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Stereoselective ring-opening polymerization of racemic lactide using alkoxy-amino-bis(phenolate) group 3 metal complexes

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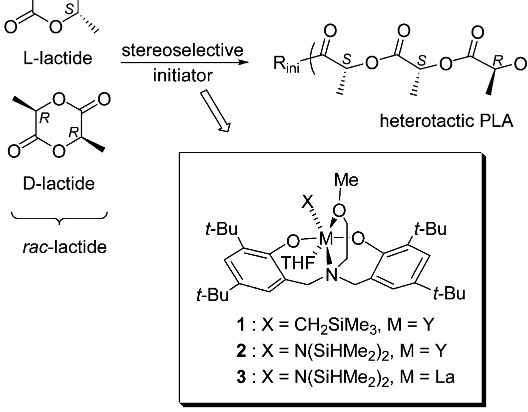
Polymerization of racemic lactide initated by alkyl- and amido-yttrium complexes of a non-chiral tetradentate alkoxy-amino-bis(phenolate) ligand proceeds rapidly, in a controlled manner, to give heterotactic-rich polylactic acid.

Thanks to its biodegradability and biocompatibility, polylactic acid (PLA) is one of the most promising materials for medical, pharmaceutical and agricultural applications.[1] PLA is conveniently prepared by ring-opening polymerization (ROP) of lactide. Polymerization of racemic lactide (D,L-*rac*-lactide) with usual non-selective initiators leads to amorphous, atactic PLA.[2] This material is of marginal importance because stereoregularity is the important factor that determines the mechanical properties, and rate of chemical and biological degradation.[1] In the last decade, many efforts have been made toward the preparation of discrete, well-characterized single-site catalysts for controlling the stereochemistry of *rac*-lactide polymerization.[3] Systems based on Mg, Ca, Zn, Al, and Sn complexes were successfully explored to prepare heterotactic and stereoblock isotactic PLA by employing the two important concepts, *i.e.* chain-end control and enantiomorphic site control.[4] Here we describe the first example of a group 3 metal complex that enables the rapid, controlled and stereoselective ROP of *rac*-lactide to form heterotactic-rich PLA and evidence the importance of the metal center on the control of stereoselectivity (Scheme 1).

Our current interest is focused on group 3 metal complexes of tetradentate alkoxy-amino-bis(phenolate) ligands (Scheme 1). Contrary to group 4 metal complexes,[5] the polymerization ability of such complexes remains largely unexplored. Recently, we have prepared yttrium-alkyl (**1**) and -amido (**2**) complexes using convenient alkane and amine elimination routes, and structurally characterized them by X-ray diffraction.[6] The parent lanthanum-amido complex **3** was prepared in 92% yield by direct treatment of $La[N(SiHMe_2)]_3(THF)_2$ [7] with 1 mol equiv of the bis(phenol) ligand. The molecular structure of **3** was established by NMR† and an X-ray diffraction study‡ (Fig. 1). In solution as in the solid state, the side-arm methoxy was found to be bound to the metal center. The La–O(Me) bond length is *ca*. 0.2 Å larger than the corresponding bond in **2** (Y(1)–O(3), 2.414(4) Å), as expected from a major influence of effective ionic radii of the metal centers.[8] Although complexes **2** and **3** show both a six-coordinate metal center with a *trans* arrangement of the amino/amido groups, and the coordinated THF molecule and methoxy side arm, the octahedral geometry in **3** is much more distorted than in **2**. In the latter complex, the {ONOO} ligand core adopts a quite symmetric binding to yttrium with the four coordinated oxygen atoms almost coplanar; the distance from the THF oxygen atom to the plane formed by the three oxygen atoms of the ligand is 0.016 Å. In contrast, the corresponding value in **3** is 1.929 Å. This strong distortion in **3** is also illustrated by the larger dihedral angle between the two phenolate planes (**2**, 30.0°; **3**, 61.8°) and the *ca*. 0.1 Å difference in the La–O(phenate) bond lengths (Y–O(phenate), 2.145(2) and 2.157(2) Å).[6]



Scheme 1

Polymerization of *rac*-lactide with yttrium complexes **1** and **2** proceeds rapidly at room temperature, equally in toluene and THF solvents in terms of activity (Scheme 1).§ Complete conversions of the monomer to PLA are achieved within 1 h for monomer-to-yttrium ratios up to 500. A ^1H NMR monitoring for the polymerization of 100 equiv of *rac*-lactide with **2** in THF at 0 °C indicated turnover frequencies up to 300 h^{-1} (26% conversion after 5 min; 50% after 10 min). As evidenced by the linear relationship between the monomer-to-metal ratio and number-average molecular masses (M_n) (Fig. 2), a good control of polymerization is achieved with this system, even at a catalyst loading of 0.2% that yielded M_n as high as 90 kg mol^{-1}. The experimental M_n values are only slightly higher (*ca*. 15–20%) from the calculated values, a deviation which may impart to the use of polystyrene standards for GPC calibration. This control of the polymerization, as well as a single type of reaction site, is also supported by the relatively low polydispersity, with M_w/M_n values ranging from 1.25 to 1.35. These values are somewhat higher than those expected for a purely

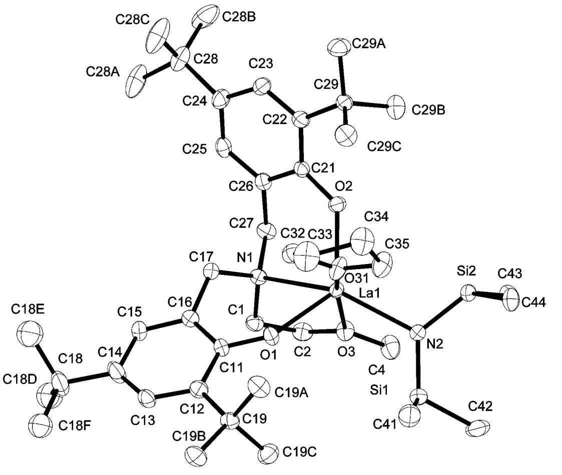


Fig. 1 The molecular structure of **3**. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and bond angles (°): La(1)–O(1) 2.229(3), La(1)–O(2) 2.315(3), La(1)–O(3) 2.647(3), La(1)–N(1) 2.662(3), La(1)–N(2) 2.413(3); O(1)–La(1)–O(2) 127.39(12).

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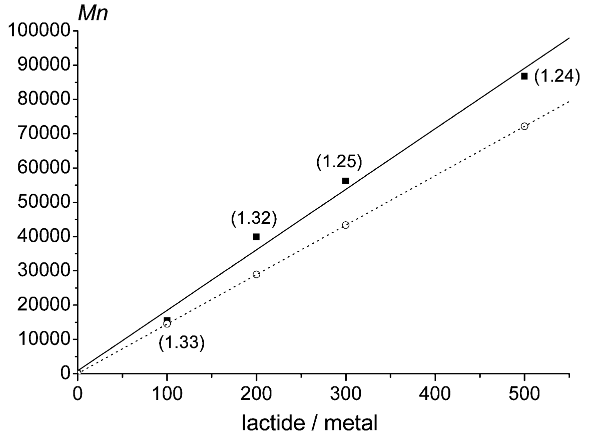

Fig. 2 Dependence of M_n on monomer-to-yttrium ratio using **2** for *rac*-LA polymerization in THF at 20 °C for 1 h (yield of PLA > 97%). –■–: M_n (GPC; polystyrene standards), ···○···: M_n (theory).

living polymerization (M_w/M_n < 1.1), and suggest that either transesterification takes place to a small extent and/or the initiation step is not very fast with respect to propagation, *i.e.* the k_p/k_i ratio is not ultimately favorable.

More importantly, the homonuclear decoupled ^{1}H NMR spectrum of the methine region of the PLA samples derived from **1** and **2** in THF at room temperature (Fig. 3a) is consistent with the formation of chains that are most predominantly heterotactic. The probability of racemic linkages,[4a,b] estimated from the relative intensity of the *rmr* (δ 5.22 ppm) and *mrm* (δ 5.140 ppm) tetrads *vs* other tetrads (*rmm*/*mmr*, δ 5.20 and 5.16 ppm; *mmm*, δ 5.145 ppm), is P_r = 0.80. Both alkyl- and amido-yttrium complexes **1** and **2** lead to the same P_r value, which is consistent with initiation of polymerization by the X (amido or alkyl) group and assistance of the [{ONOO}Ln] fragment on stereocontrol.[4b] This hypothesis is supported by the results obtained with the La complex **3**. Although **3** initiates the ROP of *rac*-lactide with similar activity and control of molar mass and polydispersity than **1** and **2** ([LA]/[**3**] = 100, THF, 1 h, 20 °C; 97% conv, M_n = 18400, M_w/M_n = 1.34), the level of heterotacticity is significantly decreased (P_r = 0.64; Fig. 3b). We assume that this change may reflect the direct influence of the metal center, *i.e. via* its ionic radius,[8] or its indirect influence on the overall conformation of the [{ONOO}Ln] fragment, as observed in the solid state (*vide supra*). Noteworthy is also the strong influence of the solvent on the level of stereoselectivity, with a neat decrease (P_r = 0.60) observed when the polymerization is carried out in toluene (Fig. 3c) instead of THF.

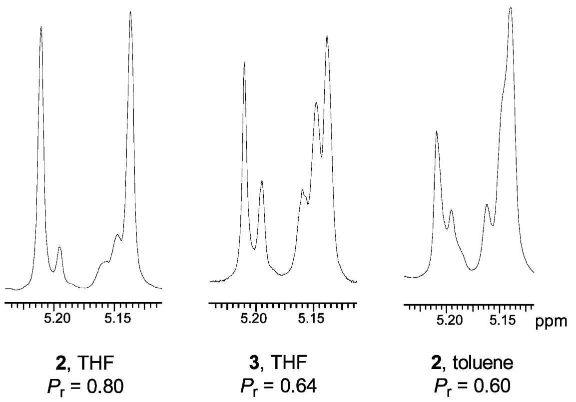

Fig. 3 ^{1}H NMR spectra (500 MHz, CDCl$_3$) of PLA methine resonances with selective decoupling of PLA methyl resonances; heterotactic PLA prepared with (*a*) **2** in THF, (*b*) **3** in THF, and (*c*) **2** in toluene.

In conclusion, we report a group 3 metal complex that acts as single-site initiator for the controlled polymerization of *rac*-lactide to heterotactic PLA. Further studies are examining thoroughly the effect of changes to the metal center and the substituents of the bis(phenolate) ligand on the polymerization behavior of these group 3 metal complexes, as well as employing **2** for the synthesis of new polyester architectures.

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Notes and references

† *Complex* **3**: To a stirred solution of La[N(SiHMe$_2$)$_2$]$_3$(THF)$_2$ (0.272 g, 0.40 mmol) in pentane (5 mL) was added a solution of alkoxy-amino-bis(phenol) ligand (0.2044 g, 0.40 mmol) in pentane (5 mL) at room temperature. The reaction mixture was stirred for 24 h and volatiles were removed under vacuum. The residue was washed with a minimal amount of cold pentane and dried under vacuum, giving **3** as a colorless powder (0.18 g, 92%). ^{1}H NMR (300 MHz, C$_6$D$_6$): δ 7.57 (d, 2H, J_{HH} = 2.3 Hz, ArH), 7.11 (d, 2H, J_{HH} = 2.5 Hz, ArH), 5.25 (m, 2H, SiH), 3.76 (b, 4H, α-CH_2 THF), 3.58 (d, 2H, J_{HH} = 12.5 Hz, ArCH_2), 3.32 (d, 2H, J_{HH} = 12.5 Hz, ArCH_2), 3.07 (s, 3H, OCH_3), 2.77 (t, 2H, J_{HH} = 5.2 Hz, NCH_2), 2.27 (m, 2H, CH_2O), 1.73 (s, 18H, C(CH_3)$_3$), 1.44 (s, 18H, C(CH_3)$_3$), 1.22 (m, 4H, β-CH_2 THF), 0.48 (d, 12H, J_{HH} = 3.0 Hz, Si(CH_3)$_2$). ^{13}C{^{1}H} NMR (75 MHz, C$_6$D$_6$): 161.8, 136.6, 135.6, 125.8, 124.3, 123.9 (s, Ar-C), 71.9 (s, CH$_2$OMe), 69.9 (s, α-CH$_2$ THF), 61.6 (s, CH$_2$Ar), 60.9(s, OCH$_3$), 50.7 (s NCH$_2$), 35.3 (s, CMe$_3$), 34.0 (s, CMe$_3$), 32.0 (s, (CH$_3$)$_3$), 30.1 (s, (CH$_3$)$_3$), 25.0 (s, β-CH$_2$ THF), 3.5 (s, Si(CH$_3$)$_2$). Single crystals of **3** toluene suitable for X-ray diffraction were grown from toluene at −35 °C. Anal. Calc. (found) for C$_{41}$H$_{73}$N$_2$O$_4$LaSi$_2$: C, 57.72 (57.91), H 8.62 (9.03), N 3.28 (3.18).

‡ *Crystal data for* **3**·*toluene*: C$_{48}$H$_{81}$LaN$_2$O$_4$Si$_2$, M = 945.24 g mol^{-1}, triclinic, $P\bar{1}$ (no. 2), a = 11.17360(10), b = 14.4669(2), c = 16.8054(2) Å, α = 100.3910(10), β = 95.6290(10), γ = 103.2940(10)°, V = 2572.61(5) Å^3, T = 100 K, Z = 2, μ(Mo-Kα) = 0.917 mm^{-1}, D_c = 1.220 g cm^{-3}, 69706 reflections measured, 17037 independent (R_{int} = 0.0818), F^2 refinement, R_1 = 0.0591, wR_2 = 0.1256, 13528 independent observed reflections [$I > 2\sigma(I)$], 537 parameters. CCDC reference number 222716. See http://www.rsc.org/suppdata/cc/b3/b314030j/ for crystallographic data in .cif or other electronic format.

§ *General polymerization procedure*: A Schlenk flask was charged with 1.0 mmol of *rac*-lactide in THF (2 mL). To this solution was added a solution of 0.01 mmol of catalyst in 0.5 mL of THF ([lactide]/[metal] = 100). The reaction mixture was stirred at room temperature for 1 h. After a small portion of the solution was sampled for NMR analysis, to determine exact conversion, the reaction was quenched with one drop of methanol. The solution was concentrated *in vacuo*, and the polymer was precipitated with excess hexane, and then dried *in vacuo* to constant weight.

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