Polymerization

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Isotactic *rac*-Lactide Polymerization with Copper Complexes: The Influence of Complex Nuclearity

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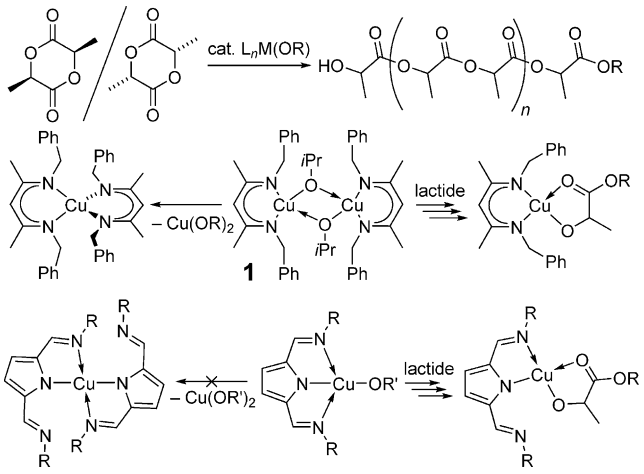
Dedicated to Professor Hans-Herbert Brintzinger on the occasion of his 80th birthday

Abstract: *Diiminopyrrolide copper alkoxide complexes, LCuOR (OR^1 = N,N-dimethylamino ethoxide, OR^2 = 2-pyridyl methoxide), are active for the polymerization of rac-lactide at ambient temperature in benzene to yield polymers with M_w/M_n = 1.0–1.2. X-ray diffraction studies showed bridged dinuclear complexes in the solid state for both complexes. While $LCuOR^1$ provided only atactic polylactide, $LCuOR^2$ produced partially isotactic polylactide (P_m = 0.7). The difference in stereocontrol is attributed to a dinuclear active species for $LCuOR^2$ in contrast to a mononuclear species for $LCuOR^1$.*

The biocompatibility of polyesters and their potential biodegradability in the human body or the environment has generated interest in the controlled polymerization of lactone monomers. In particular, the polymerization of lactide to polylactic acid (PLA) has been widely studied (Scheme 1) because PLA is marketed as a biodegradable packaging material and lactide/glycolide copolymers find medical applications as biodegradable sutures, bone grafts, or drug delivery carriers.[1–5] Although a large variety of metal complexes have been investigated for *rac*-lactide polymerization,[6–17] the factors determining stereochemistry in the coordination–insertion polymerization of *rac*-lactide often remain unclear. It is well established that chain-end control by the growing polymer chain typically leads to a preference for alternating *RR*,*SS*-insertion, which can lead to highly stereoregular heterotactic PLA given sufficient bulk of the spectator ligands.[18] Isoselective polymerization is rare outside group 13 metal catalysts and mechanisms of stereocontrol are often poorly understood. In salan aluminum complexes, for example, Gibson et al. reported in 2004 a drastic change in stereocontrol from highly isotactic (P_m = 0.70) to highly heterotactic (P_m = 0.04) upon simple exchange of phenyl for 2,4-dichlorophenyl substituents.[19] Only recently, Kol et al. showed that the polymerization is autoinhibiting for dichlorophenyl substituents and requires chain transfer to a catalyst centre of opposite chirality to continue.[20] In another example, Williams et al. reported a likewise dramatic change of stereocontrol from highly isotactic (P_m = 0.75) in lutetium phosphasalen complexes to heterotactic (P_m = 0.28) in the analogous lanthanum complex and attributed this to increased ligand flexibility.[21]



Scheme 1. Copper diketiminate and diiminopyrrole complexes in lactide polymerization.

We have recently reported the first highly active copper-based catalysts for the polymerization of *rac*-lactide,[22–24] which was shortly followed by similar work from others.[25–29] The catalytic performance of **1** (Scheme 1) in particular was outstanding: very high activity, no evidence for side reactions or chain termination even in the absence of monomer, and narrow polydispersities even under immortal polymerization conditions. The main drawbacks of **1** were the unfavourable Schlenk equilibrium (Scheme 1), which limited catalyst optimization, and the lack of stereocontrol.[23] In an attempt to solve the former by switching from diketiminate to diiminopyrrole ligands, we actually addressed the latter due to the unexpected influence of catalyst nuclearity on polymerization stereocontrol.

Diiminopyrrolides are tridentate meridional ligands, but they are more often found in a bidentate coordination owing to the steric constraints imposed by the five-membered ring. In fact, the Cambridge Structural Database reports 11 structures with a tridentate diiminopyrrolide and 20 structures with bidentate coordination and a dangling imino group.[30] We thus hypothesized that tridentate diiminopyrrolide ligands might stabilize copper alkoxide complexes against unwanted ligand exchange in the absence of monomer (Scheme 1). However, reaction of diiminopyrrole **2**H with $Cu(OiPr)_2$ under a variety of reaction conditions did not provide heteroleptic complexes (**2**)CuO*i*Pr. Apparently, the tridentate coordination of the ligand was too disfavoured in

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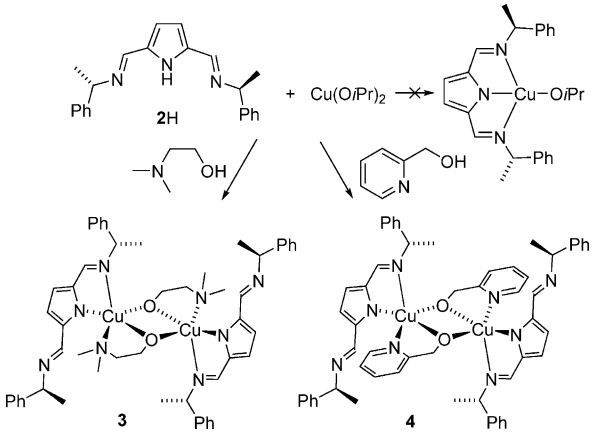
this case. Addition of either 2-pyridyl methanol or *N*,*N*-dimethylamino ethanol to the reaction, on the other hand, cleanly yielded heteroleptic complexes **3** and **4** (Scheme 2).

X-ray diffraction studies on both complexes (Figure 1, and Figures S1, S2 and Table S1 in the Supporting Information) showed that they did not crystallize as monomeric square-planar complexes but as dimers with a bridging oxygen atom.[31] Although τ-values between 0.4–0.6 argue for a coordination geometry intermediate between trigonal bipyramidal and square pyramidal,[32] the structures are best described as two square-pyramidal copper complexes: the distances between the basal ligands and the metal center are comparable to those observed in tetracoordinated copper complexes, while distances to the imino group in the apical position are significantly longer (Table S1).

Complexes **3** and **4** are active in the solution polymerization of *rac*-lactide under mild conditions (Table 1, and Table S2) and with good reproducibility (see Table 1, entries 1,2 and 3,4, respectively). Polymerizations with **4** show an induction period of 30–60 min (Figures 2 and Figures S2–S4), attributed to the requirement to dissociate



Scheme 2. Synthesis of copper complexes **3** and **4**.

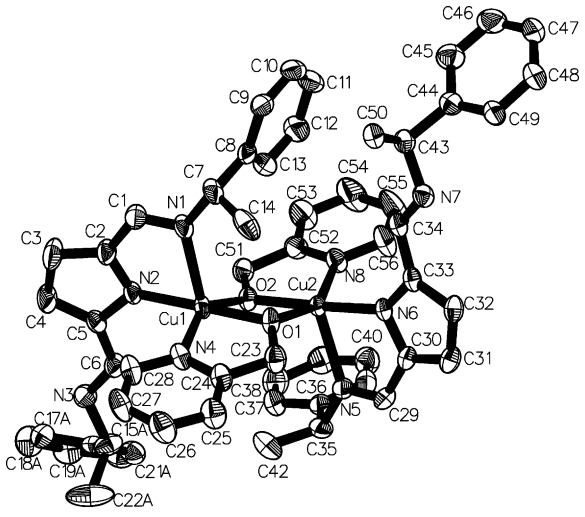


Figure 1. Crystal structure of **4**. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms and the minor part of the disordered methylbenzyl substituent omitted are for clarity.

Table 1: *Rac*-Lactide polymerizations with **3** and **4**.[a]

Entry	Catalyst	Conversion[b]	k_{obs} [h^{-1}]	P_m[c]
1	**3**	0.84/0.84	0.37(1)	0.44
2	**3**	0.89/0.90	0.36(2)	0.44
3	**4**	0.86/0.86	0.36(1)	0.68
4	**4**	0.86/0.98	0.30(1)	0.68
5	**3** + 2 pyridine	0.93/0.94	0.46(2)	0.44
6	**3** + 20 pyridine	0.98/0.98	0.51(3)	0.42
7	**3** + 40 pyridine	0.98/0.98	0.78(2)	0.44
8	**3** + 1 $C_5H_4NCH_2OH$	0.65/0.97	n. d.[d]	0.70
9	**4** + 4 $PhCH_2OH$	0.95/0.98	0.41(1)	0.70

[a] Conditions: C_6D_6, ambient temperature, [catalyst] = 1 mmol L^{-1}, i.e., [Cu] = 2 mmol L^{-1}, [lactide] = 200 mmol L^{-1}. [b] after 8 h/after 24 h. [c] Determined from homodecoupled ^1H NMR. [d] Induction period = 5–6 h, no clean pseudo-first-order behaviour.

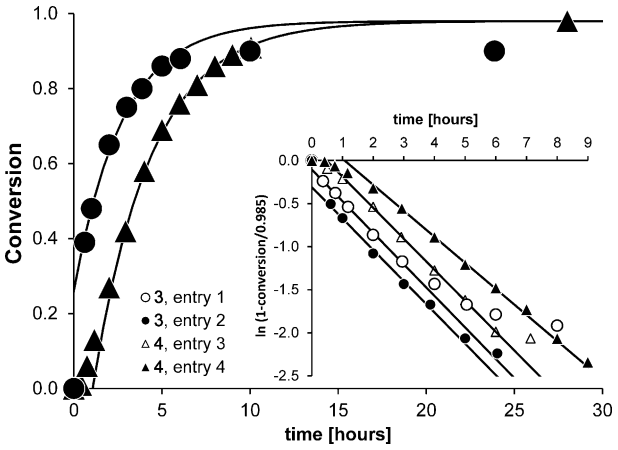
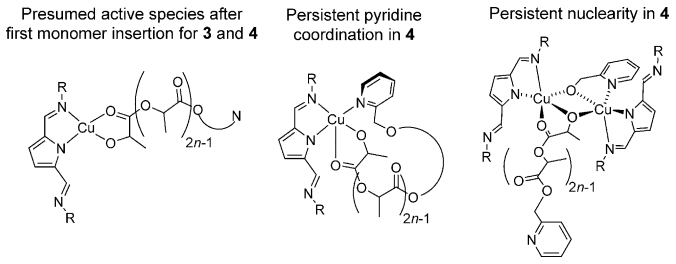


Figure 2. Conversion vs. time profiles for lactide polymerization (Table 1, entries 1–4) with **3** (circles) and **4** (triangles). The inset shows the linearized conversion–time plot for a first-order reaction.

the N donor of the chelating alcohol prior to first monomer insertion. The lack of an observable induction period for **3** indicates facile substitution of the amine ligand by lactide. Pseudo-first-order rate constants of 0.30(1)–0.37(1) h^{-1} for **3** and **4** are indistinguishable within the margin of error (Table 1). Incomplete conversions and slightly negative curvatures of the ln(conversion) vs. time plots indicate some degree of catalyst decomposition during polymerization (see the Supporting Information). In fact, when a second batch of 200 equivalents of lactide was added to the polymerization reaction after 24 h, no or greatly reduced polymerization activities were observed for **3** and **4**, respectively. All obtained polymers showed narrow polydispersities with $M_w/M_n = 1.0$–1.2 (Table S2).

Since **3** and **4** differ only in the nature of the initiating alkoxide, they should provide the same, most likely monomeric,[23] active species after the very first insertion reactions (Scheme 3). Surprisingly, **3** produces essentially atactic PLA (the typical slight heterotactic bias owing to chain-end control is observed), while **4** shows a strong isotactic preference with $P_m = 0.68$–0.70 (Table 1, entries 1–4). Based on the stronger coordination of pyridyl methoxide indicated by the induction period, a possible differentiation in the active species might

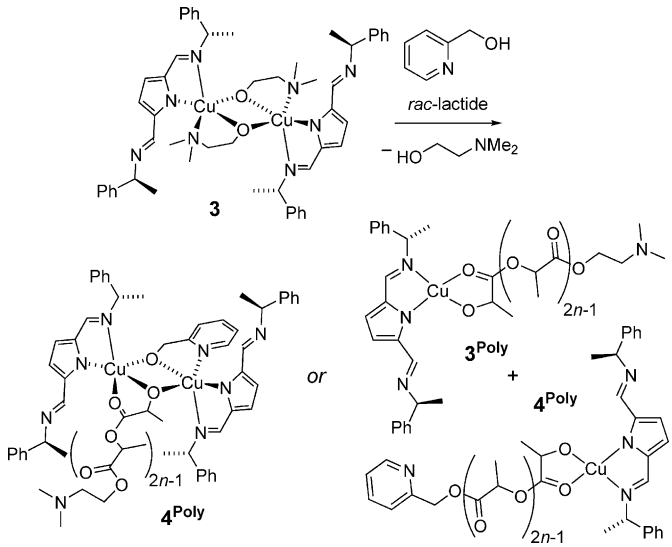


Scheme 3. Possible active species in polymerizations with **3** and **4**.

arise from persistent coordination of the pyridine group (Scheme 3). Polymerizations with **3** were thus conducted in the presence of 2, 20, or 40 equivalents of pyridine. However, while catalyst decomposition was reduced in the presence of excess pyridine (see the Supporting Information), polymerizations with **3** continued to yield essentially atactic PLA (Table 1, entries 5–7).

An alternative explanation for the impact of the initiating alcohol is based on two observations: First, insertion into pyridyl methoxide is approximately 100 times slower than later chain growth (Figure S6). Second, polymerizations with **4** afforded polymer molecular weights twice as high ($M_n = 44$–$45\ kg\,mol^{-1}$) as polymerizations with **3** ($M_n = 21$–$22\ kg\,mol^{-1}$), despite comparable conversions of lactide per catalyst. Both observations indicate that only one of the two pyridyl methoxides initiates chain growth. The unreacted pyridyl methoxide ligand is then available to retain the dinuclear nature of the complex (Scheme 3). Since UV/Vis spectra are mainly dominated by ligand-based transitions (Figure S8), the dinuclear nature of the active species of **4** was confirmed by lactide polymerization with **3** in the presence of one equivalent of pyridyl methanol. The isotacticity of the obtained polymer (Table 1, entry 8) is identical to those obtained with **4**. If the active species of **4** were mononuclear, at most half of the catalyst present could be transformed into the active species of **4** (Scheme 4) and stereoselectivities would be at best an average between **3** and **4**. Reproduction of the stereochemistry of **4** with only 0.5 equivalents pyridyl methanol per copper center thus confirms that the active species of **4** is indeed dinuclear and the crucial role of pyridyl methoxide in preserving the nuclearity of the complex. Pyridyl methanol without **3** is inactive (Table S2). Polymerizations with **4** in the presence of 2–4 equivalents of benzyl alcohol or pyridyl methanol yielded polymer with reduced molecular weight (Table S2) but unchanged isotacticity (Table 1, and Table S2). Stereocontrol is thus retained even under immortal polymerization conditions, i.e., in the presence of fast chain-transfer reactions.

Catalyst nuclearity has been reported previously to influence lactide polymerization properties,[33–49] but only in three cases was it correlated to stereocontrol: Williams et al. observed a change between heterotactic and atactic polymerization based on the nuclearity of the catalyst.[50] Stereocontrol was attributed to the presence of coordinated THF in the mononuclear catalyst. Sun et al. reported C_1-symmetric dinuclear zirconium complexes that show slightly increased isotactic preferences compared to similar mononuclear complexes.[51] For indium complexes, Mehrkhodavandi et al. correlated reduced isotacticities with increased dissociation of a dinuclear active species.[52–55] The intensively studied indium (pre-)catalysts adopt chiral coordination geometries and exhibit catalytic-site control. As expected for the polymerization of *rac*-lactide with an enantiopure site-selective catalyst, systematic variations of P_m with conversion were observed with these systems. It is unlikely that **4** follows the same mechanism. Despite the enantiopure ligand employed, the coordination geometry in dinuclear **3** and **4** is essentially centrosymmetric with a (*C*)- and an (*A*)-configurated copper atom, and polymerizations with **4** showed only random variations of P_m with conversion (Figure S7). The chirality of the N substituent is thus unlikely to be the source of the observed stereocontrol.



Scheme 4. Lactide polymerization with **3** in the presence of pyridyl methanol.

In conclusion, diiminopyrrole complex **4** is the first copper-based catalyst to show a preference for isotactic chain growth in *rac*-lactide polymerization, which is promising given the high activity and stability achieved with copper diketiminate catalysts. Stereocontrol is solely dependent on the dinuclear nature of the catalyst, which is to our knowledge unprecedented in lactide polymerization. The origin of stereocontrol might either involve catalytic-site control by a racemic mixture of C_1-symmetric complexes or chain-end control mediated by the configuration of the catalytic side.[34] While analysis of stereoerrors seems to support the latter mechanism (Figure S9), we are currently exploring further details of this mechanism, such as the influence of the chiral N substituent, of the pendant imino group, and of additional donor ligands.

Keywords: copper · homogeneous catalysis · lactide · N ligands · ring-opening polymerization

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