Polymer Bulletin 44, 31–38 (2000)

Polymer Bulletin

Controlled polymerization of DL-lactide using a Schiff's base al-alkoxide initiator derived from 2-hydroxyacetophenone

A. Bhaw-Luximon[1], **D. Jhurry**[1,*], **N. Spassky**[2]

[1] Department of Chemistry, Faculty of Science, University of Mauritius, Reduit, Mauritius
[2] Laboratoire Chimie des Polymères, UMR 7610, Université Pierre et Marie Curie,
4 Place Jussieu, 75252 Paris Cedex 05, France

Received: 4 October 1999/Accepted: 6 December 1999

Summary

The kinetics of DL-lactide polymerization was studied in CH_2Cl_2 at 25°C and in toluene at 70°C with HAPENAlOMe, a new Schiff’s base complex derived from 2-hydroxyacetophenone and ethylenediamine. A higher polymerization rate is observed with this initiator as compared to other previously reported Al-alkoxides complexes. The polymerization with HAPENAlOMe is also shown to be a living process in both solvents. Moreover, the polymerization proceeds to quite high conversion without significant occurrence of transesterification reactions as confirmed from ^{13}C NMR and SEC analysis.

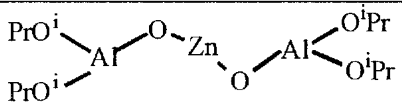
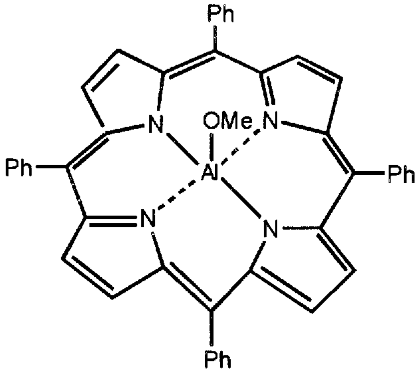
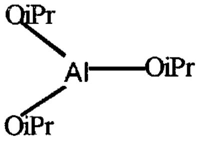
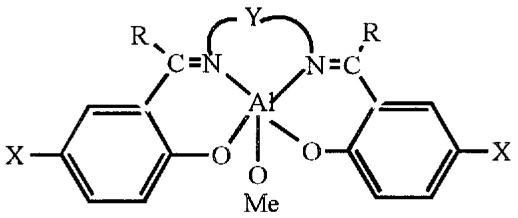
Introduction

Polyesters derived from lactides are bioresorbable and biocompatible materials. They find many applications in the biomedical field as sutures, screws, protheses and also in the design of controlled drug release devices.(1-6) The polyesters are obtained from their corresponding monomers by ring-opening polymerization [ROP] (7), with a large range of molar masses. Different types of initiators(8-14) may be used for the ROP of lactides, tin(II) octanoate(9, 10) and zinc powder or zinc lactate(11, 12) being the most commonly used in polymers for biomedical applications. However, polymerization in the presence of these initiators do not exhibit living behaviour and lead to polymers with broad molar mass distribution. The development of other initiators mostly based on aluminium alkoxides giving rise to controlled polymerization of lactides has known a growing interest during the past fifteen years. A list of such initiators is given in table 1. Aluminium alkoxide initiators exhibit a relatively low reactivity and for this reason the polymerizations must be conducted at relatively high temperature. Recently we have reported that the polymerization of both L- and DL-lactide can easily be performed in solution at room temperature with 5-chloro-Schiff's base aluminium complex(25). In some cases with aluminium alkoxide initiators, side transesterification reactions occurred as from 70% conversion, thereby leading to a broadening of the molar mass distribution(17,23). We present in this article another Schiff’s base aluminium alkoxide having the same general structure as shown in table 1 with $R=CH_3$, X=H and $Y=(CH_2)_2$ denoted as HAPENAlOMe. The latter is easily prepared from 2-hydroxyacetophenone and proves to be an effective initiator for the controlled polymerization of DL-lactide. This paper will focus on the polymerization kinetics in dichloromethane at 25°C and in toluene at 70°C. The performance of HAPENAlOMe in comparison with previously reported Schiff’s base Al-alkoxides and $Al(OiPr)_3$ under similar experimental conditions will be discussed. The living features of the polymerization will be addressed.

---

[*] Corresponding author

Table 1. Aluminium alkoxide initiators leading to controlled polymerization of lactides.

Monomer	Initiator	Structure	Reference
DL-lactide	(Al,Zn)μ-oxo alkoxide		Song and Feng(15)
D-lactide	(5,10,15,20-tetraphenyl porphinato)Al alkoxide		Inoue *et al.*(16)
L & DL-lactide	Al(O^{i}Pr)$_3$ Al-monoalkoxides	 R_2AlOR'	Kricheldorf *et al.*(8) Dubois *et al.*(17) Ropson *et al.*(18) Kowalski *et al.*(19) Baran *et al.*(20) Dubois *et al.*(21) Barakat *et al.* (22)
DL-lactide	Schiff's base Al alkoxides		SALENAlOMe: R=H, X=H, Y=$(CH_2)_2$ Le Borgne *et al.*(23) SALBinaphtAlOMe: R=H, X=H, Y= binaphthyl Spassky *et al.*(24) 5-ClSALENAlOMe: R=H, X=Cl, Y=$(CH_2)_2$ Cameron *et al.*(25)

Experimental

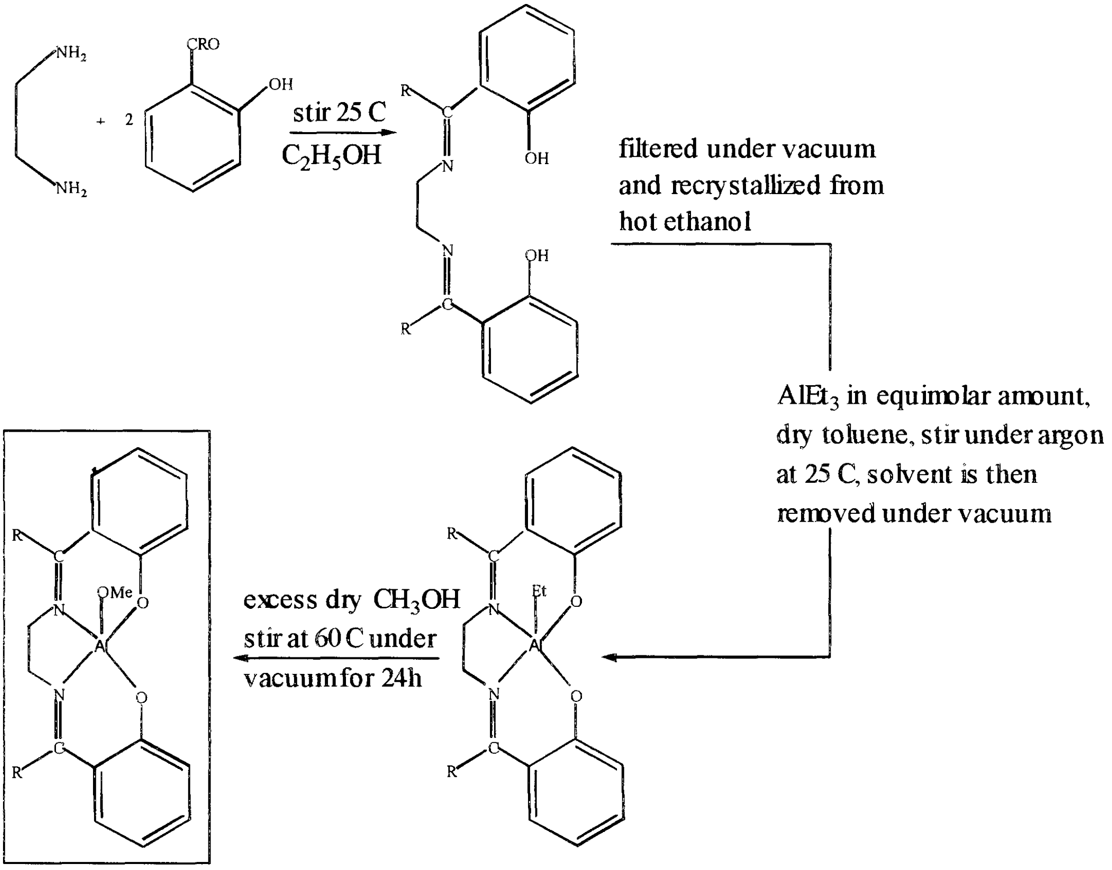
Materials

DL-lactide was obtained from Purac-Biochem as a gift. It was recrystallised three times from dry ethyl acetate, dried under vacuum and finally kept under argon. Dichloromethane was first refluxed and distilled twice over CaH_2 under nitrogen and was stored under argon. Toluene was first refluxed and then distilled over sodium under nitrogen and kept under argon.

Al(O^{i}Pr)$_3$ was used as obtained from Riedel-de-Haën.

Synthesis of initiators

The synthesis of SALENAlOMe and HAPENAlOMe was carried out according to scheme 1. The structure of HAPENAlOMe was confirmed by ^{1}H NMR in CD_2Cl_2: δ (in ppm) 7.47-7.11 (m, 4H, ArH), 6.80-6.49 (m, 4H, ArH), 3.80 (m, 1H, CH_2), 3.63 (m, 1H, CH_2), 3.50 (m, 1H, CH_2), 3.20 (m, 1H, CH_2), 2.70 (s, 3K, OCH_3), 2.31 (s, 3H, CH3), 2.24 (s, 3H, CH_3).



Scheme 1. Synthesis of SALENAlOMe (R=H) and HAPENAlOMe (R=CH_3)

Polymerization procedure

Polymerizations in dichloromethane were carried out under stirring in glass tubes at 25°C under argon in a glove box while those in toluene were conducted in Schlenk tubes at 70°C under vacuum. The initiator, solvent and monomer were in both cases introduced in the tubes inside the glove box. After the desired time of polymerization the solvent was removed under vacuum and the percentage conversion was determined by ^{1}H NMR. Then the reaction mixture was treated three times with 1M aqueous solution of acetic acid, washed with water till neutrality and dried on sodium sulphate. After filtration, the polymers were isolated by precipitation in methanol and finally dried under vacuum at 40°C.

Characterization

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using an FT Bruker 250 MHz spectrometer at 25°C.

SEC analysis was carried out with a Varian equipment (TSK4000-3000-2000 column set) using THF as eluent at a flow rate of 0.8 ml/mn under 68 atm pressure and an RI detector. Polystyrene standards were used for calibration.

Results and Discussion

Similarly to all the Al-alkoxides described in table 1, polymerization of DL-lactide with HAPENAlOMe proceeds by insertion of the monomer into the aluminium methoxide bond. This involves cleavage of the acyl-oxygen bond of DL-lactide leading to aluminium alkoxide as the growing species. One end of the polymer remains attached to aluminium through an alkoxide bond while the other end contains a methoxyester group appearing as a singlet at $\delta = 3.74$. Comparison of the signal intensities of this end-group with the methine protons of the chain enables the determination of the molar mass of the polymer with quite good accuracy (±1.5%).

A hydroxy end-group results after mild hydrolysis of the alkoxide bond with aqueous acetic acid. This transformation occurs without any change in the molar mass of the polymer.

Kinetics

The kinetics of DL-lactide polymerization using HAPENAlOMe was investigated in dichloromethane at 25°C and in toluene at 70°C at monomer concentrations of 1 M and 2 M for a ratio [M]/[I] = 50. For ease of comparison, the polymerization of DL-lactide has also been achieved (i) with SALENAlOMe (see table 1: Schiff's base Al-methoxide complex with R=H, X=H, $Y=(CH_2)_2)$ in CH_2Cl_2 and in toluene at 25°C and 70°C respectively (ii) with $Al(O^iPr)_3$ in toluene at 70°C. The extent of conversion was determined from ^1H NMR spectra by comparing the signal intensities of the monomer ($\delta = 5.01\text{-}5.11$) and polymer ($\delta = 5.11\text{-}5.27$).

The polymerization is found to be first order with respect to monomer as supported by the linear relationship between In $[M]_0/[M]$ and time (Figures 1 and 2). This also substantiates that the concentration of active species remains constant throughout the polymerization reaction. As can be noted, no induction period is observed in either solvent as the initiator is here totally soluble.

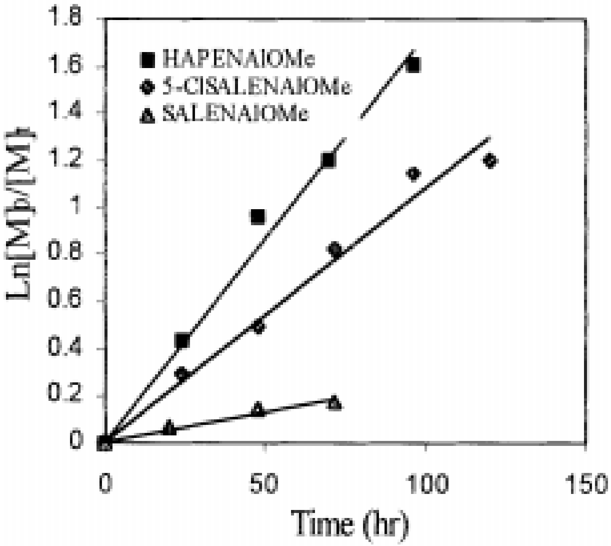


Figure 1. Determination of the order in monomer for polymerization in CH_2Cl_2 at 25°C. $[M]_0$ = 1M; [M]/[I] = 50 for HAPENAlOMe and SALENAlOMe; $[M]_0$ = 1.38M; [M]/[I] = 150 for 5-Cl-SALENAlOMe

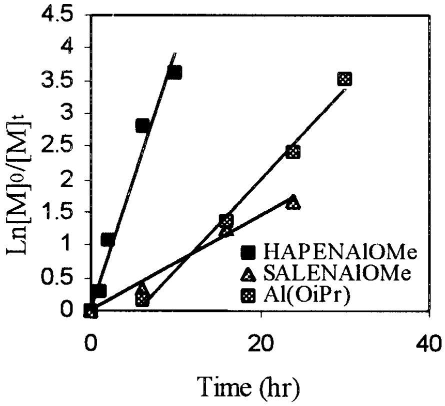


Figure 2. Determination of the order in monomer for polymerization in toluene at 70°C. $[M]_0 = 1M$; $[M]/[I] = 50$

The apparent polymerization rate constants ($k_{app}=k_p.[I]$) in the two solvents have been calculated for HAPENAlOMe, SALENAlOMe, 5-ClSALENAlOMe and $Al(O^iPr)_3$ from the slopes of the straight lines above and are listed in table 2. As can be seen, a significant increase in the polymerization rate is observed with HAPENAlOMe as compared to SALENAlOMe in both solvents. The higher reactivity of HAPENAlOMe may be explained by an increase in the polarisability of the Al-OMe bond as indicated by an upfield shift of the methyl protons (δ=2.71) in ^1H NMR compared to those of SALENAlOMe (δ=2.91). 5-ClSALENAlOMe is found to be also more reactive than SALENAlOMe although in that case a much lower concentration of initiator was used. This can be explained by the presence of chloro electron withdrawing group which could possibly enhance the electrophilicity of aluminium(24).

Table 2. Apparent polymerization rate constants for different initiators. $[M]_0 = 1$ M; $[M]/[I] = 50$

Initiator	Solvent	Temp.(°C)	k_{app}* 10^3 (hr^{-1})
HAPENAlOMe	CH_2Cl_2	25	17
	toluene	70	374
SALENAlOMe	CH_2Cl_2	25	2.4
	toluene	70	73
5-ClSALENAlOMe[a]	CH_2Cl_2	25	11
$Al(O^iPr)_3$	toluene	70	138
$Al(O^iPr)_3$[b] (17)	toluene	70	42

[a] $[M]_0 = 1.38$ M; $[M]/[I] = 150$
[b] $[M]_0 = 0.56$ M; $[M]/[I] = 417$

It is interesting to note that HAPENAlOMe is about three times more reactive than $Al(O^iPr)_3$ under similar experimental conditions. The apparent rate constant as determined by Dubois *et al.*(17) has been included in the table for comparison.

Influence of monomer concentration on kinetics

The polymerization of DL-lactide was carried out also at [M] = 2 M in CH_2Cl_2 at 25°C. Again a linear relationship was observed. The apparent rate constant of polymerization for a ratio [M]/[I] = 50 was found to be about 2.5 times greater at 2 M (Figure 3).

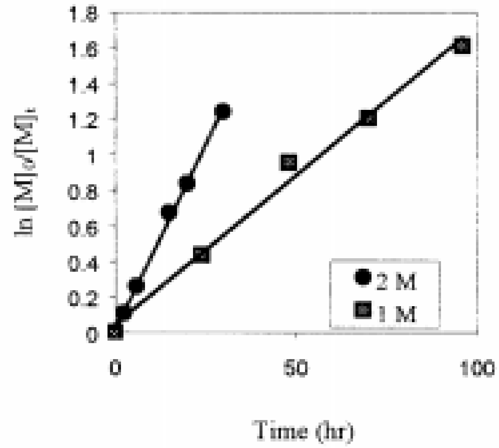


Figure 3. Effect of monomer concentration on polymerization rate in CH_2Cl_2 at 25°C. [M]/[I]=50

Molar mass v/s conversion

The DL-lactide polymerization initiated by HAPENAlOMe in both CH_2Cl_2 and toluene is a living process as shown by a linear plot of number average molar mass (M_n) v/s conversion (Figure 4).

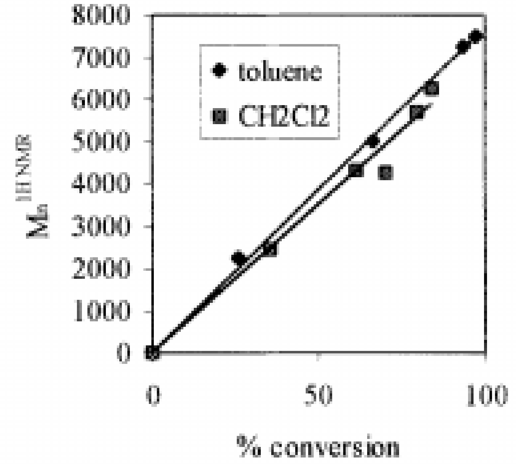


Figure 4. Variation of molar mass with % conversion in toluene at 70°C and in CH_2Cl_2 at 25°C. $[M]_0$ = 1M; [M]/[I] = 50

As can be seen in Table 3, the experimental molar masses determined by ^1H NMR are in close agreement with the predicted molar mass calculated from equation (1), whereas the correlation between the latter and the molar masses determined by SEC using polystyrene standards is not as good. A slight increase is noted in the molar mass distribution (1.1 to 1.2) with percentage conversion, but it remains however narrow as for a living polymerization.

$$M_n = [M]_0/[I] * M_r * x\% \quad ....(1) \qquad \text{where } M_r \equiv 144 \text{ g/mol}$$

$$x\% \equiv \text{percentage conversion}$$

Table 3. Polymerization of DL-lactide with HAPENAlOMe in CH_2Cl_2 at 25°C
$[M]_0$ = 1M; [M]/[I] = 50

Time (hr)	% conversion	$M_n^{calc.}$	$M_n^{1H\ NMR}$	M_n^{SEC}	$I = M_w/M_n$
24	36	2592	2450	2100	1.10
70	70	5040	5500	4600	1.16
96	80	5760	5700	4900	1.13
144	84	6048	6200	5500	1.20

Study of transesterification reactions

An interesting feature of the polymerization with HAPENAlOMe is that no significant transesterification reactions are observed during the polymerization in CH_2Cl_2 solution, while they occur only at very high extent of conversion (97%) in toluene, contrary to what has already been reported previously for $Al(O^iPr)_3$(17) and SALENAlOMe(23). These features have been substantiated by ^{13}C NMR spectra as seen in Figure 5. In the methine region, signals at 69.3 and 69.4 ppm assigned to "forbidden" tetrads *sss, ssi* and *iss*, typical of transesterification reactions are not observed for 100% conversion in CH_2Cl_2 (Figure 5a) and for 94% conversion in toluene (Figures 5b). However at prolonged polymerization time in toluene, transesterification appear in non negligible amounts at 97% conversion (Figure 5c). The percentage of transesterification can be evaluated from ^{13}C NMR spectra by known methods(26, 27) and in the latter case it is of the order of 27%. Comparison of the intensities of the tetrad signals in Figure 5a (A:B/86%:14%) and in Figure 5b (A:B/83%:17%) shows that the polymers obtained in both solvents for quantitative extent of conversion exhibit a high degree of isotacticity. This is in agreement with results previously found for SALENAlOMe initiator for which a microstructure obeying a first-order Markovian distribution of units with a reactivity ratio (r = 2.8) was found (28). The poly(DL-lactides) prepared with HAPENAlOMe were analyzed by DSC and found to exhibit sharp melting points, thereby confirming their high stereoregularity. For example, the sample prepared in dichloromethane at high conversion (84%, [M] = 1M, [M]/[I] = 50) shows a well-defined melting transition at 159°C.

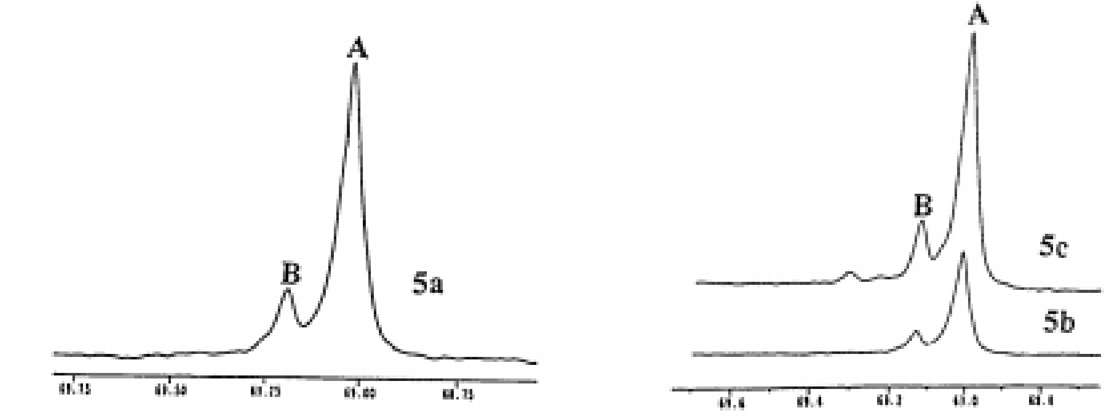


Figure 5. ^{13}C NMR spectrum ($CDCl_3$) showing <u>C</u>H tetrads of PDLLA: (a) 100% conversion in CH_2Cl_2; $[M]_0$ = 2 M, [M]/[I] = 50 (b) 94% conversion in toluene at 70°C; $[M]_0$ = 1 M, [M]/[I] = 50 (c) 97% conversion in toluene at 70°C; $[M]_0$ = 1 M, [M]/[I] = 50

Conclusion

HAPENAlOMe proves to be an interesting initiator for the controlled polymerization of DL-lactide. It has a higher reactivity than SALENAlOMe and $Al(O^iPr)_3$ and does not lead to significant transesterification reactions even at high temperature. HAPENAlOMe is also an isospecific initiator which enables the synthesis of highly isotactic polymers from a racemic monomer.

Acknowledgements

The authors are thankful to the Tertiary Education Commission (Mauritius) for providing financial support for this work and a scholarship to (ABL). Grateful acknowledgements to Prof. H Cramail (Bordeaux University) for assistance with SEC analysis and to Mr B. Jokhun (University of Mauritius) for running the NMR spectra.

References

1. Vert M, Chabot F, Leray J, Christel P (1981) Makromol Chem, Suppl 5: 30
2. Holland SJ, Tighe BJ, Gould LP (1986) J Controlled Release 4: 155
3. Vert M (1986) Macromol Chem, Macromol Symp 6: 109
4. Nieuwenhuis J (1992) Clin Mater 10: 59
5. Kharas GB, Sanchez-Riera F, Severson DK (1994) in "Plastics from Microbes: Microbial Synthesis of Polymers and Polymer Precursors", Mobley DP, Ed. Hanser, Munich: 93
6. Vert M, Li SM, Spenlehauer G, Guérin P (1992) J Mater Sci, Mater Med 3: 432
7. Lofgren A, Albertsson AC, Dubois P, Jérôme R (1995) J.M.S.-Rev Macromol Chem and Phys C35(3): 379
8. Kricheldorf HR, Berl M, Scharnagl N (1988) Macromolecules 21: 286
9. Nijenhuis AJ, Grijpma DW, Pennings AJ (1992) Macromolecules 25: 6419
10. Kricheldorf HR, Kreiser-Saunders I, Boettcher C (1995) Polymer 36: 1253
11. Chabot F, Vert M, Chapelle S, Granger P (1983) Polymer 24: 53
12. Schwach G, Coudane J, Engel R, Vert M (1996) Polym Bull 37: 771
13. Kricheldorf HR and Damrau DO (1997) Macromol Chem and Phys 198: 1753
14. Schwach G, Coudane J, Engel R, Vert M (1998) Polymer 46: 177
15. Song CX and Feng XD (1984) Macromolecules 17: 2764
16. Trofimoff L, Aida T, Inoue S (1987) Chem Lett 991
17. Dubois Ph, Jacobs C, Jerôme R, Teyssié Ph (1991) Macromolecules 24: 2266
18. Ropson N, Dubois Ph, Jérôme R, Teyssié Ph (1991) Macromolecules, 26: 6378
19. Kowalski A, Duda A, Penczek S (1998) Macromolecules 31: 2114
20. Baran J, Duda A, Kowalski A Szymanski R, Penczek S (1997) Macromol Symp 123: 93
21. Dubois Ph, Jérôme R, Teyssié Ph (1991) Macromol Chem, Macromol Symp 42/43: 103
22. Barakat I, Dubois Ph, Jérôme R, Teyssié Ph (1993) J Macromol Chem, Pure Appl Chem A31: 505
23. Le Borgne A, Wisniewski M, Spassky N (1995) Polym Prepr (Div Polym Chem, Am Chem Soc) 36(2): 217
24. Spassky N, Wisniewski M, Pluta C, Le Borgne A (1996) Macromol Chem Phys 197:2627-2637
25. Cameron PA, Jhurry D, Gibson VC, White AJP, Williams DJ, Williams S (1999) submitted to Macromol Rapid Commun
26. Bero M, Kasperczyk J, Jedlinski Z (1990) Makromol Chem 191: 2287
27. Coudane J, Ustaritz-Peyret, Schwach G, Vert M (1997) J Polym Sci: Polym Chem 35: 1651
28. Wisniewski M, Le Borgne A, Spassky N (1997) Macromol Chem Phys 198: 1227