Polylactones. 44. Polymerizations of L-Lactide Catalyzed by Manganese Salts

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POLYLACTONES. 44. POLYMERIZATIONS OF L-LACTIDE CATALYZED BY MANGANESE SALTS

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ABSTRACT

Manganese(II)chloride, bromide, acetate and L-lactate were used as catalysts for the polymerization of L-lactide. All polymerizations were performed in bulk and despite a high reaction temperature (150°C), long reaction times (192 hours) were needed to achieve nearly complete conversions. Mn L-lactate was found to be the most reactive of the four catalysts. Yet, relatively low molecular weights ($M_v = 33\,000$) and partial racemization were found under all circumstances. Furthermore, copolymerizations of L-lactide and glycolide or L-lactide and ε-caprolactone were studied. A few homopolymerizations of L-lactide catalyzed by magnesium lactate or calcium lactate were included for comparison. These more basic initiators gave even worse results.

INTRODUCTION

This work is part of a broader study dedicated to the evaluation of resorbable catalysts of the ring-opening polymerization of L-lactide [1-6]. Resorbable, in this context, means that the components of the catalysts belong to the human metabolism, and thus, can be resorbed without any toxicity problems. Manganese $^{2+}$ ions are needed in trace amounts in the human body and Mn salts such as acetate are well known to be good transesterification catalysts. For instance, manganese acetate is a standard catalyst for the synthesis of poly(ethylene terephthalate) from dimethyl terephthalate and ethylene glycol [7, 8]. However, to the best of our knowledge, no

systematic study has been performed concerning the evaluation of manganese salts as catalysts of the ring-opening polymerization of L-lactide or other lactones.

EXPERIMENTAL

Materials

$MnCl_2$, $MnBr_2$, MnI_2, MnO and Mn acetate were purchased fom Aldrich Co. (Milwaukee, Wisc. USA) and used as received. Li-L-lactate was purchased from Sigma Chemicals (Munich, Germany). Glycolide and lactide (S-grade) were purchased from Boehringer Ingelheim GmbH (Germany). They were once recrystallized from dry ethyl acetate and stored over P_4O_{10} prior to use. ε-Caprolactone was purchased from Aldrich Co. and distilled over freshly powdered CaH_2 *in vacuo*.

Mn(II)-L-lactate

$MnCl_2$ (22 mmol) was dissolved in desoxygenated water (100 ml) and added dropwise with stirring to a solution of Li-L-lactate (50 mmol) in desoxygenated water (100 ml). The clear solution was concentrated until a turbidity appeared. After standing overnight, the product was isolated by filtration and once recrystallized from water. Finally, the product was dried at 70°C over P_4O_{10}. Yield: 57%.

$C_6H_{10}O_6Mn$ (233.08)   Calcd. C 30.92   H 4.32
                                  Found   C 30.82   H 4.37

$[\alpha]_D^{20}$ - 11.04°, c = 2.5 g/dL in H_2O

Polymerizations

Homopolymerizations

Under an atmosphere of dry nitrogen L-lactide (50 mmol) and the catalyst (1 mmol or 0.25 mmol) were weighed into a 50 ml Erlenmeyer flask with silanized glass walls. The reaction vessel was closed with a glass stopper and steel spring, and completely immersed into an oil bath preheated to 150°C. Finally, the cold reaction product was dissolved in CH_2Cl_2 (40 ml), precipitated into cold methanol and dried at 40°C *in vacuo*.

Copolymerizations with Glycolide

Glycolide (12.5 mmol), L-lactide (37.5 mmol) and Mn-L-lactate (1 mmol) were weighed under dry nitrogen into a 50 ml Erlenmeyer flask with silanized glass walls. The reaction vessel was closed with a glass stopper and steel spring and completely immersed into an oil bath thermostated at 150°C. The cold product was

isolated as described above. All other copolymerizations were conducted analog-ously.

Copolymerizations with ε-Caprolactone

ε-Caprolactone (33.6 mmol), L-lactide (16.3 mmol) and Mn L-lactate (1 mmol) were weighed into a 50 ml Erlenmeyer flask with silanized glass walls and polymerized as described for A). All other polymerizations listed in Table 4 were performed analogously.

Measurements

The inherent viscosities were measured with an automated Ubelohde viscosimeter thermostated at 25°C. The DSC-measurements were conducted with a Perkin Elmer DSC-7 in aluminum pans under nitrogen. The 100 MHz ^{1}H-NMR spectra were recorded on a Bruker AC-100 FT NMR spectrometer in 5mm o.d. sample tubes. The 25.2 MHz ^{13}C NMR spectra were recorded with the same NMR spectrometer in 10 mm o.d. sample tubes. CDCl$_3$ containing TMS was used as solvent and shift reference for most NMR measurements. However, the glycolide/lactide copolyesters were measured in hexafluoroisopropanol containing DMSO-d$_6$ as shift reference.

RESULTS AND DISCUSSION

Homopolymerizations of L-lactide

Four commercial manganese salts were used for the present work, namely: MnCl$_2$, MnBr$_2$, MnI$_2$ and Mn acetate. Mn L-lactate was prepared from MnCl$_2$ and Li L-lactate. It was included in this work, because previous studies of Zn salts and Fe(II)salts had demonstrated that the lactates were the best catalysts of all salts compared in those studies.

A first series of polymerizations was conducted in bulk at 150°C using MnCl$_2$, MnBr$_2$ and MnI$_2$ as catalysts. Two monomer/initiator ratios were used and their reaction time was varied. The results summarized in Table 1. demonstrate that all three Mn halogenides gave similar results, but the yields, inherent viscosities and optical rotations obtained with MnBr$_2$ were slightly higher than those obtained with MnCl$_2$ or MnI$_2$. This point is interesting, because it parallels the results found for Zn halogenides and Fe(II) halogenides. Why the bromides gave the best results cannot be explained at this time, but the parallel between the halogenides of Zn, Fe(II) and Mn excludes the fact that impurities in individual catalysts played a key role. Further, but less satisfactory observations concerning the performance of the

Table 1. MnCl$_2$ and MnBr$_2$ -Catalyzed Polymerizations of L-lactide[a]

Polymer No.	Catalyst	M/C	time in [h]	Yield in [%]	$\eta_{inh.}$[b] in dl/g	$[\alpha]_D^{20}$ [c]
1	MnCl$_2$	500	48	17	0.10	
2		500	96	53	0.18	
3		500	192	61	0.38	- 144
4	MnCl$_2$	2000	48	5	0.11	
5		2000	96	39	0.14	
6		2000	192	55	0.32	- 147
7	MnBr$_2$	500	48	47	0.23	
8		500	96	85	0.32	
9		500	192	87	0.34	- 149
10	MnBr$_2$	2000	48	14	0.12	
11		2000	96	40	0.25	
12		2000	192	87	0.33	-152

a)   all polymerizations were conducted in bulk at 150 °C
b)   measured at 20 °C with c = 2g/l in CH$_2$Cl$_2$
c)   measured at 20 °C with c = 1g/l in CHCl$_3$

Mn halogenides are the rather low inherent viscosities (and thus molecular weights) obtained in all polymerizations listed in Table 1 along with optical rotations indicating a slight racemization.

The second series of polymerzations was performed with Mn acetate an Mn L-lactate. The data compiled in Table 2 yield the following information. Firstly, both the acetate and the lactate were more active than the halogenides as indicated by the higher yields obtained after short reaction times at the M/C ratio of 2000/1. Yields of 90% (Nos. 9 and 12, Table 2) are close to the maximum, because for thermodynamic reasons, the conversions of L-Lactide stops around 95%, and the

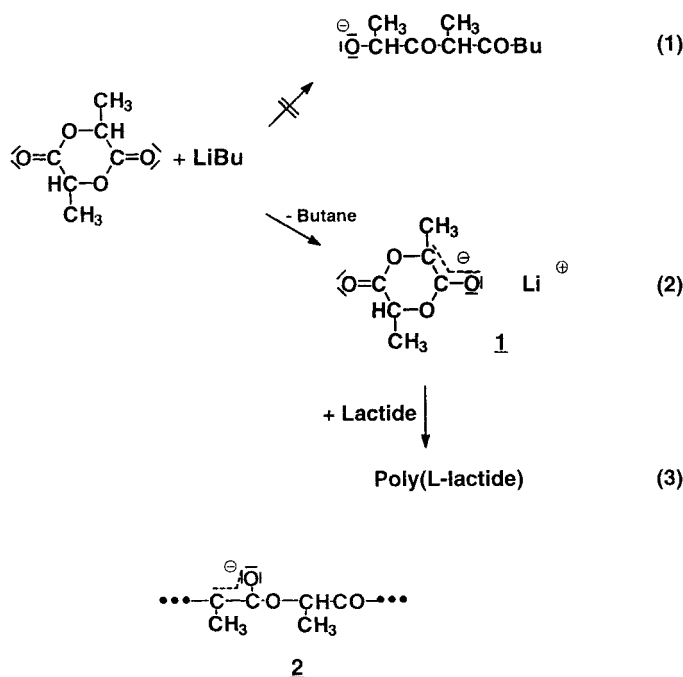Table 2. Mn Acetate and Mn L-lactate Catalyzed Polymerizations of L-lactide

Polymer No.	Catalyst	Monomer/ Catalyst	Time in [h]	Yield [a] in [%]	$\eta_{inh.}$ [b] in [dl/g]	$[\alpha]_D^{20}$ [c]
1	Mn acetate	500	48	81	0.29	
2		500	96	79	0.31	
3		500	192	87	0.29	-123
4	Mn acetate	2000	48	44	0.29	
5		2000	96	72	0.35	
6		2000	192	88	0.38	-130
7	Mn lactate	500	48	82	0.32	
8		500	96	86	0.33	
9		500	192	90	0.35	-130
10	Mn lactate	2000	48	64	0.35	
11		2000	96	78	0.33	
12		2000	192	90	0.27	-134

a)   all polymerizations were conducted in bulk at 150 °C

b)   measured at 20 °C with c = 2g/l in CH_2Cl_2

c)   measured at 20 °C with c = 1g/dl in $CHCl_3$

precipitation of the crude polylactide in methanol causes a slight fractionation. Secondly, the inherent viscosities were not significantly higher than those found for the Mn halogenide-catalyzed polymerization. Thirdly, the optical rotations were considerably lower than those observed for Mn halogenide catalyzed polyesters.

These results can be partially understood on the basis of our previous studies dealing with the anionic polymerization of L-lactide [9, 10]. For instance, it was found that the Butylanion of LiBu does not undergo a nucleophilic attack (Equation 1) but exclusively causes deprotonation (Equation 2). The resulting

lactide anion (<u>1</u>) initiates an anionic polymerization (Equation 3). The acidity of lactide is so high that even relatively weak bases (relative to the butyl anion) such as triethylamine (pK$_S$ ~11) may cause racemization by deprotonation. The pK$_S$ value of L-lactide is not exactly known, but it is reasonable to assume a value of 16 ± 2, which falls into range defined by acetone (pK$_S$ ~19) and esters of malonic acid (pK$_S$ ~12 ± 1). However, it is clear that the cyclic L-lactide is more acidic than a lactyl unit in the polymer. In the latter case, the delocalized anion (<u>3</u>) produces a double bond which is a hindrance for rotation around the C$_\alpha$-CO bond, and thus, unfavorable for entropic reasons. The deprotonation of L-lactide is not only the origin of racemization, it may also cause chain transfer according to Equation (<u>3</u>), and thus, cause a limitation of the maximum molecular weights. On the basis of these facts, it is understandable, why the acetate and lactate of manganese which are more basic than the halides reduce the optical rotation. However, it is not understandable why the molecular weights are almost identical.

Copolymerizations of L-lactide

In addition to these homopolymerizations, a series of copolymerizations with glycolide (molar ratio Glyc/Lac 1:3) was performed. MnBr$_2$ and Mn L-lactate were used as catalysts and the M/C ratio was varied between 500/1 and 2000/1. High yields were obtained at M/C = 500 but low yields at M/C = 2000, whereas the

Table 3. MnBr$_2$ and Mn L-lactate Catalyzed Copolymerization[a] of Glycolide and L-lactide (Molar Ratio 1:3)

Polymer No	Catalyst	Monomer Catalyst	Time in[h]	Yield in [%]	$\eta_{inh.}$[b] in [dl/g]	Glyc/ Lac[c]	L_{Glyc}[d]	L_{Lac}[d]	T_g [°C]
1	MnBr$_2$	500/1	48	82	0.26	0.36/1	(1.7)	(6.5)	32
2		500/1	72	89	0.24	0.34/1	(1.7)	(8.0)	27
3		2000/1	48	55	0.24	0.56/1	2.5	5.5	19
4		2000/1	72	54	0.20	0.58/1	2.7	5.3	10
5	Mn lactate	500/1	48	81	0.29	0.28/1	2.0	6.0	42
6		500/1	72	90	0.30	0.30/1	(1.9)	(5.1)	42
7		2000/1	48	43	0.27	1.33/1	2.9	4.8	32
8		2000/1	72	48	0.22	0.96/1	2.6	6.5	27

a)   all polymerizations were conducted in bulk at 150°C

b)   measured at 25 °C with c = 2g/l in TFA/CH$_2$Cl$_2$ (1:4)

c)   molar composition of the isolated copolyesters are determined by ^{1}H-NMR spectroscopy

d)   average length of the glycolide or lactide blocks as determined by ^{13}C-NMR spectroscopy

       The values in brackets have a low accurancy due to a poor signal to noise ratio.

viscosities proved to be independent of the M/C ratio (Table 3). Surprisingly, the molar compositions varied with the M/C ratios. The Glyc/Lac ratio was higher than the feed ratio (1:3) in all copolylactones. This result is not surprising, because glycolide is known to be more reactive than lactide regardless of the polymerization mechanism [11-13]. However, the difference between the experimental molar composition and the feed ratio significantly increased, when the M/C ratio was higher. Obviously the entire polymerization and transesterification process was incomplete due to the rather low reactivity of both catalysts. This conclusion is supported by the block length values derived from the CO-signals of the ^{13}C NMR spectra according to the literature [11] when measured in hexafluoroisopropanol. The average block lengths of the Glyc units were considerably higher than expected from the feed molar ratio assuming complete transesterification.

Table 4. $MnBr_2$ and Mn L-lactate Catalyzed Copolymerizations of L-lactide and ε-Caprolactone (Molar Ratio 1:2)

Polymer No.	Catalyst	Monomer/ Catalyst	Time in [h]	Yield [a] in [%]	$\eta_{inh.}$ [b] in [dl/g]	Lact./ ε–CL [c]	L_{CL} [d]	T_g [°C]	T_m [°C]
1	$MnBr_2$	500/1	48	66	0.30	1.4	3.7	-24	45
2		500/1	96	72	0.33	1.2	3.4	-23	46
3		2000/1	48	16	0.30	2.8	_e)	- 6	115
4		2000/1	96	34	0.32	1.3	3.2	- 24	43
5	Mn-lactate	500/1	48	77	0.27	1.2	2.3	- 33	--
6		500/1	96	79	0.32	1.0	2.0	- 35	--
7		2000/1	48	23	0.33	2.6	2.6	- 11	116
8		2000/1	96	48	0.39	1.7	3.7	- 24	45

a)   all polymerizations were conducted in bulk at 150°C

b)   measured at 25 °C with c = 2g/l in CH_2Cl_2

c)   molar composition of the isolated copolyester as determined by ^{1}H-NMR spectroscopy

d)   average length of the ε–CL blocks as determined by ^{13}C-NMR spectroscopy

e)   poorly resolved NMR signals

Finally, numerous copolymerizations of L-lactide and ε-caprolactone were conducted in bulk at 150°C. Again, $MnBr_2$ and Mn L-lactate were used as catalysts using M/C ratios of 500/1 and 2000/1 (Table 4). Quite analogous to the afore-mentioned copolymerizations of L-lactide and glycolide, high yields were only obtained at the lower M/C ratios, whereas the viscosity values proved to be inde-pendent of the M/C ratio. In this series, the isolated copolyesters contained some-what more lactate units than expected from the feed ratio. Figure 1 presents an exemplary illustration of the ^{1}H-NMR spectra used for the determination of the composition. The ^{13}C NMR spectra revealed that the transesterification was in most cases not complete, so that the sequences were not random as indicated by the block length values above 2.0 (illustrated in Figure 2). Also, from this point of view, the results of these copolymerizations resemble those obtained from copolymerizations
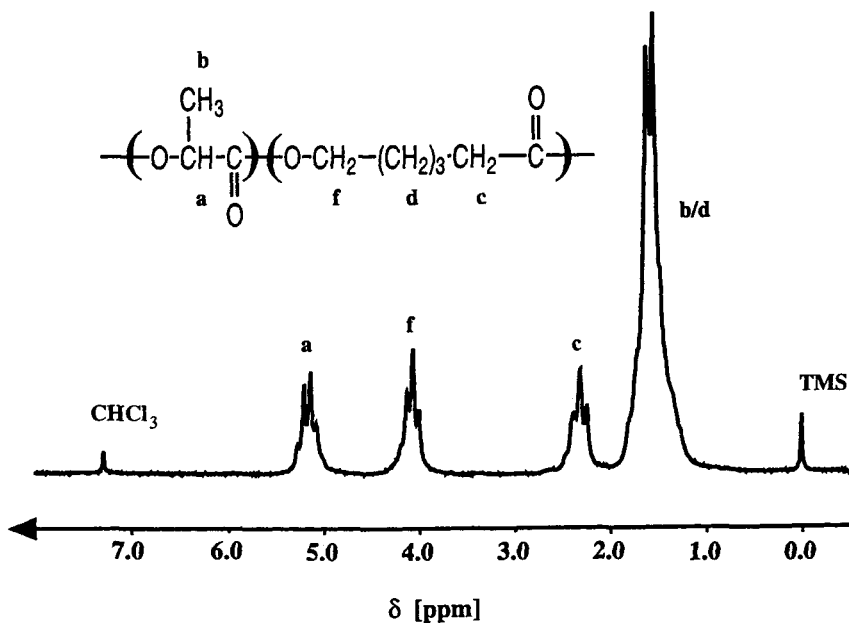
Figure 1. 100 MHz ^{1}H NMR spectrum of the L-lactide/ε-caprolactone copolymer No. 8, Table 4.
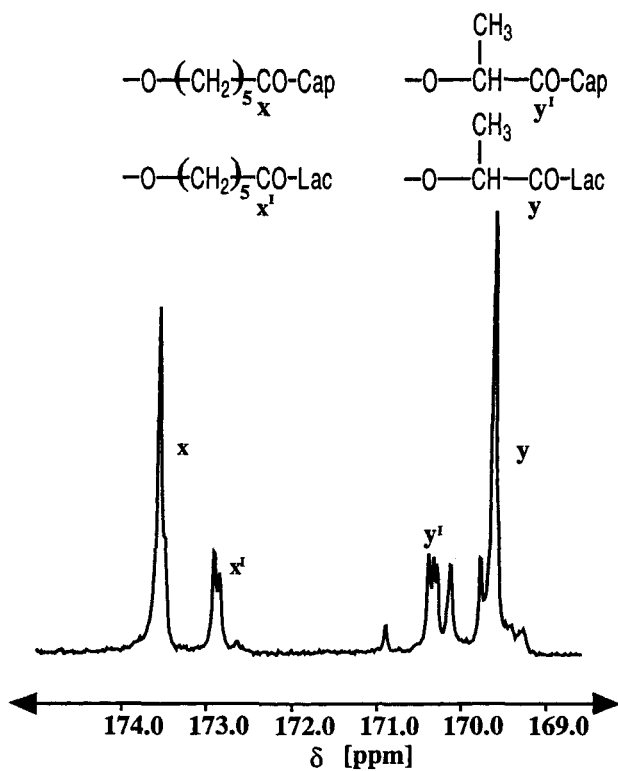
Figure 2. 90.4 MHz ^{13}C NMR spectrum (CO- signals only) of the L-lactide/ε-Caprolactone copolymer No.1, Table 4.

of glycolide. However, when Mn L-lactate was used at a M/C ratio of 500 the sequences were close to being random (Nos. 5 and 6), suggesting that Mn L-lactate was the better transesterification catalyst than $MnBr_2$.

The DSC measurements reflect and confirm this interpretation of the NMR spectra. When block lengths of the ε-CL units were above 3.0, weak melting endotherms of ε-CL blocks were detectable in the in the first heating curves of samples annealed by storage at room temperature. As illustrated by Figure 3, no endotherm was detectable in the second heating trace. However, after annealing for 24 hours at 25°C, a weak endotherm was found again in the third heating trace of sample No. 4, Table 4. In the case of samples Nos. 5 and 6, no endotherms were detectable at all in good agreement with their sequences. Interestingly, two caprolactones with relatively high Lac/CL ratios (Nos. 3 and 7, Table 4) showed two weak endotherms above 100°C, which obviously originated from small and imperfect crystallites of short L-lactide blocks.

Mg L-lactate and Ca L-lactate as Catalyst

In order to complete our evaluation of resorbable metal lactates as polymerization catalysts, one more Table summarizing Ca L-lactate homopoly-merizations of L-lactide was added (Table 5). Regardless of the reaction conditions, poor yields and low molecular weights were obtained from all polymerizations. The results obtained from Mg L-lactate initiated polymerizations were even worse than those found for Ca L-lactate, and thus, were not presented and discussed in detail. This negative tendency fits in with previous studies based on other magnesium and calcium salts [1, 2]. Obviously, the higher basicity of the magnesium and calcium salts (when compared to Mn^{2+} or Fe^{2+} salts) is responsible for the poor results. On the basis of previous studies using various bases [10] and Fe^{2+} salts [6] it was concluded that the deprotonation of L-lactide in α-position is a key reaction not only for racemization, but also as a chain transfer to the monomer. The poor results obtained here with Mg- and Ca L-lactate fit well in with this hypothesis.

CONCLUSION

The results obtained in this work with various manganese salts allow the following conclusions. All the manganese salts proved to be rather sluggish polymerization catalysts despite the good reputation as transesterification catalysts. Furthermore, all manganese salts tend to cause partial racemization and produce only low to moderate molecular weights. The more basic magnesium and calcium
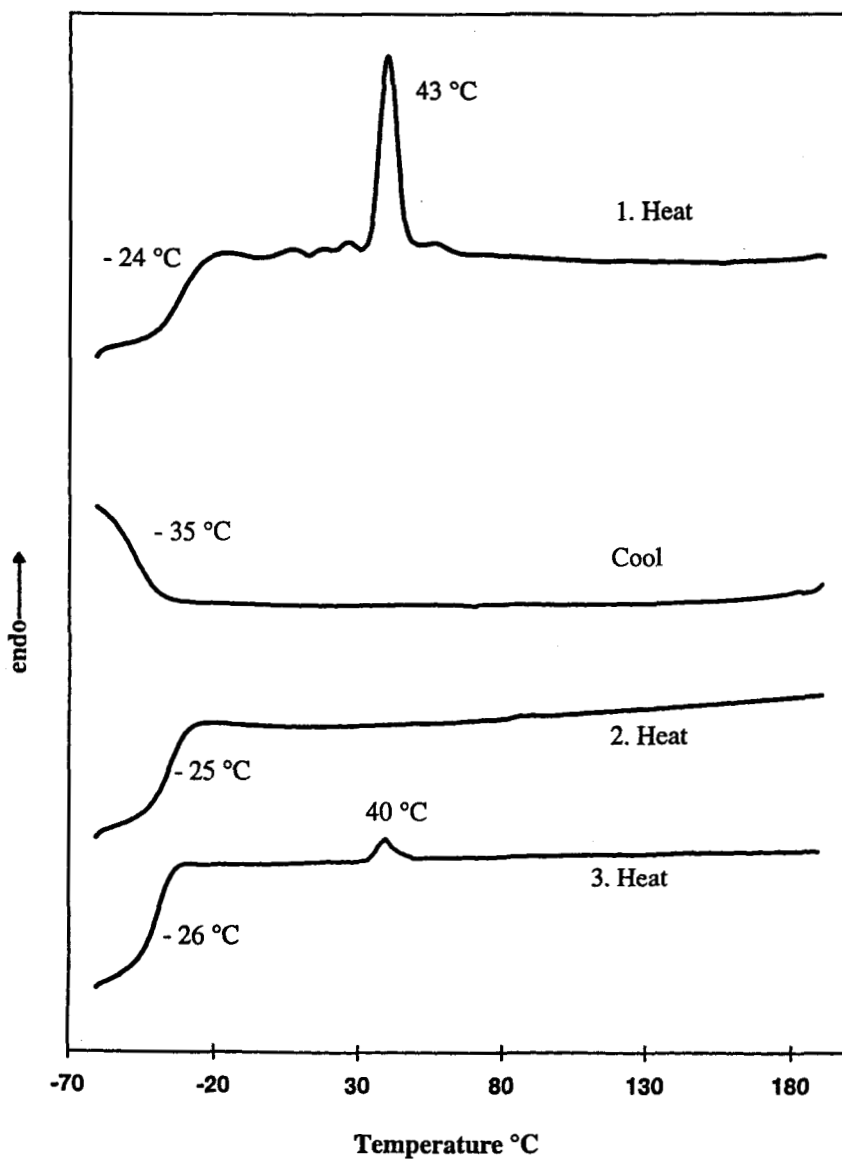
Figure 3.   DSC measurements (heating and cooling rate: 20°C/min) of the L-lactide/ε-caprolactone copolymer No. 4, Table 4.

Table 5. Ca L-lactate Catalyzed Polymerizations of L-lactide in Bulk at 120 or 150°C

Polymer No.	Monomer/ Catalyst	Temperature [°C]	Time in [h]	Yield in [%]	$\eta_{inh.}$[a] in [dl/g]
1	500	120	48	7	0.01
2	500		96	10	0.18
3	500		144	16	0.21
4	500		192	21	0.22
5	2000		48	36	0.09
6	2000		96	46	0.06
7	2000		144	46	0.06
8	2000		192	58	0.05
9	500	150	48	6	0.17
10	500		72	10	0.19
11	500		96	14	0.20
12	500		192	17	0.34
13	4000		48	47	0.06

a)   measured at 20 °C with c = 2g/l in CH_2Cl_2

lactates yield even poorer results, obviously because side reactions based on the α-deprotonation of lactide (or glycolide) are even more frequent. Taking into account our previously published results obtained with Zn L-lactate and Fe^{2+}L-lactate the order of "usefulness" of resorbable metal lactates as polymerization catalysts is the following one:

$$Zn^{2+} > Fe^{2+} > Mn^{2+} > Ca^{2+} \geq Mg^{2+}$$
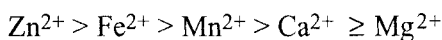
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