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Rapid and Controlled Polymerization of Lactide by Structurally Characterized Ferric Alkoxides

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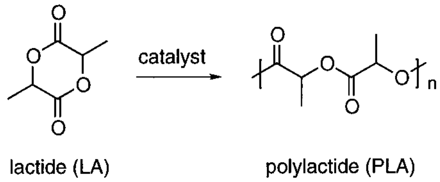
The development of discrete metal complexes for controlled polymerizations by tailoring the ligand environment can lead to highly active and selective polymerization catalysts for a variety of monomer classes. A significant current aim is to construct less expensive catalysts using nontoxic metals while retaining the benefits of discrete metal complexes.[1] These goals are especially important with respect to the polymerization of lactide (LA), a monomer derived from a renewable resource, to give polylactide (PLA),[2] a biodegradable and biocompatible polyester[3] that is garnering great interest due to its biomedical, pharmaceutical, and agricultural applications (Scheme 1).[4] To this end, compounds of metals such as tin,[5] aluminum,[6] yttrium,[7] and zinc[5a,8] have been used as catalysts for the polymerization of LA. The biomedical applications of PLA require low levels of impurities, so there is great impetus for the development of active catalysts that contain low toxicity metals. Iron is attractive in this regard, but there are few reports of iron complexes for the polymerization of LA. Ferric oxide,[9] iron porphyrins,[10] and simple iron salts including carboxylates[11] have been used, but the polymerizations are sluggish, even at high temperature (120−210 °C, hours or days), racemization invariably occurs (especially at longer reaction times), and mechanistic analysis is frequently hindered by a lack of knowledge of precatalyst structure, often because of sample inhomogeneity. Since other metal alkoxides[5b,6−8] readily polymerize LA, it seemed likely that simple ferric alkoxides would be more efficient catalysts than the previously reported iron complexes.[12] However, a search of the literature revealed no examples of neutral homoleptic ferric alkoxides that had been crystallographically characterized.[13] Here we report the synthesis and structural characterization of two ferric alkoxide complexes, including a species derived from commercial "Fe(OEt)$_3$", and their LA polymerization efficacy. The new, discrete complexes polymerize LA faster than the previously described iron compounds and exhibit controlled polymerization behavior without observable racemization.

Scheme 1



Commercially available ferric ethoxide (Strem)[14] was extracted with THF which was then removed *in vacuo*. The resulting brown residue was recrystallized from hexamethyldisiloxane to give Fe$_5$(μ_5-O)(OEt)$_{13}$, **1**, as yellow crystals. X-ray diffraction analysis revealed **1** to have a pentanuclear structure with the five iron atoms arranged in a square pyramid (Figure 1).[15] Each of the four iron atoms in the basal plane is 5-coordinate and has a distorted trigonal bipyramidal coordination geometry with the oxo and terminal alkoxide ligands occupying the axial positions. The apical Fe5 is 6-coordinate with a distorted octahedral geometry. Eight of the ethoxide ligands are μ_2 bridging and five are terminal (Fe−O = 1.810(3)−1.825(3) Å). The structure is similar to that of Y$_5$(μ_5-O)(O^{i}Pr)$_{13}$,[16] a complex that is an efficient polymerization catalyst of LA and ϵ-caprolactone,[7a,17] as well as isopropoxides of erbium,[18] indium, and ytterbium,[19] a bimetallic isopropoxide of yttrium and praseodymium,[20] and a *tert*-butoxide of lantha-

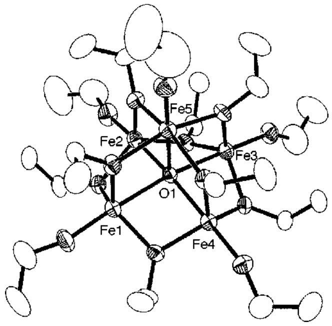


Figure 1. Representation of the X-ray crystal structure of **1** as 50% ellipsoids. Hydrogen atoms are omitted for clarity.

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[6] For example: Dubois, P.; Jacobs, C.; Jérôme, R.; Teyssié, P. *Macromolecules* **1991**, *24*, 2266−2270.

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[12] The only reports of ferric alkoxides being used to polymerize LA are by Penczek et al., who briefly mentioned using "Fe(OEt)$_3$" in THF at 80 °C. No information is provided on the source or nature of the "Fe(OEt)$_3$" used in these studies. See: (a) Penczek, S.; Duda, A.; Szymanski, R.; Biela, T. *Macromol. Symp.* **2000**, *153*, 1−15. (b) Penczek, S.; Duda, A.; Szymanski, R. *Macromol. Symp.* **1998**, *132*, 441−449. (c) Baran, J.; Duda, A.; Kowalski, A.; Szymanski, R.; Penczek, S. *Macromol. Symp.* **1998**, *123*, 93−101.

[13] Only ebullioscopic and cryoscopic data are available for some iron alkoxides that suggest dimeric or trimeric structures in solution. See: Bradley, D. C.; Mehrotra, R. C.; Gaur, D. P. *Metal Alkoxides*; Academic Press: London, New York, 1978; pp 87−88. Searches of Cambridge Structural Database (version 5.19) and the Chemical Abstracts Service database gave only one hit for X-ray structures of ferric alkoxides and that is a lithium salt of [Fe(OCH^{t}Bu$_2$)$_4$]$^-$: Bochmann, M.; Wilkinson, G.; Young, G. B.; Hursthouse, M. B.; Malik, K. M. A. *J. Chem. Soc., Dalton Trans.* **1980**, 1863−1871.

[14] Strem prepares ferric ethoxide from FeCl$_3$ and NaOEt.

[15] X-ray data for **1**: triclinic, $P\bar{1}$, yellow; a = 11.7472(10) Å, b = 12.1672(11) Å, c = 15.8347(17) Å, α = 99.2118(15)°, β = 101.2623(15)°, γ = 109.5066(14)°; 173(2) K; Z = 2; $R1$ ($I > 2\sigma(I)$) = 0.0456; GOF = 0.949.

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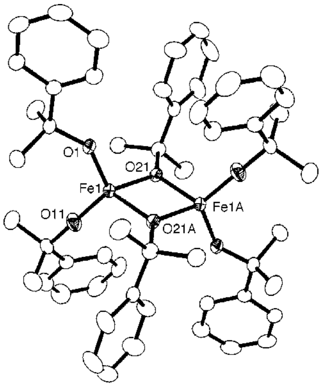

Figure 2. Representation of the X-ray crystal structure of **2** as 50% ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Fe1−O1, 1.910(1); Fe1−O11, 1.763(1); Fe1−O21, 1.970(1); Fe1−O21A, 1.963(1); Fe1···Fe1A, 3.003(1); O21−Fe1−O21A, 80.42(6); Fe1−O21−Fe1A, 99.58(6).

num.[21] These structures differ from that of **1**, however, insofar as they have μ_3 alkoxides bridging the apical metal and the four basal metals. The most closely related structure in ferric alkoxide chemistry is that of $Na_2Fe_6(\mu_6\text{-}O)(OMe)_{18}$ in which six iron atoms are octahedrally disposed about a central oxo ligand.[22]

A second complex, $Fe_2(OCMe_2Ph)_6$ (**2**), of a more sterically encumbered alkoxide was isolated in 56% yield from the reaction of $TlOCMe_2Ph$ and anhydrous $FeCl_3$, a protocol with considerable potential generality.[23] The structure of **2** was determined by X-ray crystallography (Figure 2).[24] Each 4-coordinate iron atom in the dinuclear structure has a distorted tetrahedral geometry and is ligated by four alkoxides, two of which are terminal and two are doubly bridging. To our knowledge, **2** is the first structurally characterized neutral ferric complex with solely alkoxide ligands.[13]

The catalytic behavior of **1** and **2** was studied in toluene at 70 °C with $[LA]_0 = 1$ M.[25] Under these conditions compound **1** is highly active for the controlled polymerization of LA. For example, using $[LA]_0/[Fe]_0 = 450{:}1$ we observed 97% conversion in 21 min and isolated polymer with a narrow molecular weight distribution (polydispersity index (PDI) = 1.17). ^1H NMR monitoring of conversion vs time ($[LA]_0/[Fe]_0 = 1000{:}1$) showed the reaction to be first order in [LA], with the pseudo-first-order rate constant $k_{app} = 0.03\ min^{-1}$ (Figure S1). Polymers with narrow molecular weight distributions were obtained from reactions conducted at a range of lactide-to-iron ratios (Figure 3). The linearity of this plot, in conjunction with a linear plot of M_n vs conversion for a given $[LA]_0/[Fe]_0$ ratio (Figure S2), indicates a high degree of molecular weight control. The PDI values slightly increase during the course of a polymerization at a given $[LA]_0/[Fe]_0$ ratio, perhaps due to the equilibrium nature of the polymerization or transesterification reactions.[12a,26] In further support of the controlled nature of the reaction, addition of LA to a reaction mixture at equilibrium conversion ($[LA]_0/[Fe]_0 = 50{:}1$, 11 min, $M_n = 5.0 \times 10^3$ g/mol, PDI = 1.16) resulted in further polymerization ($M_n = 41.5 \times 10^3$ g/mol, PDI = 1.23), with no observation of low molecular weight polymer in the final polymer sample by SEC (Figure S3). The initiation reaction proceeds via a coordination−insertion mechanism, as evinced by the presence of an ethoxy ester end group in the ^1H NMR spectrum of a low molecular weight polymer sample.[26a] In a reaction performed with enantiomerically pure *L*-LA, the polymer exhibited only one methine peak in the decoupled ^1H NMR spectrum, showing that epimerization does not occur.[27]

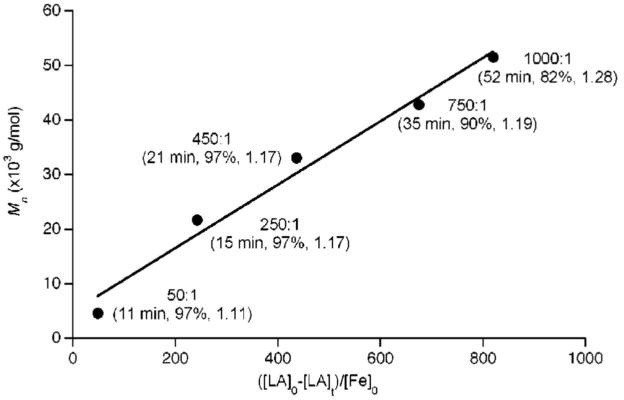

Figure 3. Dependence of M_n (vs polystyrene standards) on $([LA]_0 - [LA]_t)/[Fe]_0$. Data points represent $[LA]_0/[Fe]_0$ (time (min), % conversion, PDI).

Preliminary experiments show that the polymerization of LA by **2** proceeds similarly to the reaction promoted by **1**, although the PDI values for the product polymers were slightly higher. For example, at $[LA]_0/[Fe]_0 = 450{:}1$ we observed 98% conversion in 35 min with $M_n = 34.0 \times 10^3$ g/mol and PDI = 1.60.[28]

In conclusion, we report the straightforward preparation of two new structurally characterized ferric alkoxides that are effective initiators for the polymerization of lactide. Their polymerization behavior supersedes those of other reported iron complexes with respect to rate, molecular weight distribution control, and epimerization. The generality of their synthesis bodes well for further studies aimed at expanding the scope of polymerization reactivity and gaining mechanistic information.

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Supporting Information Available: Synthetic procedures and characterization data for all compounds (PDF) and X-ray crystallographic data files (CIF) for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] Using the same method, we have also prepared $Fe_2(OCHPh_2)_6$. Attempts to react $FeCl_3$ with NaOR or LiOR reagents instead of thallium alkoxides did not yield clean products.

[24] X-ray data for **2**: monoclinic, $P2_1/c$, yellow; $a = 12.6689(7)$ Å, $b = 19.768(11)$ Å, $c = 9.9959(5)$ Å, $\beta = 105.4340(10)$°; 173(2) K; $Z = 2$; $R1$ ($I > 2\sigma(I)$) = 0.0324; GOF = 1.026.

[25] The catalysts polymerize LA at room temperature in THF, but the results under these conditions were irreproducible (variable reaction times, yields, and/or polydispersities).

[26] (a) Kricheldorf, H. R.; Berl. M.; Scharnagl, N *Macromolecules* **1988**, *21*, 286−293. (b) Duda, A.; Penczek, S. *Macromolecules* **1990**, *23*, 1636−1639.

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[28] For further comparison to **1**, using **2** at $[LA]_0/[Fe]_0 = 1000{:}1$ we observed 95% conversion in 60 min with $M_n = 48.0 \times 10^3$ g/mol and PDI = 1.53.