Organocatalysis

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Hydrogen-Bonding Catalysts Based on Fluorinated Alcohol Derivatives for Living Polymerization**

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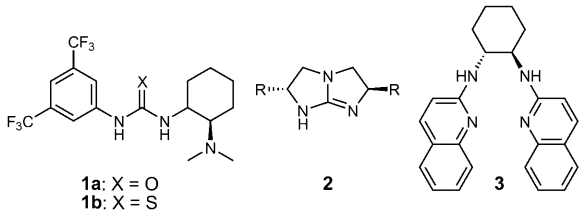
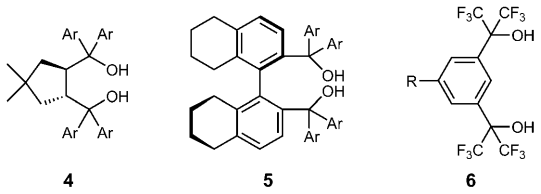
Hydrogen bonding plays a vital role in biological systems, which include the mediation of recognition between DNA base pairs, binding of ligands to receptor sites, folding of proteins into secondary structures, and enzymatic catalysis.[1] Metal-free organic catalyst systems that utilize multiple reversible noncovalent interactions to activate the substrate in a manner analogous to natural systems are of particular interest. For example, the use of urea, thiourea, guanidine, and amidine functionalities (Scheme 1) in a number of organic transformations have been investigated.[2]



Scheme 1. Representative structures of urea **1** (X = O), thiourea **1** (X = S), guanidinium **2**, and amidinium ions **3** (charges omitted).

Recently, we reported the use of a cyclic guanidine as well as a thiourea-containing bifunctional organocatalyst for the ring-opening polymerization (ROP) of lactides (LAs), wherein both catalysts are believed to proceed by hydrogen-bonding mechanisms.[3] Computational methods were used to demonstrate the importance of hydrogen-bonding activation in the ring-opening reaction of L-LAs in the presence of the organic bicyclic guanidine catalysts.[4] The ROP of LAs with thiourea-amine catalyst **1** proceeds by activation of the carbonyl group of the monomer by the thiourea to become more electrophilic, and activation of the initiating or propagating alcohol by the tertiary amine to become more nucleophilic. Mechanistic studies show that both the hydrogen-bond-donating thiourea and hydrogen-bond-accepting amine groups are necessary for high activity in LA ROP. In the case where the thiourea and amine moieties are not part of the same molecule, (−)-sparteine was found to be the most effective base for activation when used in combination with a thiourea derivative.[3b] Predictable molecular weights with narrow polydispersities were achieved with shorter reaction times and retention of stereochemistry in the resulting polylactide (PLA).

Alcohol-containing catalysts such as biphenols and chiral diols are another class of hydrogen-bond donors that have been shown to form hydrogen-bonded complexes with carbonyl-containing compounds and have been shown to accelerate a number of reactions, including Diels–Alder cycloaddition reactions (**4**–**5**; Scheme 2).[5] A number of oxidation reactions that use hydrogen peroxide have been reported to show significantly enhanced reaction rates when carried out in fluorinated tertiary-alcohol-based solvents, furthermore, computational methods suggested that hydrogen bonding promoted the catalyst activity.[6] The utility of alcohol-based catalysts for ring-opening polymerization of LA is limited by their inability to sufficiently activate the monomer as well as their tendency to act as initiator or chain transfer agents. Herein, we introduce a new hydrogen-bonding catalyst based on fluorinated tertiary alcohols, so-called hexafluoroalcohols (HFAs), for the ROP of strained heterocycles (catalyst **6**, Scheme 2). In this context, the bulky electron-withdrawing fluorinated groups serve to increase the acidity of the alcohol (increasing hydrogen bonding), while steric factors reduce the nucleophilicity of the alcohols and prevent their participation in initiation or chain-transfer



Scheme 2. Representative structures of diol hydrogen-bonding donor catalysts.

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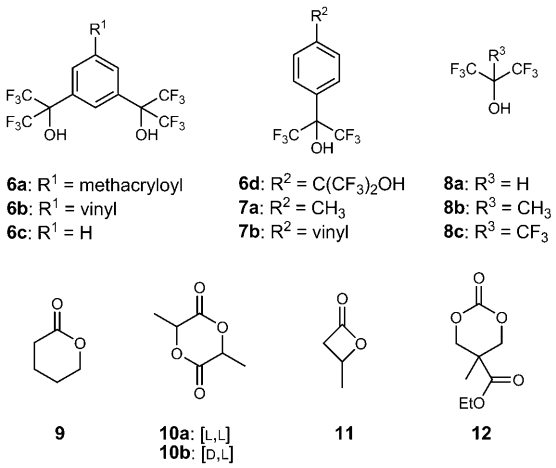
reactions. A number of HFA compounds that were surveyed as catalysts are shown in Scheme 3.

The hydrogen-bonding capability of this new catalyst platform was first investigated by using NMR spectroscopy to compare the properties of single- versus double- hydrogen-bonding catalysts. ^{13}C NMR spectroscopy was used for the identification of complexes formed by hydrogen-bonding interactions with the carbonyl groups of the catalysts **6a** and **8b**.[7] When a solution of valerolactone (VL, **9**) in C_6D_6 was titrated with either the single-hydrogen-bonding catalyst **8b** or the double-hydrogen-bonding catalyst **6a**, the carbonyl resonance in the ^{13}C NMR spectrum was observed to shift downfield (see Figure S1 in the Supporting Information). Maximum displacements of the carbonyl signal were observed for catalyst/VL mole ratios of 2 and 0.85 for catalysts **8b** and **6a**, respectively (Figure 1). These results strongly suggest that **8b** interacts with VL in a 2:1 ratio, and that **6a** interacts with VL in a 1:1 ratio. The 1:1 interaction of **6a** with VL was also confirmed by cryometric analysis (see Figure S2 in the Supporting Information).[8]



Scheme 3. Double- (**6a–d**) and single- (**7a,b** and **8a–c**) hydrogen-bonding catalysts and cyclic esters (**9**, **10a,b**, **11**), and carbonate (**12**).

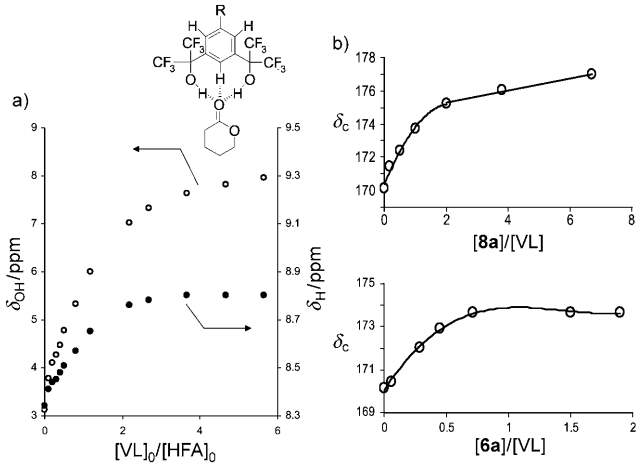


Figure 1. a) Chemical shifts in the ^1H NMR spectrum observed by titration of VL (**9**) with **6a** (solvent C_6D_6); b) ^{13}C NMR chemical shifts observed by titration of VL with **8b** (top) and **6a** (bottom; solvent C_6D_6)

The strength of the hydrogen-bonding interaction was subsequently investigated by using ^1H NMR spectroscopy. When VL was titrated into a solution of **6a** in C_6D_6, the hydroxy protons were most affected, as indicated by the large change in chemical shift of the OH resonance ($\Delta\delta = 4.82$). This shift suggests that a strong hydrogen-bonding interaction takes place between VL and the catalyst and results in the proximity of the lactone and the aromatic methine group, and causes a downfield shift of the methine resonance, which is *ortho* to both HFA functionalities (Figure 1 and Figure S1 in the Supporting Information). Similar results were observed for the single-hydrogen-bonding catalysts. The combined multinuclear NMR spectroscopy results suggest that both type of catalysts interact with the monomer through a strong intermolecular hydrogen-bonding interaction between the hydroxyl group and the carbonyl group of VL.

To gain an initial understanding of the catalytic activity of this new compound, we studied the interaction of L-lactide **10a** with the catalyst **6c**, using B3LYP/cc-pVTZ//B3LYP/6-31 + G* density functional calculations[10,11] in the presence of a continuum dielectric $\varepsilon = 2.38$ (toluene) using IEF-PCM[12] as implemented in GAMESS-US.[13] This result was compared to the corresponding interaction with a model thiourea, which has been reported to be a hydrogen-bonding catalyst (Figure 2).[2] It can be inferred that **6c** is a more potent hydrogen-bonding catalyst since the hydrogen-bonding distances are shorter than for the thiourea catalyst, and the Löwdin charges[14] assigned to the hydrogen atoms of the catalyst are correspondingly larger (0.46 versus 0.41/0.39). Initial studies on the mechanism of the rate-determining step also confirm the importance of this adduct interaction, since this mechanism occurs entirely through hydrogen bonding with the catalyst (and the base), in a manner similar to that demonstrated for the potent guanidinium catalyst.[4]

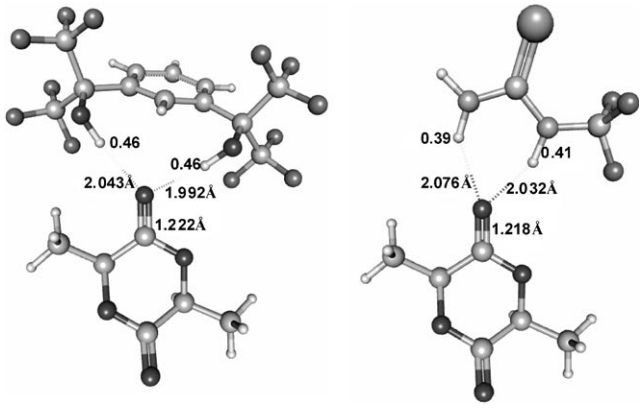
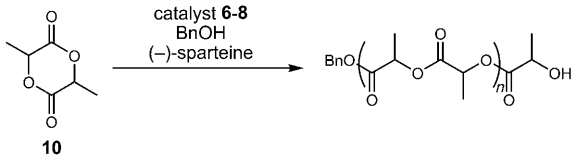


Figure 2. Comparison of L-lactide **10a** adduct with **6c** and model thiourea catalysts: hydrogen-bond lengths, carbonyl bond lengths, and partial charges on the hydrogen atoms that participate in hydrogen bonding to the oxygen atom of the carbonyl group.

The HFA compounds were surveyed as organocatalysts for the ROP of LA (Scheme 4). Polymerizations were



Scheme 4. ROP of a lactide by HFA catalysts.

conducted at ambient temperature using an alcohol initiator, such as benzyl alcohol (BnOH), with (−)-sparteine (S) as a cocatalyst base. It is important to note that without the cocatalysts, no polymerization was observed for any of the HFA catalysts at the concentrations surveyed. The ROP of L-lactide **10a** was evaluated in CH_2Cl_2 for a [**10a**]/[BnOH]/[S]/[catalyst] ratio of 200:1:1:5 ([**10a**]$_0$ = 1 M), and the relative conversions were determined by using ^{1}H NMR spectroscopy (Table 1 and Figure 3; a typical ^{1}H NMR spectrum is shown in Figure S3 in the Supporting Information and confirms the structure and end-group fidelity. ^{13}C NMR analysis (Figure S4 in the Supporting Information shows no evidence of racemization, with only one peak in the carbonyl region). Catalysts **6b, 6c**, and **8b** proved to be more active than **6a** and **6d** as well as **7a** and **7b**. The broader PDI (polydispersity index) of the poly(lactide) produced using catalyst **8a** (Table 1, entry 12) indicates that **8a** can participate in the reaction (presumably because of lower steric hindrance). Catalyst **8c** did not show any activity towards polymerization, irrespective of the catalyst concentration; this inactivity is likely a result of its steric bulk. Combinations of catalysts **6c**, **6b**, or **8b**/BnOH/S show activities toward the ROP of lactide comparable to that of the previously studied thiourea/BnOH/S system (see the Supporting Information).

Table 1: Properties of poly(L-lactide)s obtained using HFA catalysts.[a]

Entry	Cat.	t [h]	Conv.[c] [%]	M_n[d] [g mol^{-1}]	PDI
1	**6a**	52	47	15300	1.09
2	**6a**	91	68	21300	1.09
3	**6b**	52	73	25900	1.07
4	**6b**	91	95	27500	1.08
5	**6c**	47	72	19000	1.06
6	**6d**	47	26	5900	1.08
7	**6d**	72	30	5900	1.07
8	**7a**	49	12	3700	1.08
9	**7a**	121	15	4400	1.08
10	**7b**	52	27	11800	1.07
11	**7b**	91	54	20300	1.09
12	**8a**	23	91	12900	1.28
13	**8b**	23	23	9500	1.06
14	**8b**	26	13[b]	3300	1.08
15	**8b**	50	75	22400	1.09
16	**8c**	143	0	–	–

[a] Reaction was performed in CH_2Cl_2 with BnOH as an initiator. L,L-lactide [**10a**]$_0$ = 1 M, [**10a**]/[catalyst]/[BnOH]/[S] = 200:5:1:1. [b] [**10a**]/[catalyst]/[BnOH/[S] = 200:250:1:1. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by size-exclusion chromatography.

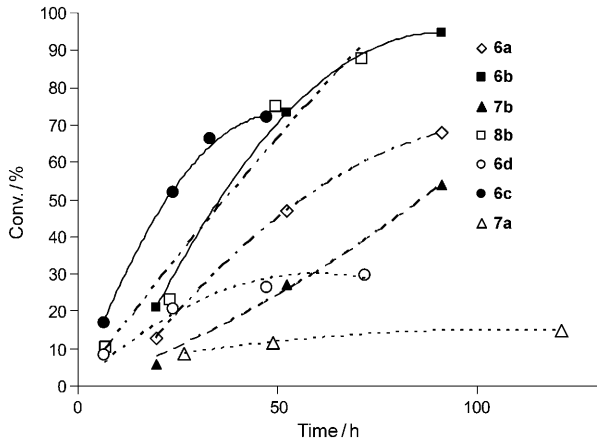


Figure 3. Time-conversion curves obtained from ROPs of LA in CH_2Cl_2 at RT ([**10a**]/[catalyst]/[BnOH]/[S] = 200:5:1:1; [**10a**]$_0$ = 1 M).

The molecular weight (M_n) values obtained with each catalyst (determined by gel permeation chromatography (GPC) analysis) vary linearly with the conversion (Figure 4). The linearity of this plot demonstrates the controlled character of each polymerization and indicates that little chain transfer occurs (Figure 4).[9] End-group fidelity was investigated by the formation of an oligomer that contained pyrene butanol as an initiator. This procedure, which could be followed with the refractive index (RI) and UV detectors in the GPC setup, demonstrated that the pyrene group was attached to the chain end (Figure S4 in the Supporting Information). ^{1}H NMR spectroscopy was also used to confirm the presence of the initiating (pyrene) and terminal (hydroxy) chain ends (Figure S5 in the Supporting Information). To provide further support for the living nature and end-group control of this polymerization, two chain-extension experiments were also successfully performed from an initial polymerization using D,L-lactide **10b** ([**10b**]$_0$ = 2.95 M; [**10b**]/[BnOH]/[S]/[**6c**] = 500:1:5:50) carried out at room temperature for 19 hours to give a polylactide with M_n = 43000 g mol^{-1} (PDI = 1.13), as determined by size-exclusion chromatography (relative to polystyrene standards). Additional **10b** (3.5×10^{-3} mol, 0.4 equivalents) was added to this solution and the solution was allowed to react for an additional 23 hours. The molecular weight of the sample increased to 99000 g mol^{-1} (PDI = 1.15). This solution was charged again with 4.2×10^{-3} mol (0.45 equivalents) of

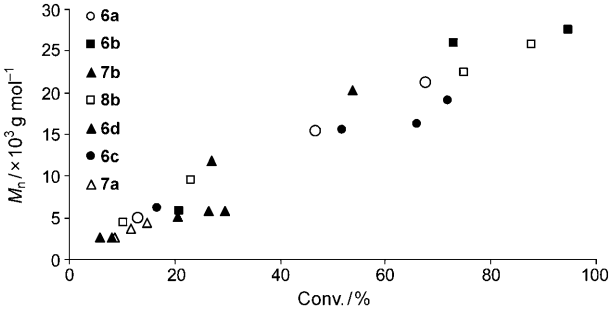


Figure 4. Plot of M_n (estimated by GPC) versus LA conversion (estimated by ^{1}H NMR; CH_2Cl_2, RT, [**10a**]$_0$ = 1 M, [**10a**]/[catalyst]/[BnOH]/[S] = 200/5/1/1).

10b and diluted slightly by addition of CH_2Cl_2 (1 mL). After 71 hours, the final molecular weight of the polymer increased to 114000 g mol^{-1}, with no real change in the polydispersity (1.09). These characteristics are typical of a living system.

Finally, in order to demonstrate the versatility of these catalyst systems, we surveyed the use of β-butyrolactone (BL, **11**) and the cyclic carbonate MTC-Et (**12**; Scheme 3). In each case, BnOH and S were used as the initiator and cocatalysts, respectively (Table 2). Narrowly dispersed polymers were

Table 2: Molecular characterizations of poly(BL) and poly(MTC-Et) as obtained from HFA catalysts in different solvents.

Monomer	Cat.[a]	Solvent	t [h]	Conv. [%]	M_n[d] [g mol^{-1}]	PDI
11	**6a**	C_6D_6	138[b]	71	6500[c]	1.05
11	**6a**	C_6D_6	357[b]	52	10600[d]	1.10
12	**6c**	CH_2Cl_2	7.5	51	2100[c]	1.13
12	**6c**	CH_2Cl_2	22.5	88	3200[c]	1.13

[a] 0.2 equiv of sparteine ([catalyst]/[S] = 5). [b] Reaction performed at 50 °C. [c] BnOH initiator, DP (degree of polymerization) target: 100. [d] Determined by size-exclusion chromatography. [e] BnOH initiator, DP target: 425.

obtained with molecular weights that followed the degree of conversion, which demonstrated the generality of these catalysts toward other strained heterocycles.

A new hydrogen-bonding motif based on fluorinated tertiary alcohols has been described, and its ability to activate electrophilic substrates was demonstrated by NMR spectroscopy, cryometric analysis, and computational methods. The catalytic activity of the hydrogen-bonded catalysts towards ROP produced narrowly dispersed polymers of predictable molecular weights from selected strained heterocycles.

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