Macromol. Symp. ***144****, 257–267 (1999)*

SYNTHESIS OF ALIPHATIC POLYESTERS BY CONTROLLED RING-OPENING POLYMERIZATION OF CYCLIC ESTERS. CHARACTERIZATION, PROPERTIES, TRANSESTERIFICATION REACTIONS.

Nicolas SPASSKY[1*], Vesna SIMIC[1], Liliane G. HUBERT-PFALZGRAF[2],
Maurizio S. MONTAUDO[3]

1 - Laboratoire de Chimie des Polymères - UMR 7610 - Université P. et M. Curie – Paris, France

2 - Laboratoire de Chimie Moléculaire, Université de Nice - Nice Sophia Antipolis, France

3 - Istituto per la Chimica e Tecnologica dei Materiali Polimerici, CNR – Catania, Italia

ABSTRACT:

The polymerization of (D,L)-Lactide at room temperature in solution using $Y(OCH_2CH_2OiPr)_3$ and $Ln_5(\mu\text{-}O)(OiPr)_{13}$ with Ln = La, Sm, Y, Yb as initiators was studied. According to kinetic data, a controlled type polymerization is observed for most of the systems. La μ-oxoisopropoxide is the most reactive initiator, but leads to a substantial broadening of molecular weight distribution at high conversions. The nature of transesterification reactions was studied by SEC, ^{13}C NMR and MALDI-TOF MS techniques. For Sm and Y-μ-oxo initiators only limited intermolecular ester exchange occurs, while with La μ-oxoinitiator and with $Y(OCH_2CH_2OiPr)_3$ initiator, but after a long time of the polymerization reaction, both inter and intramolecular transesterification occur with formation of cyclics.

INTRODUCTION

Aliphatics polyesters are important biodegradable materials having various applications in biomedical, pharmacological and environmental fields (Ref. 1-5). The most efficient way to synthesize these polymers is the ring-opening polymerization of corresponding cyclic esters using ionic type initiators. (Ref. 6) In order to obtain polymers with well-defined characteristics (structure, molecular weight) initiators leading to a controlled type process are suitable. Among metallic alkoxides, aluminium alkoxides are the most studied initiators allowing the controlled polymerization of ε-caprolactone and lactides (Ref. 7-12). The selectivity parameter, which can be expressed by the ratio of the propagation rate constant to chain transfer rate constant was very carefully examined in the group of Lodz and a general quantitative determination of selectivity was described and applied for aluminium type initiators and some others (Ref. 13,14). The stereochemical aspects of the controlled ring-opening polymerization of chiral cyclic esters was recently discussed by

CCC 1022-1360/99/$ 17.50+.50/0

our group (Ref. 15). Several groups have shown that lanthanide alkoxides exhibit a very high reactivity for the polymerization of lactones and lactides, for some of them a living type behaviour was observed (Ref. 16-21).

The aim of this paper is to report our recent results in the field of polymerization of cyclic esters more particularly lactides, using some lanthanide alkoxides and to discuss the selectivity of these systems with some emphasis on the characterization of transesterification reactions.

RESULTS AND DISCUSSION

Kinetic data for lanthanide alkoxide initiators

Two families of lanthanide alkoxide initiators were used for the polymerization of lactides : μ-oxoisopropoxide initiators $Ln_5(\mu\text{-}O)(OiPr)_{13}$ and namely yttrium tris-alkoxide $Y(OCH_2CH_2OiPr)_3$.

The preparation and the characterization of (μ-oxo) alkoxide initiators was already described (Ref. 22). They are cluster compounds in which five lanthanide atoms are linked to a single central oxygen. The polynuclear structure of the oxo species is retained in solution. Sm and Yb initiators are very soluble in dichloromethane (DCM), while Y and La initiators are less soluble in DCM but are more soluble in toluene. Thus, the latter initiators were dissolved in the required volume of toluene and the solution of lactide in DCM was added to the solution of initiator in toluene. For homogeneity of experimental conditions the same amount of toluene was added in all experiments whatewer the initiator.

Some typical results of (D,L)-lactide polymerization in dichloromethane/toluene solution at room temperature using La, Sm, Y, Yb initiators are given in Table 1.

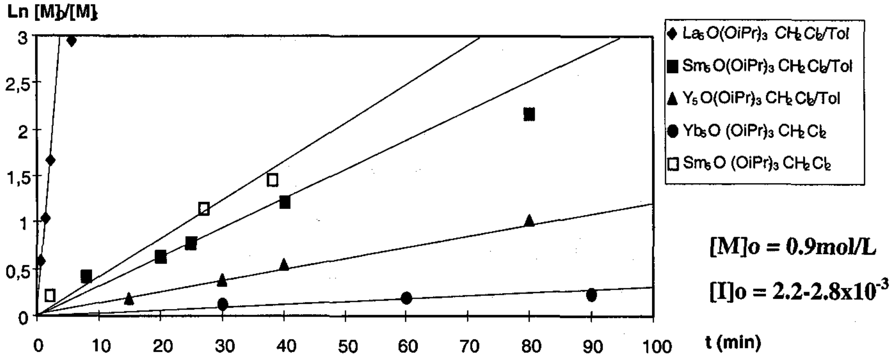
Table 1. Polymerization of (D,L)-lactide using Ln_5 (μ-O)(OiPr)$_{13}$ initiators in dichloromethane/toluene (80 : 20) solution at room temperature

$[M]_o = 0.9$ mol/L $[M]_o/[I]_o = 68 - 70$

N°	Inititator	Time (min)	Conv (%)	Mn(a) (calc.)	Mn(b) (SEC)	MWD (SEC)	n (c)
1	La	1.25	65	2500	3600	1.15	1.8
2		5.75	95	3640	5000	1.57	1.85
3		60	97	3700	4300	2.14	2.2
4	Sm	25	46	1850	2180	1.29	2.6
5		80	82	3250	3350	1.29	2.6
6	Y	80	62	2400	2000	1.20	2.7
7		100	73	2800	2600	1.20	2.7
8	Yb (d)	350	34	1200	1000	1.28	2.9
9		1340	65	2250	1900	1.18	3.0

(a) on the basis of 2.6 sites/Ln (b) SEC in THF ; corrected molecular weight using a correcting factor 0.58 (c) number of active sites from SEC (d) in CH_2Cl_2 solution $[M]_o/[I]_o = 61$

Kinetic data of these systems were examined. The semi-logarithmic kinetic plots $Ln[M]_0/[M]_t$ versus time are linear (Fig. 1) which accounts for the stability of active centres all along the polymerization, a fast initiation (compared to propagation) and the absence of termination reaction. The range of reactivity found for different metals in initiators is La>>Sm>Y>>Yb. The molar mass increases linearly with the monomer conversion (Fig. 2). This suggests that no significant transfer reactions occur. Both of these findings are in favour of a living type behaviour.



$[M]o = 0.9 mol/L$

$[I]o = 2.2\text{-}2.8x10^{-3}$

Fig 1 : Semi-logarithmic plots of (D,L)-lactide conversion in time initiated by different $Ln_5O(OiPr)_{13}$ initiators in solution at room temperature

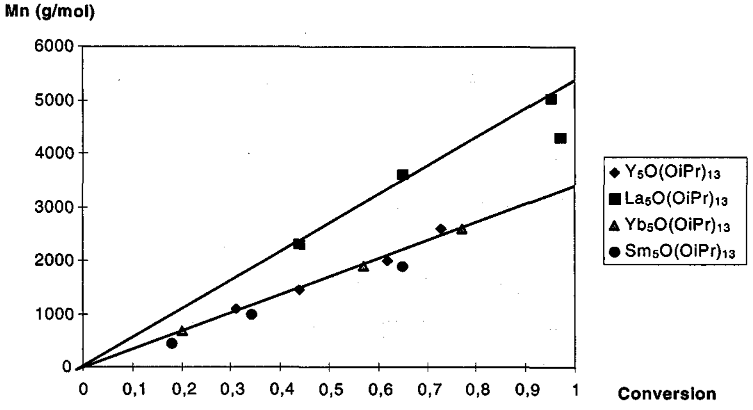


Fig 2 : Molecular weight (Mn) as a function of conversion for the $Ln_5O(OiPr)_{13}$ initiated polymerization of (D,L)-lactide in solution at room temperature.

The La system shows however some difference in the slope of molar mass (Fig. 2). It is the most reactive system for which the polymerization, in the given conditions, is achieved in a few minutes and at the end of the reaction a substantial broadening of molecular weight distribution (MWD) is observed.

Yttrium tris-alkoxide initiator $[Y(OCH_2CH_2OiPr)_3]_2$ was prepared according to the described procedure (Ref. 23). It was found to be a dimer by molecular weight measurements. Some results of the polymerization of (D,L)-lactide in DCM solution at room temperature are presented in Table 2.

Table 2. Polymerization of (D,L)-lactide in dichloromethane solution at room temperature using $[Y(OCH_2CH_2OiPr)_3]_2$ as initiator $[M]o = 0.9$ mol/L

N°	$[M]_o/[Y]_o$	Time (min)	Conv (%) (a)	Mn (calc) (b)	Mn (NMR)	Mn (SEC) (c)	MWD (c)
10	70	2	60	2000	2150	1800	1.14
11	70	5	76	2550	2400	2000	1.14
12	70	25	89	3000	2900	2300	1.13
13	400	30	42	8100	7100	8000	1.22
14	400	70	93	17900	-	14300	1.23
15	400	12960	98	18900	-	14000	1.70

(a) determined from ^1H NMR. (b) calculated on the basis of one polymer chain per alkoxide group. (c) SEC in THF ; molecular weight using a correcting factor for polylactide (0.58)

At first glance it appears from the table that the MWD remains narrow until high conversions.

The kinetic data show some differences with the previously studied initiators. The semi-logarithmic plots (Fig. 3) are no longer linear from the beginning of reaction. The shape of curves is typical of slowly initiated reactions. However, according to results given in Table 2, a reasonable agreement is found between calculated and experimental molar masses at different conversions. Therefore a living type behaviour is again observed, which is also confirmed by a clean preparation of block copolymers. The effect of the nature of the solvent on the kinetics was studied next (Fig. 4). In THF solution, the semi-logarithmic plot is linear from the beginning. The overall kinetic behaviour is not very different in THF or DCM solution and narrow MWD is found for both initiators at any stage of conversion .

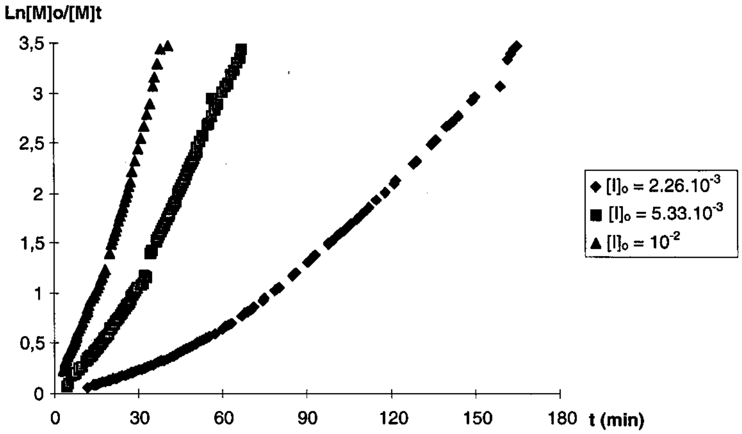


Fig 3 : Semi-logarithmic plots of (D,L)-lactide ($[M]_0$ = 0.8 mol/L conversion in time initiated by $[Y(OCH_2CH_2OiPr)_3]_2$ initiator in dichloromethane at room temperature.

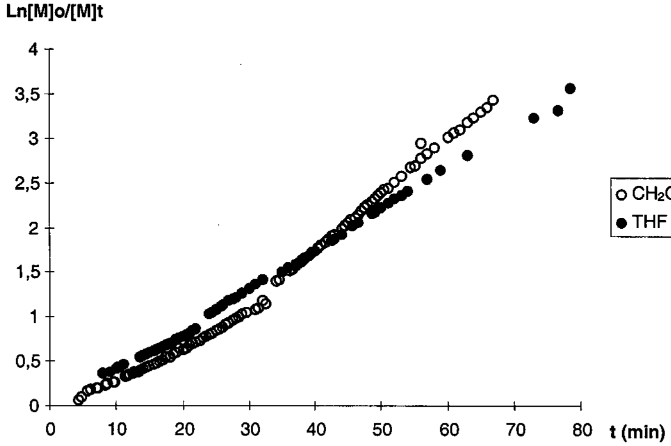


Fig 4 : Effect of the nature of the solvent on the kinetics of (D,L)-lactide polymerization using $Y(OCH_2CH_2OiPr)_3$ as initiator.

At the very beginning of the reaction the degree of aggregation of the initiator species is most probably different in both solvents and solvation phenomena may occur.

A comparison between the reactivity of lanthanide initiators bearing different ligands may be established. In Fig. 5 the kinetics behaviour of three different yttrium initiators is presented for identical experimental conditions.

It is clear that the (μ-oxo) cluster compound $Y_5O(OiPr)_{13}$ is the less reactive initiator, while the two tris-alkoxide initiators exhibit the same high reactivity. The latter initiators are based on alkoxyalkoxide ligands OC_2H_4OR. The ether functionnality acts on intramolecular Lewis base site leading thus to a bridging-chelating behaviour of the ligand. The degree of aggregation (x) of the metallic species is, to some degree controlled by the steric hindrance of the ether site, with x = 10 for the methoxyethoxide and x = 2 for the isopropoxyethoxide. Nevertheless for lactide polymerization they show the same reactivity suggesting thus the same reactive intermediate.

La_5(μ-oxo) cluster remains the most reactive of all of the initiators. A rough comparison of reactivities based on the time of half reaction gives the following range :

	La_5 (μ-oxo)	$Y(OCH_2CH_2OiPr)_3$	Sm_5 (μ-oxo)	Y_5(μ-oxo)	Yb_5(μ-oxo)
t ½ (min)	<1	5	30	50	700

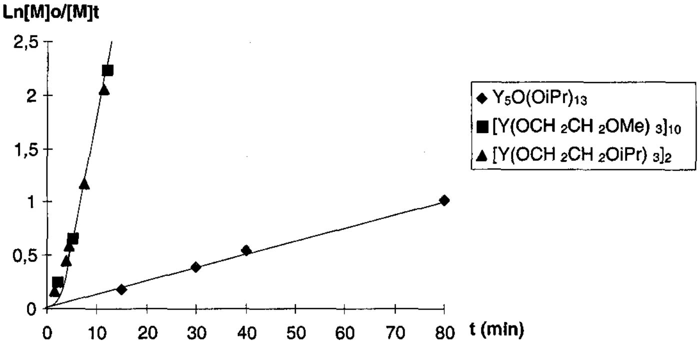


Fig 5 : Effect of the nature of the ligand on the kinetics of (D,L)-lactide polymerization with different yttrium alkoxide initiators.

The number of active sites (alkoxide initiating groups) per metal (n) can be derived from SEC molar mass measurements. It was found that for Y tris-alkoxide initiator each of the three alkoxide groups is initiating a polymer chain from the beginning of the reaction, thus n = 3. In the case of $Ln_5(\mu\text{-}O)(OiPr)_{13}$ initiators the expected number of sites is 2.6 (13/5). However for the La cluster, it was found, that n is 1.8 at half-reaction and reach only a value of 2.2 at complete conversion. For the Sm initiator n varies between 2.2 and 2.6 and for Y, n = 2.6 on all of range the scale of conversion. These findings are not explained yet, but a similar behaviour was found with some other cyclic esters.

In the case of aluminium isopropoxide initiators, two coexisting trimeric and tetrameric aggregates have been identified and their reactivities with different cyclic esters (ε-caprolactone, lactide) established. To day, detailed informations on the existence of molecular species of different nuclearity are lacking for most of μ-oxo lanthanoid alkoxides (Ref. 24).

Transesterification reactions

Transesterification reaction is a side reaction which is found for all of the polymerization reactions of cyclic esters. Two types of transesterification reactions are possible :

- Intermolecular chain transfer, in which one growing chain attacks another chain. In such a reaction the number of macromolecules does not change but there is a redistribution of polymer segments (reshuffling) and the MWD (Mw/Mn) changes. A substantial broadening may be observed.
- Intramolecular chain transfer (back-biting), in which the growing end chain attacks its proper chain with formation of cyclics. In this process the number of macromolecules changes.

Most of the lactide polymerizations were found to be accompanied by ester-exchange reactions producing some broadening of the MWD and a reshuffle of configurational units. Transesterification reactions can be identified by ^{13}C NMR analysis (Ref. 25, 26), by size exclusion chromatography (SEC) (Ref. 8, 13,14) and also by MALDI-TOF MS (Ref. 27). The change in MWD is easily determined by SEC technique and we have indeed observed the broadening of MWD for some initiators, e.g., samples n° 2 and 3 for the La cluster in Table 1. Ester exchange may appear after a prolonged time of polymerization , e.g., sample n° 15 in the case of polymerization with yttrium tris-alkoxide (table 2).

The selectivity or the degree of livingness of a given system may be determined by measuring the ratio of rate constant of propagation (kp) and the rate constant of side reaction (transesterification) (k_{tr}) and this allows to quantify the importance of the side reaction. This was done in the group of Lodz and selectivity parameters k_p/k_{tr} were determined for ε-caprolactone (Ref. 14) and lactide (Ref. 28) polymerizations. A correlation between the MWD and the selectivity parameter was established (Ref. 14, 29).

This general kinetic treatment was established for systems with intermolecular chain transfer.

Up to now we have not determined the propagation constants and the selectivity parameters in our systems. The observation of cyclics is possible by SEC technique (Ref. 8) and we have indeed observed the presence of small amounts of low molar mass oligomers, for example in the case of the La initiator, which can be assigned to cyclics. The observed decrease of Mn of the polymer is another argument for a side reaction with formation of cyclics, but the latter were never isolated and fully characterized.

The ^{13}C NMR technique allows also to observe and to quantify transesterification reactions (Ref. 26). The information is obtained from additional signals observed in methine and in carbonyl regions which cannot be described by pair-addition Bernouillian statistics but result from the stereosequence rearrangement due to transesterification reaction.

We have examined carbonyl and methine regions in ^{13}C NMR spectra of three samples of poly (D,L)-lactides (n° 13, 14, 15 in Table 2) prepared with yttrium tris-alkoxide initiator. The intensity of ssi tetrad in methine signal allow to estimate the transesterification contributions (Ref. 36) which were found to be approximatively equal 10, 17 and 27% respectively for the cited samples. It is worthy to mention that transesterification coefficient introduced by Bero et al (Ref. 26) is modified in the case of a stereoselective process as reported by Coudane et al (Ref. 30).

MALDI-TOF MS analysis of several polylactide samples from Table 1 and Table 2 were performed . It was found for poly (D,L)-lactides prepared with tris-alkoxide initiator that at moderate conversion (sample n° 13, Table 2) only open-chain odd and even oligomers are found, while for samples at higher conversion signals corresponding to cyclic oligomers clustered with Na^+ (indicated by a star) appear in substantial amounts (sample n° 15, Fig. 6 a). These results clearly indicate the occurence of exchange ester reactions both intermolecular and intramolecular, the latter one leading to the formation of cyclic compounds.

The same analysis was performed on polymers prepared with (μ-oxo) cluster lanthanide alkoxides as initiators.

In the spectra of polymers prepared with Sm and Y initiators only open-chain polymers were observed with a reduced ester exchange intermolecular process.With La initiator, a considerable broadening of MWD is observed at high conversions (samples n° 2 and 3, Table 1) and again together with open-chain oligomers, signals corresponding to cyclic compounds appear (Fig.6 b). The different type of species which appear in different spectra are presently examined and a quantitative approach of ester exchange is under study (Ref. 31). Lanthanoid isopropoxides are known to be active catalysts for the interchange reaction of the alkoxy groups between two kind of esters (Ref. 32).

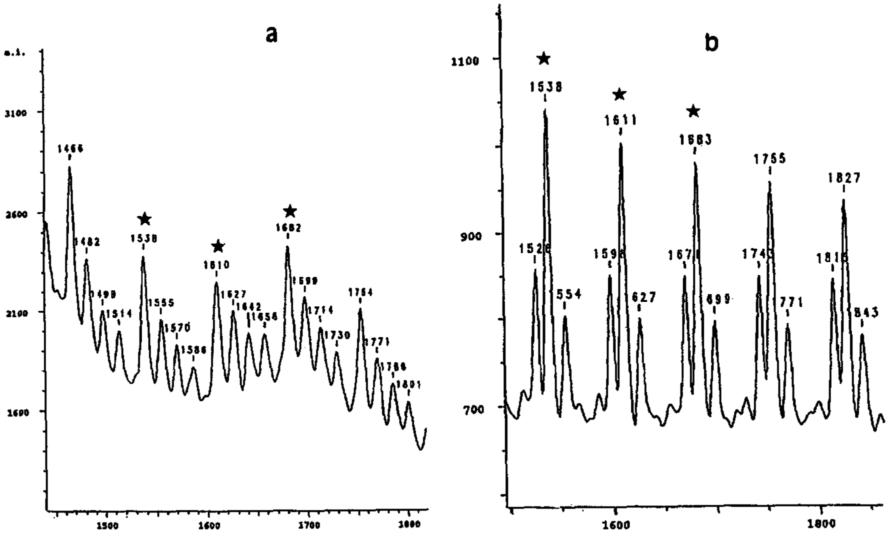


Fig 6 : MALDI-TOF MS spectra of poly(D,L)-lactides prepared with (a) Y(OCH$_2$CH$_2$OiPr)$_3$ (sample 15, Table 2) and (b) La$_5$(μ-O)(OiPr)$_{13}$ (sample 3, Table 1).

CONCLUSION

Lanthanide alkoxide are reactive initiators leading for most of them to a controlled type polymerization of (D,L)lactide in solution at room temperature.

La (μ-oxo) cluster is the most reactive initiator but involves important ester exchange reactions at high conversions. Y(OCH$_2$CH$_2$OiPr)$_3$ appears to be the most appropriate initiator combining high reactivity and limited side reactions during the course of polymerization.

The study of transesterification reactions by several techniques reveals that aside the usual intermolecular process, for two of the initiator systems intramolecular ester exchange reaction occurs also with formation of cyclics.

REFERENCES

(1) S.J. Holland, B.J. Tighe, L.P. Gould, *J. Controlled Release*, **4**, 155 (1986)

(2) M. Vert, S.M.Li, G. Spenlenhauer, P. Guérin, *J. Mater. Sci., Mater. Med.*, **3**, 432 (1992)

(3) H.M.Müller, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **32**, 477 (1993)

(4) R.G. Sinclair, *J. Macromol. Sci., Pure Appl. Chem.*, A **33**, 585 (1996)

(5) M. Vert, F. Chabot, J. Leray, P. Christel, *Makromol. Chem., Suppl.* **5**, 30 (1981)

(6) A. Löfgren, A.C. Albertsson, P. Dubois, R. Jérôme, *J. Macromol. Sci. Rev., Macromol. Chem. Phys.*, C **35**, 379 (1995)

(7) H.R. Kricheldorf, M. Berl, N. Scharnagl, *Macromolecules*, **21**, 286 (1988)

(8) P. Dubois, C. Jacobs, R. Jérôme, P. Teyssié, *Macromolecules*, **24**, 2266 (1991)

(9) M. Wisniewski, A. Le Borgne, N. Spassky, *Macromol. Chem. Phys.* **198**, 1227 (1997)

(10) A. Duda, S. Penczek, *Macromolecules*, **28,** 5981 (1995)

(11) A. Kowalski, A. Duda, S. Penczek, *Macromolecules*, **31**, 2114 (1998)

(12) P. Degée, P. Dubois, R. Jérôme, *Macromol. Chem. Phys.* **198,** 1973 (1997)

(13) S. Penczek, R. Szymanski, A. Duda, *Macromol. Symp.*, **98,** 193 (1995)

(14) J. Baran, A. Duda, A. Kowalski, R. Szymanski, S. Penczek, *Macromol. Symp.*, **123**, 93 (1997)

(15) N. Spassky, C. Pluta, V. Simic, M. Thiam, M. Wisniewski, *Macromol. Symp.*, **128**, 39 (1998)

(16) S.J. Mc Lain, T.M. Ford, N.E. Drysdale et al, *Polym. Prepr. (Div. Polym. Chem. Am. Chem. Soc.)* **33**, 463, (1992) ; **35**, 534 (1994)

(17) W.M. Stevels, M.J.K. Ankoné, P.J. Dijkstra, J. Feijen, *Macromol. Chem. Phys.*, **196**, 1153 (1995)

(18) A. Le Borgne, C. Pluta, N. Spassky, *Macromol. Chem. Rapid. Comm.* , **15**, 955 (1995)

(19) M. Yamashita, Y. Takemoto, F. Ihara, H. Yasuda, *Macromolecules*, **29**, 1978 (1996)

(20) W.N. Stevels, M.J.K. Ankoné, P.J. Dijkstra, J. Feijen, *Macromolecules,* **29**, 6132 (1996)

(21) V. Simic, N. Spassky, L.G. Hubert-Pfalzgraf, *Macromolecules,* **30,** 7338 (1997)

(22) O. Poncelet, W.J. Sartrain, L.G. Hubert-Pfalzgraf, K. Folting, K.G. Caulton, *Inorg. Chem.*, **28,** 263 (1989)

(23) O. Poncelet, L.G. Hubert-Pfalzgraf, J.C. Daran, R. Astier *J. Chem. Soc., Chem. Comm.*, **1849**, (1989)

(24) P. S. Coan, L. G. Hubert-Pfalzgraf, K. G. Caulton, *Inorg. Chem.*, **31**, 1262, (1992)

(25) F. Chabot, M. Vert, S. Chapelle, P. Granger, *Polymer,* **24**, 53 (1983)

(26) M. Bero, J. Kasperczyk, Z. Jedlinski, *Makromol. Chem.* **191**, 2287 (1988)

(27) G. Montaudo, M.S. Montaudo, C. Puglisi, F. Samperi, N. Spassky, A. Le Borgne, M. Wisniewski, *Macromolecules*, **29**, 6461 (1996)

(28) J. Baran, A. Duda, A. Kowalski, R. Szymanski, S. Penczek, *Macromol. Rapid Comm.*, **18,** 325 (1997)

(29) R. Szymanski, *Macromol. Theory Simul*, **7**, 27 (1998)

(30) J. Coudane, C. Ustariz-Peyret, G. Schwach, M. Vert, *J. Polym. Sci. A, Polym. Chem.*, **35**, 1651 (1997)

(31) N. Spassky, V. Simic, M.S. Montaudo, Macromolecules, (to be published)

(32) T.Okano, Y. Hayashizaki, J. Kiji, *Bull. Chem. Soc. Jpn.*, **66**, 1863 (1993)