DOI: 10.1002/masy.200900101

Bulk Ring Opening Polymerization of L-Lactide with Calcium methoxide

Marcos Lopes Dias, Luiz Carlos Palermo, Alexandre C. Silvino*

Summary: Bulk ring opening polymerization (ROP) of L-lactide (LA) initiated by calcium methoxide ($Ca(OMe)_2$) was investigated in LA/Ca molar ratio from 100 to 5000 and reaction times up to 3h at 180 °C. $Ca(OMe)_2$ showed good activity as ROP catalyst, particularly at high catalyst concentration. The polymerization shows a linear relationship between $\overline{M}_n$ and reaction time, typical of a controlled process. The increase of LA/Ca molar ratio decreases the conversion which was maximum (66%) when the polymerization was carried out at 180 °C and LA/Ca = 100. Semicrystalline poly(L-lactic acid) (PLLA) with moderate $\overline{M}_n$ varying from 8,500 to 19,500 and polydispersities from 1.20 to 1.44 were obtained. The increase of LA/Ca molar ratio decreased $\overline{M}_n$, increased the degree of crystallinity and decreased racemization processes which can be controlled by the polymerization condition. Racemization could be reduced by using low catalyst concentration.

Keywords: bulk polymerization; calcium methoxide; L-lactide; racemization; ROP

Introduction

Polylactides (PLA) are interesting polymers due to combination of characteristics like bioresorption, biocompatibility and biodegradation. They can be applied in biomedical, pharmaceutical and packaging areas and are considered "Green Polymers", since they come from renewable agricultural resources by combination of fermentation and polymerization.[1–3]

Poly(L-lactic acid) (PLLA), which is an important member of the family, is synthesized from L-lactide ring opening polymerization (ROP), producing a semi-crystalline polymer with a variable melting temperature (T_m), depending on the degree of stereocontrol imposed by the catalyst/initiator used in the polymerization process.[4–6]

The most used catalyst to synthesize high molecular weight, high stereoregular and consequently high melting temperature PLLA is Sn(II) 2-ethylhexanoate, also known as tin octoate ($SnOct_2$).[7] However, tin compounds are relatively cytotoxic and catalytic residues are difficult to remove from the polymer. Thus the use of tin compounds must be limited when PLLA is used in medical and pharmaceutical applications.[8] Due to this possible toxicity, several catalysts based on more compatible metals like Li, Zn, Ca, Mg e Fe(II) have been studied.[9,10] With this regard, calcium compounds are very interesting, but few papers have reported the bulk ROP polymerization of lactides with Ca compounds.

Kricheldorf[11] was the first to report the bulk polymerization of L-lactide with calcium compounds (oxide, carbonate and stearate). These compounds produced brown high viscosity liquids after 48h at 180 °C. The molecular weight and microsctructure of the products were not reported. CaH_2 was used as catalyst in the synthesis of triblock PLA/PEO/PLA copolymers by polymerization of L-lactide in the presence of a bifunctional OH-terminated poly(ethylene glycol).[12–13] The same compound was used in the synthesis of four-arm PLA oligomers.[14]

Instituto de Macromoléculas Professora Eloisa Mano, Universidade Federal do Rio de Janeiro, CP. 68525, 21945-970 Rio de Janeiro, RJ Brazil
E-mail: mldias@ima.ufrj.br

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Authors reported that the calcium compound led to some racemization. Calcium dimethoxide and *in-situ* generated calcium dimethoxide prepared from calcium complexes were investigated as initiators for bulk and solution ROP of lactones in mild conditions, resulting in good yields and polymers with controlled molecular weight.[15–19] Nevertheless, in these works only one example of bulk ROP of lactide was presented, with no report on the microstructure and properties of the polymer.

Solution polymerization of LA with calcium complexes containing amino-imino ligands in presence of alcohols were also reported to result in polymers with relatively high molecular weight, narrow polydispersity and high conversion.[20]

We have investigated in detail the bulk ROP of L-lactide with several calcium compounds in conditions similar to those used in industrial production of PLLA. No previous report of bulk polymerization with calcium methoxide ($Ca(OMe)_2$) exploring the reaction conditions was found in literature. So, in this work the bulk polymerization of L-lactide using ($Ca(OMe)_2$) was investigated, aiming to achieve additional information on the influence of reaction conditions on the polymer structure and properties.

Experimental Part

Materials

L-Lactide (Boehringer) was crystallized from ethyl acetate. The final free acid content measured by potentiometric titration was lower than 1 meq/kg. $Ca(MeO)_2$ 97% (Sigma-Aldrich), chloroform and ethanol (Vetec, Brazil) were used as received.

Polymerization

Polymerization reactions were carried out in schlenk flasks and all reactant manipulation was done in glove-bag under nitrogen atmosphere. Bulk polymerization of lactide was carried out in Schlenk flasks at 180 °C for 3 hours under inert nitrogen atmosphere. After reactions, the polymers were dissolved in chloroform, precipitated in ethanol, filtered under vacuum and dried in an oven at 40 °C for 24 hours. The polymer was then redissolved, reprecipitated, filtered under vacuum and dried in an oven. This second purification aimed to remove traces of color due to the catalyst. The conversion was calculated from the weight of monomer and polymer after purification.

Polymer Characterization

Size exclusion chromatography (SEC) was carried out in a Waters chromatographic system at 25 °C with a set of two Styragel columns (HT3 and HT6E) by using THF as solvent, flow rate of 1.0 mL/min, polymer concentration 0.2%. Monodisperse polystyrene standards were used for calibration. ^{13}C-NMR spectra were recorded at room temperature with a Varian Mercury VX-300 FT-NMR spectrometer operating at 75 MHz (^{13}C) using tetramethylsilane (TMS) as an internal reference. Polymers were analyzed in $CDCl_3$ solution. Chemical shifts (δ) were given in ppm and differences in the microstructure were evaluated according to literature.[21–22] Differential scanning calorimetry (DSC) was carried out in a TA DSC equipment. Samples were subject to different thermal cycles: a first heating from 25 °C to 200 °C at 10 °C.min^{-1}, a quenching from 200 °C to 25 °C at about 50 °C/min, a 2nd heating from this temperature to 200 °C at 10 °C.min^{-1}, a 2nd cooling to 25 °C and a 3rd heating to 200 °C at 10 °C.min^{-1}. Crystallization temperatures were investigated from exothermic peaks of crystallization on 2nd heating (cold crystallization) (T_{ch}) and on 2nd cooling (T_{cc}) scans. The degree of crystallinity was calculated from the melting enthalpy (106 J.g^{-1} used for 100% crystalline PLLA).[23] Wide angle X-ray diffraction (WAXD) was performed in a Miniflex Rigaku diffractometer (30 kV, 15 mA) with a copper X-ray tube (CuKα, $\lambda = 1.5418$ Å).

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Results and Discussion

Bulk Lactide ROP with $Ca(OMe)_2$

It is very well know that in ROP of lactides, monomer molecules are inserted between preformed metal-oxygen bonds of the catalyst molecule in the propagation step of polymerization.[6,7] When the catalyst/initiator molecule has no alkoxide group the initiation is assumed to occur via the reaction with hydroxyl impurities in the medium. In this study, $Ca(OMe)_2$ was chosen because it contains this type of bond in the molecular structure and initiation is facilitated. However, it is also know that $Ca(OMe)_2$ has limited solubility in organic medium and polymerization initiated with the compound can occur as heterogeneous reaction system. Thus, polymerizations were carried out by using LA/Ca molar ratio from 100 to 5000 in order to see the influence of catalyst concentration on the reaction.

The results of bulk ROP of LA with $Ca(OMe)_2$ at 180 °C in five LA/Ca molar ratio from 100 to 5000 and 3 h reaction are presented in Table 1. After the end of polymerization, in all cases the reaction medium was a brown solid material. After purification, performed through precipitation in a chloroform solution with addition of ethanol, the polymer material became a pale cream colored powder.

As shown in Table 1, conversion decreased as the LA/Ca was increased. The higher attained conversion at 3h reaction was 66% at LA/Ca = 100. These results are similar to those observed in reactions initiated with $SnOct_2$, where at higher LA/Sn molar ratio the reaction is slower, leading to lower conversion in 3 h reaction.[24]

The obtained PLLAs presented monomodal SEC curves and number average molecular weights ($\overline{M}_n$) from 8500 to 19500 with narrow molecular weight distribution ($\overline{M}_w/\overline{M}_n$ from 1.20 to 1.44). Table 1 also shows that $\overline{M}_n$ and polydispersity decreased when the LA/Ca molar ratio increased. These results are however different from those observed with tin compounds in which the increase of the monomer/initiator ratio generates polymers with higher molecular weights.[24]

It is important to mention that only in the LA/Ca = 5000 the catalyst was completely soluble in the reaction medium. In the other cases, although a considerable amount of catalyst was soluble in the molten LA, part of the catalyst was not soluble and therefore not accessed by monomer molecules, which means that nominal concentration was not the true concentration of active species.

Figure 1 presents the evolution of conversion with reaction time and shows that conversion increases linearly with reaction times up to 3 h. The study showed also a linear relationship between $\overline{M}_n$ and the polymerization time.

Plot of $\overline{M}_n$ versus conversion is shown in Figure 2. This plot also shows a linear relationship between $\overline{M}_n$ and conversion that agrees well with the theoretical linear relationship that is representative of a living or controlled polymerization.

Table 1.
Effect of LA/Ca on the polymerization of L-lactide with $Ca(OMe)_2$ at 180°C (reaction time = 3 h)

Run	LA/Ca molar ratio	$\overline{M}_n$	$\overline{M}_w/\overline{M}_n$	Conversion (%)
1	100	19500	1.44	66.0
2	250	18600	1.39	42.0
3	500	13400	1.24	14.5
4	1000	12800	1.22	5.0
5	5000	8500	1.20	< 1.0

Structure of PLLAs

Main PLA ^{13}C NMR signals appeared at 16.4 (CH_3), 68.7 (CH), and 169.3 ppm (C = O). The expanded region of methine and carbonyl of ^{13}C NMR spectra of PLLAs obtained with $Ca(OMe)_2$ at different LA/Ca molar ratio are presented in Figure 3. These data show that the polymer obtained at LA/Ca = 100 presented a large number of microstructural errors due to racemization. Thus, this polymer is less stereoregular. Polymers obtained at molar ratio 1000 and 5000 presented microstruc-

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

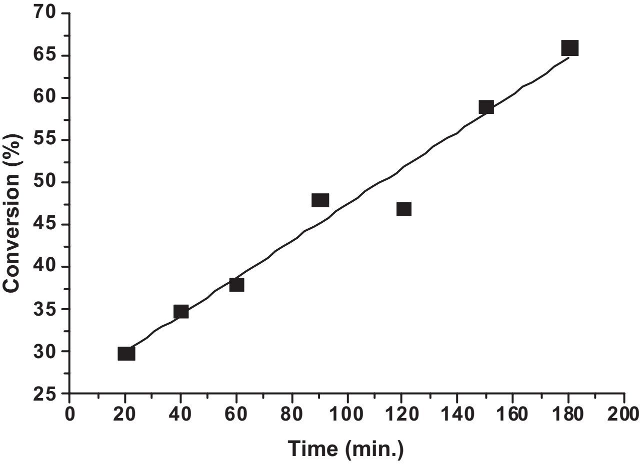

Figure 1.
Plot of L-lactide conversion versus reaction time for polymerization initiated by $Ca(OMe)_2$ at 180 °C and molar ratio LA/Ca = 100.

ture with higher stereoregularity, evidenced by the higher intensity of mmm tetrade peaks and lateral signals of lower intensities. Integration of carbonyl region gives mmm% = 49 and 90% for polymers synthesized at LA/Ca = 100 and 1000, respectively. It is interesting to note that chain regularity can be controlled by the polymerization condition and that racemization can be reduced by using lower concentration of catalyst.

It is also important to mention that the spectra of PLLAs obtained at LA/Ca = 1000 and 5000 exhibited extra signals with low intensities at 20.20 and 66.45 ppm besides those characteristic of isotactic PLA sequences and racemization. According the literature,[12] these signals can be ascribed to -CH_3 and -CH of OH-ended lactyl units, respectively. These end groups were probably observed due to the lower molecular weight of these samples and were

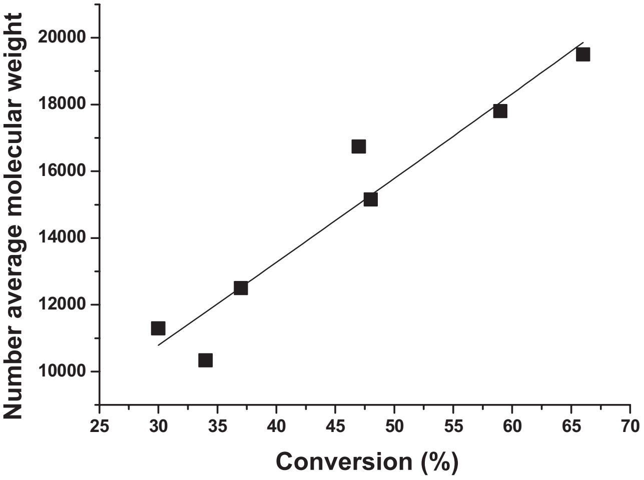

Figure 2.
Number average molecular weight ($\overline{M}_n$) as a function of conversion for polymerization initiated by calcium methoxide at 180 °C with ratio LA/Ca = 100.

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

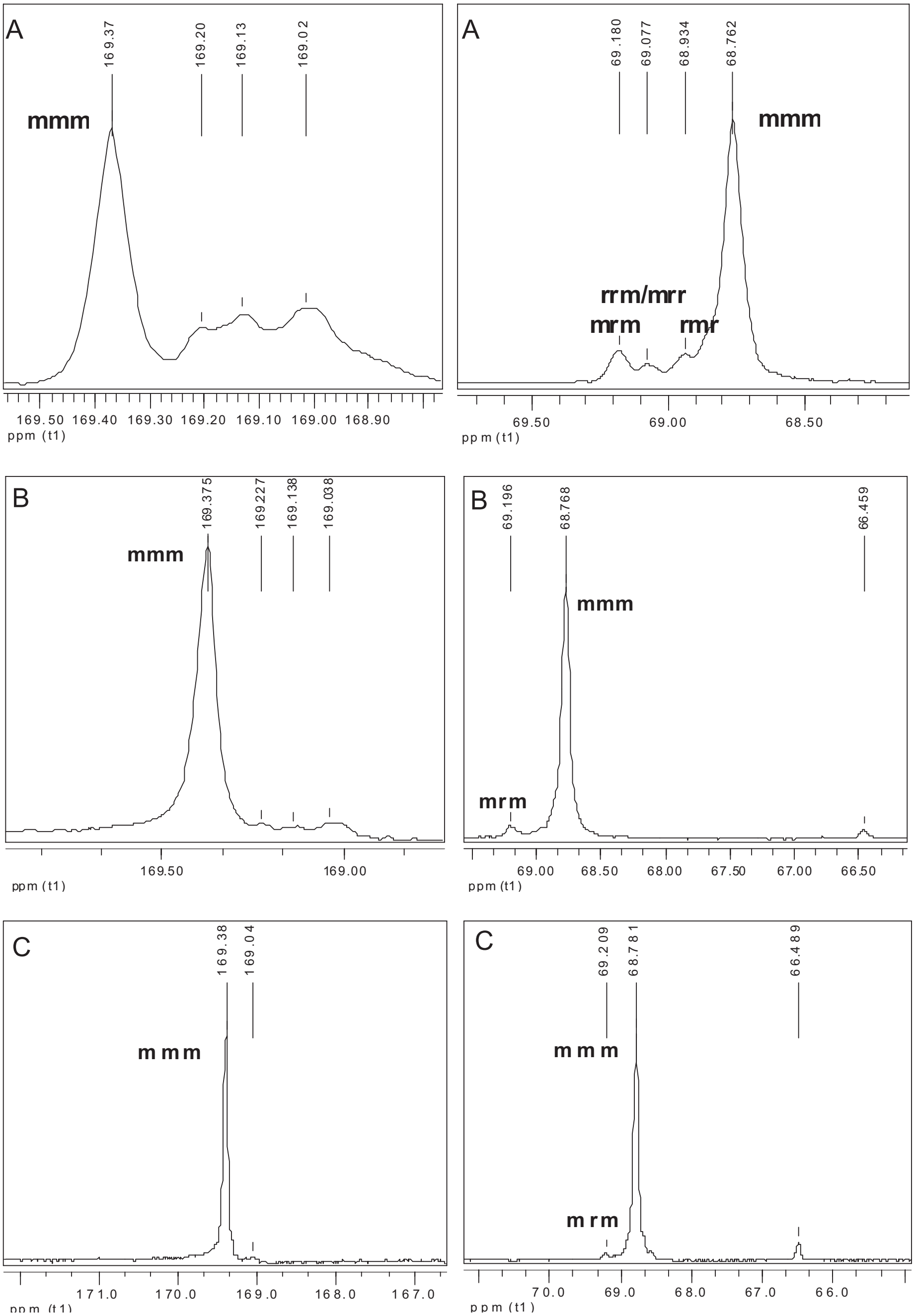

Figure 3.
Carbonyl and methine region of ^{13}C NMR spectra of PLLAs obtained with $Ca(OMe)_2$ at 180 °C for LA/Ca = 100 (A), LA/Ca = 1000 (B) and LA/Ca = 5000 (C).

probably produced by the break of Ca-O growing chain bond by moisture at the end of reaction.

Polymer Thermal Properties

DSC traces of the PLLA powders obtained by chloroform solution precipitation in

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

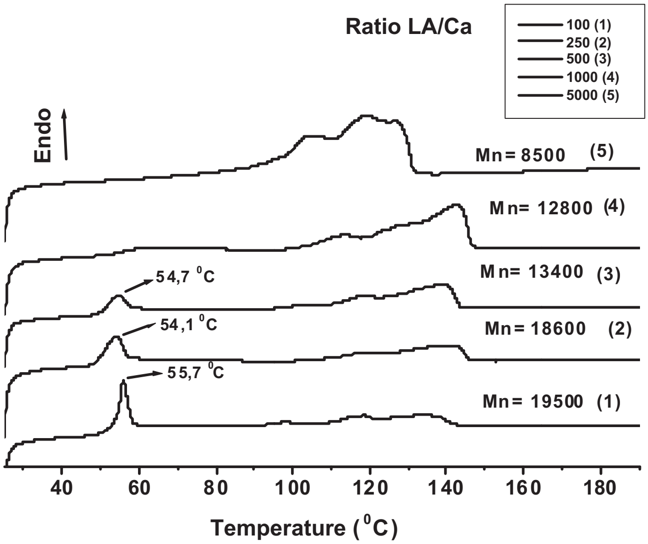

Figure 4.
DSC traces (1st heating run) of PLLA obtained with $Ca(OMe)_2$ at 180 °C and different LA/Ca.

Table 2.
Thermal Properties and Degree of Crystallinity of PLLAs obtained with $Ca(OMe)_2$ at 180 °C (reaction time = 3 h)

LA/Ca Molar Ratio	T_g [b] (°C)	T_{ch} [b] (°C)	T_m [a] (°C)	X_c [a] (%)
100	49.6	–	98.4 / 118.4 /134.2	12.8
250	49.0	–	118.8 / 140.5	15.4
500	49.6	–	104.8 / 119.0/ 138.9	22.0
1000	47.7	106.0	111.1 / 142.7	38.1
5000	40.4	75.0	105.4 / 119.0	64.5

[a]Determined from the first heating curves; [b]Determined from the 2nd heating.

ethanol after the end of polymerization showed that the polymers are semicrystalline (Figure 4). Table 2 shows the thermal transitions and degree of crystallinity of PLLAs. Tg between 40 and 50 °C which increases with $\overline{M}_n$ (Figure 5) and

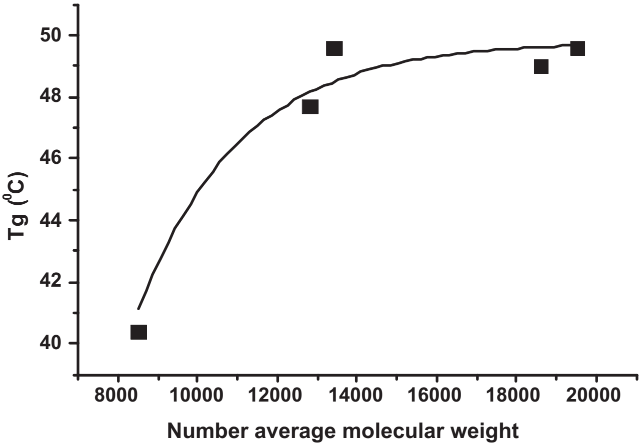

Figure 5.
Tg versus $\overline{M}_n$ of PLLAs obtained with $Ca(OMe)_2$.

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

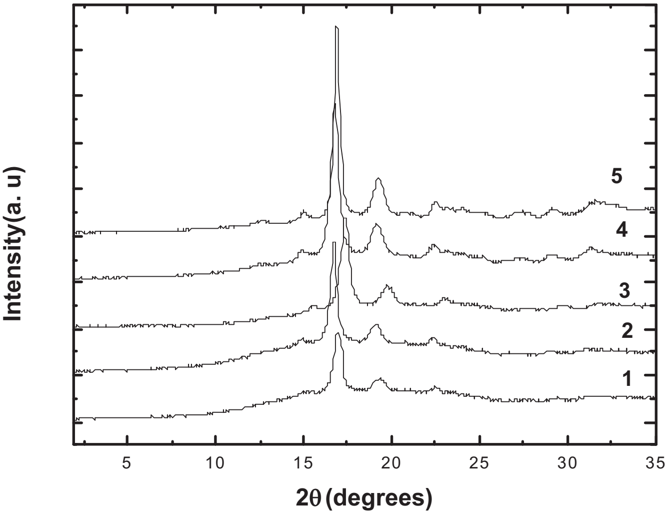

Figure 6.

WAXD curves of PLLA obtained by bulk polymerization of the L-lactide with calcium methoxide LA/Ca ratio = 100 (1); 250 (2); 500 (3); 1000 (4); 5000 (5).

multimoldal endotherms related to crystals melting were observed in these samples.

The PLLAs presented low T_m due to stereoerrors in the chain. Probably due to the lower chain regularity, no T_m was observed at 2nd and 3rd heating runs. The increase in LA/Ca molar ratio caused, in addition of a decrease in the molecular weight, an increase in the stereoregularity and degree of crystallinity of PLLAs.

An interesting enthalpic relaxation phenomenon was observed near the Tg of the polymer powders. The intensity of the transition decreased when the LA/Ca molar ratio increased, which means also the transition decreased when molecular weight decreased and crystallinity increased. Only the PLLAs prepared with higher LA/Ca molar ratio showed cold crystallization.

Polymer Morphology

X-ray diffraction analyzes of obtained PLLA samples confirmed the relatively high degree of crystallinity, particularly in polymers obtained at LA/Ca = 1000 and 5000, respectively (Figure 6, Curves 4 and 5). This high crystallinity is indicated by the profile of WAXD curves which presented more intense and narrow crystalline reflections in these samples.

Conclusion

This work demonstrates $Ca(OMe)_2$ has significant activity as catalyst/initiator for LA bulk polymerization at high temperature. The polymerization presents a linear relationship between conversion and $\overline{M}_n$ with polymerization time representative of a controlled process. Yields around 66% and $\overline{M}_n = 19{,}500$ are attained in 3 h at 180 °C. PLLAs show relatively narrow polydispersity ($\overline{M}_w/\overline{M}_n = 1.2$) and crystallinity, although significant racemization is observed in reactions carried out at low LA/Ca molar ratio. It demonstrates that chain regularity can be controlled by the polymerization condition and that racemization can be reduced by using lower concentration of catalyst. It also shows that the increase in LA/Ca molar ratio causes a decrease in the molecular weight and an increase in the degree of crystallinity of PLLAs.

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Acknowledgements: The authors wish to thank CAPES and CNPq for financial support.

[1] V. Simic, V. Girardon, N. Spassky, L. G. Hubert-Pfalzgraf, A. Duda, *Polym. Degrad. Stab.* **1998**, *59*, 227.
[2] V. Krikorian, D. J. Pochan, *Chem. Mater.* **2003**, *15*, 4317.
[3] Q. Zhou, M. Xanthos, *Polym. Degrad. Stab.* **2008**, *93*, 1450.
[4] J. H. Chang, Y. U. An, G. S. Sur, *J. Polym. Sci.* **2003**, *41*, 94.
[5] M. A. Paul, M. Alexandre, P. Degée, C. Henrist, A. Rulmont, P. Dubois, *Polymer* **2003**, *44*, 443.
[6] L. T. Lim, R. Auras, M. Rubino, *Prog. Polym. Sci.* **2008**, *33*, 820.
[7] H. R. Kricheldorf, *Chemosphere* **2001**, *43*, 49.
[8] Z. Wei, L. Liu, C. Qu, M. Qi, *Polymer* **2009**, *50*, 1423.
[9] H. Y. Chen, H. Y. Tang, C. C. Lin, *Polymer* **2007**, *48*, 2257.
[10] R. H. Platel, L. M. Hodgson, C. K. Williams, *Polym. Rev.* **2008**, *48*, 11.
[11] H. R. Kricheldorf, A. Serra, *Polym. Bull.* **1985**, *14*, 497.
[12] S. M. Li, I. Rashkov, J. L. Espartero, N. Manolova, M. Vert, *Macromolecules* **1996**, *29*, 57.
[13] I. Rashkov, N. Manolova, S. M. Li, J. L. Espartero, M. Vert, *Macromolecules* **1996**, *29*, 50.
[14] K. A. George, F. Schué, T. V. Chirila, E. Wentrup-Byrne, *J. Polym. Sci., Polym. Chem.* **2009**, *47*, 4736.
[15] Z. Y. Zhong, M.J. K. Ankone, P. J. Dijkstra, C. Birg, M. Westerhausen, J. Feijen, *Polym. Bull.* **2001**, *46*, 51.
[16] Z. Y. Zhong, P. J. Dijkstra, C. Birg, M. Westerhausen, J. Feijen, *Macromolecules* **2001**, *34*, 3863.
[17] Z. Y. Zhong, S. Schneiderbauer, P. J. Dijkstra, M. Westerhausen, J. Feijen, *J. Polym. Environ.* **2001**, *9*, 31.
[18] Z. Y. Zhong, S. Schneiderbauer, P. J. Dijkstra, M. Westerhausen, J. Feijen, *Polym. Bull.* **2003**, *51*, 175.
[19] M. S. Hill, P. B. Hitchcock, *Chem. Commun.* **2003**, 1758.
[20] H. Y. Chen, H. Y. Tang, C. C. Lin, *Polymer* **2007**, *48*, 2257.
[21] T. M. Ovitt, G. W. Coates, *J. Am. Chem. Soc.* **2002**, *124*, 1316.
[22] S. Shyamroy, B. Garnaik, S. Sivaran, *J. Polym. Sci., Polym. Chem.* **2005**, *43*, 2164.
[23] J. R. Sarasua, A. L. Arraiza, P. Balerdi, I. Maiza, *J. Mat. Sci.* **2005**, *40*, 1855.
[24] D. R. Witzke, R. Narayan, *Macromolecules* **1997**, *30*, 7075.

Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim