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Well-defined Ti₄ pre-catalysts for the ring-opening polymerisation of lactide

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The synthesis and full characterisation of four discrete tetrametallic titanium complexes is reported. These well-defined compounds are isostructural in the solid state and share the same general formula: Ti₄(μ-O)L₄ (L = 1, 2, 3 or 4). Using a combination of NMR techniques the complexes are found to be stable in solution, even at elevated temperatures. Further studies show that the carboxylate moieties of the supporting amine bis(phenolate) ligands can be displaced by a more strongly coordinating solvent. This reversible process causes the coordinatively saturated Ti₄(μ-O)L₄ complexes to separate into two Ti₂(μ-O)L₂ subunits which we envisaged would be catalytically active. Proof-of-concept experiments establish that all four of these complexes display catalytic activity in the ring-opening polymerisation of rac-lactide. These aggregates can therefore be viewed as air and moisture stable pre-catalysts for a range of reactions.

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Introduction

There is a wealth of fascinating chemistry which exists at the interface of homogeneous and heterogeneous catalysis. For example, reducing the particle size of a heterogeneous catalyst is generally accompanied by a favourable increase in reaction rate. Upon reaching the size of small nanoparticles ambiguity often arises in defining the catalytically-active species as these unsupported particles/clusters are unstable. Therefore the synthesis of stable and well-defined polymeric complexes is of great interest. Solvothermal reactions have been shown to be useful in creating polymeric complexes. However, greater synthetic control can be achieved by sequentially linking monometallic species through metal-metal bonds or bridging ligands, such as o xo or carboxylate. By supporting each metal centre with a suitable ligand, we can create a stable aggregate whilst also solubilising the complex for dynamic analysis at the atomic scale. Additionally the ligand has the potential to direct the assembly of the metal complex, tailor the properties of the complex and influence the activity of the catalyst.

With low toxicity and high relative abundancy titanium is an ideal choice for sustainable catalysis. This is particularly true for polymerisation reactions such as the production of polylactide, a biodegradable plastic which finds application in food packaging and medical implants. Titanium(IV) catalysts have been used extensively for the ring-opening polymerisation (ROP) of lactide in conjunction with many different ligands with some examples featuring an o xo-bridged titanium core. These complexes often also feature alkoxy initiating groups that are ultimately incorporated into the polymer chains. As a result these complexes are often more accurately described in the literature as initiators rather than catalysts. A reusable catalyst would not require regeneration of the initiator.

Amine bis(phenolate) ligands have been exploited in the ROP of lactide for their ability to strongly bind metals and ease of modification. For example, a variety of donors can be installed on the pendant arm and the phenol moieties can be appended with a range of substituents, both of which can be used to affect catalysis. We noted that no amine bis(phenolate) ligands featuring a carboxylate group on the pendant arm had been reported for application in the ROP of cyclic esters. Moreover, the ambidentate carboxylate group on the pendant arm had been reported for application in the ROP of cyclic esters. Finally, the carboxylate could also bridge to other metal centres leading to expansion of the metal complex into an aggregate. Herein, we present the synthesis, characterisation and design of a robust, air- and water-stable, tetrametallic titanium catalyst for use in the ring-opening polymerisation of rac-lactide.
Scheme 1. Synthetic route to the ligand precursors 1-4(H)₃ and their consequent reaction to form the titanium clusters 5-8.

Results and discussion

Synthesis of ligands and metal complexes

A general reaction scheme for compounds 1-8 is shown in Scheme 1. Compound 1(H)₃ was synthesised by two successive reductive aminations. Synthesis of compound 2(H)₃ has been reported using a one-pot Mannich condensation. Modified Mannich condensation procedures based on literature precedents were developed to obtain compounds 3(H)₃ and 4(H)₃. In contrast to the other compounds, 3(H)₃ could not be isolated cleanly in the work up. In this instance the product was precipitated, as a white solid, from a viscous aqueous mixture by lowering the pH with dilute, aqueous hydrochloric acid. Synthesis of ligand 4(H)₃ was problematic and various reaction conditions for the Mannich condensation reaction were explored to improve the yield (see Experimental for details). The deactivating nature of the fluoro group in the reagent 4-fluorophenol was presumed to inhibit the nucleophilic aromatic substitution step of the Mannich condensation. However, using a similar procedure to that used to obtain 3(H)₃, a low yield (7% conversion) of 4(H)₃ could be isolated by column chromatography. The second method, a triethylamine-catalysed Mannich condensation, was also low yielding (14% yield) but due to a simpler work-up was found to be the most satisfactory synthetic method to obtain ligand 4(H)₃.

Dry THF suspensions of compounds 1-4(H)₃ were then treated with one equivalent of Ti(OiPr)₄, under an atmosphere of N₂, to give clear yellow/orange solutions of the resultant complexes. Deionised water (four equivalents) was added under basic conditions to effect the formation of Ti–O–Ti bridges and resulted in the formation of yellow/orange precipitates. The suspensions were concentrated under vacuum and the solids removed by filtration under N₂ to yield non-crystalline samples of compounds 5-8 respectively. These compounds were further purified by trituration using THF (5,6,8) or toluene (7).

Synthesis of ligands and metal complexes

Diffraction quality crystals of each of the titanium compounds 5-8 were grown by vapour diffusion (5,6,8) or slow evaporation (7). Single crystal X-ray diffraction studies of 5-8 showed a common tetranuclear titanium complex Ti₄(μ₂-O)₂L₄ (L = 1-4, Figure 1). Aggregates 5 and 8 have pseudo S₄ symmetry about the Ti₄(μ₂-O)₂(μ₂-COO)₄ core. In contrast 6 and 7 contain actual S₄ symmetry as indicated by their space group symmetry of I4. The Ti₄ core is bound by two oxo ligands and four carboxylate ligands. The longer Ti-carboxylate bridges (cf. Ti–O–Ti) result in an ordered, natural elongation of a tetrahedron whereby the four titanium centres form the vertices of a tetragonal disphenoid.

Complex 5 consists of a total of four supporting ligands (1), four titanium centres and two bridging oxo ligands resulting in the overall formula of Ti₄(μ₂-O)₂L₄. Each titanium centre is bound to all but one of the donor atoms of the amine bis(phenolate) ligand resulting in a distorted octahedral geometry. The remaining oxygen atom of the carboxylate moiety bridges to an adjacent metal; we define this as ‘bridging’ and the other as ‘native’. The complex is overall neutral, confirmed by the absence of counter-ions in the asymmetric unit. The charges upon the four deprotonated amine bis(phenolate) ligands and two oxo ligands are balanced by the four titanium(IV) centres. The bridging carboxylate group is formally an LX donor but as might be expected for a delocalised moiety the mean distances of the native and bridging carboxylate carbon-oxygen bonds, 1.263(3) Å and 1.253(2) Å respectively, do not differ significantly. Furthermore, the average bond distance between a titanium centre and the oxygen from the native carboxylate is 2.012(1) Å whereas the average bond distance between a titanium and the oxygen from an adjacent carboxylate is 2.094(2) Å. The lack of significant difference in bond lengths can be explained by delocalisation of the electronic charge within the structure.

Table 1 Means and deviations of selected bond lengths (Å) and angles (°) for compounds 5-8.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Deviation (Å)</th>
<th>Deviation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti–(μ₂-O)</td>
<td>1.821(2)</td>
<td>±0.004</td>
<td>0.23</td>
</tr>
<tr>
<td>Ti–(μ₂-O)–Ti</td>
<td>1.45(8)</td>
<td>±0.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Ti–OPh</td>
<td>1.83(2)</td>
<td>±0.004</td>
<td>0.21</td>
</tr>
<tr>
<td>Ti–Onative</td>
<td>2.017(2)</td>
<td>±0.005</td>
<td>0.27</td>
</tr>
<tr>
<td>Ti–ObridgedCO</td>
<td>2.095(2)</td>
<td>±0.003</td>
<td>0.14</td>
</tr>
<tr>
<td>TiOnative–CO</td>
<td>1.266(4)</td>
<td>±0.005</td>
<td>0.36</td>
</tr>
<tr>
<td>TiObridged–CO</td>
<td>1.257(4)</td>
<td>±0.003</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Figure 1 Crystallographic representations of compound 5. From left to right: asymmetric unit; coordination sphere of the titanium metal centres; the tetragonal disphenoid formed by the four titanium centres. Solvent of crystallisation and hydrogen atoms omitted for clarity. Ti = Light blue; C = Grey; N = Blue; O = Red.

This implies the two carboxylate oxygens can consecutively alternate between L and X type donation with each titanium centre conserving an oxidation state of +4. We anticipate that these delocalised carboxylate groups will have the potential to stabilise a metal centre during redox processes associated with a catalytic cycle. Despite the observed delocalisation we classify each amine bis(phenolate) ligand as a formal LX$_3$ type donor with the native carboxylate oxygen acting as an X donor to satisfy an oxidation state of +4 to each titanium centre.

Selected bond distances and angles for the crystals structures of 5-8 are presented in Table 1. These are in agreement with similar titanium amine bis(phenolate) complexes and related Ti compounds which contain bridging oxo moieties. The Ti–O–Ti bridges in compounds 5-8 adopt a bent conformation with an internal angle of 145.7(1)$^\circ$ to accommodate the bridging carboxylate interactions. Both native and bridging Ti–OCO bonds are found to be shorter than the L-type donation found in a pendant CH$_2$CH$_2$OMe group but longer than an X-type CH$_2$CH$_2$O$^-$ group. A bridging CH$_2$CH$_2$O$^-$ group with a L- and X-type donation shows comparable Ti–OCO distances to those found in compound 5. A further example consisting of a salicylaldiminato titanium complex featuring bridging carboxylates also shares similar native and bridging Ti–OCO and TiO–CO bond distances to compound 5.

Analysis of geometrical parameters in compounds 5-8 showed no significant deviation (< 0.5%). From this, we can infer that 5-8 are isostructural and the R-groups screened in this work have had little effect on observed bond lengths within the aggregates. Moreover, the nature of the R group has not diminished the formation of this clearly favourable Ti$_4$(μ-O)$_2$L$_4$ species.

Solution NMR characterisation

Compounds 5-8 were further characterised by $^1$H and $^{13}$C NMR spectroscopy as well as $^{19}$F NMR spectroscopy in the case of 8. It was observed that $^1$H NMR spectra of 5 in [D$_6$]DMSO were broadened in comparison to the spectra obtained in CDCl$_3$ (see Figure S1). This was found to occur in both the $^1$H and $^{13}$C NMR spectra of 5. To investigate the cause of this broadening, the D1 delay was increased to 12 s and the sample concentration was decreased to determine if the spectral broadening was due to relaxation effects or aggregation in solution. No change in the peak widths was observed, therefore these causes were eliminated. An EXSY NMR experiment of 5 in [D$_6$]DMSO confirmed that the broadened $^1$H signals were due to their involvement in an exchange process (Figure S2). We suggest this is the result of an equilibrium between the dimeric (Ti$_4$)
Selected proton assignments from NMR studies labelled in the crystal structure of 6. Through-space contacts specific to the dimeric structure, shown by purple fragmented bonds, are present in the ROESY spectrum (see Figure S4). Intramolecular proton distances from single crystal X-ray diffraction data: H_{D1} ••• H_{Me1}, 2.785(1) Å; H_{D1} ••• H_{B1}, 3.165(1) Å; H_{D1} ••• H_{Me2}, 3.235(1) Å and H_{D2} ••• H_{Me1}, 3.612(1) Å. Solvent of crystallisation and selected hydrogen atoms omitted for clarity. Ti = Light blue; C = Grey; N = Blue; O = Red.
and monomeric forms (Ti$_2$, Scheme 2). To further investigate this exchange process the $^{19}$F NMR spectra of compound 8 in CDCl$_3$ confirms the sole presence of the Ti$_4$(μ-$\sigma$-O)$_4$L$_4$ species in solution. However, in a more strongly coordinating solvent such as [D$_6$]DMSO we observe signals associated with several different species, all of which are accompanied by spectral broadening (Figure S3) indicating that we are observing an exchange process. The monomeric form is proposed on the basis that the bridging carboxylates were identified as the most labile group, participating in L-donation whilst the native X-type donation conserves the +4 oxidation state of the titanium centres. Although the titanium centres in 5 are fully saturated, the presence of a suitable donor or substrate could potentially disrupt the aggregate allowing for interactions with the titanium centres. This implied that although no vacant site is apparent in the solid state structures of compounds 5-8, an active species could be generated if a substrate were to bind to the metallic core.

Due to the instability of 5 in the presence of a strong donor solvent we sought to undertake further NMR based investigations to better understand the reactivity of these complexes. Using the crystal structures of 5-8, through-space contacts that could only be observed if the dimeric form existed in solution were identified (Figure 2). The presence or absence of these contacts would elucidate whether the monomeric or dimeric form is characterised by the NMR spectra in CDCl$_3$. NOESY/EXSY and ROESY NMR experiments were undertaken. No NOE or exchange signals were observed for samples of 5-8 in CDCl$_3$, which can be expected for molecules in the mass range of 1000 to 2000 Da. A ROESY experiment did show cross-coupling signals for all samples of 5-8. In conjunction with COSY and HSQC NMR experiments, the individual methylene and aromatic proton environments were assigned (Figure S4). For example, the ROESY experiment of compound 6 revealed through-space contacts with methyl protons H$_{Me1}$ and H$_{Me2}$ that enabled the assignment of H$_6$ and H$_7$ as aromatic protons ortho to the methyl R group. Since H$_4$ and H$_6$ showed through-bond coupling from the COSY experiment, H$_6$ could be distinguished from H$_{Me1}$. The individual methylproton signals could be paired per methylene group using C-H correlation and through-bond coupling. Individual proton assignments were made by using through-space contacts, specifically the relationships between H$_{Me1}$•••H$_E$ and H$_{Me2}$•••H$_{Me2}$ were key to achieving this. With these assignments, the methylene-aromatic region was inspected. Cross-coupling peaks were found for H$_E$•••H$_{Me1}$ and H$_{Me2}$•••H$_{Me2}$ and these were identified as distinct to the dimeric form from the crystal structure.

Additionally, the through-space contacts for H$_{Me1}$•••H$_{Me2}$ and H$_{Me2}$•••H$_{Me2}$ were also observed and further support the presence of the dimeric form. These cross-coupling peaks are in agreement with the intramolecular hydrogen distances (< 5 Å) obtained from the crystal structures (Figure 2). From this evidence, we can ascertain the NMR spectra in a weakly coordinating solvent are of the dimeric forms of compounds 5-8. Exploiting the solubility of the complex enabled us to gain insight into its behaviour in solution and potential application in catalysis through analysis of the three-dimensional structure by combining solid- and solution-state techniques.

A variable temperature NMR study in [D$_6$]toluene of 8 was performed to test the thermal stability of the dimeric structure in a weakly-coordinating solvent (Figure S5). Coalescence of the methylene bridge signals was of interest since this would be indicative of hemi-lability in the ligand upon heating. No coalescence was observed in the temperature range from −40°C to 80°C. In addition, identical NMR spectra were obtained at 20°C before and after heating to 80°C. This shows that the aggregates are thermally stable. If the dimeric structure were to dissociate to the monomeric structure, the apparition of different chemical environments or broadening of the signals would be anticipated but no such change in the NMR spectra was observed. The variable temperature NMR experiment produced similar spectra across the temperature range −40°C to 80°C with no coalescence of signals. The aggregates are thermally stable in a weakly-coordinating solvent but we have already shown that they can be disrupted with a more strongly-coordinating solvent. It is reasonable to expect that a diester, such as lactide, will have a similar, disruptive effect on the aggregate. It is therefore more accurate to describe these Ti$_4$ compounds as pre-catalysts that
are capable of forming the active species in situ under the polymerisation conditions we describe.

**Melt polymerisation of rac-lactide**

Compounds 5-8 exhibited thermal stability leading us to propose that they would be well-suited to catalyse the ROP of lactide in the melt. To verify the stability of the catalyst under these conditions, the $^1$H NMR spectra for 6 and a quenched sample of 6 from a reaction with lactide-to-titanium ratio of 10:1 in the melt at 130°C were inspected. All the $^1$H NMR signals for 6 were found to be present at similar chemical shift and integrations. Further analysis by COSY and ROESY NMR experiments confirmed the dimeric structure of catalyst 6 was recovered after reaction, asserting the catalyst was stable under the reaction conditions and can be recovered.

Initial polymerisations were performed with 5 as catalyst in the melt polymerisation of rac-lactide at 130°C with a monomer-to-titanium ratio of 300:1. Low conversion (17%) of the monomer to the polymer was observed after 24 h. Benzyl alcohol was introduced at the same concentration as titanium to act as an initiator in the catalytic reaction but this was not found to increase the rate of ROP after 24 h. In comparison it was found that the addition of an alkyl R-group to the phenolate (6 and 7) significantly increased the conversion after 24 h. An increase in the solubility of 6 and 7 (with respect to 5) correlated with an upward trend in catalytic activity ($5 < 6 < 7$). Finally, catalyst 8 was of interest for two reasons: to investigate the effect of an electron withdrawing substituent and to make the catalyst more polar to increase solubility in the melt. This catalyst gave the highest conversion after 24 h at 91%. The increased catalytic activity of 8 could be rationalised by either electronic effects or solubility imparted by the fluoro group. However, earlier inspection of the crystal structures revealed the compounds 5-8 are isostructural indicating that the R group has little electronic influence over the complex. Therefore, it is likely the increase in catalytic activity for catalyst 8 is due to its increased solubility in molten lactide. Furthermore, the crystal structures of 5-8 show the R groups are facing the exterior of the aggregate where they affect the primary solvation sphere. This would support that the improved solubility is the cause of the increase in catalytic activity between 5 and 8.

Bulk polymerisation with 8 was repeated with a monomer-to-titanium ratio of 600:1 to further test the activity of the catalyst. This led to a conversion of 66% after 24 h. The polymerisation was repeated with time extended to 48 h and the conversion reached 96%. A similar increase in conversion was observed with Entries 11 and 12 when increasing the polymerisation time. As expected, increasing the polymerisation time led to an increase in conversion. This suggests the catalyst is not deactivated until the polymerisation is terminated at the desired time.

From Entries 11 and 12, it can be seen that addition of benzyl alcohol has hindered the polymerisation. We observed lower conversion, shorter polymer chain lengths and higher polydispersity indices (PDIs) in comparison to entries 8 and 9. This is attributed to benzyl alcohol displacing the growing polylactide chains from the metal centres, resulting in an increase in the rate of transesterification reactions. Noticeably, the gel permeation chromatography (GPC) traces exhibited bimodal molecular weight distributions with shoulders as well as evidence of unimodal high molecular weight chains (ca. 90000 Da). The high molecular weight chains are likely due to intermolecular transesterification whereas the bimodal traces occur from intramolecular transesterification, whereby the difference in hydrodynamic volume between linear polylactide and macycyclic polylactide results in the appearance of a shoulder peak.$^{47,48}$ Generally, the addition of benzyl alcohol had a negative effect on the conversion for these systems, confirming that an accompanying initiator is not a necessity for catalysts 5-8 to ring-open lactide. With the

**Table 2** Melt polymerisation of rac-lactide with catalysts 5-8 at 130°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst [M]$_0$/[Ti]$_0$</th>
<th>Additive Time Conv. (%)</th>
<th>$M_w$/[$M_n$/$M_d$]</th>
<th>$M_w$/[$M_n$/$P_d$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 300 BnOH 24 h 11 6700  1120 1.06 0.53</td>
<td>1.35 0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 300 BnOH 24 h 11 6700  1120 1.06 0.53</td>
<td>1.35 0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 300 - 24 h 46 3150 8470 1.12 0.66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6 300 BnOH 24 h 40 4380 4560 1.10 0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7 300 - 24 h 84 1110 16000 1.41 0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7 300 BnOH 24 h 86 8530 5690 1.49 0.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7 300 - 24 h 91 22300 20000 1.59 0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8 600 - 24 h 66 15700 23500 1.36 0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>8 600 - 48 h 96 42000 41200 1.50 0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8 300 BnOH 24 h 84 10500 6050 1.73 0.59</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>11</td>
<td>8 600 BnOH 24 h 64 11800 /7140 1.76 0.54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>8 600 BnOH 48 h 78 24700 /9100 1.59 0.56</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

$^a$ Conversion from $^1$H NMR spectra evaluated by integration of the methine regions of polylactide versus lactide. $^b$ Polymer number average molar mass determined from GPC traces. $^c$ Calculated polymer molecular weight by $^1$H NMR end-group analysis. $^d$ Polydispersity indices ($M_w$/[$M_n$/) obtained from GPC traces. $^e$ Calculated from analysis of the homonuclear decoupled $^1$H NMR spectrum of the polymer sample. $^f$ From unresolved peaks – see discussion.
of these systems, the catalysts showed reasonable control over the ROP of rac-lactide with PDI values ranging between 1.12 and 1.59 where conversion exceeded 40%.\textsuperscript{47,48} Comparison of these results to other Ti(IV) systems is difficult as the majority are initiated by pre-existing metal alkoxides, something which is not present in our complexes (5-8). Moreover, our Ti\textsubscript{4} pre-catalyst requires activation \textit{in situ} and therefore our systems unsurprisingly show lower activity when compared to other initiators featuring a Ti–O–Ti core.\textsuperscript{23,25} Despite this, 5-8 retain the advantage of being air- and water-stable pre-catalysts that are capable of ring-opening unpurified lactide and can be collected and reused due to the absence of a pre-existing initiating group.

The microstructure of the polylactide samples was investigated by $^1$H NMR. Determination of the polymer chain lengths by end-group analysis correlates well with most of the polymer chain lengths obtained from GPC traces. This supports the view that linear polylactide terminated by water was obtained from catalysts 5-8. We assume the water incorporated into the polymer chains was present in the lactide used. Inspection of the methine region by homonuclear decoupled proton NMR enabled the determination of the probability of racemic enchainment, $P_r$.\textsuperscript{49,50} The values presented in Table 2 indicate polymers produced using catalysts 5-8 display a slight tendency for heterotactic enchainment.

A correlation between increased conversion and longer polymer chain length can be seen from the data in Table 2. Longer chain lengths were obtained for catalyst 8 at similar conversion to catalyst 7. It could be thought that the increased solubility of 8 allows for better mass transfer of the catalyst during the melt polymerisation, leading to longer polymer chains. The higher conversion and longer polymer chain lengths showed that maximising homogeneity was beneficial for these systems.

Figure 3 Suggested active species in the melt polymerisation of rac-lactide. The monomeric Ti$_2$(μ-O)L$_2$ structure is stabilised by the growing polylactide chains bound to the titanium centres and denoted by PLA.

Melt polymerisation active species

Solution polymerisation experiments are commonly used to determine the kinetics of the ROP of lactide. The nature of the solvent was shown to be critical to the stabilisation of the dimeric Ti\textsubscript{4} pre-catalysts over the monomeric Ti$_2$ form. In the case we present, relevant kinetic data could only be obtained in molten lactide, which is problematic without specialised equipment.\textsuperscript{51} As an alternative approach, we used a variety of solution-state NMR experiments to probe the active species.
Compounds 5-8 exhibited lability in strong donor solvents, a comparable environment to the molten lactide 'solutions' in the catalytic system. We propose that the active species involves a transition from the saturated dimeric Ti₄(μ-O)₂L₄ to the monomeric Ti₂(μ-O)L₂ form stabilised by coordinated polylactide chains, allowing access to all four titanium centres. Rotation about the Ti–O–Ti bridge would relieve any steric strain caused by the growing chains (Figure 3). To gain further insight into the proposed active species during polymerisation, a control ¹H NMR experiment involving the mixing of rac-lactide and catalyst 6 in CDCl₃ was carried out to probe for interactions between the two molecules. We observed an upfield shift of specific proton signals when compared to the ¹H NMR of the pure catalyst (Figure S6). The shift in proton signals not accompanied by the same shift of vicinal protons is indicative of a localised interaction between the catalyst and rac-lactide. The protons in question are highlighted in the space-filling model of 6 in its dimeric form (Figure 4). It was noted that protons H₁ and H₂ are inaccessible to the solvation sphere and cannot interact directly with rac-lactide. The upfield shift of these proton signals is symptomatic of greater magnetic shielding, which can be explained by greater proximity to the face of an aromatic ring or carboxylate. It can be envisaged that rac-lactide interacts with the catalyst causing a bending of the phenolate rings, resulting in more pronounced magnetic shielding of individual protons. To locate possible areas rac-lactide can interact with 6, the solvent-accessible void space in the crystal structure of 6 was calculated (Figure 4). This revealed four areas, highlighted in yellow, that correspond to the only sterically-viable approach pathway rac-lactide can take to displace the bridging carboxylate and access the titanium centres, ultimately leading to the monomeric Ti₂(μ-O)L₂ form. In conjunction with the localised proton signal shifts, we find this is supportive of the proposed active species (Figure 3). At this moment in time, the structure of the active species can only be inferred and we are undertaking further work in pursuit of additional structural proof.

**Conclusions**

Four amine bis(phenolate) ligands have been used to synthesise well-defined tetrametallic titanium complexes 5-8. Single crystal X-ray diffraction studies showed these discrete complexes were isostructural, demonstrating that varying the R-groups of the ligand has minimal influence on the overall architecture of the complex. When examining their catalytic activity we did observe a significant difference in the rate with which these complexes polymerised rac-lactide. Qualitatively, we observed those complexes which were most soluble in molten lactide were also those which achieved the highest rates of ROP and longest polymer chain lengths. We therefore ascribe the increased rate of ROP to those catalysts that have the highest concentration in solution whilst also noting that as the reaction proceeds, the concentration of PLA increases and the reaction medium becomes increasingly polar. We are undertaking further investigations to establish the full effect the changes of R-group have on the overall electronic structure of the complex. Critical to understanding the behaviour of these complexes has been the detailed NMR studies. These allowed us to assign individual protons in the ¹H NMR spectra using a range of 2D NMR experiments. In particular, through-space contacts from a ROESY were identified as being specific to the dimeric form found in
the crystal structure confirming its presence in solution and establishing its stability in variable temperature NMR experiments. Broadening of the NMR spectra in a donor solvent highlighted exchange processes were occurring on the NMR timescale. We observed that these tetrametallic complexes are, in a strong donor solvent, in equilibrium with two dimetallic sub-units which are themselves stabilised by the donor solvent molecules. The relative stability of these two species is intrinsically linked to the carboxylate bridges. We propose that weakening these bridges will facilitate formation of the active dimetallic species and ultimately increase the rate with which our catalysts can ROP lactide. As a result we can conclude that these aggregates are only being activated in situ by the presence of the substrate. The use of benzyl alcohol, a common additive used to improve the performance of similar catalysts, was found to reduce conversion of the monomer and promote unfavourable side-reactions. Inspection of the polymer microstructure indicated we were producing slightly heterotactic linear polylactide chains, unsurprising considering the nature of our catalyst. Now that the proof-of-concept work has been completed, we are focusing our efforts on the inclusion of chirality into the ligand framework through the use of single enantiomer amino acids in the ligand synthesis to increase the selectivity of the reaction.

Experimental details
General considerations
The starting materials were purchased from Sigma-Aldrich and Acros. Dry solvents were purified in an MBRAUN SPS-800 and stored over 4 Å molecular sieves under a dry nitrogen atmosphere. NMR spectroscopy data was acquired with a Bruker AVIII 300 MHz instrument or Bruker AVIII 400 MHz at 298 K. Nanoelectrospray ionisation (NSI) mass spectra were obtained by the EPSRC National Mass Spectrometry Facility (NMSF), Swansea, UK. Elemental microanalysis was carried out on an Exeter CE-440 Elemental Analyse. Single crystal X-ray diffraction data was acquired using a Bruker Apex-II operating at 100 K with Mo-Kα radiation or the synchrotron at beamline number 11.3.1, Advanced Light Source, Berkeley, USA. The Advanced Light Source is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231. CCDC 1483652, 1483653, 1483654 and 1483655 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Molecular weights (Mn) and molecular mass distributions (Mw/Mn) of polymers were determined by GPC at 35°C using THF as eluent with a 8 flow rate of 1.0 mL min⁻¹. The experimental values were obtained relative to a calibration curve using polystyrene standards, which were corrected by universal calibration and a factor of 0.58. See SI for further experimental details.

Ligand precursor synthesis
Compound 1(H)₂:

bis-(2-hydroxybenzyl)-amino acetic acid3,4

Under N₂, glycine (1.50 g, 20 mmol) was dissolved in a solution of sodium hydroxide (0.80 g, 20 mmol) in methanol (50 mL). Salicylaldehyde (2.12 mL, 20 mmol) was added to yield a yellow solid in suspension which then dissolved to give a clear yellow solution. Sodium borohydride (0.83 g, 22 mmol) was added slowly to yield a white precipitate in a clear colourless solution. After 15 mins stirring, the reaction mixture was evaporated to dryness and the resulting white solids dissolved in water (20 mL) and acidified to pH 4 with 1 M aqueous hydrochloric acid. The white precipitate was filtered, dried and weighed (3.128 g, 86%).

This was identified as the monophenolate adduct by the presence of the substrate. The use of benzyl alcohol, a common additive used to improve the performance of similar catalysts, was found to reduce conversion of the monomer and promote unfavourable side-reactions. The aqueous phase was concentrated, acidified with 1 M aqueous hydrochloric acid to pH 4 to yield a white solid that was filtered, rinsed with chloroform and recrystallised from methanol. Yield (1.816 g, 32%); δ 10.73 (br, ArOH), 6.97 (m, 4H, ArH), 7.12 (m, 4H, ArH), 6.77 (m, 4H, ArH), 3.77 (s, 4H, CH₂); δ 172.55, 156.93, 130.60, 129.08, 122.99, 119.32, 115.85, 53.86, 53.40; HRMS (NSI⁺): m/z calcd for C₃₆H₃₅NO₄: 528.23; found 528.2435; elemental analysis calcd (%) for C₃₆H₃₅NO₄: C 66.89, H 5.96, N 4.87; found: C 66.77, H 5.83, N 4.65.

Compound 2(H)₂:

bis-(2-hydroxy-5-methylbenzyl)-amino acetic acid35

Sodium hydroxide (0.80 g, 20 mmol) was dissolved in methanol (60 mL) with p-cresol (4.326 g, 40 mmol) and glycine (1.50 g, 20 mmol). Paraformaldehyde (1.20 g, 40 mmol) was added and the reaction mixture was heated to reflux for 48 h under N₂. The suspension turned clear and the reaction was quenched with water (120 mL) and washed with diethyl ether (5 × 50 mL). The aqueous phase was concentrated, and the reaction mixture was added to 1 M aqueous hydrochloric acid to pH 4 to yield a white solid that was filtered and recrystallised from methanol. Yield (0.836 g, 13%); δ H NMR (300 MHz, [D₆]DMSO): 6 10.49 (br, ArOH), 6.97 (m, 4H, ArH), 6.72 (m, 2H, ArH), 3.79 (s, 2H, CH₂), 3.34 (s, 4H, CH₂), 2.19 (s, 3H, CH₃); δ 171.86, 154.15, 130.68, 129.04, 127.17, 121.96, 115.21, 53.31, 52.83, 20.13; HRMS (NSI⁺): m/z calcd for C₃₆H₃₄NO₄: 516.1543 [M⁺H⁺]; found 516.1544; elemental analysis calcd (%) for C₃₆H₃₄NO₄: C 66.85, H 6.71, N 4.44; found: C 66.86, H 6.57, N 4.24.

Compound 3(H)₂:

bis-(5-tert-butyl-2-hydroxybenzyl)-amino acetic acid

Sodium hydroxide (0.80 g, 20 mmol) was dissolved in methanol (30 mL) with p-tert-butylphenol (6.009 g, 40 mmol) and glycine (1.50 g, 20 mmol). Paraformaldehyde (1.20 g, 40 mmol) was added and the reaction mixture was heated to reflux for 48 h under N₂. The suspension turned clear and the reaction was quenched with water (120 mL) and washed with diethyl ether (3 × 30 mL). The aqueous phase was concentrated on the rotary evaporator. The resulting viscous liquid was acidified with 1 M aqueous hydrochloric acid from pH 10 to pH 4 to yield a white solid that was filtered, triturated with chloroform and recrystallised from methanol. Yield (3.279 g, 41%); δ H NMR (300 MHz, [D₆]DMSO): 6 10.54 (br, ArOH), 7.12 (m, 4H, ArH), 6.72 (d, 4H, ArH), 3.75 (s, 4H, CH₂), 3.19 (s, 2H, CH₂), 1.22 (s, 18H, CH₃); δ 172.59, 154.57, 141.28, 127.25, 125.56, 121.99,
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and dried at 40°C under vacuum. In dichloromethane and the polymers precipitated with excess methanol. The collected polymers were washed with methanol and dried at 40°C under vacuum.

**Compound 4(H):**

bis-(5-fluoro-2-hydroxybenzyl)-amino acetic acid

**Method A:** Following the same procedure as for compound 2(H), brown solids were obtained. The product was isolated by column chromatography with 10: dichloromethane: methanol as eluent as a light brown solid. Yield (0.466 g, 7%).

**Method B:** To a mixture of ethanol (15 mL) and water (2 mL) was added glycine (0.8258 g, 11 mmol), 4-fluorophenol (2.803 g, 25 mmol), triethylamine (0.500 mL, 4 mmol) and 37 wt% formaldehyde solution (3.30 mL, 40 mmol). The solution was heated to 50°C for 10 days followed by stirring at RT for 24 h. The light brown precipitate was filtered and recrystallised from methanol.

**Compound 5:**

After trituration from THF, the yellow solids were dried and weighed. Yield (0.334 g, 49%); 1H NMR (400 MHz, CDCl3): δ 7.26 (m, 2H, ArH), 7.01 (m, 2H, ArH), 6.86 (m, 3H, ArH), 6.72 (td, 1H, ArH), 3.77 (d, 1H, CH3), 3.30 (d, 1H, CH3), 3.17 (d, 1H, CH3), 3.06 (d, 1H, CH3).

**Compound 6:**

After trituration from THF, the yellow solids were dried and weighed. Yield (0.388 g, 53%); 1H NMR (400 MHz, CDCl3): δ 7.03 (td, 2H, ArH), 6.79 (d, 2H, ArH), 6.72 (dd, 2H, ArH), 3.74 (d, 1H, CH3), 3.29 (d, 1H, CH3), 3.10 (d, 1H, CH3), 2.88 (d, 1H, CH3).

**Compound 7:**

After trituration from toluene, the orange solids were dried and weighed. Yield (0.451 g, 50%); 1H NMR (400 MHz, CDCl3): δ 7.25 (dd, 1H, ArH), 7.19 (dd, 1H, ArH), 7.01 (d, 1H, ArH), 6.92 (d, 1H, ArH), 6.76 (d, 1H, ArH), 6.72 (d, 1H, ArH), 3.78 (d, 1H, CH3), 3.41 (d, 1H, CH3), 3.20 (d, 1H, CH3).

**Compound 8:**

After trituration from THF, the orange solids were dried and weighed. Yield (0.336 g, 49%); 1H NMR (400 MHz, CDCl3): δ 6.97 (m, 2H, ArH), 6.80 (m, 4H, ArH), 3.76 (d, 1H, CH3), 3.23 (d, 2H, CH3), 3.16 (d, 1H, CH3), 3.01 (d, 1H, CH3), 2.70 (d, 1H, CH3); 13C NMR (100 MHz, CDCl3): δ 181.77, 162.00, 158.09, 157.19, 156.56, 155.69, 154.81, 126.05, 125.98, 125.83, 125.76, 117.21, 117.13, 116.66, 116.59, 116.45, 116.22, 116.14, 115.98, 115.92, 115.74, 64.48, 61.94, 59.63; 13F NMR (376.5 MHz, CDCl3): δ −121.61 (sxt, ArF).

**Melt polymerisation procedure**

Under N2, a 5 mL vessel was charged with rac-lactide (1.00 g, 6.94 mmol) and appropriate amounts of catalyst and, if required, benzyl alcohol. The vessel was sealed and immersed in an oil bath at 130°C. Once the polymerisation time was reached, the vessel was removed from the oil bath and the reaction terminated by the addition of methanol (5 mL). The solids were dissolved in dichloromethane and the polymers precipitated with excess methanol. The collected polymers were washed with methanol and dried at 40°C under vacuum.

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References