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 Hot Paper

First Use of Thiosquaramides as Polymerization Catalysts: Controlled ROP of Lactide Implicating Key Secondary Interactions for Optimal Performance

Gaël Printz,^[a] Dmytro Ryzhakov,^[b] Christophe Gourlaouen,^[a] Béatrice Jacques,^[a] Samir Messaoudi,^[b] Françoise Dumas,^[b] Franck Le Bideau,^{*[b]} and Samuel Dagorne^{*[a]}

We herein report the first use of thiosquaramides as polymerization catalysts, which are shown to be effective for the controlled ROP of lactide in the presence of an alcohol source and NEt_3 . Comparison of their catalytic performances with the less acidic squaramides are also discussed. The observed catalytic activity of variously *N*-substituted thiosquaramides suggest that a balanced NH Brønsted acidity is required for optimal performance. Most interestingly and rather unexpectedly, DFT-supported calculations on thiosquaramide-mediated

lactide ROP catalysis suggest that secondary interactions between the thiosquaramide *N*-substituents and the incoming lactide (presently of type C-H $\cdots\pi$ -arene) are crucial for catalytic activity. Though this type of interactions is quite common in organo-catalysis, it has rarely been evidenced to play a key role in the area of organo-catalyzed polymerizations. Such catalyst substituents/substrate interactions may well play a significant role in the catalytic performances of various other systems.

Introduction

Over the past two decades, organocatalyzed ring-opening polymerization (ROP) of cyclic polar monomers has emerged as a sustainable alternative to traditional metal-based ROP processes that frequently incorporate toxic and/or expensive metal sources.^[1] In addition to being metal-free, the wide structural variety of readily available organocatalysts, including chiral derivatives, has led to major progress in the field of ROP catalysis with the development of highly effective organo-catalysts to afford metal-free polymers.^[2] In this area, ROP organocatalysis proceeding through hydrogen-bonding (HB) activation of the monomer/initiator by the catalyst is an attractive ROP approach to access well-defined materials under mild reaction conditions. In the area, ureas and thioureas derivatives have been by far the most studied organocatalysts for cyclic esters ROP,^[3] with such catalysts acting as hydrogen

bond (HB) donors for monomer activation. More recently developed HB donor catalysts such as squaramides have also received attention in the ROP of cyclic esters such as lactide.^[4] Though known since 1966,^[5] thiosquaramides, which are the thio analogues of squaramides (see for instance **1a–4a** in Scheme 1), were only recently used as organocatalysts,^[6] probably due to difficulties encountered in their preparation.^[7] A comparison of squaramides and thiosquaramides reveals two notable physico-chemical features that may favor the use of thiosquaramides in homogenous catalysis.^[8] Contrary to squaramides forming head-to-tail ladder networks *via* interaction between hydrogen bond donor (NH) and acceptor (CO) functions, thiosquaramides have a lower tendency to self-aggregate leading to a higher solubility than their oxo-analogues.^[6] The second favorable feature of thiosquaramides is their stronger Brønsted acidity. Thus, based on computational and experimental studies, they are, on average, 6.4 pKa units more acidic than the corresponding squaramides.^[8] Following the seminal work of Rawal et al. in 2017 evaluating thiosquaramides as HB donor catalysts in the conjugate addition of barbituric acids to nitroolefins,^[6] a few other organocatalyzed reactions involving such compounds were reported,^[9] showing an improvement of both yields and enantioselectivities when compared to the use of the corresponding squaramides. Despite the enhanced acidity/HB donor ability of thiosquaramides, of interest for stronger monomer activation, thiosquaramide-catalyzed polymerization of cyclic polar monomers is thus far unknown. In fact, to our knowledge, the use of thiosquaramides as polymerization catalysts is not documented.

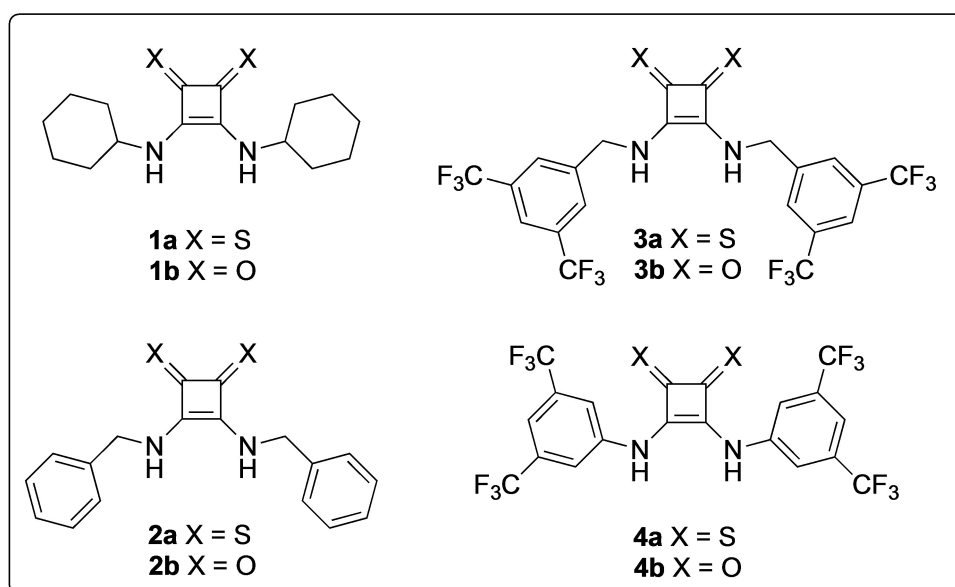
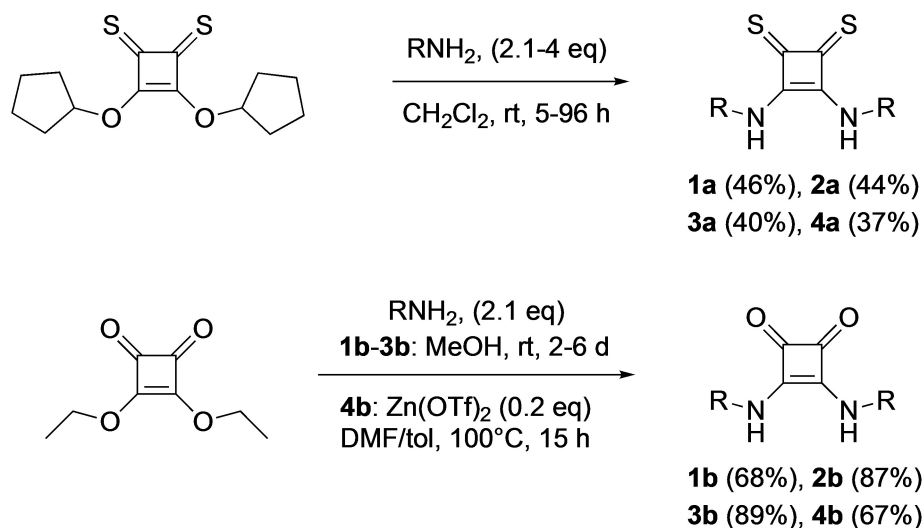
Poly(lactic acid) (PLA), a biodegradable,^[10] biocompatible,^[11] and renewable aliphatic polyester,^[12] is currently attracting significant attention with notable applications ranging from the biomedical area^[13] to food packaging.^[14] Its annual production worldwide should reach 300,000 tons in 2024. The most

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Scheme 1. Studied thiosquaramides (1a–4a) and squaramides (1b–4b) and their synthesis.

efficient and economical synthesis of PLA relies on ring opening polymerization (ROP) of lactides and its industrial production currently involves a Sn-based catalyst, whose toxicity is well established.^[15] The development of novel organocatalysts is of particular interest for lactide ROP and numerous systems have been reported in the area over the past twenty years, in particular using HB-donor type catalysts such as thioureas in association with an initiator and a base acting as a HB acceptor.^[3,4]

Here, we report on the first use of thiosquaramides (1a–4a, Scheme 1) able to act as organocatalysts in polymerization catalysis. Specifically, we show that 1a–4a are effective catalysts for the controlled ROP of lactide (in the presence of BnOH or MeO-PEG-OH as initiators and Et₃N as a HB acceptor) to produce well-defined PLA. Factors controlling their activity, comparison of their performances with the corresponding squaramides (1b–4b, Scheme 1), complete kinetic studies as

well as a DFT-estimated ROP mechanism are provided. As discussed below, besides the expected influence of Brønsted acidity on ROP performance, the key role of secondary catalyst/monomer CH $\cdots\pi$ interactions for optimal catalytic activity are also uncovered.

Results and Discussion

Thiosquaramides 1a–4a were synthesized according to a literature procedure from reaction of the robust dicyclopentyl dithiosquarate with the corresponding amines under mild conditions (CH₂Cl₂, rt), and were isolated in moderate yields (37–46% yield, Scheme 1).^[7] Squaramides 1b–4b were synthesized according to slightly modified literature procedures (see SI).

Preliminary ROP tests with **1a–4a** performed in the absence of NEt_3 with a $\text{LA}/\text{BnOH}/\mathbf{1a-4a}$ mixture in a 600/30/1 ratio showed no ROP activity after 96 h (CH_2Cl_2 , room temperature). Species **1a–4a** were then tested as lactide ROP catalysts in the presence of BnOH (acting as initiator) and NEt_3 (for initiator activation). The results are compiled in Table 1. As initial screening, ROP tests were run using **1a–4a** under identical conditions (25 h, CH_2Cl_2 , rt; entries 1–4, Table 1). Satisfyingly, in combination with BnOH (30 equiv. vs. catalyst) and NEt_3 (10 equiv. vs. catalyst) and starting with 600 equiv. of L -LA, the N -benzyl substituted thiosquaramides **2a** and **3a** quantitatively (or nearly in the case of **3a**) polymerize L -LA in a controlled manner to afford well-defined and narrow disperse PLLA in high conversion, as concluded from GPC and NMR data (entries 2 and 3, Table 1). In contrast, the N -Cy substituted **1a** is much less active with a 33% conversion to PLA (from 600 equiv) under identical conditions. Likewise, the bis-aniline derivative **4a**, though the most acidic thiosquaramide of the **1a–4a** series, also displays moderate ROP activity (entry 4, Table 1). In all cases, the PLA M_n values match well the expected theoretical M_n values, in line with a controlled ROP process.

Table 1. ROP of L -LA catalyzed by thiosquaramides **1a–4a** and squaramides **1b–4b** (for comparison) in the presence of NEt_3 and BnOH in a 600/30/10/1 $\text{LA}/\text{BnOH}/\text{NEt}_3/\text{Cat}$ ratio.

Entry	Cat.	conv (%) ^a	$M_n(\text{theo})^b$ (g/mol)	$M_n(\text{exp})^c$ (g/mol)	\mathcal{D}^d
1	1a	33	950	1030	1.18
2	2a	100	2880	2750	1.13
3	3a	90	2600	2400	1.09
4	4a	27	780	670	1.22
5	1b	35	1000	1150	1.20
6	2b	35	1000	740	2.18
7	3b	77	2200	2060	1.06
8	4b	85	2448	2158	1.12

NMR data and MALDI-TOF analysis of the produced PLA agree with the production of linear and OBn-ester-ended PLA, in line with BnOH acting as ROP initiator. MALDI-TOF data are also consistent with the absence of substantial transesterification reaction as the ROP proceeds. Also, no apparent epimerization of the PLA chain occurs as the ROP proceeds under the studied conditions with the formation of PLLA as deduced from homodecoupled ^1H NMR data of a crude PLA sample produced from a 600/30/10/1 L -LA/ $\text{BnOH}/\text{Et}_3\text{N}/\mathbf{3a}$ ROP run (see SI). Using *rac*-LA instead of L -LA as a monomer source and **3a** as catalyst (600/30/10/1 *rac*-LA/ $\text{BnOH}/\text{Et}_3\text{N}/\mathbf{3a}$) led to a similar catalytic activity but with the production of atactic PLA, indicating the absence of any stereoselectivity in the ROP process.

ROP kinetic data gathered for **1a–4a** systems support a well-controlled polymerization in all cases including: i) an observed first order reaction rate relative to LA (Figure 1) and ii) a linear correlation between the PLA M_n values and the monomer conversion (Figure 2 in the case of **1a**; for additional kinetic data, see SI). From the k_{obs} values in Figure 1, catalysts **2a** and **3a** are roughly five and ten times more active than **1a** and **4a**, respectively, indicating no clear correlation between ROP activity and thiosquaramide acidity under the studied conditions: from the nature of the nitrogen substituents in **1a–4a**, it can be qualitatively estimated that Brønsted acidity decreases in the following order: **4a** > **3a** > **2a** > **1a** (*vide infra* for further discussion). Noticeably, catalysts **1a–4a** were all found to be soluble under the studied catalytic conditions ruling out solubility issues to rationalize the observed ROP performances for **1a–4a**.

For comparison, the ROP performances of the squaramide analogues **1b–4b** were evaluated under identical conditions (entries 5–8, Table 1) also showing controlled ROP processes with these catalysts. Interestingly and contrasting with the **1a–4a** systems, the most acidic catalysts of the **1b–4b** family, *i.e.* **3b** and **4b**, are the most effective squaramide catalysts with 77% and 85% conversion to PLA, respectively (starting from 600 equiv. of L -LA, CH_2Cl_2 , rt, 25 h), yet with a lower catalytic

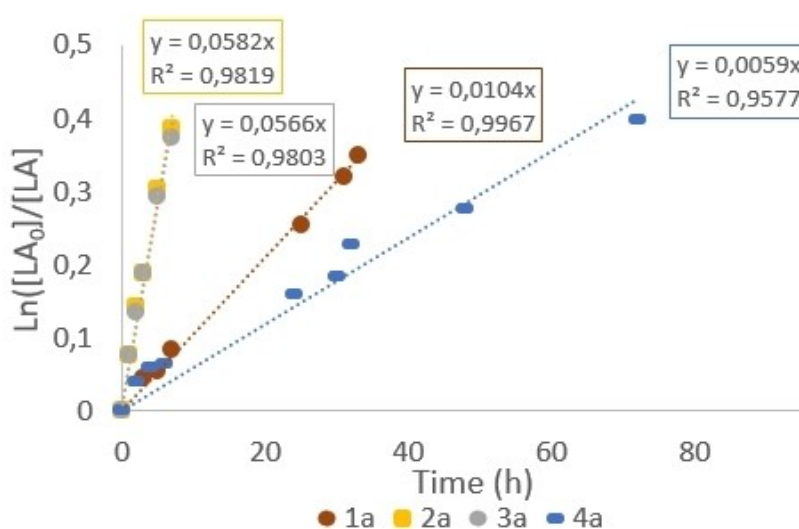


Figure 1. Plot of $\ln([LA]_0/[LA])$ vs. reaction time with thiosquaramide derivatives **1a–4a** in the ROP of L -LA in the presence of BnOH and NEt_3 . Conditions: 600/30/30/1 equivalents (L -LA/ $\text{BnOH}/\text{NEt}_3/\mathbf{1a-4a}$), $[L\text{-LA}]_0 = 5$ M, room temperature, CH_2Cl_2 .

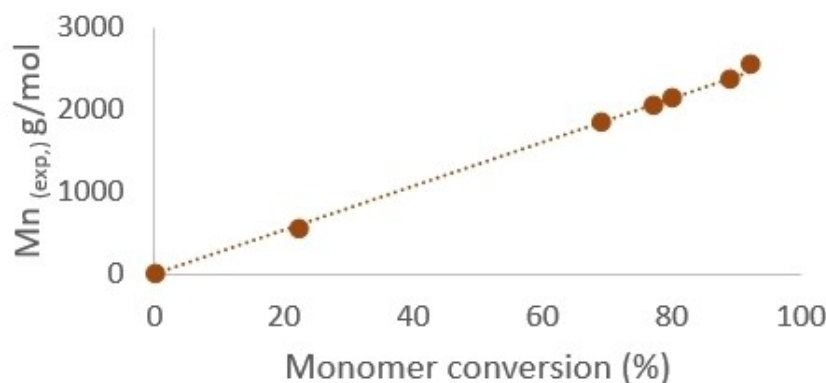


Figure 2. Plot of M_n vs. lactide conversion of the ROP mediated by catalyst **1a** in the presence of BnOH and Et₃N. Conditions: $[L-LA]_0 = 5$ M, 600/30/30/1 L-LA/BnOH/NEt₃/1 **a** ratio, rt, CH₂Cl₂.

performance than the most active thiosquaramide systems **2a** and **3a**. The least acidic catalysts **1b** and **2b** only afforded a moderate conversion to PLA (35% conversion; entries 5 and 6, Table 1). Strikingly, when comparing the activity of **1a–4a** to **1b–4b**, as derived from kinetic data (for squaramides, see Figure S8, SI), the ROP catalyzed by **2a** proceeds about seven times faster than with the (less acidic) squaramide analogue **2b**, while, on the contrary, (the more acidic) **4a** is six times slower than (the less acidic) **4b**. These data suggest that high ROP activity in these multi-component catalytic systems (Cat/NEt₃/BnOH) requires a finely tuned catalyst acidity/HB ability so that to allow substantial monomer activation while limiting strong co-catalyst binding or/and side reactions between catalyst and co-catalyst. Cocatalysts binding effects resulting into a lower lactide ROP activity have been documented in the case of DBU/thiourea (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) catalytic systems.^[16]

Being the most active catalysts along with **2a**, catalyst **3a** was further investigated for optimization and the results are compiled in Table 2, with all runs leading to the production of

chain-length-controlled and narrow disperse PLA. In particular, the catalytic activity was optimized showing that **3a** may mediate the ROP of 530 equiv. of L-LA within 6 h at rt, with an initial lactide feed of 600 equiv. vs. **3a**; entry 1, Table 2). Higher catalyst loading at constant monomer feed (entries 2 and 3, Table 2) led to increased ROP activity with, at best, a 92% conversion to PLA within 3 h when using a 600/30/30/4 L-LA/BnOH/NEt₃/**3a** ratio. As can be expected, decreasing the loading in NEt₃ or BnOH led to lower ROP performances (entries 4–7, Table 2), reflecting the key role of NEt₃ for initiation and polymer chain-end activation. Nevertheless, even at lower BnOH loading, **3a** remains efficient and allowed the production of PLA with higher M_n values (entries 8 and 9, Table 2). Thus, for instance, starting from a 600/30/30/4 L-LA/BnOH/NEt₃/**3a** catalytic system led to the production of well-defined PLA ($M_n = 29650$ g·mol⁻¹, $\mathcal{D} = 1.06$) in high conversion (86%) within 26 h at rt. Moreover, catalyst **3a** may also be exploited to access metal-free well-defined PEG-*b*-PLLA block co-polymer, an amphiphilic material of biomedical importance,^[17] with the use of MeO-PEG-OH ($M_n = 2000$ g·mol⁻¹) as a ROP macro-initiator

Table 2. ROP of L-LA mediated by **3a**/BnOH/Et₃N in various ratios for optimization of the catalytic performances.

Entry	L-LA/BnOH/NEt ₃ / 3a	Conv (%) ^a	Time (h)	$M_n(\text{theo})^b(\text{g/mol})$	$M_n(\text{exp})(\text{g/mol})^c$	\mathcal{D}^d
1	600/30/30/1	88	6	2530	2450	1.13
2	600/30/30/2	93	5	2700	2400	1.12
3	600/30/30/4	92	3	2650	2550	1.11
4	600/30/20/1	81	6	2330	2400	1.17
5	600/30/5/1	75	32	2160	1750	1.12
6	600/10/10/1	81	32	7000	5200	2.07
7	600/10/5/1	65	48	5600	4100	1.07
8	600/2/30/1	56	39	24200	26500	1.04
9	600/2/20/2	86	26	37150	29650	1.06
10 ^e	600/30/10/1	25	27	2800	2950	1.07
11 ^e	600/30/10/1	72	70	4100	4700	1.09

Conditions (except indicated otherwise): $[L-LA]_0 = 5$ M, rt, CH₂Cl₂. ^a determined by ¹H NMR. ^b Calculated as $M_n(\text{theo}) = [L-LA]_0/[BnOH]_0 \times M_{L-LA} \times \text{conversion}/100$. ^c Measured by GPC in THF (30 °C) with polystyrene standards and corrected by applying the correcting factor 0.58. ^d $\mathcal{D} = M_w/M_n$; measured by GPC in THF (30 °C). ^e MeO-PEG-OH was used as an alcohol initiator.

(entries 10 and 11, Table 2). Thus, **3a** mediates the ROP of *L*-LA (72% conversion from 600 equiv) in the presence of a 30/10/1 MeO-PEG-OH/NEt₃/**3a** to afford narrow disperse PEG-*b*-PLLA ($M_n = 4700 \text{ g}\cdot\text{mol}^{-1}$, $\mathcal{D} = 1.06$), as deduced from all characterization data (GPC, NMR, MALDI-TOF, see SI). A ¹H NMR DOSY measurement of an isolated PEG-*b*-PLLA sample (CDCl₃, rt) also confirmed copolymer formation with all NMR resonances correlating to an identical diffusion coefficient (see SI).

While organocatalyzed ROPs of lactide has been intensively studied over the past fifteen years leading to numerous highly active systems,^[3] literature comparison of the present thiosquaramide/NEt₃ bi-component catalysts is most relevant with thioureas associated with NEt₃ as co-catalyst. When used in combination with NEt₃ and an alcohol source for initiation, thioureas are significantly less active than thiosquaramides in *L*-LA ROP with high conversion in PLA only achieved after 72 h at room temperature despite high catalyst loading (typically 10% mol).^[18] Recent studies have however demonstrated that the association of thioureas with much stronger Brønsted bases such as DBU and *N*-heterocyclic carbenes may lead to highly active systems in lactide ROP, able for instance to quantitatively convert 200 equiv. of LA to well-defined PLA within 2–3 h at room temperature.^[19]

Kinetic studies and control experiments. To better understand the mechanism of the ROP process mediated by these systems, detailed kinetic studies were carried out with organocatalyst **3a**. Thus, the dependence of the ROP reaction rate on [**3a**], [NEt₃] and [BnOH] was determined for each component by performing several ROP runs at constant initial concentrations for two of them but at different concentrations in the third, leading to a set of different k_{obs} values in each case. A linear correlation between k_{obs} and the concentration in [**3a**], [NEt₃] and [BnOH] was observed, thus indicating a first order dependence of the reaction rate relative to [**3a**], [NEt₃] and [BnOH] (see Figure 3 for k_{obs} dependence on [**3a**] and the SI for additional data). Thus, the ROP reaction rate constant is of the type $k_{\text{obs}} = k_p[\mathbf{3a}][\text{NEt}_3][\text{BnOH}]$. This is a similar rate law to that previously established for thiourea systems (in the presence of base and an initiator) for which a dual activation of the monomer (through HB with the thiourea) and the initiator/polymer chain-end (HB-accepting character of the base) was proposed to operate.^[20,1b]

For further understanding, control stoichiometric experiments involving catalyst components (**3a**, NEt₃ and BnOH) were

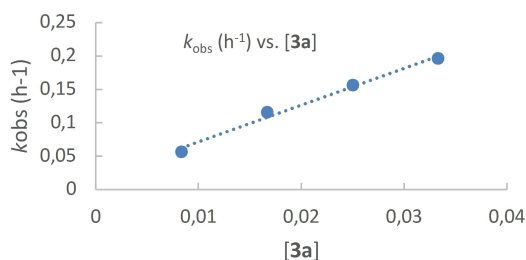


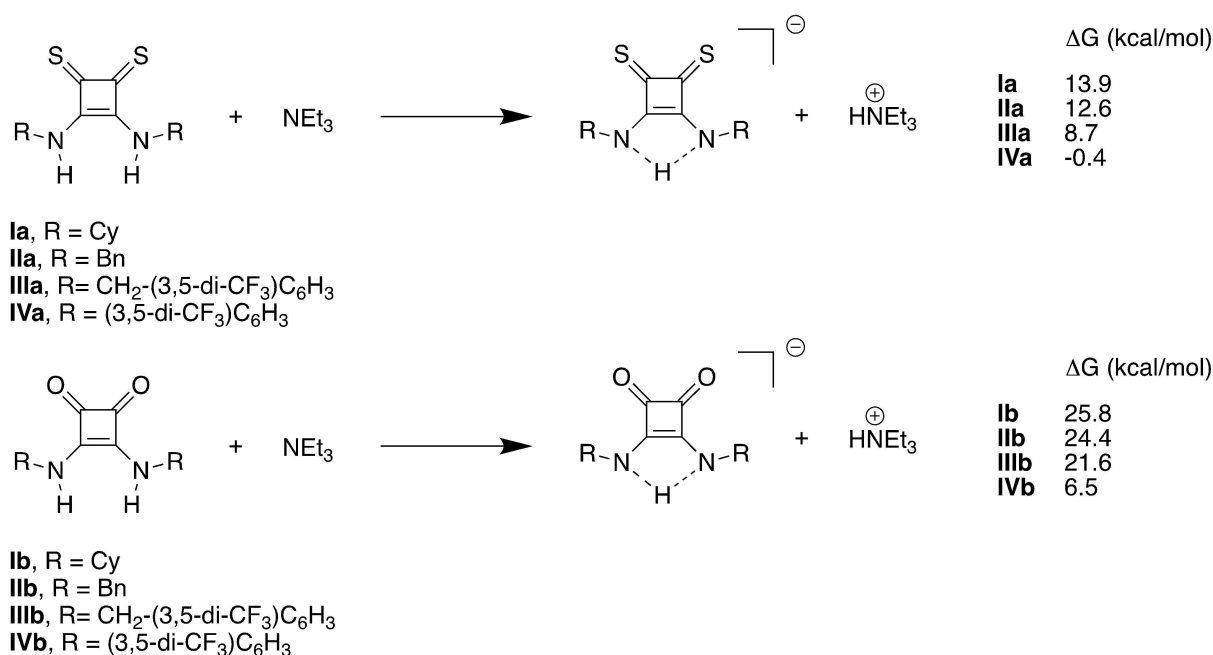
Figure 3. Plot of k_{obs} (h⁻¹) vs. concentration in **3a** in the ROP of *L*-LA at constant initial concentrations of *L*-LA, BnOH and NEt₃. Conditions: [*L*-LA]₀ = 5 M, *L*-LA/BnOH/NEt₃: 600/30/30, rt, CH₂Cl₂.

also ¹H NMR monitored (CDCl₃, rt) to probe interactions between these components (see Figures S17 and S18, SI).^[21] Only the most notable features are discussed herein. While thiosquaramide **3a** is poorly soluble in CDCl₃ (rt), the addition of 1 equiv. of NEt₃ yields a soluble mixture, with a significant downfield shift of the NEt₃ groups (δ 2.90 and 1.19 ppm) versus free NEt₃ (δ 2.31 and 0.82 ppm) by ¹H NMR, suggesting the formation of an adduct between **3a** and NEt₃ presumably through HB between the *N*-H and NEt₃ moieties. The addition of 1 equiv. of *L*-LA to the latter mixture only led to a minor additional downfield shift of the NEt₃ signals (δ 3.12 and 1.30 ppm). A 1/1/1 **3a**/NEt₃/BnOH mixture also displayed similar ¹H NMR NEt₃ chemical shifts (δ 3.09 and 1.29 ppm). Less significant ¹H NMR shifts of the NEt₃ groups (δ 2.52 and 1.03 ppm) are observed in the 1/1 NEt₃/BnOH mixture (δ 2.52 and 1.03 ppm) relative to free NEt₃, suggesting a weaker interaction of NEt₃ with BnOH vs. **3a**. Contrasting with NEt₃, interactions between BnOH and **3a** appear minimal based on ¹H NMR data with the ¹H NMR chemical shifts for BnOH in a 1/1 **3a**/BnOH (δ 4.70, PhCH₂, and 1.30, OH, ppm) being nearly identical (though slightly broader) compared to those of free BnOH (δ 4.70 and 1.63 ppm). Though qualitative, all these ¹H NMR data agree with the initial formation of an adduct between **3a** and NEt₃ as the major species upon combination of catalytic components **3a**, NEt₃ and BnOH.

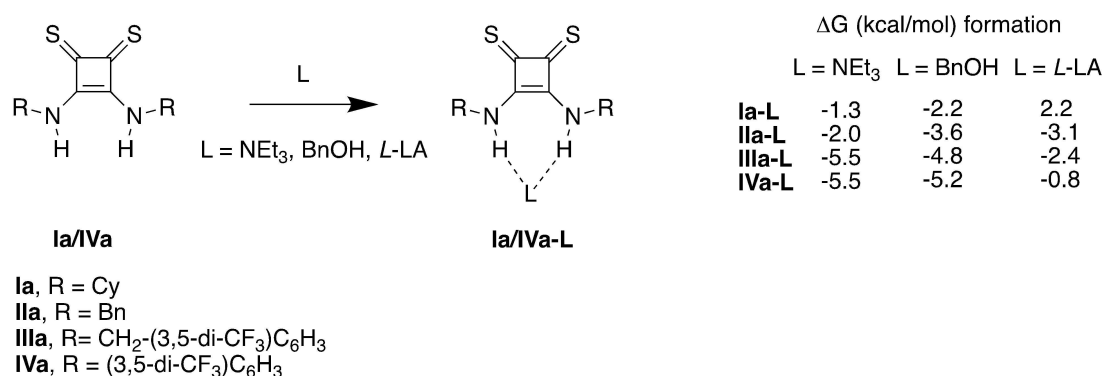
DFT calculations on properties/interactions of catalytic components and *L*-LA. Further knowledge of the present catalytic systems as well as their interactions with *L*-LA monomer was gained through DFT computation (ω B97XD/6-31+G** theory level, energies estimated in CH₂Cl₂ via a PCM model). First, the Brønsted acidity of thiosquaramides **1a–4a** and squaramide analogs **1b–4b** (models **1a–IVa** and **1b–IVb**, respectively) was evaluated by estimation of Gibbs free enthalpy of their deprotonation reaction by NEt₃; the results are summarized in Scheme 2.

As expected, when comparing thio- and squaramides with identical *N*-substituents, the reactions of **1a–IVa** with NEt₃ are clearly more thermodynamically favorable than those with **1b–IVb**, in line with the stronger acidity of **1a–IVa**. Within each series, an increased acidity is observed going from **1a/1b** to **IVa/IVb** following the stronger electron withdrawing character of the *N*-substituents. Remarkably, it should be noted the most acidic model of the computed species, *i.e.* **IVa**, reacts exergonically with NEt₃ ($\Delta G = -0.4 \text{ kcal}\cdot\text{mol}^{-1}$). This means that, under catalytic conditions, thiosquaramide **4a** may, at least partially, be deprotonated by NEt₃. The latter may significantly impact catalytic activity through possible side reactions involving the *in situ* formed conjugate base of **4a** and [HNEt₃]⁺. Such acid/base-related side reactions may be detrimental to ROP activity and rationalize the fact that **4a** is the least effective thiosquaramide ROP catalyst (Table 1, entries 1–4).

Second, to complement the control experiments discussed above with thiosquaramide **3a**, interaction energies between thiosquaramides **1a–4a** and NEt₃, BnOH and *L*-LA were computed, through the formation of the corresponding adducts **1a/IVa–L** (*L* = NEt₃, BnOH and *L*-LA; Scheme 3) and associated stabilization energies. As expected, the reaction between



Scheme 2. DFT-estimated (ω B97XD/6-31 + G** theory level) Gibbs free energies of deprotonation of (thio)squaramides by NEt₃ (values estimated in CH₂Cl₂).



Scheme 3. DFT-estimated (ω B97XD/6-31 + G** theory level) Gibbs free energies of formation of adducts between thiosquaramides **Ia-IVa** and L (L = NEt₃, BnOH and L-LA values; estimated in CH₂Cl₂).

thiosquaramide models **Ia-IVa** and NEt₃ leads to adducts **Ia-NEt₃** to **Iva-NEt₃**, an exergonic process in all cases (ΔG going from -5.5 to -1.3 kcal.mol⁻¹). The stability trend of such adducts follows the HB ability and acidity trend, with adducts **Illa-NEt₃** and **Iva-NEt₃** being the most stable of the series ($\Delta G = -5.5$ kcal.mol⁻¹). A similar stability trend is computed considering the interaction of **Ia-IVa** and BnOH, with the exergonic formation of adducts **Ia-BnOH** to **Iva-BnOH** (ΔG going from -5.2 to -2.2 kcal.mol⁻¹). In contrast and unexpectedly, the complexation energies of L-LA to **Ia-IVa** do not follow the HB/acidity trend, with the adduct **Ila-LA** being the most stable ($\Delta G = -3.1$ kcal.mol⁻¹) followed by **Illa-LA** ($\Delta G = -2.4$ kcal.mol⁻¹). The formation of **Iva-LA**, derived from the association of the most acidic thiosquaramide and L-LA, is only slightly exergonic ($\Delta G = -0.8$ kcal.mol⁻¹), while the interaction between the least acidic **Ia** and L-LA is endergonic ($\Delta G = 2.2$ kcal.mol⁻¹). Importantly, it should be noted that the most

stable thiosquaramide-lactide adducts correspond to the most active catalysts in lactide ROP, *i.e.* with thiosquaramides **2a** and **3a**.

To better understand the higher stability of adduct **Ila-LA**, Non-Covalent Interactions (NCI) analysis was performed (Figure 4), showing that the presence of stabilizing secondary interactions of the type C-H... π -arene between the N-Bn phenyl rings and the C-H groups of the lactide monomer likely rationalizes the observed stability. A similar type of stabilization probably accounts for the exergonic formation of **Illa-LA** ($\Delta G = -2.4$ kcal.mol⁻¹).

Overall, the computed complexation energies derived from interactions between catalytic components and L-LA suggest that: i) NEt₃, BnOH and LA may readily form weakly interacting adducts with **1a-4a** (with at most a 5.5 kcal.mol⁻¹ stabilization upon substrate coordination), thus indicating such adducts may all readily exist and interchange under the studied catalytic

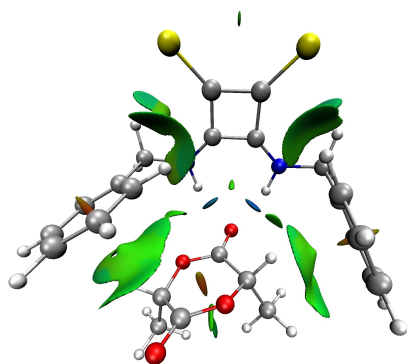


Figure 4. Non covalent interactions (NCI) isosurface ($\eta = 0.65$) for model lactide adduct **IIa-LA**, as estimated by DFT calculations at the ω B97XD/6-31 + G** theory level. Green areas correspond to attractive Van der Waals interactions.

conditions, and ii) the formation of the lactide-thiosquaramide adducts is exergonic (except for **Ia**) and the more stable adducts **IIa-LA** ($\Delta G = -3.1 \text{ kcal.mol}^{-1}$) and **IIIa-LA** ($\Delta G = -2.4 \text{ kcal.mol}^{-1}$) correspond to the most efficient catalysts **2a** and **3a**. This strongly suggests such lactide adducts are key intermediates for the ROP reaction to occur.

DFT-estimated ROP mechanism. The mechanism of the ring-opening reaction of *L*-LA catalyzed by thiosquaramide **2a** in the presence of BnOH and NEt_3 was then computed at the ω B97XD/6-31 + G** theory level (CH_2Cl_2 as solvent) and is depicted in Figure 5. Starting from adduct **IIa-LA** in the presence of BnOH activated through HB with NEt_3 ($\Delta G = 1.2 \text{ kcal.mol}^{-1}$), a NEt_3 -assisted nucleophilic attack of the BnOH moiety at the lactide C=O coordinated to **IIa** may readily occur at little energy cost through transition state **TS1** ($\Delta G = 16.2 \text{ kcal.mol}^{-1}$). This leads to the formation of intermediate **V** ($\Delta G = 0.7 \text{ kcal.mol}^{-1}$), in which the incorporated OBn group is now H-bonded to the generated $[\text{HNEt}_3]^+$ cation. From **V**, ring-opening may proceed via transient formation of intermediate **V'** ($\Delta G = 5.5 \text{ kcal.mol}^{-1}$), and then intramolecularly through low energy transition state **TS2** ($\Delta G = 10.1 \text{ kcal.mol}^{-1}$) to afford the ring-opening product **VI** ($\Delta G = 2.8 \text{ kcal.mol}^{-1}$). Note that the latter product features a terminal alcohol function H-bonded to NEt_3 and thus prone to undergo a subsequent lactide ring-opening reaction under catalytic conditions. Overall, the present mechanism agrees with a rather low experimental barrier ($16.2 \text{ kcal.mol}^{-1}$), in line with a catalytic process occurring at room temperature. Also, it suggests that the rate-determining step of the catalysis is thus the nucleophilic attack of the alcohol moiety on the lactide-**2a** adduct, further indicating that

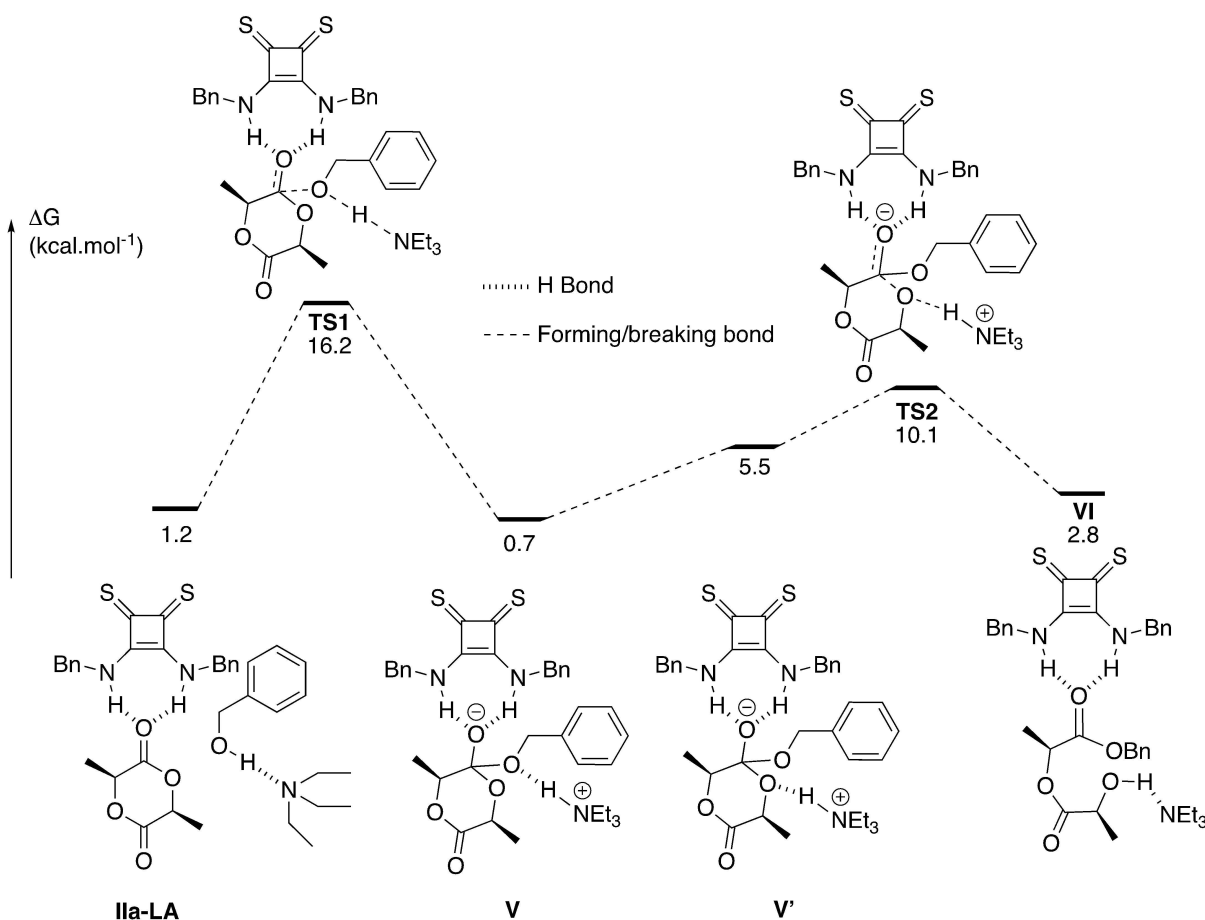


Figure 5. DFT-estimated mechanism of *L*-LA ring-opening mediated by model squaramide **IIa** in the presence of NEt_3 and BnOH (ω B97XD/6-31 + G** theory level). All energies are reported in CH_2Cl_2 (introduced through a PCM model).

the presence/concentration of such adduct is crucial for catalytic efficiency. This step involves all catalytic components as well as *L*-LA, which is consistent with the experimentally determined rate law of the ROP process (*vide supra*).

For comparison, lactide ring-opening was also DFT-studied with catalyst thiosquaramide **1a** (model **1a**), the least active catalyst of the series, in the presence of BnOH and NEt₃. As expected, a similar mechanism to that discussed with **2a** likely proceeds (see Figure S20, Supporting Information). Interestingly, the rate-determining step energetics and the experimental barrier with **1a** (16.6 kcal.mol⁻¹) are nearly identical to those with **2a**, though the latter is five to six times more active in lactide ROP than the former (Figure 1). Based on overall DFT data, the only notable energy difference between systems **1a** and **2a** is the stability difference of the lactide-thiosquaramide adducts (relative to the corresponding free components, see Scheme 3). Rather than kinetic/energy barrier factors, the higher catalytic performance of **2a** may be driven by thermodynamics, and thus due to the more favored formation (and thus higher concentration under catalytic conditions) of lactide adduct **2a**-LA relative to other adducts of the series.

Conclusions

In conclusion, a set of various N-substituted thiosquaramides were first introduced as polymerization catalysts through their use in the controlled lactide ROP to produce well-defined PLLA at room temperature in the presence of BnOH and NEt₃, and overall perform better than their squaramide analogues. Combined experimental and DFT computation studies established that a HB ROP catalysis occurring *via* an activated monomer/activated chain-end mechanism is likely operative in these systems. Of more importance, the present study clearly shows that, though the stronger Brønsted acidity/HB-donor ability of HB-type catalysts may improve catalytic efficiency, a fine acid/base balance is required between the catalyst and co-catalyst (NEt₃ in the present case) for optimal catalytic activity. Last and probably of most significance, the role of (unexpected) secondary interactions (C-H... π interactions) between *L*-LA and thiosquaramide *N*-substituents of **2a** and **3a**, appear crucial in the present systems for effective lactide activation and thus an efficient ROP process. Though this type of interactions is expected to be quite common in organo-catalysis,^[22] it has rarely been evidenced to play a key role in organo-catalyzed polymerizations.^[3] Such catalyst substituents/substrate interactions may also play a significant role in the catalytic performances of numerous other organo-/organometallic-catalyzed ROP of cyclic esters.^[23]

Experimental Section

All experiments were performed under nitrogen atmosphere using standard Schlenk techniques or in a MBraun Unilab glove box. Dichloromethane was first dried through a solvent purification system (MBraun SPS) and stored for at least a couple of days over activated molecular sieves (4 Å) in a glovebox before use. CD₂Cl₂

was purchased from Eurisotope (CEA, Saclay, France), degassed under a N₂ flow, and stored over activated molecular sieves (4 Å) in a glovebox before use. BnOH was dried for 24 h over activated molecular sieves (4 Å) before use. All other chemicals were purchased on Sigma-Aldrich and were used as received. NMR spectra were recorded on BrukerAC 300, or 600 MHz NMR spectrometers. Chemical shifts are given in ppm. Mass spectra were recorded at the Mass Spectrometry Department of the University of Strasbourg. Mass spectra were acquired by using a MALDI-TOF-TOF Autoflex II TOF-TOF (Bruker Daltonics, Bremen, Germany) equipped with a nitrogen laser (λ =337 nm). An external multipoint calibration was performed before each measurement with a standard peptide mixture and a standard protein mixture (which depended on the mass range analyzed). Scan accumulation and data processing were performed with FlexAnalysis 3.4 software. *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenyldiene]malononitrile (DTCB) and 2,5-dihydroxybenzoic acid (DHB) was used as matrix for the analysis of the PLLA samples. Size exclusion chromatography (SEC) analysis was performed by using a SEC system (with SEC columns temperature set at 30 °C) equipped with a Shimadzu RID10A refractometer detector using HPLC-grade THF as an eluent. For all GPC samples, 3 mg of the polymer sample was dissolved in 1 mL of THF and 25 μ L of the resulting solution was injected for analysis. Molecular weights and \bar{M}_w were calculated using polystyrene standards. The molecular weight number (M_n) values corrected with the appropriate correction factor (0.58 for PLA).

General procedure for ROP of *L*-LA mediated by **1a**–**4a**/**1b**–**4b** in the presence of BnOH

All polymerization experiments were prepared and performed under a nitrogen atmosphere in a glove box at room temperature. The appropriate amount of *L*-LA monomer (600 equiv. vs. catalyst, 6 mmol, 865 mg) and catalyst **1a**–**4a**/**1b**–**4b** (10 μ mol) were charged in a vial equipped with a Teflon screw-cap and dissolved in dichloromethane (5 mol L⁻¹, 1.2 mL). Then the appropriate amount of BnOH (2–30 equiv, 20 μ mol – 300 μ mol, 2–31 μ L) and NEt₃ (2–30 equiv., 20 μ mol–300 μ mol, 7–42 μ L) were added to the reaction mixture. The mixture was stirred for the appropriate time with the conversion being periodically monitored by ¹H NMR spectroscopy. An excess of methanol was added to quench the reaction mixture leading to polymer precipitation. The polymer was washed several times with methanol, dried under vacuum and analysed by using ¹H NMR spectroscopy, GPC analysis and MALDI-TOF mass spectrometry.

Supporting Information

Experimental procedures, all characterization data (NMR, GPC, MS data), DFT calculations details.

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Conflict of Interests

There are no conflicts to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

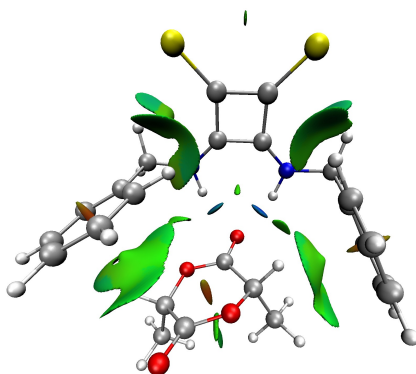
Keywords: Organocatalysis · polymerization · secondary interactions · thiosquaramide · squaramide

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RESEARCH ARTICLE

The use of thiosquaramides as polymerization catalysts is shown to be effective for the controlled ROP of lactide in the presence of an alcohol source and NEt_3 . Comparison of their catalytic performances with less acidic squaramides is also discussed. DFT-supported calculations on thiosquaramide-mediated lactide ROP catalysis suggest that secondary interactions between the thiosquaramide *N*-substituents and the incoming lactide (presently of type $\text{C-H}\cdots\pi$ -arene) are crucial for catalytic activity.



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1 – 10

First Use of Thiosquaramides as Polymerization Catalysts: Controlled ROP of Lactide Implicating Key Secondary Interactions for Optimal Performance

