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(Thio)Amidoindoles and (Thio)Amidobenzimidazoles: An Investigation of Their Hydrogen-Bonding and Organocatalytic Properties in the Ring-Opening Polymerization of Lactide

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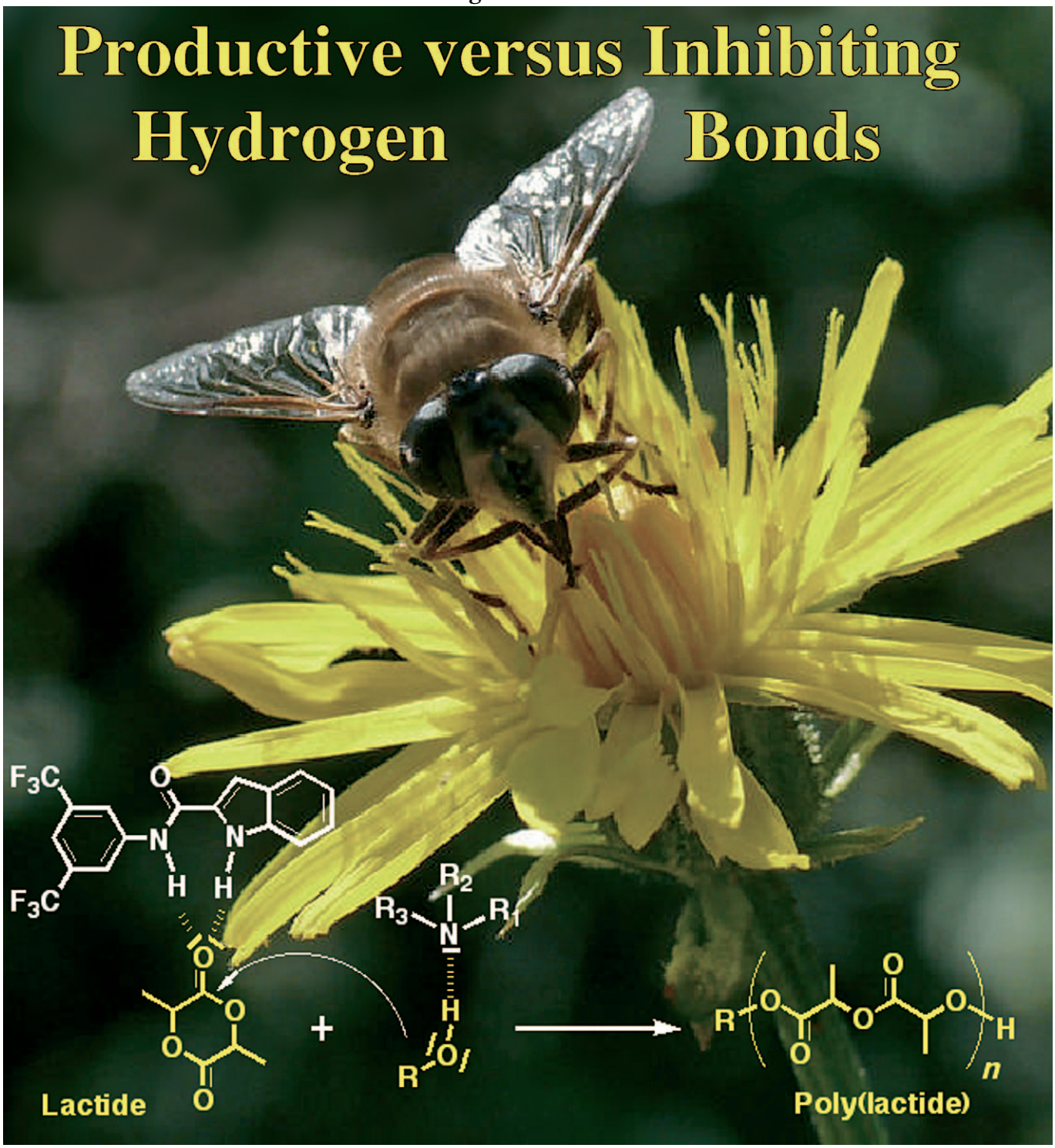

Abstract: The mechanism of the ring-opening polymerization (ROP) of lactide catalyzed by two partner hydrogen-bonding organocatalysts was explored. New amidoindoles **4a**,**c**, thioamidoindoles **4b**,**d**, amidobenzimidazoles **5a**,**c**, and thioamidobenzimidazoles **5b**,**c** were synthesized and used as activators of the monomer. In the solid state and in solution, compounds **4** and **5** showed a propensity for self-association, which was evaluated. (Thio)-Amides **4** and **5** do catalyze the ROP of lactide in the presence of a cocatalyst, tertiary amine **3a** or **3b**, which activates the growing polymer chain through hydrogen-bonding. Reactions were conducted in 2–24 h at 20 °C; conversion yields ranged between 22 and 100 %. A detailed study of the intermolecular interactions undertaken between the participating species showed that, as expected, simultaneous weak hydrogen bonds do exist to activate the reagents. Moreover, interactions have been revealed between the partner catalysts **4/5**+**3**. ROP catalyzed by these partner activators is thus governed by multiple dynamic equilibria. The latter should be judiciously adjusted to fine-tune the catalytic properties of (thio)-amides and organocatalysts, more generally.

Keywords: hydrogen bonds · lactides · organocatalysis · partner catalysts · ring-opening polymerization

Introduction

Organocatalyzed polymerization is an emerging field of research.[1] It represents an elegant alternative to organometallic and enzymatic catalyses, 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 cyclic esters, diesters, and carbonates.[2] From a mechanistic point of view, it has been demonstrated that these ROPs can be promoted by organocatalysts by means of the activation of the reagents through temporary covalent bonds or weak interactions. The strategies encompass the activation of the monomer, that is, the electrophile (using Brønsted acids,[3] alcohols,[4] 4-dimethylaminopyridine (DMAP) derivatives,[5] phosphines,[6] N-heterocyclic carbenes[7]); the activation of the growing polymer chain, that is, the nucleophile (using basic phosphazenes,[8] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)[9]); or the dual activation of both monomer and chain end (thiourea derivatives[10] and 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)[11]). Among the organocatalysts, thioureas[12] have shown promising results in the access of polymers with controlled molar masses, operating under mild conditions (20 °C, loading of catalyst below 10 mol %). This remarkable catalytic activity relies on their ability to promote hydrogen bonds with the monomer and thus the smooth increase of its electrophilicity. Additionally, a hydrogen-bond-acceptor cocatalyst partner, generally a tertiary amine, is required to increase the nucleophilicity of the initiator and the growing polymer chain. These catalytic systems can be a unique compound such as Takemoto's catalyst **1**,[13] or two independent molecules such as thiourea **2**+ amine **3** (Scheme 1). Under drastic anhydrous conditions, at 20 °C for over 24 h, catalyst **1** (5 mol % in dichloromethane, 5 mol % of initiator) allows 97 % conversion of lactide into a poly(lactide) with a narrow dispersity and controlled molar masses, as the experimental degree of polymerization (DP) matches with the theoretical one (moles of monomer polymerized/moles of initiator). The ROP of lactide was also efficient over 24 h in the presence of thiourea **2** and cocatalyst dimethylcyclohexylamine (Me_2NCy) **3a** or (−)-sparteine (Sp) **3b** (Scheme 1). Notably, due to the better hydrogen-bonding properties of **3b** versus **3a**, the combination of **2**+**3b** allowed a complete polymerization reaction within 2 h, whereas the time of the reaction in the presence of the partners **2**+**3a** was 24 h.

A remaining drawback of previously reported procedures is that satisfying conversion requires extensive and tedious preparation of dry reagents and performing the reactions in a glove box.

Therefore, new hydrogen-bonding organocatalysts are highly desirable, especially versatile ones. They should be available through a rapid synthesis and should be efficient at room temperature under relaxed and less energy-consuming conditions. Our interest in supramolecular chemistry[14] prompted us to design hydrogen-bonding catalysts for the ROP of lactide. In this context, amides, which are modular compounds with easy synthetic access, were anticipated to be polymerization promoters through hydrogen-bonding. We recently showed that, in the presence of (−)-sparteine, an activated amidoindole **4a** is an efficient organocatalyst.[15] We demonstrated that both NH groups from the amide and the indole moieties participate in the hydrogen-bonding of

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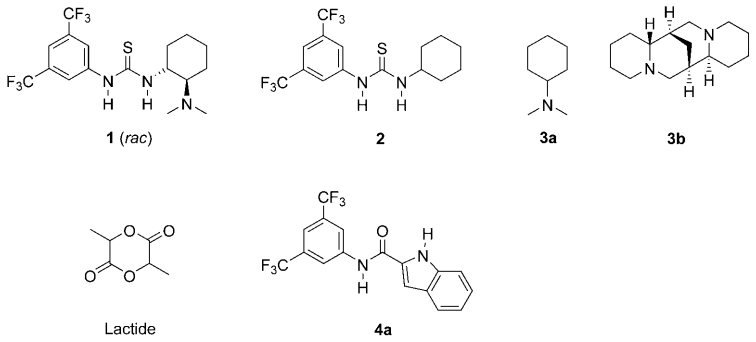
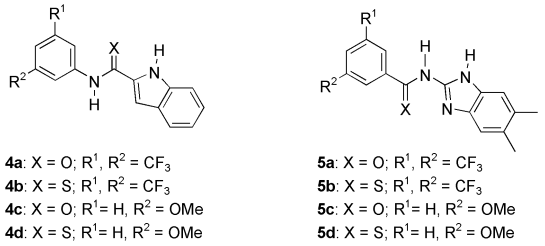


Scheme 1. Molecular structures of thioureas **1** and **2**, tertiary amines **3a**,**b** and amide **4a** as hydrogen-bonding organocatalysts for ring-opening polymerization of lactide.

lactide, thus allowing its total conversion in 2 h. Moreover, an X-ray structure of a hydrogen-bonded complex between a ROP organocatalyst and the monomer was reported for the first time. To deepen and broaden our investigation, we decided to explore the behavior of two series of amides and related thioamides that bear an indole (compounds **4**) or a benzimidazole group (compounds **5**), as a second hydrogen-bond donor (Scheme 2).



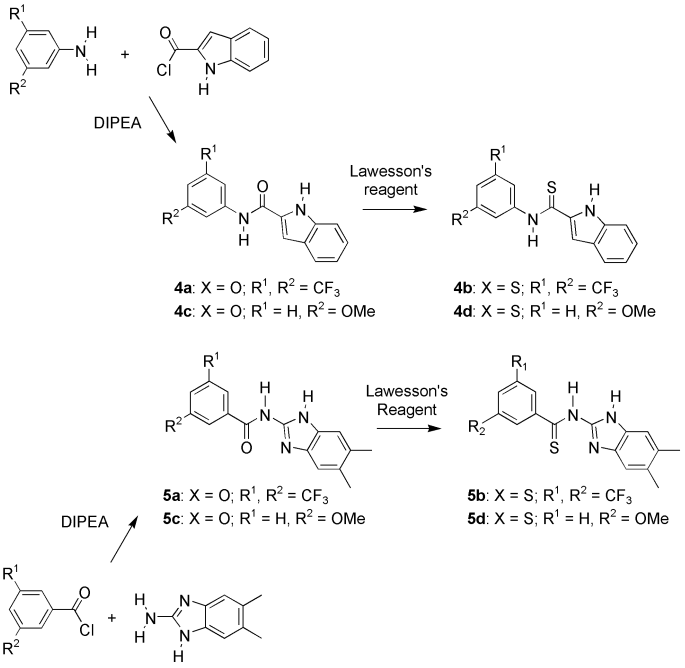
Scheme 2. Molecular structures of hydrogen-bonding organocatalysts **4** and **5**.

In compounds **4a–d** and **5a–d**, the global geometry of the hydrogen-bond donor subunits is different and may have an impact upon the catalytic properties. Besides, the strength of the hydrogen-donor properties of the NH−C=X group could also be modulated by two factors: 1) the nature of the X atom, oxygen (amide function), or sulfur (thioamide function); 2) the electronic density on the phenyl group, from electron-deficient derivatives (**4a**,**b** and **5a**,**b**) to electron-rich compounds (**4c**,**d** and **5c**,**d**). Classically, thioamides are better hydrogen-bond donors and less subject to self-aggregation. Electron-deficient substituents should increase the hydrogen-bond donor properties of the corresponding compounds. Finally, the effect of the cocatalyst in these ROPs will also be evaluated using two tertiary amines **3a** or **3b**, as hydrogen-bond acceptors of a different strength.[9b]

The possible disadvantage of this approach is the potential formation of hydrogen bonds between the partner activators, that is, **4** or **5** with **3**, which could hamper the reaction efficiency. Consequently, a detailed supramolecular mechanism of ROP involving partner organocatalysts will be explored. Herein, we report the synthesis and the in-depth catalytic properties of new hydrogen-bonding organocatalysts for the polymerization of lactide, in connection with their aggregative properties.

Results and Discussion

Synthesis of the catalysts: the straightforward preparation of new compounds **4** and **5** was achieved in one or two steps from commercial reagents (Scheme 3).

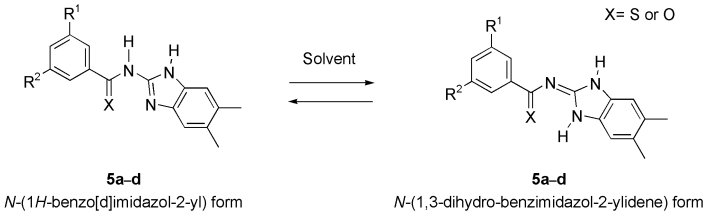


Scheme 3. Straightforward synthesis of (thio)amides **4** and **5**. DIPEA = diisopropylethylamine.

In detail, amidoindoles **4a** and **4c** were obtained by condensation of the aniline derivatives on the corresponding acid chloride (freshly prepared), in 90 and 73% yield, respectively.[16] A similar procedure[17] was achieved to synthesize amidobenzimidazoles **5a** and **5c** in 45 and 73% yield, respectively, from the benzoyl chloride derivatives and 2-amino-5,6-dimethyl-benzimidazole.[18] Thioamido-related compounds were obtained by thionation of the oxo compounds using Lawesson's reagent in toluene heated at reflux.[19] Molecules **4b** and **4d** were isolated in 78 and 81% yield, respectively. Compounds **5b** and **5d** were also obtained in excellent yields: 97 and 93%, respectively.

Interestingly, based upon ^{1}H NMR spectra in [D$_6$]DMSO and CDCl$_3$, (thio)amidobenzimidazoles **5a–d** appeared to be in equilibrium between the classical *N*-(1*H*-benzo[*d*]imidazol-2-yl) structure and its *N*-(1,3-dihydro-benzimidazol-2-

ylidene) tautomer (Scheme 4). For instance, all compounds **5** displayed similar ^{1}H NMR spectra ([D$_6$]DMSO, 4 mM): the two NH groups appeared as a broad signal at $\delta = 12.1$–12.5 ppm for amides **5a**,**b** or $\delta = 13.4$–13.5 ppm for thioamides **5b–d** (see the Supporting Information). In our analyses, spectroscopic data did not allow for the discrimination between the two forms. As previously reported,[20] this tautomeric equilibrium may be favored by hydrogen bonding between (thio)amidobenzimidazoles **5** or between **5** and the solvent.



Scheme 4. The tautomeric equilibrium of compound **5**.

Concerning hydrogen-bonding properties, this tautomeric equilibrium is anticipated to influence the catalytic properties of the series **5a–d** in ROP reactions, as the solvent of choice for these polymerizations is dichloromethane.

All catalysts were found to be fairly soluble in dichloromethane. In the presence of lactide, this solubility was increased, which allows one to undertake reactions under classical conditions (20 °C, 5 mol % with respect to monomer, that is, 35 mM). This behavior is probably due to specific intermolecular interactions between the hydrogen-bonding catalysts and lactide as a hydrogen-bond acceptor. This is clearly supported by the weak interactions between reagents and catalysts (see below), unrevealed so far.

X-ray diffraction: Single crystals of compounds **4a**, **4c**, **5c**, and **5d** were grown in dichloromethane and/or chloroform subjected to slow pentane vapor diffusion. To the best of our knowledge, very few crystallographic descriptions of amidoindole,[21] thioamidoindole,[22] and amidobenzimidazole[23] have been reported. Notably, the first structure of a thioamidobenzimidazole (**5d**) is described herein. Interestingly, in the crystal, the tautomeric *N*-(1*H*-benzo[*d*]imidazol-2(3*H*)-ylidene)benzothioamide) form is observed. All molecules adopt centrosymmetric monoclinic space groups. The crystal lattice is stabilized by strong intermolecular hydrogen bonds as usually encountered for amides[24] and thioamides.[25] The experimental hydrogen-bond geometries (lengths, angles) are in the range of those usually found in literature.[24d]

The crystal of **4a** belongs to the space group $P2_1/a$ in which the molecules are packed in layers. The layers are separated by a distance of approximately 2.9 Å, which corresponds to F···F interactions between the CF_3 substituents situated at the extremities of the layers. In the layers, the two aromatic parts of the molecules are non-coplanar (angle between the two aromatic parts: 16.7(3)°). Compounds **4a** form centrosymmetric dimers (Figure 1), internally tied with symmetrical hydrogen bonds between the carbonyl group (acceptor) and the H–N of the indole (donor) moiety (distance (d) of N–H····O=C = 2.35 Å). Interestingly, the N–H of the amide spacer is not involved in the dimer but it is linked through a hydrogen bond to the carbonyl group of another dimer ($d = 2.41$ Å) that lies in a quasi-parallel plane (interdimer plane distance ≈ 3.4 Å). A herringbone packing is formed in the solid with an angle of 87° between the planes of the dimers (see the Supporting Information).

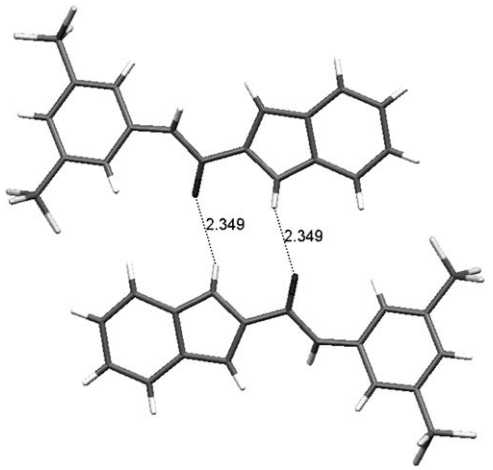


Figure 1. Hydrogen-bonded dimer of compounds **4a** in the crystal.

Compound **4c** crystallizes in the monoclinic space group $P2_1/n$ (Figure 2). In the solid, the molecules are not totally flat (angle equal to 15.9(1)° between the two aromatic parts). They are packed in quasi-coplanar dimers in which the molecules are linked by two strong symmetrical hydrogen bonds that involve the N–H (donor) of the indole moiety and the carbonyl group acceptor (d(N–H····O=C) = 2.04 Å). Here again, the N–H of the amide spacer does not

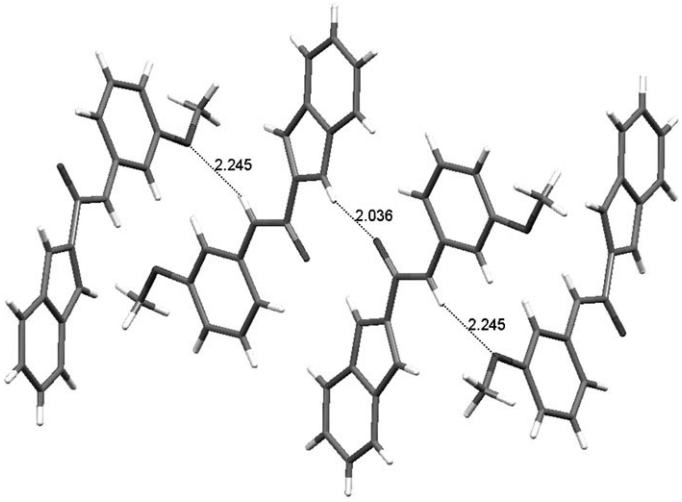


Figure 2. Hydrogen-bonded packing of compounds **4c** in the crystal.

participate in the cohesion of the centrosymmetric dimer; it interacts with the oxygen of the methoxy group of the neighboring dimer (d(N−H····O−CH_3) = 2.24 Å). These dimers are stacked in a herringbone mode and form an angle of 70°.

Amidobenzimidazole **5c** crystallizes in the monoclinic space group $P2_1/a$ (Figure 3). The asymmetric unit includes two independent molecules of **5c** and one disordered molecule of solvent on a site partially occupied by molecules of chloroform (80%) and dichloromethane (20%). In this asymmetric unit, both independent molecules are not flat, as the two aromatic parts of the molecules form an angle of 36.2(1) and 42.7(1)° for the two molecules, respectively. Of note, the amide link is situated in the benzimidazole plane. These two independent molecules are not in the same plane and displayed an average twisted angle of 27° (taking benzimidazole carbons plus C=O to build each average plane). These two compounds are associated by hydrogen bonds that involve only the N−H of the amide spacer and the nitrogen lone pair of the benzimidazole moiety (d = 2.03 and 2.08 Å, respectively). The carbonyl groups are symmetrically hydrogen-bonded with the N−H of benzimidazole group that belongs to another asymmetric unit (d = 2.21 and 2.22 Å), as indicated in Figure 3. Finally, these hydrogen-bonded molecules form infinite ribbons in the crystals in which the C=O and N−H groups are all involved.

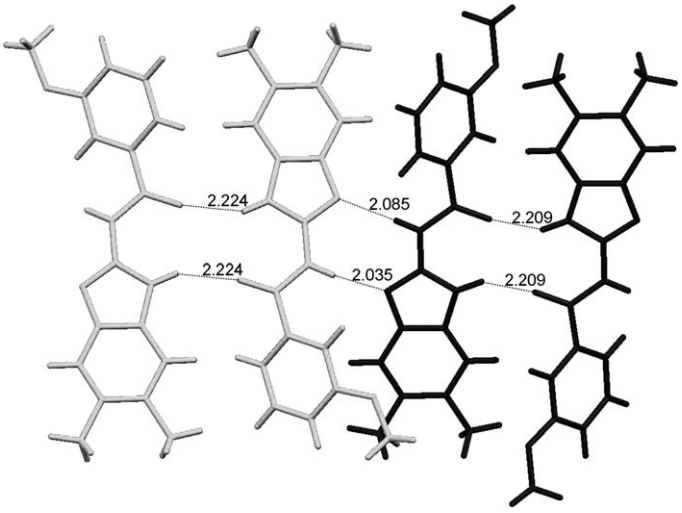


Figure 3. Hydrogen-bond packing of compounds **5c** in the crystal.

The crystal of **5d** belongs to the centrosymmetric monoclinic space group $C2/c$ (Figure 4). In the crystal, this thioamidobenzimidazole exhibits the tautomeric *N*-(1*H*-benzo[*d*]imidazol-2(3*H*)-ylidene) form, in which the two nitrogen atoms of the benzimidazole hold a hydrogen atom. In the molecular structure, the five-atom ring of the benzimidazole is symmetrical, as shown by the bond lengths (see the Supporting Information), and the N−C bond, which links the benzimidazole moiety and the (thio)amide, is shortened compared with that of **5c** (1.369(4) and 1.380(4) Å in **5c** and 1.346(3) Å in **5d**, respectively). Within **5d**, the thiobenzimidazole moiety forms an angle of 38.6(1)° with the anisyl ring. The molecules are organized in centrosymmetric dimers that involve one of the N−H units of the imidazole ring and the nitrogen of the spacer (d(N−H···N) = 1.97 Å), whereas the other N−H and the C=S thiocarbonyl group are not implicated in such directional hydrogen bonds. Several short contacts also participate in the cohesion of the solid (see the Supporting Information).

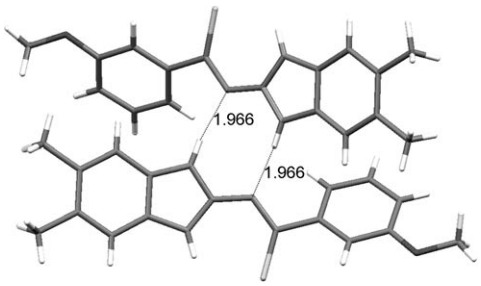


Figure 4. Hydrogen-bonded dimer of compound **5d** in the crystal.

Inspection of the molecular packing of these new (thio)amides shows that the latter could be classed in two categories (Table 1). Concerning **4a** and **4c**, the centrosymmetric hydrogen-bonded dimers only involve the C=O and the N−H of the indole moiety, whereas the N−H of the linker (amide) is not directly implicated. In **5c** and **5d** crystals, the N−H of the amide spacer is strongly involved in the dimer (or ribbonlike) cohesion. Additionally, **5d** presents an imine tautomeric form in the dimer. Finally, if these dimeric forms also exist in solution (see above), in **4a** and **4c** the amido N−H can be available for extra hydrogen-bonded linkage such as the one necessary for the activation of the lactide. In contrast, hydrogen-bond donors in **5c** and **5d** are embedded within the aggregates and should not be as available as those present in **4a** and **4c**. This would rationalize the experimental data presented hereafter: the relative catalytic efficiency of the compounds and/or the preferential molecular conformations experienced in solution.

Table 1. Hydrogen bond lengths [Å] and angles [°] in monocrystals **4a**, **4c**, **5c**, and **5d**.

	$N-H_{amide}\cdots O=C$	$N-H_{arom}\cdots O=C$	Other hydrogen bonds	∢D−H···A[a]
4a	2.41	2.35	–	143.9, 147.6
4c	–	2.04	2.24 ($NH_{amide}\cdots$OMe)	161.4, 161.4
5c	–	2.22, 2.21	2.03, 2.08 ($N-H_{arom}\cdots N$)	149.9, 139.9, 158.9, 151.8
5d	–	–	1.97 ($N-H_{arom}\cdots N=C$)	172.1

[a] Respective angles of the hydrogen bonds, from column 2 to column 4.

Molecular interactions in solution: Based on the observations in the solid state, we decided to investigate the propensity of the catalysts to self-aggregate in solution. Titrations monitored by ^{1}H NMR ($CDCl_3$) spectroscopy were conducted on compounds **2** (as a model), **4**, and **5** in the 0.5–35 mM concentration range. NMR spectra showed concentration-dependent chemical shifts, except for compounds **4b** and **4d** (see the Supporting Information). The variations mainly concern the amide NH groups and, to a lesser extent, some aromatic or aliphatic protons. These observations were interpreted as the formation of hydrogen-bonded complexes between complementary X=C–NH moieties. Experimental data were fitted with a model of dimerization (except compound **2**, which oligomerizes) and the corresponding binding constants K_{dimer} are reported in Table 2.

Table 2. Maximum variation of the chemical shifts (δ_{max} in ppm) for compounds **2**, **4a**, **4c**, and **5a–d** and the corresponding constants of dimerization (K_{dimer} in M^{-1}) in $CDCl_3$.[a,b]

	2	**4a**[c]	**4c**	**5a**	**5b**	**5c**	**5d**
$\Delta\delta_{max}$	+0.51	+0.18	+0.27	−0.66	+1.11	−0.25	−0.24
K_{dimer}[c]	6[d]	4	5	226	66	195	190

[a] Monitoring protons at 20°C in the 0.5–35.0 mM concentration range. [b] Estimated error ±15%. [c] Measured in CD_2Cl_2. [d] Data fitted with an isodesmic model.

Taken as a reference catalyst in the ROP of lactide, thiourea **2** showed moderate aggregative properties (K_{aggreg} = 6 M^{-1}) that had not been previously reported. Amidoindoles **4a** and **4c** form dimers with a small association constant (K_{dimer} = 4 and 5 M^{-1}, respectively). Notably, thioamidoindoles **4b** and **4d** do not aggregate ($\Delta\delta_{max} < 0.05$ ppm). This behavior is expected for thiocarbonyls because the latter are less efficient hydrogen-bond acceptors than their oxo derivatives.[26] Interestingly, even if the values of the self-association constants are weak (4–6 M^{-1}), approximately 15–20% of dimer is present in solution under the ROP conditions (concentration of catalyst = 35 mM).

Benzimidazoles **5** display a different behavior. All proton NMR spectroscopic signals were largely affected by increasing the concentration. Compounds **5** form tighter hydrogen-bonded dimers (K_{dimer} = 66–226 M^{-1}) than those of compounds **4** ($K_{dimer} \leq 5$ M^{-1}). Only thio derivative **5b** is associated in a looser manner. Under the experimental ROP conditions (i.e., 35 mM), approximately 60–80% of (thio)benzimidazoles **5** are aggregated. Therefore, a complementary geometry of hydrogen-bond acceptor and donor within (thio)amides **5** probably favors dimerization, as previously shown in the solid state. This result has obviously to be taken into account for the evaluation of the catalytic activity.

Catalytic properties in ROP reactions: Molecules **4** and **5** were tested as organocatalysts in the ROP of lactide, chosen as a model monomer. Classical conditions were employed: concentration of lactide at 0.7 M in dichloromethane, 20°C, using biphenylmethanol as the initiator (5 mol%) and a co-catalyst **3a** or **3b** (5 mol%) as an activator of the initiator/polymer growing chain (Table 3). All experiments were conducted under anhydrous conditions (dry reagents and solvents) and in the presence of 4 Å molecular sieves to trap residual water, a competitor of the catalysts in the hydrogen-bonding process. An independent experiment proved that the activated or nonactivated molecular sieves had no catalytic effect upon reactions. Time reactions were programmed between 24 and 72 h to evaluate the kinetics. When, in the presence of **3b**, the conversion of the monomer became over 50%, the crude polylactides were characterized by the average molar mass determined by ^{1}H NMR spectroscopy, M_n(NMR), and size-exclusion chromatography (SEC; M_n(SEC)). The index of dispersity (PDI) was also determined from the SEC analysis.

Under these conditions, over 24 h the catalytic property of the individual components was evaluated with preliminary tests. Reactions achieved in the presence of the initiator and in the absence of organocatalyst **3** and **4**/**5** gave no con-

Table 3. ROP conditions and properties of the poly(lactide)s.[a]

Entry	Catalyst (5 mol%)	t [h]	Conversion [%][b] **3a**	**3b**	M_n(theor)[c]	M_n(NMR) (**3b**)	M_n(SEC)[d] (**3b**)	PDI[d] (**3b**)
1	**1**	24	95	100	3070	3210	5150	1.08
2	**1**+H_2O 5 mol%	24	46	–	3070	–[e]	–[e]	–[e]
3	**1**+H_2O 50 mol%	24	0	0	3070	–	–	–
4	**2**	24	85	100	3070	2633	5420	1.10
5	**2**	48	95	–	2920	2778[f]	3970[f]	1.06
6	**4a**	24	72	100 (2 h)	3070	3070	4460	1.07
7	**4a**	48	95	–	2920	3498[f]	4190[f]	1.06[f]
8	**4b**	24	43	53	1630	1480	1907	1.05
9	**4b**	48	63	59	1810	1769	2119	1.05
10	**4c**	24	53	74	2270	2489	2850	1.07
11	**4d**	24	54	71	2180	2489	3200	1.07
12	**5a**	24	23	33	1010	760	–	–
13	**5a**	48	35	56	1720	n.d.[g]	1720	1.06
14	**5a**	72	49	83	2550	n.d.[g]	2576	1.06
15	**5b**	24	20	31	950	904	–	–
16	**5c**	24	24	20	610	616	–	–
17	**5d**	24	28	28	860	904	–	–

[a] Conditions: lactide 0.7 M in CH_2Cl_2, catalyst **4** or **5** (5 mol%), tertiary amine **3** (5 mol%), biphenylmethanol as initiator (5 mol%), 4 Å molecular sieves, 20°C. [b] Determined by ^{1}H NMR spectroscopy. [c] Theoretical molar mass when conversion was 100%. [d] Determined by size-exclusion chromatography. [e] Not measured when conversion was lower than 50%. [f] Experiment achieved in the presence of amine **3a**. [g] n.d. = not determined.

version of the monomer. The ROP of lactide conducted in the presence of the initiator plus organocatalyst **4**/**5**, without partner amine **3**, resulted in a conversion lower than 10%. Polymerization in the presence of the initiator plus amine **3**, without organocatalyst **4** or **5**, allowed the conversion of approximately 10% of lactide with **3a** and 15–20% with **3b**. These results demonstrated that individual ROP partners have a low catalytic efficiency.

Table 3 shows the conditions of the ROP experiments in the presence of different organocatalysts **1**, **2**, **4**, or **5** and a cocatalyst **3** and the characterization of the resulting polylactides. Molar masses determined by NMR spectroscopy (M_n(NMR)) are in good agreement with the theoretical value (M_n(theor)), whereas molar weights determined by SEC are overestimated, as they are calculated versus polystyrene standards.

Under our conditions, in the presence of molecular sieves, thioureas **1** and **2** allowed a very good conversion (85–100%; Table 3, entries 1, 4, and 5), especially when the cocatalyst was **3b**, which is recognized as a better hydrogen-bond acceptor than **3a**.[9b] Moreover, the polylactides with a narrow dispersity and predictable average number molar mass were obtained in reasonable time (24 h). The catalytic efficiency of **1** and **2** under our conditions is thus identical to that previously reported.[10]

The inhibiting properties of water in ROP triggered by hydrogen-bonding catalysts were demonstrated in entries 2 and 3 of Table 3. Indeed, an increase of the quantities of water (5 and 50 mol% with respect to lactide) in the reaction medium resulted in the progressive decrease of the percentage of monomer conversion (95, 46, and 0%, respectively). Reactions were therefore systematically run in the presence of 4 Å molecular sieves (five beads in 1 mL of reaction medium).

Each compound **4**/**5** was found to be active and allowed the conversion of lactide in 24 h with 20 to 100% yield. As expected, the ROP of lactide appeared to be strongly dependent upon the nature of the partner organocatalysts. Notably, all polymers had a narrow dispersity (polydispersity index (PDI) = 1.05–1.07) coupled with an experimental number average molar mass M_n(NMR), which is in agreement with the theoretical (M_n(theor)) assuming the formation of one chain per initiator molecule (Table 3). Variation of the [monomer]/[initiator]([M]/[I]) ratio from 20 to 50 and 100 led to narrowly dispersed polymers (PDI = 1.12 and 1.11, respectively), again with masses that match the theoretical ones (M_n(SEC) = 8398 and 12030 g mol^{-1}, respectively, to be compared to their M_n(theor) = 7384 and 14584 g mol^{-1}; see the Supporting Information). Besides, ^{13}C NMR spectroscopy indicates that the polymers exhibit a fully isotactic structure, thereby suggesting the absence of side transesterification reactions that would yield racemization (see the Supporting Information). Additionally, a chain-extension experiment was successfully realized: firstly, the polymerization of lactide was conducted under standard conditions (Table 3, entry 6: 100% conversion, M_n(theor) = 3064 g mol^{-1}, M_n(SEC) = 3070 g mol^{-1}, and PDI = 1.07, after 24 h) and, secondly, the same quantity of lactide was added. After 24 h, the conversion was total and the resulting polylactide had similar characteristics (M_n(theor) = 5944 g mol^{-1}, M_n(SEC) = 7569 g mol^{-1} and PDI = 1.12). All this supported that a controlled process is indeed occurring in these organocatalyzed ROP reactions.

Catalysts **4**+**3** (Table 3, entries 6–11) were more efficient than compounds **5**+**3** (entries 12–17) and provided poly(lactides) in 24 h, with a conversion ranging from 43 to 100%. Additionally, the catalytic activity of (thio)amides **4a–d** was slightly influenced by the hydrogen-bond acceptor character of amine **3** (entries 6, 8, 10, and 11). In the presence of the better hydrogen-bond activator **3b**, the percentage of conversion was higher: 71–100% compared to 53–72% when **3a** was employed as a cocatalyst. Notably, quantitative conversion with **4a** was obtained in 2 h in the presence of **3b** (entry 6 indicates the conversion after 2 h). These observations can be ascribable to the better hydrogen-bond donor character of amine **3b**.[9b,10] This assumption will be checked by the measurement of the corresponding association constants (see below). For partner catalysts **4a–d**+**3a**, conversion was significantly increased when reaction time was extended to 48 h (entries 5, 7, and 9), thereby indicating that polymerization is still going on and that chain ends are not deactivated. This phenomenon was already observed with thiourea **2** (entry 5). Kinetics of these ROP reactions can be slow in some cases and it is dependent upon the activation efficiency of both partner catalysts.

Nevertheless, additional parameters have to be taken into account to better understand the structure–activity relationships. Concerning the hydrogen-bonding catalysts **4**, the catalytic activity of the NH group appeared to be dependent upon two main structural factors: the electron density of its phenyl substituent and the nature of the linker onto the indole substituent (C=O or C=S). Compound **4a** with an electron-withdrawing group is the most active catalyst of the series (Table 3, entry 6, 72–100% conversion). Its corresponding electron-donating derivative **4c** and its thioamide derivative **4b** are less active and allow for 53–74% (entry 10) and 43–53% conversion (entry 8), respectively. These observations can be explained by two opposite phenomena: in the structure of **4c**, the amido NH is less acidic than in **4a** and thus it is a worse hydrogen-bond donor than **4a**, whereas in compound **4b**, the acidity of NH is largely increased (in acetonitrile, pK_a(S=C−NH) = 11–13 and pK_a(O=C−NH) = 17)[26] and thus might be partly inhibited by the basic species present in the solution, that is, the cocatalyst **3** (see below). Interestingly, catalyst **4c** was as efficient as its thio derivative **4d**. In this case, due to the electron-rich aromatic substituent, the NH group is a poorer hydrogen-bond donor whatever the nature of the C=X bond.

Given a 24 h reaction time, (thio)amidobenzimidazoles **5a–d** were moderate catalysts (20–33% conversion; Table 3, entries 12, 15–17) whatever the nature of the aromatic substituent and the nature of the cocatalyst **3**. When the reaction time was increased to 48 or 72 h (entries 13 and 14), the activity of hydrogen-bonding catalyst **5a** was increased, es-

pecially in the presence of cocatalyst **3b** (35 and 49% conversion with **3a** and 56 and 83% conversion with **3b**). The kinetics of catalysts **5** is slower than that observed for compounds **4**. This observation can be rationalized by the strong dimerization of **5**, which embeds the active NH group.

Supramolecular insight into the ROP reactions: Partner organocatalysts have been poorly studied in the ROP reactions. In this field of research, to the best of our knowledge, only one binding constant of $39\,M^{-1}$ was measured in C_6D_6 between thiourea **2** and valerolactone,[9b] which represents a rough model for the ROP of lactide in dichloromethane. In a first approach, we can speculate that these hydrogen-bonding compounds **4**/**5** and **3**, respectively, activate the monomer and the initiator/growing chain in a similar manner to the thiourea organocatalysts (Scheme 5, framed equilibria). However, we have already demonstrated that organocatalysts **4** and **5** can self-aggregate in a dimeric form. Thus an extra equilibrium, K_{dimer}, is present in the reaction medium and should be considered in the mechanism (Scheme 5).

Unexpected results reported in Table 3 (entry 8) prompted us to investigate the interactions between the different reagents using the model catalysts **2**, **4a**, and **4b**. Titrations monitored by ^{1}H NMR spectroscopy were achieved in $CDCl_3$ to demonstrate intermolecular interactions between the multiple components of the reaction (Table 4): 1) catalyst and lactide (equilibrium K_1), 2) initiator and cocatalyst **3** (equilibrium K_2), 3) catalyst and cocatalyst **3** (equilibrium K_3). Knowing that molecules **2**–**4** self-aggregate, the host concentration was fixed at 4–8 mM to minimize this side phenomenon.

Table 4. Binding constants K_{1-3} ($CDCl_3$, M^{-1}) between the molecules involved in the ROP of lactide.[a,b]

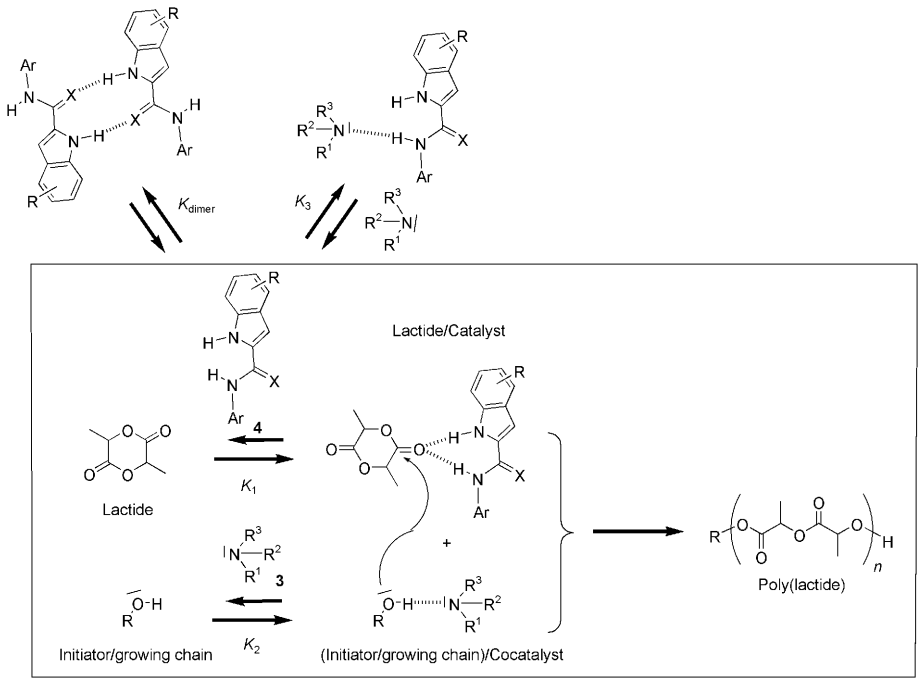
Host/guest	Lactide	**3a**	**3b**
2	$K_1=2$	$K_3=2$	$K_3=6$
ROH[c]	–	$K_2=2$[d]	$K_2=2$[d]
4a	$K_1=2$	$K_3=6$	$K_3=14$
4b	$K_1=3$	$K_3<1$	$K_3=57$

[a] Titrations were monitored by ^{1}H NMR spectroscopy at 20°C, using a 2 mM concentration of host **2**, **4a**, or **4b** and a 2–25 mM of guest lactide **3a**, **3b**, or ROH. [b] Estimated error ±15%. [c] ROH is the initiator 4-biphenylmethanol. [d] Host concentration was 20 mM.

At first, the expected interactions between cocatalysts and reagents were investigated to prove the supramolecular activation (framed equilibria in Scheme 5). Indeed, catalysts **2**, **4a**, and **4b** are weakly associated to the lactide in (1:1) stoichiometry ($K_1 \approx 2$–$3\,M^{-1}$). For (thio)amidoindoles **4a** and **4b**, both NH groups from the (thio)amide and the indole moieties were involved in the complexation of lactide (see the Supporting Information). As expected from hydrogen-bond-donating properties, activated amide groups ($\Delta\delta \approx 0.7$ ppm) were more affected than NH from the indole ($\Delta\delta \approx 0.07$–$0.2$ ppm). These observations are in favor of the participation of both NH groups in the complexation of the C=O group from the lactide.

Initiator ROH does not self-aggregate (see the Supporting Information) and it interacts with the cocatalysts **3a** and **3b** to form weak complexes ($K_2=2\,M^{-1}$). These values corroborate the activation of the monomer and the initiator/growing chain by tertiary amines **3**, but the two interactions appeared to be in the same order, contrary to the expected hydrogen-bond-donating classification (**3a** would be a lesser hydrogen-bond donor than **3b**).[9b,10b] Interestingly, the observed difference in the catalytic power of amine **3a** and strained diamine **3b** might rely on a more complex hydrogen-bonding system. Further investigations will be carried out.

Broadening the scope of the possible hydrogen bonds, we found that the catalysts **2**, **4a**, and **4b** do also interact with the cocatalyst **3** within an undesired hydrogen-bonding equilibrium (K_3), which could hamper the ROP. Titrations concerning thiourea **2** showed that this catalyst interacts with the cocatalysts **3a** and **3b**. The corresponding binding constants K_3 are 2 and $6\,M^{-1}$, respectively, and are in the same range as the other hydrogen-bonding constants K_1 and K_2. For **4a** and **4b**, host–guest titrations showed that NH groups ($\Delta\delta \approx 0.06$–$0.9$ ppm) as well as sev-



Scheme 5. Multiple hydrogen-bonding equilibria involving the reagents and catalysts **4**+**3** during the ring-opening polymerization of lactide. (A similar process is postulated for catalysts **5**.)

eral aromatic or aliphatic protons were largely affected ($\Delta\delta \approx 0.1$–0.5 ppm) by these interactions. In this equilibrium, hydrogen bonding probably occurs between the NH of the (thio)amides **4** and the nitrogen atom of **3**. In the presence of amine **3a**, the association constants K_3 that involve catalysts **4** were in the same range ($\leq 6\,M^{-1}$) as those found between the catalysts and their desired guests (K_1 and K_2), whereas in the presence of **3b** these K_3 values were larger (≈ 14–$57\,M^{-1}$). This result showed that partner catalysts can self-inhibit through undesired hydrogen bonding. Nevertheless, as all supramolecular species are in equilibrium, the progress of the ROP reaction appeared mainly driven by the balance between the four equilibria present in solution (K_{dimer}, K_1–K_3).

A remarkable value was noticed between organocatalyst **4b** and (−)-sparteine **3b**, which bind much more strongly ($K_3 \approx 57\,M^{-1}$). This result can explain the poorer catalytic properties of thioamide **4b** in the presence of the basic amine **3b** relative to those obtained with the cocatalyst **3a**, which is a weaker base (Table 3, entries 8 and 9).

Intermolecular interactions do exist between the different hydrogen-bond donor and acceptors in solution. The dynamic equilibria are favorably shifted towards the formation of the polylactide in a controlled manner (predictable M_n and narrow PDI), especially when the organocatalyst interacts poorly with itself or with its cocatalyst.

Conclusion

Activated (thio)amides that bear a second hydrogen-bond donor group, **4** and **5**, were straightforwardly synthesized and tested as organocatalysts for the ROP of lactide. Hydrogen-bonding networks within crystal structures of compounds **4a**, **4b**, **5c**, and **5d** revealed tight dimers, which, in some cases, embedded the NH amide group necessary for catalysis. Notably, the first X-ray structure of thioamidobenzimidazole tautomer **5d** is described. Investigation of the self-association properties in solution proved that molecules **4** and **5** form weak and strong dimers, respectively. In the case of series **5**, these self-associations probably decrease the availability of the active NH group for the monomer activation, whatever the nature of cocatalyst **3**. In the efficient series **4**, we showed that the catalytic power of the NH group is better when the aromatic substituent is electrodeficient and when NH is an amide versus thioamide.

We demonstrated that the hydrogen-bonding partner catalysts do play their role by activating the monomer and the polymer growing chain, respectively. Notably, for the first time, undesirable hydrogen bonds between the partner catalysts were highlighted. Some associations were strong and thus inhibit the catalytic power of the new (thio)amides. In a general manner, as hydrogen-bonding catalysts may be involved in multiple equilibria in the reaction medium, binding partners should be judiciously chosen to tune the outcome of the polymerization.

Experimental Section

General preparation of the amidoindoles: A mixture of indole-2-carboxylic acid (483 mg, 3.0 mmol) and thionyl chloride (2.2 mL, 30 mmol) in CH_2Cl_2 (10 mL) was heated at reflux for 1 h under nitrogen and evaporated to dryness. The residue was dried under vacuum for 1 h and dissolved in CH_2Cl_2 (10 mL), and a solution of the corresponding aniline (2.5 mmol) and *N*,*N*-diisopropylethylamine (517 mg, 4.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 15 min and heated at reflux for 16 h. After extraction and concentration in vacuo, the crude solid was purified by column chromatography.

General preparation of the amidobenzimidazoles: A solution of the corresponding benzoyl chloride (3.3 mmol) in THF (5 mL) was added dropwise to a solution of 2-amino-5,6-dimethylbenzimidazole (484 mg, 3.0 mmol) and *N*,*N*-diisopropylethylamine (1.0 mL, 5.7 mmol) in THF (15 mL). The mixture was stirred at room temperature for 16 h under nitrogen atmosphere and evaporated to dryness. The residue was extracted and eventually purified by column chromatography.

General preparation of the thioamidoindoles and thioamidobenzimidazoles: A solution of the corresponding amidobenzimidazole or amidobenzimidazole (0.5 mmol) and Lawesson's reagent (0.5 mmol) in toluene (15 mL) was heated at reflux for 16 h under nitrogen and evaporated to dryness. The residue was purified by column chromatography.

NMR spectroscopic titrations: Deuterated solutions were freshly prepared and dried in the presence of 4 Å molecular sieves. Association constants between host and guest (K_1–K_3) as well as the dimerization binding constants (K_{dimer}) were determined using titrations monitored by ^{1}H NMR spectroscopy (host signals) in $CDCl_3$. For determination of K_1–K_3, a solution (100 μL) of host (≈ 20 mM) was introduced in each NMR spectroscopic 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 ($\Delta\delta$ ppm versus guest concentration) were fitted using the nonlinear curve-fitting procedure with a (1:1) binding equation using the WinEqNMRprogram.[27] Concerning K_{dimer} evaluation, a stock solution of host (≈ 30 mM) in $CDCl_3$ was used to prepare the diluted NMR spectroscopy tubes (12 to 15) required for each titration. The titration data ($\Delta\delta$ ppm versus host concentration) were fitted with a dimerization model using Excel.[28] For thiourea **2**, the isodesmic aggregation model was more accurate.[29]

Typical experimental procedure for ROP reactions: Under nitrogen and in a dry Schlenk tube, the organocatalyst (35 μmol), the initiator (4-biphenylmethanol, 35 μmol), lactide (700 μmol), 4 Å molecular sieves (5 beads), dry dichloromethane (1 mL), and amine **3** as a cocatalyst (35 μmol) were successively introduced. The reaction mixture was stirred at 20 °C under nitrogen for the indicated period. The reaction mixture was filtered and concentrated in vacuo. Conversion was determined by ^{1}H NMR spectroscopy and integrating the signals of the methine proton in both the residual lactide and the polymer. Polymer molar masses and the dispersity index were measured by size-exclusion chromatography (SEC) using a PL-GPC50 Plus apparatus equipped with RI and UV detectors and Tosoh G4000HXL, G3000HXL, and G2000HXL columns (eluent: THF, flow rate 1.0 mL min^{-1}, temperature: 40 °C, calibrated with polystyrene standards).

X-ray structural analysis: Detailed crystal structures, cell parameters, and *R* values for **4a**, **4c**, **5c**, and **5d** are reported in the Supporting Information. CCDC-749820 (**5c**), 749821 (**4c**), 749822 (**5d**), and 749823 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] a) F. Nederberg, E. F. Connor, M. Möller, T. Glauser, J. L. Hedrick, *Angew. Chem.* **2001**, *113*, 2784–2787; *Angew. Chem. Int. Ed.* **2001**, *40*, 2712–2715; b) N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer, J. L. Hedrick, *Chem. Rev.* **2007**, *107*, 5813–5840; c) D. Bourissou, S. Moebs-Sanchez, B. Martin-Vaca, *C. R. Chim.* **2007**, *10*, 775–794; d) A. P. Dove, *Chem. Commun.* **2008**, 6446–6470.

[2] a) F. Nederberg, B. G. G. Lohmeijer, F. Leibfarth, R. C. Pratt, J. Choi, A. P. Dove, R. M. Waymouth, J. L. Hedrick, *Biomacromolecules* **2007**, *8*, 153–160; b) R. C. Pratt, F. Nederberg, R. M. Waymouth, J. L. Hedrick, *Chem. Commun.* **2008**, 114–116.

[3] a) H. R. Kricheldorf, I. Kreiser, *Makromol. Chem.* **1987**, *188*, 1861–1873; b) F. Sanda, H. Sanada, Y. Shibasaki, T. Endo, *Macromolecules* **2002**, *35*, 680–683; c) X. Lou, C. Detrembleur, R. Jérôme, *Macromolecules* **2002**, *35*, 1190–1195; d) P. V. Persson, J. Schröder, K. Wickholm, E. Hedenström, T. Iversen, *Macromolecules* **2004**, *37*, 5889–5893; e) S. Gazeau-Bureau, D. Delcroix, B. Martin-Vaca, D. Bourissou, C. Navarro, S. Magnet, *Macromolecules* **2008**, *41*, 3782–3784.

[4] O. Coulembier, D. P. Sanders, A. Nelson, A. N. Hollenbeck, H. W. Horn, J. E. Rice, M. Fujiwara, P. Dubois, J. L. Hedrick, *Angew. Chem.* **2009**, *121*, 5272–5275; *Angew. Chem. Int. Ed.* **2009**, *48*, 5170–5173.

[5] a) F. Nederberg, E. F. Connor, T. Glauser, J. L. Hedrick, *Chem. Commun.* **2001**, 2066–2067; b) reference [1a].

[6] M. Myers, E. F. Connor, T. Glauser, A. Mock, G. Nyce, J. L. Hedrick, *J. Polym. Sci. Polym. Chem. Ed.* **2002**, *40*, 844–851.

[7] a) E. F. Connor, G. W. Nyce, M. Myers, A. Möck, J. L. Hedrick, *J. Am. Chem. Soc.* **2002**, *124*, 914–915; b) O. Coulembier, B. G. G. Lohmeijer, A. P. Dove, R. C. Pratt, L. Mespouille, D. A. Culkin, S. J. Benight, P. Dubois, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 5617–5628; c) A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, D. A. Culkin, E. C. Hagberg, G. W. Nyce, R. M. Waymouth, J. L. Hedrick, *Polymer* **2006**, *47*, 4018–4025; d) W. Jeong, J. L. Hedrick, R. M. Waymouth, *J. Am. Chem. Soc.* **2007**, *129*, 8414–8415.

[8] a) L. Zhang, F. Nederberg, R. C. Pratt, R. M. Waymouth, J. L. Hedrick, C. G. Wade, *Macromolecules* **2007**, *40*, 4154–4158; b) L. Zhang, F. Nederberg, J. M. Messman, R. C. Pratt, J. L. Hedrick, C. G. Wade, *J. Am. Chem. Soc.* **2007**, *129*, 12610–12611.

[9] a) R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2006**, *128*, 4556–4557; b) B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. G. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 8574–8583; c) X. Sun, J. P. Gao, Z. Y. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 8130–8131.

[10] a) A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2005**, *127*, 13798–13799; b) R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, P. N. P. Lundberg, A. P. Dove, H. Li, C. G. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 7863–7871.

[11] A. Chuma, H. W. Horn, W. C. Swope, R. C. Pratt, L. Zhang, B. G. G. Lohmeijer, C. G. Wade, R. M. Waymouth, J. L. Hedrick, J. E. Rice, *J. Am. Chem. Soc.* **2008**, *130*, 6749–6754.

[12] Recent reviews about bifunctional thioureas: a) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; b) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem.* **2005**, *117*, 817–821; *Angew. Chem. Int. Ed.* **2005**, *44*, 807–811; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; d) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427.

[13] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem.* **2005**, *117*, 4100–4103; *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035.

[14] a) C. Givelet, B. Tinant, L. Van Meervelt, T. Buffeteau, N. March-and-Geneste, B. Bibal, *J. Org. Chem.* **2009**, *74*, 652–659; b) M.-L. Dumartin, C. Givelet, P. Meyrand, B. Bibal, I. Gosse, *Org. Biomol. Chem.* **2009**, *7*, 2725–2728; c) C. Givelet, T. Buffeteau, F. Arnaud-Neu, V. Hubscher-Bruder, B. Bibal, *J. Org. Chem.* **2009**, *74*, 5059–5062.

[15] S. Koeller, J. Kadota, A. Deffieux, F. Peruch, S. Massip, J.-M. Léger, J.-P. Desvergne, B. Bibal, *J. Am. Chem. Soc.* **2009**, *131*, 15088–15089.

[16] Adapted from: C. Kuehm-Caubère, P. Caubère, B. Jamart-Grégoire, A. Negre-Salvayre, D. Bonnefont-Rousselot, J.-G. Bizot-Espiard, B. Pfeiffer, D.-H. Caignard, B. Guardiola-Lemaître, P. Renard, *J. Med. Chem.* **1997**, *40*, 1201–1210.

[17] Adapted from: J. Sluka, J. Danek, P. Bedrnik, Z. Budesinsky, *Collect. Czech. Chem. Commun.* **1981**, *46*, 2703–2708.

[18] N. J. Leonard, D. Y. Curtin, K. M. Beck, *J. Am. Chem. Soc.* **1947**, *69*, 2459–2461.

[19] a) M. Jesberger, T. P. Davis, L. Barner, *Synthesis* **2003**, 1929–1958; b) T. Ozturk, E. Ertas, O. Mert, *Chem. Rev.* **2007**, *107*, 5210–5218.

[20] a) E. V. Nosova, G. N. Lipunova, A. A. Laeva, V. N. Charushin, *Russ. J. Org. Chem.* **2005**, *41*, 1671–1677; b) J. P. Powers, S. Li, J. C. Jaen, J. Liu, N. P. C. Walker, Z. Wang, H. Wesche, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2842–2845.

[21] a) S. Ianelli, M. Nardelli, D. Belletti, B. Jamart-Grégoire, C. Caubère, P. Caubère, *Acta Crystallogr. Sect. C* **1995**, *51*, 1341–1345; b) G. W. Bates, M. E. Light, M. Albrecht, P. A. Gale, *J. Org. Chem.* **2007**, *72*, 8921–8927.

[22] a) J. Li, D.-Q. Shi, W.-X. Chen, *Heterocycles* **1997**, *45*, 2381–2384; b) L. Jing, F. He-Liang, S. Jie, C. Wei-Xing, *Acta Crystallogr. Sect. C* **1997**, *53*, 320–322.

[23] a) B. Yang, Y.-F. Xia, S. Bi, S.-S. Zhang, *Acta Crystallogr. Sect. E* **2006**, *62*, o4200–o4202; b) M. G. Fisher, P. A. Gale, M. E. Light, *New J. Chem.* **2007**, *31*, 1583–1584.

[24] a) L. Leiserowitz, G. M. J. Schmidt, *J. Chem. Soc. A* **1969**, 2372–2382; b) L. Leiserowitz, M. Tuval, *Acta Crystallogr. Sect. B* **1978**, *34*, 1230–1247; c) P. Dauber, A. T. Haggler, *Acc. Chem. Res.* **1980**, *13*, 105–112; d) R. Taylor, O. Kennard, W. Versichel, *Acta Crystallogr. Sect. B* **1984**, *40*, 280–288; e) M. C. Etter, *Acc. Chem. Res.* **1990**, *23*, 120–126.

[25] a) C. N. Sundaresan, S. Dixit, P. Venugopalan, *J. Mol. Struct.* **2004**, *693*, 205–209; b) G. Pavlovic, V. Tralic-Kulenovic, M. Vinkovic, D. Vikic-Topic, I. Matanovic, Z. Popovic, *Struct. Chem.* **2006**, *17*, 275–285.

[26] a) T. Sifferlen, M. Rueping, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 2067–2093; b) R. Frank, M. Jakob, F. Thunecke, G. Fischer, M. Schutkowski, *Angew. Chem.* **2000**, *112*, 1163–1165; *Angew. Chem. Int. Ed.* **2000**, *39*, 1120–1122.

[27] J. M. Hynes, *J. Chem. Soc. Dalton Trans.* **1993**, 311–312.

[28] P. R. Mitchell, H. Sigel, *Eur. J. Biochem.* **1978**, *88*, 149–154.

[29] T. H. Lilley, H. Linsdell, A. Maestre, *J. Chem. Soc. Faraday Trans.* **1992**, *88*, 2865–2870.

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