

Ring-Opening Polymerization of L-Lactide Efficiently Triggered by an Amido-Indole. X-ray Structure of a Complex between L-Lactide and the Hydrogen-Bonding Organocatalyst

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Organocatalyzed polymerization has gained much interest in the past few years.¹ Among the variety of catalysts, hydrogen-bonding structures such as thioureas² have proved to be efficient in the Ring-Opening Polymerization (ROP) of lactide.³ Remarkably, the resulting polymers display predictable average molar masses and narrow dispersity. This controlled process was proposed to be activated by a supramolecular mechanism which involves appropriate hydrogen bonds between the catalysts and the reactive components (initiator, monomer, and growing chain).

Our expertise in the field of H-bonding receptors⁴ prompted us to investigate new H-bonding architectures designed for the ROP of lactide. In these lines, we anticipated that amides provided with suitable electron-withdrawing groups can also activate the electrophilicity of the lactide and thus trigger the ring opening in the presence of weak nucleophilic species (initiator and growing chain). A series of *N*-(3,5-bis(trifluoromethyl)phenyl) amides **1a–e**, prepared *via* an expeditious route, were tested to evaluate the effects of the substituents upon their H-donor properties and their catalytic activity (Scheme 1).

Aromatic derivatives **1a–c** were selected to compare the electronic effects of the phenyl moiety upon the reaction. Compounds **1d–e** were tested to gain information on the activity of more extended aromatic derivatives together with the influence of a second H-bond donor site. Polymerizations were conducted in dichloromethane at 20 °C, at different reaction times, in the presence of (–)-Sparteine **2**, as a second catalyst to activate the initiator and the growing chain through H-bonding (Table 1). This tertiary amine is known as the most efficient H-bond acceptor in the ROP reaction^{3b} and gave the most satisfying results in our hands. Along this study, L-lactide was chosen as the monomer because it allows preparation of isotactic polymers, provided that no transesterification reactions occur.

The electron-deficient aromatic **1c** (54% conv.) allowed a higher conversion than the related nonsubstituted one **1b** (34% conv.) and the electron-richer derivative **1a** (22% conv.), probably due to the reinforcement of H-bonding between the catalyst and the monomer. The indene catalyst **1d** (34% conv.) is as efficient as compound **1b** (34% conv.). These results demonstrated for the first time that organocatalyzed ROP of L-lactide can be achieved by activated amides. Notably, the activating power of *N*-(3,5-bis(trifluoromethyl)phenyl)-1*H*-indole-2-carboxamide **1e** (100% conv. in 2 h) appeared to be at least equivalent to those of the thiourea

Scheme 1. Activated Amides **1** and (–)-Sparteine **2** as ROP Cocatalysts

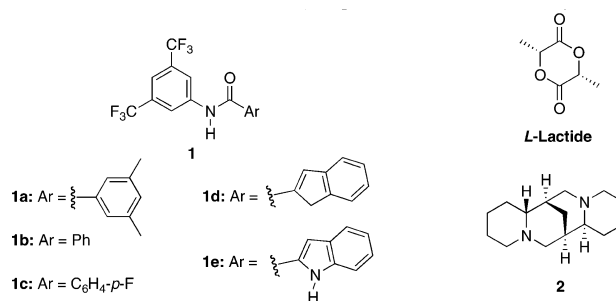


Table 1. Catalytic Properties of Amides **1** in the ROP of L-Lactide^a

catalyst	1a	1b	1c	1d	1e
reaction time	24 h	24 h	24 h	24 h	2 h
% conv. ^b	22	34	54	34	100

^a Reaction conditions: lactide 0.7 M in dichloromethane at 20 °C, catalysts **1** and **2** (5% mol), 4-biphenylmethanol as an initiator (5% mol), and 4 Å molecular sieves. ^b Determined by ¹H NMR.

derivatives,^{3b} the latter being checked under our experimental conditions (95–100% in 2 h).

SEC analysis of the poly(L-lactide) generated by the tandem **1e** + **2** catalysts (5% mol each) in the presence of 4-biphenylmethanol as initiator (5% mol) indicated the formation of a polymer with a biphenylmethoxy head and with a number average mass ($M_{n, SEC} = 3460$ g/mol) in close agreement with the theoretical one ($M_n = 3064$ g/mol, DP = 20 at 100% conv.) and a very narrow dispersity (PDI = 1.08), as expected for a controlled polymerization process. Indeed, along the reaction, M_n of the polymer increases in direct proportion with the monomer conversion, while the dispersity stands close to 1 (see Supporting Information (SI)). Finally, ¹³C NMR analysis of the poly(L-lactide), in the stereosensitive methine carbon region (69–70 ppm), only indicates the presence of a mmm tetrad corresponding to a fully isotactic structure. These experimental observations corroborate the controlled character of the ROP triggered by the new H-bonding catalyst **1e**.

To better understand the H-bonding properties of **1e**, semiempirical molecular modeling was performed on **1e** as well as mixtures of **1e** and L-lactide (see SI). AM1 experiments showed that **1e** can display two different H-bonding forms. At first, it can exhibit an extended conformation with both NH groups directed in opposite directions, on both sides of the (O=C)–C_{Ar} bond. Thus a single molecule of **1e** can interact with L-lactide, through a single H-bond

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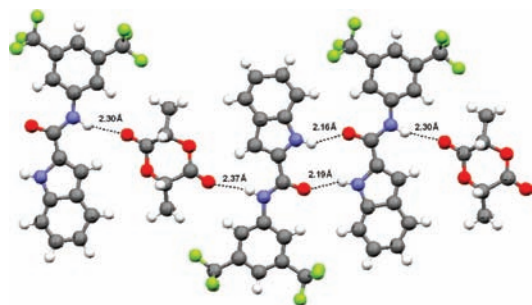


Figure 1. Molecular packing of **1e** and L-lactide, showing the H-bond distances in one layer. Oxygen atoms are represented in red, nitrogen in blue, and fluorine in green.

between its amide NH group and the carbonyl of an L-lactide. Second, in this extended conformation, **1e** can form a H-bonded dimer (**1e**)₂ through the complementary oxo-indole moieties. Then, (**1e**)₂ exhibits two identical H-bonds between its available NH amide groups and the carbonyl group of two L-lactides, as seen for a single **1e**. Third, compound **1e** can adopt a pinched conformation and could interact with L-lactide through a double H-bond. From these calculations, H-bond distances and angles are similar in both conformations of **1e**.

Single crystals of a complex between **1e** and L-lactide suitable for X-ray analysis have been obtained from a chloroform solution subjected to slow pentane vapor diffusion.⁵ For the first time, interactions between these two species are directly highlighted (Figure 1). The crystals belong to the space group *P1* (*Z* = 1) with six independent molecules of **1e** and three of L-lactide, in the asymmetric unit. In the crystal, the molecules are packed in layers (interlayer separation: *ca.* 3.2 Å).

Molecules **1e** are arranged in head-to-tail dimers where the N–H of the indole moiety is tightly H-bonded⁶ with the carbonyl group of the amide linker. These H-bonds are not identical and vary from 2.11 to 2.19 Å. The N–H of the amide in the linker is H-bonded to the C=O of the L-lactide (length ranging from 2.22 to 2.45 Å). H-bond angles are *ca.* 150°–155° in the dimer and *ca.* 150°–162° between the amide donor and the carbonyl group of L-lactide, as usually found in the literature.⁶

Inspection of the molecular packing underlines that, within (**1e**)₂, each molecule **1e** forms a H-bonded complex with one L-lactide. Nevertheless, no pincher conformation involving the participation of the two N–H of **1e** is observed in the solid. Although, this X-ray structure has not been considered as a snapshot of the supramolecular scaffold triggering the polymerization process, it however strongly demonstrates the propensity of the amido-indole to dimerize and the participation of the N–H of the amide group in interacting with the L-lactide in a H-bonded complex.

Remarkable properties of **1e** were further investigated in solution. Self-aggregation of **1e** (0.8–29 mM) was monitored by NMR. Only the chemical shifts of the NH group of the indole moiety are concentration dependent in CDCl₃. This result proved the formation of the H-bonded oxo-indole dimer (**1e**)₂ in solution with a self-association constant of 4 M⁻¹. Then, under the condition of polymerization, only *ca.* 20% of **1e** is self-associated. An NMR titration between **1e** (4.3 mM) and the L-lactide showed that these

(host/guest) partners are weakly associated in a 1:1 ratio (*K*_a = 5 M⁻¹ in CDCl₃). This observation supports the activation of L-lactide by a molecule of catalyst. According to the ¹H NMR spectra, the NH group of the amide is mainly affected ($\Delta\delta = +0.74$ ppm) by the formation of the complex with the L-lactide, while the NH of the indole participates in the complexation to a lesser extent ($\Delta\delta = +0.21$ ppm). This observation corroborates the hypothesis that, in solution, the H-bonding activation mainly occurs between the carbonyl group of the monomer and the amide group of **1e**. In a dynamic equilibrium, **1e** probably exists in its extended and pinched conformations which both activate the monomer. Taking into account these data, it is assumed that, under the conditions of polymerization, **1e** (35 mM) displays two different H-bonding donors, available for catalysis: an amide (extended **1e**, alone or as a minor dimeric form) and an amido-indole (pinched **1e**) species. Investigations are currently in progress to establish the degree of involvement of the dimeric species in this activation.

In summary, the new hydrogen-bonding amide **1e** is demonstrated to be an efficient organocatalyst for the ROP of L-lactide into poly(L-lactides) with controlled dispersity and molecular weight. It is assumed that the exceptional reactivity of amido-indole **1e** rests on its ability to display a preferential NH bond between its amide group and the L-lactide and an additional H-bonding activation *via* a pincher form. These studies have also shown that the already known thiocarbonyl-based thiourea organocatalyst is not unique. Additionally, **1e** has allowed for the first time the direct observation and characterization of a 1:1 complex between a catalyst and an ROP monomer. Also, the magnitude of the 1:1 interaction between the catalyst and the monomer has been revealed and measured in the reaction solvent.

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Supporting Information Available: Crystallographic data, molecular modeling, characterization of polymers and complexes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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