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Ring Opening Polymerization of DL-Lactide Using A Supramolecular Sulfonamide – Tertiary Amine Organocatalytic System

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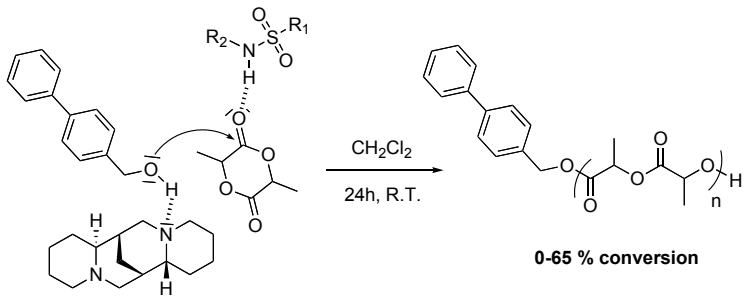
Graphical Abstract



Abstract: Sulfonamides are common ligands for organometallic catalysis in the Ring Opening Polymerization (ROP) of cyclic esters. In our quest for original Hydrogen-bonding catalytic systems, our goal was to use a sulfonamide derivative as an electrophilic activator of DL-lactide in partnership with a tertiary amine, as a nucleophilic activator of the initiator and growing polymer chain. Several sulfonamides were synthesized and tested in the ROP of DL-lactide. The impact of sulfonamide substituents was analyzed to better understand the H-bonds involved in the process.

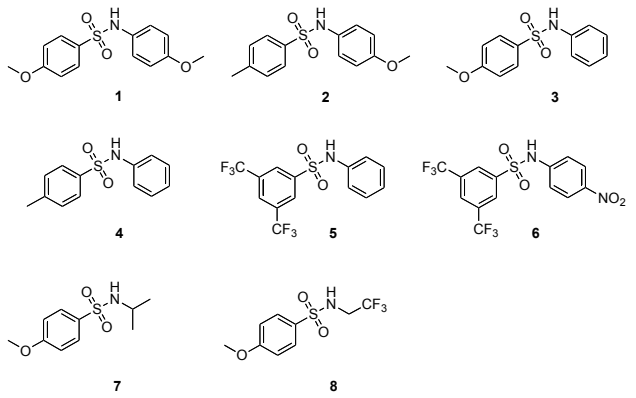
Keywords: *Sulfonamides, Sparteine, Ring Opening Polymerization, Lactide, Organocatalysis, Hydrogen bond*

1. Introduction

Organocatalyzed polymerization is a blossoming field of research.[1] It represents an elegant alternative to organometallic and enzymatic catalysis, as it allows, within 24 h, the preparation of polymers with controlled average molar masses, narrow dispersities, and without any metallic residues. Organocatalyzed polymerization was essentially developed for the ring-opening polymerization (ROP) of lactide, lactones, and carbonates.[2] From a mechanistic point of view, the organocatalysts promoted ROP by activating the reagents through temporary covalent bonds or weak interactions. The supramolecular strategies encompass the activation of the monomer (electrophile) using Brønsted acids[3], alcohols[4], (thio)amidoindoles[5], (thio)amido-benzimidazoles[5], or the activation of the growing polymer chain (nucleophile) using tertiary amines like (-)-sparteine, dimethylcyclohexylamine[6] or the dual activation of both monomer and chain end (thiourea derivatives[6,7]). In the continuation of our work on H-bonding catalysts (amides[5] and phenol[8] derivatives), we investigated herein new supramolecular architectures designed for the ROP of lactide. Along these lines, we anticipated that sulfonamides provided with suitable substituents could also activate lactide (enhanced electrophilicity) and thus trigger ring opening polymerization, in the presence of a second catalyst, devoted to activate the initiator and the growing chain. Recently, sulfonamides were employed as ligands within metallic complexes that catalyzed the ROP of lactide and ε–caprolactone.[9] In 2010, while our study was underway, Bourissou, Martin-Vaca *et al.* showed that bis-sulfonamides + DMAP were able to trigger the polymerization of DL-lactide.[10] They demonstrated that a H-bond probably occurred between the sulfonamide catalyst and the monomer. Percentages of conversion were high (≥ 95%) depending on reaction time and catalyst/initiator loadings. Polylactides were narrowly dispersed (Dispersity, $D \leq 1.10$) and the molar masses

were close to the theoretical ones, which indicated a living process. This work aims to evaluate the relevance of a H-bonding catalytic system, based on a mono-sulfonamide and a tertiary amine, towards the ROP of DL-lactide.

2. Results and discussion



Scheme 1: Structure of mono-sulfonamides **1**–**8**.

To estimate the impact of the substituents on H-bonding properties, sulfonamides were provided with donating and/or withdrawing groups (Scheme 1). Aromatic substituents on the amine group (compounds **1**–**6**) were also compared to aliphatic derivatives (series **7**–**8**). The synthesis of organocatalysts **1**–**8** was straightforward, through a condensation between the corresponding commercially available amines and sulfonyl chlorides, using a modified protocol[11] (see experimental section). The yields were excellent (82–98 % for catalysts **1**–**5** and **8**) except for aniline **6** (48 %), which was poorly activated towards nucleophilic addition, and compound **7** (43%), in which synthesis was not yet optimized.

As classically proposed for a supramolecular mechanism for ROP (see Graphical Abstract), the hydrogen bond donor catalyst creates an interaction with DL-lactide, on the oxygen atom of its carbonyl group. Therefore, the temporary connection increases the polarization of the C=O bond and facilitates the polymerization of the monomer. The action of the H-bond acceptor catalyst, such as a tertiary amine, is similar and directed towards the nucleophiles, *i.e.* the initiator and the growing polymer chain. In this study, commercially available (-)-sparteine (Sp) and dimethylcyclohexyl amine ($CyNMe_2$) were chosen as cocatalysts in partnership with sulfonamides **1**–**8**.

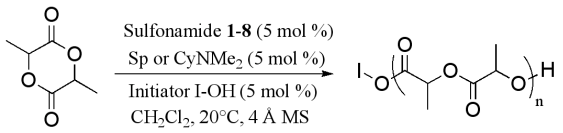
To demonstrate the existence of H-bonding between mono-sulfonamides and lactide, a titration monitored by ^{1}H NMR ($CDCl_3$) was achieved between compound **8** and DL-lactide (see experimental section). An association constant of 5 M^{-1} (1:1 stoichiometry) was determined. This low value is in the same range as those observed for other H-bonding catalysts employed in ROP of DL-lactide (2–27 M^{-1}), and thus, it does not preclude the catalytic properties of mono-sulfonamides.[5b]

As preliminary results, the role of each catalyst was evaluated. Under the usual ROP conditions (Table 1), any sulfonamide employed as the unique catalyst did not trigger polymerization (0% conv.). Besides, we already demonstrated that, in 24 h at 20 °C, Sp by itself allows 20% conversion whereas $CyNMe_2$ induces only 13% conversion, due to its loose interaction with the nucleophile.[8] Thus, the combination of donor and acceptor H-bonding catalysts should increase the monomer conversion, through a double targeted activation.

Organocatalyzed ROP of DL-lactide (1M) was conducted in dichloromethane at 20 °C, in 24 h, in the presence of the catalytic system sulfonamide–tertiary amine (Sp or $CyNMe_2$) at 5 mol % , biphenylmethanol (5 mol %) as the initiator and 4 Å molecular sieves (Table 1). The conversion of DL-lactide was generally low: 22-28% using $CyNMe_2$ + sulfonamides **1**–**8**, and 15-27 % using Sp + **1**–**5** or **7**. Notably, no conversion was observed in the presence of Sp + **6**, while the highest conversion was obtained with catalysts Sp + **8** (65%). The latter crude oligomers were characterized by ^{1}H NMR and Size Exclusion Chromatography (Molar masses Mn = 3000g.mol^{-1}, dispersity = 1.20).

A first hypothesis accounting for low conversion was the possible self-aggregation of the sulfonamide species in dichloromethane, at the concentration of 50 mM (experimental conditions of ROP). As a model, self-aggregation of compound **1** was determined through a titration monitored by ^{1}H NMR ($CDCl_3$) and the corresponding dimer association constant was 130 M^{-1}. This value is higher than the average binding constant between sulfonamide and the monomer (around 5 M^{-1}). By extrapolation, in these cases of 13-20% conversion of DL-lactide, we could speculate that the sulfonamide as a dimer cannot properly activate the monomer and thus oligomerization was limited to ~ 20–28% in the presence of the tertiary amine. This phenomenon could be specially observed when sulfonamides were provided with electron-donating aromatic or aliphatic substituents.

Table 1: Organocatalysed polymerization of DL-lactide using sulfonamide + tertiary amine catalysts.[a,b]



Sulfonamide	(-)-Sparteine % conv.	$CyNMe_2$ % conv.
none	20	13
1	26	23
2	27	24
3	21	23
4	24	24
5	15	26
6	0	22
7	22	24
8	65	28

[a] Conditions: DL-lactide 1M in CH_2Cl_2, 24h, 20°C, 5 mol % in catalytic system (sulfonamide: amine, 1/1), 4-biphenylmethanol (I-OH) as initiator (5 mol %). [b] Conversion was determined by ^{1}H NMR.

As a second hypothesis, sulfonamide and tertiary amine could interact more strongly together than with their expected partners, *i.e.* the monomer and the initiator / growing chain respectively. Thus, their catalytic activity would be moderate. As an example, compounds **5** and **6** having an electron-withdrawing group, allowed the lowest conversion of monomer in presence of the better activator, Sp (15% and 0%, respectively), probable due to increased H-bondings between the catalysts. To support this idea, a complementary titration was undertaken between sulfonamide **8** and Sp, and the latter compounds appeared to be interacting with an association constant of 147 M^{-1}. This value is far larger than the average binding constant between the sulfonamide and the monomer. Knowing that sulfonamide **8** allowed the highest conversion in presence of Sp, it could be predicted that H-bonding between the other sulfonamides and Sp could be stronger, precluding the expected H-bonding abilities of the whole system. Indeed, the undesired H-bonds were present in the global equilibrium, then decreasing the progress of the polymerization reaction, especially with sulfonamides having efficient electron-withdrawing aromatic groups.

However, in contrast to the other H-bond donors, sulfonamide **8** was designed with an electron-donating group (aromatic) and a moderate electron-withdrawing group (CH_2CF_3). So the partial charge on its hydrogen atom was tuned to properly interact with DL-lactide, allowing a conversion of 65%, in the presence of Sp. Indeed, desired interactions between catalysts and reactants could be promoted, specifically by tuning the H-bond donating properties of sulfonamides, as shown with the catalytic couple sulfonamide **8** + Sp.

3. Conclusion

A new dual catalytic system composed of a mono-sulfonamide (**1**–**8**) and a tertiary amine (Sp or $CyNMe_2$) was tested towards the ring opening polymerization of DL-lactide, under classical conditions. Along the study, the electronic impact of the sulfonamide substituents upon the catalytic properties was evaluated. The best conversion after 24 h (65 %) was observed with the catalytic couple sulfonamide **8** + Sp. Concerning the other systems, it has been demonstrated through titrations monitored by ^{1}H NMR that H-bondings between the catalysts existed and that sulfonamide could self-aggregate. Thus the sulfonamide group had a great propensity for multiple H-bonding, which prevents the possibility of controlling the desired activation of the monomer, within a reaction mixture of several H-bond partners. To improve the catalytic properties of sulfonamide + tertiary amine system in ROP, efforts should be directed towards tuning the H-bond donating properties of sulfonamide, by for example using suitable aliphatic substituents.

4. Experimental Section

Procedure for the synthesis of sulfonamides 1-8 [11]: A solution of freshly distilled aniline derivative (1 mmol) and sulfonyl chloride (1.5 mmol) in pyridine (2 mL) was stirred for 72 h at room temperature under nitrogen. A HCl solution (5 mL, 2N) was added dropwise and then ethyl acetate (15 mL). The organic phase was washed with a saturated solution of NaCl (3x20 mL), dried over Na_2SO_4, filtrated and then concentrated in vacuum.

Procedure for the ring opening polymerization of DL-lactide: Under nitrogen, in a dry Schlenk tube, dry dichloromethane (0.5 mL) was successively introduced, DL-lactide (1 mmol), sulfonamide catalyst **1**–**8** (5 mol %), the amine cocatalyst (5 mol %), 4-biphenylmethanol (5 mol %), and 4 Å molecular sieves (5 beads). The reaction mixture was stirred at 20 °C under nitrogen for 24 h. The reaction mixture was filtered and concentrated in a vacuum. Conversion was determined by ^{1}H NMR, integrating the signals of the methylene proton (adjacent to the carbonyl group) in both the residual lactide and the polymer.

Procedure for titrations monitored by ^{1}H NMR: Deuterated solutions were freshly prepared and dried in

the presence of 4 Å molecular sieves. Association constants between host and guest as well as dimerization binding constants were determined using titrations monitored by ^{1}H NMR (host signals) in $CDCl_3$. A solution (100 µL) of host (~20 mM) was introduced in each NMR tube (12 to 15 experiments per titration). Increasing aliquots of guest stock solution (~ 70 mM) were added and the total volume (500 µL) was adjusted with $CDCl_3$. The titration data (Δδ ppm *versus* guest concentration) were fitted using the nonlinear curve-fitting procedure with a (1:1) binding equation using WinEqNMRprogram.[12] Concerning K_{dimer} evaluation, a stock solution of host (~ 30 mM) in $CDCl_3$ was used to prepared the diluted NMR tubes (12 to 15) required for each titration. The titration data (Δδ ppm *versus* host concentration) were fitted with a dimerization model using Excel.[13]

N-(4-methoxyphenyl)-4-methoxybenzenesulfonamide **1**. Yield: 84%. ^{1}H NMR ($CDCl_3$, 300 MHz) : δ (ppm) = 7.62 (d, J = 9 Hz, 2H); 6.96 (d, J = 9 Hz, 2H); 6.88 (d, J = 9 Hz, 2H); 6.76 (d, J = 9 Hz, 2H); 6.38 (sl, 1H); 3.83 (s, 3H); 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 55.6; 56.5; 113.4; 126.7; 127.2; 133.6; 157.5; 163.8.

N-(4-methoxyphenyl)-4-methylbenzenesulfonamide **2**. Yield: 94%. ^{1}H NMR (DMSO, 300 MHz): δ (ppm) = 10.06 (s, 1H); 7.77 (d, J = 8.1 Hz, 2H); 7.53 (d, J = 7.9 Hz, 2H); 7.18 (d, J = 8.7 Hz, 2H); 7.0 (d, J = 8.7 Hz, 2H); 3.87 (s, 3H); 2.72 (s, 3H). ^{13}C NMR (DMSO, 75 MHz): δ (ppm) = 18.9; 53.1; 112.2; 121.3; 124.7; 127.6; 128.2; 134.6; 140.9; 154.4.

N-Phenyl-4-methoxybenzenesulfonamide **3**. Yield: 93%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.70 (d, J = 8.9 Hz, 2H); 7.14 (m, 5H); 6.88 (d, J = 8.9 Hz, 2H); 6.62 (sl,1H); 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 56.2; 114.7; 121.4; 124.7; 129.9; 132.5; 138.6; 163.8.

N-Phenyl-4-methylbenzenesulfonamide **4**. Yield: 90%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.01 (s, 1H); 7.72 (d, J = 7.9 Hz, 2H); 7.24 (m, 5H); 7.12 (d, J = 7.9 Hz, 2H); 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 21.4; 121.2; 124.8; 127.1; 129.5; 136.2; 136.3; 136.9; 143.5.

N-Phenyl-3,5-bis(trifluoromethyl)benzenesulfonamide **5**. Yield: 98%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.14 (sl, 2H); 8.02 (s, 1H); 7.28 (m, 5H); 6.79 (sl, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 122.9; 126.6; 127.5; 129.8; 132.5; 138.9; 141.5.

N-4-nitrophenyl-3,5-bis(trifluoromethyl)benzenesulfonamide **6**. Yield: 48%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.28 (dd, J_1 = 2.1 Hz, J_2 = 6.9 Hz, 2H); 8.06 (dd, J_1 = 2.2 Hz, J_2 = 6.9 Hz, 2H); 8.30 (s, 2H); 8.42 (s, 1H); 11.3 (sl, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 115.4; 117.8; 124.3; 125.7; 129.6; 134.6; 140.2; 152.5.

N-isopropyl-4-methoxybenzenesulfonamide **7**. Yield: 43%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.92 (sl, 1H); 7.78 (d, J = 6.9 Hz, 2H); 7.06 (d, J = 7.0 Hz, 2H); 4.03 (s, 3H); 3.87 (m, 1H); 1.87 (d, J = 6.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 25.2; 51.3; 58.6; 116.5; 129.4; 139.2; 160.3.

N-(2,2,2-trifluoroethyl)-4-methoxybenzenesulfonamide **8**. Yield: 82%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.12 (sl, 1H); 7.83 (d, J = 7.5 Hz, 2H); 7.15 (d, J = 7.3 Hz, 2H); 4.16 (s, 3H); 3.85 (q, J = 9.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 57.2; 65.4; 118.3; 127.6; 132.7; 139.5; 165.7.

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