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Titanium pyridonates and amidates: novel catalysts for the synthesis of random copolymers<sup>†</sup>

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A series of pyridonate and amidate supported titanium alkoxides have been isolated. These complexes can be readily prepared in high yield, under mild reaction conditions in only two steps from commercially available (Ti(NMe<sub>2</sub>)<sub>4</sub>). We have furnished one of the rare examples of discrete catalysts for random copolymer synthesis.

There have been great advances in the initiator systems available for the ring-opening polymerisation (ROP) of lactide (LA) and caprolactone (CL), including systems that produce very high molecular weight polymers and exhibit exquisite LA-stereocontrol under ambient conditions.1 Titanium catalysts have not, as yet, shown such high levels of reactivity and control during polymerisation. Although Ti-mediated homopolymerisations cannot yet compete with alternative metal initiators, the low toxicity<sup>2</sup> of titanium makes it attractive for the synthesis of copolymers with potential biomedical application.<sup>3</sup> For example, high molecular weight homopolymer for application in drug-delivery materials can result in poor biodegradation or detrimental "bursts" of drug release.<sup>4</sup> Seppälä and co-workers have shown that random copolymers offering alternative mechanical properties to traditional homopolymers can be advantageous for such specialised applications.<sup>4b,5</sup> PLA, characterised as hard and brittle with low maximum strain, and PCL, known to be tough with high maximum strain, can be combined into copolymers offering high levels of strain yet a range of physical properties "from weak elastomers to tougher thermoplastics".<sup>5b</sup> As a result blends, block or random copolymers of PLA and PCL may offer a desirable, tunable combination of properties suitable for a range of applications in biomedical science. While copolymerisations are an intense area of investigation with a range of metal centres,<sup>3,6</sup> such reactivity with discrete titanium initiators has rarely been reported.<sup>6a</sup> Indeed very few examples of random

copolymer formation have been realised with designed catalysts.<sup>6</sup> Exploring catalyst structure/polymer properties is of fundamental importance to our understanding of copolymerisations and realising their potential in real-life applications.

We have previously reported the synthesis of bis(pyridonate)and bis(amidate)-metal-amido complexes of the Group 4 transition metals as excellent precatalysts for the catalytic synthesis of amines.<sup>7–10</sup> However, Group 4 pyridonate and amidate complexes have not yet been explored for their potential in ROP. Yttrium amidate complexes on the other hand have been exploited in this role,<sup>11</sup> whereby trisligated complexes have been shown to produce high molecular weight PCL.<sup>11*a*</sup> However, the moisture sensitivity of such yttrium initiators is a limitation to their application toward scalable, functionalised polymer synthesis. Pyridonate or amidate titanium alkoxides could provide an alternative robust platform for investigating ligand stereoelectronic effects upon ROP, combined with the desirable bio-compatibility of titanium (Scheme 1).

Synthesis of bis(pyridonate)- or bis(amidate)-titaniumbis(dialkylamido) complexes is facile, by reaction of neutral amide or pyridone proligands with commercially available transition metal tetrakis(dialkyl)amido complexes at room temperature.<sup>7</sup> However, synthesis and rigorous characterisation of the related alkoxides has thus far remained elusive, likely due to complex aggregate formation during attempted reactions of  $Ti(O^{i}Pr)_{4}$  with pyridonate and amidate proligands. However, we were pleased to find that a sequential protonolysis approach, by reaction of  $Ti(NMe_2)_{4}$  with proligand, followed by reaction with isopropanol in one pot, furnishes a range of pyridonate- or amidate-titanium-alkoxides in excellent yield.<sup>12</sup>



**Scheme 1** Synthesis of pyridonate- and amidate-supported titanium-alkoxides and their application in polymerisation.

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Experimental details and full spectroscopic analysis data. CCDC 882572. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc37201k



**Fig. 1** Pyridonate- and amidate-titanium-alkoxides **1–5** were synthesised in high yield from Ti(NMe<sub>2</sub>)<sub>4</sub>. Right: ORTEP representation of the solid state molecular structure of **1**, thermal ellipsoids set at 50%, selected bond lengths (Å) Ti–O1 2.003(1), Ti–O2 1.986(1), Ti–N1 2.219(1), Ti–N2 2.250(2), Ti–O3 1.785(1), Ti–O4 1.766(1), C1–O1 1.318(2), C1–N1 1.344(3), C7–O2 1.325(2), C7–N2 1.347(2) and angles (°) N1–Ti–O1 62.72(5), N2–Ti–O2 62.51(5), N1–C1–O1 111.8(2), N2–C7–O2 111.5(2).

To the best of our knowledge, these are the first examples of fully characterised and mononuclear pyridonate- and amidate-titanium-alkoxides (Fig. 1).

6-Methyl-, 3-methyl- and 3-phenyl-pyridonate complexes (1, 2 and 3) have been synthesised in the first instance to provide a direct comparison of steric bulk adjacent to nitrogen versus the oxygen heteroatom. Crystals of 1 can be grown from hexanes at -30 °C and it can be seen that the ligand binds unsymmetrically through the N,O chelate.<sup>12</sup> The Ti-O1 and Ti-N1 bond lengths are 2.003(1) Å and 2.219(1) Å respectively. Such asymmetric binding modes have been previously reported for pyridonate group 4 bis(dialkylamido) complexes,<sup>13</sup> but are in contrast to previously reported bis(amidate)-bis(dialkylamido) complexes (vide infra).<sup>8</sup> The robust nature of these complexes is astonishing; heating complexes 1 to 3 in refluxing ethanol for up to 64 h does not result in ligand protonolysis and precipitation of Ti oxides as may be expected, instead the pyridonate ligand remains coordinated to the metal.<sup>12</sup> The highly sterically hindered amidate alkoxides 4 and 5 also form readily, but 5 shows broadened signals in the <sup>1</sup>H NMR spectrum at room temperature, associated with fluxional ligand binding on the NMR timescale. Heating the sample to 95 °C results in a simplified NMR spectrum. Although X-ray quality crystals of these titanium amidates could not be obtained, characterisation by VT-NMR spectroscopy and HRMS suggest that discrete monomeric species form. This would be consistent with the previously reported monomeric bis(diethylamido) precursor.<sup>8b</sup> Interestingly, in the solid state the diethylamido species is  $C_2$  symmetric and exhibits bond lengths for Ti-O<sub>amidate</sub> 2.146(1) Å and Ti-N<sub>amidate</sub> 2.156(1) Å, indicating a far more delocalised N,O-chelate than that exhibited by the pyridonates described above. Considering the varying steric and electronic attributes of these related ligand sets, it is interesting to examine their different catalytic activities.

We first investigated the homopolymerisation of LA and CL using catalysts 1 to 5 in the melt state (Table 1). As anticipated  $M_n$  and PDIs are modest compared to alternative metal initiators,<sup>1</sup> but are competitive with leading Ti examples.<sup>14,15</sup> Differences between observed and theoretical  $M_n$  ( $M_n$ theo) may be consistent with transesterification processes.<sup>12</sup> Some PLA chain-end stereocontrol is observed and it is interesting to note the shift in stereocontrol in moving from pyridonate initiators 2 and 3, where there is an isotactic bias, to amidates 4 and 5 where there is a slight preference for heterotacticity. Another

Table 1 Melt-phase homopolymerisation of rac-LA and ε-CL

Entry	Cat.	Monomer	Yield <sup>a</sup> (%)	$M_n^b$ (g mol <sup>-1</sup> )	$M_{\rm n}$ theo <sup><math>c,12</math></sup>	$PDI^{b}$	$P_{\rm m}{}^d$
1	1	LA	88	13 800	19030	1.17	0.49
2	2		90	14 120	19460	1.21	0.46
3	3		81	22 220	17 510	1.22	0.46
4	4		95	23 040	20 540	1.17	0.55
5	5		93	25 440	20110	1.16	0.53
6	1	CL	98	39 400	16780	1.29	_
7	2		98	22 810	16780	1.38	_
$8^e$	3		96	21 360	16440	1.28	_
9 <sup>f</sup>	4		98	20 860	16780	1.48	_
$10^{e,g}$	5		85	27 470	14550	1.33	_
			c17				

PLA: 130 °C, 24 h, [LA]/[Ti] = 300, 0.5 g. PCL: 100 °C, 16 h, [CL]/[Ti] = 300, 0.5 ml. <sup>*a*</sup> Isolated yield. <sup>*b*</sup> Determined by GPC. <sup>*c*</sup>  $M_n$ theo = ([M]/2[Ti] × %Yield × MW). <sup>*d*</sup> <sup>1</sup>H{<sup>1</sup>H} NMR spectrum. <sup>*e*</sup> Bimodal GPC trace. <sup>*f*</sup> 1 h. <sup>*g*</sup> 2 h.

intriguing facet is the increase in PLA  $M_n$  on moving from 6-methyl-pyridonate, **1**, to 3-methyl-pyridonate, **2**, which is further enhanced when **3**, with a bulkier substituent in the 3-position, is employed. This trend is reversed during PCL synthesis (compare entries 6, 7 and 8): we questioned whether this tunability during homopolymerisations coupled with the unusual ability to afford efficient PLA *and* PCL formation could be exploited for the synthesis of random copolymers.

To date, few examples of well-characterised initiators are known to facilitate the copolymerisation of LA and CL,<sup>6</sup> and the present state-of-the-art is Al Schiff-base or salen complexes.<sup>6d,f</sup> Examples of CL/LA random copolymers where there is a 1 : 1 incorporation of both monomers are rare simply because there is a propensity for LA to polymerise first, followed by CL incorporation at a lower rate.<sup>16</sup> Alternatively, an initiator which facilitates randomisation through transesterification can be used, thus avoiding this formation of block-like polymers, instead resulting in short average sequence lengths<sup>17</sup> (an ideal random copolymer will have  $L_{CL} = L_{LL} = 2^{16a,6d}$ ). Complexes 1, 2 and 3 form random copolymers in excellent yield using a low catalyst loading compared to leading salan/salen examples.<sup>6b,d</sup> We also observe excellent levels of CL and LA incorporation without the need for an excess CL feed.  $M_{\rm p}$  is competitive with previously reported values using well-defined initiators with a 1:1 monomer feed (e.g. 22320 using initiator 3 vs.  $13900^{6b}$ 16 300,<sup>6c</sup> and 21 600<sup>6d</sup>), Table 2. An initial attempt to increase the incorporation of CL into the random copolymer, by moving to reaction conditions which favour CL homopolymerisation i.e. lower reaction temperature, did not affect the polymer composition as hoped, but in fact led to predominantly PLA with only 12% CL

Entry	Catalyst	Yield <sup>a</sup> (%)	CL/LA <sup>b</sup> (mol%)	$L_{\rm CL}/L_{\rm LL}^c$	$M_{ m n}$ $({ m g mol}^{-1})^d$	$M_{\rm n}$ theo <sup>e, 12</sup> (g mol <sup>-1</sup> )	PDI <sup>d</sup>	
1	1	82	45/55	1.8/3.4	18750	19600	1.41	

Table 2 Malt phase conclumentian of a CL and real /

1	1	82	45/55	1.8/3.4	18750	19600	1.41
2	<b>1</b> <sup>f</sup>	60	29/71	_	28780	20 3 20	1.36
3	2	83	52/48	1.9/2.9	19070	19280	1.29
4	3	86	43/57	1.7/3.5	22320	19690	1.38
5	4	68	64/36	3.1/2.4	19190	18740	1.37
6	5	63	5/95	_	23660	21400	1.38

Conditions: 130 °C, 24 h, [monomer]/[Ti] = 600, 0.5 g (3.45 mmol) LA, 0.38 ml (3.45 mmol) CL. <sup>*a*</sup> Isolated yield. <sup>*b*</sup> Ratio of CL/LA determined by <sup>1</sup>H NMR. <sup>*c*</sup> Average chain length determined by <sup>13</sup>C{<sup>1</sup>H} NMR. <sup>*d*</sup> Values determined by GPC analysis. <sup>*e*</sup>  $M_n$ theo = ([CL]/2[Ti] ×  $\%_{CL}$  × 114.14) + ([LA]/2[Ti] ×  $\%_{LA}$  × 144.13). <sup>*f*</sup> 100 °C, 18 h, then 130 °C, 7 h.



copolymerisation; (b) monitoring the presence of LA homodiads ( $\blacktriangle$ ), CL homodiads ( $\blacksquare$ ) and heterodiads ( $\times$ ) over time.

(entry 2). The change from initiator **1** to **2**, resulted in a decrease in PDI and more importantly a reduction in  $L_{\rm LL}$  and a decrease in the LA content (48%). A  $T_{\rm g}$  of -3.3 °C is obtained for copolymer synthesised using **2**, where the theoretical value is -20.8 °C,<sup>16</sup> while  $T_{\rm m}$  was not observed. Pushing the reactivity trends further, to 3-phenyl-pyridonate **3**, results in an increase in  $M_{\rm n}$ , but a return to higher levels of LA incorporation. Although the yield with initiator **4** is modest, an unusual preference for CL incorporation is observed. In contrast, PLA dominates when bulkier amidate complex **5** is employed.

Investigation of the carbonyl region of the 13C(1H) NMR spectrum reveals that all of the copolymers undergo transesterification.<sup>17</sup> Reaction monitoring of polymerisation catalysed by 3 shows rapid polymerisation of LA to form longer chains of PLA (6 h: L<sub>CL</sub> 1.5; L<sub>LL</sub> 5.7) with CL reacting modestly (Fig. 2a). CL/LA ratios remain static after 10 h, where there is also a concomitant increase in the presence of heterodiads (CL-LA bonds), thereby reiterating the randomising effect of transesterification (Fig. 2b). After 10 h  $L_{LL}$  and  $L_{CL}$  reach their final observed values, however,  $M_n$ is 12 550 g mol<sup>-1</sup> and the PDI is 1.48 (compared to 22 320 g mol<sup>-1</sup> and 1.38 in the final isolated polymer). This data suggests that the polymer chain continues to grow after the 10 h time period through transesterification.<sup>18,19</sup> Methanol soluble (*i.e.* low mass) fractions of the quenched reaction solutions were subjected to qualitative MALDI-TOF analysis. Low mass cyclic species and short linear chains composed of half lactide units can be seen. The methyl ester peak, resulting from methanol-quenched transesterifications, is also present in the <sup>1</sup>H NMR spectrum.<sup>12</sup>

In conclusion, novel bis(pyridonate)- and bis(amidate)-titaniumalkoxides have been isolated in excellent yield. All can be prepared under mild reaction conditions from a common precursor,  $Ti(NMe_2)_4$ . The complexes have been used in the polymerisation of LA and CL and are the first examples of polymerisation initiated by this class of titanium compound. Most importantly, these titanium initiators can be used for copolymer synthesis with short sequence lengths, close to 1 : 1 monomer incorporation and good  $M_n$  due to transesterification. We plan to further exploit our synthesis of random copolymers with these readily modified ligand sets to access a family of polymerisation catalysts affording a large scope of  $M_n$ , sequence length and level of transesterification. Such synthetic results, polymer characterization and rheological investigations will be reported shortly.

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