A study of the ring-opening of lactides and related cyclic esters by Ph_2SnX_2 and Ph_3SnX compounds (X = NMe_2 , OR)[†]

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Ph₃SnX reacts with L-lactide in the order $X = NMe_2 \sim OMe \gg OPr^i > OBu^t$ in the initial ring-opening event. The rate of ring-opening of methyl substituted 1,4-dioxane-2,5-diones decreases with methyl substitution and ring-opening of 3,3,6,6-tetramethyl-1,4-dioxane-2,5-dione is not observed. From studies of the reaction between Ph₃SnOPr^{*i*} and L-lactide the activation parameters $\Delta H^{\neq} = 13(1)$ kcal mol⁻¹ and $\Delta S^{\neq} = -37(3)$ eu have been determined. Ph₃SnNMe₂ reacts with cyclic esters and propylene carbonate at low temperatures to give isolable ring-opened products. The compound Ph₃Sn[OCHMeC(O)OCHMeC(O)X] (where $X = NMe_2$, OMe) are labile in solution at room temperature, yielding Ph₃Sn[OCHMeC(O)X] and Ph₃Sn[OCHMeC(O)]_nX, where $n \ge 3$, by transesterification, along with other minor products due to phenyl/ OR group transfer (*i.e.*, Ph₄Sn). Ph₂Sn(NMe₂)₂ and L-lactide react to give Ph₂Sn[OCHMeC(O)OMe₂]₂ by ring-opening of L-lactide followed by rapid amidation. A related compound, Ph₂Sn[OCHMeC(O)OPr^{*i*}]₂, is also formed in the reaction between Ph₂Sn(OPr^{*i*})₂ and L-lactide but is more labile toward further ring-opening of L-lactide.

Introduction

Interest in polylactides, PLAs, arises from their numerous potential applications, which range from environmentally friendly packaging materials¹ to drug-delivery agents,² biodegradable sutures^{2,3} and polymer scaffolds for tissue engineering.⁴ Ring-opening polymerization (ROP) of lactides (LA; L-, D-, rac- and meso- forms) to form polylactides by single-site metal alkoxide precursors has attracted considerable recent attention⁵ since the properties of a given PLA are determined by its molecular weight, molecular weight distribution and molecular microstructure. Recent successes in the development of single-site catalysts include the preparation of syndiotactic^{5a} and heterotactic5c polymers along with control of polydispersity. An excellent review documents recent endeavors in this field.⁶ Much attention has been directed to understanding the stereosequences (the arrangement of the R and S chiral centers) of PLA with recent work by Hillmyer and coworkers addressing this issue by use of high resolution NMR spectroscopy.

It is, however, fair to state that little is really understood in terms of what controls the intimate mechanistic steps of polymerization, how stereoselectivity is achieved and what factors influence the relative rates of ROP *versus* the often deleterious side reactions involving transesterification and chain transfer. For example, it is not clear why sterically demanding and chiral Tp*M(OR) compounds,^{5e} **A**, of magnesium or zinc should yield only poor stereoselectivity when less sterically demanding achiral diiminato compounds **B** achieve significant stereoselectivity (>90%) under similar reaction conditions (Fig. 1).^{5d,5g}

We reasoned that much might be learned from a study of the reactivity of Ar₃SnX and Ph₂SnX₂ precursors in their reactions with lactides and related cyclic esters since, unlike Tp or betadiiminate (BDI) ligands, reversible metal-ligand dissociation in solvents such as benzene and methylene chloride could safely be ruled out. To date, there have been a number of interesting papers that have dealt with the polymerization of cyclic esters such as LA by tin(II) catalyst precursors⁸ but there are few examples utilizing tin(IV) catalysts.⁹ These Ar₃SnX and Ph₂SnX₂ precursors are kinetically slow relative to tin(II) and other zinc(II) and magnesium(II) catalysts. This allows for the possibility to study in isolation the three components of metal-mediated anionic lactide polymerization, namely the initial ring-opening event, the propagating reaction (also known as ring-opening polymerization, ROP) and the side



Fig. 1 Zinc and magnesium catalyst precursors for the polymerization of lactide.

 $[\]dagger$ Electronic supplementary information (ESI) available: preparation and characterization data for Ar₃SnX, Ph₂SnNMe₂ and Ph₂Sn(OPrⁱ)₂ compounds [X = NMe₂, OMe, OPrⁱ, OBuⁱ, OPh, OCH(CF₃)₂, PPh₂ and Ar = Ph, *o*-MeC₆H₄]; NOE data and NMR spectra available. See http://www.rsc.org/suppdata/nj/b3/b300101f/



Scheme 1 The three components of lactide polymerization: ring-opening, propagation and side reactions (transesterification and chain transfer).

reactions such as chain transfer and transesterification (Scheme 1).

If the relative rates of initial ring-opening, $k_{\rm ro}$, and subsequent propagation, $k_{\rm prop}$, markedly differ such that $k_{\rm ro} > k_{\rm prop}$ it should be possible to isolate products where just one LA monomer has been ring-opened. We first observed this for Ph₃SnNMe₂ and L-lactide¹⁰ and have expanded our findings here. Specifically we have systematically investigated the effect of three parameters on the ring-opening event. (1) The effect of X, the initiating group, in Ph₃SnX on the ringopening of LA. (2) The effect of methyl substitution on the cyclic monomer as in LA vs. GL (where GL = glycolide). (3) The effect of altering the Ar groups (the spectator ligands) on the Sn(rv) initiator. The results from this study are discussed below whilst a detailed description of the propagation kinetics¹¹ and side reactions of transesterification and chain transfer utilizing R₂SnX₂ and R₃SnX catalyst precursors will be discussed in subsequent publications.

Results and discussion

Ar₃SnX and Ph₂SnX₂ compounds

The dimethylamido compounds were all synthesized in a similar manner from the metathetic reaction between Ar_3SnCl and $LiNMe_2$ in benzene or THF to yield the corresponding Ar_3SnNMe_2 compounds, where Ar = Ph and *o*-MeC₆H₄, which were air-sensitive, white or colorless oils or waxy solids. $Ph_2Sn(NMe_2)_2$ was prepared in an analogous fashion from Ph_2SnCl_2 and 2 equiv. of LiNMe₂.

The corresponding alkoxides Ar_3SnOR and $Ph_2Sn(OR)_2$ were prepared by alcoholysis of the appropriate dimethylamides (R = Me, Pr^i , $CH(CF_3)_2$, Bu^i and Ph). Ph_3SnPPh_2 was likewise synthesized by treatment of Ph_3SnNMe_2 with excess $HPPh_2$. These compounds were similarly air-sensitive, white or colorless waxy solids or oils and were purified by vacuum distillation or crystallization. Characterization data for all compounds reported here are given in the Electronic supplementary information (ESI). The Ar₃SnOR compounds ($R = Bu^t$ and Pr^i) were stable at 100 °C in anhydrous toluene for several days as evidenced by ¹H and ¹¹⁹Sn NMR spectroscopy.

Discrete ring-opened lactide and related cyclic ester derivatives of Sn(IV)

These new compounds, described below, have been characterized by NMR [¹H, ¹³C{¹H}, ¹¹⁹Sn] and IR spectroscopy, mass spectrometry and, in many cases, by elemental analyses. Data are reported in the Experimental in addition to our previous preliminary report on this chemistry.¹⁰

(a) Ring-opening of L-lactide by Ph_3SnX where $X = NMe_2$, OMe, OPrⁱ, OCH(CF₃)₃, OBu^t, OPh and PPh₂. In order to investigate the effect of the initiating group on the ring-opening of L-lactide a variety of Ph_3SnX compounds $[X = NMe_2,$ OMe, OPr^{*i*}, OCH(CF₃)₂, OBu^{*t*}, OPh and PPh₂] were synthesized and treated with equiv. of L-lactide (Scheme 2). It is apparent from Scheme 2 that electronic and steric properties of the initiating group influence not only the ring-opening of L-lactide but also the stability of the ring-opened product. Scheme 2 reveals that Ph₃SnNMe₂ and Ph₃SnOMe rapidly ring-open L-lactide at room temperature in benzene to form the discrete and isolable products Ph₃Sn[OCHMeC(O)OCH-MeC(O)X where $X = NMe_2$ or OMe. The ¹H NMR spectrum of Ph₃Sn[OCHMeC(O)OCHMeC(O]NMe₂) is shown in Fig. 2, along with an assignment of the ligand resonances. The latter is possible from a COSY spectrum.

Ph₃Sn[OCHMeC(O)OCHMeC(O)OMe] is less stable than the analogous NMe₂ compound and is more susceptible to intermolecular transesterification leading to Ph₃Sn[OCHMe-C(O)OMe] and Ph₃Sn[OCHMeC(O)]_nOMe, where n > 3 (see below for a discussion of stabilities and side reactions of these complexes).



Scheme 2 Reactions between Ph₃SnX compounds and L-lactide indicating the effect of initiating group. Compounds in boxes are isolable species.

The steric effect of X on ring-opening of L-lactide is best illustrated in the comparison between Ph₃SnOMe, Ph₃SnOPr^{*i*} and Ph₃SnOBu^{*i*}, where the order of reactivity decreases with increasing steric bulk of X. This is the inverse of the basicity of the alkoxide anions: Bu^{*i*}O > Pr^{*i*}O > MeO. Unlike Ph₃SnOMe, both Ph₃SnOPr^{*i*} and Ph₃SnOBu^{*i*} require heating in benzene (45–50 °C) to accomplish appreciable ring-opening. This decrease in reactivity for the more bulky X groups may reflect the increased steric crowding about the tin(IV) center, thereby suppressing the ability of L-lactide to coordinate to the tin(IV) metal center prior to ring-opening (Scheme 1). In addition, the X group may be too bulky to attack the ester carbonyl carbon atom. Furthermore, it appears that Ph₃Sn[OCH-MeC(O)OCHMeC(O)X] with X = OPr^{*i*} is more stable (Fig. 3) (forming a stable, isolable product) than for X = OBu^{*i*}, which probably is a result of two effects: (1) the relative rates of ringopening, k_{ro} , and propagation or ROP,¹¹ k_{prop} , are such that $k_{ro} > k_{prop}$ for $X = OPr^{i}$ but $k_{prop} > k_{ro}$ for $X = OBu^{i}$, and (2) the poorer ability of the –C(O)OBuⁱ group to chelate either inter- or intramolecularly to the tin(IV) center (see below for a discussion of the stability of these compounds).

A more pronounced effect of $k_{\text{prop}} > k_{\text{ro}}$ was seen in the reactions involving Ph₃SnX and L-lactide (1:1 equiv.) where $X = \text{OCH}(\text{CF}_3)_2$, OPh and PPh₂. Here heating in benzened₆ was required (73 and 94 °C, Scheme 2) before any reaction was observed and then only a small amount of Ph₃SnX was consumed and no discrete compounds of formula Ph₃Sn[OCHMeC(O)OCHMeC(O)X)] were detected by ¹H NMR spectroscopy. We can conclude that the observed rate order for the initial rate of ring-opening of L-lactide, which is $X = \text{NMe}_2 \sim \text{OMe} > \text{OPr}^i > \text{OBu}^t > \text{OPh} > \text{OCH}(\text{CF}_3)_2 > \text{PPh}_2$,



Fig. 2 ¹H NMR spectrum in benzene- d_6 of Ph₃Sn[OCHMe-C(O)OCHMeC(O)ONMe₂]. Notice the inequivalent NMe₂ methyl signals.



Fig. 3 ¹H NMR spectrum in benzene- d_6 of Ph₃Sn[OCHMe-C(O)OCHMeC(O)OPr^{*i*}]. Notice the inequivalent OPr^{*i*} methyl signals.

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represents a combination of electronic and steric factors. The rate is enhanced by the nucleophilicity/basicity of the anion X^- and is suppressed by steric factors. For $X = NMe_2$, OMe and OPr^{*i*}, $k_{ro} > k_{prop}$ but for $X = OCH(CF_3)_2$, OPh and PPh₂, $k_{prop} > k_{ro}$. The influence of steric factors is further underscored by the observation that (*o*-MeC₆H₄)₃-SnNMe₂ and L-lactide do not react!.

(b) Kinetics of the ring-opening event. A reaction scheme for the initial ring-opening event can be represented by eqn. (1),

(a)
$$\mathbf{A} + \mathbf{B} \xrightarrow[k_{-1}]{k_{-1}} \mathbf{C} \quad K_{eq}$$

(b) $\mathbf{C} \xrightarrow{k_2} \mathbf{D}$ (1)

where A represents the Ph₃SnX compound, B the L-lactide, C a kinetically labile adduct or reactive intermediate and D, the product of the ring-opening event. In the reaction scheme the rate of formation of the ring-opened product, d[D]/dt, is given by eqn. (2), according to the steady-state approximation.

$$\frac{d[D]}{dt} = \frac{k_2 \cdot k_1 [A] [B]}{k_{-1} + k_2}$$
(2)

There are two limiting situations: (i) for $k_{-1} \gg k_2$, $k_{obs} = k_2 \cdot k_1 / k_{-1} \sim k_2 \cdot K_{eq}$ and (ii) for $k_2 \gg k_{-1}$ when $k_{obs} = k_1$. In other cases the reaction scheme does not simplify and $k_{obs} = k_2 \cdot k_1 / (k_{-1} + k_2)$.

If the ring-opened product D closely resembles A then further reaction with substrate B can be expected and we will arrive at a kinetic situation where $k_{\rm prop} \sim k_{\rm ro}$. However, in order to study the initial ring-opening event and have this make a meaningful or at least a chemically interesting comparison with the ring-opening polymerization (propagation), $k_{\rm ro}$ must be greater but not very much greater than k_{prop} . In this study this situation is obtained for Ph₃SnOPr^{*i*} and we have examined the kinetics of the ring-opening event as a function of temperature (29 to 81 °C) in benzene- d_6 . The reactions were followed by ¹H NMR spectroscopy by simultaneously following the decrease in L-lactide, the loss of SnOPrⁱ signals and the growth of the product Ph₃Sn[OCHMeC(O)OCHMeC(O)OPr^{*i*}] (see Experimental). The reaction proceeded as expected based on the reaction scheme shown in eqn. (1). Most significantly there was no evidence by NMR spectroscopy for the formation of a 1:1 adduct, supporting the notion that C is a reactive intermediate, with K_{eq} being small, not detected by NMR spectroscopy. This is further corroborated by the fact that ¹¹⁹Sn NMR spectra of Ph_3SnOPr^i in toluene- d_8 at low temperatures are insensitive to the presence of excess lactide. Kinetic data are summarized in Table 1.

From a plot of $\ln(k/T)$ vs. 1/T (Fig. 4) we can obtain an estimate of the activation parameters: $\Delta H^{\neq} = 13(1)$ kcal mol⁻¹ and $\Delta S^{\neq} = -37(3)$ eu. These are entirely reasonable values for the metal-mediated anionic ring-opening reaction proposed in Scheme 1. The enthalpy of activation is quite modest as

Table 1 Kinetics data for the 1:1 reaction between Ph_3SnOPr^i and Llactide leading to formation of $Ph_3Sn[OCHMeC(O)OCHMeC(O)OPr^i]$ at various temperatures and in the presence of donors

Entry	$k_{\rm obs}/{\rm mol}^{-1}~{\rm dm}^3~{\rm s}^{-1})$	<i>T</i> /°C
1	$2.0(2) \times 10^{-5}$	29
2	$4.1(2) \times 10^{-5}$	49
3	$1.3(2) \times 10^{-4}$	61
4	$6.1(2) \times 10^{-4}$	81
5 ^{<i>a</i>}	$1.6(2) \times 10^{-5}$	29
6 ^{<i>b</i>}	$3.0(2) \times 10^{-5}$	29
^{<i>a</i>} With 5 equiv	. of propylene carbonate. ^b With 5 equi	v. of pyridine.



Fig. 4 Plot of $\ln(k_{obs}/T)$ vs. 1/T for the reaction between Ph₃SnOPr^{*i*} and L-lactide (1:1).

expected for attack on a carbonyl group coordinated to the metal by an adjacent nucleophilic alkoxide ligand. The negative and modest magnitude of the entropy of activation is typical of many bimolecular processes and does not imply a uniquely high order in the transition state.

Since 4-coordinate tin(IV) compounds are well known to be able to increase their coordination numbers in associative reactions we examined the kinetics of the ring-opening of L-lactide by Ph₃SnOPr^{*i*} in the presence of added donors, specifically propylene carbonate (PC) and pyridine (py) (Table 1). Given that neither is susceptible to ring-opening but that both molecules could compete in a reversible association to tin(IV) with Llactide, according to the scheme outlined in eqn. (1), the rate of ring-opening, k_{ro} , could be supressed. The added ligand, py or PC, was in five-fold excess of the lactide concentration. At 29 °C we observed no supression in the rate constant, k_{obs} , and for py a slight increase in k_{obs} was observed, which may be due to subtle changes in solvent polarity that, in turn, enhance the rate of ring-opening (Table 1).

(c) Ring-opening of related cyclic esters by Ph₃SnX where $X = NMe_2$ and OPr^{*i*}. It has been shown that the nature of the initiating group X and the ancillary ligands Ar can control the ring-opening event of L-lactide. However, it is not clear whether related cyclic esters have the same propensity to ring-open as L-lactide and, if so, whether there will be any regiospecificity in ring-opening of an unsymmetrical cyclic ester. To address these issues we have studied the reactions between Ph₃SnX compounds, where $X = NMe_2$ or OPr^{*i*}, and a variety of cyclic esters that are closely related to L-lactide (Scheme 3).

Ph₃SnNMe₂ was shown to react regioselectively with the asymmetrically substituted cyclic ester 3,3,6-trimethyl-1,4-dioxane-2,5-dione to give Ph₃Sn[OCMe₂C(O)OCHMeC(O)NMe₂] whilst Ph₃SnOPr^{*i*} reacts with 3-methyl-1,4-dioxane-2,5-dione (methylglycolide) to give Ph₃Sn[OCHMeC(O)OCH₂C(O)OPr^{*i*}] (95%). In both cases nucleophilic attack occurs at the lesshindered (and more electrophilic) carbonyl moiety (Scheme 3). The ¹H NMR spectrum of the compound Ph₃Sn[OCMe₂-C(O)OCHMeC(O)NMe₂] can be found in the ESI.

As is apparent, there is only one regioisomer for $Ph_3Sn[OCMe_2C(O)OCHMeC(O)NMe_2]$ and the specific isomer is established with confidence based on the presence or absence of coupling to $^{119}Sn/^{117}Sn$ in the ^{1}H and



Scheme 3 Reactions between Ph_3SnX (X = NMe₂, OPr^i) and methyl substituted lactide derivatives.

 $^{13}C{^{1}H}$ spectra. This compound is notably less kinetically labile than its L-lactide counterpart and does not participate in self transesterification as observed for Ph₃Sn[OCHMe-C(O)OCHMeC(O)NMe₂]. (See below for a discussion of the stabilities of these compounds.)

Treatment of Ph₃SnOPrⁱ with 1,4-dioxane-2,5-dione (glycolide) (1:1) does not lead to the isolable compound $Ph_3Sn[OCH_2C(O)OCH_2C(O)OPr']$ but rather to polyglycolide (Scheme 3), uggesting that the rates of ring-opening and chain propagation are similar such that subsequent glycolide molecules are able to insert readily into the already formed ring-opened product. The relative stability of the Ph₃Sn[CMe₂-C(O)OCHMeC(O)NMe2] and Ph3Sn[CHMeC(O)OCHMe-C(O)X (X = NMe₂, OPr^{*i*}) complexes (see above) is presumably related to the poorer substrate activation of the cyclic ester monomers by the ring-opened product relative to initial activation by Ph₃SnOPrⁱ or Ph₃SnNMe₂. This leads to the initial rate of ring-opening being greater than the subsequent rate of ROP ($k_{\rm ro} > k_{\rm prop}$). In contrast, the less hindered glycolide (and to a lesser extent methylglycolide) molecules can more readily coordinate to the tin center than L-lactide or 3,3,6-trimethyl-1,4-dioxane-2,5-dione, resulting in $k_{\rm prop} \ge k_{\rm ro}$.¹² Ring-opening is not observed when Ph_3SnNMe_2 is treated with the tetramethylated cyclic ester derivative, 3,3,6,6-tetramethyl-1,4-dioxane-2,5-dione. This result complements the regiospecific ring-opening observed for the 3,3,6-trimethyl-1,4-dioxane-2,5-dione cyclic ester by Ph_3SnNMe_2 , for which no activation was observed for the more hindered carbonyl ester.

Hence the degree of methyl substitution on the cyclic ester has a considerable effect on the relative rates and regiospecificity of ring-opening: the less hindered cyclic esters more rapidly ring-open in a less regiospecific fashion. In addition, the reactivity of the 1:1 ring-opened products is also related to the degree of methyl substitution in that the most kinetically persistent compounds are those with a high degree of methyl substitution of the cyclic ester. This "stability" may arise from the higher degree of steric crowding about the tin(tv) metal center in the more heavily substituted ring-opened systems, which supresses further bimolecular reactions.

Ph₃SnNMe₂ has also been shown to ring-open the cyclic carbonate, propylene carbonate, to give a mixture of the two regioisomers Ph₃Sn[OCH₂CHMeOC(O)NMe₂] and Ph₃Sn[OCHMeCH₂OC(O)NMe₂]. The relative ratio of these regioisomers was little changed in reactions carried out at -78 °C.



n > 2

Scheme 4 Reaction between Ph_2SnX_2 compounds (X = NMe₂, OPr^{*i*}) and L-lactide, indicating rapid intramolecular inter-chain esterification/ amidation.

(d) Reaction between Ph_2SnX_2 and L-lactide where $X = NMe_2$ or OPr^i . $Ph_2Sn(NMe_2)_2$ and L-lactide (1:1) react in benzene to give $Ph_2Sn[OCHMeC(O)NMe_2]_2$ by an initial ring-opening event, following by a rapid intramolecular amidation (Scheme 4). This reaction is conceptually similar to that seen between Ph_3SnNMe_2 (2 equiv.) and L-lactide (1 equiv.), where the initially formed $Ph_3Sn[OCHMeC(O)OCHMe-C(O)NMe_2]$ compound is also seen to react quickly with Ph_3SnNMe_2 to give $Ph_3Sn[OCHMeC(O)NMe_2]$ by an intermolecular amidation (see below).

The compound Ph₂Sn[OCHMeC(O)NMe₂]₂ has two IR bands, at 1596 and 1609 cm⁻¹, assignable to the organic amide moiety. These values are considerably lower than those found for Ph₃Sn[OCRMeC(O)OCHMeC(O)NMe₂] (R = H or Me) compounds whose infrared spectra of the C(O)NMe₂ moieties show characteristic bands at *ca*. 1600–1650 cm⁻¹, notably lower than the ester carbonyl groups, which are at *ca*. 1700– 1750 cm⁻¹. Furthermore, the ¹¹⁹Sn NMR spectrum of Ph₂Sn[OCHMeC(O)NMe₂]₂ is also significantly different from that of the other compounds and shows complex variable temperature behavior similar to that recently observed for the analogous Me₂Sn(OAr)₂ compound.¹³ It is believed that this, together with the lower values of v(CO), is evidence for intraor intermolecular amide group coordination to Sn (see below). Regrettably, crystals suitable for a single crystal X-ray determination were not obtained.

In an analogous fashion $Ph_2Sn(OPr^i)_2$ reacts with L-lactide (1:1) to form $Ph_2Sn[OCHMeC(O)OPr^i]_2$ (Scheme 4). This compound is much more susceptible to further L-lactide ring-opening than $Ph_2Sn[OCHMeC(O)NMe_2]_2$, making it impossible to isolate the OPr^i containing compound in its pure form. Presumably the OCHMeC(O)NMe_2 moiety forms a stronger, more stable chelate to Sn than does the OCHMeC(O)OPrⁱ moiety. (See below for a discussion of stability and NOE data.)

The relative stability of these two compounds manifests itself in the polymerization studies where, depending upon which initiating group is used, NMe₂ vs. OPrⁱ, striking differences are observed in the molecular weight distribution and polymer type (chains or cycles).¹¹

(e) Stability and reactivity of the ring-opened products, $Ph_3Sn-(cyclic ester)-X$ and $Ph_2Sn-[(cyclic ester)-X]_2$. 1:1 reactions between Ph_3SnX or Ph_2SnX_2 and cyclic esters have lead to the formation of, in some cases, discrete compounds that have sufficient stability for isolation and characterization.

None of these compounds are, however, indefinitely persistent in solution or at elevated temperatures {with the exception of $Ph_2Sn[OCHMeC(O)NMe_2]_2$ }. It is clear from the above discussions that some of these compounds exhibit greater stability than others. It is believed that this stability arises from the formation of chelating C(O)X end groups to tin(tv) (Fig. 5).

NOE difference spectra were obtained for $Ph_3Sn[OCHMe-C(O)OCHMeC(O)NMe_2]$, $Ph_3Sn[OCMe_2C(O)OCHMeC(O)N-Me_2]$ and $Ph_2Sn[OCHMeC(O)NMe_2]_2$ compounds (see ESI). These indicate a significant ${}^1H\cdots {}^1H$ interaction involving the *ortho*-phenyl protons and the methine protons of the ligand. We propose that this arises from reversible chelation of the ligand through 5- and 8-membered rings of the type shown in **C**, **D** and **E** (Fig. 5). Although 5-membered rings are preferred over 8-membered rings, the latter may be favored by the terminal amide groups in the Sn[OCHMeC(O)NMe_2]_2 moiety.

The compounds $Ph_3Sn[OCHMeC(O)OCHMeC(O)X]$ (where $X = NMe_2$, OPr^i , OMe) display kinetic lability toward a ligand redistribution reaction that arises from intermolecular transesterification (Scheme 5, reaction i). This reaction proceeds over several hours at room temperature and is accelerated by heat in benzene- d_6 or toluene- d_8 solution and can readily be followed by ¹H NMR spectroscopy (see ESI for $X = NMe_2$). From these studies the stability of

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Fig. 5 Possible 5- and 8-membered rings of Ar₃SnOP compounds.



Scheme 5 Reactivity of Ph₃Sn-(cyclic ester)-X and Ph₂Sn-[(cyclic ester)-X]₂ compounds towards transferreactions.

Ph₃Sn[OCHMeC(O)OCHMeC(O)X] compounds follows the order $X = NMe_2 > OPr^i > OMe$, where the OMe compound is impossible to isolate free from any transesterification reactions. This observed order of stability probably reflects both the superior chelating ability of the –C(O)NMe₂ moiety (if an 8-membered chelate forms) and steric factors where the – C(O)OMe group provides less steric protection through chelation to tin(iv) *versus* the corresponding –C(O)OPrⁱ moiety. If chelation to the metal center is strong then Sn–OR migration (which is necessary for transesterification) will be less facile.

The transesterification products, $Ph_3Sn[OCHMeC(O)X]$ (where $X = NMe_2$, OMe) can be independently prepared from the direct reaction between Ph_3SnX (2 equiv.) and L-lactide (1 equiv.) (Scheme 5, reaction ii). This reaction is similar to that seen between $Ph_2Sn(NMe_2)_2$ and L-lactide (1:1 ratio), where the initially formed $Ph_2Sn[OCHMeC(O)OCHMe C(O)NMe_2](NMe_2)$ rapidly undergoes an intramolecular transamidation reaction to give $Ph_2Sn[OCHMeC(O)NMe_2]_2$ (see above).

Remarkable stability is seen for the $Ph_3Sn[OCMe_2-C(O)OCHMeC(O)NMe_2]$ compound where no transesterification is seen, even upon heating (Scheme 5, reaction iii). This increased stability must arise from the presence of the tin(IV) tertiary alkoxide, SnOCMe_2R, and the increased shielding of the ketonic C=O group. Both factors suppress intermolecular reactions.

The lability of ligand exchange in these reactions is also manifest by the fact that some Ph_4Sn and $Ph_2Sn[OCHMe-C(O)NMe_2]_2$ are also formed (as identified by mass spectrometry and ¹H, ¹³C and ¹¹⁹Sn NMR spectroscopy) in the decomposition of $Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2]$ (Scheme 5, reaction iv). These side-reactions become more prevalent upon heating to 60-80 °C.

A very important observation was the stability of $Ph_2Sn[OCHMeC(O)NMe_2]_2$, which does not experience aryl

group migration whilst all $Ph_3Sn[OCHMeC(O)OCHMe-C(O)X]$ compounds do (Scheme 5, reactions iv and v). This has significant ramifications in ROP studies since the kinetic analysis is not complicated by the formation of kinetically inactive species such as Ph_4Sn .

Concluding remarks

The reactions between Ph₃SnX and Ph₂SnX₂, where $X = NMe_2$ or an alkoxide, and L-lactide have allowed us to examine the influence of the initiator group on the rate of ring-opening. The order of reactivity $X = NMe_2 \sim OMe >$ $OPr^i > OBu^t > OPh > OCH(CF_3)_2 > PPh_2$ clearly implicates the combined influence of electronic and steric factors. The importance of steric factors is also seen in the complete lack of reactivity between $(o-MeC_6H_4)_3SnNMe_2$ and L-lactide and between Ph₃SnNMe₂ and the tetramethylated cyclic ester, 3,3,6,6-tetramethyl-1,4-dioxane-2,5-dione. The ring-opened products Ph₃Sn[OCHMeC(O)OCHMeC(O)X] were shown to be kinetically labile to an intermolecular transesterification reaction and the stability of the -OCHMeC(O)NMe2 ligand can be understood in terms of chelation via the nucleophilic carbonyl group, which is stabilized by the NMe₂ group to form a 5-membered ring involving Sn. From the studies of the kinetics of the ring-opening event in the 1:1 reaction between Ph₃SnOPr^{*i*} and L-lactide the activation parameters $\Delta H^{\neq} = 13(1)$ kcal mol⁻¹ and $\Delta S^{\neq} = -37(3)$ eu have been determined. These are entirely consistent with a bimolecular reaction wherein the tin-alkoxide moiety adds across the ketonic C-O bond of the lactide. The metal center serves to assist in the activation of the C=O moiety by acting as a weak electrophile while the neighboring alkoxide ligand participates in the nucleophilic attack on the carbon of the coordinated carbonyl moiety. It is reasonable to suppose that this is slow for Sn(IV) relative to say Sn(II), Zn(II) and Mg(II) because the Sn–OR bond is notably less polar.

Experimental

General considerations

Caution: organotin(IV) compounds are highly toxic and require appropriate handling!

The manipulation of air-sensitive compounds involved standard Schlenk line and dry box techniques. All solvents were distilled under nitrogen from alkali metals (sodium or sodium/potassium alloy) and stored over 4 Å molecular sieves. L-Lactide was purchased from Aldrich and sublimed prior to use. Propylene carbonate was purchased from Aldrich and was degassed and stored over activated sieves. o-Bromotoluene, chlorotriphenyltin(IV), tetrachlorotin(IV), magnesium turnings, benzene-d₆, toluene-d₈, anhydrous tert-butanol and iso-propanol were purchased from Acros Scientific whilst diphenyltin(IV) dichloride was purchased from Alfa Aesar. Benzene- d_6 and toluene- d_8 were dried over sodium and vacuum transferred to a Schlenk flask containing activated molecular sieves. All aryl bromides were stored over calcium hydride and tetrachlorotin(IV) was stored over phosphorus pentoxide whilst all other reagents were used as received. The (o-MeC₆H₄)₃SnCl complex was synthesized by literature procedures¹⁴ where the Grignard reagent was generated in either THF or diethyl ether from magnesium and the appropriate arylbromide. This Grignard reagent was then treated in situ with tetrachlorotin(IV) (4:1), dissolved in either benzene or hexanes, to afford Ar₄Sn. The Ar₃SnCl complex is formed from reaction between Ar₄Sn and tetrachlorotin(IV) (3:1) via the Kocheshkov redistribution reaction.¹⁵ Lithium dimethylamide was synthesized by treating n-butyllithium in hexanes with excess dimethylamine at -78 °C. After allowing the reaction mixture to warm to room temperature, the solvent and excess amine were removed to quantitatively yield white lithium dimethylamide. Synthesis of lactide-like compounds such as 3-methyl-1,4-dioxane-2,5-dione (methylglycolide) and 3,3, 6-trimethyl-1,4-dioxane-2,5-dione were based on reported methods.16

The synthesis of Ar_3SnNMe_2 (Ar = Ph, *o*-MeC₆H₄,) and Ph₂Sn(NMe₂)₂ complexes was based on the reported synthesis¹⁷ of Ph₃SnNMe₂ and Ph₂Sn(NMe₂)₂ where Ar_3SnCl or Ph₂SnCl₂ was treated with 1 or 2 equiv. of LiNMe₂, respectively. The major difference in the synthesis was that LiNMe₂ was not generated *in situ*. The full preparation and characterization of Ph₃SnX and Ph₂Sn(NMe₂)₂ compounds where $X = NMe_2$, OMe, OPr^{*i*}, OPh, OBu^{*t*}, OCH(CF₃)₂, PPh₂ is given in the ESI.

Measurements and analyses

¹H, ¹³C{¹H} and ¹¹⁹Sn spectra were obtained from either Bruker DPX-400 or DRX-500 NMR spectrometers using either benzene- d_6 or toluene- d_8 solvents. Spectra were referenced internally to the residual protio impurities for ¹H and ¹³C (C₆D₆ δ 7.15 ¹H, 128.0 ¹³C; C₆D₅CD₃ δ 2.09) or externally to Me₄Sn ($\delta = 0$) for ¹¹⁹Sn. Infrared data were obtained from a Perkin Elmer Spectrum GX spectrophotometer with samples sandwiched between potassium bromide or sodium chloride plates as Nujol[®] mulls (solids) or as neat liquids/semi-solids. Mass spectra were obtained with a Mircomass QTOF. Elemental analyses were performed by Atlantic Microlab, Inc., with samples sealed under nitrogen in glass ampoules.

Syntheses

toluene solution (0°C 10 mL) of dimethylamidotriphenyl-

Ph₃Sn[OCHMeC(O)OCHMeC(O)NMe₂]. To a cooled

tin(IV) (0.39 g, 1.00 mmol), a toluene (10 mL) solution of L-lactide (0.14 g, 1.00 mmol) was slowly added. The colorless reaction solution was stirred for 30 min after which time the toluene was removed under vacuum to give an opaque semisolid (yield 0.42 g, 78%). Anal. calcd for C₂₆H₂₉NO₄Sn: C. 58.02; H, 5.43; N, 2.60; found: C, 58.08; H, 5.88; N, 2.85. IR (liquid)/cm⁻¹: 3081 w, 2987 w, 2934 w, 1755 m, 1713 m, 1667 s, 1617 m, 1480 m, 1429 s, 1403 w, 1376 w, 1331 w, 1303 w, 1259 m, 1235 m, 1192 m, 1148 s, 1075 s, 1024 m, 997 m, 938 w, 870 w, 812 w, 730 vs, 699 vs, 501 m, 450 m. ¹H NMR (400 MHz, benzene- d_6): δ 0.99 [d, CHMe-C(O)NMe₂, 3H], 1.53 (d, SnOCH*Me*, 3H), 2.11 (s, NMe₂, 3H), 2.47 (s, NMe2, 3H), 4.75 (q, SnOCHMe, 1H), 4.83 [q, C/MeC(O)NMe₂, 1H], 7.16 (m, *m*-H and *p*-H, 9H), 7.80 (dd, *o*-H, 6H, $J_{\rm HH}$ 7.9 and 1.5 Hz, ^{119/117}Sn satellites $J_{\rm SnH}$ ¹¹⁷Sn 64, ¹¹⁹Sn 49 Hz). ¹³C{¹H} NMR (126 MHz, benzened₆): δ 16.30 [s, CHMeC(O)NMe₂], 23.25 (s, SnOCHMe), 35.31 (s, NMe₂), 35.74 (s, NMe₂), 68.55 [s, CHMeC(O)NMe₂], 69.24 (s, SnOCHMe, ^{119/117}Sn satellites J_{SnC}^{117} Sn 46, ¹¹⁹Sn 44 Hz), 128.83 (s, *m*-C), 129.45 (s, *p*-C), 137.27 (s, *o*-C, ^{119/117}Sn satellites J_{SnC} 47 Hz), 142.21 (s, ipso-C), 168.74 [s, CHMe- $C(O)NMe_2$], 180.74 [s, SnOCHMeC(O)O]. ¹¹⁹Sn NMR (149 MHz, benzene- d_6): δ -124 (s). ESI-HRMS (m/z) calcd for C₂₆H₂₉NO₄Sn [MNa⁺]: 562.1016; found: 562.1056 (7.1 ppm).

Ph₂Sn[OCHMeC(O)NMe₂]₂. To a cooled toluene solution (0°C 10 mL) of bis(dimethylamido)diphenyltin(IV) (72 mg, 0.20 mmol), a toluene (15 mL) solution of L-lactide (29 mg, 0.20 mmol) was slowly added. The colorless reaction solution was stirred for 30 min after which time a white precipitate formed, which was filtered off to give the title complex (yield 78 mg, 77%). Anal. calcd for $C_{22}H_{30}N_2O_4Sn$: C, 52.31; H, 5.99; found: C, 51.54; H, 5.92. IR (Nujol)/cm⁻¹: 1609 vs, 1596 vs, 1404 w, 1330 w, 1256 w, 1180 w, 1129 s, 1074 m, 1047 w, 906 w, 781 w, 730 m, 704 m, 656 w, 637 w, 551 w, 456 m, 443 m.¹H NMR (400 MHz, benzene- d_6): δ 1.43 (d, SnOCHMe, 6H), 1.87 (s, NMe2, 6H), 2.26 (s, NMe2, 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, $J_{\rm HH}$ 7.6 and 1.2 Hz, ^{119/117}Sn satellites: $J_{\rm SnH}$ ¹¹⁷Sn 75, ¹¹⁹Sn 59 Hz). ¹³C{¹H} NMR (126 MHz, benzene- d_6): δ 22.85 (s, SnOCH*Me*), 35.42 (s, NMe₂), 35.93 (s, NMe₂), 66.13 [s, SnOCHMeC(O)NMe₂, ^{119/117}Sn satellites: $J_{\rm SnC}$ 36 Hz], 127.83 (s, *m*-C), 128.36 (s, *p*-C), 136.88 (s, *o*-C, ^{119/117}Sn satellites: $J_{\rm SnC}$ 47 Hz), 152.83 (s, *ipso*-C), 181.39 (s, CO). ¹¹⁹Sn NMR (149 MHz, benzene- d_6 , 300 K): δ –346 (br s). ¹¹⁹Sn NMR (187 MHz, THF- d_8 , 300 K): δ -350 (br s); (233 K): δ -360 (s), -362 (br); (213 K): δ -360 (s, 3Sn), -362 (s, 1Sn). ESI-HRMS (m/z) calcd for C₂₂H₃₀N₂O₄Sn [MNa⁺]: 529.1125; found: 529.1130 (0.9 ppm).

Ph₃Sn[OCMe₂C(O)OCHMeC(O)NMe₂]. To a cooled toluene solution (0 $^{\circ}$ C 10 mL) of dimethylamidotriphenyltin(IV) (0.39 g, 1.00 mmol), a toluene (10 mL) solution of 3,3,6trimethyl-1,4-dioxane-2,5-dione (0.13 g, 1.00 mmol) was added slowly. The colorless solution was stirred for 30 min after which time the toluene was reduced and hexanes were added to the reaction, which was then cooled to $-20 \,^{\circ}\text{C}$ for 12 h, causing precipitation of the complex. Subsequent filtration afforded the title complex (yield 0.39 g, 71%). Anal. calcd for C₂₇H₃₁NO₄Sn: C, 58.72; H, 5.63; N, 2.54; found: C, 58.40; H, 5.60; N, 2.42. IR (Nujol)/cm⁻¹: 3062 m, 3042 m, 1695 m, 1507 w, 1481 m, 1429 s, 1354 m, 1311 m, 1260 w, 1168 s, 1116 w, 1077 s, 1025 m, 1007 w, 997 w, 916 vw, 888 vw, 845 w, 789 w, 762 vw, 731 vs, 702 s, 661 m, 619 vw, 570 w, 531 w, 448 m. ¹H NMR (500 MHz, benzene- d_6): δ 1.06 (d, CHMe-CONMe₂, 3H), 1.56 (s, SnOCMe₂, 3H), 1.65 (s, SnOCMe₂, 3H), 2.12 (s, NMe2, 3H), 2.47 (s, NMe2, 3H), 4.87 [q, CHMe-C(O)NMe₂, 1H], 7.17 (m, *p*-H, 3H), 7.23 (m, *m*-H, 6H), 7.87 (dd, *o*-H, 6H, $J_{\rm HH}$ 8.2 and 1.3 Hz, ^{119/117}Sn satellites: $J_{\rm SnH}$ ¹¹⁷Sn 64, ¹¹⁹Sn 48 Hz). ¹³C{¹H} NMR (125 MHz, benzene- d_6): δ 16.38 [s, CH*Me*C(O)NMe₂], 29.50 (s, SnOC*Me*₂), 29.94 (s, SnOC*Me*₂), 35.38 (s, NMe₂), 36.77 (s, NMe₂), 67.02 [s, CHMe-C(O)NMe₂], 73.31 (s, SnOCMe₂, ^{119/117}Sn satellites: J_{SnC} 29 Hz), 128.72 (s, *m*-C), 129.36 (s, *p*-C), 137.32 (s, *o*-C, ^{119/117}Sn satellites: J_{SnC} 44 Hz), 143.19 (s, *ipso*-C), 168.66 [s, CHMe-C(O)NMe₂], 183.01 [s, SnOCMe₂C(O)]. ¹¹⁹Sn NMR (187 MHz, benzene-*d*₆): δ –141 (s). ESI-LRMS (*m*/*z*): 554 [MH⁺].

Ph₃Sn[OCHMeC(O)OCHMeC(O)OPrⁱ]. iso-Proproxytriphenyltin(IV) (0.13 g, 0.32 mmol) was added to L-lactide (45 mg, 0.31 mmol) in benzene. The colorless solution was stirred for 1 day at 60 °C after which time the benzene was removed to afford a white semi-solid compound (yield 0.10 g, 58%). Anal. calcd for C₂₇H₃₀O₅Sn: C, 58.62; H, 5.47; found: C, 57.90; H, 5.22. IR (Nujol)/cm⁻¹: 1740 vs, 1457 s, 1261 m, 1071 vs, 800 s, 730 s 698 s. ¹H NMR (500 MHz, benzene- d_6): δ 0.78 [d, CHMeC(O)OCHMe2, 3H], 0.92 (d, OCHMe2, 3H), 1.03 (d, OCHMe2, 3H), 1.58 (d, SnOCHMe, 3H), 4.79 (q, SnOCHMe, 1H), 4.84 [overlapping signals: q, CHMeC(O)OCHMe2; sept., OCH(CH₃)₂1H], 7.15 (m, *p*- and *m*-H, 6H), 7.87 (dd, *o*-H, 6H) $J_{\rm HH}$ 8.4 and 1.4 Hz, ^{119/117}Sn satellites: $J_{\rm SnH}$ ¹¹⁷Sn 62, ¹¹⁹Sn 46 Hz). ¹³C{¹H} NMR (125 MHz, benzene- d_6): δ 16.47 [s, CHMeC(O)OCHMe2], 21.32 (s, SnOCHMe2), 21.43 (s, SnOCHMe2), 28.11 (s, SnOCHMe), 68.94 [s, CHMeC(O)-OCHMe₂)], 69.15 (s, SnOCHMe), 70.13 (s, SnOCHMe₂) 128.76 (s, m-C), 129.23 (s, p-C), 137.31 (s, o-C), 142.01 (s, ipso-C), 169.39 [s, CHMeC(O)OCHMe2], 180.58 [s, SnOCH-MeC(O)]. ¹¹⁹Sn NMR (187 MHz, benzene- d_6): δ –123 (s).

Ph₃Sn[OCHMeC(O)OCHMeC(O)OMe]. Methoxyoxytriphenyltin(IV) (93 mg, 0.24 mmol) dissolved in benzene (40 mL) was slowly added to L-lactide (35 mg, 0.24 mmol) in benzene (40 mL). The colorless solution was stirred for < 5 min at room temperature after which time the benzene was removed to afford a clear liquid, which was extracted with hexane to remove any unreacted L-lactide. Removal of the hexane gave 82 mg (64%) of the title compound. This compound readily undergoes self-transesterification, hence the product has only been characterized by NMR spectroscopy. ¹H NMR (400 MHz, benzene- d_6): δ 1.00 [d, CHMeC(O)OMe, 3H], 1.55 (d, OCHMe, 3H), 3.15 (s, OMe, 3H), 4.77 and 4.81 [overlapping q, SnOCHMeC(O)OCHMeC(O)OMe, 2H], 7.16 (m, *p*- and *m*-H, 6H), 7.85 (d, *o*-H, 6H, $^{119/117}$ Sn satellites: J_{SnH} ¹¹⁷Sn 63, ¹¹⁹Sn 49 Hz). ¹³C{¹H} NMR (100 MHz, benzene- d_6): δ 16.46 [s, CH*Me*C(O)OMe], 23.20 (s, SnOCH*Me*₂), 51.68 (s, O*Me*), 69.37 [s, CHMeC(O)OMe], 71.86 (s, SnOCHMe), 128.90 (s, *m*-C), 129.37 (s, *p*-C), 137.26 (s, *o*-C, $^{119/117}$ Sn satellites: J_{SnH} $^{117/119}$ Sn 45 Hz), 141.89 (s, *ipso*-C), 170.19 [s, CHMeC(O)OMe], 180.43 [s, SnOCHMeC(O)]. ¹¹⁹Sn NMR (149 MHz, benzene- d_6): $\delta - 121$ (s).

Reaction between Ph₃SnNMe₂ and propylene carbonate. To a cooled toluene solution (0 °C, 10 mL) of dimethylamidotriphenyltin(IV) (0.39 g, 1.00 mmol) a toluene-hexane (50:10 mL) solution of propylene carbonate (0.10 g, 1.00 mmol) was added slowly. The colorless solution was stirred for 30 min at 0°C after which time the toluene was removed. An opaque semisolid, 0.23 g, of a mixture of Ph₃SnOCH₂CHMeOC(O)NMe₂ and Ph₃SnOCHMeCH₂OC(O)NMe₂ (40:60) was identified by ¹H NMR spectroscopy (see below). Modification of the reaction conditions (RT and -50 °C) did not cause a change in product ratio. IR (liquid)/cm⁻¹: 3066 m, 3049 m, 3019 w, 2966 m, 2931 m, 2870 m, 1810 br m, 1702 br vs, 1580 w, 1569 wv, 1495 m, 1482 m, 1455 m, 1430 s, 1397 s, 1375 m, 1304 w, 1275 m, 1262 m, 1193 vs, 1153 m, 1120 m, 1077 m, 1023 w, 997 m, 939 w, 860 w, 799 w, 770 m, 730 vs, 699 vs, 661 w, 618 w, 539 w, 451 s, 370 vw, 386 w, 374 s. ¹H NMR (500 MHz, benzene- d_6): δ 1.21 (d, SnOCHMeCH₂) and 1.28 (d, SnOCH₂CHMe), 2.37 and 2.56 [overlapping br s, OC(O)NMe₂), 4.05 (dd, overlapping H_a and H_b, SnOCH₂- CHMe), 4.25 (dd, overlapping H_a and H_b , SnOCHMeCH₂), 4.40 (sextet, SnOCHMeCH₂), 5.28 (sextet, SnOCH₂CHMe) 7.15 (m, *m*- and *p*-H), 7.67 (m, *o*-H).

Kinetics analysis

Standard solutions of Ph₃SnOPr^{*i*} and L-lactide were made in benzene- d_6 and stored in the dry box. Appropriate aliquots of both reagents were transferred to a J. Young¹⁰ NMR tube. The total volume was made up to 800 µL with benzene- d_6 to ensure a constant initial L-lactide concentration (0.039 M). The reaction temperatures were regulated *via* a thermostatically controlled oil bath.

An overall second-order process, first-order in both Ph₃SnOPr^{*i*} [A] and L-lactide [B], was assumed. The rate of disappearance of both [A] and [B] {based on the formation of Ph₃SnOCHMeC(O)OCHMeC(O)OPr^{*i*} [C]} was determined by plotting ln([B]/[A]) vs. time (s). The rate constants for these reactions were determined from the gradient of the graph via $m = k([B_o] - [A_o])$.

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