Ring-Opening Polymerization of the Cyclic Ester Amide Derived from Adipic Anhydride and 1-Amino-5-pentanol

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ABSTRACT: The ring-opening polymerization of the cyclic ester amide (cEA, **2**) (systematic name, 1-oxa-7-aza-cyclotridecane-8,13-dione)—prepared from adipic anhydride and 1-amino-5-pentanol—in the melt at temperatures above 145 °C with $Bu_2Sn(OMe)_2$, $Ti(OBu)_4$, Al(O-*sec*-Bu)$_3$, or Sn(octoate)$_2$ as initiator yields the poly(ester amide) (PEA, **3**) (systematic name, poly(5-(5-oxypentylcarbamoyl)pentanoate) with regular microstructure. This poly(ester amide) is a semicrystalline material with a melting point of 108 °C. The elementary chain growth reaction proceeds by a coordination insertion mechanism in analogy to the polymerization of lactones. The monomer-to-initiator ratio and the conversion determine the number-average molecular weight. By using hydroxy telechelic poly(ethylene oxide) with Sn(octoate)$_2$ as initiator poly(ester amide)-*block*-poly(ethylene oxide) and poly(ester amide)-*block*-poly(ethylene oxide)-*block*-poly(ester amide) were obtained. Kinetic studies for different monomer-to-initiator ratios, different temperatures and initiators reveal that the ring-opening polymerization is a first-order reaction with respect to the monomer and shows no termination and transfer reactions.

Introduction

The ring-opening polymerization (ROP) of cyclic ester amides from α-hydroxy acids and α-amino acids—known as depsipeptides[1] or morpholine diones—has been studied intensively in the past decade.[2−11] The polymerization is usually performed in the melt at temperatures $T > 100$ °C using transition metal initiators and proceeds according to a chain growth reaction. From a mechanistic point of view, the ROP of cyclic ester amides has obvious similarities to the ROP of lactones and occurs via a coordination insertion mechanism.[12−17] The active species is generated upon acyl-oxygen cleavage under exclusive participation of the ester group. By using macroinitiators derived from poly(ethylene oxide), A−B and B−A−B block copolymers with enhanced hydrophilicity were obtained.[18−22] The cyclic six-membered depsipeptide monomers were synthesized by cyclization of a linear precursor.[23,24]

Reports on ROP of cyclic ester amides with larger rings have scarcely been mentioned in the literature. We prepared cyclic diester diamides (14-membered rings) of α-amino acids and β-hydroxy acids and cyclic ester amides (11-membered rings) of ϵ-amino acids and β-hydroxy acids by ring-enlargement reactions of corresponding hydroxyacyl diketopiperazines or hydroxyacyl lactames.[25] The 14-membered rings could not be polymerized; however, different substituted 11-membered rings were successfully polymerized.[26−28]

This paper reports on the synthesis and ring-opening polymerization of 1-oxa-7-aza-cyclotridecane-8,13-dione, a 13-membered cyclic ester amide prepared from adipic anhydride and 1-amino-5-pentanol. Kinetic aspects of the ROP at different monomer to initiator ratios, different temperatures, and using different initiators are investigated. Using poly(ethylene oxide) macroinitiators, a series of A−B and B−A−B block copolymers were prepared.

Experimental Part

Materials. Adipic acid (Bayer AG, 99%) and 1-amino-5-pentanol (Fluka, 96%), were used as received. 5-(5-Hydroxypentylcarbamoyl)-pentanoic acid (**1**) and poly(ester amide) **3** were prepared according to the literature.[29] Before polymerization the monomer 1-oxa-7-aza-cyclotridecane-8,13-dione (**2**) was sublimed at 120 °C and 10^{-2} mbar. The initiators aluminum(III) *sec*-butylate (Al(O-*sec*-Bu)$_3$, Aldrich, 99.99%), tin(II) 2-ethylhexanoate (Sn(octoate)$_2$, Aldrich), titanium(IV) butoxide ($Ti(OBu)_4$, Acros, 99%), and dibutyldimethoxytin(IV) ($Bu_2Sn(OMe)_2$, Aldrich) were used without further purification. The monomer, initiators, and purified reagents were stored under nitrogen. Dimethylformamide (DMF, 99%) was refluxed over CaH_2 for several hours and distilled before use. The monofunctional poly(ethylene oxide)s (MPEO 2000, MPEO 5000, MPEO 10000, MPEO 20000) and bis(hydroxy) functional poly(ethylene oxide)s (PEO 2000, PEO 6800, PEO 11800, PEO 20000) of narrow molecular weight distribution ($M_w/M_n \approx 1.1$) from Shearwater Polymers Inc. were used as received.

Polymerizations were carried out in nitrogen atmosphere. Nitrogen (Linde) was passed over molecular sieves (4 Å) and finely distributed potassium on aluminum oxide.

Measurements. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 FT-NMR spectrometer at 300 and 75 MHz, respectively. Chloroform ($CDCl_3$), dimethyl sulfoxide (DMSO-d_6), and trifluoroacetic acid (TFA-*d*) were used as solvents, and tetramethylsilane (TMS) served as an internal standard.

Gel permeation chromatography (GPC) analyses were carried out using a high-pressure liquid chromatography pump (Bischoff HPLC pump 2200) and a refractive index detector (Waters 410). The eluting solvent was dimethylacetamide (DMAc) with 2.44 g·L^{-1} LiCl with a flow rate of 0.8 mL·min^{-1} at 80 °C. Four columns with MZ-DVB gel were applied: length of each column 300 mm, diameter 8 mm, diameter of gel particles 5 μm, and nominal pore widths 100, 100, 10^3, and 10^4 Å. Calibration was achieved using polystyrene standards of narrow molecular weight distribution from Polymer Standard Service Mainz.

Differential scanning calorimetric analyses were performed with a Netzsch DSC 204 under nitrogen with a heating rate of 10 K·min^{-1}. Calibration was achieved using indium standard samples.

Thermogravimetric analyses were performed on a TG 209 with a TA-System-Controller TASC 412/2 and kinetic software from Netzsch.

C, H, N elemental analyses were performed with a Carlo Erba MOD 1106 instrument.

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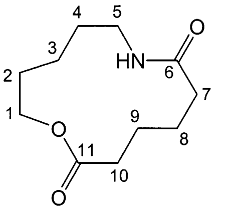
Preparation of the Monomer. Method a. 5-(5-Hydroxypentylcarbamoyl)pentanoic acid[29] (**1**) (5.84 g, 25.3 mmol) and Ti(OBu)$_4$ (170 mg, 0.5 mmol) were heated for 16 d at 170 °C and 10^{-2} mbar. The cyclic ester amide **2** was collected by sublimation. Yield: 3.44 g, 16.1 mmol (64%). Mp: 142−143 °C.

Method b. Poly(ester amide)[29] **3** (1.06 g, 5.0 mmol) and Bu$_2$Sn(OMe)$_2$ (29.5 mg, 0.1 mmol) were heated for 16 d at 170 °C and 10^{-2} mbar. The cyclic ester amide **2** was collected by sublimation. Yield: 0.65 mg, 3.1 mmol (61%). Mp: 142−143 °C.



2

^{1}H NMR (DMSO-d_6): $\delta = 1.35$ (m, 4H, CH$_2$−3/4), 1.53 (m, 4H, CH$_2$−2/8), 1.63 (m, 2H, CH$_2$−9), 2.02 (m, 2H, CH$_2$−7), 2.26 (m, 2H, CH$_2$−10), 3.04 (d/tr, 2H, CH$_2$−5, $^3J = 4.5$ Hz, $^3J = 5.7$ Hz), 4.00 (tr, 2H, CH$_2$−1, $^3J = 5.3$ Hz), 7.67 (br s, 1H, NH) ppm.

^{13}C NMR (DMSO-d_6): $\delta = 20.55$ (C-3, 1C), 23.89 (C-9, 1C), 26.16 (C-8, 1C), 26.96 (C-2, 1C), 27.37 (C-4, 1C), 34.49 (C-10, 1C), 35.96 (C-7, 1C), 36.79 (C-5, 1C), 62.10 (C-1, 1C), 172.25 (C-6/11, 1C), 172.42 (C-6/11, 1C) ppm.

^{1}H NMR (CDCl$_3$): $\delta = 1.49$ (m, 4H, CH$_2$−3/4), 1.67 (m, 4H, CH$_2$−2/8), 1.80 (m, 2H, CH$_2$−9), 2.27 (m, 2H, CH$_2$−7), 2.37 (m, 2H, CH$_2$−10), 3.31 (d/tr, 2H, CH$_2$−5, $^3J = 4.5$ Hz, $^3J = 5.7$ Hz), 4.16 (tr, 2H, CH$_2$−1, $^3J = 5.3$ Hz), 5.58 (br s, 1H, NH) ppm.

^{13}C NMR (CDCl$_3$): $\delta = 20.75$ (C-3, 1C), 24.11 (C-9, 1C), 26.26 (C-8, 1C), 27.13 (C-2, 1C), 27.45 (C-4, 1C), 34.83 (C-10, 1C), 36.41 (C-7, 1C), 37.93 (C-5, 1C), 62.34 (C-1, 1C), 173.12 (C-6/11, 1C), 173.68 (C-6/11, 1C) ppm.

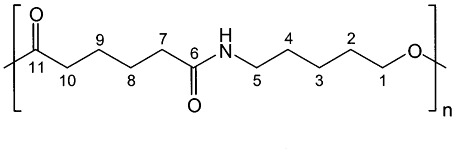
^{1}H NMR (TFA-d): $\delta = 1.62$ (m, 2H, CH$_2$−3), 1.85 (m, 4H, CH$_2$−2/4), 1.94 (m, 4H, CH$_2$−8/9), 2.62 (m, 2H, CH$_2$−7), 2.87 (m, 2H, CH$_2$−10), 3.72 (tr, 2H, CH$_2$−5, $^3J = 5.3$ Hz), 4.37 (tr, 2H, CH$_2$−1, $^3J = 5.3$ Hz) ppm.

^{13}C NMR (TFA-d): $\delta = 22.49$ (C-3, 1C), 25.39 (C-8/9, 1C), 27.36 (C-2/4, 1C), 27.77 (C-2/4, 1C), 28.31 (C-8/9, 1C), 35.08 (C-10, 1C), 36.01 (C-7, 1C), 43.77 (C-5, 1C), 67.08 (C-1, 1C), 179.95 (C-6/11, 1C), 182.47 (C-6/11, 1C) ppm.

IR (KBr): 3306 (s), 2956 (s), 2929 (s), 2866 (m), 1721 (s, C═O stretching, ester), 1645 (s, C═O stretching, amide I), 1551 (s, amide II), 1439 (m, O−CH$_2$), 1333 (m), 1292 (s), 1258 (s), 1155 (s, C−O stretching), 1075 (w), 1063 (w), 1005 (w), 744 (m), 703 (m) cm^{-1}.

Anal. Calcd for C$_{11}$H$_{19}$NO$_3$ (213.27): C, 61.95; H, 8.98; N, 6.57. Found: C, 61.97; H, 9.27; N, 6.51.

Ring-Opening Polymerization of Cyclic Ester Amide 2. Poly(ester amide) 3. All glass vessels were heated in vacuo prior to use, filled with inert gas, and handled in a stream of dry inert gas. The monomer was weighed under nitrogen directly into the reaction vessel, and was melted in a preheated oil bath under permanent stirring. For polymerization the initiator was added to the monomer melt. Cyclic ester amide **2** (427 mg, 2.00 mmol) and Bu$_2$Sn(OMe)$_2$ (5.9 mg, 0.02 mmol) were reacted for 1 h at 145 °C. The polymerization was terminated by cooling to room temperature. The product was dissolved in DMF (5 mL) at 60 °C and precipitated in diethyl ether (120 mL). Yield: 376 mg (88%).



3

GPC in DMAc with 2.44 g·L^{-1} LiCl: M_n = 18 600, M_w = 31 800, M_w/M_n = 1.71.

^{1}H NMR (DMSO-d_6): $\delta = 1.27$ (m, 2H, CH$_2$−3), 1.35 (m, 2H, CH$_2$−4), 1.48 (m, 4H, CH$_2$−8/9), 1.53 (m, 2H, CH$_2$−2), 2.04 (m, 2H, CH$_2$−7), 2.27 (m, 2H, CH$_2$−10), 3.03 (d/tr, 2H, CH$_2$−5, $^3J = 6.0$ Hz), 3.97 (tr, 2H, CH$_2$−1, $^3J = 6.4$ Hz), 7.77 (br s, 1H, NH) ppm.

^{13}C NMR (DMSO-d_6): $\delta = 22.76$ (C-3, 1C), 24.03 (C-8/9, 1C), 24.69 (C-8/9, 1C), 27.77 (C-2, 1C), 28.70 (C-4, 1C), 33.15 (C-10, 1C), 34.93 (C-7, 1C), 38.12 (C-5, 1C), 63.55 (C-1, 1C), 171.57 (C-6/11, 1C), 172.72 (C-6/11, 1C) ppm.

^{1}H NMR (DMSO-d_6, 100 °C): $\delta = 1.33$ (m, 2H, CH$_2$−3), 1.43 (m, 2H, CH$_2$−4), 1.56 (m, 6H, CH$_2$−2/8/9), 2.09 (m, 2H, CH$_2$−7), 2.28 (m, 2H, CH$_2$−10), 3.07 (d/tr, 2H, CH$_2$−5, $^3J = 6.4$ Hz), 4.02 (tr, 2H, CH$_2$−1, $^3J = 6.4$ Hz), 7.34 (br s, 1H, NH) ppm.

^{13}C NMR (DMSO-d_6, 100 °C): $\delta = 22.28$ (C-3, 1C), 23.58 (C-8/9, 1C), 24.13 (C-8/9, 1C), 27.33 (C-2, 1C), 28.14 (C-4, 1C), 32.83 (C-10, 1C), 34.54 (C-7, 1C), 37.81 (C-5, 1C), 62.98 (C-1, 1C), 171.11 (C-6/11, 1C), 171.95 (C-6/11, 1C) ppm.

^{1}H NMR (TFA-d): $\delta = 1.54$ (m, 2H, CH$_2$−3), 1.85 (m, 8H, CH$_2$−2/4/8/9), 2.60 (m, 2H, CH$_2$−7), 2.83 (m, 2H, CH$_2$−10), 3.64 (tr, 2H, CH$_2$−5, $^3J = 7.2$ Hz), 4.29 (tr, 2H, CH$_2$−1, $^3J = 6.4$ Hz) ppm.

^{13}C NMR (TFA-d): $\delta = 24.73$ (C-3, 1C), 25.29 (C-8, 1C), 27.02 (C-9, 1C), 29.34 (C-2/4, 1C), 29.48 (C-2/4, 1C), 35.18 (C-7/10, 2C), 44.81 (C-5, 1C), 68.36 (C-1, 1C), 180.36 (C-6/11, 1C), 181.12 (C-6/11, 1C) ppm.

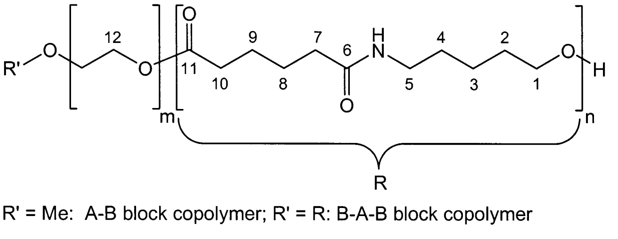
IR (KBr): 3312 (s), 3086 (w), 2941 (s), 2867 (s), 1735 (s, C═O stretching, ester), 1638 (s, C═O stretching, amide I), 1547 (s, amide II), 1464 (m, O−CH$_2$), 1421 (w), 1377 (m), 1270 (m), 1242 (w), 1178 (s, C−O stretching), 1144 (m), 1062 (w), 973 (m), 734 (m), 705 (m), 586 (w) cm^{-1}.

For kinetic experiments after selected reaction times samples were drawn in a stream of dry inert gas and analyzed by means of NMR and GPC.

The thermal stability of poly(ester amide) **3** was determined by thermogravimetric analysis: a 5% mass loss is observed at 290 °C, a 50% mass loss is observed at 354 °C, and a 90% mass loss at 414 °C.

Ring-Opening Polymerization of Cyclic Ester Amide 2 Using Poly(ethylene oxide) PEO 2000 and Sn(octoate)$_2$ as Initiator. Poly(ethylene oxide) PEO 2000 (40 mg, 0.02 mmol) and Sn(octoate)$_2$ (174 μL of a 0.229 M solution in toluene, 0.04 mmol) were stirred for 45 min at 145 °C. Cyclic ester amide **2** (640 mg, 3.00 mmol) and 500 μL of toluene were added at room temperature to this mixture. To obtain a homogeneous system the mixture was heated to 145 °C and then toluene was removed at room temperature and reduced pressure. For polymerization, the mixture was stirred for 48 h at 145 °C. The polymerization was terminated by cooling to room temperature. The product was dissolved in DMAc (5 mL) at 60 °C and precipitated in diethyl ether (150 mL). To remove unreacted macroinitiator, the product was washed with water. Yield: 600 mg (88%).

GPC in DMAc with 2.44 g·L^{-1} LiCl: M_n = 20 200, M_w = 38 000, M_w/M_n = 1.88.



R' = Me: A-B block copolymer; R' = R: B-A-B block copolymer

^{1}H NMR (DMSO-d_6): $\delta = 1.27$ (m, 2H, CH$_2$−3), 1.37 (m, 2H, CH$_2$−4), 1.48 (m, 4H, CH$_2$−8/9), 1.55 (m, 2H, CH$_2$−2), 2.05 (m, 2H, CH$_2$−7), 2.28 (m, 2H, CH$_2$−10), 3.02 (d/tr, 2H, CH$_2$−5, $^3J = 6.0$ Hz, $^3J = 6.4$ Hz), 3.51 (s, 4H, CH$_2$−12), 3.98 (tr, 2H, CH$_2$−1, $^3J = 6.4$ Hz), 7.78 (tr, 1H, NH, $^3J = 5.3$ Hz) ppm.

^{13}C NMR (DMSO-d_6): $\delta = 22.73$ (C-3, 1C), 24.01 (C-8/9, 1C), 24.66 (C-8/9, 1C), 27.74 (C-2, 1C), 28.67 (C-4, 1C), 33.14 (C-

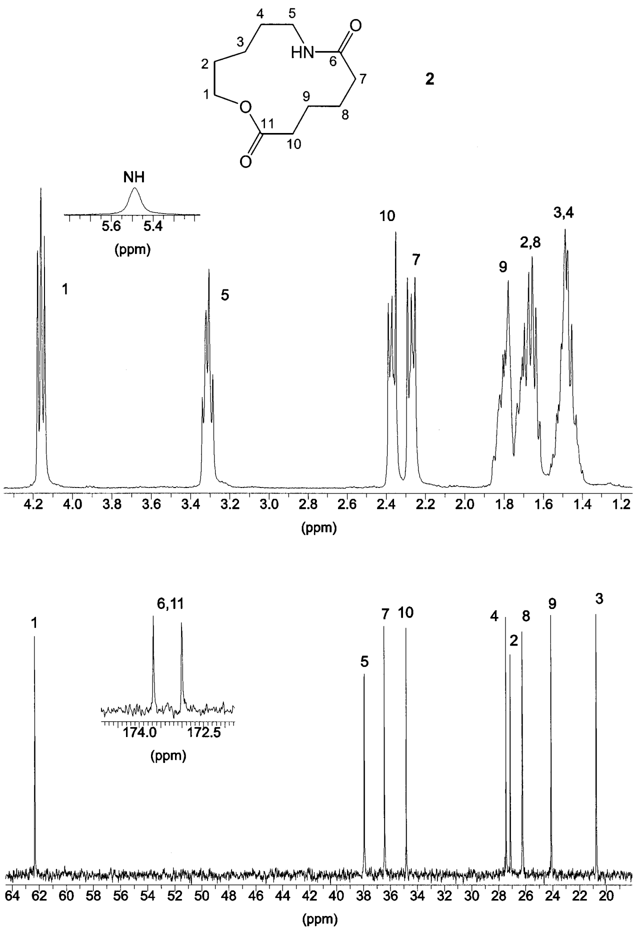
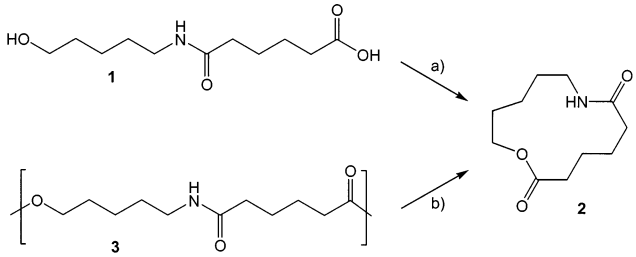


Figure 1. ^1H and ^{13}C NMR spectrum of cEA **2** in $CDCl_3$ with assignment of the resonances.

Scheme 1. Synthesis of the Cyclic Ester Amide 2 (1-Oxa-7-aza-cyclotridecane-8,13-dione): (a) $Ti(OBu)_4$, 170 °C, 10^{-2} mbar; (b) $Bu_2Sn(OMe)_2$, 170 °C, 10^{-2} mbar



10, 1C), 34.92 (C-7, 1C), 38.11 (C-5, 1C), 63.52 (C-1, 1C), 69.70 (C-12, 2C), 171.55 (C-6/11, 1C), 172.70 (C-6/11, 1C) ppm.

Results and Discussion

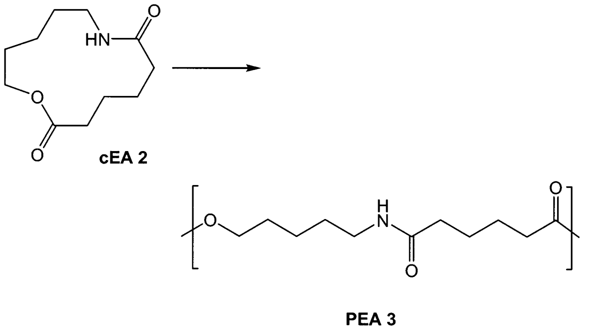
Monomer Synthesis. Cyclic ester amide **2** was prepared by thermal ring-closing depolymerization according to a method described for the preparation of cyclic aliphatic carbonates.[30] In the first step in the presence of a suitable catalyst, polycondensation occurs. Then at temperatures up to 200 °C, ring-closing depolymerization yields the cyclic monomer, which is isolated by distillation or sublimation. The starting material 5-(5-hydroxypentylcarbamoyl)pentanoic acid (**1**) was obtained by selective conversion of adipic anhydride with 1-amino-5-pentanol. We studied the polycondensation of this α-hydroxyl-ω-carboxyl amide **1** at different temperatures and found that up to a temperature of 140 °C the poly(ester amide) **3** is obtained in high yield; however, when the temperature is raised to 170 °C depolymerization occurs with formation of the cyclic ester amide **2** (Scheme 1).[29] No side products and no higher oligomers were detected. We assume that the ring formation occurs by a back biting reaction from the activated hydroxy end group of the polymer. The cyclic ester amide **2** is a crystalline material with a melting point of 142−143 °C. The ^1H and ^{13}C NMR spectra (Figure 1), the IR spectrum and the elemental analysis clearly reveal the cyclic nature of the product. ^1H NMR spectra show for each methylene group adjacent to the functional groups characteristic resonances in accord with a uniform microstructure: CH_2O (δ = 4.16 ppm, 62.34 ppm), CH_2NH (δ = 3.31 ppm, 37.93 ppm), CH_2COO (δ = 2.37 ppm, 34.83 ppm), and CH_2CONH (δ = 2.27 ppm, 36.41 ppm). For comparison reasons, the NMR spectra of cEA **2** in dimethyl sulfoxide (DMSO-d_6) and trifluoroacetic acid (TFA-d) are given in the Experimental Part.

Table 1. Reaction Conditions and Results of the Ring-Opening Polymerization of CEA 2 in Bulk

no.	I	$[M]_0/[I]_0$	T/°C	t/min	M_n[a]	M_w/M_n[a]	X_p/%[b]
1	$Bu_2Sn(OMe)_2$	50	145	15	16 900	1.79	99
2	$Bu_2Sn(OMe)_2$	100	145	60	30 200	1.84	96
3	$Bu_2Sn(OMe)_2$	250	145	360	25 500	2.14	76
4	$Bu_2Sn(OMe)_2$	100	160	30	24 600	1.89	97
5	$Bu_2Sn(OMe)_2$	100	175	15	22 200	1.79	98
6	$Ti(OBu)_4$	100	145	15	20 600	1.87	98
7	Al(O*sec*Bu)$_3$	50	145	15	11 200	1.51	98
8	Sn(octoate)$_2$	100	145	600	8400	1.50	26

[a] Determined by GPC in DMAc with 2.44 g·L^{-1} LiCl. [b] Conversion (X_p) determined by ^1H NMR spectroscopy in TFA-d.

Polymerization of cEA 2 and Characterization of PEA 3. The cyclic ester amide **2** was polymerized in bulk at temperatures above the melting point of the monomer with a variety of nucleophilic initiators, i.e., $Bu_2Sn(OMe)_2$, $Ti(OBu)_4$, Al(O-*sec*-Bu)$_3$ or Sn(octoate)$_2$. As will be shown later, the polymer obtained is an alternating poly(ester amide) with a regular microstructure (eq 1). Some typical results obtained are summarized in Table 1. With $Bu_2Sn(OMe)_2$, $Ti(OBu)_4$, or Al(O-*sec*-Bu)$_3$ as initiator in all cases high polymer yields were obtained. With Sn(octoate)$_2$ the yields are low; however, the system Sn(octoate)$_2$/ROH gives good results as will be shown for the synthesis of block copolymers. The values of M_w/M_n = 1.8 are relative high for a controlled polymerization. This is explained by transesterification reactions. The rate constant of propagation and of transesterification are evidently of the same order of magnitude; due to the high temperature employed for polymerization the selectivity coefficient—the ratio of the rate constant of propagation and of back biting[31]—is close to 1 and thus a chain length distribution close to the most probable distribution



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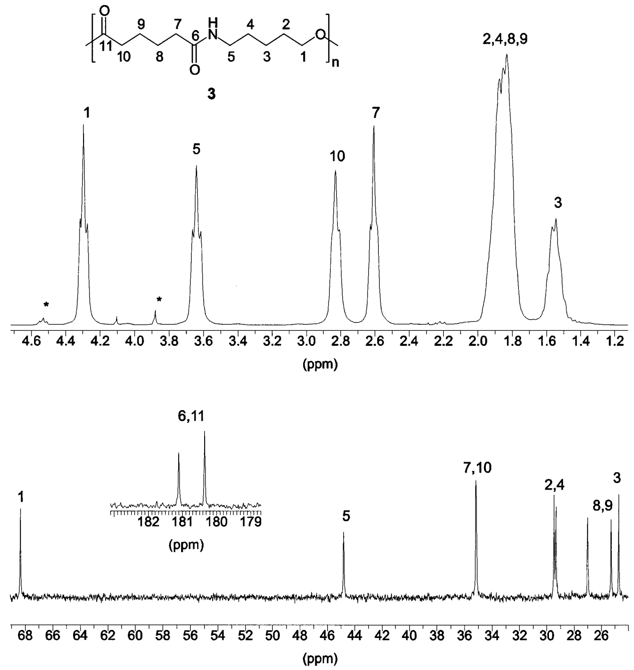


Figure 2. ^{1}H and ^{13}C NMR spectrum of the poly(ester amide) **3** in TFA-*d* with assignment of the resonances (∗, resonances of the end groups). Polymerization in bulk at 145 °C with $Bu_2Sn(OMe)_2$ as initiator $[M]_0/[I]_0 = 100$.

(with $M_w/M_n = 2$) is obtained. Transesterification, however, does not change the microstructure of the alternating poly(ester amide). The lowest value for M_w/M_n is obtained with Al(O-*sec*-Bu)$_3$ as initiator; this corresponds to the low transesterification rate constant found for Al-based active species in the ROP of lactones and of cyclic carbonates.[32]

All poly(ester amide)s prepared show a unimodal molecular weight distribution in GPC analyses. The ^{1}H NMR and ^{13}C NMR spectra show characteristic resonances for an alternating poly(ester amide); only one series of diads is observed (Figure 2). The existence of only one signal in the ^{13}C NMR spectrum for each carbon is indicative of the alternating regular microstructure of the poly(ester amide) **3**. The signals of small intensity in the ^{1}H NMR spectrum at $\delta = 3.90$ ppm and $\delta = 4.55$ ppm were assigned to $-COOCH_3$ and $-CH_2$-$OCOCF_3$ end groups.

The poly(ester amide) **3** is a semicrystalline material with a melting point of 108 °C. The endotherm at the melting transition may show two peaks or one peak with a shoulder, indicating the existence of two crystalline modifications.

Kinetic Aspects. The influence of three parameters on the kinetics of the ROP of cEA **2** were investigated: (i) The influence of the monomer-to-initiator ratio was studied for $[M]_0/[I]_0 = 50$, 100, and 250 at 145 °C with $Bu_2Sn(OMe)_2$ as initiator. (ii) The influence of the temperature was studied above the melting temperature of the monomer (Mp: 142−143 °C) at 145, 160, and 175 °C with $Bu_2Sn(OMe)_2$ and $[M]_0/[I]_0 = 100$. (iii) The influence of the initiator was studied for $Bu_2Sn(OMe)_2$, $Ti(OBu)_4$, and Sn(octoate)$_2$ as the initiator at 145 °C and $[M]_0/[I]_0 = 100$. At selected reaction times samples were analyzed: by ^{1}H NMR spectroscopy for monomer conversion and by GPC for the number-average molecular weight. The monomer conversion was obtained by comparison of the integrals of the CH_2O group of the monomer ($\delta = 4.40$ ppm) and the polymer ($\delta = 4.30$ ppm). Figure 3 shows the ^{1}H NMR spectra for a monomer conversion of 48% and 89%. Since these resonances are well resolved, the conversions are reliable. The GPC curves of the products obtained for the ROP of the cEA **2** at 145 °C with $Bu_2Sn(OMe)_2$ as initiator ($[M]_0/[I]_0 = 50$) after 0.5, 2, and 9 min are shown in Figure 4. In the beginning of the reaction, oligomers are clearly detected in the GPC trace; with time the maximum of the elution curve shifts to lower elution volumes and the concentration of oligomers decreases.

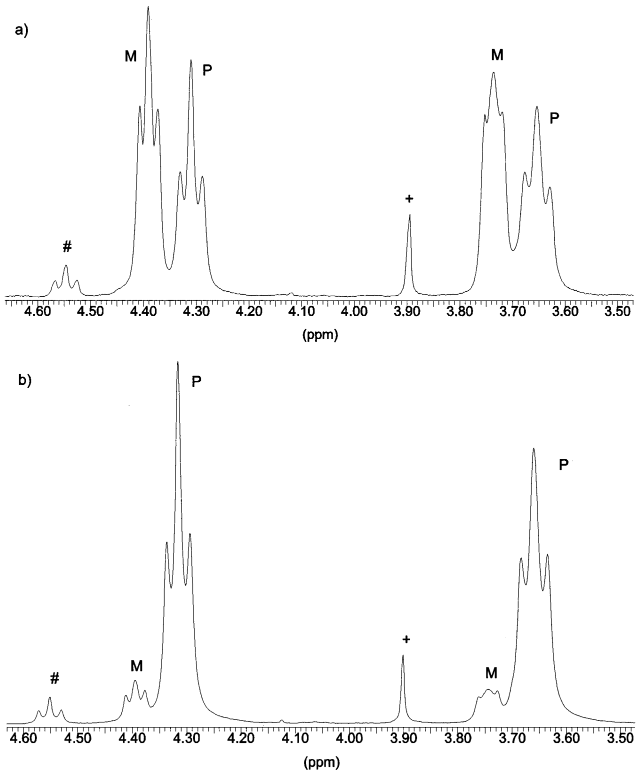


Figure 3. ^{1}H NMR spectra in TFA-*d* of the product of ring-opening polymerization of the cEA **2** in bulk with $Bu_2Sn(OMe)_2$ as initiator: (a) monomer conversion is 48%; (b) monomer conversion is 89%. Key: (M) resonances of the monomer; (P) resonances of the polymer; (#) CH_2O; (+) COOMe end group).

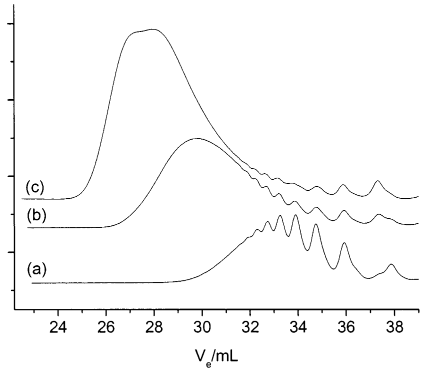


Figure 4. GPC trace of poly(ester amide)s **3** in DMAc/2.44 g·L^{-1} LiCl. Polymerization in bulk at 145 °C with $Bu_2Sn(OMe)_2$ as initiator $[M]_0/[I]_0 = 50$ at various reaction time (conversion): (a) 0.5 min (19%); (b) 2 min (48%);(c) 9 min (96%).

(a) Influence of the Monomer-to-Initiator Ratio. For a controlled polymerization, the reaction rate should decrease and the molecular weight increase with increasing $[M]_0/[I]_0$. The first-order plots for the polymerization of cEA **2** with $Bu_2Sn(OMe)_2$ as initiator are

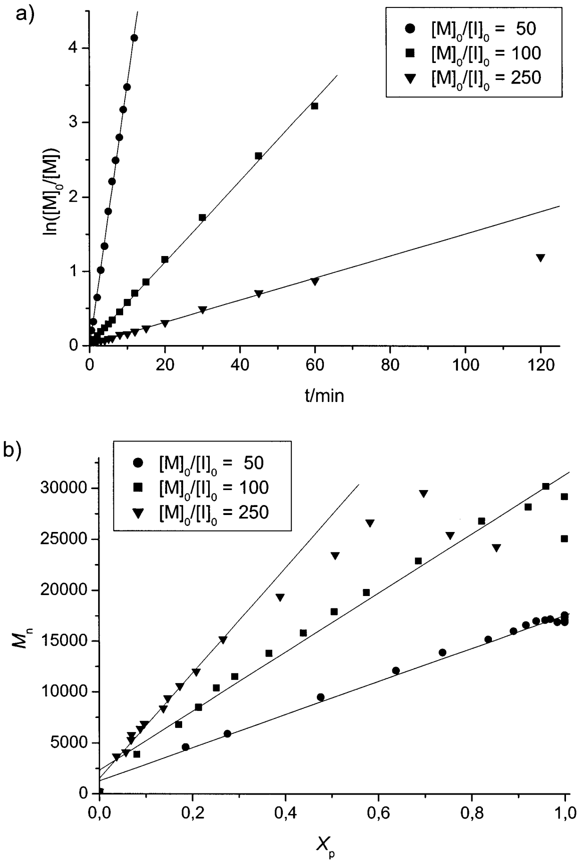


Figure 5. Polymerization of cEA **2** in bulk with $Bu_2Sn(OMe)_2$ as initiator at 145 °C ($[M]_0/[I]_0 = 50$, $[M]_0/[I]_0 = 100$, $[M]_0/[I]_0 = 250$): (a) first-order kinetic plot; (b) number-average molecular weight M_n as a function of conversion X_p.

linear for $[M]_0/[I]_0 = 50$ and 100 up to high conversion (Figure 5a). For $[M]_0/[I]_0 = 250$, the plot is linear up to 60 min and then deviates from linearity, which is indicative of termination reactions. No induction period is observed, which is typical of polymerization reaction in which initiation is faster than propagation. From the slope of the straight lines the apparent rate constants were determined to be $k[P^*] = 57.89 \times 10^{-4}\ s^{-1}$ for $[M]_0/[I]_0 = 50$, $9.53 \times 10^{-4}\ s^{-1}$ for $[M]_0/[I]_0 = 100$, and $2.58 \times 10^{-4}\ s^{-1}$ for $[M]_0/[I]_0 = 250$. The ratio of the values $k[P^*]$ for different monomer-to-initiator ratios should correspond to the ratio of the concentration of active species: the ratio expected is 1:0.5:0.2; the ratio experimentally found is 1:0.16:0.04. This means that the lower the concentration of active species is, the higher is the influence of accidental chain termination. To obtain information on transfer reactions, the dependence of M_n on conversion was studied (Figure 5b). The values obtained by GPC using polystyrene standards are not absolute values; however, a linear dependence of M_n on conversion indicates that transfer reactions are absent. For $[M]_0/[I]_0 = 50$ and 100 the dependence is linear up to quantitative conversion. For $[M]_0/[I]_0 = 250$ where the concentration of active species is lowest, deviations form linearity are observed starting with a conversion of 40%. It should be mentioned that the M_n vs conversion plots do not pass throughout the coordinates origin which is tentatively explained by the method of determination of M_n by GPC using polystyrene standards and the relative high molecular weight of the monomer initiator adduct.

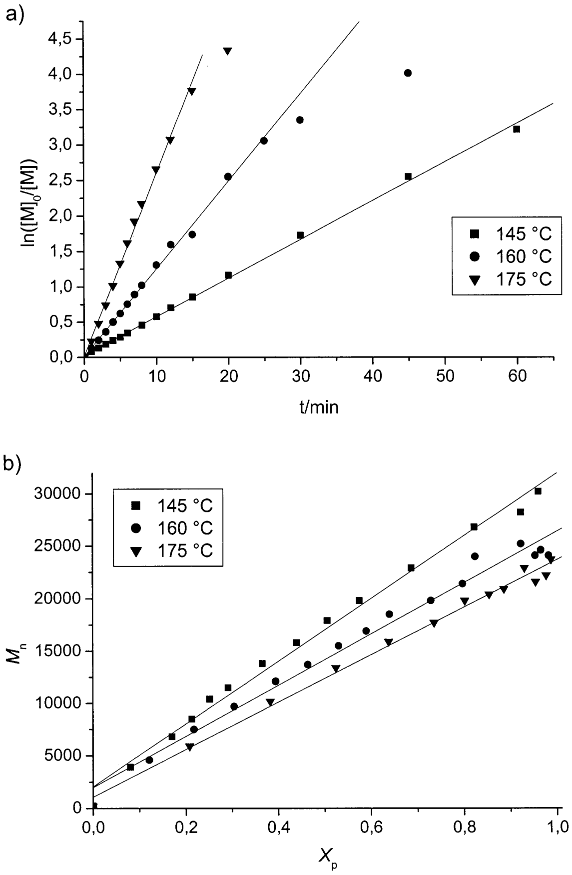


Figure 6. Polymerization of cEA **2** in bulk with $Bu_2Sn(OMe)_2$ as initiator ($[M]_0/[I]_0 = 100$) at 145, 160, and 175 °C: (a) first-order kinetic plot; (b) number-average molecular weight M_n as a function of conversion X_p.

For the M_n vs conversion plot based on the $[M]_0/[I]_0$ ratio the ratio of the M_n values is expected to be 1:2:5. From the slope of the straight lines the calculated ratio is 1:1.9:3.1. This result is in contradiction to the relative concentration of active species found in the first-order plots, which would lead to a higher ratio of the M_n values. Further investigations are necessary to explain this experimental result. We have excluded the possibility of a thermal polymerization, since at 145 °C the cyclic monomer is stable for at least 3 h.

(b) Influence of Temperature. The influence of temperature on the ROP of the cEA **2** was studied for $Bu_2Sn(OMe)_2$ as the initiator at $[M]_0/[I]_0 = 100$. A conversion > 90% is reached after 50 min at 145 °C, after 20 min at 160 °C, and after 10 min at 175 °C. First-order plots at all three temperatures are linear up to high conversion (Figure 6a). From the slope of the straight lines the apparent rate constants $k[P^*]$ were determined: $44.33 \times 10^{-4}\ s^{-1}$ for 175 °C, $20.38 \times 10^{-4}\ s^{-1}$ for 160 °C, and $9.53 \times 10^{-4}\ s^{-1}$ for 145 °C. According to Arrhenius the activation energy was estimated to be $E_a = 80\ kJ \cdot mol^{-1}$ which is similar to that for lactones.[33] The dependence of M_n on conversion for all three experiments (Figure 6b) is linear up to high conversion. This means that in the temperature range studied no transfer reactions are detectable. Since in all three experiments the same $[M]_0/[I]_0$ was used, all points should be on the same straight line. The differences in Figure 6b result primarily from the inaccuracy in the weight of the starting materials; an additional error arises from the determination of the conversion by NMR and the determination of M_n by GPC.

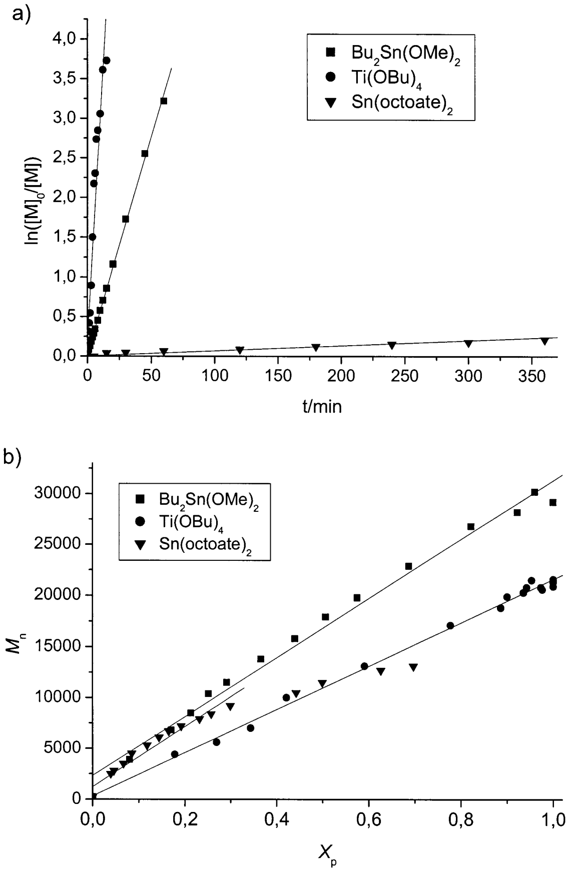
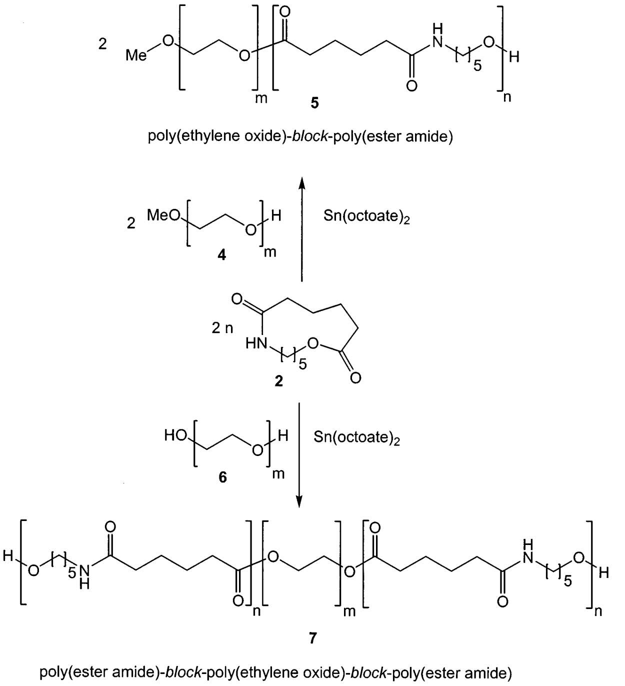


Figure 7. Polymerization of cEA **2** in bulk at 145 °C with $Bu_2Sn(OMe)_2$, $Ti(OBu)_4$, and $Sn(octoate)_2$ as initiator ($[M]_0/[I]_0 = 100$): (a) first-order kinetic plot; (b) number-average molecular weight M_n as a function of conversion X_p.

Scheme 2. Synthesis of A−B and B−A−B Block Copolymers via Ring-Opening Polymerization of cEA 2 in the Melt with Hydroxy-Functional Poly(ethylene oxide) as Initiator and Sn(octoate)₂ as Catalyst



(c) Influence of the Initiator. The influence of the initiator on the course of the ROP of cEA **2** was studied for $Bu_2Sn(OMe)_2$, $Ti(OBu)_4$, and $Sn(octoate)_2$ as initiators at 145 °C and $[M]_0/[I]_0 = 100$. A conversion >90% is reached after 5 min for $Ti(OBu)_4$ and after 50 min for $Bu_2Sn(OMe)_2$ as initiator. With $Sn(octoate)_2$ a slow increase of conversion is observed; 20% conversion is reached after 6 h. According to the literature $Sn(octoate)_2$ is a catalyst, with residual water being the initiator.[10] A control experiment showed that the low conversion is not due to a thermal polymerization. For $Bu_2Sn(OMe)_2$ and $Ti(OBu)_4$ as initiators the polymerization is first order with respect to the monomer (Figure 7a), chain termination is not detectable. The apparent rate constants $k[P^*]$ determined from the slope of the straight lines are as follows: $50.27 \times 10^{-4}\ s^{-1}$ for $Ti(OBu)_4$ as initiator and $9.53 \times 10^{-4}\ s^{-1}$ for $Bu_2Sn(OMe)_2$ as initiator. From the ratio of the values $k[P^*]$ the ratio of the corresponding rate constants of propagation can be calculated. This ratio is 2.6 assuming that $Bu_2Sn(OMe)_2$ starts two chains and $Ti(OBu)_4$ starts four chains. For $Sn(octoate)_2$ as the catalyst the reaction is also first order but slow; the apparent rate constant is $0.19 \times 10^{-4}\ s^{-1}$. The dependence of M_n on conversion for $Bu_2Sn(OMe)_2$, and $Ti(OBu)_4$ as initiators (Figure 7b) is linear; transfer reactions can be excluded. A comparison of the results obtained reveal that for the ratio $[M]_0/[I]_0 = 100$, the M_n values obtained for $Bu_2Sn(OMe)_2$ are higher by a factor of about two at equal monomer conversion. This means that for $Ti(OBu)_4$ the number of chains is twice as high as expected from the number of alkoxide residues in the initiators. For $Sn(octoate)_2$ as a catalyst at conversions higher than 30%, deviations from linearity are observed, indicating the presence of chain transfer reactions.

Synthesis and Characterization of Block Copolymers. Block copolymers with poly(ethylene oxide) and poly(depsipeptide) blocks with a variety of architectures have been prepared in the last years[18−22] starting with cyclic depsipeptides and an initiating system comprising hydroxytelechelic poly(ethylene oxide) and $Sn(octoate)_2$. From a mechanistic point of view, cEA **2** should be polymerizable with the same initiating system.

For the synthesis of block copolymers comprising an alternating poly(ester amide) block with adipic acid and 1-amino-5-pentanol repeating units and a poly(ethylene oxide) block (Scheme 2) the cEA **2** was polymerized with mono- (MPEO **4**, $Me\text{-}(O-CH_2-CH_2)_x-OH$) and bis(hydroxy)-functional poly(ethylene oxide)s (PEO **6**, $H-(O-CH_2-CH_2)_x-OH$) of various molecular weights (MPEO 2000, MPEO 5000, MPEO 10000, MPEO 20000, PEO 2000, PEO 6800, PEO 11800, PEO 20000) in combination with $Sn(octoate)_2$ as the catalyst ($[Sn(octoate)_2]_0/[OH]_0 = 1$). With MPEO as initiator, A−B block copolymers **5** are obtained; with PEO as initiator, B−A−B block copolymers **7** are obtained. To activate all hydroxy groups and to initiate all chains at the same time poly(ethylene oxide) was treated first with $Sn(octoate)_2$ to generate the active species, then the monomer was added ($[cEA]_0/[OH]_0 = 75$) and the mixture was heated to 145 °C for polymerization. The polymerization was terminated by cooling to room temperature. The block copolymer was isolated by dissolving the product in DMF and precipitating in ether. GPC analysis of the crude product (Figure 8a) shows beside residual monomer ($V_e = 40$ mL) a bimodal distribution for the polymer. The peak at $V_e = 30$ mL corresponds to unreacted MPEO 5000 and the peak at $V_e = 26$ mL to the block copolymer. Purification of the

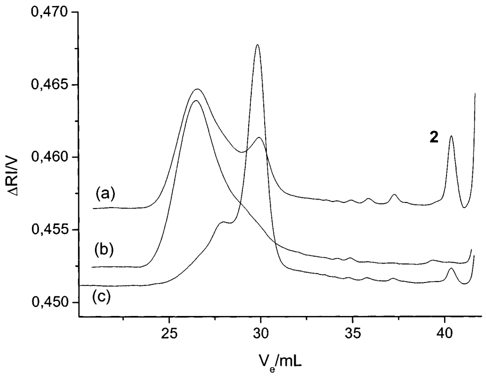


Figure 8. GPC trace in DMAc/2.44 g·L^{-1} LiCl: (a) crude product obtained by polymerization of cEA **2** with MPEO 5000/Sn(octoate)$_2$; (b) poly(ethylene oxide)-*block*-poly(ester amide) **5** (purified product); (c) water-soluble fraction.

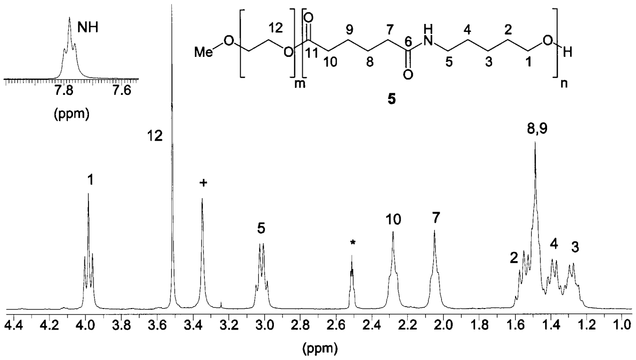


Figure 9. ^{1}H NMR spectrum of an A–B block copolymer **5** of cEA **2** and MPEO 2000 **4** (Table 2, no. 1) in DMSO-d_6 (+ = H$_2$O, $*$ = DMSO).

Table 2. Reaction Conditions and Results of the ROP of cEA 2 with Mono- and Bifunctional Poly(ethylene oxide) Macroinitiators (MPEO, PEO) with Sn(octoate)$_2$ as a Catalyst in the Melt at T = 145 °C ([cEA]$_0$/[OH]$_0$ = 75, [Sn(octoate)$_2$]$_0$/[OH]$_0$ = 1, t = 48 h)

no.	macroinitiator	X_p/%^{a} of cEA	(EO)/ mol %^{b}	(EO)/ mol %^{c}	M_n^{d} (M_w/M_n)	yield/ %^{e}
1	MPEO 2000	100	38	30	18 500 (1.76)	88
2	MPEO 5000	89	60	38	25 700 (1.83)	67
3	MPEO 10000	78	75	61	24 000 (1.84)	49
4	MPEO 20000	76	86	69	27 000 (1.67)	37
5	PEO 2000	100	23	23	20 200 (1.88)	88
6	PEO 6800	57	51	62	22 800 (1.79)	51
7	PEO 11800	71	64	67	23 300 (1.84)	56
8	PEO 20000	68	75	67		56

[a] Conversion (X_p) determined by ^{1}H NMR spectroscopy of the crude product. [b] mol % of EO repeating units in the feed. [c] mol % of EO repeating units in the block copolymer determined by means of ^{1}H NMR spectroscopy (purified product). [d] Determined by GPC in DMAc with 2.44 g·L^{-1} LiCl. [e] Determined from the weigh-out quantity.

crude material by extraction with water results in a water-insoluble fraction—the block copolymer—with a tailing to lower molecular weight (Figure 8b) and a water-soluble fraction consisting mainly of unreacted MPEO 5000 (Figure 8c). NMR spectroscopic analysis of the water-soluble fraction confirmed the selective removal of unreacted macroinitiator.

Table 3. Thermal Properties of A–B and B–A–B Block Copolymers^a

no.	macroinitiator	T_m/°C	ΔH_m/J·g^{-1}	T_c/°C	ΔH_c/J·g^{-1}
1	MPEO 2000	106	59.1	46	−26.7
2	MPEO 5000	108	54.2	46	−22.0
3	MPEO 10000	106 64^b	40.3 34.6^b	33	−54.2
4	MPEO 20000	108 64^b	43.4 30.8^b	32	−48.4
5	PEO 2000	107	47.4	49	−19.9
6	PEO 6800	107 49^b	47.6 29.9^b	42 −29^b	−21.4 −11.4^b
7	PEO 11800	108 56^b	40.1 26.0^b	27	−47.7
8	PEO 20000	104 59^b	48.8 29.4^b	30	−47.4
9	PEO 2000	55^b	158.4^b	12^b	−152.4^b
10	PEA **3**	108	36.8	41	

[a] T_m and T_c are the temperatures in the peak maximum. [b] These data refer to the PEO blocks; all other data refer to the PEA blocks.

The composition of the purified copolymers was determined by ^{1}H NMR spectroscopy (Figure 9). Beside the resonances for the PEA block(s) the singlet at δ = 3.51 ppm is assigned to the ethylene oxy repeating units of the PEO block. The composition of the block copolymer was determined by integration of this singlet and of one of the well resolved signals for the ester amide repeating unit. The results from the block copolymer synthesis are presented in Table 2. The higher the M_n value of the macroinitiator the lower the conversion of cEA **2**. Two reasons may account for this result: (i) At higher M_n values the concentration of the monomer and of the active species decreases. (ii) The longer the polymer chain of the initiator is, the less accessible the active species will be. In addition initiation efficiency decreases with increasing M_n. Bifunctional initiators show higher initiation efficiency at similar amount of PEO; however, we do not know the content of A–B diblock in the B–A–B triblock copolymer. The thermal characteristics of these block copolymers as determined by DSC measurements (Table 3) reveal a phase separated system for the block copolymers with a poly(ethylene oxide) block of M_n > 5000. The thermal properties of the PEA domains in the block copolymer are similar to those of the homopolymer.

Conclusions

Ring-opening polymerization of cEA **2** occurs with high rate at temperatures above the melting point of the monomer. Kinetic data of the polymerization support the absence of termination and transfer reactions up to high conversion. These results indicate that the polymerization is controlled and are supported by the preparation of block copolymers.

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