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Single-Site Catalysis by Bimetallic Zinc Calixarene Inclusion Complexes

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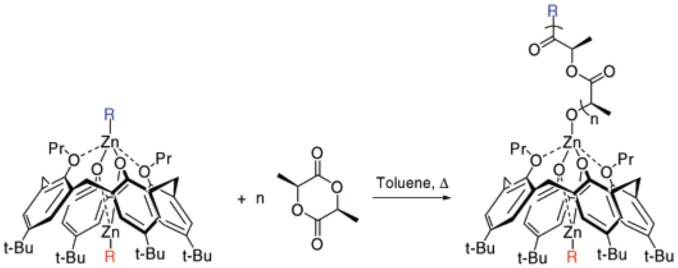
ABSTRACT



Bimetallic alkylzinc calixarene inclusion complexes were prepared and used in the ring-opening polymerization of L-lactide. Polymers with high molecular weight and a low degree of polydispersity were obtained. ^{1}H NMR and diffusion NMR experiments suggest that a single-site mechanism is operative.

Bimetallic zinc complexes lie at the core of a variety of catalytic processes, ranging from enzymatic transformations to asymmetric organic synthesis.[1,2] Generally, enzymatic and organic catalysts possessing bimetallic zinc fragments are believed to involve the tandem participation of both zinc atoms in the catalytic cycle.[3,4] This assumption is often supported by X-ray structure analyses of a number of catalytically active species, which show both zinc atoms in close proximity to each other (normally 3−5 Å apart).[5−8] While both zinc atoms are essential for catalysis, the exact nature of their involvement in the catalytic cycle is often hard to evaluate, and meticulous kinetic analysis is required.[9−11]

To determine the participation mode of two zinc centers in close proximity to each other in a catalytic cycle, it is important to develop a model catalytic bimetallic system that (a) has two zinc atoms in close proximity to each other, (b)

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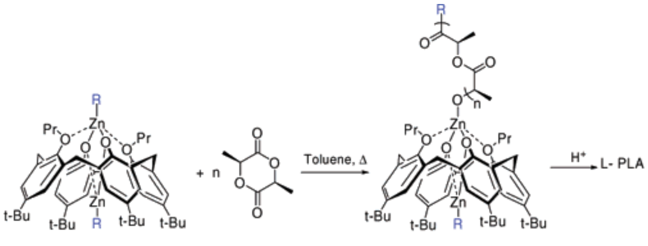
is kinetically stable, and (c) allows easy monitoring of processes taking place in the system during and after the catalysis. If one of the zinc centers is sterically inaccessible, the catalytic reaction would indicate that a single-site mechanism can operate in a bimetallic Zn system.

Recently, we reported a general strategy toward the preparation of bimetallic ethylzinc inclusion complex **1a** and its 1,3-dialkylcalixarene analogues.[12] While both zinc atoms in **1a** share the same aryl oxide framework, the calixarene entrapment protects one of the ethylzinc fragments from an attack by an organic substrate. Thus, these complexes appear to be ideal for mechanistic studies on reactivity modes in bimetallic systems.

As a model reaction we chose the ring-opening polymerization (ROP) of L-lactide. Poly(lactic acid) (PLA) is an important polymer within the broad family of polyesters that received a great deal of recent attention due to its biocompatible and biodegradable properties.[13] It is also used as the hydrophobic core in block copolymers for drug delivery.[14] We found that complex **1a** catalyzes the ROP of L-lactide at temperatures above 60 °C in toluene to produce poly(lactic acid) with a low degree of polydispersity (Scheme 1). Quenching the reaction with aqueous NH_4Cl, followed by polymer precipitation with hexane, gives pure PLA in over 90% isolated yield and free **1a**, confirming that the polymerization is not initiated by the calixarene aryloxide attack at L-lactide. Use of the di-3,3,3-trifluoropropyl analogue of **1a** showed no presence of fluorine in the PLA obtained after the acidic workup.

Scheme 1



1: R= Et (**a**), Me (**b**)

2a, b

The initiation step appears to be the rate-determining one, as large amounts of unreacted **1a** were observed in solution even after completion of the polymerization. This observation is consistent with the fact that the ethylzinc group is a relatively poor nucleophilic initiator and is significantly less reactive than the zinc alkoxide formed after the first insertion step. As a result, the obtained polymers have high molecular weights even at a low L-lactide/**1a** ratio. Switching from the ethylzinc-initiating group to the methylzinc in **1b**, dramatically improved the catalyst's performance. Polymers with very high molecular weight and a low degree of polydispersity were obtained at different substrate-to-catalyst ratios (Table 1). Under the reaction conditions, about 25% of the catalyst reacted, providing the polymers with molecular weights four-times higher than the theoretical values.[15] The unreacted catalyst that remained in solution after the addition of hexane could be recycled and used in further polymerization reactions.

Table 1. Polymerization Properties of Complexes **1a**,**b**

	catalyst	LA/**1** ratio[a]	conversion,[b] %	M_n[c] (kDa)	PDI[c]
1	**1a**	200	98	72	1.45
2	**1b**	50	98	60	1.16
3	**1b**	100	97	103	1.11
4	**1b**	200	98	143	1.06

[a] Solvent, toluene (2 mL); concentration of catalyst 1 μmol/mL, 15 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GPC using polystyrene standards.

^{1}H NMR spectroscopy provided crucial information regarding the reactivity mode of **1** in the ROP of L-lactide. Due to their distinct positions in the complex, the hydrogen atoms of the external and internal methylzinc moieties of the complexes were found to resonate at 0.01 and −2.32 ppm, respectively (Figure 1a). No changes in the ^{1}H NMR spectra were observed upon heating of **1** in C_6D_6 at 60 °C. When the external group initiates the ROP at 60 °C, a new signal of the internal guest methylzinc moiety, next to that of the starting material, appears in the ^{1}H NMR spectrum (Figure 1b). After the reaction completion and repeated precipitation with hexane, the ^{1}H NMR spectrum of the pure polymer shows only the signal of the calixarene-entrapped unreacted methylzinc group at −2.18 ppm, **2b** (Figure 1c).

Further corroboration of the single-site process came from the ^{1}H NMR diffusion experiments.[16,17] Figure 2 shows a stack plot of the signal decay as a function of the gradient strength (g) for the three different polymers **2b** shown in Table 1. The signal decay of both the backbone and the Zn−Me end-group signals are shown. Figure 3 shows the normalized signal decay as a function of the diffusion weighting of the three different PLA polymers prepared, along with the signal decay of the calixarene methylzinc

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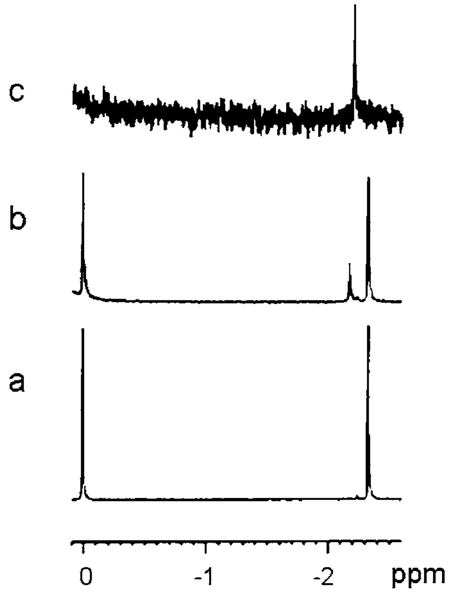


Figure 1. Section of the ^{1}H NMR spectra showing the signals of internal and external methylzinc moieties of the calixarene catalyst recorded (a) before, (b) during, and (c) after the polymerization.

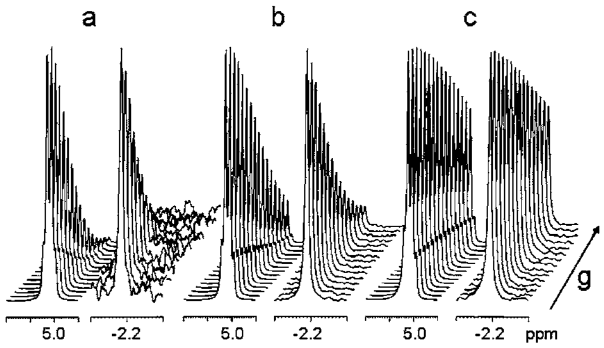


Figure 2. ^{1}H NMR stack plots of the signal decay as a function of the gradient strength (g) for the polymers and their respective end-groups obtained when the LA/**1b** ratios were (a) 50, (b) 100, and (c) 200.

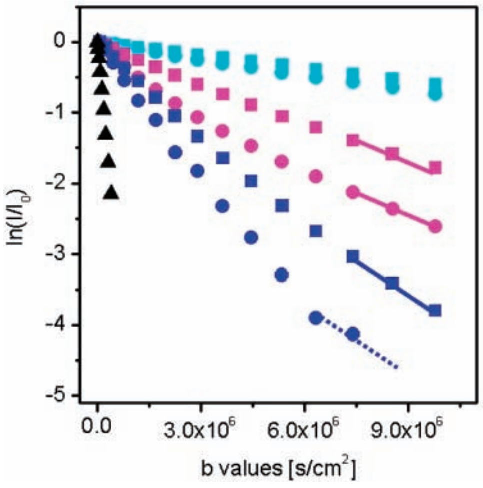


Figure 3. Normalized signal decay ($\ln(I/I_0)$) as a function of the diffusion weighting (b values, $b = \gamma^2 g^2 \delta^2(\Delta - \delta/4)$) for **1b** (▲), the backbone (■), and end-group (◆) signals of the polymers when the LA/**1b** ratios were 50 (blue), 100 (magenta), and 200 (turquoise). The error bars are smaller than the symbols used.

complex **1b**. As expected, the normalized signal decay of **1b** is much larger than that of the polymers due to its much higher diffusion coefficient. For the polymers, the normalized signal decay follows the polymer molecular weight showing the smallest signal decay for the highest molecular-weight polymer consistent with its smaller diffusion coefficient. However, Figure 3 also shows an apparent discrepancy between the normalized signal decay of the polymers and their respective end-groups. While the signal decay of the polymer, as deduced from the backbone signals, could be fitted to a monoexponential function, the signal decay of the end-groups were clearly non monoexponential. Therefore, the signal decays of the end-groups were analyzed using the low- and high-b-value ranges (low and high diffusion weighting). The diffusion coefficients extracted from these analyses are summarized in Table 2. These results show that the polymer end-groups indeed have much lower diffusion coefficients than the (0.557 ± 0.005) × 10^{-5} cm^2 s^{-1} observed for complex **1b**. More importantly, it was found that the diffusion coefficients extracted for the end-group signals in the high-b-value range are nearly identical to those of the backbone signals of the polymers, indicating that the polymers and these end-group signals represent a single chemical entity. It is conceivable that the non-monoexponential decay of the end-group signals in the diffusion experiment is a result of the much higher sensitivity of the end-group signal to low molecular weight strands, which is negligible for the backbone signal of the polymer.

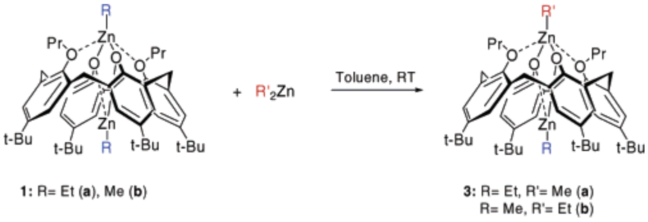
Table 2. Diffusion Coefficients (D) of the Three Polymers Prepared at Different Catalyst/Monomer Ratios and Their Respective End-Groups

	diffusion coefficients		
system[a]	D(benzene) ($\times 10^5$ cm^2 s^{-1})	D(polymer)[b] ($\times 10^7$ cm^2 s^{-1})	D(end-group)[c] ($\times 10^7$ cm^2 s^{-1})
1:50	2.08 ± 0.04	3.97 ± 0.04	7.70 ± 0.80
60 kDa			4.10 ± 0.50
1:100	2.04 ± 0.01	1.84 ± 0.02	4.80 ± 0.10
103 kDa			2.10 ± 0.30
1:200	2.00 ± 0.09	0.61 ± 0.01	1.25 ± 0.07
143 kDa			0.66 ± 0.01

[a] **1b**/L-lactide ratio. [b] Obtained from the decay of the backbone signal of the polymer at 1.3 ppm. [c] Obtained from the signal decay in the low and high diffusion weighting ranges (low and high b values, respectively) of the end-group signal of the polymer at −2.2 ppm.

To ensure that calixarene conformational changes do not play a role during the catalytic process, we prepared complexes **3a**,**b** (Scheme 2)[18] which have unequivalent alkylzinc groups inside and outside the calixarene cavity. Complexes **3a** and **3b** showed polymerization activities similar to **1b** and **1a**, respectively. The end-groups of polymers initiated by **3a** and **3b** demonstrated perfect overlay in the ^{1}H NMR spectra with respective end-groups of polymers obtained from **1a** and **1b**. When an approximately 1:1.5 mixure of **1a** and **3b** was used in catalysis, the same ratio was found for the polymer end-groups in the ^{1}H NMR spectrum (Figure 4a,b).

Scheme 2



1: R= Et (**a**), Me (**b**)

3: R= Et, R'= Me (**a**)
R= Me, R'= Et (**b**)

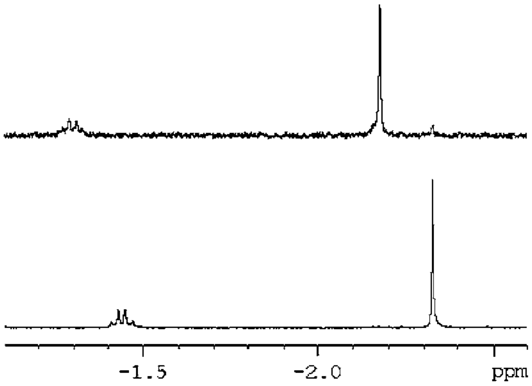
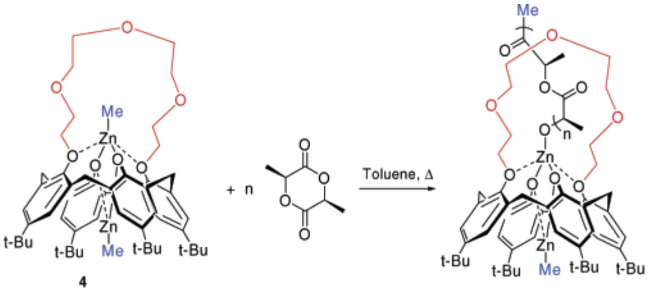


Figure 4. (a) Internal alkylzinc NMR region for a mixture of **1a** and **3b** before the polymerization (bottom). (b) Internal alkylzinc NMR region of the polymer (top).

A mixture of **1b** and **3a** also gave the same ratio in the final product. In both cases, a single GPC trace was observed (Supporting Information). Thus, the catalyst's activity only depends on the external alkylzinc group (the initiator) and is independent of the alkylzinc group inside the calixarene cavity. Finally, we found that complex **4** catalyzes the ROP of L-lactide under the same reaction conditions (Scheme 3), confirming that the monomolecular activation pathway is operative.

Scheme 3



The overall data clearly demonstrate that the second Zn atom remains immersed in the calixarene cavity throughout the polymerization process and does not participate in catalysis. While it still might play an important structural role, these results represent the first *direct* example of the single-site bimetallic catalytically active zinc system.

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Supporting Information Available: Experimental details including selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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