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Living Polymerization of Lactide Using Titanium Alkoxide Catalysts

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Summary: Several titanium isopropoxides have facilitated the ring opening polymerization of *l*-lactide (LA) and *rac*-lactide in toluene solution at various polymerization temperatures via a coordination insertion mechanism. Depending on catalysts, the controlled/living poly(*l*-lactide), or the heterotactic-biased poly(*rac*-lactide) were obtained. The stereochemical microstructure of polylactide (PLA) was determined from homonuclear decoupled ^{1}H NMR spectral studies. Such spectra of PLA derived from *rac*-LA featured the characteristic five-methine resonance pattern, whereas corresponding spectra derived from *l*-LA exhibited only one methine peak.

Keywords: living polymerization; polylactide; ring opening polymerization; tacticity; titanium

Introduction

Polylactide (PLA) polymers are biodegradable, biocompatible and non-toxic materials that are proving to be important as, for example, controlled drug-release devices, absorbable sutures, medical implants for orthopedic use, disposable degradable plastic articles and scaffolds for tissue engineering.[1]

The design and synthesis of efficient metal alkoxide complex catalysts toward the ring-opening polymerization (ROP) of lactide (LA) has attracted considerable attention in the fields of catalysis, organometallic chemistry and polymer chemistry for the past few decades.[2] Many elements of metal and non-metal (e.g., of lithium, carbon, nitrogen, magnesium, aluminum, calcium, iron, zinc, lanthanide, zirconium, germanium and tin) have been used as catalytic centers in active LA polymerization, and many catalysts including those elements afford materials with controlled molecular weights and narrow molecular weight distributions (see Figure 1).

Despite the fact that outstanding initiators have been found among these systems for the polymerization of LA, the search for new catalysts for generating well-defined polylactide

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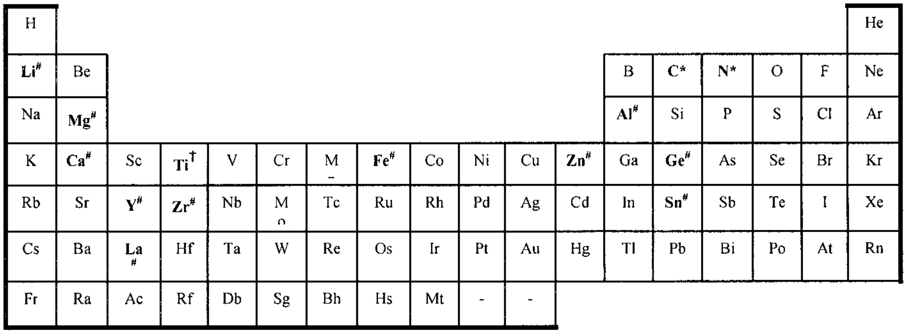

H																	He
Li#	Be											B	**C***	**N***	O	F	Ne
Na	**Mg#**											**Al#**	Si	P	S	Cl	Ar
K	**Ca#**	Sc	**Ti†**	V	Cr	M -	**Fe#**	Co	Ni	Cu	**Zn#**	Ga	**Ge#**	As	Se	Br	Kr
Rb	Sr	**Y#**	**Zr#**	Nb	M o	Tc	Ru	Rh	Pd	Ag	Cd	In	**Sn#**	Sb	Te	I	Xe
Cs	Ba	**La** **#**	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	-	-							

Figure 1. Metal (denoted by #) or non-metal (denoted by *) sources used in the ring-opening polymerization of lactide. No examples for living/controlled PLA catalysts including Ti (denoted by †) metal center before our works.

still remains of interest. In view of the well known significant number of similarities in the chemistries of tin and titanium, we were somewhat surprised to find that few explorations of titanium alkoxides as prospective catalysts in this polymerization process have been reported, although they are well known to homogeneously catalyze olefin polymerization.[3] In addition, the bond dissociation energy between metal atoms and oxygen atoms of the initiating group is important because this bond should be cut in the initial stage of the polymerization. The bond dissociation energy(ΔH_f^{298}) of Ti-O (662(16) kJ/mol) is somewhat higher than that of Sn-O (548(21) kJ/mol) and much lower than that of La-O (799(13) kJ/mol) or Y-O (715(30) kJ/mol).[4] This means titanium alkoxides could be good candidates for the ROP of LA because the Sn complex is a well-known catalyst in the industrial production of PLA. Table 1 summarizes the bond dissociation energy of various kinds of M-O bonds.

Table 1. Bond dissociation energy (ΔH_f^{298}, kJ/mol) of M-O bond.

Type of Bond	ΔH_f^{298}	Type of Bond	ΔH_f^{298}
Al-O	512(4)	La-O	799(13)
Sn-O	548(21)	Y-O	715(30)
Zn-O	284.1	Mg-O	394(35)
Fe-O	409(13)	Ti-O	662(16)

Recently, we reported that several titanium isopropoxides showed reasonably good catalytic activity in the solution and bulk homopolymerization of *l*-LA and *rac*-LA at various polymerization temperatures.[5] Details on the preparation and structure as well as catalytic characterization with respect to PLA polymerization of titanium isopropoxides have been and will be reported elsewhere. [5] We herein wish to report a brief overview of our studies demonstrated in pursuing a more precise understanding on the catalytic ability of titanium propoxides for the solution polymerization of LA. In addition, we wish to report the dependence of controlled polymerization on the the number of titanium metal centers in the complex. In this regard, we will use four kinds of titanium isopropoxides such as tetranuclear-, trinuclear-, dinuclear- and mononuclear-titanium isopropoxide as catalysts for the ROP of LA.

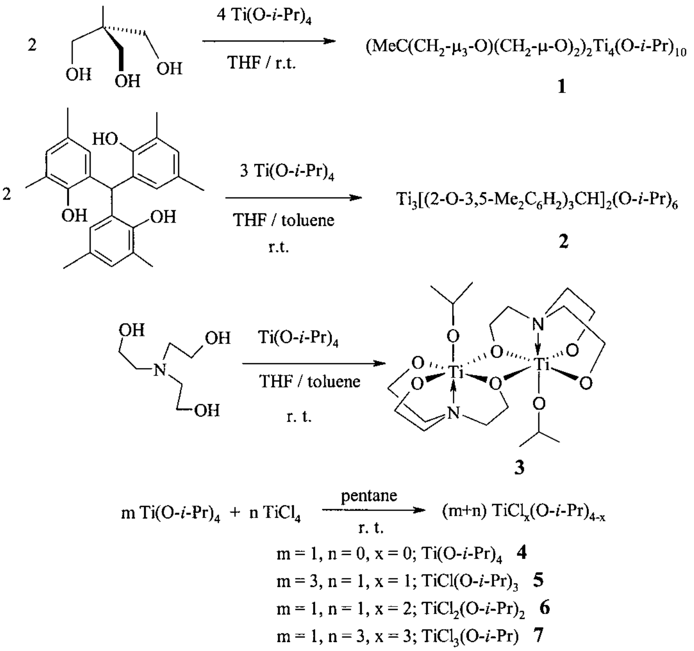

Figure 2. Synthetic route for the catalysts **1** – **7**.

Experimental

Preparation of Catalysts. Seven catalysts were prepared according to the literature procedure[5] and their synthetic routes are outlined in Figure 2. All reactions were carried out under argon using standard Schlenk and glove box techniques.[6]

Measurements. ^1H and $^{13}C\{^1H\}$ spectra were recorded at ambient temperature on a Varian VXR-400 NMR spectrometer using standard parameters. The chemical shifts are referenced to the residual peaks of $CDCl_3$ (7.24 ppm, ^1H NMR; 77.0 ppm, $^{13}C\{^1H\}$ NMR). Molecular weights of polymers were determined by gel permeation chromatography (GPC) at room temperature with THF as the eluent (1 mL/min) using a Waters 510 pump, a Waters 717 Plus Autosampler, four Polymer Laboratories PLgel columns (100, 500, 10^4, 10^5 Å) in series, and a Wyatt Optilab DSP interferometric refractometer as a detector. The columns were calibrated with polystyrene standards.

Results and Discussion

Tetranuclear titanium isopropoxide (1) for the controlled polymerization of LA.

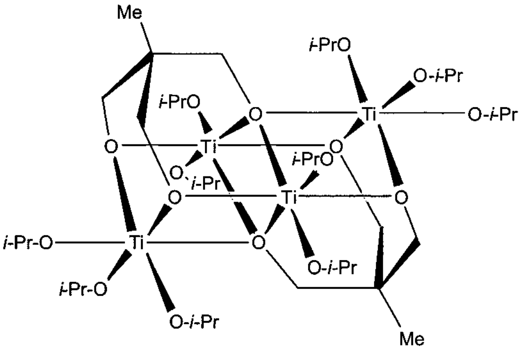

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Figure 3. Schematic drawing for compound **1**.

Compound **1** was chosen as a catalyst for the polymerization of LA because of the following advantages.

(1) Compound **1** contains ten O-*i*-Pr groups, one or more of which could act as an initiator for producing *iso*-propoxy terminated PLA. Many known multinuclear titanium complexes contain more than one type of alkoxy or aryloxy group (*e.g.*, OR and OR' or OAr and OAr') in their structures.

(2) Compound **1** has good solubility in almost all organic solvents including toluene, a solvent commonly used in LA polymerization, whereas many homoleptic compounds of the type $Ti_x(OR)_y$ and oxo-bridged alkoxides of the type $Ti_xO_y(OR)_z$

exhibit poor solubility in standard organic solvents.

(3) Compound **1** has reasonable stability in the solid state and in the solution state at ambient temperature over an extended period of time.

(4) Compound **1** has slight thermal instability in toluene at elevated temperatures. We anticipated that the thermal instability of **1** could play a role in enhancing the initiation rate during polymerization.

(5) Compound **1** is a kinetic product as well as a thermodynamic product. Whenever one equivalent of 1,1,1-*tris*(hydroxymethyl)ethane and excess Ti(O-*i*-Pr)$_4$ was mixed in THF solution, only **1** could be obtained (see Figure 2); however, the compositions of other homoleptic titanium cluster compounds are sensitive to the ratios of the starting materials.

Table 2 shows compound **1** has the catalytic activity for the solution polymerization of LA. Interestingly, the PDI values of PLA made with **1** (which range from 1.33 to 1.52) rise quite linearly with the number average molecular weight (Mn) and the [LA]/[Ti] ratio (Figure 4, Table 2, entries 1 – 4). This implies that the polymerization process is a reasonably controlled one. In addition, the linearity of the slope in Figure 4 indicates that all isopropoxide groups in **1** could be active in the initiation step. The high y intercepts observed for the lines in Figure 4 can be ascribed to a tendency for **1** to engage in a slow initiation step in solution.

Table 2. Solution Polymerization Data for LA in the Presence of **1**.[a]

run	type of LA	LA / Ti	Tp (°C)	time (h)	obtained polymer (g)	yield (%)	M_w [b]	M_n [b]	PDI [b]
1	*l*-LA	100	70	24	1.54	77	8,100	6,100	1.33
2	*l*-LA	200	70	24	1.71	86	13,300	9,100	1.46
3	*l*-LA	300	70	24	1.86	93	17,000	11,300	1.50
4	*l*-LA	400	70	24	1.97	99	20,700	13,600	1.52
5	*rac*-LA	100	70	24	1.50	75	8,800	7,200	1.22

[a] Polymerization conditions: 2 g of lactide, [LA]/[P] = 300, toluene 30 mL.

[b] Weight average molecular weight (M_w), number average molecular weight (M_n) and PDI (M_w/M_n) were determined by GPC.

It is worth noting that the ^{1}H NMR spectrum of PLA produced by **1** in solution shows an hydroxy as well as an *i*-Pr ester chain terminus, suggesting that initiation occurs through insertion of the O-*i*-Pr group from compound **1** into LA. This is further supported by a homonuclear decoupled ^{1}H NMR spectrum which reveals only one resonance and five resonances in the lactide methine region for poly(*l*-LA) and poly(*rac*-LA), respectively.[7]

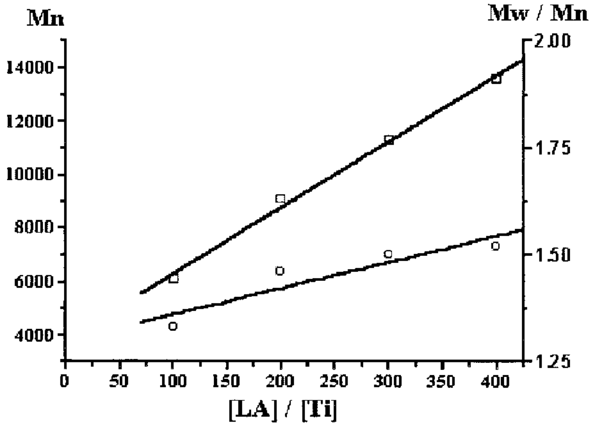
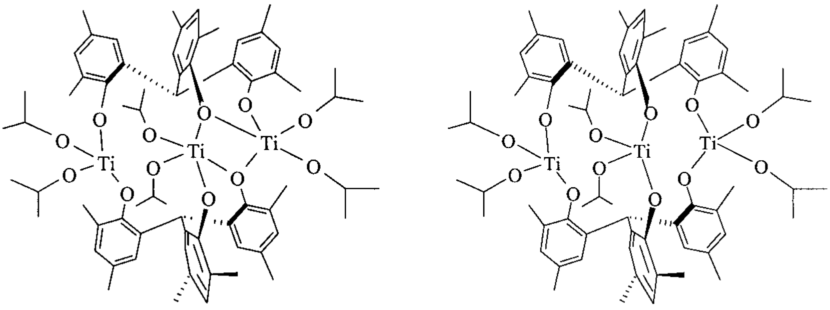


Figure 4. Plot of M_n (upper line) and PDI (lower line) vs polystyrene standards for PLA as a function of [LA]/[Ti] at 70 °C in toluene in the presence of **1**.

Trinuclear titanium isopropoxide (2) for the controlled polymerization of LA. Like compound **1**, compound **2** is a kinetic product as well as a thermodynamic product. Only **2** is obtained when one equivalent of tris(2-hydroxy-3,5-dimethylphenyl)methane and excess Ti(O-*i*-Pr)$_4$ was mixed in a THF solution (see Figure 2). **2** also has good solubility in normal organic solvents. Interestingly, the initial solution ^{1}H and ^{13}C spectra of **2(solid)**, determined by X-ray crystallography, in C_6D_6 are consistent with C_3 symmetry (Figure 5(a)). Although this result is also in accord with **2(soln)/2(solid)** fluxionality, new peaks appear over time in the ^{1}H NMR spectrum of **2(soln)** in C_6D_6, at the expense of the resonances in the initial spectrum until only a spectrum in agreement with **2(solid)** is present. Experiments aimed at understanding the origin of this interesting phenomenon are under way.

Complex **2** was used as a catalyst in the ring opening polymerization of *l*-LA in toluene solution at 130°C [where the **2(soln)** structure is presumed to dominate] using a [LA]/[**2**] ratio of 200 with [LA] = 2.8 M. Table 3 shows compound **2** has considerable catalytic activity for the solution polymerization of LA.



2(solid) **2(soln)**

Figure 5. Schematic drawing for (a) compound **2(solid)** determined by X-ray crystallography and (b) the proposed structure of **2(soln)**.

Table 3. Solution Polymerization Data for LA in the Presence of **2**.

run [a]	type of LA	time (min)	yield (%) [b]	conv. (%) [c]	M_n [d]	PDI [d]
1	*l*-LA	120	15	18	4,900	1.15
2	*l*-LA	240	25	32	9,000	1.12
3	*l*-LA	300	30	40	11,400	1.12
4	*rac*-LA	300	41	50	12,100	1.16
5	*l*-LA	360	42	45	12,600	1.16
6	*l*-LA	390	45	53	14,900	1.14
7	*l*-LA	510	54	67	18,000	1.36
8	*l*-LA	720	81	95	25,400	1.35

[a] Polymerization conditions: 2 g of lactide, polymerization temperature = 130°C, [LA]/[Ti] = 200, toluene 5 mL. [b] Isolated yield. [c] Conversion determined via intergration of methine resonances of LA and PLA ($CDCl_3$). [d] Weight average molecular weight (M_w), number average molecular weight (M_n) and PDI (M_w/M_n) were determined by GPC.

Greater than 90% conversion to PLA occurred within 12 h. The level of polymerization control was high, as was shown by the linear increase in M_n with conversion and the low polydispersity index (PDI) of the polymer produced as shown in Figure 6. However, the PDI values also increased with conversion. It is worth noting that after workup, the ^1H NMR spectrum of the PLA produced with **2(soln)** shows an hydroxy as well as an *i*-Pr ester chain terminus, suggesting that initiation occurs through insertion of the O-*i*-Pr group from compound **2(soln)** into LA via a coordination insertion mechanism. This is further supported by a homonuclear decoupled ^1H NMR spectrum which reveals only one resonance in the LA methine region for poly(*l*-LA). It is worth noting that epimerization of the chiral centers in poly(*l*-LA) does not occur, according to this spectrum.

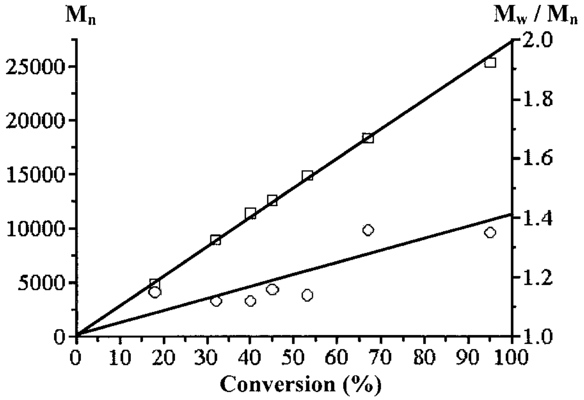


Figure 6. Plot of Mn (open squares, GPC) vs. monomer conversion (determined by ^1H NMR spectroscopy), with polydispersity indices indicated by open circles (GPC).

Dinuclear titanium isopropoxide (3) for the controlled polymerization of LA. Many elements in the periodic table have been employed as core atoms atranes (traditionally understood to posses three five-membered rings) synthesized from triethanolamine, including the main group and transition metal elements.[8] Especially, titanatranes have usually been used in the field of olefin polymerization catalysis.[9] In this regard, compound **3** was selected as the catalyst for the ROP of LA. Interestingly, the X-ray analysis of **3** reveals that its molecular structure features a solid-state dinuclear property with an oxo bridge (see Figure 7). The four oxygen atoms of the ethylene arms form the equatorial plane and the axial sites are occupied by a nitrogen atom of the tripodal ligand, triethanolamine, and an oxygen atom of the isopropoxide group.

Table 4 shows compound **3** has catalytic activity for the solution polymerization of LA. PLA polymers with narrow PDI values were obtained from reactions conducted with a fixed [LA]/[Ti] ratio of 300 at 70 °C. The linear relationship between Mn and the conversion shown in Figure 8 (Table 4, entries 1 – 5), implies that polymerization was substantially controlled. At the higher polymerization temperature of 130 °C and at the higher [LA]/[Ti] ratio of 300, the PDI value for PLA using initiator **3** increases (M_n = 25,400, PDI = 1.35, Table 4 entry 6), but a significant increase in polymer yield did not occur.

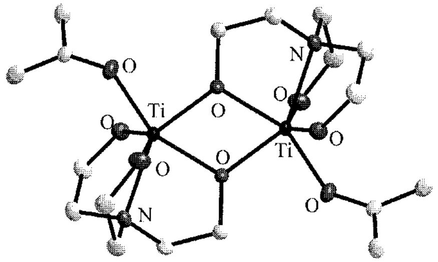


Figure 7. X-ray structure for **3**.

Table 4. Solution Polymerization Data for LA in the Presence of **3**.

entry	monomer type[a]	[LA] / [Ti]	T[b] (°C)	Time (h)	Yield[c] (%)	M_n[e]	PDI[e]
1	*l*-LA	300	70	3	7 (8)[d]	2,800	1.09
2	*l*-LA	300	70	10	21 (25)[d]	10,000	1.15
3	*l*-LA	300	70	14	29 (31)[d]	12,500	1.08
4	*l*-LA	300	70	17	28 (35)[d]	13,300	1.07
5	*l*-LA	300	70	36	58 (70)[d]	28,000	1.03
6	*l*-LA	300	130	24	81	25,400	1.35

[a] Solvent: 30 mL of toluene, 2 g of LA. [b] Oil bath temperature: 130 (± 3) °C. [c] Isolated Yield.
[d] Conversion determined via integration of the methine resonances of LA and PLA ($CDCl_3$).
[e] The weight average molecular weights (M_w), the number average molecular weights (M_n) and the polydispersity indices (PDI = M_w/M_n) were determined by GPC.

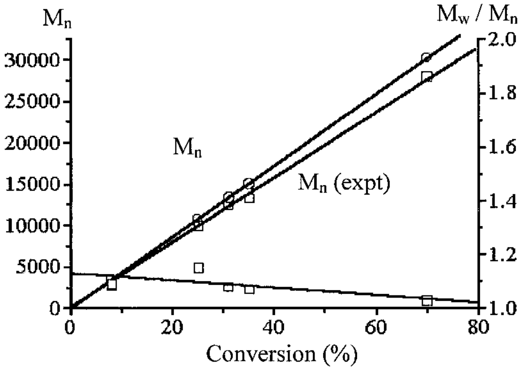


Figure 8. Plot of M_n and PDI values (employing polystyrene standards) for PLA as a function of conversion at 70 °C in toluene with [LA]/[Ti] = 300 using **3** as the catalyst. M_n(theory) was calculated from the formula of (M_w of LA) x ([LA]/[Ti]) x (conversion).

Mononuclear titanium isopropoxides (4 – 7) for heterotactic-biased PLA. Compounds **5** - **7** were obtained by the reaction of **4** with the appropriate amount of $TiCl_4$ in pentane at room temperature. Unlike slightly viscous **5**, compounds **6** and **7** precipitated as white solids within 20 minutes after combination of the reactants. To avoid generation of by-products and mixtures of **5** – **7**, a solution of $TiCl_4$ in dry pentane was added dropwise to exactly the appropriate number of equivalents of **4** in pentane while stirring rapidly at room temperature for 10 min. After washing thoroughly with cold pentane, these titanium compounds were used as catalysts for making PLA or as starting materials for other titanium alkoxides. Compounds **5** – **7** were soluble in toluene, dichloromethane and ether.

Table 5. Solution polymerization of LA using **4** – **7**.

entry	catalyst	Lactide type	[LA]/ [Ti]	T[c] (°C)	Time (h)	Yield[d] (%)	M_n[f]	PDI[f]
1	**4**	*l*-LA[a]	300	70	24	85	14,300	2.01
2		*rac*-LA[a]	300	70	24	70	9,200	1.83
3	**5**	*l*-LA[b]	200	70	4	15 (20)[e]	4,200	1.10
4		*l*-LA[b]	200	70	16	55 (58)[e]	12,800	1.06
5		*l*-LA[b]	200	70	20	65 (69)[e]	15,100	1.08
6		*l*-LA[b]	200	70	24	81 (85)[e]	18,400	1.10
7		*l*-LA[b]	300[g]	70	36[g]	78	27,300	1.12
8		*rac*-LA[b]	200	70	24	87	16,300	1.07
9	**6**	*l*-LA[a]	200	70	6	26	5,600	1.10
10		*rac*-LA[a]	200	70	6	28	5,200	1.08
11	**7**	*l*-LA[a]	300	130	24	53	51,100	1.20
12		*rac*-LA[a]	300	130	24	48	37,000	1.20

[a] Solvent: 40 mL of toluene, 2 g of LA. [b] Solvent: 30 mL of toluene, 2 g of LA. [c] Oil bath temperature: 130 (± 3) °C. [d] Isolated Yield. [e] Conversion determined via integration of the methine resonances of LA and PLA ($CDCl_3$). [f] The weight average molecular weights (M_w), the number average molecular weights (M_n) and the polydispersity indices (PDI = M_w/M_n) were determined by GPC. [g] Continuation polymerization after equibrium was estabilished (see main text).

Even though the polymerizations were carried out in toluene, **4** gave rise to PLA with a high PDI value, which may be associated with the dissociation of more than one O-*i*-Pr group from **4**, thus generating more than one initiating site (Table 5, entries 1 – 2). On the other hand, **5** and **6**, which contain more than one chlorine atom, generated PLA with very narrow PDI values (Table 5, entries 3 –10). This suggests that the presence of chlorine atoms in chlorotitanium alkoxides may permit only one O-*i*-Pr group to dissociate. In keeping with this suggestion, the methine region in the homonuclear decoupled ^1H NMR spectrum of poly(*rac*-LA) derived from **7** displayed *rmr* and *mrm* tetrads that were much more intense than expected [as was also observed under bulk polymerization conditions for this catalyst (Figure 9(d))]. In progressing from **4** to **7** (Table 5, entries 2, 8, 10 and 12), the intensity in the ^1H NMR spectra of heterotactic-biased poly(*rac*-LA) increased. This result is consistent with that predicted from a Bernouillian analysis of totally random poly(*rac*-LA).[7] The methine region in the homonuclear decoupled ^{1}H NMR spectrum of poly(*rac*-LA) derived from **6** and **7** displays *rmr* and *mrm* tetrads which are much more intense than expected. These observations are consistent with a heterotactic-biased poly(*rac*-LA) since the *rmr* microstructure can only arise from two consecutive D-L or L-D interchanges. Each *rmr* tetrad is accompanied by two *mrm* tetrads in agreement with the NMR integration (Table 5, entries 10 and 12). The preference for heterotacticity in our poly(*rac*-LA) is not as strong as reported previously by Coates et al.[10a] and Kasperczyk et al.,[10b] but our tacticity bias is similar to that reported by Gibson and coworkers.[10c]

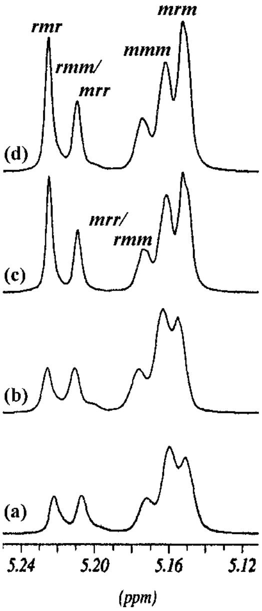


Figure 9. Methine region of homonuclear decoupled ^{1}H-NMR spectra for poly(*rac*-LA) produced by (a) **4**, (b) **5**, (c) **6** and (d) **7** under bulk polymerization conditions.

For a further investigation of the degree of control in these polymerizations, we selected catalyst **5**. The PDI values of PLA obtained with **5** ranged from 1.06 to 1.12. These values vary linearly with M_n and with the conversion as shown in Figure 10(a) (Table 5, entries 3 – 6), implying a very substantially controlled polymerization process. The controlled nature of these polymerizations was further confirmed by a polymerization resumption experiment that resulted in further ROP of LA. In this experiment (Table 5, entry 7), an additional 100 equivalents of LA monomer was added to the reaction medium corresponding to that of entry 6 in Table 5. The GPC traces in Figure 10(b) show that the molecular weight increased for the final polymer (peak e, M_n = 27,300, PDI = 1.12) relative to the initial product (peak d, M_n = 18,400, PDI = 1.10).

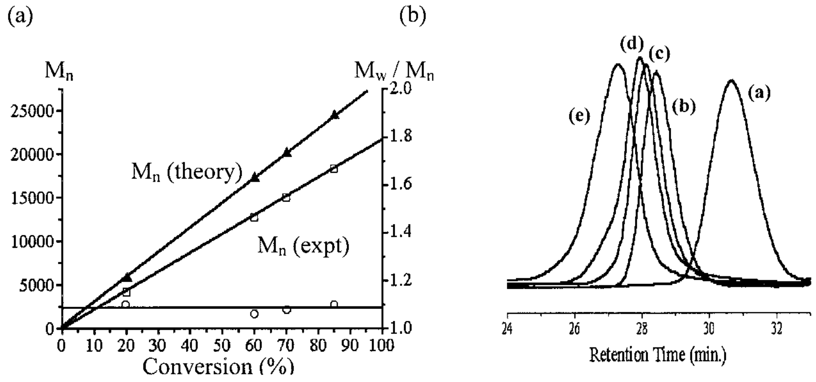


Figure 10. (a) Plot of M_n and PDI values (employing polystyrene standards) for PLA as a function of conversion at 70 °C in toluene with [LA]/[Ti] = 200 using **2** as the catalyst. M_n(theory) was calculated from the formula (M_w of LA) x ([LA]/[Ti]) x (conversion). (b) GPC traces of isolated PLA produced with **2** ([LA]/[Ti] = 200) at (a) 4 hr, (b) 16 hr, (c) 20 hr, (d) 24 hr and (e) 36 hr. The corresponding PDI values are 1.10, 1.06, 1.08, 1.10 and 1.12, respectively.

Conclusion

PLA was prepared by the ROP of LA via a coordination-insertion mechanism by four kinds of titanium isopropoxides containing from one titanium to four titaniums within the complex. Controlled/living polymerization has nothing to do with the number of metal centers within the complex; however, suitable selection of titanium alkoxides containing non-labile ligands yielded tailor-made PLA.

Acknowledgements

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