Polymer 51 (2010) 4329–4335

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Synthesis and characterization of biodegradable polylactides and polylactide-block-poly(Z-lysine) copolymers

Ya-Liu Peng [a], Yong Huang [a], Hui-Ju Chuang [a], Chen-Yuan Kuo [b], Chu-Chieh Lin [a,*]

[a] Department of Chemistry, National Chung Hsing University, Taichung 402, Taiwan, ROC
[b] Department of Biological Engineering, Yung-Ta Institute of Technology and Commerce, Pingtung 909, Taiwan, ROC

ARTICLE INFO

Article history:
Received 20 April 2010
Received in revised form
7 July 2010
Accepted 10 July 2010
Available online 17 July 2010

Keywords:
L-Lactide
Peptide
Lithium

ABSTRACT

The reaction of (R,R)-trans-1,2-bis(2,4,6-triisopropylbenzenesulfonamidato)cyclohexane (^{RR}TBSC-H_2, **1**) with MN[Si(CH_3)$_3$] in tetrahydrofuran (THF) produces [(^{RR}TBSC)$_2$M$_4$(THF)$_4$] (**2**: M = Li, **3**: M = Na, **4**: M = K). Experimental results show that all three complexes **2**–**4** are active toward the ring-opening polymerization of L-lactide and compound **2** efficiently catalyzes the polymerization of L-lactide in the presence of a variety of alcohols in a controlled fashion with very narrow polydispersity index. In addition, a variety of biodegradable poly(L-lactide)-block-poly(N$_\xi$-carbobenzyloxy-L-lysine) block copolymers with different ratios have also been synthesized using poly(L-lactide) containing amino chain end (PLLA-NH_2) as a macroinitiator.

1. Introduction

Biodegradable polyesters, such as poly(ε-caprolactone) (PCL), polylactide (PLA) and their copolymers have been attracting considerable attention owing to their potential applications in biomedical fields such as absorbable sutures and delivery medium for the controlled release of drugs [1]. The most convenient method for synthesis of these polyesters is the ring-opening polymerization (ROP) of cyclic esters (e.g., ε-caprolactone (ε-CL) and L-lactide (LLA)). Due to the advantages of well controlled molecular weight and low polydispersity (PDI), many chemists have focused on the development of new catalysts for ring-opening polymerization. In this aspect, complexes coordinated with suitable ligands play an important role not only in molecular weight control and molecular weight distribution, but also in the production of stereoregular polyesters. Recently, several excellent review articles related to the polymerization of cyclic esters have been published [2].

In addition, polypeptides and their copolymers are alluring materials both as applications for biomedicine and in architectures of a variety of polymers due to their outstanding properties such as biodegradability and biocompatibility, as well as self-assembly and formation of liquid crystals [3,4]. In order to modify and enhance the property of polymers for use in certain fields, various preparation methods have been developed for the preparation of diblock and triblock polypeptides [5]. In terms of the biomedical purposes, the polymerization procedure catalyzed/initiated by low toxic metals coordinated with sufficient ligands seems suitable. The development of low toxic metal complexes supported by sufficient ligand as catalysts for ROP of cyclic esters has attracted attention [6,7]. Herein, we report on the preparation of three novel low toxic Group 1 metal complexes and use them as catalysts for ROP reactions of LA. The activities and stereoselectivities of these complexes are presented. Poly(lactide)-block-poly(N$_\xi$-carbobenzyloxy-L-lysine) (PLA-b-PZLys) copolymer is prepared using PLA as initiators.

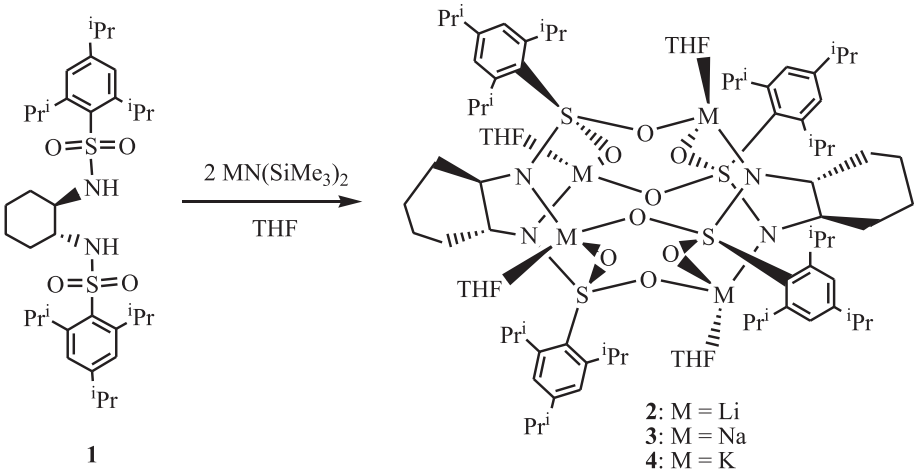
2. Experimental section

2.1. General

All manipulations were carried out under a dry nitrogen atmosphere and all glass wares were flame-dried under vacuum before using. Solvents were dried by refluxing at least for 24 h over sodium/benzophenone (hexane, toluene and tetrahydrofuran (THF)) and freshly distilled prior to use. L-Lactide (LLA) and *rac*-lactide (RLA) were purified from the recrystallization of the toluene solution. Lithium bis(trimethylsilyl)amide (LBA, dissolved in hexane, 1 M, Fluka), sodium bis(trimethylsilyl)amide (SBA,

* Corresponding author. Tel.: +886 4 22840412; fax: +886 4 22862547.
E-mail address: cchlin@mail.nchu.edu.tw (C.-C. Lin).

0032-3861/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2010.07.016



Scheme 1.

dissolved in THF, 1 M, Aldrich), potassium bis(trimethylsilyl)amide (PBA, dissolved in toluene, 0.5 M, Aldrich), (2,4,6)-triisopropyl benzenesulfonyl chloride (Acros), 3-aminopropan-1-ol (Aldrich), benzyl chloroformate (Fluka), and piperidine (Aldrich) were used without further purification. 3-Benzyloxycarbonylaminopropan-1-ol (Z-ROH) was obtained according to the method reported by Blagbrough et al. [8]. Nξ-carbobenzyloxy-L-lysine N-carboxyanhydride (Z-Lys-NCA) [9] and (R,R)-trans-1,2-bis-(2,4,6-triisopropylbenzenesulfonamidato)cyclohexane (^{RR}TBSC-H_2, **1**) [10] were prepared according to the literature methods. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Mercury-400 spectrometer with chemical shifts given in ppm from the internal TMS. Microanalyses were performed using a Heraeus CHN-ORAPID instrument. Infrared spectra were obtained from a Bruker Equinox 55 spectrometer. The gel permeation chromatography (GPC) measurements were performed on a Hitachi L-7100 system equipped with a differential JASCO RI-2031Plus detector using THF (HPLC grade) as an eluent. The chromatographic column was Phenomenex Phenogel 5 μ 10^3 Å and the calibration curve is made by polystyrene standards to calculate number average of molecular weight (Mn). A typical GPC measurements description was exemplified by the measurement of $PLLA_{25}$ (the number 25 indicates [M]/[Z-ROH]). $PLLA_{25}$ (0.025 g) was dissolved in THF (4.975 g, HPLC grade) and the solution was filtered through a filter (13 mm Millex-HN Filter 0.45 mm NY Nonsterile). The resulting filtration (0.25 mL) was then injected into the GPC with the flow eluent rate of 1 mL min^{-1} at 40 °C. The GPC results were calculated by SISC chromatography data solution 1.0 edition using polystyrene as a standard.

2.2. Synthesis of (^{RR}TBSC)$_2$Li$_4$(THF)$_4$] (**2**)

Lithium bis(trimethylsilyl)amide (4.1 mL, 1.0 M in hexane, 4.1 mmol) was added slowly to an ice cold solution (0 °C) of TBSC-H_2 (1.292 g, 2.0 mmol) in tetrahydrofuran (20 mL). The ice bath was removed and the temperature was increased to room temperature. The mixture was stirred for another 3 h under a nitrogen atmosphere and was then evaporated to dryness under vacuum. The residue was dissolved in hexane (30 mL) and filtered through celite. The resulting hexane solution was cooled to −18 °C and colorless crystals were obtained after one week. Yield: 1.25 g (78%). Anal. Calcd for $C_{88}H_{144}Li_4N_4O_{12}S_4$: C, 65.81; H, 9.04; N, 3.49%. Found: C, 65.51; H, 9.17; N, 3.34%. ^{1}H NMR (d^6-benzene, ppm) δ 7.27 (S, 8H, *Ph*); 5.04 (m, *J* = 7.2 Hz, 8H, *o*-C(*H*)Me_2ArSO_2); 3.58 (m, 32H, OCH_2CH_2); 3.23 (m, 4H, CH_2CHNSO_2Ar); 2.73 (m, *J* = 6.8 Hz, 4H, *p*-C(*H*)Me_2ArSO_2); 1.66 (m, 4H, CH_2); 1.43 (d, *J* = 7.2 Hz, 48H, CH_3,);

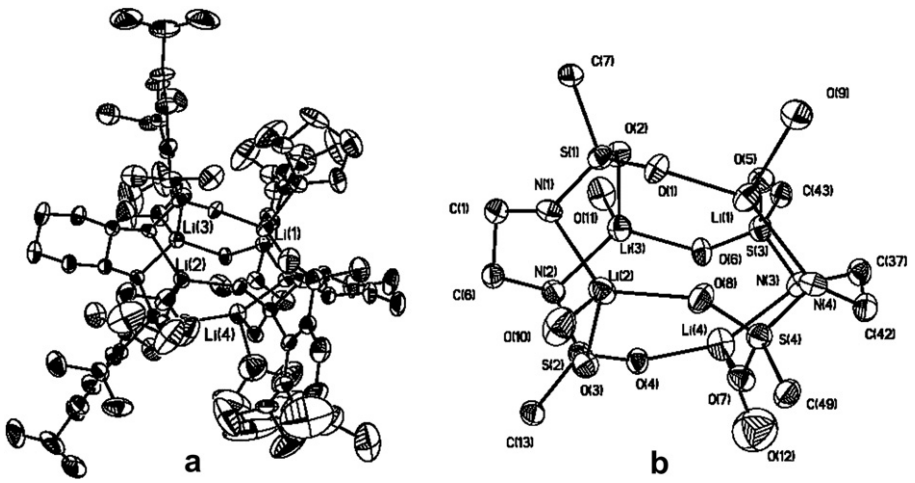


Fig. 1. (a) The ORTEP of complex **2** (only Li atoms were labeled), all H atoms are omitted for clarity. (b) The core structure of complex **2**, all coordinated THF molecules, two cyclohexyl groups and four aromatic groups are reduced to the terminal O atoms, ethylene groups and the terminal C atoms respectively and all H atoms are omitted for clarity.

Table 1
Selected bond lengths (Å) and bond angles (deg) of complex **2**.

Li(1)-O(1)	1.958(10)
Li(1)-O(5)	2.010(10)
Li(1)-O(9)	2.051(12)
Li(1)-N(4)	2.213(11)
Li(2)-O(10)	1.964(11)
Li(2)-O(8)	2.013(11)
Li(2)-O(3)	2.012(10)
Li(2)-N(1)	2.113(11)
Li(3)-O(6)	1.952(10)
Li(3)-O(11)	1.976(11)
Li(3)-O(2)	1.986(11)
Li(3)-N(2)	2.096(11)
Li(4)-O(7)	1.944(12)
Li(4)-O(4)	1.966(12)
Li(4)-O(12)	2.352(18)
Li(4)-N(3)	2.214(13)
S(1)-N(1)	1.538(4)
S(1)-O(1)	1.459(4)
S(1)-O(2)	1.470(4)
S(1)-N(1)	1.538(4)
S(2)-O(3)	1.461(4)
S(2)-O(4)	1.470(4)
S(2)-N(2)	1.539(5)
S(3)-O(5)	1.469(4)
S(3)-O(6)	1.463(4)
S(3)-N(3)	1.551(5)
S(4)-O(7)	1.453(4)
S(4)-O(8)	1.474(4)
O(1)-Li(1)-O(5)	108.8(5)
O(1)-Li(1)-O(9)	96.4(4)
O(5)-Li(1)-O(9)	98.9(5)
O(1)-Li(1)-N(4)	139.4(6)
O(5)-Li(1)-N(4)	100.0(4)
O(9)-Li(1)-N(4)	107.0(5)
O(10)-Li(2)-O(8)	97.7(4)
O(10)-Li(2)-O(3)	101.5(5)
O(8)-Li(2)-O(3)	106.4(5)
O(10)-Li(2)-N(1)	111.4(5)
O(8)-Li(2)-N(1)	130.6(5)
O(3)-Li(2)-N(1)	105.6(4)
O(6)-Li(3)-O(11)	102.8(5)
O(6)-Li(3)-O(2)	107.5(5)
O(11)-Li(3)-O(2)	100.4(5)
O(6)-Li(3)-N(2)	120.8(5)
O(11)-Li(3)-N(2)	111.2(5)
O(2)-Li(3)-N(2)	111.8(5)
O(7)-Li(4)-O(4)	111.0(6)
O(7)-Li(4)-N(3)	99.5(5)
O(4)-Li(4)-N(3)	146.5(7)
O(7)-Li(4)-O(12)	92.9(6)
O(4)-Li(4)-O(12)	92.2(6)
N(3)-Li(4)-O(12)	100.1(6)

1.41–1.21 (br, 8H, CH_2); 1.17 (d, J = 6.8 Hz, 24H, CH_3); 1.06 (m, 32H, OCH_2CH$_2$). ^{13}C NMR (d^6-benzene, ppm) δ 147.24 (SO_2Ar, C1); 144.36 (SO_2Ar, C4); 123.13 (SO_2Ar, C2); 115.10 (SO_2Ar, C3); 67.94 (OCH$_2$CH$_2$); 61.43 (CH$_2$CHNSO$_2$Ar); 35.98 (*p*-*C*(H)Me$_2$ArSO$_2$); 34.30 (*o*-*C*(H)Me$_2$ArSO$_2$); 32.84 (*o*-CH(*C*H$_3$)$_2$ArSO$_2$); 31.27 (*p*-CH(*C*H$_3$)$_2$ArSO$_2$); 29.22 (CH$_2$CH$_2$C(H)NSO$_2$Ar); 25.62 (OCH$_2$CH$_2$); 23.92 (*C*H$_2$CH$_2$C(H)NSO$_2$Ar).

2.3. Synthesis of [^{RR}TBSC]$_2$Na$_4$[THF]$_4$ (**3**)

The preparation method for compound **3** is similar to that for compound **2** with sodium bis(trimethylsilyl)amide (4.1 mL, 1.0 M in THF, 4.1 mmol) was used. Yield: 1.35 g (81%). Anal. Calcd for $C_{88}H_{144}N_4Na_4O_{12}S_4$: C, 63.28; H, 8.69; N, 3.35%. Found: C, 63.05; H, 8.70; N, 3.27%. ^{1}H NMR (d^6-benzene, ppm) δ 7.29 (S, 8H, *Ph*); 4.88 (m, J = 6.8 Hz, 8H, *o*-C(*H*)Me$_2$ArSO$_2$); 3.59 (m, 32H, OCH_2CH$_2$); 2.84 (m, 4H, CH$_2$C*H*NSO$_2$Ar); 2.78 (m, J = 6.4 Hz, 4H, *p*-C(*H*)Me$_2$ArSO$_2$); 1.64 (m, 4H, CH_2); 1.48 (d, J = 6.8 Hz, 48H, CH_3); 1.44–1.27 (br, 8H, CH_2); 1.22 (d, J = 6.4 Hz, 24H, CH_3); 1.17 (m, 32H, OCH_2CH$_2$). ^{13}C NMR (d^6-benzene, ppm) δ 149.20 (SO_2Ar, C1); 141.97 (SO_2Ar, C4); 122.89 (SO_2Ar, C2); 111.31 (SO_2Ar, C3); 67.37(OCH$_2$CH$_2$); 61.04 (CH$_2$CHNSO$_2$Ar); 36.35 (*p*-*C*(H)Me$_2$ArSO$_2$); 34.41 (*o*-*C*(H)Me$_2$ArSO$_2$); 32.62 (*o*-CH(*C*H$_3$)$_2$ArSO$_2$); 29.47 (*p*-CH(*C*H$_3$)$_2$ArSO$_2$); 27.63 (CH$_2$CH$_2$C(H)NSO$_2$Ar); 25.61 (OCH$_2$CH$_2$); 24.59 (*C*H$_2$CH$_2$C(H)NSO$_2$Ar).

2.4. Synthesis of [^{RR}TBSC]$_2$K$_4$[THF]$_4$ (**4**)

The preparation method for compound **4** is similar to that for compound **2** with potassium bis(trimethylsilyl)amide (8.2 mL, 0.5 M in hexane, 4.1 mmol) was used. Yield: 1.37 g (79%). Anal. Calcd for $C_{88}H_{144}K_4N_4O_{12}S_4$: C, 60.93; H, 8.37; N, 3.23%. Found: C, 61.14; H, 8.71; N, 3.03%. ^{1}H NMR (d^6-benzene, ppm) δ 7.31 (S, 8H, *Ph*); 4.83 (m, J = 6.4 Hz, 8H, *o*-C(*H*)Me$_2$ArSO$_2$); 3.61 (m, 32H, OCH_2CH$_2$); 2.78 (m, 4H, CH$_2$C*H*NSO$_2$Ar); 2.72 (m, J = 6.0 Hz, 4H, *p*-C(*H*)Me$_2$ArSO$_2$); 1.61 (m, 4H, CH_2); 1.55 (d, J = 6.4 Hz, 48H, CH_3); 1.47–1.24 (br, 8H, CH_2); 1.23 (d, J = 6.0 Hz, 24H, CH_3); 1.21 (m, 32H, OCH_2CH$_2$). ^{13}C NMR (d^6-benzene, ppm) δ 151.17 (SO_2Ar, C1); 139.89 (SO_2Ar, C4); 121.57 (SO_2Ar, C2); 110.23 (SO_2Ar, C3); 67.41 (OCH$_2$CH$_2$); 60.83 (CH$_2$CHNSO$_2$Ar); 37.63 (*p*-*C*(H)Me$_2$ArSO$_2$); 33.21 (*o*-*C*(H)Me$_2$ArSO$_2$); 31.58 (*o*-CH(*C*H$_3$)$_2$ArSO$_2$); 30.96 (*p*-CH(*C*H$_3$)$_2$ArSO$_2$); 26.21 (CH$_2$CH$_2$C(H)NSO$_2$Ar); 25.41 (OCH$_2$CH$_2$); 24.89 (*C*H$_2$CH$_2$C(H)NSO$_2$Ar).

2.5. General procedures for the polymerization of lactides

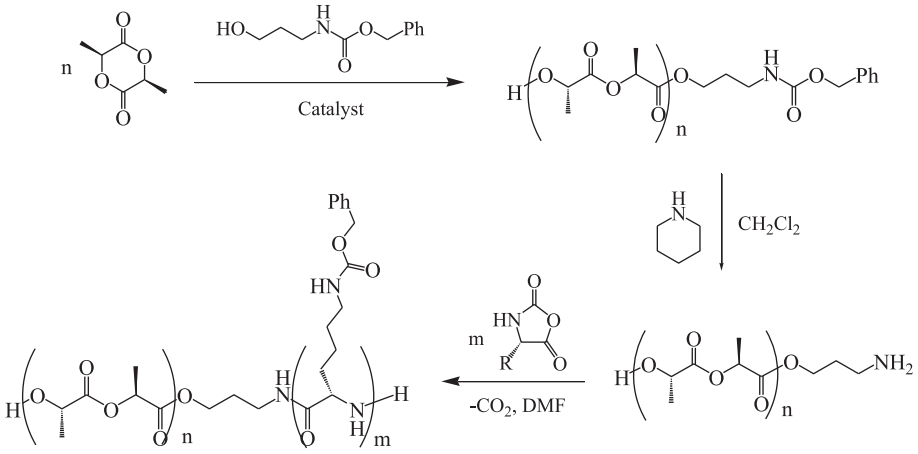
A typical polymerization procedure for polylactides was exemplified by the synthesis of PLLA$_{25}$ (the number 25 indicates the designed [LA]/[Z-ROH] ratio). A toluene (1.0 mL) solution of Z-ROH (0.10 mmol) was added to a rapidly stirred solution of [TBSC]$_2$Li$_4$[THF]$_4$ (0.161 g, 0.10 mmol) and L-lactide (0.36 g, 2.5 mmol) in toluene (15 mL). The resulting mixture was stirred at 28 °C for 2.5 h and the reaction was quenched by the addition of an excess 0.35 N acetic acid solution. The solution was then poured into n-hexane (100 mL) giving a white precipitate. The white precipitate was redissolved in dichloromethane and then precipitated into n-hexane. The obtained white precipitate was dried under vacuum giving white powder. Yield: 0.314 g (87.2%).

2.6. General procedures for the preparation of polylactide with amine end chain

A typical procedure for the synthesis of polylactide with amine chain end (PLA-NH$_2$) was illustrated as the following reactions. PLLA$_{25}$ (1.0 g) containing benzyloxycarbonylamino (NHZ) group in the end chain (PLLA$_{25}$-NHZ) was mixed with piperidine (1.0 mL) in CH_2Cl_2 (20 mL) at room temperature and was stirred for 3.5 h. Volatile materials were removed *in vacuo* yielding white powder. The powders were redissolved in THF (10 mL) and hexane (60 mL) was added resulting white precipitate. The white precipitate was then dried *in vacuo*. Yield: 0.893 g (89.3%).

2.7. General procedures for the preparation of poly(L-lactide)-b-poly(N_ξ–(Z)-L-lysine) block copolymers

General procedures for the preparation of poly(L-lactide)-*b*-Poly(N_ξ–(Z)-L-lysine) block copolymers were exemplified as the following reaction. PLLA$_{25}$-NH$_2$ (38 mg, 0.010 mmol) was dissolved in dried dimethylformamide (DMF) (5.0 mL) in a tube reactor. Z-Lys-NCA (30.63 mg, 0.10 mmol) in DMF (5.0 mL) was quickly injected into the reactor. The mixture was stirred in an N_2 gas flow



Scheme 2.

system allowing the evolution of CO_2. After all monomers had been consumed, which was monitored by ^{1}H NMR and IR spectroscopic methods, the polymer was precipitated by plunging into 80 mL methanol (containing 1 mL conc. HCl). Yield: 55.47 mg (86.4%).

2.8. X-ray crystallographic studies

A suitable crystal of complex **2** was sealed in a thin-walled glass capillary under a dry nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing ω (width of 0.3° per frame). The absorption correction was based on the symmetry–equivalent reflections using the SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences and confirmed by using the structure solution. The structure was solved by direct method using an SHELXTL package. All non-H atoms were located from successive Fourier maps, and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms.

3. Results and discussion

3.1. Synthesis and characterization of complexes

[^{RR}TBSC]$_2$Li$_4$[THF]$_4$ (**2**) was prepared by the reaction of ^{RR}TBSC-H_2 with 2 M equivalents of LBA in THF at room temperature, as shown in Scheme 1. Complexes **3** and **4** were obtained in a procedure similar to that for **2,** using SBA for **3** and PBA for **4**, respectively. These compounds were confirmed by elementary analyses as well as NMR spectroscopic methods. ^{1}H NMR spectrum of compound **2** showed two resonance peaks at 1.43 and 1.17 ppm for the methyl groups of the isopropyl groups in the phenyl ring with a ratio of 1:2 indicating that compound **2** is a highly symmetric complex. Similar results were observed for compounds **3** and **4** with the chemical shifts of 1.48, 1.22 ppm in complex **3** and 1.55, 1.23 ppm in complex **4**, respectively. The resonances for the methine protons of the isopropyl groups were 5.04, 2.73 ppm in complex **2**; 4.88, 2.78 ppm in complex **3** and 4.83, 2.72 ppm in complex **4**. This result was further verified by the X-ray structural determination of compound **2**.

Suitable crystals of complex **2** for X-ray single crystal structure determination were obtained by slowly cooling the hexane solution of complex **2**. The ORTEP of compound **2** is profiled in Fig. 1. The molecular structure of complex **2** illustrates a tetranuclear character in which each lithium atom was tetrahedral coordinated to one oxygen atom of a THF molecule, two oxygen atoms and one nitrogen atom of ^{RR}TBSC ligand. The N, O, O atoms of each sulfonamide group coordinated to three different Li atoms to form a cage structure in the core. The average S–O bond length of 1.465 Å was somewhat longer than typical S=O double bond (1.41 Å) [11]. The S–N bond length ranged from 1.538 to 1.551 Å, which was somewhat shorter than the distance for a normal S–N single bond (1.64 Å) indicating a double bond character in S–N bonding. The selected bond lengths and bond angles are listed in Table 1. The crystal data and the cif file of complex **2** are provided as Supporting

Table 2
Ring-opening polymerization of L-lactide catalyzed by complexes **2**, **3** and **4**.[a]

Entry	Catalyst	[M]/[Z-ROH]	Time(h)	Mn(GPC)[b]	Mn(NMR)[c]	PDI[d]	Yield(%)[e]
1	**2**	100	2.5	14600	14700	1.07	90.1
2	**3**	100	0.333	15800	16500	1.25	89.4
3	**4**	100	0.167	15100	16700	1.31	91.2
4	**2**	25	2.5	4000	4100	1.13	87.2
5	**2**	50	2.5	7900	7900	1.09	88.9
6	**2**	75	2.5	12400	12300	1.08	89.5

[a] Reaction conditions: [Catalyst]/[Z-ROH] = 1, 16 mL toluene, 28 °C.
[b] Obtained from GPC and corrected by timing 0.58. [16].
[c] Calculated from ^{1}H NMR spectrometry.
[d] Obtained from GPC.
[e] Isolated yield.

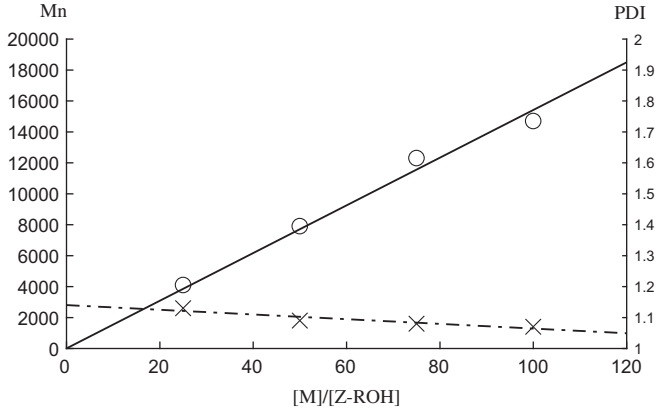


Fig. 2. Polymerization of LLA catalyzed by **2** in toluene at 28 °C. The relationship between Mn (O), PDI (×) of polymer and the initial mole ratio [M]/[Z-ROH] is shown.

Table 3
Ring-opening polymerization of *rac*-lactide catalyzed by complexes **2**[a], [17].

Entry	Time(h)	Solvent	Temp.(°C)	Mn(GPC)[b]	Mn(NMR)[c]	PDI[d]	Yield(%)[e]	Pr[f]
1	2.5	toluene	28	14900	14400	1.06	92.4	0.54
2	20	THF	28	14900	14900	1.08	91.2	0.62
3	30	THF	0	14800	14900	1.06	90.5	0.71
4	48	THF	−30	14700	14600	1.04	91.7	0.82

[a] Reaction conditions: [Monomer]:[**2**]:[Z-ROH] = 100:1:1.
[b] Obtained from GPC and corrected by timing 0.58 [16].
[c] Calculated from ^{1}H NMR spectrometry.
[d] Obtained from GPC.
[e] Isolated yield.
[f] Pr is the probability of racemic linkages between monomer units and is determined from the methine region of the homonuclear decoupled ^{1}H NMR spectrum:8 (a),14 [mmm] = [2(1−Pr)^2 + Pr(1−Pr)]/2; [mrm] = [Pr^2 + Pr(1−Pr)]/2; [mmr] = [rmm] = [Pr(1−Pr)]/2; [rmr] = Pr^2/2 [15b].

information. To the best of our knowledge, only a few lithium sulfonamides have been structurally characterized [12].

3.2. Ring-opening polymerization of L-lactide catalyzed by 2–4

The catalytic activities of complexes **2**, **3** and **4** toward ROP of L-lactide using Z-ROH as an initiator were tested in the same conditions (Scheme 2, Table 2, entries 1–3). Time required for the completion of the ROP reaction was 2.5 h for complex **2**, 20 min for complex **3** and 10 min for **4**, respectively. This result revealed that the order of activity was **2** < **3** < **4** as expected. However, the PDI values of PLLA obtained from [^{RR}TBSC]$_2$Na$_4$[THF]$_4$ and [^{RR}TBSC]$_2$K$_4$[THF]$_4$, respectively (entry 2 and 3) were much higher than the PDI values obtained from [^{RR}TBSC]$_2$Li$_4$[THF]$_4$ (entry 1). In entries 2 and 3, the Mn(NMR) values were much higher than the Mn(theoretical) and Mn(GPC) values. The unexpected higher molecular weight could be due to the low initiation efficiency of the initiator/catalyst system.

Based on these experimental results, complex **2** was believed to be the most suitable catalyst for ROP of lactides. Therefore, the catalytic activity of complex **2** toward polymerization of LA was systematically investigated (Table 2, entries 4–6). A linear relationship between number-average molecular weight and monomer-to-initiator ratio ([M]/[I]) exists as shown in Fig. 2. The Mn values obtained from GPC is almost the same as the values obtained from ^{1}H NMR studies and the PDIs are very narrowed (1.07–1.13) implying the "living" character of the polymerization process. It is interesting to note that the catalytic reaction would be performed in a mild temperature without transesterification which is always observed in other lithium complexes [6b,13].

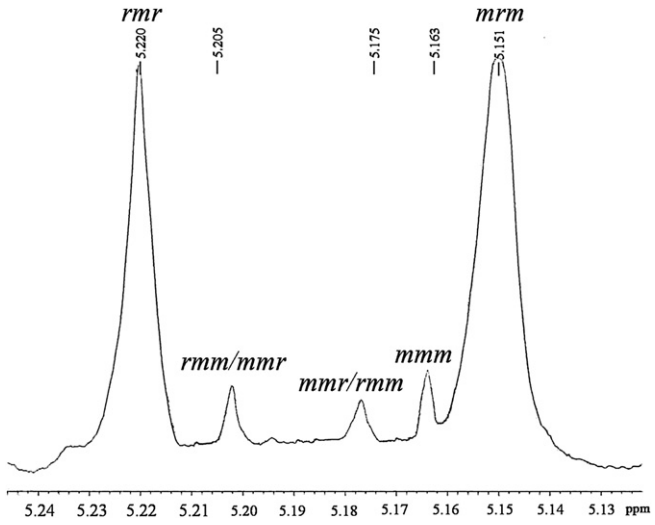


Fig. 3. Homonuclear decouple ^{1}H NMR spectrum of the methane region of heterotactic PLA prepared from the polymerization of *rac*-LA catalyzed by **2** in the presence of Z-ROH in THF at −30 °C.

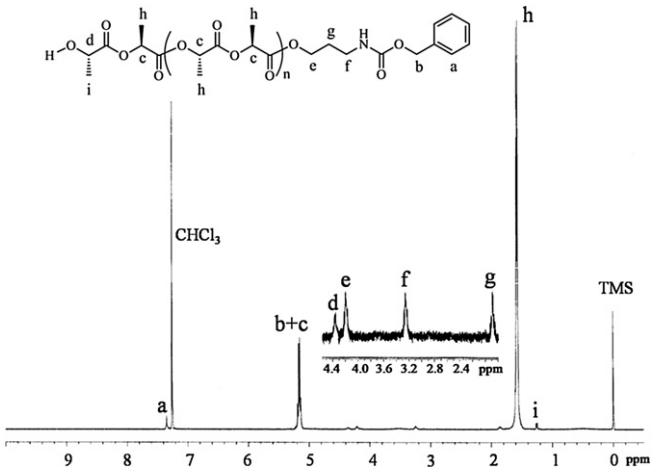


Fig. 4. ^{1}H NMR spectrum of polylactide bearing -NHZ end group (PLLA$_{25}$-NHZ) in $CDCl_3$.

3.3. Stereoselectivity of complex 2

It is well known that the physical and degradation properties of PLA are dramatically dependent on the stereochemistry of PLA [14]. For example, optical pure poly(L-lactide) is a semicrystalline polymer with a melting point around 180 °C. However, poly(*meso*-lactide) is an amorphous polymer. In addition, the equivalent mixture of poly (L-lactide) and poly(D-lactide) (PDLA) forms a crystalline stereocomplex with a melting temperature up to 230 °C. Due to these excellent properties, many efforts have focused on the development of metal complexes for high stereoselectivity of PLA [15]. Therefore, the polymerizations of RLA catalyzed by complex **2** were also performed, and the stereoselectivity was determined by the homonuclear decoupled ^{1}H NMR spectra. Experimental results show that by changing the solvent from toluene to THF at 28 °C, the *Pr* value is in somewhat increased from 0.54 to 0.62 but the reaction rate decreased dramatically (Table 3, entries 1 and 2) probably due to the coordination of THF to metal center slowing the reaction rate and therefore enhancing the stereoselectivity. After lowering the temperature from 28 to 0 °C, the *Pr* value increased from 0.62 to 0.71 (entry 3). Furthermore, the heterotactic PLA with *Pr* up to 0.82 can be achieved at −30 °C (Table 3, entry 4 and Fig. 3). The *Pr* values increase with the polymerization temperature decrease is probably due to decreasing reaction rate at low temperature which allows the complex to reorganize and enhancing the stereoselectivity.

Table 4
Characterization of poly(L-lactide) before and after deprotection.

Entry	Polymer	Before deprotection		After deprotection		
		Mn(GPC)[a]	PDI[b]	Mn(GPC)[a]	PDI[b]	Mn(NMR)[c]
1	PLLA$_{25}$	4000	1.13	3900	1.15	3900
2	PLLA$_{50}$	7900	1.09	7900	1.10	7900
3	PLLA$_{100}$	14600	1.07	14600	1.07	14700
4	PRLA$_{100}$	14700	1.04	14700	1.05	14500

[a] Obtained from GPC and corrected by timing 0.58 [16].
[b] Obtained from GPC.
[c] Calculated from ^{1}H NMR spectrum.

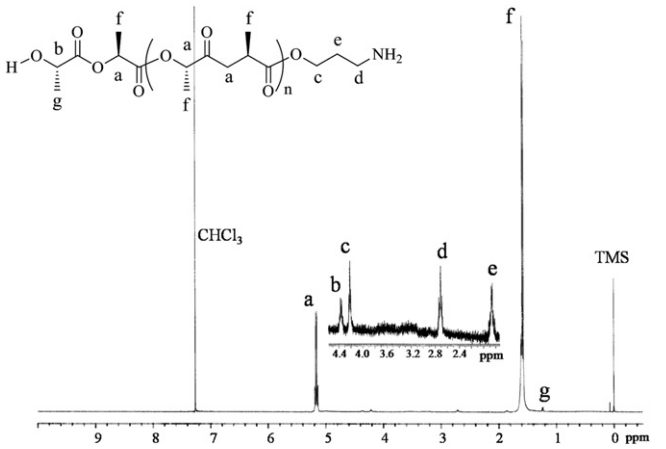


Fig. 5. ^{1}H NMR spectrum of polylactide containing $-NH_2$ end group ($PLLA_{25}$-NH_2) in $CDCl_3$.

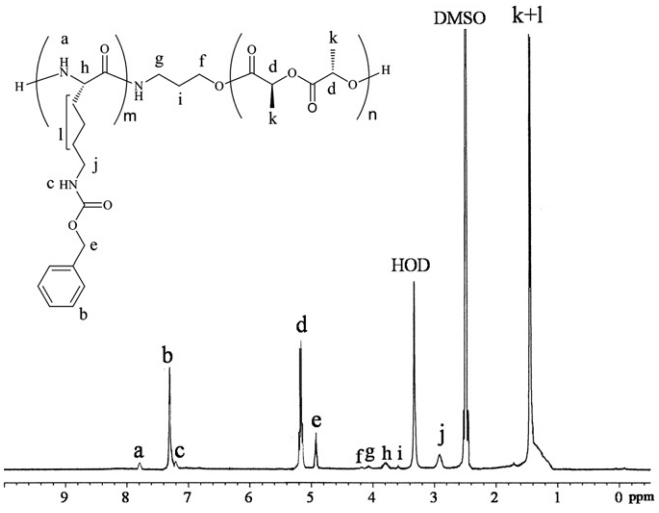


Fig. 6. ^{1}H NMR spectrum of the block copolymer $PLLA_{25}$-*b*-$PZLys_{10}$ in d_6-DMSO.

3.4. Syntheses of polylactide-b-N_ξ-(Z)-L-lysine block copolymer

A variety of PLLA-*b*-P(Z-Lys) block copolymers with a different PLLA/P(Z-Lys) ratio were easily prepared as shown in Scheme 2. The ^{1}H NMR spectra of $PLLA_{25}$ was chosen for illustration purposes. The first step was the deprotection of the PLA-NHZ (Fig. 4 shows the ^{1}H NMR spectrum of the polymer before deprotection) by treating the polymer with piperidine in CH_2Cl_2 in ambient temperature for 3.5 h. Then the Z group of the PLA was cracked given a PLA with the amine group in the chain end (Table 4). This can be verified by the comparison of the ^{1}H NMR spectra of $PLLA_{25}$-NHZ (Fig. 4) and $PLLA_{25}$-NH_2 (Fig. 5). It is worth noting that the molecular weight of the PLAs remained the same before and after the deprotection, indicating no side reactions occurred. However, the reaction time for the deprotection process must be limited under 4 h, or else degradation of the PLA occurs. This phenomenon can be detected by ^{1}H NMR spectroscopic studies.

The second step was the polymerization of Z-Lys-NCA using PLA-NH_2 as a macroinitiator. By treatment of PLA-NH_2 with Z-Lys-NCA in DMF at an atmosphere of N_2 gas, evolution of CO_2 was observed indicating the polymerization Z-Lys-NCA. The reaction time was determined according to ^{1}H NMR studies of PLLA-b-PZLys. A series of PLLA-b-PZLys with different PLLA/PZLys ratio was prepared as shown in Table 5. The theoretical values of Mn obtained from GPC were consistent with ^{1}H NMR results. The GPC spectrum of $PLLA_{25}$-b-$PZLys_{10}$ (Fig. 7) showed only one signal and the molecular weight was higher than its macroinitiator, $PLLA_{25}$ suggesting the formation of the block copolymer. Since self-assembly of PLLA-b-PZLys have occurred [5b], the Mn and PDI values obtained can not be considered reliable. ^{1}H NMR spectrometry was used to estimate the Mn values of PLLA-b-PZLys block copolymers as in previous reports [5]. The ^{1}H NMR spectrum of the $PLLA_{25}$-b-$PZLys_{10}$ is shown in Fig. 6 and the PLLA/PZLys ratio was determined by the integration of d and g. Experiment results revealed the polymerization of Z-Lys-NCA was well controlled and the molecular weight obtained was as expected.

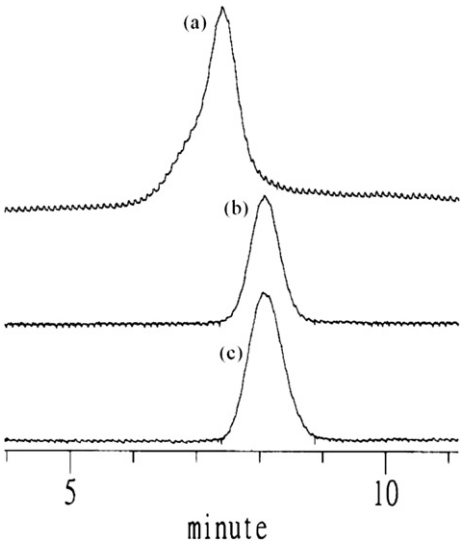


Fig. 7. GPC profiles of (a) the $PLLA_{25}$-b-$PZLys_{10}$ copolymer, (b) the $PLLA_{25}$-NH_2 (which was obtained after deprotection of $PLLA_{25}$-NHZ), and (c) the $PLLA_{25}$-NHZ before deprotection.

Table 5
Characteristics of different PLLA-b-PZLys copolymers.

Entry	Polymer	PLA		PZLys	
		Mn(GPC)[a]	Mn(NMR)[b]	Mn(Cal.)[c]	Mn(NMR)[b]
1	$PLLA_{25}$-$PZLys_{10}$	3900	3900	2600	2500
2	$PLLA_{25}$-$PZLys_{20}$	3900	3900	5200	5000
3	$PLLA_{50}$-$PZLys_{10}$	7900	7900	2600	2400
4	$PLLA_{50}$-$PZLys_{20}$	7900	7900	5200	5100
5	$PLLA_{100}$-$PZLys_{10}$	14600	14700	2600	2300
6	$PRLA_{100}$-$PZLys_{10}$	14700	14500	2600	2400

[a] Obtained from GPC and corrected by timing 0.58 [16].
[b] Obtained from ^{1}H NMR estimation [5d].
[c] Theoretical values of PZLys.

4. Conclusions

Three novel, low toxic metal complexes **2**, **3** and **4** are synthesized and characterized by spectroscopic methods. Single crystal X-ray structural determination of **2** reveals a rare cage structure composed of 7,8,7 rings. Catalytic results indicate that the lithium complex **2** is a suitable catalyst for ROP of lactides and has medium stereoselectivity in polymerization of *rac*-lactide. A variety of PLA-b-PZLys block copolymers can be prepared by the polymerization of Z-Lys-NCA, using PLA-NH_2 as a macroinitiator.

Acknowledgement

Financial support from the National Science Council of the Republic of China is gratefully appreciated.

Appendix. Supporting information

Supplementary data associated with article can be found in the online version, at doi:10.1016/j.polymer.2010.07.016.

References

[1] (a) Hovestadt W, Muller JA, Hocker H. Macromol Chem Rapid Commun 1990;11:271;
(b) Hutchinson FG, Furr BJA. In: Fawcett AH, editor. High value polymers. Cambridge: The Royal Society of Chemistry; 1991. Science Park;
(c) Hovestadt W, Keul H, Hocker H. Polymer 1992;33:1941;
(d) Swift G. Acc Chem Res 1993;26:105;
(e) Gref R, Minamitake Y, Peracchia MT, Trubetskov V, Torchilin V, Langer R. Science 1994;263:1600;
(f) Jeong B, Bae YH, Lee DS, Kim SW. Nature (London) 1997;388:860;
(g) Nakamura T, Shimizu Y, Takimoto Y, Tsuda T, Li YH, Kiyotani T, et al. J Biomed Mat Res 1998;42:475;
(h) Uhrich KE, Cannizzaro SM, Langer R, Shakesheff KM. Chem Rev 1999;99:3181;
(i) Langer R. Acc Chem Res 2000;33:94–101.
[2] (a) O'Keefe BJ, Hillmyer MA, Tolman WB. J Chem Soc Dalton Trans 2001;15:2215;
(b) Lindblad MS, Liu Y, Albertsson AC, Ranucci E, Karlsson S. Adv Polym Sci 2002;157:139;
(c) Dechy-Cabaret O, Martin-Vaca B, Bourissou D. Chem Rev 2004;104:6147;
(d) Wu JC, Yu TL, Chen CT, Lin CC. Coord Chem Rev 2006;250:602.
[3] (a) Deming TJ. Adv Drug Deliv Rev 2002;54:1145;
(b) Tomczak MM, Glawe DD, Drummy LF, Lawrence CG, Stone MO, Perry CC, et al. J Am Chem Soc 2005;127:12577;
(c) Haynie DT, Palath N, Liu Y, Li B, Pargaonkar N. Langmuir 2005;21:1136;
(d) Kricheldorf HR. Angew Chem Int Ed 2006;45:5752.
[4] (a) Klok HA, Lecommandoux S. Adv Mater 2001;13:1217;
(b) Boduch-Lee KA, Chapman T, Petricca SE, Marra KG, Kumta P. Macromolecules 2004;37:8959.
[5] (a) Kricheldorf HR, Hauser K. Biomacromolecules 2001;2:1110;
(b) Caillol S, Lecommandoux S, Mingotaud AF, Schappacher M, Soum A, Bryson N, et al. Macromolecules 2003;36:1118;
(c) Rong G, Deng M, Deng C, Tang Z, Piao L, Chen X, et al. Biomacromolecules 2003;4:1800;
(d) Fan Y, Chen G, Tanaka J, Tateishi T. Biomacromolecules 2005;6:3051;
(e) Schappacher M, Soum A, Guillaume SM. Biomacromolecules 2006;7:1373;
(f) Hellaye ML, Fortin N, Guilloteau J, Soum A, Lecommandoux S, Guillaume SM. Biomacromolecules 2008;9:1924;
(g) Yu H, Gu X, Shen X, Li Y, Duan Y. J App Polym Sci 2009;112:3371.
[6] (a) Ko BT, Lin CC. J Am Chem Soc 2001;123:7973;
(b) Hsueh ML, Huang BH, Wu J, Lin CC. Macromolecules 2005;38:9482;
(c) Chen HY, Zhang J, Lin CC, Reibenspiesa JH, Miller SA. Green Chem 2007;9:1038.
[7] (a) Ho RM, Chiang YW, Tsai CC, Lin CC, Ko BT, Huang BH. J Am Chem Soc 2004;126:2704;
(b) Ho RM, Lin FH, Tsai CC, Lin CC, Ko BT, Hsiao BS, et al. Macromolecules 2004;37:5985.
[8] Geall AJ, Blagbrough IS. Tetrahedron 2000;56:2449.
[9] Ben-Ishai D, Katchalski E. J Am Chem Soc 1952;74:3688.
[10] Takahashi H, Kawakita T, Ohno M, Yoshioka M, Kobayashi S. Tetrahedron 1992;48:5691–700.
[11] (a) Balsells J, Mejorado L, Phillips M, Ortega F, Aguirre G, Somanathan R, et al. Tetrahedron: Asymmetry 1998;9:4135;
(b) Haas A, Klare Ch, Betz P, Bruckmann J, Kru1ger C, Tsay YH, et al. Inorg Chem 1996;35:1918.
[12] (a) Dillon REA, Stern CL, Shriver DF. Chem Mater 2000;12:1122;
(b) Brouillette D, Irish DE, Taylor NJ, Perron G, Odziemkowski M, Desnoyers JE. Phys Chem Chem Phys 2002;4:6063;
(c) Zhao J, Song H, Cui C. Organometallics 2007;26:1947.
[13] Yu TL, Wu CC, Chen CC, Huang BH, Wu J, Lin CC. Polymer 2005;46:5909.
[14] (a) Tsujit H, Ikada Y. Macromolecules 1993;26:6918;
(b) MacDonald RT, McCarthy SP, Gross RA. Macromolecules 1996;29:7356;
(c) Huang J, Lisowski MS, Runt J, Hall ES, Kean RT, Buehler N, et al. Macromolecules 1998;31:2593;
(d) Sarasua JR, Prud'homme RE, Wisniewski M, Borgne AL, Spassky N. Macromolecules 1998;31:3895;
(e) Drumright RE, Gruber PR, Henton DE. Adv Mater 2000;12:1841.
[15] (a) Ovitt TM, Coates GW. J Am Chem Soc 1999;121:4072;
(b) Cheng M, Attygalle AB, Lobkovsky EB, Coates GW. J Am Chem Soc 1999;121:11583;
(c) Radano CP, Baker GL, Smith MR. J Am Chem Soc 2000;122:1552;
(d) Chamberlain BM, Cheng M, Moore DR, Ovitt TM, Lobkovsky EB, Coates GW. J Am Chem Soc 2001;123:3229;
(e) Zhong Z, Dijkstra PJ, Feijen J. J Am Chem Soc 2003;125:11291;
(f) Majerska K, Duda A. J Am Chem Soc 2004;126:1026;
(g) Hormnirun P, Marshall EL, Gibson VC, White AJP, Williams DJ. J Am Chem Soc 2004;126:2688;
(h) Nomura N, Ishii R, Yamamoto Y, Kondo T. Chem Eur J 2007;13:4433;
(i) Chisholm MH, Gallucci JC, Quisenberry KT, Zhou Z. Inorg Chem 2008;47:2613.
[16] (a) Baran J, Duda A, Kowalski A, Szymanski R, Penczek S. Macromol Rapid Commun 1997;18:325;
(b) Biela T, Duda A, Penczek S. Macromol Symp 2002;183:1;
(c) Save M, Schappacher M, Soum A. Macromol Chem Phys 2002;203:889.
[17] (a) Kricheldorf HR, Boettcher C, Tönnes KU. Polymer 1992;33:2817;
(b) Coudane J, Ustariz-Peyret C, Schwach G, Vert M. J Polym Sci Part A Polym Chem 1997;35:1651;
(c) Zell MT, Padden BE, Paterick AJ, Thakur KAM, Kean RT, Hillmyer MA, et al. Macromolecules 2002;35:7700.