Use of pyrazoles as ligands greatly enhances the catalytic activity of titanium iso-propoxide for the ring-opening polymerization of 1-lactide: a cooperation effect†

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Using TiOiPr4 with a pyrazole ligand for one-pot LA polymerization improved catalytic activity compared with using TiOiPr4 only. At 60 °C, TiOiPr4 with furPz exhibited a higher catalytic activity (approximately 3-fold) than TiOiPr4. At room temperature, TiOiPr4 with BuPz exhibited a higher catalytic activity (approximately 17-fold) than TiOiPr4. High molecular mass PLA ($M_n$GPC = 51,100, and $Đ$ = 1.10) could be produced by using TiOiPr4 with furPz in melt polymerization ([TiOiPr4] : [furPz] = 1000 : 1 : 1 at 100 °C, 240 min). The crystal structure of MePz2Ti2OiPr7 revealed the cooperative activation between two Ti atoms during LA polymerization.

1. Introduction

Petrochemical plastics are extensively used in modern society; however, widely discarded plastic waste pollutes the environment continually because bacteria cannot decompose it naturally within a short period. To accelerate the environmental degradation of polymers, biodegradable polylactide (PLA) has been developed for creating a sustainable society. PLA-based biomaterials are used in various fields because of their biocompatible and permeable physical properties. One of the methods of PLA synthesis is the Lewis acidic metal-catalyzed ring-opening polymerization (ROP) of cyclic esters.

For biomaterials, metal residuals present in resulting PLA are a serious problem, and using catalysts with non-cytotoxic metals is a straightforward approach to solving this problem. Because of the non-cytotoxic property and strong Lewis acidity of titanium, Ti complexes are commonly used catalysts in LA ROP. Numerous Ti complexes bearing various ligands such as calix[4] arene, Schiff base, salen, salan, phenolate, aminophenolate, benzotriazole phenolate, phosphinophenolate, thiophenolate, bis-phenolate-N-heterocyclic carbene, pyridonate, and pyrrolide have been reported to exhibit considerable catalytic activity or controllability, which is contributed by ligands. However, for most studies, focusing on materials is inconvenient, because the synthesis and purification of Ti catalysts are time-consuming processes. An efficient method of fabricating PLA without time-consuming Ti catalyst-base synthesis and purification is necessary. Herein, commercially available Ti alkoxides was also used catalysts for cyclic esters polymerization. Recently, dinuclear Ti complexes bearing hydrazine-bridging Schiff base ligands (Fig. 1) were reported to exhibit

Fig. 1 Strategy of dinuclear Ti complexes in LA polymerization inspired by the literature.
a high catalytic activity of LA polymerization because of the cooperation between two Ti atoms. Based on this study, if pyrazole is added to LA polymerization with titanium iso-propoxide (TiOiPr4) as a catalyst, bringing two Ti atoms close together to enable dinuclear cooperation is possible. Following this strategy, several pyrazole derivatives (Fig. 2) were added to LA polymerization with a TiOiPr4 catalyst to investigate dinuclear cooperation relative to the mixture of TiOiPr4 and pyrazole.

2. Experimental section

2.1 Chemicals

Standard Schlenk techniques and a N2-filled glovebox were used all over the isolation and treatment of all the compounds. Solvents, L-lactide (LA), and deuterated solvents were purified prior to use. LA, thioPz, MePz, BuPz, PhPz, furPz, thioPz, Tz, pyPz, and MeOPz were purchased from Aldrich. ClPz was prepared following literature procedures. 1H and 13C NMR spectra were recorded on a Varian Gemini 2000-200 (200 MHz for 1H and 50 MHz for 13C) spectrometer. Chemical shifts (in ppm) of 1H NMR spectra were referenced to tetramethylsilane (δ = 0 ppm) in CDCl3, as an internal standard, and chemical shifts of 13C NMR spectra were reported in ppm referenced to the center line of a triplet at 77.0 ppm of CDCl3. Microanalyses were performed using a Heraeus CHN-O-RAPID instrument. The gel permeation chromatography (GPC) measurements were performed on a Jasco PU-2080 PLUS HPLC pump system equipped with a differential Jasco RI-2031 PLUS refractive index detector using THF (HPLC grade) as an eluent (flow rate 1.0 mL min⁻¹ at 40 °C). The chromatographic column was JORDI Gel DVB 10⁻⁵ A, and the calibration curve was made by primary polystyrene standards to calculate molar masses of PLA. Values of Mn, were obtained through gel permeation chromatography (GPC) times 0.58.

2.2 Synthesis of MePz2Ti2OiPr7

A mixture of MePz (0.96 g, 10 mmol) and TiOiPr4 (2.84 g, 10 mmol) in toluene (20 mL), was stirred at room temperature for 24 h. Volatile materials were removed under vacuum to give light yellow mud, and then hexane was transferred to be the suspension. The light-yellow powder was obtained after filtering, and was recrystallized in toluene to form the crystal. Yield: 1.15 g (33%). 1H NMR spectrum (CDCl3, 200 MHz, Fig. S1†) was complex, but it could be assigned that two β-Hs were at 5.59 and 5.43 ppm, and the methine protons of

![Pyrazole derivatives used in this study.](Image)

Table 1. L-Lactide polymerization with the mixture of TiOiPr4 and pyrazole derivatives as catalysts in toluene

| Entry | Ligand [TiOiPr4 : L] | Time (min) | Conv. (%) | M_w (g mol⁻¹) | M_n (g mol⁻¹) | kobs (min⁻¹) |
|-------|---------------------|------------|-----------|---------------|---------------|--------------|
| 1a    | thioPz (1 : 0.5)    | 50         | 85        | 3900          | 3300          | 1.30         |
| 2a    | thioPz (1 : 1)      | 45         | 88        | 4700          | 4600          | 1.51         |
| 3a    | thioPz (1 : 2)      | 125        | 84        | 7000          | 6000          | 2.10         |
| 4a    | thioPz (1 : 4)      | 220        | 99        | 7400          | 6500          | 2.02         |
| 5     | thioPz (1 : 1)      | 10         | 87        | 2300          | 2200          | 1.27         |
| 6     | L free              | 22         | 92        | 2100          | 1600          | 1.75         |
| 7     | ClPz (1 : 1)        | 13         | 94        | 7100          | 4400          | 1.68         |
| 8     | ClPz (1 : 1)        | 14         | 89        | 1900          | 1800          | 1.13         |
| 9     | BuPz (1 : 1)        | 9          | 95        | 2100          | 1700          | 1.23         |
| 10    | furPz (1 : 1)       | 10         | 94        | 2500          | 2000          | 1.25         |
| 11    | furPz (1 : 1)       | 5          | 86        | 2200          | 2100          | 1.23         |
| 12    | furPz (1 : 1)       | 15         | 88        | 2000          | 2000          | 1.18         |
| 13    | furPz (1 : 1)       | 10         | 92        | 6500          | 3000          | 1.38         |
| 15    | Tz (1 : 1)          | 20         | 87        | 1900          | 1800          | 1.12         |
| 16    | MePz (1 : 1)        | 16         | 88        | 1800          | 1700          | 1.10         |
| 17a   | MePz (1 : 1)        | 25         | 89        | 3900          | 3600          | 1.27         |
| 18a   | MePz (1 : 1)        | 24         | 80        | 5300          | 4300          | 1.27         |
| 19a   | MePz (1 : 1)        | 45         | 87        | 8500          | 7900          | 1.32         |
| 20a   | MePz (1 : 1)        | 95         | 90        | 13 100        | 12 500        | 1.49         |
| 21a   | L—H-TiOPr6 2a        | 50         | 89        | 3100          | —             | 1.25         |

* In general, the reaction was carried out in 5 mL toluene with [LA] = 2 M at 60 °C for LA polymerization ([LA] [TiOiPr4]: 50 : 1). The data were determined using 1H NMR analysis. Values of M_n, were corrected considering Mark−Houwink factor (0.58) from poly styrene standards in THF.

### References

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isopropyl oxide were at 4.92–4.28 ppm, and dimethyl groups of MePz were at 2.39 and 2.14 ppm.

### 3. Results and discussion

#### 3.1 Polymerization of LA

Table 1 presents the conditions for optimizing LA polymerization by using a mixture of TiOiPr4 and thioPz as the catalyst. Entries 1–5 in Table 1 reveal that the 1 : 1 ratio of TiOiPr4 and thioPz ([LA] : [TiOiPr4] : [thioPz] = 1 M, [TiOiPr4] = 10 mM) exhibited the fastest polymerization rate. When [LA] was increased to 2 M with 40 mM of [TiOiPr4], after 10 min, the conversion became 87%. Under this condition ([LA] = 2 M, [LA] : [TiOiPr4] : [thioPz] = 50 : 1 : 1 in 5 mL toluene), various pyrazole derivatives were used to analyze LA polymerization, and all pyrazole derivatives improved the catalytic activity of TiOiPr4, except thioPz and Tz in the following order: furPz > thioPz > PhPz > MeOPz > thioPz = thioPz > ClPz > PhPz > Tz. Although MePz improved the catalytic activity of TiOiPr4, it provided low controllability (dispersity, D = 1.68). To solve this problem, the TiOiPr4 concentration was decreased from 20 to 13.4 mM, and the D value was decreased to 1.10. LA polymerization using TiOiPr4 (13.4 mM) as a catalyst with MePz was systematically investigated with the [LA]/[TiOiPr4] ratio ranging from 50 to 300 (entries 16–20). The results revealed that LA polymerization was controllable, confirmed by the linear relationship between [LA]0/[TiOiPr4] and Mn,pc (Fig. 3). However, the controllability in the [LA]/[TiOiPr4] ratio of 300 (D = 1.49, entry 20 in Table 1) was low, and it may be ascribed to transesterification because of the long polymerization time at 60 °C. Fig. 3 revealed that four isopropoxides of TiOiPr4 could be initiators to initiate LA. TiOiPr4 with thioPz exhibited a higher catalytic activity (3.5 folds) in LA polymerization than L-H-TiOPr6 (entry 21)

A survey of LA ROP using Ti complexes as catalysts revealed that few Ti catalysts could polymerize LA at room temperature. Therefore, LA polymerization was conducted at room temperature (Table

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### Table 2  L-Lactide polymerization with the mixture of TiOiPr4 and pyrazole derivatives as catalysts in CH2Cl2 at room temperature$a$

| Entry | Ligand (TiOiPr4 : L) | Time (min) | Conv. $^b$ (%) | $M_{n,pc}^c$ (g mol$^{-1}$) | $M_{n,pc}^d$ (g mol$^{-1}$) | $D^e$ | $k_{obs} \times 10^{3}$ (min$^{-1}$) |
|-------|----------------------|------------|----------------|-----------------------------|-----------------------------|------|-------------------------------|
| 1     | L free               | 4290       | 85             | 1600                        | 1700                        | 1.25 | 0.3                           |
| 2     | furPz                | 450        | 80             | 900                         | 1000                        | 1.12 | 3.0                           |
| 3     | MePz                 | 1670       | 85             | 1300                        | 1200                        | 1.08 | 0.9                           |
| 4     | ClPz                 | 720        | 85             | 1100                        | 1200                        | 1.08 | 2.0                           |
| 5     | thioPz               | 370        | 88             | 1100                        | 1000                        | 1.07 | 5.0                           |
| 6     | ClPz                 | 1335       | 89             | 1400                        | 1200                        | 1.12 | 1.0                           |
| 7     | furPz                | 540        | 90             | 1000                        | 1100                        | 1.08 | 4.0                           |
| 8     | thioPz               | 660        | 84             | 1200                        | 1200                        | 1.08 | 2.0                           |
| 9     | thioPz               | 660        | 87             | 1200                        | 1100                        | 1.08 | 2.4                           |
| 10    | MePz                 | 660        | 85             | 1200                        | 1200                        | 1.08 | 2.0                           |
| 11    | Tz                   | 1670       | 87             | 1400                        | 1300                        | 1.11 | 0.7                           |
| 12$^a$| furPz                | 315        | 95             | 1400                        | 1200                        | 1.08 | —                             |
| 13$^a$| furPz                | 310        | 88             | 1600                        | 1500                        | 1.09 | —                             |
| 14$^a$| furPz                | 450        | 88             | 1800                        | 1800                        | 1.11 | —                             |
| 15$^a$| furPz                | 510        | 89             | 2100                        | 2200                        | 1.27 | —                             |
| 16$^a$| furPz                | 390        | 84             | 700                         | 800                         | 1.13 | —                             |
| 17$^a$| +100 LA              | 895        | 92             | 1800                        | 1900                        | 1.09 | —                             |
| 18$^a$| +100 LA              | 1495       | 83             | 2300                        | 2200                        | 1.16 | —                             |
| 19$^a$| +100 LA              | 2000       | 72             | 2600                        | 2600                        | 1.14 | —                             |
| 20$^a$| furPz                | 240        | 52             | 31100                       | 31100                       | 1.10 | —                             |
| 21$^a$| L free               | 240        | 52             | 31100                       | 31100                       | 1.26 | —                             |

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*a In general, the reaction was carried out in 2.5 mL CH2Cl2 with [LA] = 2 M at room temperature for LA polymerization ([LA] : [TiOiPr4] = 25 : 1).

*b The data were determined using $^1$H NMR analysis. $^c$ Values of $M_{n,pc}$ were corrected considering Mark–Houwink factor (0.58) from polystyrene standards in THF. $^d$ [LA] : [TiOiPr4] : [furPz] = 37.5 : 1 : 1, [TiOiPr4] = 0.08 M in 2.5 mL CH2Cl2. $^e$ [LA] : [TiOiPr4] : [furPz] = 43.75 : 1 : 1, [TiOiPr4] = 0.08 M in 2.5 mL CH2Cl2. $^f$ [LA] : [TiOiPr4] : [furPz] = 50 : 1 : 1, [TiOiPr4] = 0.08 M in 2.5 mL CH2Cl2. $^g$ [LA] : [TiOiPr4] : [furPz] = 62.5 : 1 : 1, [TiOiPr4] = 0.08 M in 2.5 mL CH2Cl2. $^h$ [LA] : [TiOiPr4] : [furPz] = 25 : 1 : 1, [TiOiPr4] = 0.08 M in 2.5 mL CDCl3. $^i$ After the conversion of the reaction (entry 16) was 84%, LA (0.72 g) was transferred into the solution. $^j$ After the conversion of the reaction (entry 17) was 83%, LA (0.72 g) was transferred into the solution. $^k$ [TiOiPr4] : [furPz] = 1000 : 1, melt reaction at 100 °C. $^l$ [LA] : [TiOiPr4] = 1000 : 1, melt reaction at 100 °C.
to determine whether the addition of pyrazole ligands can enhance the catalytic ability of TiOiPr₄ at room temperature. In addition, reducing the polymerization temperature may improve the controllability of Ti catalysts.

All pyrazole derivatives improved the catalytic activity of TiOiPr₄, in the following order: BuPz > furPz > Hpz > pyPz > ClPz = thioPz = MeOPz > PhPz > MePz > Tz (Table 2). In the CH₂Cl₂ solution, the pyrazole ligand provided the benefit of considerable improvement of the catalytic reaction. For example, kₖobs of TiOiPr₄ with BuPz was 17 times higher than that of TiOiPr₄, and kₖobs of TiOiPr₄ with furPz was 13 times higher than that of TiOiPr₄. In addition, the controllability of TiOiPr₄ with all pyrazole derivatives was improved (D = 1.07–1.12). Although TiOiPr₄ with BuPz revealed the highest polymerization rate, BuPz is overly expensive. Therefore, furPz was used as a ligand with TiOiPr₄ as a catalyst to polymerize LA with various ratios of [LA]/[TiOiPr₄] (entries 12–19, Table 2). The [LA]/[TiOiPr₄] ratio from 37.5 to 62.5 was investigated, and the molecular mass (MₙGPC) of PLA increased from 1400 to 2100. According to the solubility of LA in CH₂Cl₂, the limit of the [LA]/[TiOiPr₄] ratio is 62.5 (1.80 g of LA in 2.5 mL CH₂Cl₂), and PLA with high molecular mass PLA cannot be synthesized by increasing the [LA]/[TiOiPr₄] ratio.

To investigate the living property of TiOiPr₄ with the pyrazole ligand in LA polymerization, first, LA was polymerized ([LA] : [TiOiPr₄] : [furPz] = 100 : 4 : 4 in CDCl₃, entry 16 in Table 2). After 390 min, the conversion was 84%, and 100 equivalents of LA were reloaded into the solution (entry 17 in Table 2). However, the polymerization time increased to 895 min with a 92% conversion. Subsequently, 100 equivalents of LA were reloaded into the solution (entry 18 in Table 2), and the polymerization rate decreased. After 1495 min, the conversion was 83%, and 100 equivalents of LA were reloaded into the solution (entry 19 in Table 2). The solution could not be stirred after 2000 min with a 72% conversion. The slower LA polymerization rate can be ascribed to the higher viscosity of the polymerized solution. On the basis of the linear relationship between MₙGPC and ([LA]₀ × conv.)/[TiOiPr₄], (entries 7, and 12–19 in Table 2 and Fig. 4), TiOiPr₄ with the pyrazole ligand demonstrated a high controllability with narrow D for LA polymerization. To confirm that PLA with high molecular mass can be synthesized using TiOiPr₄ with the pyrazole ligand, LA was polymerized using TiOiPr₄ with furPz ([LA] : [TiOiPr₄] : [furPz] = 1000 : 1 : 1 at 100 °C without solvent, entry 20 in Table 2). After 240 min, the conversion was 93%, and PLA (MₙGPC =

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![Fig. 4](image-url)  
**Fig. 4** Linear plots of MₙGPC versus ([LA]₀ × conv.)/[TiOiPr₄]. Blue solid dots indicate Đs.

![Fig. 5](image-url)  
**Fig. 5** ¹H NMR spectrum of PLA (entry 13 in Table 2).

![Fig. 6](image-url)  
**Fig. 6** MALDI-TOF spectrum of PLA (entry 13 in Table 2).
(51 100, and $D = 1.10$) was obtained. Compared with LA polymerization using TiOiPr$_4$ without furPz (240 min, conv. = 52%, $M_{n, GPC} = 31,600, D = 1.26$, entry 21 in Table 2), adding furPz to LA polymerization improved the polymerization rate and enhanced the controllability for producing PLA.

The $^1$H nuclear magnetic resonance (NMR) spectrum of PLA (entry 2 in Table 2 and Fig. 5) confirmed the presence of one isopropyl oxide group (peak a) and a hydroxyl chain end (peak c), suggesting that initiation occurred through insertion of an isopropyl oxide into LA. The matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrum of PLA (entry 5 in Table 2 and Fig. 6) revealed the presence of isopropyl oxide group at the end of the PLA chain.

### 3.2 Synthesis and characterization of MePz$_2$Ti$_2$OiPr$_7$

To determine what was the real catalysis mechanism in the polymerization process, the reaction of MePz and TiOiPr$_4$ (1 : 1) in toluene was investigated. Fig. 7 illustrates the crystal of MePz$_2$Ti$_2$OiPr$_7$ (CCDC 1568213, Table S4†). However, the $^1$H NMR spectrum (Fig. S3†) revealed that MePz$_2$Ti$_2$OiPr$_7$ was impure. The crystal data of MePz$_2$Ti$_2$OiPr$_7$ indicated that the Ti–Ti distance was 3.2322(14) Å, which is slightly shorter than that of LBu-TiOPr$_6$ distance (3.242 Å), and it implied the cooperative activation can occur in this system. To prove that MePz$_2$Ti$_2$OiPr$_7$ is the real catalyst in LA polymerization, the crystal of impure MePz$_2$Ti$_2$OiPr$_7$ was used as a catalyst in LA polymerization with the polymerization condition of entry 17 of Table 1 ([LA] : [MePz$_2$Ti$_2$OiPr$_7$] = 100 : 0.5, [MePz$_2$Ti$_2$OiPr$_7$] = 6.7 mM at 60 °C in 15 mL toluene). After 16 min, the conversion was 95% with $M_{n, GPC} = 4900, D = 1.56$, and $k_{obs} = 0.203$ (min$^{-1}$), and the results were similar to the results of entry 17 of Table 1 (conversion was 89% after 25 min).

### 4. Conclusions

Our strategy of using TiOiPr$_4$ with pyrazole ligand for one-pot LA polymerization successfully improved the catalytic activity compared with using TiOiPr$_4$ only. The crystal structure of MePz$_2$Ti$_2$OiPr$_7$ revealed cooperative activation between two Ti atoms during LA polymerization. These results can provide a straightforward approach to synthesize PLA by using TiOiPr$_4$ as a catalyst. In future, we intend to investigate the mechanism of LA polymerization.

### Conflicts of interest

There are no conflicts to declare.

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