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Metalloenzyme inspired dizinc catalyst for the polymerization of lactide

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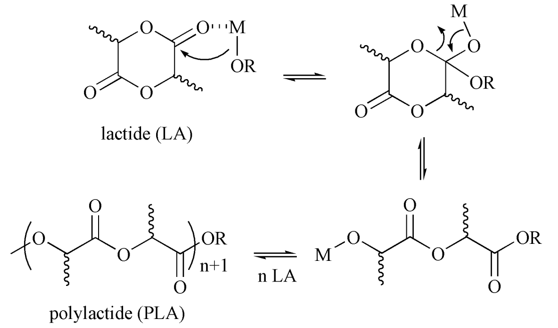
A new dizinc–monoalkoxide complex supported by a dinucleating ligand was structurally characterized and shown to be a highly active catalyst for the controlled polymerization of lactide.

Polylactide (PLA) has received acclaim as an attractive alternative to petrochemically derived polyolefins due to its utility (*e.g.*, biomedical and packaging applications), biodegradability, and synthesis from lactide (LA), a monomer that can be harvested from renewable resources such as corn or beets.[1] Metal alkoxides often are used to catalyze the ring-opening polymerization of LA and related cyclic esters.[2,3] We aim to design and structurally define single-site metal–alkoxide LA polymerization catalysts comprising biocompatible metals (*e.g.*, Zn[4] or Fe[5]) in order to undertake mechanistic studies on well characterized systems, exert tight control over the polymerization process, and prepare useful materials.[3]

The ring-opening polymerization is generally thought to occur *via* a coordination–insertion pathway (Scheme 1), whereby the metal ion serves to activate the carbonyl toward attack by the metal-bound alkoxide initiator or growing chain.[6] An intriguing mechanistic analogy may be drawn between this process and the hydrolysis reactions performed by a large class of enzymes that have in common active sites with two or more metal ions (typically divalent) held in close proximity.[7] While mechanistic models for this diverse array of enzymes differ in detail, a common theme has emerged that stresses the cooperative action of the metal ions to rationalize the observed high catalytic efficiency and substrate specificity. According to this general notion, one or more of the metal ions binds a water molecule or an amino acid side chain, causing a reduction in pK_a and thereby activating it to participate as a nucleophile. In addition, one or more of the metal ions binds substrate, increasing its electrophilicity and susceptibility to nucleophilic attack. Additional rate-enhancement may arise from stabilization of the resulting anionic intermediate or transition state by the Lewis-acidic metal ions. These notions have inspired studies of the hydrolytic reactivity of bimetallic and higher nuclearity complexes,[8] including dizinc compounds that ring-open β-lactams.[9] We considered that analogous complexes might be useful in cyclic ester polymerizations that may proceed by a similar multimetallic substrate activation pathway. In preliminary support of this hypothesis, we describe herein a new dizinc–monoalkoxide complex that polymerizes LA rapidly and in controlled fashion under mild conditions.



Scheme 1 Coordination–insertion mechanism for LA polymerization.

Treatment of a solution of 2,6-bis{*N*-(2-dimethylaminoethyl)-*N*-methyl}-4-methylphenol[10] in THF with a mixture of EtZnCl[11] and Et_2Zn, followed by addition of EtOH and crystallization afforded **1** as white needles in 60% yield (Fig. 1).† ‡ Complex **1** is structurally analogous to a methoxo-bridged compound with nitrate coligands that was reported as a β-lactamase model.[9] In **1**, both zinc atoms have distorted pentacoordinate geometries with Zn(1) being closer to square pyramidal (τ = 0.34,[12] Cl(1) in the axial position) and Zn(2) being closer to trigonal bipyramidal (τ = 0.52, O(2) and N(3) in axial positions). The two bridging oxygen atoms are asymmetrically placed between the two zinc atoms with the phenoxy oxygen [O(1)] lying closer to Zn(2) and the ethoxy oxygen [O(2)] closer to Zn(1) by ~0.1 Å in each case. ^1H NMR spectra (CD_2Cl_2, −75 to 25 °C) showed retention of the dizinc structure of **1** in solution. However, the presence of broadened resonances at 25 °C that sharpened and split (reversibly) upon cooling indicated fluxionality. The data are consistent with interconversion between isomers with and without mirror symmetry (*e.g.*, *meso* and *RR*/*SS* diastereomers, respectively), presumably *via* pseudorotation and/or N-inversion processes that we are unable to distinguish at present.

Complex **1** rapidly polymerized D,L-LA in CH_2Cl_2 at room temperature; at a $[LA]_0/[\mathbf{1}]_0$ ratio of 300 with $[LA]_0$ = 1 M, greater than 90% conversion to PLA occurred within 30 min ($k_{app} = 9 \times 10^{-4}\ s^{-1}$, reaction first order in [LA], *vide infra*).§ The level of polymerization control was high, as shown by the linear increase in M_n with conversion and the low polydispersity indices (PDI, M_w/M_n) of the product polymers (Fig. 2). In support of livingness in the polymerization, when 300 eq. of LA was added to a reaction mixture at full conversion ($[LA]_0/[\mathbf{1}]_0$ = 100, M_n = 20.6 kg mol^{-1} by size exclusion chromatography (SEC), PDI = 1.19), polymerization continued, yielding PLA with M_n = 64.9 kg mol^{-1}, PDI = 1.17, and no detectable amount of initial polymer remaining (SEC). The ^1H NMR spectrum of PLA prepared using a $[LA]_0/[\mathbf{1}]_0$ ratio of 50 showed

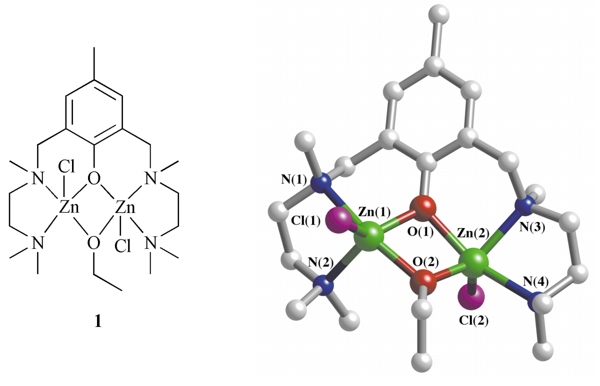


Fig. 1 Drawing of compound **1** and a representation of its X-ray crystal structure. Selected bond lengths (Å); Zn(1)–Zn(2) 3.176(1), Zn(1)–O(1) 2.112(4), Zn(2)–O(1) 1.997(3), Zn(1)–O(2) 1.975(4), Zn(2)–O(2) 2.060(4), Zn(1)–Cl(1) 2.3197(15), Zn(2)–Cl(2) 2.3396(13).

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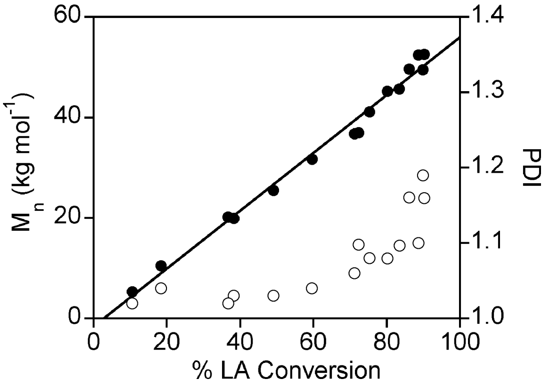

Fig. 2 Plot of M_n (filled circles, SEC) *vs.* monomer conversion (determined by ^{1}H NMR), with polydispersity indices indicated by open circles (SEC). *Conditions*: $[LA]_0/[\mathbf{1}]_0 = 300$, $[LA]_0 = 1$ M, CH_2Cl_2, 25 °C.

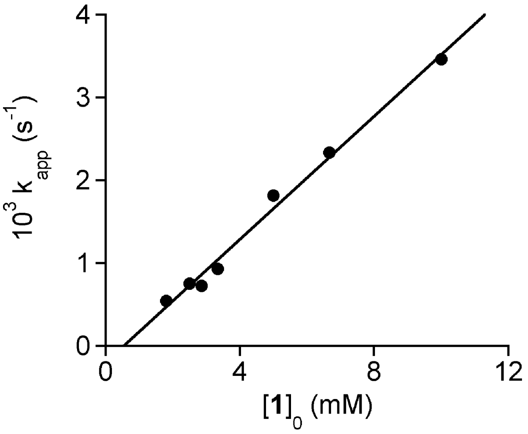

Fig. 3 Plot of k_{app} values, determined from principal component analysis of *in situ* FTIR spectra acquired during the polymerization of LA, as a function of the initial concentration of **1**. The line represents a best fit to the data ($R = 0.996$). *Conditions*: $[LA]_0 = 1$ M, CH_2Cl_2, 25 °C.

ethoxide end groups (indicative of a coordination insertion mechanism) in the amount expected for initiation by every molecule of **1**. ^{1}H NMR spectral analysis also showed that D,L-LA yielded atactic PLA.[13] In addition, PLA derived from L-LA was isotactic, signifying no epimerization of stereogenic centers during the polymerization.

Preliminary kinetics studies monitored by *in situ* FTIR spectroscopy (ReactIR) indicate a first order dependency on [LA]. Moreover, a first order dependency in [**1**] is indicated by a linear plot of k_{app} *vs.* $[\mathbf{1}]_0$ (Fig. 3), with a slope equal to the second order rate constant $k_{prop} = 0.37$ M^{-1} s^{-1} and a nonzero *x*-intercept indicative[5] of a trace impurity in the LA and/or solvent that slightly reduces the effective catalyst concentration.[14] The rate law $d[LA]/dt = k_{prop}[LA][\mathbf{1}]$ is consistent with a bimetallic coordination insertion mechanism involving enchainment of LA at the dizinc site of **1**,[15] as well as with the absence of kinetically significant aggregation phenomena.[5]

In conclusion, we have prepared and structurally characterized a new dizinc–alkoxide complex that is a highly active catalyst for the controlled polymerization of LA. Further insights will be provided by ongoing studies of the scope and mechanism of polymerizations catalyzed by **1** and mononuclear analogs.

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Notes and references

† *Synthesis of* **1**: the compound 2,6-bis{*N*-(2-dimethylaminoethyl)-*N*-methyl}-4-methylphenol[10] (2 g, 4 mmol, 1 eq.) was dissolved in THF at −20 °C and ZnEtCl[11] (0.8 g, 6 mmol, 1.5 eq.) and $ZnEt_2$ (6 mL of a freshly distilled 1 M solution in hexanes, 6 mmol, 1.5 eq) were added into the solution of ligand and gas evolution was observed. The solution was stirred for 20 h at room temperature, after which EtOH (0.71 mL, 12 mmol, 3 eq.) was carefully added. The suspension was stirred for a further 20 h, the solvent was removed, and the residue was washed with pentane (3 × 50 mL). Crystallization from THF–diethyl ether yielded the product as white needles (1.6 g, 2.4 mmol, 60%).

Selected spectroscopic data for **1**: ^{1}H NMR: δ(250 MHz, CD_2Cl_2, 25 °C) 1.19 (t, 3H, OCH_2CH_3), 2.17–2.73 (m, 30 H), 2.99 (d, 2H, CH_2NMe), 3.84 (q, 2H, OCH_2CH_3), 4.30 (d, 2H, CH_2NMe), 6.76 (s, 2H, C_6H_2(Me)O), δ (250 MHz, CD_2Cl_2, −75 °C) 1.08 (m, 3H, OCH_2CH_3), 2.00–2.53 (m, 30 H), 3.00 (d, 2H, CH_2NMe), 3.74 (m, 2H, OCH_2CH_3), 4.22 (d, 2H, CH_2NMe), 6.76 (s, 2H, C_6H_2(Me)O) for one set of isomers, δ (250 MHz, CD_2Cl_2, −75 °C) 1.08 (m, 3H, OCH_2CH_3), 2.00–2.53 (m, 30 H), 2.98 (m, 2H, CH_2NMe), 3.54 (m, 2H, OCH_2CH_3), 4.28 (d, 1H, CH_2NMe), 4.36 (d, 1H, CH_2NMe), 6.72 (s, 1H, C_6H_2(Me)O), 6.73 (s, 1H, C_6H_2(Me)O), for the other isomers; Anal. Calc. (found) for $C_{21}H_{40}N_4O_2Zn_2Cl_2$: C 43.60 (43.18), H 6.97 (6.76), N 9.68 (9.55)%.

‡ *Crystal data* for **1**: $C_{25}H_{48}N_4O_3Zn_2Cl_2$, $M = 654.31$, orthorhombic, space group $Pca2_1$, $a = 17.3944(17)$, $b = 14.6134(14)$, $c = 11.9982(12)$ Å, $V = 3049.8(5)$ Å^3, $Z = 4$, $D_c = 1.425$ Mg m^{-3}, μ(Mo-Kα) = 1.780 mm^{-1}, $T = 173(2)$ K, white needles, 5355 independent measured reflections, F^2 refinement, $R_1 = 0.0437$, $wR_2 = 0.1212$, 4507 independent observed reflections $[|F_o| > 4\sigma(|F_o|), 2\theta < 50°]$, 326 parameters. CCDC 189527. See http://www.rsc.org/suppdata/cc/b2/b206437e/ for crystallographic data in CIF or other electronic format.

§ *Typical polymerization procedure*: complex **1** (0.0219 g, 0.038 mmol, 1 eq.) and D,L-LA (0.546 g, 3.8 mmol, 100 eq.) were weighed into a silylated glass vial in the dry box. Alumina filtered CH_2Cl_2 (3.8 mL) was added and the solution stirred at room temperature. After stirring for the allotted time period an aliquot (1 mL) was withdrawn from the glove box, exposed to air, and hexanes added to precipitate the polymer. The volatile components were removed and the sample dried *in vacuo*. Percentage conversion was determined by integration of monomer *vs.* polymer methine resonances in the ^{1}H NMR spectrum of the crude product (in $CDCl_3$). Size exclusion chromatograhy (SEC) data were recorded on a HP1100 high pressure liquid chromatograph (HPLC) with a flow rate of 1.00 cm^3 s^{-1} using THF as the eluent. The columns were calibrated against polystyrene standards. The HPLC was equipped with a HP refractive index detector and three Jordi polydivinylbenzene columns of 10^4, 10^3 and 100 Å pore sizes.

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15. A pathway involving only one Zn ion in **1** cannot be discounted with the available data.