DOI: 10.1002/chem.200902518

Development of Amino–Oxazoline and Amino–Thiazoline Organic Catalysts for the Ring-Opening Polymerisation of Lactide

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Abstract: The ring-opening polymerisation of lactide by a range of amino–oxazoline and amino–thiazoline catalysts is reported. The more electron-rich derivatives are demonstrated to be the most highly active and polymerisation is well controlled, as evidenced by the linear relationship between the molecular weight and both the monomer conversion and the monomer-to-initiator ratio. Mechanistic studies reveal significant interactions between the monomer, initiator and catalyst and that the polymerisation is first order with respect to each of these components. These observations indicate that the polymerisation operates by a general base/pseudo-anionic mechanism.

Keywords: lactides · organocatalysis · polyesters · ring-opening polymerization

Introduction

The ring-opening polymerisation of lactide (LA) provides a convenient route to the synthesis of poly(lactide)s, PLAs.[1–6] When performed under optimal conditions in the presence of a suitable catalyst, this methodology displays many of the characteristics of a living polymerisation, including predictable molecular weights (based on the monomer/initiator ratio), narrow polydispersities and high levels of control over the polymer end groups. Additionally, ROP enables the synthesis of high-molecular-weight polymers, which in combination with their biodegradability and derivation from renewable resources, is encouraging their investigation as environmentally friendly packaging materials in addition to their biomedical applications.[1,7–12]

The ROP process can be mediated by a wide range of catalysts, including metal-based complexes, enzymes and small-molecule organics. Undoubtedly the most widely explored field in this area has been the development and application of discrete metal complexes from a wide portion of the periodic table.[3–5] While these studies have led to the discovery of a range of catalysts with high activities and/or high selectivities (including stereocontrolled ROP), the polymers produced contain the catalytic metal residues used in their synthesis. For applications in biomedicine and microelectronics and to overcome concerns regarding leaching of these residues into the environment after disposal of the resultant PLAs, the costly removal of the metal residues must be carried out. The application of both enzymatic and organocatalytic methodologies enable the synthesis of PLAs without the need for removal of metallic residues.

Enzymatic processes are highly efficient for the ROP of ε-caprolactone or larger less strained cyclic esters and, to date, have shown relatively low activities towards lactide ROP.[4,13–15] Recently, the development of small-molecule organic catalysts for ROP has led to the discovery of a range of species that are proposed to operate by monomer-activated and supramolecular mechanisms.[2,4,6,16] Following the report by Hedrick et al. in 2001 on the controlled ROP of LA by DMAP,[17] several further reports have disclosed organocatalytic ROP by other nucleophilic catalysts, such as NHCs,[18–22] supramolecular monomer/chain end activation catalysts including cyclodextrins[23,24] and thiourea-amines[25,26] and general base catalysis by guanidine and phosphazene bases.[27–30] These reports have led to the discovery of some of the most highly active catalysts reported to date, which display high selectivities for ROP over trans-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902518.

esterification and the ability to control the tacticity of the polymer chains at low temperatures.[29,31,32]

However, many of these catalyst systems do not offer a great deal of flexibility within their design to enable structure–property relationships to be obtained and thus further enable understanding and optimisation of their behaviour. Herein, we report a modular synthesis for amino–oxazoline and amino–thiazoline species and detail their application as catalysts in a mechanistic study of the organocatalytic ROP of lactide.

Results and Discussion

Oxazoline-based compounds provide a synthetically versatile unit that have been widely applied as ligands for metal-based catalysts in a wide range of processes.[33–36] The structural similarities between 2-amino derivatives and the highly active 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), recently applied in ring-opening polymerisation studies by Hedrick and Waymouth,[28] are clear (Figure 1). Both possess a three-

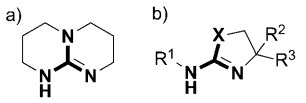
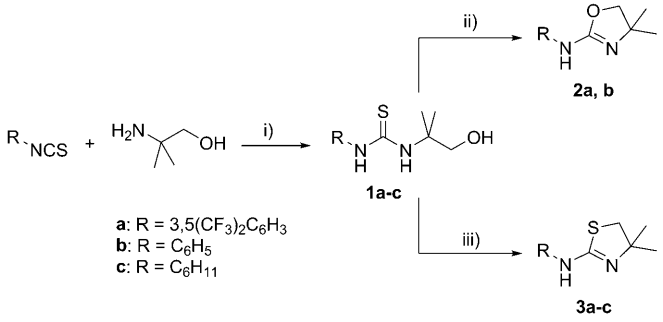


Figure 1. a) 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD). b) Amino–oxazoline (X = O) and amino–thiazoline (X = S) compounds.

centred N=C–NH unit, but access to analogues of TBD is synthetically challenging whereas the modular synthesis of amino–oxazoline and amino–thiazoline compounds makes them an attractive option to explore the effect of structure on ROP behaviour and further understand the polymerisation mechanism.

Both oxazoline (**2a**,**b**) and thiazoline catalysts (**3a–c**) were synthesised via common thiourea intermediates (**1a–c**) that were prepared by the addition of equimolar amounts of isothiocyanate and amine/aniline in THF at ambient temperature (Scheme 1). Amino–oxazoline compounds were accessed by ring-closure under basic conditions in the presence



Scheme 1. Synthesis of thiourea, amino-oazoline and amino–thiazoline compounds. i) THF; ii) NaOH, TsCl, THF, H_2O; iii) HCl.

of tosyl chloride, whereas ring-closure under acidic conditions led to the realisation of the corresponding amino–thiazoline compounds (Scheme 1).[33,36–38] Ring closure incorporating O or S (or mixtures thereof) can be readily identified by ^{1}H NMR spectroscopic analysis of the products. The chemical shift of the endocyclic methylene proton resonances are highly dependant on the adjacent heteroatom, such that the oxazoline derivatives display much lower-field resonances (typically $\delta \approx 4$ ppm) than the thiazoline analogues (typically $\delta \approx 3$ ppm). In this manner, amino–oxazoline and amino–thiazoline compounds were prepared to investigate the influence of electronic structure on their behaviour as catalysts for the ROP of lactide. Notably, ring closure of **1c** under basic conditions to provide the corresponding amino–oxazoline resulted in the isolation of a mixture of O- and S-heterocyclic compounds, comparable to that reported by Heinelt et al.,[38] thus only further investigation with the thiazoline derivative was pursued.

Amino–oxazoline compounds **2a** and **2b** and amino–thiazoline compounds **3a–c** were evaluated as catalysts for the ROP of lactide. At ambient temperature in CH_2Cl_2 and 7 mol% catalyst loading (relative to monomer), the ROP of *rac*-LA initiated from *neo*-pentanol (target degree of polymerisation, DP = 100) was investigated. This initial screening of the catalyst activity (Table 1) revealed that thiazoline de-

Table 1. Data for the polymerisation of *rac*-lactide by using amino–oxazoline and amino–thiazoline catalysts.[a]

Entry	Catalyst	Target DP[b]	t [h]	Conv.[c] [%]	DP[c]	M_n[d] [g mol^{-1}]	PDI[d]
1	**2a**	100	48	0	–	–	–
2	**2b**	100	48	9	8	500	1.33
3	**3a**	100	48	0	–	–	–
4	**3b**	100	48	11	10	1000	1.39
5	**3c**	100	36	95	100	15400	1.04
6	**3c**	50	28	94	45	7000	1.07
7	**3c**	25	16	95	20	3900	1.10
8	**3c**	10	8	94	9	2800	1.10
9[e]	**3c**	100	34	94	100	17900	1.08
10[f]	**3c**	100	32	98	100	20400	1.09

[a] Conditions: 7 mol% catalyst, [LA] = 4.6 M in $CDCl_3$, 22 °C. [b] Determined from the monomer/initiator ratio. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by GPC. [e] At 40 °C. [f] At 60 °C.

rivatives with electron-withdrawing aryl groups resulted in lower ROP activities. In all cases, atactic polymers of predictable DPs with narrow polydispersities (1.04–1.10) were obtained.

Compound **3c** with a 2-cyclohexylamino substitution on the thiazoline ring was noted to be the most active catalyst, therefore, further investigations were focused on elucidating the behaviour of this catalyst in the ROP of lactide. The polymerisation mediated by **3c** resulted in poly(lactide) that exhibited a number average molecular weight, M_n, of 15400 g mol^{-1} and a narrow polydispersity (1.04), which indicates that the polymerisation was well controlled. Further evidence of this control was obtained by demonstration of a linear dependence of M_n on monomer conversion, with low

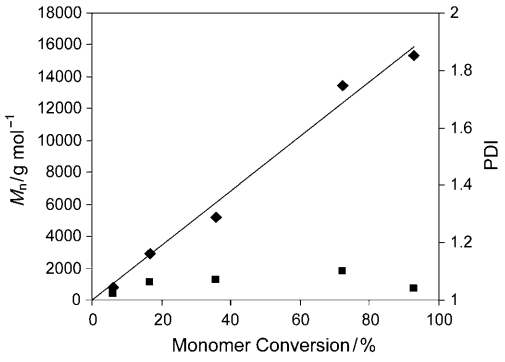


Figure 2. Graph of average molecular weight (M_n [g mol^{-1}]) against monomer conversion [%] and PDI for the polymerisation of *rac*-lactide mediated by **3c** (DP100).

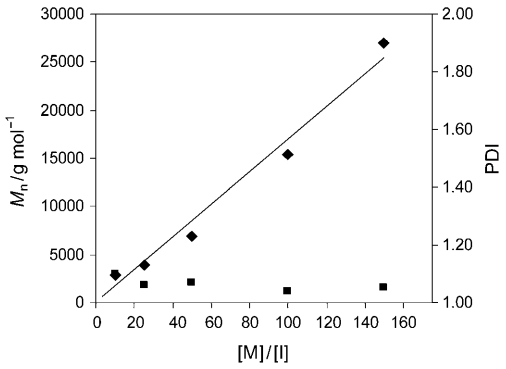


Figure 3. Graph of average molecular weight (M_n [g mol^{-1}]) against [M]/[I] and PDI for the polymerisation of *rac*-lactide mediated by **3c**.

polydispersity values being maintained throughout the polymerisation (Figure 2). Variation of the monomer-to-initiator ratio revealed a linear dependence with a polymer molecular weight of between 20 and 150 equivalents of LA; again the polydispersities remained low (Figure 3).

The initiator efficiency was investigated by analysis of the DP10 PLA by ^{1}H NMR and MALDI-TOF MS (Figure 4). The ^{1}H NMR spectrum reveals a singlet at $\delta = 0.93$ ppm that corresponds to the *tert*-butyl methyl groups and a multiplet at $\delta = 3.84$ ppm that corresponds to the methylene resonance from the initiator in a 9:2:16 ratio (Me/CH_2/polymer CH), which indicates that a DP8 polymer was isolated. Accordingly, the MALDI-TOF MS (Figure 4, bottom) reveals a single distribution corresponding to the sodium-charged PLA with a single *neo*-pentyl end group. Additionally, an exclusive spacing of 144 Da (at 94% monomer conversion) is observed, with the absence of a distribution spaced at 72 Da that strongly suggests that the catalysts are highly selective towards ROP over transesterification. Extension of the reaction time to 12 d for the DP100 PLA (M_n = 15400 g mol^{-1}; PDI = 1.04), however, revealed a reduction in molecular weight (M_n = 12500 g mol^{-1}) and a slight broadening of PDI (1.32) that suggests that at significantly increased time periods transesterification side reactions occur to a low extent. Investigation of the ROP of L-lactide results in the observation of low levels of monomer epimerisation as evidenced by the appearance of methyl signals corresponding to *meso*-lactide ($\delta = 1.68$ ppm) throughout the

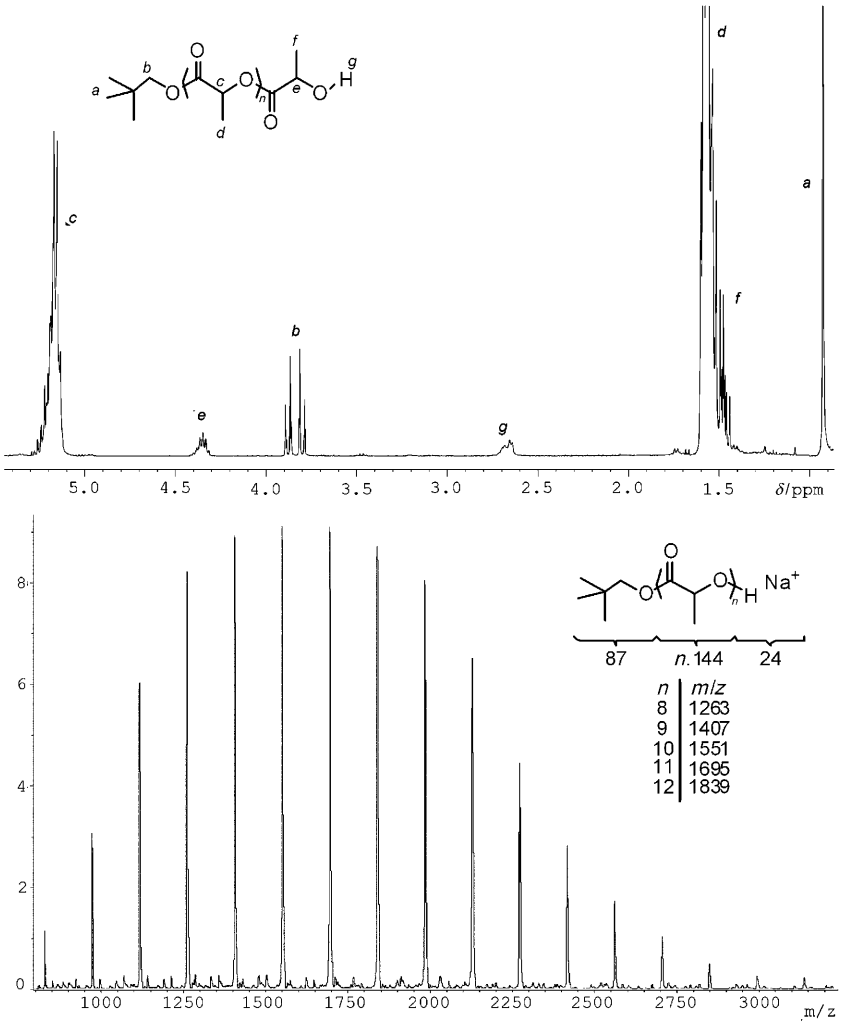


Figure 4. ^{1}H NMR spectrum (top) and MALDI-TOF MS (bottom) of PLA (DP10) initiated from *neo*-pentanol.

polymerisation and the presence of a *sss* tetrad resonance ($\delta = 69.4$ ppm) in the ^{13}C NMR spectrum (see the Supporting Information). Homonuclear decoupled ^{1}H NMR analysis of this polymer revealed that the *iii* tetrad represented around 75% of the tetrad sequences.

Given the preference of the system towards ROP over transesterification, we also decided to investigate the polymerisation at elevated temperature with a view to increasing the activity of the polymerisation system. Interestingly, investigation of the ROP of *rac*-LA ([M]/[I] = 100, [M] = 0.69 M) in $CDCl_3$ at 40 and 60 °C revealed very little rate enhancement over that observed at 22 °C, such that 94 and 98% monomer conversions were observed within 34 and 32 h at 40 and 60 °C, respectively (cf. 95% monomer conversion within 32 h at 22 °C; see Table 1). We postulate that this observation results from the decreased strength of the supramolecular interactions postulated to occur in the transition state of the rate-determining step of the polymerisation.[39,40]

These observations led us to further investigate the polymerisation kinetics and the interactions between the catalyst, monomer and initiator. Notably, the observable timescale of the polymerisations enables direct study of the polymerisation mechanism of lactide with this class of catalyst for the first time.

Kinetic studies of the polymerisation of *rac*-lactide mediated by **3c** by using *neo*-pentanol as an initiator in $CDCl_3$ at 22 °C were performed by monitoring monomer conversion (determined by the integration of methine resonances of the monomer vs. the polymer) by ^{1}H NMR spectroscopy. Given the three components the rate law can be assumed to follow Equation (1).

$$-\mathrm{d}[\mathrm{LA}]/\mathrm{d}t = k_\mathrm{p}[\mathrm{LA}]^x \cdot [\textit{neo}\text{-pentanol}]^y \cdot [\mathbf{3c}]^z \quad (1)$$

Analysis of the semilogarithmic plots (Figure 5) reveals that the polymerisation is first order with respect to the monomer. Experiments in which the [*neo*-pentanol] was varied and the [LA] and [**3c**] were kept constant ($[\mathrm{LA}]_0 = 4.6$ M; $[\mathbf{3c}]_0 = 0.31$ M) were conducted to identify the order with respect to the initiator (*neo*-pentanol). For each [*neo*-pentanol], these experiments revealed a linear relationship between $\ln[\mathrm{LA}]_0/[\mathrm{LA}]_t$ and time with a zero intercept. A plot of $\ln k_{app}$ against ln[*neo*-pentanol] for each experiment revealed a linear relationship with a gradient of 1.05 ± 0.12 (see the Supporting Information), which approximates to the polymerisation being first order with respect to initiator, within experimental error. Repeat of this process at constant [LA] and [*neo*-pentanol] ($[\mathrm{LA}]_0 = 2.7$ M; [*neo*-pentanol]$_0$ = 0.11 M) enabled the order with respect to the catalyst (**3c**) to be determined (Figures 5 and 6) as 0.91 ± 0.11. Again, this result approximates to the polymerisation being first order with respect to the catalyst, confirmed by the direct linear relationship between k_{app} and [**3c**] (see the Supporting Information). In this case, the deviation from a rate order of one with respect to the catalyst is more significant, however, these observations suggest that the rate law follows Equation (2), which identifies that a molecule of monomer, initiator and catalyst are involved equally in the rate-determining step.

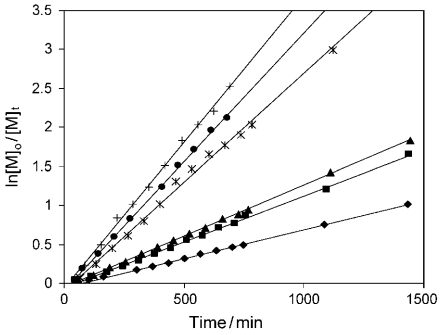


Figure 5. Semilogarithmic plot of time vs. monomer conversion for the polymerisation of *rac*-lactide by *neo*-pentanol/**3c** at 22 °C in $CDCl_3$. [LA] = 2.7 M; [*neo*-pentanol] = 0.11 M +: [**3c**] = 0.41 M; ●: [**3c**] = 0.34 M; ∗: [**3c**] = 0.27 M; ▲: [**3c**] = 0.14 M; ■: [**3c**] = 0.095 M; ◆: [**3c**] = 0.068 M.

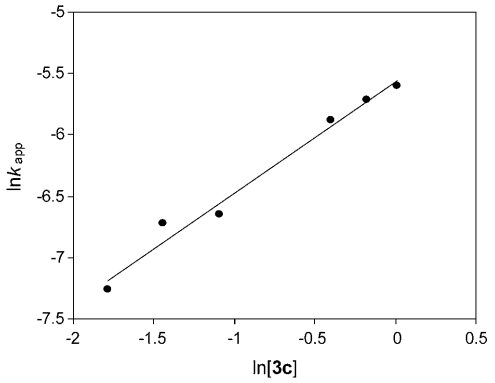


Figure 6. Graph of ln[**3c**] vs. ln[k_{app}] for the polymerisation of *rac*-lactide by *neo*-pentanol/**3c** at 22 °C in $CDCl_3$. [LA] = 2.7 M; [*neo*-pentanol] = 0.11 M.

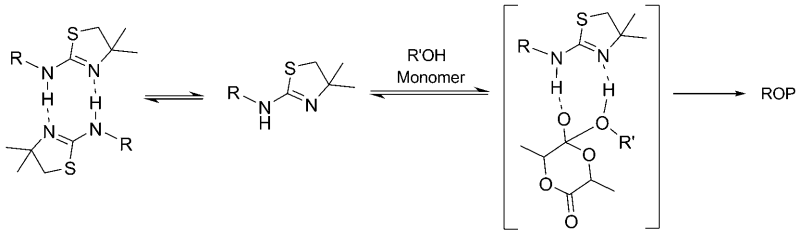
$$-\mathrm{d}[\mathrm{LA}]/\mathrm{d}t = k_\mathrm{p}[\mathrm{LA}] \cdot [\textit{neo}\text{-pentanol}] \cdot [\mathbf{3c}] \quad (2)$$

To further elucidate mechanistic information relating to the polymerisation, we undertook a series of experiments to probe the interactions between the components of the reaction mixture. Examination of the ^{1}H NMR spectrum of a mixture of **3c** and lactide in $CDCl_3$ in a 1:38 ratio at 22 °C led to only small shifts of the N*H* and cyclohexyl C*H* resonances (N*H*: from $\delta = 4.14$ (free) to 4.15 ppm; C*H*: from $\delta =$ 3.39 (free) to 3.36 ppm). As such, further work focused on the application of δ-valerolactone as a benzene-soluble cyclic ester model compound to facilitate observation of supramolecular interactions between the species. The ^{1}H NMR spectrum of a mixture of **3c** and δ-valerolactone in a 1:18 ratio in C_6D_6 at 22 °C ([**3c**] = 0.035 M; [δVL] = 0.52 M) revealed a notable shift in the highly sensitive N*H* resonance from $\delta = 3.55$ to 4.17 ppm and a smaller shift in the cyclohexyl C*H* resonance from $\delta = 3.68$ to 3.70 ppm, which indicates a significant interaction between the species. Com-

parable studies with mixtures of **3c** and *neo*-pentanol in a ratio of 16:1 ([**3c**] = 0.035 M; [*neo*-pentanol] = 0.002 M) revealed no significant shift in the N*H* or cyclohexyl C*H* resonance of **3c** and a minor shift in the *neo*-pentanol CH_2 and CH_3 resonance from $\delta = 2.99$ and 0.79 ppm to $\delta = 3.03$ and 0.81 ppm, respectively, which indicates a weak interaction between the two species under these conditions. In all cases the O*H* resonance could not be observed, due either to an overlap with another resonance or to broadening as a consequence of rapid exchange on the NMR timescale. Notably, the N*H* resonance of **3c** was also observed to shift significantly during the course of this titration. Further investigation of the effect of concentration of **3c** upon the chemical shift of the N*H* resonance revealed a concentration-dependant shift from $\delta = 4.60$ to 3.05 ppm and the cyclohexyl C*H* resonance shifted from $\delta = 3.61$ to 3.66 ppm upon dilution from a 1.5 to 0.035 M C_6D_6 solution. These observations suggest that a concentration-dependant dimerisation of the catalytic species exists in solution, in addition to the hydrogen-bonding interactions between the catalyst and lactone and the catalyst and alcohol. Notably, this concentration-dependant monomer–dimer equilibrium rationalises the apparent deviation in the catalyst order of one. Under conditions at which [**3c**] is high, free **3c** will predominate as a dimer that must be broken up to allow monomeric **3c** to mediate the ring-opening process. In extreme cases in which all catalyst exists in the dimeric form but is required to be monomeric to mediate the rate-determining step of the polymerisation, the rate order would equal 0.5. The lowering of the rate order with respect to **3c**, tending towards 0.5 at higher catalyst concentrations, suggests that the monomer–dimer equilibrium plays an important role in the polymerisation process.

These observations are consistent with ROP being mediated by a general base/pseudo-anionic mechanism that involves stabilisation of transition states by hydrogen bonding. To differentiate between a mechanism involving activation of the initiator/chain end solely by the thiazoline nitrogen, ROP was attempted by using the commercially available 2-methylthiazoline as the catalyst. Under conditions identical to those applied above, no polymerisation activity was observed over 24 h. This is consistent with the increased activity of TBD-catalyzed ROP over basic catalysts that do not possess an amine proton, such as 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU).

These observations support the theoretical results independently reported by Rice and co-workers[39] and Simon and Goodman[40] for the analogous TBD-catalyzed polymerisation, and indicate that the catalyst species serves to stabilise the transition state of the rate-determining step of the polymerisation involving lactide, alcohol and catalyst by concurrent hydrogen-bonding interactions between the catalyst, monomer and propagating chain end/initiator. Additionally, these studies reveal that the catalyst is in a rapid, concentration-dependant equilibrium between its monomeric and dimeric forms (Scheme 2).



Scheme 2. Key interactions between the catalyst, monomer and alcohol in the ROP of lactide mediated by **3c**.

To investigate if a relationship exists between these supramolecular interactions between the catalyst, monomer and alcohol and the catalyst activity, the chemical shifts of key ^{1}H NMR resonances for the interactions between **2b**, **3a** and **3b** and δ-valerolactone and *neo*-pentanol were investigated. After saturation of a solution of the respective amino–oxazoline or amino–thiazoline compound in C_6D_6 with δ-valerolactone ($\approx$13 equiv) under conditions comparable to those described above ([catalyst] = 0.035 M), the chemical shifts of the N*H* and the *ortho*-phenyl proton were recorded. These spectra with aminothiazoline compounds **3a** and **3b** did not reveal the presence of an N*H* proton, which is presumably a result of broadening of the resonance, yet the same resonance for the amino–oxazoline compound **2b** was observed to shift downfield by $\delta = 0.94$ ppm. However, the *ortho*-phenyl protons could all be observed to undergo a downfield shift, with the magnitude of the shift correlating to the electronic environment of the catalyst such that the difference in chemical shift was in the order **3a** > **2b** > **3b** (> cyclohexyl C*H* shift in **3c**; see the Supporting Information). Further investigation of the interaction of the catalyst species with *neo*-pentanol ([catalyst] = 0.035 M; [catalyst]/[*neo*-pentanol] $\approx$ 20) revealed that the most electron rich species resulted in the largest change of chemical shift for both the *neo*-pentyl CH_2 and CH_3 resonances (i.e., **3c** > **3b** > **2b** > **3a**). These data show that, as may be expected, the more electron-deficient compounds result in a stronger interaction with cyclic esters but a weaker interaction with added alcohol.

Clearly, subtle changes to the electronic nature of the catalyst structure affect the ability to mediate the ROP reactions of these compounds. These studies also demonstrate that ROP activity is clearly not dominated by either component and that both hydrogen-bonding sites are required to be available to obtain efficient catalysis, further supporting the proposed mechanism. Additional experimental and theoretical studies are planned to provide greater understanding of these complex interactions.

Conclusion

We have reported the synthesis of a versatile and modular catalyst system and its application to the ROP of LA, namely, amino–oxazoline and amino–thiazoline compounds. The electronic structure of the compounds has been demonstrated to have a large effect on their activity, such that the most active catalysts are those with electron-rich alkyl groups and endocyclic sulfur heteroatoms. The optimum catalyst structure, **3c**, produces polymers with good control over molecular parameters and displays a resistance to transesterification. Mechanistic and kinetic studies have suggested that this catalyst operates by a general base (quasi-anionic) mechanism that is comparable to the other "superbase" ROP catalysts with the involvement of hydrogen bonding between catalyst, monomer and alcohol. Such experimental observations provide an excellent base for the foundation of further rational catalyst design around this template to provide a new family of tuneable organic catalysts.

Experimental Section

Materials: *rac*-Lactide and L-lactide (Aldrich) were purified by recrystallisation from dry dichloromethane and sublimed twice before use. Dichloromethane and $CDCl_3$ for polymerisations was refluxed over CaH and then distilled, degassed and stored under a nitrogen atmosphere. All alcohol initiators were dried over suitable drying agents, distilled and degassed. 1-(2-Hydroxy-1,1-dimethylethyl)-3-phenylthiourea (**1b**),[36] 1-(2-hydroxy-1,1-dimethylethyl)-3-cyclohexylthiourea (**1c**)[33] and 2-phenylamino-4,4-dimethyloxazoline (**2b**)[36] were synthesised according to literature procedures. Organic catalysts were dried by dissolution in dry THF and subsequent stirring at 60 °C over CaH for 18 h before filtration and drying under vacuum. All other chemicals and solvents were obtained from Aldrich and used as received.

General considerations: All manipulations were performed under moisture- and oxygen-free conditions either in a nitrogen-filled glovebox or by standard Schlenk techniques. Gel-permeation chromatography (GPC) was used to determine the molecular weights and polydispersities of the synthesised polymers. The system comprised a Polymer Laboratories Midas autosampler and LC1120 HPLC pump equipped with a guard column (Polymer Laboratories PLGel 5 μM, 50×7.5 mm), two mixed D columns (Polymer Laboratories PLGel 5 μM, 300×7.5 mm) and a Polymer Laboratories ERC-7515A differential refractive index (DRI) detector. The mobile phase (eluent) was chloroform/triethyl amine (95:5) at a flow rate of 1.0 mLmin^{-1} and samples were calibrated against linear poly(styrene) standards (540 to 2.9×104 gmol^{-1}) by using Cirrus 3.0 software; elution time was standardised against that of toluene. ^1H and ^{13}C NMR spectra were recorded by using a Bruker DPX-300, DPX-400, AC400 or DRX-500 spectrometer at 293 K unless stated. Chemical shifts are reported as δ in parts per million (ppm) and referenced to the chemical shift of the residual solvent resonances ($CDCl_3$: ^1H $\delta=7.26$ ppm; ^{13}C $\delta=77.16$ ppm). Mass spectra were acquired by using a Bruker Micro-TOF (ESI^+) or a Bruker Esquire200 ESI mass spectrometer. MALDI-TOF mass spectrometry was performed by using a Bruker Daltonics Ultraflex II MALDI-TOF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at $\lambda=337$ nm with positive-ion TOF detection performed by using an accelerating voltage of 25 kV. Solutions of *trans*-2-[3-(4-tertbutylphenyl)-2-methyl-2-propylidene]malonitrile as the matrix (0.3 μL of a 10 gL^{-1} solution in acetone), sodium trifluoroacetate as the cationisation agent (0.3 μL of a 10 gL^{-1} solution in acetone) and analyte (0.3 μL of a 1 gL^{-1} CH_2Cl_2 solution) were applied sequentially to the target followed by solvent evaporation to prepare a thin matrix/analyte film. The samples were measured in reflectron ion mode and calibrated by comparison to 2×103 and 5×103 gmol^{-1} poly(ethylene glycol) standards. Elemental analyses were performed by Warwick Analytical Services.

Synthesis of 1-(2-hydroxy-1,1-dimethylethyl)-3-[3,5-bis(trifluoromethyl)-phenyl]thiourea (1a): 2-Amino-2-methylpropanol (1.9 mL, 19.5 mmol) was added to a solution of (3,5-bis(trifluoromethyl)phenyl)isothiocyanate (5.3 g, 19.5 mmol) in THF (150 mL). The solution was stirred for 18 h before the solution was reduced under vacuum. The resultant oil was diluted in a small volume of dichloromethane, precipitated into stirred petroleum ether (40/60), collected by filtration and dried in vacuo to give a white solid (yield 6.2 g, 17.2 mmol, 88%). ^1H NMR ($CDCl_3$, 400 MHz): $\delta=10.60$ (brs, 1H; N*H*), 8.06 (s, 2H; *o*-Ar), 7.63 (s, 1H; *p*-Ar), 6.37 (s,1 H; N*H*), 3.66 (s, 2H; CH_2OH), 1.39 ppm (s, 6H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=180.8$ (NC(S)N), 140.8 (Ar-*ipso*), 131.9 (^2J(C,F)=33 Hz, *C*CF_3), 123.1 (^1J(C,F)=273 Hz, *C*F_3), 123.2 (Ar-*o*), 118.3 (Ar-*p*), 71.2 (*C*Me_2), 58.2 (*C*H_2OH), 24.5 ppm (*C*H_3); MS (ESI^+): *m*/*z*: 361.0 [*M*H]$^+$; elemental analysis calcd (%) for $C_{13}H_{14}N_2SOF_6$: C 43.3, H 3.9, N 7.8; found: C 43.2, H 3.9, N 7.8.

Synthesis of 2-[3,5-bis(trifluoromethyl)phenyl]amino-4,4-dimethyloxazoline (2a): The procedure was adapted from that previously reported by Munslow et al.[36] Tosyl chloride (2.5 g, 13.1 mmol) in THF (5 mL) was added dropwise to a stirred solution of **1a** (3.0 g, 8.3 mmol) in THF and 10 M aqueous sodium hydroxide (7.5 mL, 2:1 vol). After stirring for 18 h, the THF was removed under vacuum and the residue was partitioned with Et_2O (150 mL) and H_2O (100 mL). The aqueous layer was extracted with Et_2O (2×50 mL) before the combined organic fractions were dried over $MgSO_4$, filtered and reduced under vacuum to give **4** as a white solid that was extracted and recrystallised from hexanes (yield 1.0 g, 3.1 mmol, 37%). ^1H NMR ($CDCl_3$, 400 MHz): $\delta=7.52$ (s, 2H; *o*-Ar), 7.45 (s, 1H; *p*-Ar), 4.18 (s, 2H; CH_2), 1.37 ppm (s, 6H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=155.9$ (NC(-O)=N), 130.8 (^2J(C,F)=33 Hz, *C*CF_3), 122.5 (^1J(C,F)=273 Hz, *C*F_3), 121.7 (Ar-*o*), 114.3 (Ar-*p*), 78.5 (*C*Me_2), 56.4 (*C*H_2), 26.3 ppm (*C*H_3); MS (ESI^+): *m*/*z*: 327.0931 [*M*H]$^+$; elemental analysis calcd (%) for $C_{13}H_{12}N_2OF_6$: C 47.9, H 3.7, N 8.6; found: C 47.8, H 3.7, N 8.6.

Sample procedure for synthesis of amino–thiazoline: The procedure was adapted from that previously reported by Crust et al.[33] Concentrated HCl (100 mL) was slowly added to **1a** (3.0 g, 8.3 mmol). The solution was heated under reflux at 95 °C for 4 h. After cooling, the solution was diluted with H_2O (20 mL) and made basic by the addition of Na_2CO_3 in an ice bath (CAUTION: addition should be made in small portions because the reaction is exothermic and leads to vigorous effervescence). The solid was collected by filtration and washed with H_2O (20 mL) before being dissolved in chloroform (50 mL), then dried over $MgSO_4$. Removal of drying agent by filtration and reduction of the solution under vacuum gave in a white solid, 2-[3,5-bis(trifluoromethyl)phenyl]amino-4,4-dimethylthiazoline (**3a**), that was extracted and recrystallised from hexanes (0.7 g, 2.0 mmol, 24%). ^1H NMR ($CDCl_3$, 400 MHz): $\delta=7.52$ (s, 1H; *p*-Ar), 7.45 (s, 2H; *o*-Ar), 3.11 (s, 2H; CH_2), 1.36 ppm (s, 6H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=161.9$ (NC(-S)=N), 150.6 (Ar-*ipso*), 131.1 (^2J(C,F)=33 Hz, *C*CF_3), 122.4 (^1J(C,F)=272 Hz, *C*F_3), 121.5 (Ar-*o*), 115.4 (Ar-*p*), 59.4 (*C*Me_2), 41.5 (*C*H_2), 26.5 ppm (*C*H_3); MS (ESI^+): *m*/*z*: 343.0710 [*M*H]$^+$; elemental analysis calcd (%) for $C_{13}H_{12}N_2SF_6$: C 45.6, H 3.5, N 8.2; found: C 45.65, H 3.5, N 8.2.

2-Phenylamino-4,4-dimethylthiazoline (3b): This compound was isolated from **1b** as a white solid (yield 1.1 g, 5.3 mmol, 39%); ^1H NMR ($CDCl_3$, 400 MHz): $\delta=7.28$ (t, ^3J(H,H)=8.1 Hz, 2H; *m*-Ar), 7.07 (d, ^3J(H,H)=8.7 Hz, 2H; *o*-Ar), 7.06 (t, ^3J(H,H)=8.6 Hz, 1H; *p*-Ar), 3.05 (s, 2H; CH_2), 1.36 ppm (s, 6H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=160.3$ (NC(-S)=N), 148.9 (Ar-*ipso*), 128.9 (Ar-*m*), 123.1 (Ar-*o*), 121.8 (Ar-*p*), 77.1 (*C*Me_2), 43.0 (*C*H_2), 27.7 ppm (*C*H_3); MS (ESI^+): *m*/*z*: 207.0950 [*M*H]$^+$; elemental analysis calcd (%) for $C_{11}H_{15}N_2S$: C 64.0, H 6.8, N 13.6; found: C 64.0, H 6.8, N 13.5.

2-Cyclohexylamino-4,4-dimethylthiazoline (3c): This compound was isolated from **1c** as a white solid (yield 1.03 g, 4.9 mmol, 54%); ^1H NMR ($CDCl_3$, 400 MHz): $\delta=4.17$ (brs, 1H; N*H*), 3.39 (m, 1H; NC*H*), 3.08 (s, 2H; SCH_2), 1.98 (m, 2H; Cy-*H*), 1.33 (s, 6H; CH_3), 1.05–1.75 ppm (m,

8H; Cy-*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.6 (N*C*(-S)=N), 53.7 (Cy-*C*H), 46.0 (S*C*H_2), 28.3 (*C*H_3), 33.7, 25.6, 24.7 ppm (Cy-C*H*$_2$); MS (ESI$^+$): *m*/*z*: 213.1417 [*M*H]$^+$; elemental analysis calcd (%) for $C_{11}H_{20}N_2S$: C 62.2, H 9.5, N 13.2; found: C 62.1, H 9.5, N 13.1.

General polymerisation procedure: In a typical experiment, the chosen alcohol initiator (0.05 mmol) was added to a scintillation vial or ampoule containing a solution of catalyst (**3c**) (0.05 mmol) and *rac*-lactide (0.144 g, 1 mmol) in dichloromethane or toluene (1.25 mL) under an atmosphere of nitrogen. The sealed scintillation vial or ampoule was then stirred at the desired temperature for the allotted time period before being quenched by precipitation in petroleum ether (40/60), collected by filtration and dried in vacuo.

Acknowledgements

The Research Councils UK (RCUK) are acknowledged for funding a fellowship for A.P.D. We gratefully acknowledge the support provided by the Warwick Innovative Manufacturing Research Centre (WIMRC) for financial support and the EPSRC (EP/C007999/1) for the purchase of the Bruker Ultraflex MALDI-TOF MS instrument in addition to the provision of funding, including a studentship for M.J.S. to support this work (EP/D079136/1). The GPC equipment used in this research was obtained through Birmingham Science City: Innovative Uses for Advanced Materials in the Modern World (West Midlands Centre for Advanced Materials Project 2), with support from Advantage West Midlands (AWM) and part-funded by the European Regional Development Fund (ERDF). Dr David Fox (University of Warwick) is thanked for helpful discussions.

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Received: September 11, 2009
Revised: February 15, 2010
Published online: April 13, 2010

