Articles

Polylactones. 51. Resorbable Networks by Combined Ring-Expansion Polymerization and Ring-Opening Polycondensation of ϵ-Caprolactone or DL-Lactide

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ABSTRACT: The ring-expansion polymerization of ϵ-caprolactone (ϵ-CL) was initiated with 2,2-dibutyl-2-stanna-1,3-dioxepane (DSDOP) or 2,2-dibutyl-2-stanna-1,3-dioxaundecane (DSDUC) and the molecular weights of the resulting cyclic polylactones were controlled by the monomer/initiator (M/I) ratio. Addition of benzene-1,3,5-tricarbonyl chloride yielded networks in a one-pot procedure. An analogous series of networks was prepared from a resorbable tricarboxylic acid trichloride based on glycerol and glutaric acid. After extraction of the soluble byproducts all these gels were isolated in yields of 60−90%. After swelling in $CDCl_3$, these gels were so mobile that relatively sharp signals of all protons were detectable, allowing for a determination of the cross-linking density. The glass-transition temperatures (T_g's), melting temperatures (T_m's), melting enthalpies (ΔH_m's), and swelling factors showed the expected dependence on the cross-linking density, i.e., on the M/I ratio of the polymerization process. Four more gels were prepared from racemic DL-lactide, and their glass transition temperatures and swelling factors were measured. These gels were amorphous and consisted exclusively of nontoxic building blocks familiar with the human metabolism.

Introduction

This work is part of broader study on the preparative usefulness of the ROPPOC concept, which means the direct combination of ring-opening polymerization and ring-opening polycondensation. Resorbable networks having tailored pore sizes were selected as new aims of this synthetic strategy, because they may be useful as host components of drug-delivery systems. In a previous paper[1] biodegradable networks were prepared via a tetrafunctional initiator, a stanylenated glucose glycoside. However, this initiator proved to be instable under the reaction conditions and insoluble in numerous inert solvents. In the present work we present a new approach that is not affected by such limitations. Furthermore, this approach combines three useful properties. First, it may be performed in a one-pot procedure. Second, it allows an easy control of the pore size via the M/I ratio of the ring-opening polymerization. Third, it allows the synthesis of networks consisting of components and connecting groups that are 100% compatible with the human metabolism. Networks based on polylactone segments were also prepared by other authors[2−7] in a two-step procedure. Polylactone diols were prepared by ring-opening polymerization involving diols or triols as co-initiators and cross-linked in a separate step. In one case a diisocyanate based on lysine was used, and gels mainly consisting of resorbable components were obtained.[3]

Experimental Section

Materials. ϵ-Caprolactone (ϵ-CL), 1,4-butanediol, 1,8-octanediol, glycerol, glutaric anhydride, benzene-1,3,5-tricarboxylic acid (trimesic acid), and dibutyltin dimethoxide were purchased from Aldrich Co. (Milwaukee, WI). The ϵ-CL was distilled in vacuo over freshly powdered calcium hydride. 1,4-Butanediol, 1,8-octanediol, and glycerol were azeotropically dried with toluene and distilled over a short-path apparatus in vacuo. The trimesic acid was transformed into its acid chloride (trimesoyl chloride) in refluxing thionyl chloride with dropwise addition of a solution containing 1 mL of dimethylformamide in 10 mL of chloroform. It was purified by two distillations. The DL-lactide was a gift of Boehringer (Ingelheim, Germany). It was recrystallized from dry ethyl acetate and dried over P_4O_{10}. DSDOP was prepared from dibutyltin dimethoxide and dry 1,4-butanediol as described previously.[8]

2,2-Dibutyl-2-stanna-1,3-dioxaundecane. Dibutyltin dimethoxide (0.1 mol) and dry 1,8-octanediol (0.1 mol) were weighed into a 100 mL round-bottom flask equipped with a Claisen head and cooler for distillation of the liberated methanol. The reaction vessel was placed into an oil bath preheated to 100 °C, and the temperature was slowly raised to 160 °C. After 2 h the temperature was lowered to 100 °C, and a vacuum of 10^{-1} mbar was gradually applied for 4 h. After cooling, the complete removal of methanol and methoxy groups was checked by ^{1}H NMR spectroscopy. Neither attempts to crystallize the viscous product nor attempts to distill it over a short-path apparatus were successful. Yield: 99%.

Anal. Calcd for $C_{16}H_{34}O_2Sn$ (377.1): C, 50.96; H, 9.09. Found: C, 50.75; H, 9.21%. ^{119}Sn NMR ($CDCl_3$/Me_4Sn): δ = −102 (broad), −183 (sharp) ppm.

Glycerol Trisglutarate Trichloride. Dry glycerol (0.1 mol), freshly distilled glutaric anhydride (0.3 mol), and a catalytic amount of pyridine were dissolved in dry dioxane (150 mL) and refluxed for 8 h. The crude product was isolated by evaporation of dioxane and pyridine and was spectroscopically identified as glycerol trisglutarate. The crude product and chlorotrimethylsilane (0.32 mol) were then dissolved in dry

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dioxane (500 mL). Triethylamine (0.32 mol) dissolved in dry dioxane (50 mL) was added droqwise with rapid stirring. The reaction mixture was refluxed for 4 h, cooled with ice, and filtered under exclusion of moisture. Again the crude product was separated from the dioxane and from the excess of triethylamine, and it was identified as glycerol trisglutaroyl−trimethylsilyl ester by ^{1}H NMR spectroscopy. The crude trimethylsilyl ester was dissolved in dry chloroform together with an excess of thionyl chloride and stirred at room temperature for 24 h. The temperature was then gradually raised, and the reaction mixture was refluxed for 2 h. After evaporation of chloroform and thionyl chloride the crude product was flash evaporated three times with dry toluene to remove the remaining thionyl chloride. Anal. Calcd. for $C_{18}H_{23}Cl_3O_9$ (489.7): C, 44.15; H, 4.73; Cl, 21.72. Found: C, 44.00; H, 5.12; Cl, 21.03%. ^{1}H NMR ($CDCl_3$/TMS): $\delta = 2.01$ (m, 6H), 2.44 (t, 6H), 3.02 (t, 6H), 4.21 (m, 4H), 5.27 (m, 1H) ppm.

Polymerizations. (*1*) *Networks of Polycaprolactone Cross-Linked with Benzene-1,3,5-tricarbonyl Chloride.* Dry ϵ-caprolactone (50 mmol) was weighed into a small glass reactor with silanized glass walls (pretreatment with Me_2SiCl_2). The initiator DSDOP (**1a**) was injected in form of a 1 M solution in dry toluene. The reaction vessel was closed with a glass stopper and steel spring and immersed into an oil bath thermostated at 60 °C. After 2 h of reaction a mechanical glass stirrer was placed into the reaction vessel, and the benzene-1,3,5-tricarbonyl chloride dissolved in dry toluene (25 mL) was added. The reaction mixture was then stirred at 60 °C for 6 h. After cooling to room temperature the reaction mixture was transferred into a Soxhlet extractor, and soluble byproducts were extracted with dry dichloromethane for 72 h. Finally, the gels were separated from the dichloromethane and dried in vacuo at 40 °C.

Analogous polymerizations initiated with **1a** were performed at 80 °C/2 h and with DSDUC (**1b**) as the initiator at 60 °C/2 h.

(*2*) *Networks of Polycaprolactone Cross-Linked with Glycerol Trisglutarate Trichloride.* The amounts and the procedure is identical to (1), but glycerol trisglutarate trichloride in a solution of dry toluene (25 mL) was used as the cross-linking agent.

(*3*) *Networks of Poly-*DL*-lactide Cross-Linked with Glycerol Trisglutarate Trichloride.* Dry racemic DL-lactide (50 mmol) was weighed into a small glass reactor with silanized glass walls (pretreatment with Me_2SiCl_2). The initiator DSDOP was injected in form of a 1 M solution in dry toluene. The reaction vessel was closed with a glass-stopper and steel spring and immersed into an oil bath thermostated at 60 °C. After 6 h a mechanical glass stirrer was placed into the reaction vessel, and the cross-linker glycerol trisglutarate trichloride solved in 25 mL of dry toluene was added. The reaction mixture was then stirred at 60 °C for 18 h. After cooling to room temperature, the reaction mixture was transferred into a Soxhlet extractor, and soluble byproducts were extracted with dry dichloromethane for 72 h. Afterward, the gels were dried in vacuo at 40 °C.

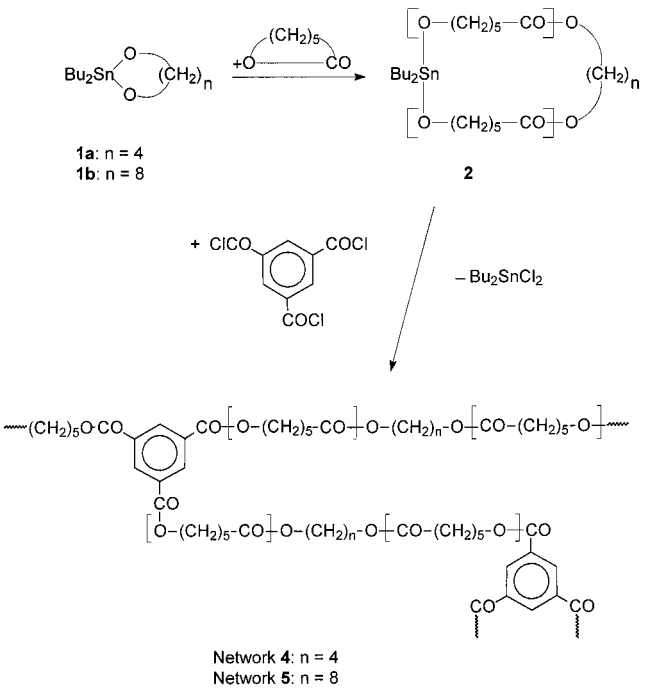
Measurements. The DSC measurements were conducted on a Perkin Elmer DSC-7 in aluminum pans under nitrogen.

The 400 MHz ^{1}H NMR spectra were recorded with a Bruker AM 400 FT NMR spectrometer in 5 mm o.d. sample tubes. $CDCl_3$ containing TMS served as solvent and shift reference.

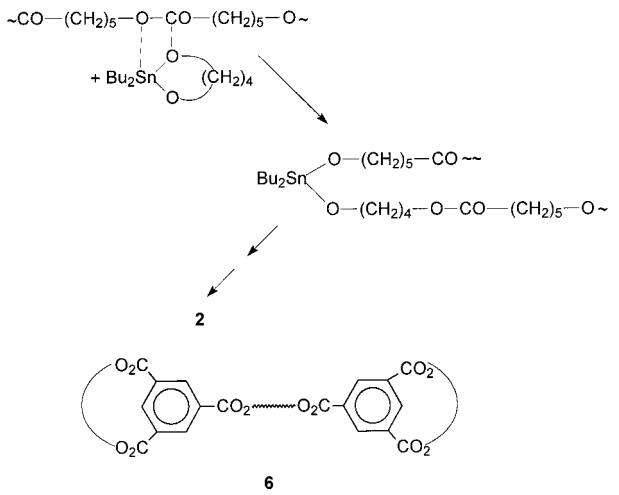
Results and Discussion

Cross-Linking with Trimesoyl Chloride. The synthetic strategy explored in this work is based on the ring-expansion polymerization of lactones or lactides initiated by cyclic tin alkoxides such as **1a** (DSDOP) or **1b** (DSDUC). The resulting cyclic polylactones containing two reactive Sn−O bonds were then subjected to a ring-opening polycondensation with a tri- or multifunctional carboxylic acid chloride such as trimesoyl chloride (Scheme 1). This polycondensation step yielded the network with elimination of Bu_2SnCl_2.

Scheme 1



Scheme 2



As previously reported,[9] it is characteristic for DSDOP (**1a**) initiated polymerizations of ϵ-CL that the initiation step is slower than the propagation steps. This difference has the consequence that at short reaction times and moderate temperatures (≤60 °C) the average degree of polymerization ($\overline{DP}$) is initially higher than the monomer initiator ratio (M/I). However, DSDOP (**1a**) like other tin alkoxides can also react with the polylactone chain according to Scheme 2. This slower equilibration reaction consumes the initially unreacted initiator and reduces the $\overline{DP}$ until it equals M/I. Furthermore, this equilibration enhances the polydispersity. At 80 °C the difference between initiation and propagation rates diminishes, and the equilibration (Scheme 2) is faster. Moreover, the larger ring of **1b** is more reactive than **1a**, and the initiation of ϵ-CL is as rapid as the propagation, so that the $\overline{DP}$ parallels the M/I ratio even at 60 °C and short reaction times (≤1 h).

Because of these kinetic peculiarities, three series of network syntheses were performed. First, four DSDOP (**1a**) initiated polymerizations were conducted at 60 °C

Table 1. Yields and Properties of Networks Prepared from ϵ-Caprolactone with Various Cyclic Initiators and Trimesoyl Chloride as Cross-Linking Agent

polymer	initiator	temp (°C)	M/I[a] (feed)	M/Cr[b] (feed)	M/Cr[c] (^{1}H NMR)	yield[d] (%)	T_g[e] (°C)	T_m[e] (°C)	ΔH_m[e] (J/g)	SF in toluene[f]	SF in CH_2Cl_2[f]
4a	DSDOP	60	20	30	29	67	−54	48	59	9.0	17.0
4b	DSDOP	60	40	60	62	88	−55	53	68	10.5	20.0
4c	DSDOP	60	60	90	87	76	−59	56	71	13.0	25.5
4d	DSDOP	60	100	150	190	55	−60	57	70	24.5	32.5
4a′	DSDOP	80	20	30	23	73	−54	49	48	9.5	13.5
4b′	DSDOP	80	40	60	55	68	−58	54	62	13.0	18.6
4c′	DSDOP	80	60	90	90	64	−59	54	63	17.0	23.5
4d′	DSDOP	80	100	150	150	58	−61	56	64	23.0	34.0
5a	DSDUC	60	20	30	40	81	−55	45	54	12.0	17.0
5b	DSDUC	60	40	60	64	80	−58	53	63	13.5	18.5
5c	DSDUC	60	60	90	78	76	−59	55	64	16.0	21.0
5d	DSDUC	60	100	150	140	63	−61	56	62	24.0	30.0

[a] Molar M/I ratio used for the ring-expansion polymerization (Scheme 1). [b] Molar monomer/trimesoyl chloride ratio. [c] Molar monomer/trimesoyl unit ratio found in the isolated gels. [d] After 72 h of extraction with refluxing CH_2Cl_2. [e] DSC measurements with a heating rate of 10 °C/min. [f] Swelling factor (volume expansion) after equilibration with an excess of "solvent".

with variation of the M/I. The resulting gels were labeled **4a**−**d** (Table 1). Second, four analogous **1a**-initiated polymerizations were conducted at 80 °C, and the isolated gels were listed under **4a′**−**d′** in Table 1. Third, four network syntheses were performed at 60 °C with DSDUC (**1b**) as initiator, and the resulting gels were labeled **5a**−**d**. The crude gels were mechanically removed from the reactor and extracted with hot CH_2Cl_2 prior to their characterization. After this extraction no Bu_2SnCl_2 was detectable in the gels by ^{1}H NMR spectroscopy. The extracted gels were isolated in yields between 55 and 88%. The losses have two sources: first, the mechanical workup procedure and, second, the formation of soluble reaction products which were extracted with CH_2Cl_2. Soluble reaction products may be a consequence of incomplete cross-linking and a consequence of cyclization (e.g., structure **6**) even at 100% conversion of the functional groups. A detailed study of the soluble byproducts was not intended in this work, but a study of cyclization reaction in polycondensations of trifunctional monomers is in progress.

The swelling of all gels was studied in three solvents of quite different structure: acetone, dichloromethane, and toluene. In the case of the series **4a**−**d**, **4a′**−**d′**, and **5a**−**d** the volume expansion was determined in the form of swelling factors which are listed in Table 1. Little swelling was found when acetone was used, and thus, no data were reported for this solvent. The good swelling of the poly(ϵ-CL) networks in CH_2Cl_2 was paralleled by good swelling in $CDCl_3$. Therefore, it was possible to record ^{1}H NMR spectra of the swollen gels. As demonstrated by the spectrum presented in Figure 1, the mobility of the swollen gels was so high that relatively narrow signals were obtained even at the highest density of cross-links. Interestingly, this high mobility also concerned the cross-links themselves, so that a rather sharp signal of the trimesoyl units was detectable. Therefore, the ^{1}H NMR spectra proved the network structure and allowed the determination of the cross-link density. The ϵ-CL/trimesoyl feed ratios and the experimental ratios determined from the isolated networks were listed as M/Cr ratios in Table 1. Taking into account a margin of error of at least ±5%, the experimental M/Cr ratios showed an acceptable agreement with the feed ratios for all three series of networks with exception of **4d**. Surprisingly, the relatively slow initiation and equilibration of DSDOP (**1a**) at 60 °C did not result in chain segments ($\overline{DP}$s) significantly exceeding the M/I ratios with exception of **4d**. Obviously, the total

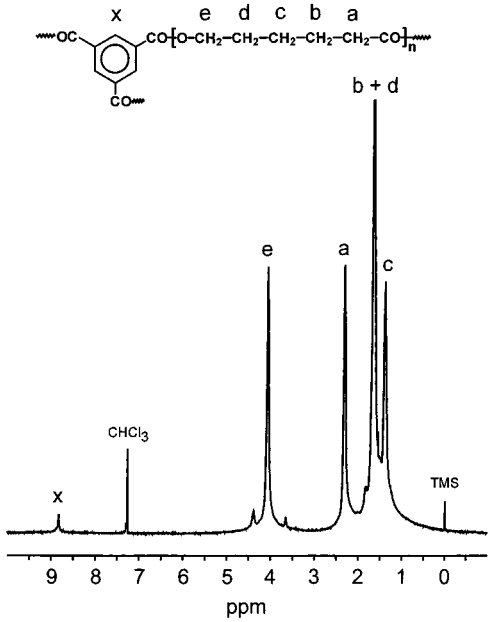


Figure 1. The 400 MHz ^{1}H NMR spectrum of the poly(ϵ-CL) network **4a** (M/I = 20/1) swollen in $CDCl_3$.

reaction time sufficed for an almost complete equilibration of this initiator before the condensation steps set in. On the basis of these results the lower reaction temperature of 60 °C was also used in further experiments (see below), because a lower temperature is favorable for a complete mixing of cyclic polylactones (**2**) with the cross-linking agent before the gelation stops the stirring.

The swelling factors determined for the networks of all three series roughly parallel the M/I ratios and thus confirm the structure and cross-link density as determined by ^{1}H NMR spectroscopy (Table 1). Furthermore, DSC measurements of the carefully dried gels of the three series were recorded. As demonstrated by the values listed in Table 1, the expected trends were indeed found. Higher cross-link density reduced both melting temperature and melting enthalpy, and the glass-transition temperature increased correspondingly. Figure 2 illustrates that the first heating curve shows two melting endotherms, whereas only one broad endotherm is observable in the second and third heating curve. With lower cross-link density sharper endotherms were observed (curve C, Figure 2).

Table 2. Yields and Properties of Networks Prepared with Glycerol Trisglutarate Trichloride as Cross-Linking Agent

polymer	Mon[a]/Init.	yield[b] (%)	T_g[c] (°C)	T_m[c] (°C)	ΔH_m[c] (J/g)	SF in toluene[d] (20 °C)	SF in CH_2Cl_2[d] (20 °C)	SF in acetone[d] (20 °C)
10a	20/1	80	−54	51	64.0	14.0	16.0	9.4
10b	40/1	76	−56	54	66.0	14.5	21.0	10.1
10c	60/1	82	−58	55	66.5	16.0	25.0	11.2
10d	100/1	75	−59	57	69.0	19.0	29.0	11.5
11a	20/1	84	49			12.0	14.5	10.5
11b	40/1	90	48			15.5	23.0	19.5
11c	60/1	76	47			17.5	29.5	26.5
11d	100/1	60	35			26.0	42.5	37.0

[a] Molar M/I ratio used for the ring-expansion polymerization. [b] After 72 h of extraction with refluxing CH_2Cl_2. [c] DSC measurements with a heating rate of 10 °C/min. [d] Swelling factor after equilibration with an excess of "solvent".

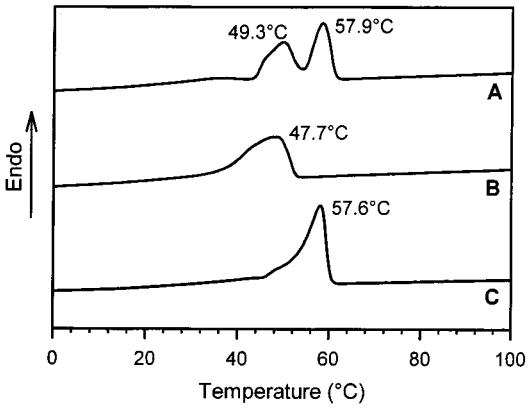


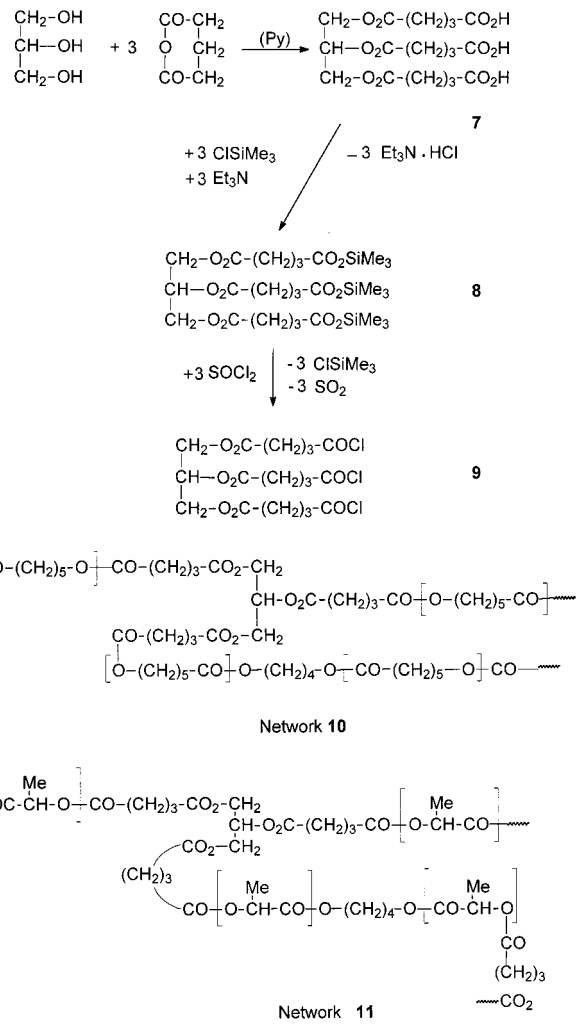
Figure 2. DSC measurements (heating/cooling rate: 10 °C/min) of (A) the poly(ϵ-CL) network **4a**, first heat, (B) second heat, and (C) **4d**, first heat.

Cross-Linking with Glycerol Trisglutaroyl Chloride. Trimesoyl chloride has two advantages as cross-linking agent: first, it is commercially available, and second, it is favorable for the ^{1}H NMR spectroscopic detection of the cross-links. However, little is known about its toxicity, and for a potential medical or pharmaceutical application of biodegradable networks nontoxic cross-links are desirable. A nontoxic tri- (or tetra-)functional acid chloride was neither commercially available nor described in the literature. Therefore, the acid chloride **9** was prepared from glycerol and glutaric anhydride according to Scheme 3. Unfortunately, the tricarboxylic acid **7** did not crystallize and decomposed upon attempted distillation over a short-path apparatus in a vacuum of 10^{-3} mbar. To avoid side reaction during the chlorination, the crude tricarboxylic acid **7** was silylated, and the trissilyl ester **8** was chlorinated with $SOCl_2$ in refluxing chloroform. A 400 MHz ^{1}H NMR spectrum suggested a purity around 97% for the crude acid chloride **9**, and satisfactory results of elemental analyzes were obtained.

Using the new cross-linking agent **9**, a series of poly(ϵ-CL) networks were prepared at 60 °C (labeled **10a**−**d**). The yields, DSC data, and swelling factors are summarized in Table 2. In principle, the same trends were found as for the networks cross-linked with trimesic acid. However, all these properties show slightly less variation than in the case of **4a**−**d**. The only speculative explanation we can forward at this time is that the cross-linking reaction was less efficient when the less reactive trimesoyl chloride was used. Signals of the cross-links were not detectable in the ^{1}H NMR spectra of **10a**−**d** because they were obscured by the intensive signals of the ϵ-CL units.

The successful synthesis of the networks **10a**−**d** prompted us to extend this approach to racemic DL-lactide. The high melting point of this monomer (mp ∼ 125−127 °C) required a solvent for the ring-expansion polymerization. Therefore, the entire synthesis was conducted in concentrated chloroform solution at 60 °C. The lower reactivity of racemic DL-lactide required a reaction time of 24 h. The gels were isolated in yields of 60−90% (Table 2). The good swelling in $CDCl_3$ allowed measurements of ^{1}H NMR spectra which revealed signals of the cross-linking units (Figure 3). These poly(DL-lactide) networks also showed good swelling properties in dichloromethane, toluene, and acetone as indicated by the swelling factors compiled in Table 2. These swelling factors roughly parallel the M/I ratios and thus represent an indirect proof of the expected structure. In this connection it should be mentioned that both classes of networks, those based on ϵ-CL and those

Scheme 3



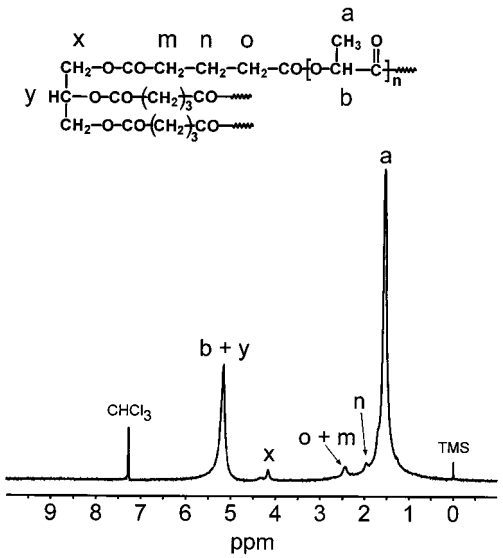


Figure 3. The 400 MHz ^{1}H NMR spectrum of the poly(DL-lactide) network **11a** (M/I = 20/1) swollen in $CDCl_3$.

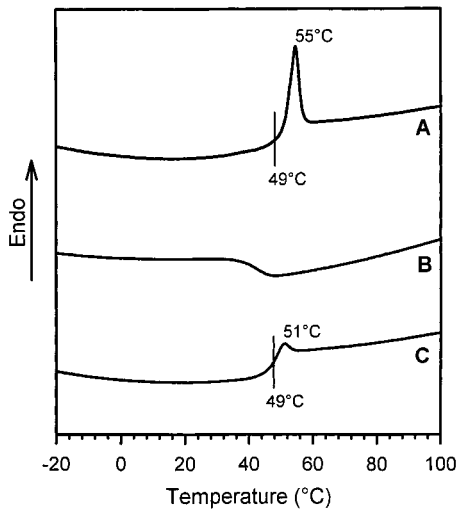


Figure 4. DSC measurements (heating/cooling rate: 10 °C/min) of the poly(DL-lactide) network **11a** (M/I = 20/1): (A) first heating, (B) first cooling, (C) second heating.

derived from DL-lactide, swell in more solvents than listed in Tables 1 and 2. For instance, they swell in tetrahydrofuran, dimethyl sulfoxide, and *N*-methylpyrrolidone.

Since poly(DL-lactide)s having nearly or exactly random stereosequences cannot crystallize, only glass-transition temperatures were detectable in the DSC curves. As illustrated by Figure 4, these DSC curves are remarkable, because the glass transitions are combined with a strong enthalpy change (Figure 4, curve A). In the second and third heating curves this enthalpy change is much weaker but still detectable (curve C). Obviously, this enthalpy change results from a frozen in orientation of the poly(DL-lactide) segments, which relaxes slowly upon thermal equilibration. This effect was also observed for non-cross-linked polylactides, but it was particularly strong in the case of our gels.

Conclusion

The results obtained in the present work allow the conclusion that the combined ring-expansion polymerization and polycondensation (ROPPOC synthesis) allows an easy synthesis of biodegradable networks. This new approach based on cyclic tin initiators, on one hand, and tri- (or multi-)functional acid chlorides is quite versatile. It can be performed with lactones and cyclic diesters, and it allows a proper control of the segment lengths (cross-linking density) of the gels via the M/I ratio of the polymerization process. Networks exclusively consisting of components familiar to the human metabolism can easily be prepared and may be useful for pharmaceutical or medical applications.

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