Communication

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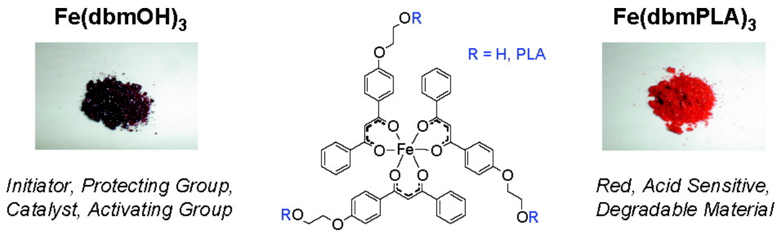

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Iron Tris(dibenzoylmethane)-Centered Polylactide Stars: Multiple Roles for the Metal Complex in Lactide Ring-Opening Polymerization

Jessica L. Gorczynski, Jianbin Chen, and Cassandra L. Fraser*

Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, Virginia 22904

Received May 11, 2005; E-mail: fraser@virginia.edu

Iron (III) tris(dibenzoylmethane) (dbm) derivatives play multiple roles in the synthesis and resulting properties of metal-centered poly(lactic acid) (PLA) stars. Specifically, features of the iron complex serve as a dbm protecting group, a ring-opening polymerization (ROP) initiator, catalyst and activating group, and as responsive functional elements (i.e., chromophores, reactive centers) in the resulting material. These findings underscore the utility of iron β-diketonate (βdk) catalysts for lactide ROP[1] and report a new way of introducing bioactive dbm and responsive $Fe(dbm)_3$ into a biocompatible and biodegradable polymer matrix, which is of potential importance for drug delivery. Dbm derivatives are isolated from turmeric and licorice and are common additives in sunscreens.[2] Moreover, dbm functions as a cancer preventative agent in model systems,[3] and iron and other metal dbm complexes serve as cancer therapeutics.[4]

Tin(II) 2-ethylhexanoate, $Sn(oct)_2$, is a common catalyst for the controlled ROP of lactide in the presence of alcohol initiators.[5] Previous studies with the dbmOH initiator (**1**) in $Sn(oct)_2$-catalyzed ROP of ϵ-caprolactone showed that reactions were not controlled to high monomer conversion, and rates were low compared to nonligand-based alcohol initiators[6] (dbmOH: $M_n = 5600$, 31 h, 30% conversion; ethylene glycol: $M_n = 14\,300$, 8 h, 30% conversion). D,L-Lactide polymerizations behave similarly.[7] GPC traces show high molecular weight (MW) byproducts when dbmPLA **4** with $M_n > 10$K is targeted. Control reactions suggest that coordination of tin to dbm may be responsible for altered catalyst activity and polymerization behavior.[6]

One way of addressing this issue is to use metal chelation as a *protecting group strategy*.[8] To test this idea, the maroon complex $Fe(dbmOH)_3$ (**2**), produced by reaction of dbmOH with NaH and $FeCl_3$, was used as an *initiator* in lactide polymerization. Reactions with $Sn(oct)_2$ were controlled to higher monomer conversion, and rates increased dramatically (Table 1, entry 4 vs 1). Surprisingly, polymerizations without $Sn(oct)_2$ gave similar results in terms of reaction rates and polymer products (entry 5 vs 4)! Thus, $Fe(dbmOH)_3$ serves not only as an initiator and a dbm protecting group but as a *catalyst* as well,[9] combining multiple functions in a single reagent.

Preliminary kinetics studies for $Fe(dbmOH)_3$ showed good MW control to ~70% monomer conversion.[10] When purified $Fe(dbmPLA)_3$ was resubmitted to reaction with additional lactide, chain extension was noted, indicating that the embedded catalyst and OH chain ends remained active. Related $Fe(dbm)_3$ and $Fe(acac)_3$[1] (acac = acetylacetonate) also function as catalysts to form dbmPLA (**4**) and BnPLA (**6**) from dbmOH and benzyl alcohol initiators. Iron ROP catalysts typically act as Lewis acids to activate the monomer carbonyl or initiator as an alkoxide or carboxylate.[11] For labile iron β-diketonate complexes,[1,12] alcohol or carbonyl donors must compete with dbm or acac for metal binding. Polymerizations with $Fe(acac)_3$ (entries 3 and 8) were faster than those with $Fe(dbm)_3$ (entries 2 and 7). The presence of βdks in both the catalyst and the initiator (6 equiv of βdk/Fe; entries 2 and 3) may explain the longer reaction times that are observed for dbmOH relative to BnOH (3 equiv of βdk/Fe; entries 7 and 8). Comparing $Fe(dbmOH)_3$ with the BnOH/$Fe(dbm)_3$ system (entries 5 and 7), the Fe:dbm:OH loadings are identical, but polymerization with the single component system **2** is faster. To rule out the possibility that the rate increase arises from chelation to the ether-alcohol moiety in **1**, p-$CH_3(CO)PhOCH_2CH_2OH$ was tested as the initiator with $Fe(dbm)_3$ as the catalyst, and reaction times were comparable to BnOH/$Fe(dbm)_3$ (40 vs 35 min, respectively). The rate enhancement noted for the multifunctional reagent $Fe(dbmOH)_3$, from which polymer chains grow as the reaction proceeds, may be due to faster ligand exchange for the bulkier polymeric $Fe(dbmPLA)_3$ catalyst. Overall, shorter reaction times or lower temperatures are noted for these Fe βdk systems versus related bulk polymerizations with Fe catalysts.[1,11]

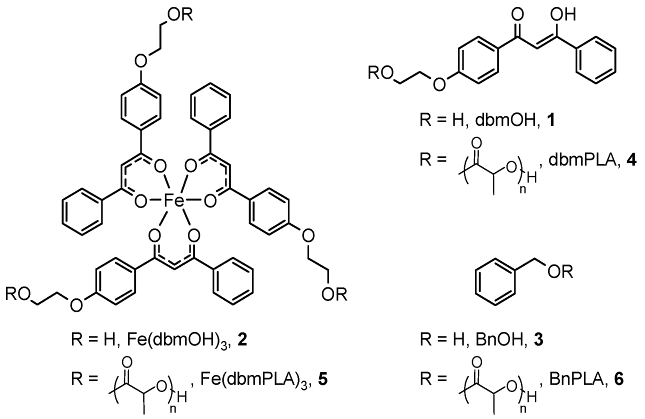

Figure 1. Alcohol initiators and the corresponding polylactide products.

Polymer products were analyzed by GPC in THF with refractive index (RI) and UV/vis detection at either $Fe(dbm)_3$ λ_{max} ($n \rightarrow d^*$)[13] = 480 nm or dbm λ_{max} ($\pi \rightarrow \pi^*$) = 360 nm. For $Fe(dbmPLA)_3$ **5**, the UV/vis trace ($\lambda = 480$ nm) shows that the metal-centered polymer was obtained with control ($M_n = 23\,200$; PDI = 1.06;[14] ~70% monomer conversion) (Figure 2, left). The RI trace, in contrast, is bimodal, with a 3:1 MW ratio between the two peaks. The high MW peak contains *$Fe(dbm)_3$ chromophores*, whereas the low MW peak does not. UV/vis detection at $\lambda = 360$ nm shows that *dbm chromophores* are present in both peaks (data not shown). Partial ligand dissociation from $Fe(dbmOH)_3$ or $Fe(dbmPLA)_3$ during polymerization or GPC analysis may explain these observations.

Reactions involving dbmOH and $Fe(dbm)_3$ lead to polymers with bimodal GPC traces from both the UV/vis ($\lambda = 480$ nm) and RI detectors, indicating multiple $Fe(dbm)_3$-containing products. Ligand exchange during polymerization or product isolation may generate a mixture of mono-, bis-, and tris-dbmPLA iron complexes, $Fe(dbm)_n(dbmPLA)_{3-n}$ ($n = 0-2$). Similar observations were noted

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Table 1. GPC Data, Reaction Times, and Yields for DbmPLA, $Fe(dbmPLA)_3$, and BnPLA Obtained from Initiators **1**−**3** with Different Catalysts[a]

								Demetalated Products[d]		
entry	initiator	catalyst	M_n calcd	M_n[b]	PDI[b]	time (min)	yield[c] (%)	M_n[b]	PDI[b]	yield (%)
1	dbmOH	$Sn(oct)_2$	11 095	6000	1.15	360	63			
2	dbmOH	$Fe(dbm)_3$	11 095	6100/15 500[e]	*e*	540	75[f]	8400	1.13	90
3	dbmOH	$Fe(acac)_3$	11 095	7300/19 700[e]	*e*	180	74[f]	8100	1.12	95
4	$Fe(dbmOH)_3$	$Sn(oct)_2$	33 340	20 100[g]	1.12[g]	10	83	8600	1.33	84
5	$Fe(dbmOH)_3$	none	33 340	23 200[g]	1.06[g]	10	66	8100	1.16	89
6	BnOH	$Sn(oct)_2$	10 920	8500	1.18	25	89			
7	BnOH	$Fe(dbm)_3$	10 920	8400	1.31	35	67[f]	7800	1.37	88
8	BnOH	$Fe(acac)_3$	10 920	9200	1.23	15	76[f]	9200	1.23	95

[a] Reactions run in bulk at 130 °C. Lactide:1° ROH:$Sn(Oct)_2$ 75:1:1/50. Lactide:1° ROH:$Fe(dbm)_3$ or $Fe(acac)_3$ 75:1:1/3. [b] Determined by GPC/RI detection except where indicated; 0.58 correction factor applied to all data.[15] [c] Not corrected for monomer consumption. [d] After HCl treatment. From **1** or **2**: dbmPLA; from **3**: BnPLA. [e] Bimodal RI and UV GPC traces. [f] Not corrected for catalyst present. [g] Determined by GPC/UV detection ($\lambda = 480$ nm).

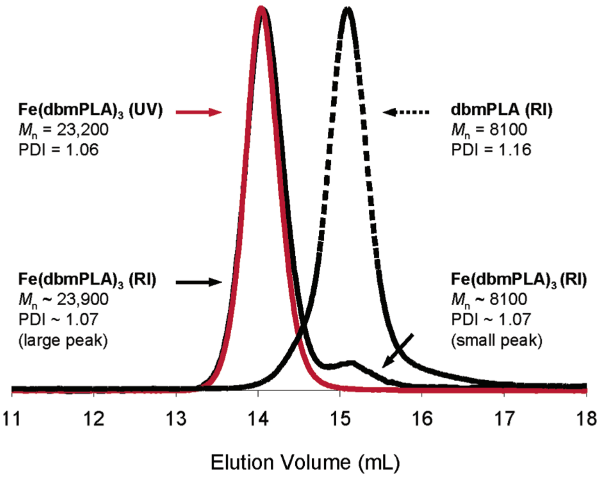

Figure 2. GPC overlay of $Fe(dbmPLA)_3$ and the corresponding dbmPLA macroligand obtained after demetalation by acid treatment.

for reactions with dbmOH and $Fe(acac)_3$ (UV/vis: $\lambda = 437$ nm). BnPLA preparations, in contrast, showed no evidence of $Fe(dbm)_3$ or $Fe(acac)_3$ chromophores coincident with polymer RI peaks by GPC, although the red catalyst remained entrapped in the polymer product after precipitation, which previously has been associated with a coordination−insertion mechanism.[11]

Iron dbmPLA complexes generated from **2**, or **1** with either $Fe(dbm)_3$ or $Fe(acac)_3$ as the catalyst, can be demetalated by HCl treatment (Table 1, right). DbmPLA macroligands are typically produced in good yield with low PDIs (entries 2−5), suggesting that backbone degradation by acid-catalyzed ester hydrolysis is negligible. Figure 2 compares the GPC RI traces for $Fe(dbmPLA)_3$ and the corresponding dbmPLA macroligand obtained after demetalation. The MW of the resulting dbmPLA is ~1/3 that of the Fe star; no UV/vis absorption is seen at 480 nm. Demetalation of $Fe(dbmPLA)_3$, **5**, illustrates how the labile $Fe(dbm)_3$ core can serve as a *reactive center*. Acid treatment also removes the red color of $Fe(dbm)_3$ and $Fe(acac)_3$ catalysts from BnPLA samples. To test the integrity of the dbm metal binding site after demetalation, a dbmPLA macroligand ($M_n = 8100$, entry 5) was recombined with $FeCl_3$ in the presence of Et_3N. The molecular weight and extinction coefficient of the reconstituted product ($M_n = 22\,200$, $\epsilon = 3840$ M^{-1} cm^{-1}) correspond well to those seen for the $Fe(dbmPLA)_3$ starting material ($M_n = 23\,200$, $\epsilon = 3880$ M^{-1} cm^{-1}).

In summary, the iron complex, $Fe(dbmOH)_3$, plays multiple roles in the synthesis of $Fe(dbmPLA)_3$ and its component dbmPLA macroligands, serving as a protecting group, initiator, catalyst, activating group, and functional elements (i.e., chromophores or reactive centers) in the resulting material. By exploiting the multifunctionality of the metal, $Fe(dbmPLA)_3$ complexes can be prepared quickly and conveniently from the metalloinitiator $Fe(dbmOH)_3$, with no additional catalyst. Studies with dbmOH and BnOH demonstrate the broader utility of $Fe(dbm)_3$ and $Fe(acac)_3$ catalysts in ring-opening polymerization. Demetalation with aqueous HCl produces dbmPLA macroligands suitable for chelation to other metals. These materials advance fundamental understanding of coordination chemistry with polymeric ligands and show promise for applications in the fields of biomedicine, photonics, and supported catalysis.

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Supporting Information Available: Experimental details for the synthesis and characterization of $Fe(dbmOH)_3$, $Fe(dbmPLA)_3$, dbmPLA (by demetalation), and BnPLA (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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