

# Ring-opening of lactides and related cyclic monomers by triaryltin(IV) alkoxides and amides†

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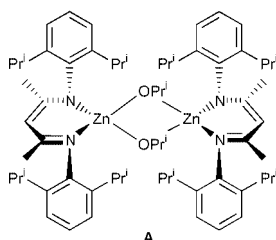
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$\text{Ar}_3\text{SnX}$ , where  $\text{Ar} = p\text{-MeC}_6\text{H}_4$ ,  $p\text{-CF}_3\text{C}_6\text{H}_4$  or  $\text{Ph}$  and  $\text{X} = \text{O}^t\text{Bu}$  or  $\text{NMe}_2$ , are catalyst precursors for the ring-opening of lactides in benzene at  $80^\circ\text{C}$  and the rate of ring-opening of lactides and a variety of related cyclic monomers is influenced by  $\text{Ar}$  and  $\text{X}$  such the chemistry of the ring-opening event and the initially formed product may be examined.

The ring-opening polymerization of lactides (*L*, *D*, *rac* and *meso*) by well-defined coordination complexes is a topic of current interest since polylactides (PLAs) have numerous applications ranging from bulk packing materials<sup>1</sup> to drug delivery reagents,<sup>2</sup> artificial sutures<sup>2,3</sup> and scaffolds<sup>4</sup> for tissue engineering. There have been some exciting recent reports documenting stereoselective polymerization of *rac*- and *meso*-lactides to give heterotactic, isotactic and syndiotactic PLAs.<sup>5</sup> Much remains to be learned at this time, however, since very little is known about the details of factors controlling the rate of ring-opening, the stereoselectivity of this event and the deleterious side reactions of both intra- and inter-chain transfer and transesterification reactions, which can lead to loss of control of stereochemistry and molecular weight of PLAs. For example, the  $\beta$ -diiminate complex  $[(\text{BDI})\text{Zn}(\text{OPr}^i)]_2$  shown in **A** is reported to give >90% heterotactic PLA from *rac*-lactide



at  $25^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$ <sup>5c</sup> whereas the related magnesium complex gives atactic polymer under similar conditions with rapid transesterification.<sup>6</sup>

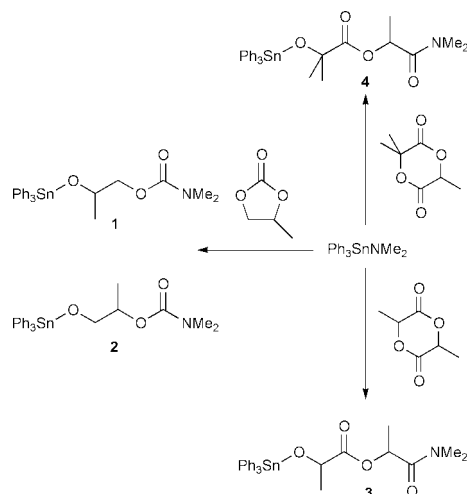
The stereocontrol in the polymerization of *rac*-lactide by  $[(\text{BDI})\text{Zn}(\text{OPr}^i)]_2$  has been attributed to end-group control which is fostered by the bulky BDI ligand, yet even bulkier ligands such as pyrazolylborate LMOR complexes [ $\text{L} = (\text{3-Bu}^t\text{pz})_3\text{BH}$ ,  $\text{M} = \text{Mg}$  and  $\text{Zn}$ ] show little stereoselectivity.<sup>7</sup> We reasoned that much might be learned from studies of the kinetics of reactions employing  $\text{Ar}_3\text{SnOR}$  catalyst precursors since, unlike trispyrazolylborate ligands or other tridentate ligands, reversible bond breaking is not likely for the  $\text{Sn-C}$  and  $\text{Sn-O}$  bonds under mild conditions. Moreover the influence of electronic and steric factors can be examined by the use of *para*- and *meta*-substituents on the aryl ligands. We report here on initial findings from studies involving  $\text{Ar}_3\text{SnX}$  precursors, where  $\text{Ar} = p\text{-MeC}_6\text{H}_4$ ,  $p\text{-CF}_3\text{C}_6\text{H}_4$  or  $\text{Ph}$  and  $\text{X} = \text{O}^t\text{Bu}$  or  $\text{NMe}_2$ .

The compounds  $\text{Ar}_3\text{SnX}$  were prepared from either meta-theric reactions involving the respective  $\text{Ar}_3\text{SnCl}$  compound and  $\text{LiNMe}_2$  or by an alcoholysis reaction involving  $\text{Ar}_3\text{SnNMe}_2$  and  $\text{Bu}^t\text{OH}$  in hydrocarbons.<sup>‡</sup> The compounds are white, hydrocarbon-soluble, microcrystalline materials with the exception of  $(p\text{-MeC}_6\text{H}_4)_3\text{SnNMe}_2$  which is a colorless oil. These compounds were characterized by  $^1\text{H}$ ,  $^{13}\text{C}\{\text{H}\}$  and  $^{119}\text{Sn}$  NMR spectroscopy (and for  $\text{Ar} = p\text{-CF}_3\text{C}_6\text{H}_4$  by  $^{19}\text{F}$ ) together with mass spectrometry, IR spectroscopy and elemental analysis. These compounds were found to be kinetically inert at  $80^\circ\text{C}$  in benzene, conditions under which ring-opening polymerization (ROP) of lactides was subsequently studied.

In a typical polymerization reaction 50 equivalents of lactide was allowed to react with the  $\text{Ar}_3\text{SnX}$  compound in  $\text{C}_6\text{D}_6$  at  $80^\circ\text{C}$  (or in some instances at 52, 67 and  $70^\circ\text{C}$ ) and the reaction was monitored with time by NMR spectroscopy. Reactions were quite slow requiring *ca.* 3 days to approach 90% conversion. From the plots of  $-\ln(A/A_0)$  vs. time (where  $A$  = concentration of lactide) we can estimate the rates of consumption of lactide to be  $k_{\text{obs}} = 2.8(1) \times 10^{-6}$  and  $2.0(1) \times 10^{-6} \text{ s}^{-1}$  for  $\text{X} = \text{NMe}_2$  and  $\text{Ar} = p\text{-CF}_3\text{C}_6\text{H}_4$  and  $\text{Ph}$ , respectively. In reactions between  $\text{Ph}_3\text{SnO}^t\text{Bu}$  and *L*-lactide, we can also obtain a reasonable estimate of the rate of the initial ring-opening event,  $k_{\text{ro}} = 2.8(1) \times 10^{-6} \text{ s}^{-1}$  which is faster than the rate of propagation  $k_{\text{prop}} = 1.4(1) \times 10^{-6} \text{ s}^{-1}$ . From studies of the rates of polymerization reactions with temperature we have obtained estimates of the enthalpy and entropy of activation for the ring-opening event for  $\text{Ar} = \text{Ph}$  and  $\text{X} = \text{NMe}_2$  at a [lactide]:[catalyst] ratio of 50 to 1:  $\Delta H^\ddagger = 12(1) \text{ kcal mol}^{-1}$  and  $\Delta S^\ddagger = -51(5) \text{ cal K}^{-1} \text{ mol}^{-1}$ . The rather large entropy of activation is consistent with a bimolecular reaction with a highly ordered transition state. However, the role of solvation has not been examined. It is noteworthy that these polymerization reactions are slower than those recently reported for a tin(II) catalyst system employing  $(\text{BDI})\text{SnOPr}^i$ <sup>8</sup> as an initiator and also that whereas the latter shows a preference for heterotactic, *rmr* and *mrm*, tetrads in the polymerization of *rac*-lactide, no such preference is found in reactions employing  $\text{Ar}_3\text{SnX}$  precursors. The rate of polymerization is probably influenced by the relative polarity of the  $\text{Sn-OR}$  bond which is greater for  $\text{Sn(II)}$  than  $\text{Sn(IV)}$  but, given the relative size of  $\text{Sn(II)}$  vs.  $\text{Sn(IV)}$  ( $0.69 \text{ \AA}$ ),<sup>9</sup> the stereoselectivity attributed to end-group control involving the  $\text{SnOC}^*\text{HMeC}(\text{O})\text{OC}^*\text{HMeC}(\text{O})\text{OP}$  unit of the growing polymer chain must arise from the pocket created by the two 2,6-diisopropylphenyl ligands in the  $(\text{BDI})\text{M}(\text{OR})$  catalyst systems.

Although the  $\text{Ar}_3\text{SnX}$  precursors are kinetically inert at  $80^\circ\text{C}$  in benzene-*d*<sub>6</sub> for several days and the system that is initially active in the polymerization can be reasonably represented by  $\text{Ar}_3\text{Sn}(\text{OP})$ , where  $\text{OP}$  represents the growing polymer chain, with the onset of polymerization,  $\text{Ar}_4\text{Sn}$  compounds are formed (as identified by  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{119}\text{Sn}$  NMR as well as electrospray mass spectrometry).  $\text{Ar}_4\text{Sn}$  compounds are inactive and the systems that are believed to be catalytically active are  $\text{Ar}_{3-n}\text{Sn}(\text{OP})_n$ , where  $n = 1$  or  $2$ . The formation of  $\text{Ar}_4\text{Sn}$  clearly implicates the facility of chain transfer and, in addition, from studies of molecular weight distributions with time, we

† Electronic supplementary information (ESI) available: additional experimental data. See <http://www.rsc.org/suppdata/cc/b1/b102896k/>

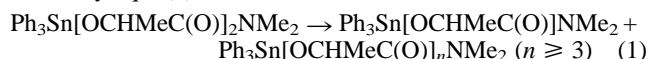


Scheme 1

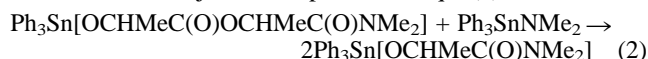
observe extensive transesterification. Thus, even the seemingly simple and kinetically slow system for the ROP of lactides employing  $\text{Ar}_3\text{SnX}$  precursors has proved to be complicated.

One important point to emerge from these studies is the rate of ring-opening of lactide and related monomers occurs much more rapidly when  $\text{X} = \text{NMe}_2$  than for  $\text{X} = \text{OBu}^t$ . Thus, at room temperature,  $\text{Ph}_3\text{SnNMe}_2$  in benzene ring-opens the cyclic oxygenates shown in Scheme 1. The regiochemistry of the ring-opening event can be reliably determined from NMR studies.<sup>‡</sup> The  $\text{Sn}-\text{O}^{13}\text{C}$  carbon shows coupling to  $^{119}\text{Sn}$  and the amide methyl protons appear as two singlets due to the restricted rotation about the  $\text{C}-\text{NMe}_2$  bond. Notable here is the ring-opening of propylene carbonate (PC) to give **1** and **2** (Scheme 1) a required step in the ring-opening decarboxylation polymerization of PC by tin catalysts at higher temperatures.<sup>10</sup>

The ring-openings shown in Scheme 1 convert an  $\text{Sn}-\text{NMe}_2$  group to an  $\text{Sn}-\text{OR}$  group and at  $25^\circ\text{C}$  no further insertion/ring-opening occurs. The compounds are, however, not indefinitely persistent in solution. The compound  $\text{Ph}_3\text{Sn}[\text{OCHMeC}(\text{O})\text{OCHMeC}(\text{O})\text{NMe}_2]$  **3** which we can represent as  $\text{Ph}_3\text{Sn}[\text{OCHMeC}(\text{O})]_2\text{NMe}_2$  is labile to transesterification reactions as represented by eqn. (1).



Reaction (1) is also accompanied by chain transfer and phenyl migration yielding  $\text{Ph}_4\text{Sn}$ . The compound  $\text{Ph}_3\text{Sn}[\text{OCMe}_2\text{C}(\text{O})\text{OCHMeC}(\text{O})\text{NMe}_2]$  **4** is less labile to transesterification of the type shown in eqn. (1), presumably because of the bulky *gem*-dimethyl group, but still enters into chain/aryl group transfer. However, **4** does react with  $\text{Ph}_3\text{Sn}(\text{OBu}^t)$  to give  $\text{Ph}_3\text{SnOCHMeC}(\text{O})\text{NMe}_2$  and  $\text{Ph}_3\text{Sn}[\text{OCMe}_2\text{C}(\text{O})\text{OBu}^t]$ , products of transesterification.  $\text{Ph}_3\text{SnOCHMeC}(\text{O})\text{NMe}_2$  is formed from the reaction between  $\text{Ph}_3\text{SnNMe}_2$  and lactide (2 : 1 ratio) in benzene as the major kinetic product in eqn. (2).



Reactions employing  $\text{Ph}_2\text{Sn}(\text{NMe}_2)_2$  and lactide (1 : 1 ratio) yield  $\text{Ph}_2\text{Sn}[\text{OCHMeC}(\text{O})\text{NMe}_2]_2$  by consecutive ring-opening of lactide followed by intramolecular attack on the chain, eqn. (3).



In conclusion, these initial studies reveal that this seemingly most simple system for ring-opening polymerization of lactide is complicated by mischievous side-reactions. Insight into the latter, namely ligand exchange and transesterification and the ring-opening event can be gleaned from studies of model reactions such as those shown in reactions (1), (2) and (3).

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## Notes and references

<sup>‡</sup> General considerations: the synthesis of  $\text{R}_3\text{SnNMe}_2$  and  $\text{Ph}_2\text{Sn}(\text{NMe}_2)_2$  complexes was based on the reported synthesis<sup>11</sup> of  $\text{Ph}_3\text{SnNMe}_2$  and  $\text{Ph}_2\text{Sn}(\text{NMe}_2)_2$ . See ESI for additional spectroscopic data.<sup>†</sup>

$\text{SnPh}_3[\text{OCHMeC}(\text{O})\text{OCHMeC}(\text{O})\text{NMe}_2]$ :  $\delta_{\text{H}}$ (400 MHz,  $\text{C}_6\text{D}_6$ ): 0.99 [d,  $\text{CHMeC}(\text{O})\text{NMe}_2$ , 3H], 1.53 (d,  $\text{SnOCHMe}$ , 3H), 2.11 (s,  $\text{NMe}_2$ , 3H), 2.47 (s,  $\text{NMe}_2$ , 3H), 4.75 (q,  $\text{SnOCHMe}$ , 1H), 4.83 [q,  $\text{CHMeC}(\text{O})\text{NMe}_2$ , 1H], 7.16 (m, *m*- and *p*-H, 9H), 7.80 (dd, *o*-H, 6H,  $J_{\text{HH}}$  7.9, 1.5 Hz,  $^{119}/^{117}\text{Sn}$  satellites  $J_{\text{SnH}}$   $^{117}\text{Sn}$  64,  $^{119}\text{Sn}$  49 Hz).

$\text{SnPh}_3[\text{OCHMeC}(\text{O})\text{NMe}_2]_2$ :  $\delta_{\text{H}}$ (400 MHz,  $\text{C}_6\text{D}_6$ ): 1.43 (d,  $\text{SnOCHMe}$ , 6H), 1.87 (s,  $\text{NMe}_2$ , 6H), 2.26 (s,  $\text{NMe}_2$ , 6H), 4.87 (q,  $\text{SnOCHMe}$ , 2H), 7.21 (t, *p*-H, 2H), 7.35 (t, *m*-H, 4H), 8.37 (dd, *o*-H, 4H,  $J_{\text{HH}}$  7.6, 1.2 Hz,  $^{119}/^{117}\text{Sn}$  satellites  $J_{\text{SnH}}$   $^{117}\text{Sn}$  75,  $^{119}\text{Sn}$  59 Hz).

$\text{SnPh}_3[\text{OCMe}_2\text{C}(\text{O})\text{OCHMeC}(\text{O})\text{NMe}_2]$ :  $\delta_{\text{H}}$ (500 MHz,  $\text{C}_6\text{D}_6$ ): 1.06 (d,  $\text{CHMeCONMe}_2$ , 3H), 1.56 (s,  $\text{SnOCMe}_2$ , 3H), 1.65 (s,  $\text{SnOCMe}_2$ , 3H), 2.12 (s,  $\text{NMe}_2$ , 3H), 2.47 (s,  $\text{NMe}_2$ , 3H), 4.87 [q,  $\text{CHMeCO}(\text{O})\text{NMe}_2$ , 1H], 7.17 (m, *p*-H, 3H), 7.23 (m, *m*-H, 6H), 7.87 (dd, *o*-H, 6H,  $J_{\text{HH}}$  8.2, 1.3 Hz,  $^{119}/^{117}\text{Sn}$  satellites  $J_{\text{SnH}}$   $^{117}\text{Sn}$  64,  $^{119}\text{Sn}$  48 Hz).

**Polymerization reactions:** standard solutions of the appropriate  $\text{R}_3\text{SnX}$  complex (0.027 M) and *L*- or *rac*-lactide (0.338 M) were prepared in  $\text{C}_6\text{D}_6$  and stored in a dry-box. Aliquots (100, 50, 25 and 12.5  $\mu\text{L}$  for 25 : 1, 50 : 1, 100 : 1 and 200 : 1, respectively) of  $\text{R}_3\text{SnX}$  solutions were transferred along with an aliquot (200  $\mu\text{L}$ ) of either *L*- or *rac*-lactide to a J. Young<sup>®</sup> NMR tube. The total volume was made up to 800  $\mu\text{L}$  with  $\text{C}_6\text{D}_6$  to ensure a constant lactide concentration (0.084 M). Rates of polymerization were determined from  $^1\text{H}$  NMR data where the sum of the area of monomer and polymer peaks ( $\text{CH}$  and  $\text{CH}_3$ ) was assumed to be 100% and rates of disappearance of monomer were calculated by the subtraction of the integral of the polymer peaks from the integral of the monomer peaks and dividing by the concentration of monomer at  $t = 0$ . The natural log of this ratio was then plotted against time with a straight line being indicative of pseudo-first order kinetics. The gradient of this plot was used to determine values of  $k_{\text{obs}}$ .

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