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

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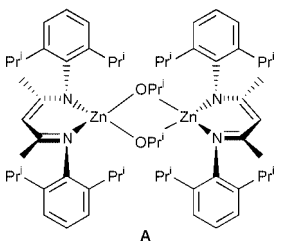
Ar_3SnX, where Ar = *p*-MeC_6H_4, *p*-$CF_3C_6H_4$ or Ph and X = OBu^t or NMe_2, are catalyst precursors for the ring-opening of lactides in benzene at 80 °C and the rate of ring-opening of lactides and a variety of related cyclic monomers is influenced by Ar and X such the chemistry of the ring-opening 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[1] to drug delivery reagents,[2] artificial sutures[2,3] and scaffolds[4] 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.[5] 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 β-diiminate complex $[(BDI)Zn(OPr^i)]_2$ shown in **A** is reported to give >90% heterotactic PLA from *rac*-lactide



A

at 25 °C in CH_2Cl_2[5c] whereas the related magnesium complex gives atactic polymer under similar conditions with rapid transesterification.[6]

The stereocontrol in the polymerization of *rac*-lactide by $[(BDI)Zn(OPr^i)]_2$ has been attributed to end-group control which is fostered by the bulky BDI ligand, yet even bulkier ligands such as pyrazolylborate LMOR complexes [L = $(3\text{-}Bu^tpz)_3BH$, M = Mg and Zn] show little stereoselectivity.[7] We reasoned that much might be learned from studies of the kinetics of reactions employing Ar_3SnOR catalyst precursors since, unlike trispyrazolylborate ligands or other tridentate ligands, reversible bond breaking is not likely for the Sn–C and 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 Ar_3SnX precursors, where Ar = *p*-MeC_6H_4, *p*-$CF_3C_6H_4$ or Ph and X = OBu^t or NMe_2.

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

The compounds Ar_3SnX were prepared from either metathetic reactions involving the respective Ar_3SnCl compound and $LiNMe_2$ or by an alcoholysis reaction involving Ar_3SnNMe_2 and Bu^tOH in hydrocarbons.‡ The compounds are white, hydrocarbon-soluble, microcrystalline materials with the exception of $(p\text{-}MeC_6H_4)_3SnNMe_2$ which is a colorless oil. These compounds were characterized by ^1H, $^{13}C\{H\}$ and ^{119}Sn NMR spectroscopy (and for Ar = *p*-$CF_3C_6H_4$ by ^{19}F) together with mass spectrometry, IR spectroscopy and elemental analysis. These compounds were found to be kinetically inert at 80 °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 Ar_3SnX compound in C_6D_6 at 80 °C (or in some instances at 52, 67 and 70 °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 $k_{obs} = 2.8(1) \times 10^{-6}$ and $2.0(1) \times 10^{-6}$ s^{-1} for X = NMe_2 and Ar = *p*-$CF_3C_6H_4$ and Ph, respectively. In reactions between Ph_3SnOBu^t and L-lactide, we can also obtain a reasonable estimate of the rate of the initial ring-opening event, $k_{ro} = 2.8(1) \times 10^{-6}$ s^{-1} which is faster than the rate of propagation $k_{prop} = 1.4(1) \times 10^{-6}$ 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 Ar = Ph and X = NMe_2 at a [lactide]:[catalyst] ratio of 50 to 1: $\Delta H^{\ddagger} = 12(1)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -51(5)$ cal K^{-1} 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 $(BDI)SnOPr^i$[8] 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 Ar_3SnX precursors. The rate of polymerization is probably influenced by the relative polarity of the Sn–OR bond which is greater for Sn(II) than Sn(IV) but, given the relative size of Sn(II) *vs.* Sn(IV) (0.69 Å),[9] the stereoselectivity attributed to end-group control involving the SnOC*HMeC(O)OC*HMeC(O)OP unit of the growing polymer chain must arise from the pocket created by the two 2,6-diisopropylphenyl ligands in the (BDI)M(OR) catalyst systems.

Although the Ar_3SnX precursors are kinetically inert at 80 °C in benzene-d_6 for several days and the system that is initially active in the polymerization can be reasonably represented by $Ar_3Sn(OP)$, where OP represents the growing polymer chain, with the onset of polymerization, Ar_4Sn compounds are formed (as identified by ^1H, ^{13}C and ^{119}Sn NMR as well as electrospray mass spectrometry). Ar_4Sn compounds are inactive and the systems that are believed to be catalytically active are $Ar_{3-n}Sn(OP)_n$, where n = 1 or 2. The formation of Ar_4Sn clearly implicates the facility of chain transfer and, in addition, from studies of molecular weight distributions with time, we

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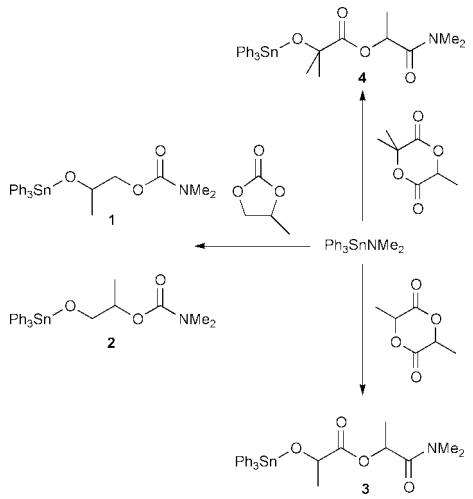

Scheme 1

observe extensive transesterification. Thus, even the seemingly simple and kinetically slow system for the ROP of lactides employing Ar_3SnX 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 X = NMe_2 than for X = OBu^t. Thus, *at room temperature*, Ph_3SnNMe_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.‡ The Sn–O^{13}C carbon shows coupling to ^{119}Sn and the amide methyl protons appear as two singlets due to the restricted rotation about the C–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 decarbonation polymerization of PC by tin catalysts at higher temperatures.[10]

The ring-openings shown in Scheme 1 convert an Sn–NMe_2 group to an Sn–OR group and at 25 °C no further insertion/ring-opening occurs. The compounds are, however, not indefinitely persistent in solution. The compound $Ph_3SnOCHMeC(O)OCHMeCONMe_2$ **3** which we can represent as $Ph_3Sn[OCHMeC(O)]_2NMe_2$ is labile to transesterification reactions as represented by eqn. (1).

$$Ph_3Sn[OCHMeC(O)]_2NMe_2 \rightarrow Ph_3Sn[OCHMeC(O)]NMe_2 + Ph_3Sn[OCHMeC(O)]_nNMe_2\ (n \geqslant 3) \quad (1)$$

Reaction (1) is also accompanied by chain transfer and phenyl migration yielding Ph_4Sn. The compound $Ph_3Sn[OCMe_2C(O)OCHMeC(O)NMe_2]$ **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 $Ph_3Sn(OBu^t)$ to give $Ph_3SnOCHMeC(O)NMe_2$ and $Ph_3Sn[OCMe_2C(O)OBu^t]$, products of transesterification. $Ph_3SnOCHMeC(O)NMe_2$ is formed from the reaction between Ph_3SnNMe_2 and lactide (2 : 1 ratio) in benzene as the major kinetic product in eqn. (2).

$$Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2] + Ph_3SnNMe_2 \rightarrow 2Ph_3Sn[OCHMeC(O)NMe_2] \quad (2)$$

Reactions employing $Ph_2Sn(NMe_2)_2$ and lactide (1 : 1 ratio) yield $Ph_2Sn[OCHMeC(O)NMe_2]_2$ by consecutive ring-opening of lactide followed by intramolecular attack on the chain, eqn. (3).

$$Ph_2Sn(NMe_2)[OCHMeC(O)OCHMeC(O)NMe_2] \rightarrow Ph_2Sn[OCHMeC(O)NMe_2]_2 \quad (3)$$

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

‡ *General considerations*: the synthesis of R_3SnNMe_2 and $Ph_2Sn(NMe_2)_2$ complexes was based on the reported synthesis[11] of Ph_3SnNMe_2 and $Ph_2Sn(NMe_2)_2$. See ESI for additional spectroscopic data.†

$SnPh_3[OCHMeC(O)OCHMeC(O)NMe_2]$: δ_H(400 MHz, C_6D_6): 0.99 [d, CH*Me*C(O)NMe_2, 3H], 1.53 (d, SnOCH*Me*, 3H), 2.11 (s, NMe_2, 3H), 2.47 (s, NMe_2, 3H), 4.75 (q, SnOC*H*Me, 1H), 4.83 [q, C*H*MeC(O)NMe_2, 1H], 7.16 (m, *m*- and *p*-H, 9H), 7.80 (dd, *o*-H, 6H, J_{HH} 7.9, 1.5 Hz, $^{119/117}$Sn satellites J_{SnH} ^{117}Sn 64, ^{119}Sn 49 Hz).

$SnPh_2[OCHMeC(O)NMe_2]_2$: δ_H(400 MHz, C_6D_6): 1.43 (d, SnOCH*Me*, 6H), 1.87 (s, NMe_2, 6H), 2.26 (s, NMe_2, 6H), 4.87 (q, SnOC*H*Me, 2H), 7.21 (t, *p*-H, 2H), 7.35 (t, *m*-H, 4H), 8.37 (dd, *o*-H, 4H, J_{HH} 7.6, 1.2 Hz, $^{119/117}$Sn satellites J_{SnH} ^{117}Sn 75, ^{119}Sn 59 Hz).

$SnPh_3[OCMe_2C(O)OCHMeC(O)NMe_2]$: δ_H(500 MHz, C_6D_6): 1.06 (d, CH*Me*C$ONMe_2$, 3H), 1.56 (s, SnOC*Me*$_2$, 3H), 1.65 (s, SnOC*Me*$_2$, 3H), 2.12 (s, NMe_2, 3H), 2.47 (s, NMe_2, 3H), 4.87 [q, C*H*MeCO)NMe_2, 1H], 7.17 (m, *p*-H, 3H), 7.23 (m, *m*-H, 6H), 7.87 (dd, *o*-H, 6H, J_{HH} 8.2, 1.3 Hz, $^{119/117}$Sn satellites J_{SnH} ^{117}Sn 64, ^{119}Sn 48 Hz).

Polymerization reactions: standard solutions of the appropriate R_3SnX complex (0.027 M) and L- or *rac*-lactide (0.338 M) were prepared in C_6D_6 and stored in a dry-box. Aliquots (100, 50, 25 and 12.5 μL for 25 : 1, 50 : 1, 100 : 1 and 200 : 1, respectively) of R_3SnX solutions were transferred along with an aliquot (200 μL) of either L- or *rac*-lactide to a J. Young® NMR tube. The total volume was made up to 800 μL with C_6D_6 to ensure a constant lactide concentration (0.084 M). Rates of polymerization were determined from ^{1}H NMR data where the sum of the area of monomer and polymer peaks (CH and 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_{obs}.

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