nature chemistry

ARTICLES

PUBLISHED ONLINE: 25 JULY 2016 | DOI: 10.1038/NCHEM.2574

Fast and selective ring-opening polymerizations by alkoxides and thioureas

Xiangyi Zhang[1], Gavin O. Jones[2], James L. Hedrick[2] and Robert M. Waymouth[1]*

Ring-opening polymerization of lactones is a versatile approach to generate well-defined functional polyesters. Typical ring-opening catalysts are subject to a trade-off between rate and selectivity. Here we describe an effective catalytic system combining alkoxides with thioureas that catalyses rapid and selective ring-opening polymerizations. Deprotonation of thioureas by sodium, potassium or imidazolium alkoxides generates a hydrogen-bonded alcohol adduct of the thiourea anion (thioimidate). The ring-opening polymerization of L-lactide mediated by these alcohol-bonded thioimidates yields highly isotactic polylactide with fast kinetics and living polymerization behaviour, as evidenced by narrow molecular weight distributions ($M_w/M_n < 1.1$), chain extension experiments and minimal transesterifications. Computational studies indicate a bifunctional catalytic mechanism whereby the thioimidate activates the carbonyl of the monomer and the alcohol initiator/chain end to effect the selective ring-opening of lactones and carbonates. The high selectivity of the catalyst towards monomer propagation over transesterification is attributed to a selective activation of monomer over polymer chains.

The development of new and versatile catalytic methods continues to drive innovation in organic chemistry[1–3] and materials science[4–6]. Polymers are ubiquitous and highly useful modern materials. Innovations in catalytic petrochemistry and polymerization methods spawned the development of petroleum-based plastics—one of the crowning achievements of the twentieth century. Nevertheless, the vast quantities of discarded plastics have stimulated efforts to generate biodegradable alternatives. Ring-opening polymerization (ROP) is a versatile synthetic method for generating well-defined macromolecules from carbocyclic or heterocyclic monomers[7]. Organocatalytic ROP of cyclic esters, carbonates and carboxyanhydrides has proven particularly useful for the generation of functional, biodegradable materials[8–12]. The rates and selectivities of organic catalysts can rival and exceed the performance of anionic, metal-based and enzymatic catalysts for ring-opening polymerization[9]. Mechanistic studies have provided key insights regarding the factors that lead not only to high rates, but also high selectivities for propagation relative to other deleterious side reactions, such as competitive transesterification, chain-transfer and chain-termination reactions[8–11].

Among the various strategies for catalysing ROP[8,9], those based on hydrogen-bond activators of either the monomer or the propagating alcohol have proven especially selective[10,13–24]. Although potent nucleophiles[25–28] or strongly basic catalysts[16,17,29–31] lead to exceptionally fast rates, these catalysts exhibit a compromise between selectivity and reactivity: increasing the nucleophilicity or basicity of the catalysts enhances the rates but also promotes transesterification and competitive nucleophilic pathways[28,32,33], resulting in broader molecular weight distributions[9]. The more selective hydrogen-bonding organocatalysts[9,10,14,15] typically exhibit lower rates, but the selectivities can be modulated by the structure and acidity of the hydrogen-bond donors[18,20–24].

The thiourea/R_3N catalyst system (TU/R_3N, Fig. 1a)[3,34–36] has been widely used in enantioselective organocatalysis[3] and is one of the most versatile catalyst systems for ROP[8–11,14,16,37]. This bifunctional catalyst system contains a general base motif (R_3N) to activate the ROH initiator/chain-end and a thiourea (TU) to active the monomer and stabilize the incipient charged tetrahedral intermediate. Despite their relatively low reactivity, one of the unique features of these catalysts is their high selectivity for ring-opening of the lactone monomer relative to transesterification of the polymer[38], resulting in narrow molecular weight distributions even at high conversions[14,15]. This latter feature is unusual for ROP catalysts[38], but has proven particularly useful for the preparation of well-defined functional oligomers for biomedical applications[39,40].

Triazabicyclodecene (TBD) is one of the most active organocatalysts for ROPs[9]. Previous computational studies[13] suggested a bifunctional catalytic mechanism, where TBD activates both the alcohol initiator and monomer through hydrogen bonding (Fig. 1b). However, the strong nucleophilicity and basicity of TBD results in competitive transesterifications (broadening the molecular weight distribution) as well as epimerizations (lowering tacticities and melting points for polylactide). As such, the polymerizations are much less controlled than the TU-amine systems, especially with extended reaction times.

Here, we report a new catalyst system (Fig. 1c) that is both active and selective for ROP, leading to very fast rates and high selectivities for ring-opening relative to transesterification and competitive deprotonation reactions, resulting in highly crystalline polymers with narrow molecular weight distributions. This new catalyst system was developed based on the hypothesis that deprotonation of a thiourea might generate a bifunctional catalyst that could activate both the alcohol initiator/chain end and the lactone monomer in a manner analogous to that proposed for the more basic guanidine TBD. Moreover, because the acidity of thioureas depends sensitively on their substitution patterns, this strategy might allow for the tuning of the basicity and hydrogen-donor ability of the thiourea anion to modulate its reactivity and selectivity.

Results and discussion

To investigate the role of thiourea anions as activators for the ROP of lactide, a mixture of sodium or potassium methoxide and

[1]Department of Chemistry, Stanford University, Stanford, California 94305-5080, USA. [2]IBM Research – Almaden, 650 Harry Road, San Jose, California 95120, USA. *e-mail: waymouth@stanford.edu

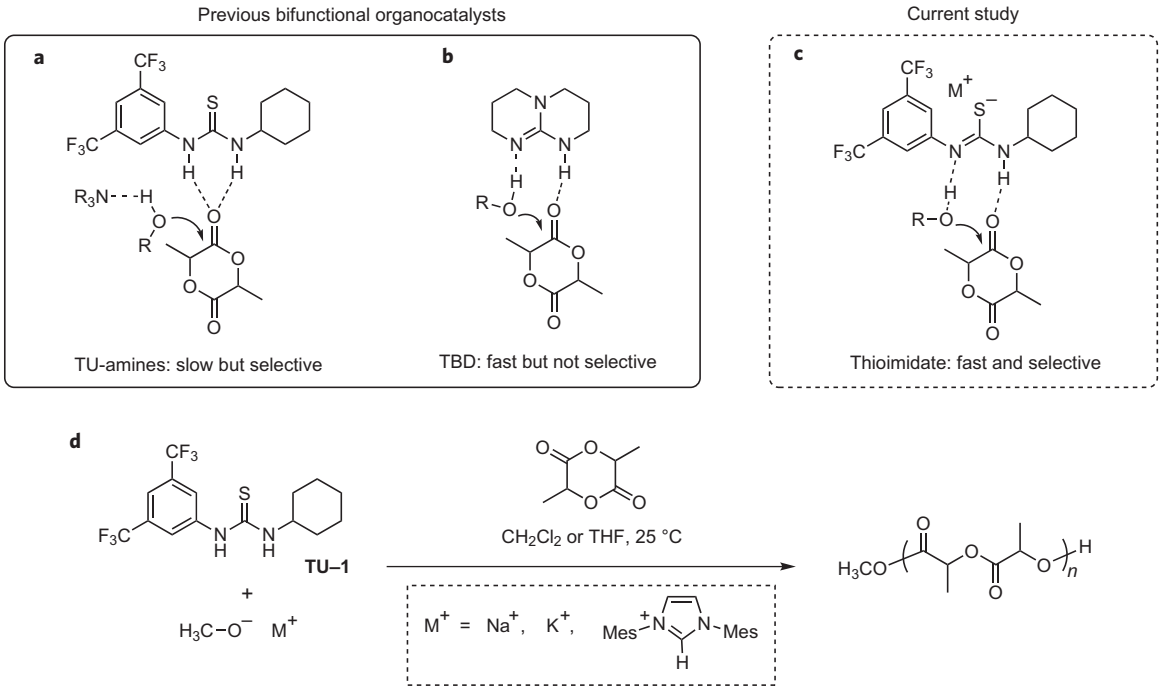

Figure 1 | Bifunctional organocatalysts. a, Thiourea/amine co-catalysts. **b**, Neutral guanidine TBD. **c**, Anionic thioimidate. **d**, Ring-opening polymerization of L-lactide catalysed by anionic thioimidates. Thioimidates were generated *in situ* by deprotonation of neutral thiourea **TU-1** with sodium, potassium or imidazolium alkoxides.

1–10 equiv. thiourea (**TU-1**) was suspended in dichloromethane and treated with 50–500 equiv. L-lactide (LA) (Fig. 1d). As shown in Table 1, this procedure leads to both rapid and controlled ROP of lactide to afford poly(lactides) (PLAs) with molecular weights that conform to those predicted theoretically ($M_{n\ theo}$) from the ratio $[LA]_0/[MOCH_3]_0$ and conversion. As this procedure is essentially an anionic polymerization of lactide[41,42] with thiourea additives, the anionic polymerizations of lactide with sodium and potassium methoxide are shown in Table 1 for comparison (entries 1 and 7, respectively). In the absence of thiourea additives, the anionic polymerization of lactide with methoxide is not only slow but also uncontrolled, leading to broad molecular weight distributions ($Đ = M_w/M_n = 1.88–2.15$) and molecular weights higher than predicted theoretically. Analysis of the resulting poly(L-lactide) by ^{1}H NMR and differential scanning calorimetry (DSC) (Supplementary Figs 1 and 2) revealed the presence of atactic sequences and a melting point of 158 °C, indicating that competitive epimerization of the monomer or polymer had occurred.

In contrast, the addition of 1–10 equiv. **TU-1** to $NaOCH_3$ results in a faster and more controlled polymerization than obtained in the absence of **TU-1** (Table 1, entries 2–6). For a monomer-to-initiator ratio of 200 ($[LA]/[NaOCH_3] = 200$) and 1–10 equiv. **TU-1** in

Table 1 | Alkoxide-initiated ROP of cyclic lactones and carbonates in the presence of TU-1.

Entry	Monomer	Initiator	$[TU]/[I]_0$	$[M]_0/[I]_0$	Per cent conversion* (time in min)	$M_{n\ theo}$† (kDa)	$M_{n\ NMR}$‡ (kDa)	$M_{n\ GPC}$§ (kDa)	$Đ$§
1	LA	$NaOCH_3$	0	200	94 (35)	27.1	58.5	32.1	2.15
2	LA	$NaOCH_3$	1	200	96 (3)	27.7	26.7	26.1	1.55
3	LA	$NaOCH_3$	5	200	94 (5)	27.1	26.6	29.0	1.22
4	LA	$NaOCH_3$	10	200	92 (6)	27.4	26.7	29.8	1.18
5	LA	$NaOCH_3$	10	100	91 (3)	13.1	11.2	14.7	1.16
6	LA	$NaOCH_3$	10	50	93 (2)	6.73	6.6	8.3	1.11
7	LA	$KOCH_3$	0	200	70 (33)	20.2	58.3	22.5	1.88
8	LA	$KOCH_3$	1	200	94 (5)	27.1	27.9	26.8	1.21
9	LA	$KOCH_3$	1.5	200	93 (5)	26.8	27.4	28.5	1.15
10	LA	$KOCH_3$	5	200	90 (6)	25.9	24.6	26.6	1.09
11	LA	$KOCH_3$	5	500	90 (45)	64.8	61.2	51.3	1.15
12	LA	PyOH/IMes‖	1	100	95 (6)	13.7	13.7	14.9	1.05
13	LA	PyOH/IMes‖	1	200	93 (22)	26.8	25.8	27.0	1.07
14¶	LA	PyOH/IMes‖,¶	1	500	91 (50)	65.6	63.3	52.8	1.09
15	δ-VL	$KOCH_3$	5	100	90 (2.5 h)	9.0	9.0	19.3	1.06
16	ε-CL	$KOCH_3$	5	100	95 (45 h)	10.9	10.3	22.8	1.10
17	TMC-Bn	$KOCH_3$	5	100	88 (30)	22.0	23.1	21.8	1.11

Reactions were run at room temperature in dichloromethane for LA and TMC-Bn or in toluene for VL and CL. $[LA]_0 = 0.69$ mol ml^{-1}, $[VL]_0 = 1.5$ mol ml^{-1}, $[CL]_0 = 3.5$ mol ml^{-1}, $[TMC\text{-}Bn]_0 = 1.0$ mol l^{-1}. *Conversion determined by ^{1}H NMR; †Theoretical M_n calculated by $MW_{mon} \times [M]_0/[I]_0 \times$ conv. + $MW_{end\ group}$ ($MW_{mon} = 144.1$ for LA, $MW_{mon} = 100.1$ for VL, $MW_{mon} = 114.1$ for CL, $MW_{mon} = 250.2$ for TMC-Bn, $MW_{end\ group} = 32$ when the initiator is $MOCH_3$, $MW_{end\ group} = 274$ when the initiator is pyrenebutanol); MW, molecular weight; ‡M_n determined by end group analysis (-C*H*(CH_3)O- in the repeat units versus end group); §M_n and $Đ = M_w/M_n$ obtained by gel permeation chromatography (GPC) in THF using polystyrene standard. M_n was corrected by a correction factor of 0.58 for PLA; ‖Reaction was initiated by a mixture of 1-pyrenebutanol, IMes and TU in the molar ratio 1:1:1; ¶Reaction was performed at $[LA]_0 = 1.0$ mol l^{-1}.

dichloromethane, lactide was converted to PLA with >90% conversion within 6 min. The molecular weight distributions of the resulting PLAs depend on the relative amount of **TU-1** to $NaOCH_3$—increasing the ratio of TU to $NaOCH_3$ significantly lowers the molecular weight distributions. In the absence of excess **TU-1** (1 equiv. relative to $NaOCH_3$), the molecular weights match those predicted from $[M]_0/[I]_0$ and conversion, but the molecular weight distributions of the obtained PLA are broader ($Đ = 1.55$). When the ratio of **TU-1** to $NaOCH_3$ was increased to 5 or 10, the molecular weight distributions decrease to 1.18. Similar polymerization behaviour was observed by adding methanol to independently synthesized sodium or potassium thioimidate salts (Supplementary Table 1). This procedure thus facilitates the use of any alcohol as an initiator.

The nature of the alkoxide counterion has a significant effect on polymerization behaviour. For a $KOCH_3$ initiator, addition of 1.0 equiv. **TU-1** results in 94% conversion after 5 min and yields PLAs with $Đ = 1.21$ (Table 1, entry 8). Even at a high monomer to initiator ratio of 500, the polymerization of L-lactide with TU/$KOCH_3$ reached high conversion in less than an hour and the resultant PLAs exhibit narrow molecular weight distributions ($Đ = 1.15$) and a molecular weight close to the theoretical value (Table 1, entry 11). Replacement of the $NaOCH_3$ initiator with $KOCH_3$ resulted in slightly slower reaction rates but narrower molecular weight distributions. (Table 1: entries 2, 8 and 3, 10; Supplementary Fig. 3). In the presence of excess **TU-1** (relative to $KOCH_3$) the molecular weight distributions are narrower, but the rate decreases (Supplementary Fig. 4).

The living nature of the polymerizations by the TU/$KOCH_3$ system was corroborated by a chain extension experiment, where the addition of 100 equiv. lactide to a pre-formed PLA of $M_n = 23$ kDa and $Đ = 1.06$ (95 lactide units) in the presence of 5:1 **TU-1**/$KOCH_3$ led to a clean chain extension to afford a PLA with M_n increased to 46 kDa (193 lactide units) while maintaining a narrow molecular weight distribution. ($Đ = 1.07$) (Supplementary Fig. 5).

The selectivity of this catalytic system is also manifested in the lack of any observable epimerization of the polylactides. Homonuclear decoupled ^{1}H NMR analysis and DSC of a PLA generated by TU/$KOCH_3$ (Table 1, entry 10) revealed it to be highly isotactic poly(L-lactide) with a melting point (T_m) of 175 °C (Supplementary Figs 1 and 2)[43]. These results indicate that the addition of the thiourea modulates the basicity of the alkoxide to enable rapid rates of ring-opening with minimal competitive deprotonation reactions. In THF, the polymerization of lactide with TU/$KOCH_3$ was slightly slower, but exhibited similar levels of control to polymerization carried out in dichloromethane (Supplementary Table 2 and Supplementary Fig. 6).

To investigate the effect of larger imidazolium counterions, we prepared another initiator/catalyst system by treating **TU-1** with equimolar amounts of 1,3-dimesitylimidazol-2-ylidene (IMes), which rapidly generates the thioimidate and the imidazolium counterion (Supplementary Fig. 7). The resulting thiourea anion/imidazolium ion in the presence of 1-pyrenebutanol mediates the polymerization of lactide more slowly than that with **TU-1**/$KOCH_3$, but generates PLAs with extremely narrow molecular weight distributions ($Đ < 1.10$), even in the absence of excess **TU-1**. Remarkably, the molecular weight distributions of the PLAs after complete monomer consumption and prolonged reaction times remained low (Supplementary Fig. 8), indicative of minimal transesterification of polymer chains. This is in contrast to other highly active organocatalysts such as *N*-heterocyclic carbenes or the guanidine TBD, where it was observed that the molecular weight distributions increase significantly at extended reaction times (Supplementary Fig. 9)[16].

The high selectivities of **TU-1**/alkoxide catalysts were also revealed by matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF MS). Shown in Fig. 2 are four PLA samples with a target degree of polymerization (DP) of 50, generated with different **TU-1**/alkoxide systems at high conversion (~90%): **TU-1**/$NaOCH_3 = 1.5$ (Fig. 2a), **TU-1**/$NaOCH_3 = 10$ (Fig. 2b), **TU-1**/$KOCH_3 = 10$ (Fig. 2c) and **TU-1**/IMes/pyrenebutanol = 1.5/1/1 (Fig. 2d). In all cases, the primary population is formed of the molecular ions with mass corresponding to the sodium adduct of linear PLAs with an alcohol end group. However, the amount of odd-numbered PLAs generated by competitive transesterifications of the polymer chains depends sensitively on the catalyst system. For the PLAs generated with the **TU-1**/$NaOCH_3$ catalyst at **TU-1**/$NaOCH_3 = 1.5$, the MALDI-TOF MS of the resulting PLAs reveal a series of ions separated by 72 mass units (Fig. 2a). The existence of both even- and odd-numbered PLAs of similar intensities is indicative of competitive transesterification of the polyester chains[38]. In contrast, MALDI-TOF MS of the PLAs generated from **TU-1**/ $NaOCH_3 = 10/1$ revealed that the ions corresponding to odd-numbered linear PLAs with m/z separated by 72 mass units decreased to ~30% of those separated by 144 mass units (Fig. 2b). These odd-numbered peaks further decreased for the **TU-1**/$KOCH_3 = 10$ catalyst system (Fig. 2c), and were barely detectable for the **TU-1**/IMes/pyrenebutanol system (Fig. 2d). These results suggest that thiourea anions in the presence of either potassium or imidazolium counterions are exceptionally well controlled with a very high selectivity for enchainment over competitive transesterification reactions.

The versatility of the TU/alkoxide system was demonstrated with other cyclic lactones and carbonate monomers. The ROPs of δ-valerolactone (VL), ε-caprolactone (CL) or trimethylenecarbonate benzylester (TMC-Bn) mediated by the **TU-1**/$KOCH_3$ (5/1) and **TU-1**/PyOH/IMes (1/1/1) systems were slower than those of lactide but exhibited exceptional control over the polymerization, with predictable molecular weights, end group fidelity and narrow molecular weight distributions (Table 1 entries 15–17, Supplementary Table 3 and Supplementary Fig. 10). The TU/alkoxide system was also used to synthesize well-defined crystalline diblock copolymers PVL-b-PLA by sequential addition of valerolactone and lactide (Supplementary Figs 11–13).

The TU/alkoxide system is both highly modular and tunable. The thiourea anion derived from *N*-phenyl, *N*-cyclohexyl thiourea (**TU-2**/$KOCH_3$) is more active than **TU-1**/$KOCH_3$ for the polymerization of CL, reaching 93% conversion in 5 h ($Đ = 1.14$, Supplementary Table 4), compared to 45 h for a similar conversion with **TU-1** (Table 1 entry 16). The thiourea anion derived from diisopropyl thiourea (**TU-3**) is even more active for the polymerization of CL (90% conversion in <1 min), but at the expense of a broader molecular weight distribution ($Đ = 1.60$, Supplementary Table 4). The thioimidate of a more acidic thiourea (bis-(3,5-ditrifluoromethylphenyl)thiourea, **TU-4**) has a much lower reactivity than that of **TU-1**, but shows equally good control over polymerizations (Supplementary Table 5). These results reveal that the activity and selectivity can be readily tuned by appropriate choice of the thioimidate anion.

Mechanistic and computational studies provide important insights into the mechanism and origin of the high selectivities of these catalyst systems. Computational investigations (using the dispersion-corrected B3LYP-D3 method with the 6-31 + G(d) basis set followed by single point energy calculations with the aug-cc-pVTZ basis set in CH_2Cl_2; Supplementary Section 'Computational methodology') reveal that ^{i}PrTU (a model for **TU-1**) reacts exergonically with $NaOCH_3$ (or $KOCH_3$) by proton transfer to form a hydrogen-bonded complex **AA** (Fig. 3a and Supplementary Fig. 17) that is 29 kcal mol^{-1} (or 33 kcal mol^{-1}) more stable than the reactants. The deprotonation of thiourea and the ability of thiourea to stabilize oxy-anions have been investigated previously[44,45]. For the hydrogen-bonded complex **AA**, the metal ion complexes to the S atom and forms a cation–π interaction[46] with the electron-deficient aryl ring.

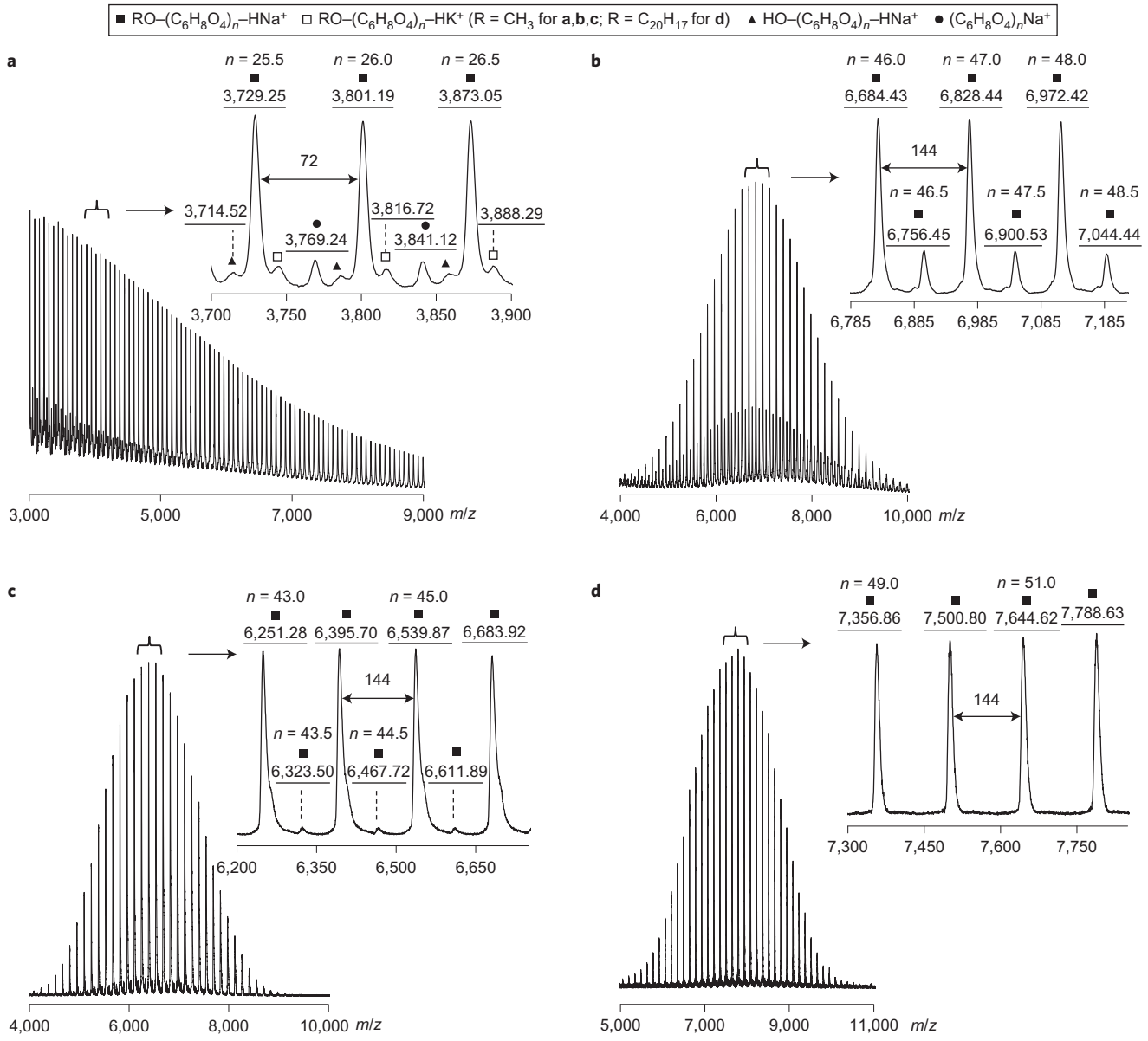

Figure 2 | MALDI-TOF MS of PLAs generated by various initiator systems with a target DP of ~50 and conversion of ~90%. a, [TU-1]/[$NaOCH_3$] = 1.5. **b**, [TU-1]/[$NaOCH_3$] = 10. **c**, [TU-1]/[$KOCH_3$] = 10. **d**, [TU-1]/[IMes]/[pyrenebutanol] = 1.5:1:1. Sodium or potassium adducts of linear PLAs with an alcohol end group (CH_3OH in **a**–**c** and pyrenebutanol in **d**) are labelled as filled and open squares, respectively, sodium adducts of linear PLAs with an H_2O end group as filled triangles, and sodium adducts of cyclic PLAs as filled circles. The number of odd-numbered PLAs differs with different initiator systems, indicating the effect of counterions and excess thiourea on the selectivity of thioimidate catalysts for ring-opening over competitive transesterifications.

These calculations were corroborated by ^{1}H NMR spectroscopy. When a 1:1 mixture of TU-1 and $NaOCH_3$ was combined in THF-d_8, ^{1}H NMR resonances of the thioimidate anion were clearly observed, as confirmed by an independent synthesis of the thioimidate salt. A comparison of the room-temperature and low-temperature (−70 °C) ^{1}H NMR spectra is consistent with a hydrogen-bonded adduct between methanol and the thioimidate anion that is in dynamic exchange (Supplementary Fig. 14).

The calculated reaction coordinate for ring-opening of lactide involves the initial formation of a reactant complex (**RC**) comprising sodium thioimidate hydrogen-bonded to both methanol and lactide (Fig. 3b and Supplementary Fig. 18). This **RC**, which is stabilized by hydrogen bonding and ionic interactions, is 40 kcal mol^{-1} more stable than the reactants. Subsequent nucleophilic attack of the bound methanol onto the carbonyl group of lactide proceeds via transition state **TS1** with an activation barrier of 17 kcal mol^{-1}. The resulting tetrahedral intermediates **INT1** and **INT 2** are stabilized by dual hydrogen bonding to the thiourea, where the proton has been transferred back to the aryl nitrogen of sodium thioimidate. The hydrogen bonding arrangement of **INT2** facilitates ring-opening of the tetrahedral intermediate with a low barrier of ~5 kcal mol^{-1} to afford **INT3**, the alcohol-terminated open chain lactide bound to sodium thioimidate. Chain propagation involves disassociation of the opened ester to give **INT4**, which binds an additional lactide monomer to afford the adduct **INT5**. These two steps are calculated to be exergonic by ~12 kcal mol^{-1}, which implies that binding of lactide to **INT4** is favoured over the intramolecular binding of the open-chain ester (**INT3**). This latter result provides some insight into the high selectivities of these catalyst systems for ring-opening of lactide relative to intra- or intermolecular transesterification reactions: the stronger affinity of **INT3** for

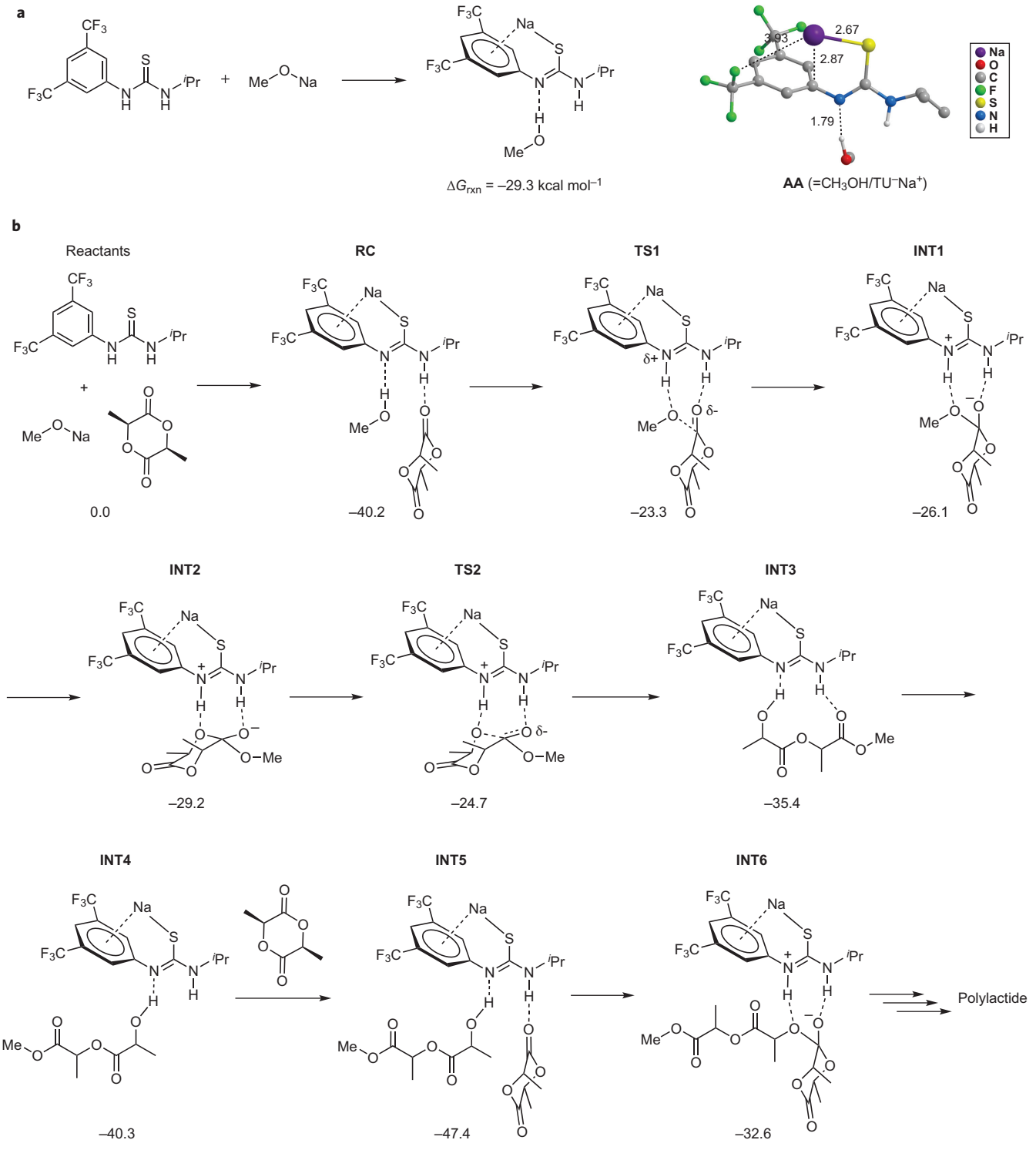

Figure 3 | Calculated energies and reaction coordinate. a, The reaction of ^{i}PrTU with sodium methoxide forms a hydrogen-bonded adduct of a thiourea anion and methanol. Atom colours are indicated in the key on the right. **b**, Mechanism for ring-opening of lactide by ^{i}PrTU and sodium methoxide. Free energies are shown in kcal mol^{-1}. DFT calculations indicate a bifunctional catalytic mechanism where the sodium thioimidate simultaneously activates monomers and reversibly shuttles protons from/to the alcohol chain end to modulate its activity. The binding of lactide monomer to the alcohol-bound thioimidate (**INT 5**) is energetically more favourable (~12 kcal mol^{-1}) than binding of the open-chain ester to the catalyst (**INT 3**).

the monomer lactide relative to other esters of the chain implies that propagation is favoured over transesterification of the open-chain esters of the polymer chain.

The calculations support the hypothesis of a bifunctional mechanism where the thioimidate anion activates both the alcohol (by hydrogen bonding with the nitrogen atom of the thioimidate) and the lactone (by hydrogen bonding with the carbonyl of the lactone). The calculations also suggest that intramolecular nucleophilic attack to form the tetrahedral intermediates (**INT1**, **INT 6**) are the highest-energy steps on the reaction coordinate (~15 kcal mol^{-1}). This calculated mechanism is closely analogous to that proposed for the guanidine TBD[13,47] and other proton shuttle catalysts[48,49].

However, in contrast to TBD, the tunable nature of the thiourea anions provides a means of modulating the strength of alcohol and lactone binding and activation. Computational studies reveal that the geometries of ^{i}PrTU/alkoxide complexes differ when the counterion is changed from Na^+ to K^+ (Supplementary Fig. 17). This observation may account for the experimentally observed counterion effects on the rates and molecular weight distributions, but further experimental and computational studies are under way to illuminate the influence of the counterions and thiourea structure on the rates and selectivities.

The intriguing indication that lactide binds more avidly than open-chain esters to alcohol adduct **INT4** prompted us to experimentally measure the relative affinity of lactones and open-chain esters to independently prepared alcohol/thioimidate adducts. Treatment of **TU-1** with KO^{t}Bu affords the ^{t}BuOH adduct of the thioimidate anion. As ^{t}BuOH is a poor initiator, we could measure and compare the binding constants of valerolactone and ethyl acetate to this adduct. Binding constants were determined by analysis of the change in ^{13}C NMR chemical shifts of the carbonyl group in a NMR titration experiment[16,50] (see Supplementary Section 'NMR titration experiment' pages 17–18 for details). The association constant for the binding of valerolactone to the TU$^{-}K^{+}$/HO^{t}Bu adduct is $24 \pm 4\ M^{-1}$, whereas the binding constant of ethyl acetate is only $5 \pm 2\ M^{-1}$ (Supplementary Fig. 15). This difference in binding constants provides a rationale for the high selectivity of these catalysts for polymerization relative to transesterification. The higher affinity of valerolactone relative to ethyl acetate for binding to the TU$^{-}K^{+}$/HO^{t}Bu would suggest that s-*cis* lactones are activated more readily than the s-*trans* esters of interchain esters, leading to the selective activation of monomer over polymer chains. We had previously suggested that the preferential binding of lactones (relative to open-chain esters) to thioureas was the origin of the high selectivities of thiourea catalysts[16]. We carried out an analogous ^{13}C NMR titration experiments with the neutral **TU-1** and valerolactone/EtOAc, and the results clearly show that lactones bind more avidly to thioureas than ethyl acetate (Supplementary Fig. 16). The results of these titration experiments provide clear experimental support for the hypothesis that the high selectivity of the thiourea catalysts (either neutrals or anions) for ROP is a consequence of the different affinities of s-*cis* esters (lactones) and s-*trans* esters for hydrogen bond donors.

In summary, we report a highly efficient catalytic system for fast and selective ROP of lactones. Operationally, this procedure is trivially simple: 1–10 equiv. of **TU-1** is added to a DCM or THF solution of sodium, potassium or imidazolium methoxide to generate alcohol adducts of thioimidate anions that rapidly mediate the living ROP of lactones (or carbonates) with narrow molecular weight distributions and minimal competitive transesterification or epimerization reactions. Mechanistic and computational studies indicate that the thioimidate anion simultaneously activates the alcohol initiator/chain-end and the lactone monomer. The high selectivity of these catalysts for propagation over transesterification correlates with the higher affinity of s-*cis* lactones relative to s-*trans* esters to these hydrogen bond donor catalysts. Compared to existing nucleophilic and hydrogen-bonding-based catalysts, this TU/alkoxide system combines the positive aspects of both fast kinetics and excellent control over the polymer structure and molecular weight distributions. The strategy of using hydrogen bond donors to modulate the reactivity of alkoxide anions could be useful for controlling other anionic polymerizations. More generally, the concept of transforming neutral hydrogen bond donor catalysts to potent bifunctional anionic catalysts is general and should prove useful for a wide range of catalytic reactions that involve the simultaneous activation of protic pro-nucleophiles and electrophiles.

Received 3 December 2015; accepted 13 June 2016;
published online 25 July 2016

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Acknowledgements

This material is based on work supported by the National Science Foundation (NSF-CHE-1306730). X.Z. acknowledges a Stanford Graduate Fellowship.

Author contributions

X.Z., R.M.W. and J.L.H. designed the experiments. X.Z. performed the experiments. G.O.J. performed the DFT calculations. All authors analysed the results and co-wrote the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to R.M.W.

Competing financial interests

The authors declare no competing financial interests.