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A well defined tin(II) initiator for the living polymerisation of lactide

Andrew P. Dove, Vernon C. Gibson,* Edward L. Marshall, Andrew J. P. White and David J. Williams

Department of Chemistry, Imperial College of Science, Technology and Medicine, Exhibition Road, South Kensington, London, UK SW7 2AY. E-mail: v.gibson@ic.ac.uk

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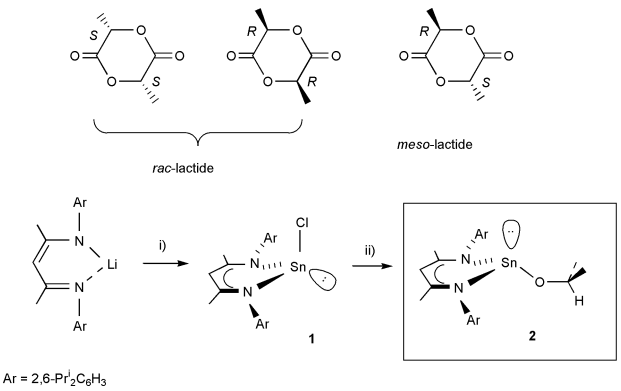
[HC{C(Me)NAr}$_2$]Sn(OPr^i) (Ar = 2,6-Pr$^i_2$C$_6$H$_3$) is shown to be an initiator for the living polymerisation of *rac*-lactide to heterotactic-enriched poly(lactide).

There is increasing interest in the design of polymers for *in vivo* applications such as sutures, artificial tissue networks and drug delivery agents. For these applications it is desirable for the polymer to be non-toxic, biocompatible and resorbable. One of the most promising classes of polymer in this field is the poly(lactide)s[1] which are readily obtained in a controlled manner *via* the living ring-opening polymerisation of lactide, the cyclic diester of lactic acid.[2]

Initiators for lactide polymerisation are typically based on alkoxide or alkanoate complexes of metals such as Al, Mg, Sn, Zn and the rare earths. Tin(II) catalysts such as Sn(ethyl hexanoate)$_2$ are generally preferred in the commercial production of poly(lactide)s[3] for medical or pharmaceutical applications owing to the low toxicity of Sn(II) compared to other metal ions [Sn(ethyl hexanoate)$_2$ is a permitted food additive in many countries]. Although a number of systems based on aluminium,[4] and more recently, magnesium[5] and zinc,[6] have been described that initiate the living ring-opening polymerisation of lactide, there have to date been no reports of well defined tin initiators. Here we describe the first example of a single-site tin catalyst for the living polymerisation of lactide.

The initiator **2** is prepared according to Scheme 1.† Treatment of $SnCl_2$ with [HC{C(Me)NAr}$_2$]Li in diethyl ether followed by crystallisation from pentane affords [HC{C(Me)-NAr}$_2$]SnCl **1** as a yellow crystalline solid. This is converted to **2** by treatment with LiOPr^i followed by recrystallisation from pentane. Crystals of **2** suitable for an X-ray structure determination‡ were grown from pentane; the structure is shown in Fig. 1.

The complex has non-crystallographic C_s symmetry with the three-coordinate tin atom adopting a tripodal geometry with inter-bond angles in the range 83.6(2)–94.1(2)°, the most acute being associated with the bite of the chelating N,N′ ligand. The Sn–N and Sn–O distances are unexceptional, and there is the expected pattern of delocalisation within the β-diketiminate ligand. The six-membered chelate ring has a boat conformation



Scheme 1 *Reagents and conditions*: i, $SnCl_2$, Et_2O, 18 h, recrystallisation from pentane, 60% yield (unoptimised); ii, LiOPr^i, Et_2O, 18 h, recrystallisation from pentane, 17% yield (unoptimised).

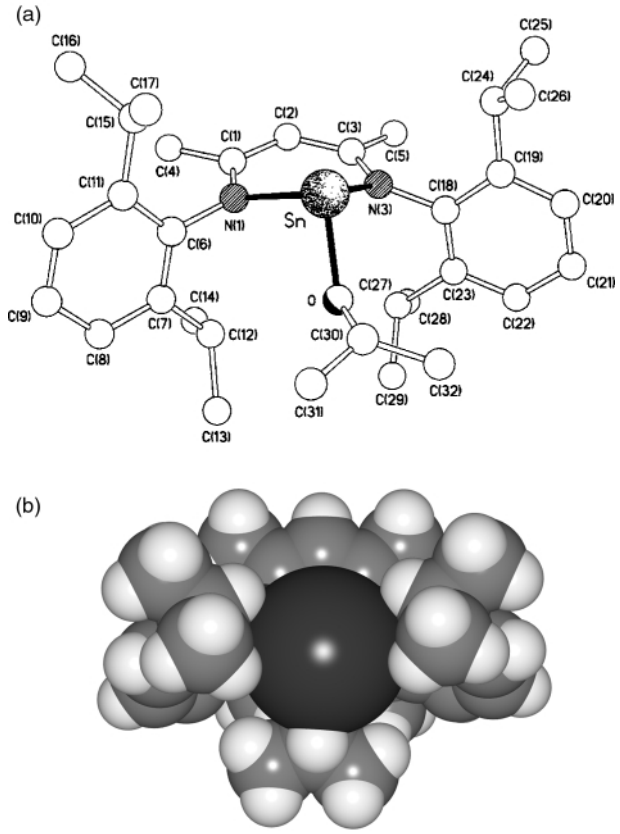


Fig. 1 (a) The molecular structure of **2**. Selected bond lengths (Å) and angles (°); Sn–O 2.000(5), Sn–N(1) 2.206(4), Sn–N(3) 2.208(4), C(1)–N(1) 1.323(6), C(1)–C(2) 1.404(7), C(2)–C(3) 1.387(7), C(3)–N(3) 1.331(6); O–Sn–N(1) 94.1(2), O–Sn–N(3) 92.5(2), N(1)–Sn–N(3) 83.6(2). (b) Space filling representation of the structure of **2** showing the exposed environment of the tin atom.

with C(2) and Sn lying 0.12 and 0.87 Å 'above' the N(1), C(1), C(3), N(3) plane; the isopropoxide oxygen atom lies 0.74 Å 'below' this plane. As a consequence of the folded chelate ring conformation, and retention of near trigonal planar geometries at the two nitrogen centres, the C(12) and C(27) isopropyl groups are drawn together, and those associated with C(15) and C(24) are folded away exposing the non-coordinated 'face' containing the stereochemically active lone pair on the tin atom [Fig. 1(b)]; the shortest intermolecular approach to the tin centre is 3.84 Å from C(13)–H.

The polymerisation of *rac*-lactide (a racemic mixture of L (*S*,*S*) and D (*R*,*R*) lactides) was initially investigated using complex **2** in CH_2Cl_2 at ambient temperature.§ Under these conditions it was found that 100 equivalents of monomer required 96 h for complete conversion (> 99% by ^{1}H NMR). The resultant polymer has a molecular weight close to that calculated from the monomer : initiator ratio (observed M_n = 17 100; calculated M_n = 14 400) and exhibits a narrow polydispersity (M_w/M_n = 1.11), characteristics of a living process. The polymerisation was then repeated at 60 °C in

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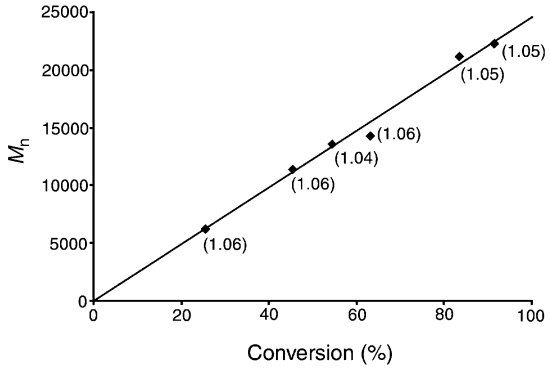

Fig. 2

toluene affording 85% conversion after 4 h, again resulting in a narrow molecular weight distribution product (M_w/M_n = 1.05). The activity of the tin catalyst is lower than that observed for the related zinc system[6] which may be in part due to the lower electrophilicity of the tin centre, and partly a consequence of the stereochemically active lone pair which may disfavour monomer binding. The living characteristics of the polymerisation are supported by the linear increase in M_n with conversion giving in each case a low polydispersity product (Fig. 2).

In order to confirm that the initiator is indeed the isopropoxide complex **2**, a ^{1}H NMR study was carried out in which increasing amounts of lactide were added to **2** in $CDCl_3$. The isopropoxide methine septet resonance at the end of the propagating chain is shifted slightly to higher frequency (0.005 ppm) relative to the unconsumed initiator (δ 4.01). New resonances for the β-diketiminate ligand substituents are also observed for the propagating species. As the number of monomer equivalents is increased, the intensities of the signals attributable to the propagating species increase relative to those of unconsumed **2**. Owing to the overlapping nature of the resonances, accurate integration has not been possible, but the addition of 5 equivalents of monomer leads to an approximately 1 : 1 mixture of initiator : propagating species. This indicates a favourable k_p/k_i ratio (the rate constant of propagation to rate constant of initiation) which is desirable for minimising the polydispersity.

The ^{1}H NMR spectrum of the poly(lactide) derived from **2** (Fig. 3) differs from the spectrum predicted from a Bernouillian analysis of totally random poly(*rac*-lactide), with the *rmr* and *mrm* tetrads much more intense than expected. These observations are consistent with a heterotactic-biased product since the *rmr* microstructure can only arise from two consecutive D–L or L–D interchanges; each *rmr* tetrad is accompanied by two *mrm* tetrads in agreement with the NMR integration. The preference for heterotacticity is not as strong as reported previously for the zinc analogue of **2**, but nonetheless represents the first example of tacticity bias arising from the polymerisation of *rac*-lactide using a tin catalyst.

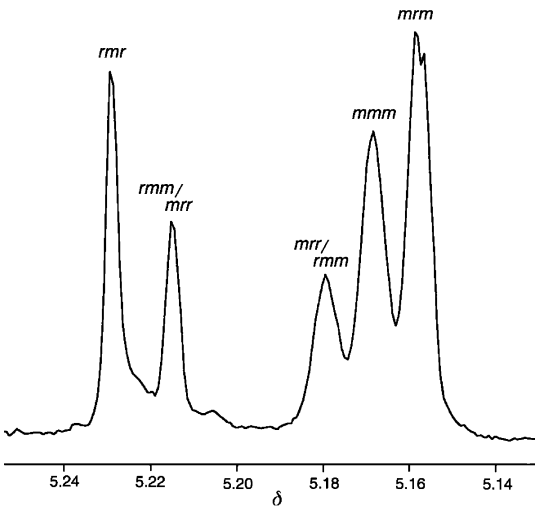

Fig. 3

Further studies are examining the effect of changes to the aryl ligand substituents on the polymerisation behaviour of the tin catalysts and their use in the ring-opening polymerisation of other cyclic ester monomers.

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Notes and references

† *Selected spectroscopic data*: for **1**: δ_H(250 MHz, C_6D_6, 25 °C) 1.06 (d, 6H, $^3J_{HH}$ 6.8 Hz, CHMe*Me*), 1.18 (d, 6H, $^3J_{HH}$ 6.9 Hz, CH*Me*Me), 1.22 (d, 6H, $^3J_{HH}$ 6.8 Hz, CHMe′*Me*′), 1.45 (d, 6H, $^3J_{HH}$ 6.6 Hz, CH*Me*′Me′), 1.61 (s, 6H, HC{C(*Me*)NAr}$_2$), 3.12 (sept, 2H, $^3J_{HH}$ 6.8 Hz, C*H*Me$_2$), 3.95 (sept, 2H, $^3J_{HH}$ 6.8 Hz, C*H*Me$_2$), 5.06 (s, 1H, *H*C{C(Me)NAr}$_2$), 7.15 (m, 6H, H_{aryl}). MS: *m/z* 572 $[M]^+$. Anal. Calc. (found) for $C_{29}H_{41}ClN_2Sn$: C, 60.91 (60.77); H, 7.22 (7.32); N, 4.90 (5.07)%. For **2**: δ_H(250 MHz, C_6D_6, 25 °C) δ 0.90 (d, 6H, $^3J_{HH}$ 6.8 Hz, OCH*Me*$_2$), 1.14 (d, 3H, $^3J_{HH}$ 6.8 Hz, CHMe*Me*), 1.24 (d, 3H, $^3J_{HH}$ 6.9 Hz, CH*Me*Me), 1.27 (d, 3H, CHMe′*Me*′), 1.54 (d, 3H, CH*Me*′Me′), 1.59 (s, 6H, HC{C(*Me*)NAr}$_2$), 3.25 (sept, 2H, $^3J_{HH}$ 6.8 Hz, C*H*Me$_2$), 3.86 (sept, 2H, $^3J_{HH}$ 6.8 Hz, C*H*Me$_2$), 4.15 (sept, 1H, $^3J_{HH}$ 6.0 Hz, OC*H*Me$_2$), 4.73 (s, 1H, *H*C{C(Me)NAr}$_2$), 7.16 (m, 6H, H_{aryl}). Anal. Calc. (found) for $C_{32}H_{48}N_2OSn$: C, 64.55 (64.28); H, 8.13 (8.08); N, 4.70 (4.90)%.

‡ *Crystal data* for **2**: $C_{32}H_{48}N_2OSn$, *M* 595.4, monoclinic, space group $P2_1/n$ (no. 14), a = 13.205(2), b = 16.680(2), c = 15.527(2) Å, β = 107.42(1)°, V = 3263.1(6) Å^3, Z = 4, D_c = 1.212 g cm^{-3}, μ(Mo-Kα) = 8.07 cm^{-1}, T = 293 K, yellow blocks; 5742 independent measured reflections, F^2 refinement, R_1 = 0.049, wR_2 = 0.112, 4038 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leqslant 50°$], 326 parameters. CCDC 151597. See http://www.rsc.org/suppdata/cc/b0/b008770j/ for crystallographic files in .cif or other electronic format.

§ *Typical polymerisation procedure*: complex **2** (0.005 g, 0.008 mmol) and *rac*-lactide (0.1181 g, 0.819 mmol) were weighed in to a 15 cm^3 glass ampoule fitted with a Teflon stopcock. The mixture was suspended in toluene (6 cm^3) and the ampoule was then sealed and transferred to an oil bath pre-heated to 60 °C. After stirring for the allotted period of time the volatile components were removed *in vacuo*. Conversion was determined by integration of monomer *vs.* polymer methine resonances in the ^{1}H NMR spectrum of the crude product (in $CDCl_3$). The polymer was purified by redissolving in CH_2Cl_2 (5 cm^3) and precipitating from rapidly stirring methanol. GPC chromatograms were recorded on a Knauer differential refractometer connected to a Gynotek HPLC pump (model 300) and two 10 μm columns (PSS) at a flow rate of 1.00 cm^3 min^{-1} using $CHCl_3$ as the eluent. The columns were calibrated against polystyrene standards with molecular weights ranging from 1560 to 128 000. Samples were filtered through a 0.45 μm filter immediately prior to injection. Analysis was performed using Version 3.0 of the Conventional Calibration module of the Viscotek SEC^3 software package.

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