, 22.5, 21.2, 20.9 (CH_3). Anal. Calcd for $(C_{33}H_{42}N_2O_{11})_n$: C, 61.67; H, 6.59; N, 4.36. Found: C, 61.50; H, 6.55; N, 4.40.

Orthoformate Derivative DL-19: White solid. See also Tables 3 and 4. IR (film, cm^{-1}): strong absorptions at 1753, 1263, and 1069. ^1H NMR ($CDCl_3$): δ 1.217 (t, ^3J = 7 Hz, 3 H, CH_3), 3.60 (q, ^3J = 7 Hz, 2 H, side chain CH_2), 4.15–4.40 (m, 6 H, 2 CH_2 and 2 CH), 5.87 (s, 1 H, side chain CH). ^{13}C NMR ($CDCl_3$): δ 154.43 (O–C(O)–O), 115.93 (ortho ester CH), 75.05 (CH), 68.22 (CH_2), 66.93 (CH_2), 60.77 (side chain CH_2), 14.96 (CH_3). Anal. Calcd for $(C_8H_{12}O_6)_n$: C, 47.06; H, 5.92. Found: C, 46.70; H, 6.00.

Orthocarbonate Derivative DL-20: white solid. See also Tables 3 and 4. IR (film, cm^{-1}): strong absorptions at 2982, 1755, 1266, 1214, 1145, and 1047. ^1H NMR ($CDCl_3$): δ 1.21 (t, ^3J = 7 Hz, 6 H, 2 CH_3), 3.715 (q, ^3J = 7 Hz, 4 H, 2 side chain CH_2), 4.27 (m, 2 H, 2 H_B of 2 CH_2), 4.315 (m, 4 H, 2 H_A of 2 CH_2 and 2 CH). ^{13}C NMR ($CDCl_3$): δ 154.39 (O–C(O)–O), 127.48 (orthocarbonate C), 74.74 (CH), 67.38 (CH_2), 60.16 (side chain CH_2), 14.98 (CH_3). Anal. Calcd for $(C_{10}H_{16}O_7)_n$: C, 48.39; H, 6.50. Found: C, 48.10; H, 6.50.

Synthesis of the Acetate Derivative D-21. A total of 1.04 g (5 mmol) of D-**6** was acetylated according to the procedure described for the acetylation of DL-**4** to yield 1.2 g (64%) of D-**21**. η_{inh} (dL/g) = 0.075 in $CHCl_3$. GPC: M_w = 6200, M_n = 5050, M_w/M_n = 1.23. DSC: T_g = 54.7 °C (from the 1st run). IR (KBr, cm^{-1}): strong absorptions at 1753, 1373, 1268, and 1218. ^1H NMR ($CDCl_3$): δ 2.05 (s, 6 H, 2 CH_3), 2.09 (s, 6 H, 2 CH_3), 4.11 (dd, $^2J_{AB}$ = 12 Hz and J = 5.5 Hz, 2 H, 2 H_B of 2 CH_2), 4.24 (dd, $^2J_{AB}$ = 12 Hz and J = 3 Hz, 2 H, 2 H_A of 2 CH_2), 5.08 (m, 2 H, 2 CH), 5.41 (d, J = 8 Hz, 2 H, 2 CH). ^{13}C NMR ($CDCl_3$): δ 69.72 (–C(O)–O), 169.60 (–C(O)–O), 154.29 (O–C(O)–O), 67.54 (CH), 65.80 (CH_2), 20.76 (CH_3), 20.53 (CH_3). Anal. Calcd for $(C_{15}O_{20}O_{11})_n$: C, 47.88; H, 5.36. Found: C, 47.50; H, 5.50.

Scheme 2



Results and Discussion

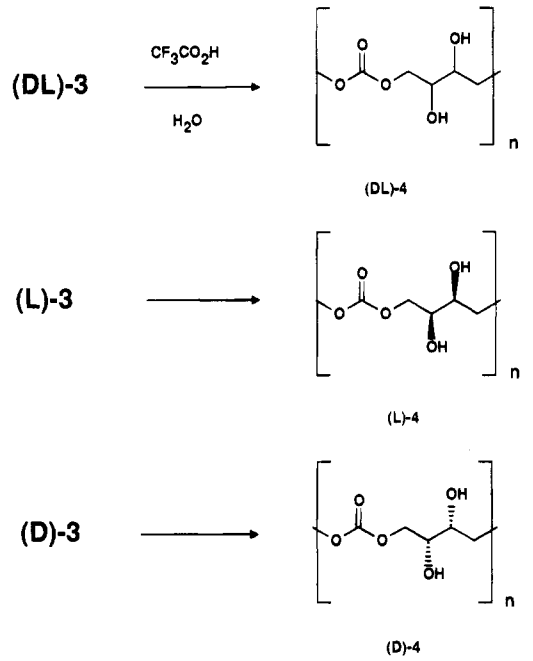
Synthesis of the PHAC's. Commercially available 2,3-*O*-isopropylidenethreitol (**1**) was reacted with diethyl carbonate in a one-pot synthesis using dibutyltin oxide as catalyst (Scheme 2). The bis(ethoxycarbonyl) derivative **2** was formed as an intermediate in situ. The polymerizations have also been carried out using **2** as the starting material, to give the same products as obtained from the one-pot synthesis under similar conditions. However, the formation of low concentrations of the corresponding seven-membered carbonate ring as an intermediate in both cases prior to the polymerization cannot be excluded yet. The synthesis of polycarbonates by reaction of diols with urea using dibutyltin oxide among other catalysts has already been described in the literature.[16] Temperatures higher than 160 °C are required for these treatments, conditions under which many functionalized polycarbonates are unstable. The dibutyltin oxide catalyzed reaction of diols with dialkyl carbonates described above proceeded under milder conditions at 120–160 °C. The polymerization can be carried out either with an enantiomer or with a racemic mixture of 2,3-*O*-isopropylidenethreitol (**1**) to give products of comparable molecular weights in similar yields under similar conditions (Table 1). Starting with D-**1** ((*R*,*R*)-**1**) and L-**1** ((*S*,*S*)-**1**), the enantiomeric products D-**3** and L-**3** were obtained, respectively. They exhibited the same $[\alpha]_D$ values with opposite signs (Table 1) and provided identical IR and NMR spectra. Starting with a DL-mixture (1:1) gave products with no significant optical activity. Since diastereomeric sequences are formed in this case, some minor differences in the coupling pattern of the ^1H-NMR spectra of DL-**3**

Table 2. Polycarbonates DL-3 from DL-1 and Diethyl Carbonate at Different Reaction Conditions

condition	M_w ($\times 10^{-3}$)	M_n ($\times 10^{-3}$)	M_w/M_n	T_g (°C)	yield (%)
a	10.70	6.45	1.66	42.0	57
b	20.30	11.10	1.83	47.0	69
c	23.40	12.70	1.84	50.1	53
d	42.00	27.20	1.54	54.5	37

[a] 24 h/120 °C/100 mbar; 24 h/120 °C/400 mbar; 24 h/120 °C/100 mbar; 24 h/120 °C/0.2 mbar. [b] 24 h/120 °C/100 mbar; 24 h/140 °C/400 mbar; 24 h/140 °C/100 mbar; 24 h/140 °C/0.2 mbar. [c] 24 h/120 °C/100 mbar; 24 h/150 °C/400 mbar; 24 h/150 °C/100 mbar; 24 h/150 °C/0.2 mbar. [d] 24 h/120 °C/100 mbar; 24 h/120 °C/1000 mbar; 24 h/120 °C/8 mbar; 30 h/140 °C/0.35 mbar; 30 h/160 °C/0.35 mbar.

Scheme 3



were observed in comparison to those of the enantiomerically pure D-3 or L-3. By varying reaction conditions such as temperature and reaction time, products of different molecular weights were prepared (Table 2), but no efforts were undertaken to optimize the polymerization reactions. At 160 °C and higher temperatures, the polymerization was accompanied by degradation, mainly into the seven-membered carbonate ring 2-oxo-1,3-dioxa-5,6-dioxy-5,6-*O*-isopropylidenecycloheptane.[17]

Following the polymerization step, the protecting groups in D-3, L-3, and DL-3 were removed with trifluoroacetic acid and water in dichloromethane to give the novel PHAC's 4 in high yields (Scheme 3). All of them gave sufficient and clean NMR and IR spectra; e.g., see Figures 1–3 for the spectra of DL-4. They also exhibited clean and simple glass transition temperatures; see, e.g., Figure 4 for the DSC of DL-4. Some minor degradation of the polycarbonate chain occurred during the deprotection step as reflected in the smaller degree of polymerization of the acetate derivatives D-7, L-7, and DL-7 in comparison to the corresponding precursors D-3, L-3, and DL-3, respectively (Table 1). This is not surprising, since the isopropylidene protecting groups were removed under acidic conditions in the presence of H_2O. If high molecular weight products are desired, other protecting groups such as benzyl ethers, which can be cleaved under neutral conditions, must be used to avoid any

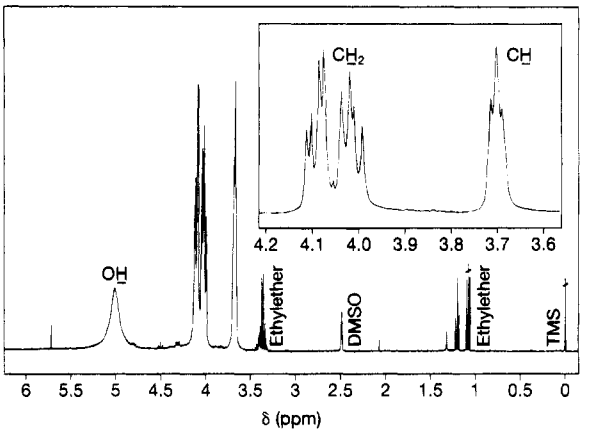


Figure 1. ^{1}H-NMR spectrum of DL-4.

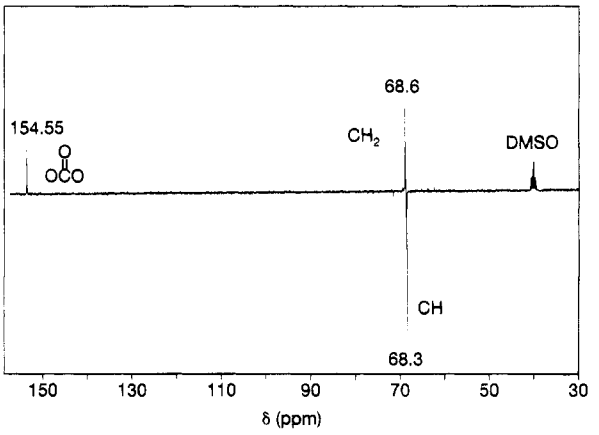


Figure 2. ^{13}C-NMR spectrum of DL-4 (J-MOD).

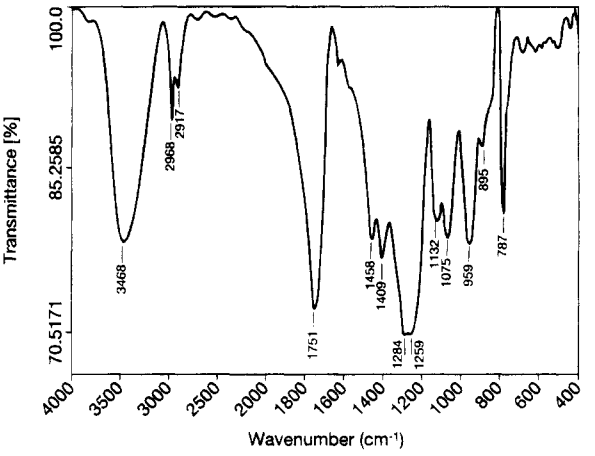


Figure 3. IR spectrum of DL-4 (KBr).

degradation during the deprotection step.

D-, L-, and DL-4 are all colorless powders, stable at room temperature under argon in a dry atmosphere. They are soluble in water, dimethylformamide, and dimethyl sulfoxide. They are insoluble or hardly soluble in dichloromethane, chloroform, tetrahydrofuran, ethyl acetate, acetone, and ethanol. In a water solution, slow degradation into monomers and smaller oligomers occurs, which can be followed by viscosimetry; see Figure 5. Since common poly(alkylene carbonate)s are not degradable in water at slightly acidic or basic pH's, the degradability of these PHAC's even in neutral water must be attributed to the presence of the free hydroxy substituents. The effect of the hydroxy substituents is not limited to an increase of the hydrophilicity of the polymer. From ^{1}H NMR of the degradation products,

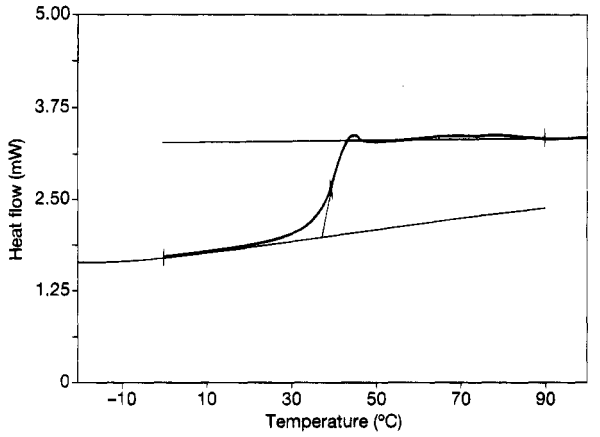


Figure 4. DSC of DL-**4** (2nd run).

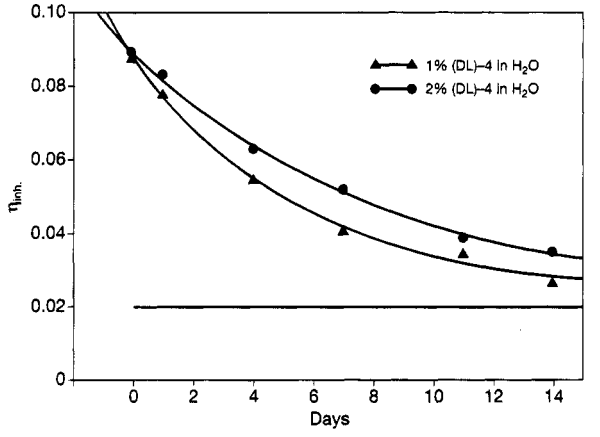
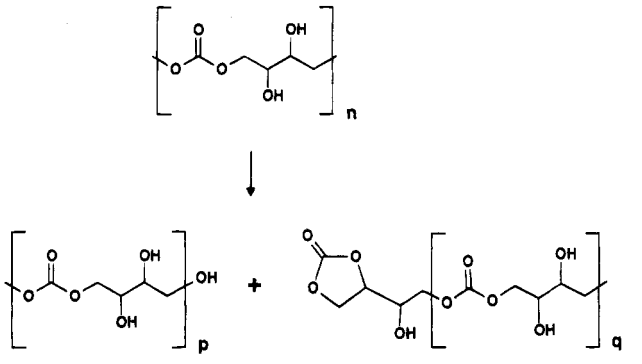


Figure 5. Degradation of DL-**4** in water.

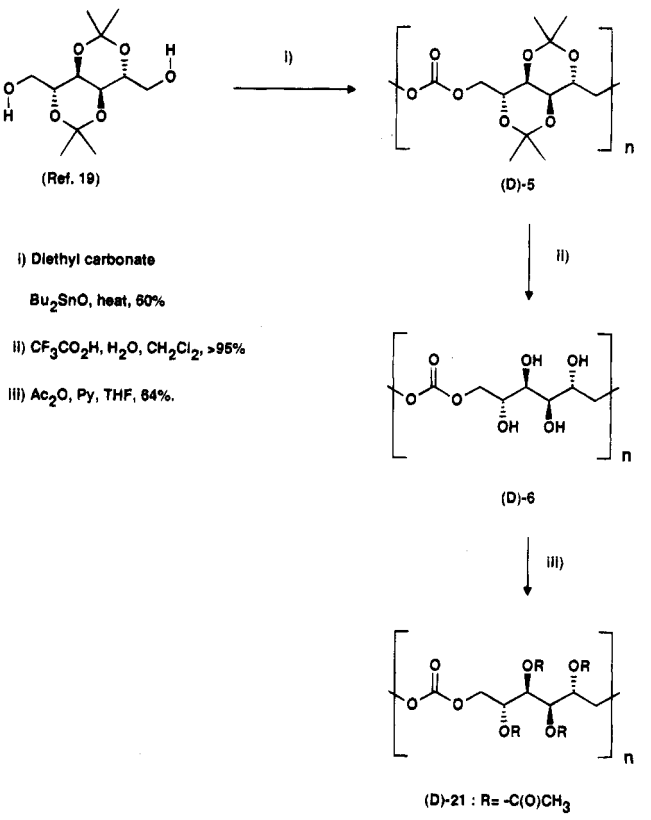
Scheme 4



we conclude a direct participation of the free hydroxy groups in the degradation: Intramolecular nucleophilic attack of a hydroxy substituent at a carbonate function leads to chain scission with a cyclic carbonate (preferably a five-ring carbonate[18]) as one end group and an alcohol as the second one (Scheme 4). The intramolecular nucleophilic attack in PHAC's is slower than that in PHOMEC,[7] since secondary hydroxy groups of the chain are attacking in PHAC's compared to conformational free primary hydroxy groups in the case of PHOMEC. This explains the relative stability of the PHAC's in comparison to PHOMEC. Subsequently, transesterification or slow hydrolysis of the formed carbonate ring may occur.

The synthetic strategy was extended to prepare PHAC's having six C atoms and four pendant hydroxy groups in each constitutional unit. Polycondensation of 2,4:3,5-di-*O*-isopropylidene-D-mannitol[19] with diethyl carbonate gave the polycarbonate D-**5** in good yield

Scheme 5



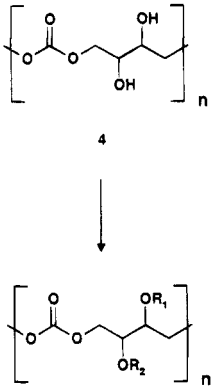
(Scheme 5). Subsequent hydrolysis of D-**5**, under the same conditions used to convert the polycarbonates **3** into the PHAC's **4**, gave D-**6** in high yield. D-**6** exhibited solubility properties similar to those of the PHAC's **4** from threitol. However, it was less sensitive to water and humidity.

Derivatizations. The synthesized carboxylic and carbonic acid ester derivatives of the PHAC's **4** are listed in Scheme 6. Depending on the reaction conditions (Table 3), complete or partial derivatization of the hydroxy groups could be achieved. The acetates D-, L- and DL-**7** were soluble in common organic solvents used for GPC, e.g., dichloromethane and tetrahydrofuran, and served as reference derivatives to calculate the approximate degree of polymerization (n) of the corresponding PHAC's under the assumption that no degradation was occurring during the mild acetylation step. The lipophilic caproate ester L-**8** and stearate ester DL-**9** are supposed to have quite different surface and absorption properties than acetates. According to ^{1}H NMR of L-**8**, 76% of the hydroxy groups were esterified and 24% were present in free condition. Thus, L-**8** comprised 52% dicaproate ester units (diunits) and 48% monocaproate ester units (monounits). This ratio was determined from the integrals of the signals at 5.352 (2 CH of diunits) and 5.205 ppm (1 CH of monunits). Analogously, 90% diunits and 10% monounits were found for DL-**9** from the integrals of the signals at 5.34 and 5.20 ppm. The polymeric structure of DL-**11** was retained even if the formylation was performed with in-situ generated formic–acetic anhydride, under acidic conditions.[20] However, a substantial decrease of the molecular weight must be faced in this case. Several carbonic acid ester derivatives of DL-**4** were also synthesized. DL-**12** and DL-**13** were prepared as hydrophilic polycarbonates, swellable in water. The ratio of diunits to monounits in DL-**13** was found to be 53:47 from the integrals of the signals at 5.18 and 5.02 ppm. DL-**14** and DL-**15**

Table 3. Reagents and Conditions for the Synthesis of the Polycarbonates 8–20

product	reagent (mol equiv) and Conditions, yield (%)
L-**8**	caproic anhydride (14.5), pyridine (0.5), DMF, rt, 20 h, 50%
DL-**9**	stearoyl chloride (3.1), pyridine (2.1), DMF/THF, rt, 28 h, 58%
DL-**10**	ethyloxayl chloride (2.2), pyridine (2.0), DMF/THF, 0 °C, 7 h, 59%
DL-**11**	see experimental part
DL-**12**	see experimental part
DL-**13**	diethyl pyrocarbonate (2.0), pyridine (2.1), THF, rt, 30 min, 79%
DL-**14**	cholesteryl chloroformate (2.1), pyridine (2.1), toluene, rt, 50 h, 72%
DL-**15**	4-(methoxycarbonyl)phenyl chloroformate (2.5), pyridine (2.2), toluene, rt, 65 h, 56%
DL-**16**	phenyl isocyanate (15.0), pyridine (0.46), THF, rt, 96 h, 23%
DL-**17**	Boc-L-phenylalanine (6), DCC (6), DMAP (catalyst), THF/DMF, rt, 2 h, 64%
DL-**18**	(*Z*)-L-leucin (6), DCC (1.0), DMAP (catalyst), THF/DMF, rt, 2 h, ca. 80%
DL-**19**	triethyl orthoformate (10.0), trifluoroacetic acid (1.1), THF, rt, 4 h, 51%
DL-**20**	tetraethyl orthocarbonate (10.0), trifluoroacetic acid (2.2), THF, rt, 18 h, 74%

Scheme 6. Ester Derivatives of the PHAC's 4



7 : R_1= R_2= -C(O)-CH_3

8 : R_1= -C(O)-$(CH_2)_4$-CH_3

R_2= R_1 or H (52:48)

9 : R_1= -C(O)-$(CH_2)_{16}$-CH_3

R_2= R_1 or H (90:10)

10 : R_1= R_2= -C(O)-CO_2Et

11 : R_1= R_2= -C(O)-H

12 : R_1= R_2= -CO_2Et

13 : R_1= -CO_2Et

R_2= R_1 or H (53:47)

14 : R_1= R_2= -C(O)-O-Cholesteryl

15 : R_1= R_2= -C(O)-O-(C_6H_4)-CO_2CH_3

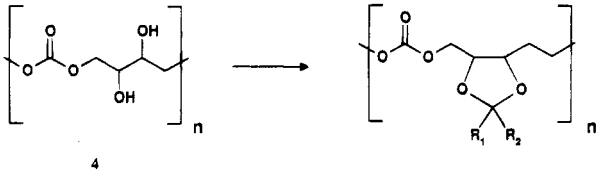
16 : R_1= -C(O)-NH-Ph

R_2= R_1 or H (86:14)

17 : R_1= R_2= BOC-L-Phenylalanyl

18 : R_1= R_2= Z-L-Leucyl

Scheme 7. Orthoester of the PHAC's 4



19 : R_1= H, R_2= OEt

20 : R_1= R_2= OEt

served as lipophilic carbonic acid ester derivatives. Finally, DL-**16** was prepared as a carbamic acid ester derivative. From the integrals of the signals at 5.30 and 5.04 ppm, 86% diunits and 14% monounits were present in DL-**16**.

As far as derivatizations of the PHAC's **4** and D-**6** with amino acids or peptides are concerned, several strategies are feasible from the results described above. The carboxyl group of the amino acids can be used to form carboxylic ester. Alternatively, the amino group can be utilized by conversion into the corresponding isocyanate, which can be reacted with the free hydroxy groups of the PHAC's to give the carbamic acid ester. Finally, amino acids having a free hydroxy group, e.g., serin, can be coupled to the PHAC's also by means of a carbonic acid ester. The carboxyl groups of both Boc-L-phenylalanine and (*Z*)-L-leucine were utilized to prepare the corresponding amino acid ester derivatives of DL-**4**.

The carboxylic and carbonic acid esters are more sensitive to basic than to slightly acidic conditions. The ethyl orthoformate derivative DL-**19** and the diethyl orthocarbonate derivative DL-**20** (Scheme 7) were synthesized as acid-sensitive derivatives of DL-**4**. Both DL-**19** and DL-**20** exhibited high acid sensitivity. With acid traces in the absence of water, crosslinking to insoluble products was observed frequently. Once purified sufficiently, both products were stable and processable. For physical properties of the PHAC derivatives **8**–**20**, see Table 4. Similar derivatizations described so far for the PHAC's **4** should also be possible with D-**6**. Acetylation of D-**6** with excess acetic ahydride gave the acetate D-**21** (Scheme 5). Other derivatizations of D-**6** are in progress.

Table 4. Selected Physical Properties of the Polycarbonates 8–20

product	M_w ($\times 10^{-3}$)	M_n ($\times 10^{-3}$)	M_w/M_n	T_g (°C)	η (dL/g)[a]
L-**8**	7.55	5.00	1.51	9.9	0.08
DL-**9**	20.35	16.40	1.24	50–80 (T_m)	0.14
DL-**10**	15.00	9.85	1.52	53.8	0.09
DL-**11**				54.3	0.065[b]
DL-**12**	15.65	10.55	1.48	49.8	0.12
DL-**13**	11.45	7.95	1.44	45.4	0.10
DL-**14**	18.15	11.60	1.56	nd	0.12
DL-**15**	22.60	13.50	1.67	90.9	0.12
DL-**16**	17.70	10.90	1.62	86.7	0.115[b]
DL-**17**	15.00	10.80	1.39	82.4	0.09
DL-**18**	19.60	16.50	1.19	50.9	0.11
DL-**19**	10.65	6.65	1.60	23.5	0.10
DL-**20**	11.75	7.75	1.52	10.8	0.10

[a] Inherent viscosity in $CHCl_3$ at 20 °C, c = 10 mg/mL, if nothing else is indicated. [b] Inherent viscosity in acetone, 20 °C, 10 mg/mL.

Degradation Studies. The degradation properties of the carboxylic acid ester DL-**11** and the carbonic acid ester DL-**12** have been investigated. The formate ester DL-**11** showed almost identical degradation in vitro and in vivo during 64 days (Figure 6). This indicates a hydrolytic cleavage of the formate ester side chains in vivo. About 80% of the implant mass was bioeroded at this time. No significant mass loss could be found for DL-**12** during the 64-day period, neither in vitro nor in vivo (Figure 7). The molecular weight of the samples also remained unchanged. This is surprising, since release of ethanol from poly[[[(ethoxycarbonyl)oxy]-methyl]ethylene carbonate] is reported in vitro in the presence of a lipase.[21] These results suggest that no significant hydrolytic cleavage of the polycarbonate

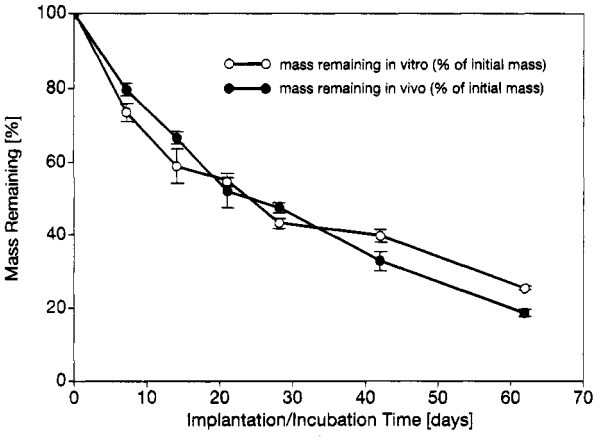


Figure 6. Degradation of DL-**11** in vitro and in vivo.

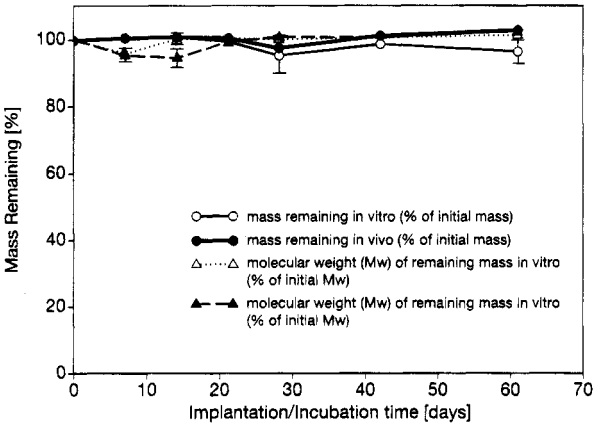


Figure 7. Degradation of DL-**12** in vitro and in vivo.

main chain is taking place in DL-**12**. In conclusion, the hydrolytic cleavage of a polycarbonate chain can be neglected during a degradation time of 64 days. Therefore, the degradation of DL-**11** must be attributed to intramolecular attacks of the free hydroxy groups on the carbonate functions of the chain, after hydrolytic cleavage of the formate ester groups. This is in accordance with the results discussed in the previous chapter and supports the proposed degradation mechanism for the PHAC's.

Conclusions

PHAC's represent a new, versatile class of bioerodible polymers. They are sufficiently stable to be derivatized by means of their pendant hydroxy groups. Although water soluble, they are unstable in aqueous media, degrading within a few days to several weeks. The degradation proceeds presumably by a special mechanism, in which the hydroxy groups are participating. As water-soluble polyols, they may replace PEG's in many applications, where the disappearance of the polymer after a certain period of time is desirable. Carboxylic and carbonic acid ester side chains of the water-insoluble PHAC derivatives are supposed to be cleavable at slightly basic conditions in vitro and in vivo, leaving behind a readily degradable backbone with free hydroxy groups. The PHAC derivatives are of interest as a matrix for controlled drug release and for medical applications. The nature of the PHAC backbone as well as of the selected derivatization will influence the physical and degradation properties of the products. The extent of derivatizations is adjustable in most cases. The PHAC's are also of particular interest for prodrug formation and for drug solubilization, since they are water soluble and can easily be reacted with a variety of substrates including amino acids. No biocompatibility problems are expected for the PHAC's, since they are built up from reduced monosaccharides. The reactions described here can presumably be extended to all other, properly protected, reduced monosaccharides and similar compounds as starting materials.

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(17) The compound sublimized at 160 °C (0.35 mbar) and higher temperatures. The racemic (DL) form had a mp of 123.5–124 °C and the following spectroscopic data: IR (KBr, cm^{-1}): 2989 (w), 1780 (s), 1168 (s), 1076 (m), 1050 (s). ^1H NMR ($CDCl_3$): δ 1.38 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.98 (dd, J = 9 and 6 Hz, 1 H), 4.13 (dd, J = 9 and 7 Hz, 1 H), 4.24 (td, J = 6 and 2 Hz), 4.45 (dd, J = 8.3 and 6 Hz, 1 H), 4.51 (t, J = 8.3 Hz, 1 H), 4.71 (ddd, J = 8.3, 6, and 2 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 154.7 (O–C(O)–O), 110.5 (O–$C(CH_3)_2$–O), 75.0 (CH), 74.6 (CH), 66.2 (CH_2), 64.8 (CH_2), 25.8 (CH_3), 25.2 (CH_3).
(18) The degradation of DL-**4** was investigated in D_2O solution. The ^1H-NMR signals of the five-ring carbonate end group appeared at δ 5.02 (m, 1 H, CH), 4.70 (t, J = 9 Hz, 1 H of CH_2), and 4.52 (dd, J = 11 Hz and J = 7.5 Hz, 1 H of CH_2) in a mixture of monomeric and oligomeric degradation products. This is in accordance with the corresponding ^1H-NMR signals of PHOMEC in D_2O, which are found at δ 5.00 (m, 1 H, CH), 4.68 (t, J = ca. 8 Hz, 1 H of ring CH_2), and 4.44 (dd, J = ca. 10 Hz and J = 8 Hz, 1 H of ring CH_2). The signals of the CH_2–OD group of PHOMEC appear as an AB system at δ 3.93 (dd, J = 14 Hz and J = 2 Hz) and 3.75 (dd, J = 14 Hz and J = 4 Hz).
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