Stereocontrolled Polymerization

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Effect of the Configuration of the Active Center on Comonomer Reactivities: The Case of ε-Caprolactone/L,L-Lactide Copolymerization**

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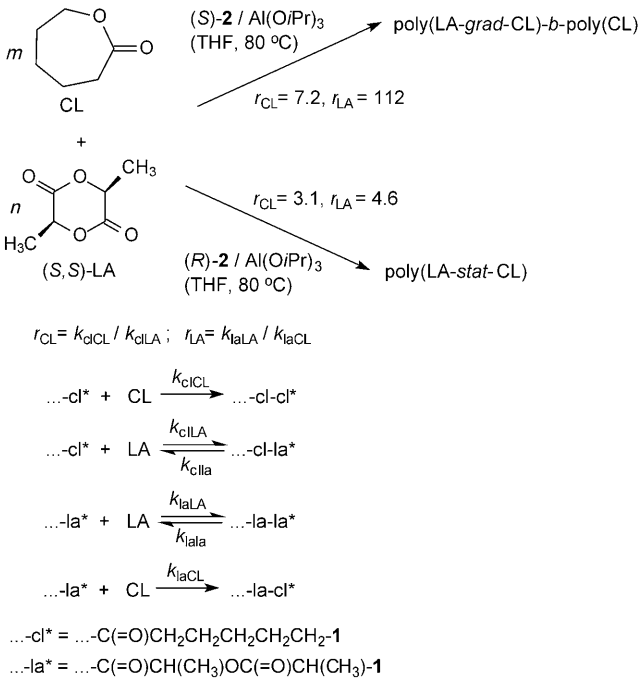
Poly(ε-caprolactone) (PCL) and poly(L-lactide) (PLA) are among the most prominent biocompatible and biodegradable synthetic polymers used in biomedical and pharmaceutical applications.[1] The synthetic route most widely used for the preparation PCL and PLA is based on ring-opening polymerization (ROP) of the corresponding monomers: ε-caprolactone (CL) and L,L-lactide ((*S*,*S*)-lactide in terms of the absolute configuration; LA). The ROP is initiated by metal alkoxides, carboxylates, or metal-free organocatalytic systems.[2] The ROP provides sufficient polymerization control and results in polymers of the required molar masses (M_n), in the wide range from 10^3 to 10^6 g mol^{-1}, and with the desired end groups and architectures. The polymerization of CL, LA, and other cyclic aliphatic esters also provides an excellent model system for fundamental studies of the thermodynamics, kinetics, and mechanism of the ROP of heterocyclic monomers.[2c,d]

Various functional parameters of PCL and PLA, such as mechanical and thermal properties, permeability, and (bio)-degradation behavior, differ considerably.[1] Thus, CL/LA copolymerization enables the properties of the resulting polyester to be tuned by varying its total composition and the distribution of the comonomer repeat units along the copolymer chain.[3–6]

The homopolymerization rates of CL and LA can also be substantially different. For example, the ratio of the absolute rate constants of propagation, k_p(CL)/k_p(LA), on aluminum trisalkoxide active species can be as high as 6.7×10^3 (THF, 20 °C).[7] Surprisingly, in the CL/LA copolymerization the LA comonomer is consumed first, and typically block (PLA-*b*-PCL) or gradient (poly(LA-*grad*-CL)) copolymers are obtained.[5] Thus, the net reactivities of CL and LA in the copolymerization are reversed relative to their reactivities in homopolymerization. Although the first reports to describe this puzzling phenomenon appeared about twenty years ago,[5a,b] there is still no consensus as to a plausible explanation on the molecular level.

Herein, we demonstrate that in the CL/LA copolymerization, the net reactivities of the CL and LA comonomers can be reversed by altering the active-center configuration to such an extent that the CL comonomer is consumed first. This striking phenomenon is of general importance, since it provides a useful tool for tuning the resultant copolymer microstructure and properties. This concept is depicted in Scheme 1.



Scheme 1. Synthesis of CL/LA copolymers with different microstructures by altering the configuration at the aluminum alkoxide active center.

The active species employed in our study was an aluminum alkoxide with a bidendate, bulky ligand of the *R* or *S* configuration, 2,2′-(1,1′-binaphthyl-2,2′-diylbis(nitrylomethilidyne))diphenoxide. This alkoxide **1** was formed through a direct reaction of the corresponding Schiff base **2** with a trimeric form of aluminum isopropoxide, {Al(O*i*Pr)$_3$}$_3$.[8]

The application of both achiral and chiral diphenolate Schiff bases of various structures led to new approaches to the stereocontrolled, enantioselective (racemate-forming, chirogenic[9]), and enantioelective (asymmetric, enantiomer-differ-

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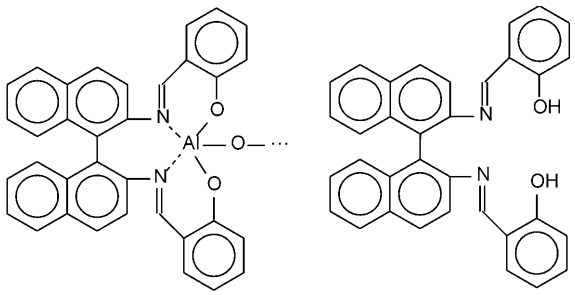

(*R*)-**1** or (*S*)-**1** (*R*)-**2** or (*S*)-**2**

entiating[9]) ROP of racemic lactide (*rac*-LA).[8,10,11] For example, kinetic measurements for the (*S*)-**1**/(*S*,*S*)-LA and (*S*)-**1**/(*R*,*R*)-LA systems showed a 28:1 preference for the polymerization of (*S*,*S*)-LA over (*R*,*R*)-LA. The application of metal-alkoxide active species with sterically extended ligands also leads to depression or even elimination of the segmental-exchange and back-biting (macrocyclization) side reactions as a result of the increase in the entropy of activation. The latter feature enables the direct preparation from *rac*-LA of well-defined multiblock or gradient stereocopolymers that are able to form stereocomplexes (see Ref. [8] and references cited therein).

Prior to the copolymerization studies, we compared the rates of CL and LA homopolymerization initiated with $Al(OiPr)_3$ and carried out in the presence of an equimolar amount (with regard to $Al(OiPr)_3$) of (*S*)-**2**. The corresponding plots in Figure 1 showing the kinetics of CL and LA consumption reveal that the presence of the bulky bidentate ligand on the aluminum alkoxide species results in a decrease in the $k_p(CL)/k_p(LA)$ ratio to 16.7. This effect is at least partially due to an increase in $k_p(LA)$: In the presence of the trisalkoxide[7] and (*S*)-**1** (present study), the $k_p(LA)$ values were determined to be 4.7×10^{-3} and $2.1\times10^{-2}\,mol^{-1}\,L\,s^{-1}$, respectively (THF, 80 °C). However, CL remains the more reactive monomer. In agreement with expectations, when the configuration of the active species **1** was altered from *S* to *R*, $k_p(LA)$ decreased to $3.4\times10^{-4}\,mol^{-1}\,L\,s^{-1}$, whereas $k_p(CL)$ remained practically unchanged owing to the achiral structure of the monomer. Thus, with (*R*)-**1**, $k_p(CL)/k_p(LA)\approx10^3$ (Figure 1).

The transformation of the active species from the aluminum trisalkoxide into the (*S*)-**1** structure does not change the general picture of the CL/LA copolymerization (Figure 2a; see Ref. [5b] for a comparison). In the early stages of copolymerization, LA reacts significantly faster than CL. Then, after approximately 90 mol% of the LA has been consumed, the copolymerization of CL accelerates to eventually reach the rate observed for its homopolymerization under otherwise identical conditions. The described kinetic behavior can be expressed quantitatively in terms of the corresponding reactivity ratios ($r_{CL}=k_{clCL}/k_{clLA}$ and $r_{LA}=k_{lalLA}/k_{laCL}$, Scheme 1) determined by using the numerical integration method (see the Experimental Section): $r_{CL}=7.2$ and $r_{LA}=112$. On the other hand, Teyssie et al. determined the reactivity ratios $r_{CL}=0.58$ and $r_{LA}=17.9$ some time ago for the copolymerization initiated with bare $Al(OiPr)_3$.[5a] Both sets of data, although the values are different, reflect favorable incorporation into the copolymer chain of repeating units derived from the LA comonomer. The differences in the r_{CL} and r_{LA} values for the initiators $Al(OiPr)_3$ and (*S*)-**2**/$Al(OiPr)_3$ are not only due to the different methods used for

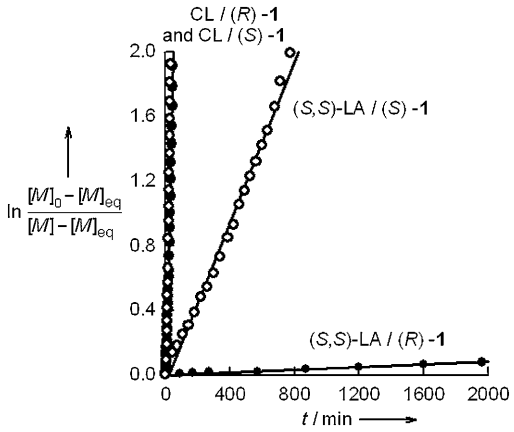

Figure 1. Comparison of the kinetics of ε-caprolactone (CL) and L,L-lactide ((*S*,*S*)-LA) homopolymerization on (*R*)-**1** (●) and (*S*)-**1** (○). Polymerization conditions: $[CL]_0=2.0$, $[(S,S)\text{-LA}]_0=1.0$, $[(R)\text{-}\mathbf{1}]=[(S)\text{-}\mathbf{1}]=2\times10^{-3}\,mol\,L^{-1}$, THF (solvent), 80 °C ($[CL]_{eq}\approx0$, $[(S,S)\text{-LA}]_{eq}=5.5\times10^{-2}\,mol\,L^{-1}$ [12]).

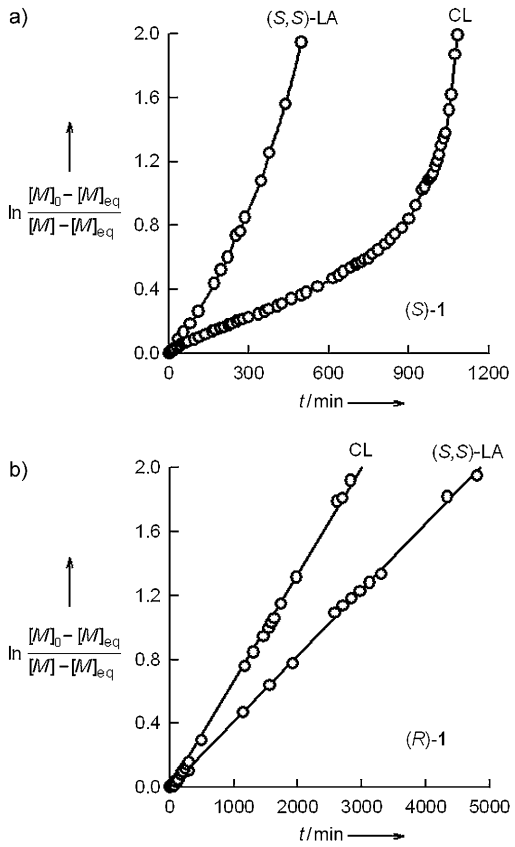

Figure 2. Kinetics of ε-caprolactone (CL)/L,L-lactide ((*S*,*S*)-LA) copolymerization initiated with equimolar a) $Al(OiPr)_3$/(*S*)-**2** and b) $Al(OiPr)_3$/(*R*)-**2** mixtures. Polymerization conditions: $[(S)\text{-}\mathbf{2}]_0=2\times10^{-3}$, $[(R)\text{-}\mathbf{2}]_0=2.5\times10^{-3}\,mol\,L^{-1}$; for the other conditions, see the legend for Figure 1.

their determination (the Mayo–Lewis method and numerical integration, respectively), but more probably to the fact that only with (*S*)-**2**/Al(O*i*Pr)$_3$ can segmental exchange and thus modification of the proportions of …-cl* and …-la* be avoided.

We wondered whether it would be possible to force the CL/LA copolymerization system to incorporate the …-cl-… and …-la-… repeating units into the copolymer chain in a more regular manner. From the viewpoint of formal kinetics, the solution to this problem requires $r_{CL} \approx r_{LA}$ and thus, on the basis of the reactivity ratios determined for the CL/LA/(*S*)-**2**/Al(O*i*Pr)$_3$ copolymerization, either an increase in r_{CL} or a decrease in r_{LA}. The results of the kinetic measurements for homopolymerization (Figure 1) suggested that the latter should be possible for a copolymerization with (*R*)-**1** as the active species. In this case, k_{clCL} would remain unchanged, whereas k_{laLA} was expected to decrease by at least one order of magnitude. Indeed, kinetic measurements performed for the LA/CL copolymerization initiated with an equimolar (*R*)-**2**/Al(O*i*Pr)$_3$ mixture (Figure 2b) revealed that CL is consumed slightly faster than the LA comonomer under the applied polymerization conditions. The reactivity ratios determined for the copolymerization are close to one another within the calculated experimental error: $r_{CL} = (3.1 \pm 1.0)$ and $r_{LA} = (4.6 \pm 1.0)$.

The microstructures of the CL/LA copolymers prepared with the initiating systems (*S*)-**2**/Al(O*i*Pr)$_3$ and (*R*)-**2**/Al(O*i*Pr)$_3$ are substantially different. The corresponding kinetic plots and reactivity ratios enable the prediction of the copolymer structures obtained as poly(LA-*grad*-CL)-*b*-poly(CL) and poly(CL-*stat*-LA) with the initiating system of *S* and *R* configuration, respectively.

Indeed, the ^{13}C NMR spectrum in Figure 3a in the range of the carbonyl-carbon-atom resonances reveals that the CL/LA copolymer prepared in the presence of the Schiff base (*S*)-**2** contains longer poly(LA) and poly(CL) sequences accompanied by statistically distributed …-cl-… and …-la-… units. Characteristic is the absence of -C(=O)(CH$_2$)$_5$OC(=O)CH(CH$_3$)OC(=O)(CH$_2$)$_5$O- heterotriads, which appear only when the segmental-exchange side reaction operates. In the spectrum of the copolymer prepared with (*R*)-**2** (Figure 3b), carbonyl signals due to the longer poly(LA) and poly(CL) sequences are practically absent, which indicates a more even distribution of the …-cl-… and …-la-… units along the copolymer chain. Signal-to-structure assignments were carried out on the basis of the spectroscopic data given in Ref. [5d].

SEC molar-mass measurements, although not perfectly conclusive because of the obvious problems associated with the determination of the copolymer molar masses, suggest that the M_n values of the CL/LA copolymers are controlled by the ratio $(M_{CL}[CL]_0+M_{LA}[LA]_0)/[OiPr]_0$. The M_n values determined with a refractive-index (RI) detector and polystyrene (PS) standards show typical deviation from the actual values as a result of a difference in the hydrodynamic volumes of the aliphatic polyesters and PS macromolecules with identical molar masses (Table 1).

In summary, we have demonstrated that in the ε-caprolactone (CL)/(*S*,*S*)-lactide (LA) copolymerization initiated by a chiral initiator, the reactivity ratios of the comonomers can be controlled by the configuration of the active species: The reactivity ratios $r_{CL} = 7.2$ and $r_{LA} = 112$ were observed for (*S*)-**2**/Al(O*i*Pr)$_3$, and $r_{CL} = 3.1$ and $r_{LA} = 4.6$ for (*R*)-**2**/Al(O*i*Pr)$_3$. Thus, by varying the stereochemical composition of the initiator, a broad range of copolymers with different microstructures, from gradient to more random, could be prepared in a controlled way. We are currently trying to uncover, on the molecular level, the origin of the differences in the relative reactivities of CL and LA in their homo- and copolymerization.

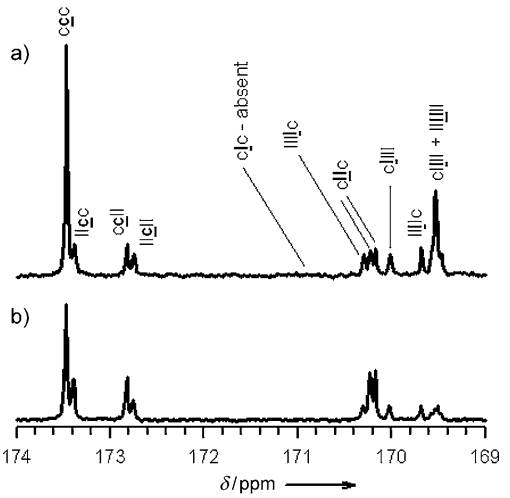

Figure 3. Comparison of the ^{13}C NMR spectra of the ε-caprolactone (CL)/L,L-lactide ((*S*,*S*)-LA) copolymers prepared with equimolar a) Al(O*i*Pr)$_3$/(*S*)-**2** and b) Al(O*i*Pr)$_3$/(*R*)-**2** mixtures in the range of the carbonyl-carbon-atom resonances. For the polymerization conditions, see the legend for Figure 2; c and l stand for -C(=O)(CH$_2$)$_5$O- and -C(=O)CH(CH$_3$)O- units, respectively.

Table 1: Comparison of theoretical and measured molar masses of the ε-caprolactone (CL)/L,L-lactide ((*S*,*S*)-LA) copolymers.

$[CL]_0/[LA]_0/[Al]_0$	M_n(theor)[a]	M_n(exptl)[b]	M_n(exptl)[c]	D[d]
1/2/0.002[e]	62100	142000	62800–95200	1.15
1/2/0.01[f]	12400	30600	13400–20300	1.10
1/2/0.005[f]	24800	46300	25200–38200	1.06
1/2/0.0025[f]	49600	80800	39300–59500	1.15

[a] Theoretical molar mass: $M_n(\text{theor}) = (M_{CL}[CL]_0+M_{LA}[LA]_0)/3[Al]_0$, in which M_{CL} and M_{LA} are the molar masses of CL and LA, respectively. [b] The experimental molar mass determined by size exclusion chromatography (SEC) with an RI detector and calibration with polystyrene standards. [c] The experimental molar mass determined by SEC with a laser light scattering detector on the basis of the assumption that $dn/dc = 0.053$ (PCL) or 0.035 mL g^{-1} (PLA). [d] $D = M_w/M_n$ measured by SEC with a laser light scattering detector. [e] Initiator: (*S*)-**2**/Al(O*i*Pr)$_3$. [f] Initiator: (*R*)-**2**/Al(O*i*Pr)$_3$.

Experimental Section

All experiments were performed by using the standard high-vacuum technique. The CL and LA monomers and the THF solvent were purified as described previously.[13] Al(O*i*Pr)$_3$ was used in its reactive,

trimeric form.[14] Compounds (*R*)-**2** and (*S*)-**2** were prepared as described in Ref. [15]. Polymerization mixtures were transferred to polarimetric cells and glass dilatometers, which were then sealed in vacuo. Kinetic measurements were carried out with a Perkin–Elmer 241 MC polarimeter (LA), and all glass dilatometers (CL) were placed in a thermostated bath (±0.05 °C). ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX 500 spectrometer. Number-average molar masses (M_n) and molar-mass distributions (M_w/M_n) of the resulting copolymers were estimated by HPLC by using an Agilent 1100 pump and a set of two PL-Gel 5μ mixed-C columns. An Optilab rex Wyatt interferometric refractometer and a Dawn Eos Wyatt laser photometer were used as detectors in series. The refractive-index increments (dn/dc) of 0.053 and 0.035 mL g^{-1} for PCL and PLA, respectively, were determined from refractive-index concentration dependencies measured at 682 nm. Astra 4.90.07 software (Wyatt Technology) was used for SEC data collection and processing. Dichloromethane was used as the eluent at a flow rate of 0.8 mL min^{-1} at room temperature.

The reactivity ratios were determined from the kinetic data in Figure 2 on the assumption that the kinetic scheme in Scheme 1 applies. The numerical-integration procedure described in reference [16] was used for this purpose.

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[1] L. S. Nair, C. T. Laurencin, *Prog. Polym. Sci.* **2007**, *32*, 762 – 798.
[2] a) D. Mecerreyes, R. Jerome, P. Dubois, *Adv. Polym. Sci.* **1999**, *147*, 1 – 59; b) B. J. O'Keefe, M. A. Hillmyer, W. B. Tolman, *J. Chem. Soc. Dalton Trans.* **2001**, 2215 – 2224; c) A. Duda, S. Penczek, *ACS Symp. Ser.* **2000**, *764*, 160 – 198; d) A. Duda, S. Penczek in *Biopolymers*, *Vol. 3b* (Eds.: A. Steinbuechel, Y. Doi), Wiley-VCH, Weinheim, **2002**, pp. 371 – 430; e) O. Coulembier, P. Degee, J. L. Hedrick, P. Dubois, *Prog. Polym. Sci.* **2006**, *31*, 723 – 747; f) N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. C. G. Lohneijer, J. L. Hedrick, *Chem. Rev.* **2007**, *107*, 5813 – 5840.
[3] a) "Polymers of Lactic Acid": G. B. Kharas, F. Sanchez-Riera, D. K. Severson in *Plastics from Microbes* (Ed.: D. P. Mobley), Hanser Publishers, Munich, **1994**, pp. 93 – 137; b) M. Hiljanen Vainio, T. Karjalainen, J. Seppala, *J. Appl. Polym. Sci.* **1996**, *59*, 1281 – 1288; c) S. I. Jeong, B. S. Kim, Y. M. Lee, K. J. Ihn, S. H. Kim, Y. H. Kim, *Biomacromolecules* **2004**, *5*, 1303 – 1309.
[4] a) C. X. Song, X. D. Feng, *Macromolecules* **1984**, *17*, 2764 – 2767; b) C. Jacobs, P. Dubois, R. Jerome, P. Teyssie, *Macromolecules* **1991**, *24*, 3027 – 3034; c) W. M. Stevels, M. J. K. Ankone, P. J. Dijkstra, J. Feijen, *Macromol. Chem. Phys.* **1995**, *196*, 1153 – 1161; d) P. J. A. In't Veld, E. M. Velner, P. van de Witte, J. Hamhuis, P. J. Dijkstra, J. Feijen, *J. Polym. Sci. Part A* **1997**, *35*, 219 – 226; e) Y. Shen, Z. Shen, Y. Zhang, K. Yao, *Macromolecules* **1996**, *29*, 8289 – 8295; f) X. Deng, Z. Zhu, Ch. Xiong, L. Zhang, *J. Polym. Sci. Part A* **1997**, *35*, 703 – 708; g) S. Pensec, M. Leroy, H. Akkouche, N. Spassky, *Polym. Bull.* **2000**, *45*, 373 – 380; h) D. Cui, T. Tang, W. Bi, J. Cheng, W. Chen, B. Huang, *J. Polym. Sci. Part A* **2003**, *41*, 2667 – 2675; i) L. Zhang, Z. Shen, C. Yu, L. Fan, *J. Macromol. Sci. Pure Appl. Chem.* **2004**, *41*, 927 – 935; j) F. Stassin, R. Jerome, *J. Polym. Sci. Part A* **2005**, *43*, 2777 – 2789; k) L. Fan, Y.-B. Xiong, H. Xu, Z. Q. Shen, *Eur. Polym. J.* **2005**, *41*, 1647 – 1653; l) A. J. Chmura, M. G. Davidson, M. D. Jones, M. D. Lunn, M. F. Mahon, A. F. Johnson, P. Khunkamchoo, S. L. Roberts, S. S. F. Wong, *Macromolecules* **2006**, *39*, 7250 – 7257.
[5] a) J. M. Vion, R. Jerome, P. Teyssie, M. Aubin, R. E. Prudhomme, *Macromolecules* **1986**, *19*, 1828 – 1838; b) P. Vanhoorne, P. Dubois, R. Jerome, P. Teyssie, *Macromolecules* **1992**, *25*, 37 – 44; c) J. Kasperczyk, M. Bero, *Makromol. Chem.* **1991**, *192*, 1777 – 1787; d) J. Kasperczyk, M. Bero, G. Adamus, *Makromol. Chem.* **1993**, *194*, 907 – 912; e) J. Kasperczyk, M. Bero, G. Adamus, *Makromol. Chem.* **1993**, *194*, 913 – 925.
[6] a) X. Zhong, D. Yu, F. Meng, Z. Gan, X. Jing, *Polym. J.* **1999**, *31*, 633 – 636; b) M. Kalmi, M. Lahcini, P. Castro, O. Lehtonen, A. Belfkira, M. Leskela, T. Repo, *J. Polym. Sci. Part A* **2004**, *42*, 1901 – 1911; c) A. Amgoune, C. M. Thomas, T. Roisnel, J.-F. Carpentier, *Chem. Eur. J.* **2006**, *12*, 169 – 179; d) M. Florczak, J. Libiszowski, J. Mosnacek, A. Duda, S. Penczek, *Macromol. Rapid Commun.* **2007**, *28*, 1385 – 1391.
[7] A. Kowalski, A. Duda, S. Penczek, *Macromolecules* **1998**, *31*, 2114 – 2122.
[8] K. Majerska, A. Duda, *J. Am. Chem. Soc.* **2004**, *126*, 1026 – 1027.
[9] K. Hatada, J. Kahovec, M. Baron, K. Horie, T. Kitayama, P. Kubisa, G. P. Moss, R. F. T. Stepto, E. S. Wilkes, *Pure Appl. Chem.* **2002**, *74*, 915 – 922.
[10] a) A. Le Borgne, V. Vincens, M. Jouglard, N. Spassky, *Makromol. Chem. Macromol. Symp.* **1993**, *73*, 37 – 46; b) N. Spassky, M. Wiśniewski, C. Pluta, A. Le Borgne, *Macromol. Chem. Phys.* **1996**, *197*, 2627 – 2637; c) M. Wisniewski, A. Le Borgne, N. Spassky, *Macromol. Chem. Phys.* **1997**, *198*, 1227 – 1238.
[11] a) C. P. Radano, G. L. Baker, M. R. Smith III, *J. Am. Chem. Soc.* **2000**, *122*, 1552 – 1553; b) T. M. Ovitt, G. W. Coates, *J. Polym. Sci. Part A* **2000**, *38*, 4686 – 4692; c) T. M. Ovitt, G. W. Coates, *J. Am. Chem. Soc.* **2002**, *124*, 1316 – 1326; d) Z. Zhong, P. J. Dijkstra, J. Feijen, *Angew. Chem.* **2002**, *114*, 4692 – 4695; *Angew. Chem. Int. Ed.* **2002**, *41*, 4510 – 4513; e) Z. Zhong, P. J. Dijkstra, J. Feijen, *J. Am. Chem. Soc.* **2003**, *125*, 11291 – 11298; f) N. Nomura, R. Ishi, M. Akakura, K. Aoi, *J. Am. Chem. Soc.* **2002**, *124*, 5938 – 5939; g) N. Nomura, R. Ishii, Y. Yamamoto, T. Kondo, *Chem. Eur. J.* **2007**, *13*, 4433 – 4451.
[12] A. Duda, S. Penczek, *Macromolecules* **1990**, *23*, 1636 – 1639.
[13] a) A. Kowalski, A. Duda, S. Penczek, *Macromol. Rapid Commun.* **1998**, *19*, 567 – 572; b) A. Kowalski, J. Libiszowski, A. Duda, S. Penczek, *Macromolecules* **2000**, *33*, 1964 – 1971.
[14] A. Duda, S. Penczek, *Macromol. Rapid Commun.* **1995**, *16*, 67 – 75.
[15] K. Da Silva Bernardo, A. Robert, F. Dahan, B. Meunier, *New J. Chem.* **1995**, *19*, 129 – 131.
[16] J. Chojnowski, M. Cypryk, W. Fortuniak, K. Rozga-Wijas, M. Scibiorek, *Polymer* **2002**, *43*, 1993 – 2001.

