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Electronic Activity Tuning of Acyclic Guanidines for Lactide Polymerization

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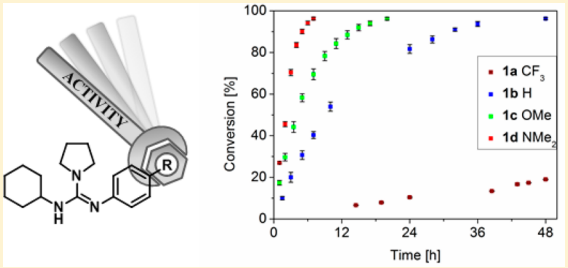
Supporting Information

ABSTRACT: Novel aromatic guanidine-based organocatalysts for the ring-opening of L-lactide were synthesized and applied in comprehensive polymerization experiments and kinetic studies. The introduction of electronically active substituents led to a significant change in activity by 2 orders of magnitude. The formed polylactide is featured with narrow polydispersity and high end-group fidelity, both characteristics that are typical for living polymerizations. Besides that, using linear free-energy relationships and DFT calculations revealed new insights into the polymerization mechanism. The formation of an adduct consisting of the catalyst and initiator/chain end turned out to be the rate-limiting step.



INTRODUCTION

The precise construction of customized materials associated with desired physical properties represents one of the essential challenges in materials science. Living polymerization techniques, for instance, are important methods to achieve a high degree of control over the polymerization process, which enables the synthesis of complex polymer architectures.[1] Organocatalysts have been attracting a significant attention[2] in the field of ring-opening polymerizations (ROP) of cyclic esters since the first approach[3] was published in 2001. The necessity to exclude metal contamination in the final polymers for biomedical[4] and microelectronic[5] applications favors the use of purely organic catalysts. Within the wide-ranging spectrum of versatile polymerization catalysts[6] the class of guanidines features an outstanding activity toward the ROP of cyclic esters.[7] Guanidines are well-known for their high Brønsted basicity as well as hydrogen bond donor and acceptor activity and therefore successfully employed in a variety of organic transformations,[8] e.g., enantioselective reactions[9] and transesterifications.[7a,10]

Specifically, guanidines such as triazabicyclodecene (TBD)[7a] or acyclic derivatives[7c] have been shown by Hedrick and Waymouth to be efficient organocatalysts for the ROP of L-lactide (LA). Polymerizations catalyzed by 0.1 mol % TBD were completed after few seconds only, yielding polylactide with a high degree of polymerization (DP = 100) combined with a narrow polydispersity (PDI = 1.19).[7a] This remarkable activity, rivaling the most active metal catalysts,[11] is due to the specific arrangement of the guanidine nitrogens, which provide a dual activation of both the monomer and the initiating alcohol via hydrogen bonds. Computational studies proved that a mechanism involving only hydrogen bonds is energetically preferred over an alternative nucleophilic pathway.[12] On the contrary, related acyclic guanidine catalysts are considerably less active as compared to TBD originating from their lower basicity, which has been attributed to the out-of-plane rotation of the pyrrolidine ring and thus to a weakened conjugation between the three guanidine nitrogens.[7c] However, the activity of such acyclic guanidines is still high and at least comparable to other organocatalysts for the ROP of lactide, such as thioureas[7b,13] or 2-amidoindoles.[14]

A detailed knowledge of the interplay of electronic factors and catalytic activity of guanidines would be worthwile in order to develop creative approaches to achieve an elevated level of control over polymerization processes, e.g., photoswitchable polymerization catalysis.[15] Hence, we synthesized various new guanidine organocatalysts **1**−**3** bearing aromatic rings in order to investigate the ability of electronically active substituents to influence their catalytic activity (Figure 1). Note that introduction of an aromatic moiety into the catalyst scaffold

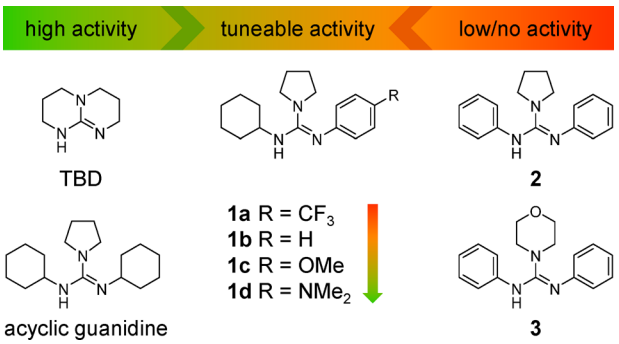


Figure 1. Guanidine organocatalysts for polymerization of lactide.

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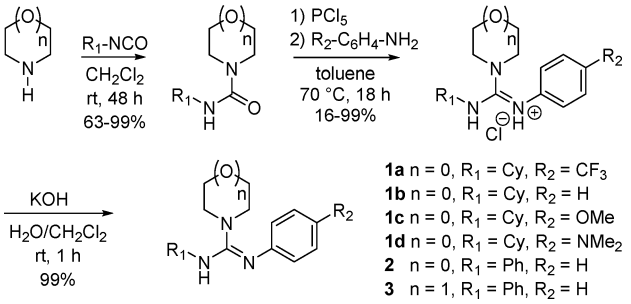
is key to achieve communication between a photoswitchable unit (to be incorporated at a later stage) and the catalytically active site.

RESULTS AND DISCUSSION

Since a modulation of the TBD scaffold is synthetically challenging, we targeted the substitution of the aliphatic residue(s) of the acyclic guanidine structure with aromatic moieties. Synthesis of the new aromatic acyclic guanidine derivatives **1**–**3** (Scheme 1) involved initial reaction of

Scheme 1. Synthesis of Aromatic Guanidines 1–3



pyrrolidine and morpholine with cyclohexyl or phenyl isocyanate, respectively. Subsequently, the formed carboxamides were transformed to their Vilsmeier salts, which were reacted *in situ* with the different aniline derivatives to give the guanidine hydrochlorides. In the final step, the hydrochlorides were exposed to a potassium hydroxide solution to obtain the free guanidines **1**–**3** quantitatively.

The catalytic activity for the ROP of lactide of the synthesized guanidines **1b**, **2**, and **3** was studied in a preliminary polymerization experiment under conditions, which are identical to the ones established by Hedrick for the case of the acyclic guanidine. Polymerizations of L-lactide in dry CH_2Cl_2 ($[LA]_0$ = 2 M) with a monomer/initiator/catalyst (M/I/C) ratio of 100:1:1 and with 1-pyrenebutanol acting as the initiator were conducted. After a reaction time of 24 h the conversion of the monomer was determined via ^{1}H NMR spectroscopy by integrating the characteristic methine proton signals of both the polymer and residual monomer. Guanidines **1b** and **2** led to a conversion of 36% and 17%, respectively, whereas compound **3** was found to be entirely inactive, even at higher catalyst loadings of 10 mol %. These results indicate a significantly lower activity as a result of replacing the cyclohexyl rings with aromatic phenyl moieties. The electron density of the guanidine nitrogens is therefore delocalized over the π system of the adjacent aromatic moieties, which has apparently a detrimental impact on the associated basicity[16] and thus on the catalytic activity. Furthermore, by exchanging the pyrrolidine structure with morpholine, which is in general less basic[17] ($pK_a(H_2O)$ = 11.3 vs. 8.5), the catalytic activity is entirely lost.

After these initial experiments the lead structure **1b** was further modified in order to fine-tune the respective catalytic activity by introducing electronically active substituents, which are compatible with the reaction conditions and do not engage in side reactions such as transesterification. To investigate the influence of the electronic properties of guanidines **1a**–**1d** the M/I/C ratio was decreased to 50:1:1 with the aim to achieve reasonable reaction times for complete monomer conversion. During the polymerization process aliquots were taken from the reaction mixture at different times, treated with excess of benzoic acid, and analyzed by ^{1}H NMR spectroscopy. All polymerization experiments were conducted at least three times. Clearly, the guanidine catalysts **1a**–**1d** show a significant difference in their activity (Figure 2). The polymerization times

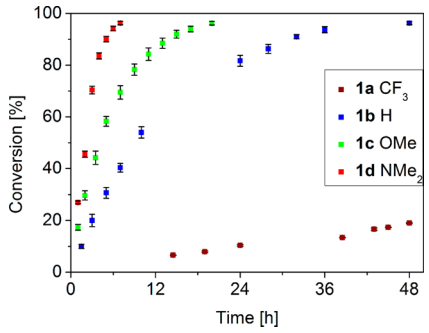
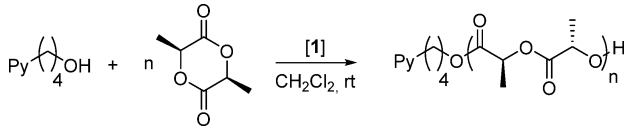


Figure 2. Monomer conversion vs time for ROP of L-lactide catalyzed by **1a**–**1d** with M/I/C ratio = 50:1:1. Experiments performed in triplicate (error bars represent standard deviation).

are ranging from 7 h for **1d** with a dimethylamino group as a strong electron donor to 48 h for **1b** without any activating group attached (Table 1). By adding a trifluoromethyl

Table 1. Polymerization of L-Lactide Using Guanidine Catalysts 1[a]



entry	catalyst	DP	time [h]	conv[b] [%]	M_n[b] [g mol^{-1}]	PDI[c]	k_{app} [10^{-3} h^{-1}][d]
1	**1a**	50	48	19	n.d.	n.d.	4 ± 0.3
2	**1b**	50	48	96	7500	1.06	73 ± 4
3	**1c**	50	20	97	7900	1.07	167 ± 11
4	**1d**	50	7	99	7500	1.06	602 ± 23
5	**1d**	100	34	96	12800	1.04	n.d.
6	**1d**	150	72	92	19100	1.08	n.d.
7	**1d**	200	96	85	26100	1.18	n.d.

[a]Reaction conditions: $[LA]_0$ = 2 M in CH_2Cl_2 with 1-pyrenebutanol as initiator. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by GPC in THF (calibrated with polystyrene standards). [d]Derived from first-order kinetic relationship. n.d. = not determined.

substituent as electron-withdrawing group, the activity of **1a** is drastically reduced, which is displayed by a monomer conversion of only 19% after 2 days.

Furthermore, polylactide with higher molecular weights (DP = 100–200) could be obtained with **1d** as catalyst in prolonged reaction times. The yielded polylactide is characterized by narrow polydispersity (PDI = 1.04–1.18), which is typically associated with living polymerization processes. The living character of the ROP is furthermore affirmed by the linear relationship of the molecular weight M_n vs monomer conversion, even until late stages of the polymerization (see Supporting Information). Moreover, the overlap of the RI and the UV traces of the GPC measurements shows a complete integration of the pyrene-based initiator into the polymer backbone (see Supporting Information). The molecular weights determined by end-group analysis via ^{1}H NMR

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spectroscopy are close to the theoretical target M_n values corresponding to quantitative monomer conversion (see Supporting Information). Concerning the stereochemistry of the polymer no epimerization of the methyl group is observed in the ^{13}C NMR spectra. In addition, differential scanning calorimetry (DSC) of PLA with DP = 100 revealed a melting point T_m = 158 °C, which exactly matches previously reported melting temperatures of isotactic PLA[13c] (see Supporting Information).

In order to compare the performance of the catalysts more precisely, the rate constants were determined by (pseudo) first-order kinetic plots of $\ln([M]_0/[M]_t)$ vs time revealing a linear relationship (Figure 3). As apparent from the different

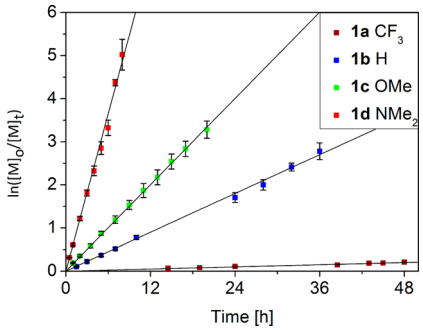

Figure 3. Kinetic analysis of the polymerization reaction according to a (pseudo) first-order rate law (lines show the linear fits).

polymerization outcome the derived rate constants are highly dependent on the nature of the substituent ranging from k_{app} = 4×10^{-3} h^{-1} for **1a** to $k_{app} = 6 \times 10^{-1}$ h^{-1} for **1d**, thereby giving raise to a difference in activity by a factor of 150 (Table 1).

With these rate constants in hand it is now possible to obtain a better mechanistic understanding of the rate-determining step during the polymerization process by using linear free-energy relationships. When correlating the rate constants to the Hammett constants[18] of the respective substituents by applying the classical Hammett equation a linear relationship with a negative slope is obtained (Figure 4). The associated reaction

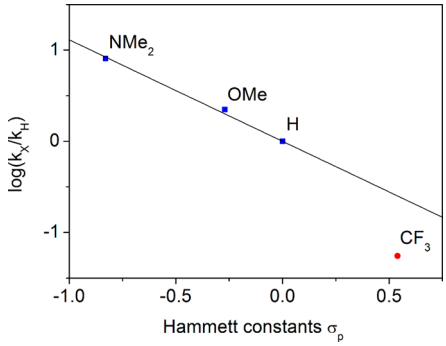

Figure 4. Application of the Hammett equation to the rate constants k_{app} and the respective Hammett constants σ_p of the substituents.[18]

constant $\rho = -1.1$ implies a slightly positively charged transition state. This is in accordance with the basic character of the guanidines, leading to a strong interaction and thus activation of the initiating alcohol/propagating chain end by formation of an alcohol adduct during the rate-limiting step. The deviation of **1a** from the linear correlation furthermore suggests that below a certain basicity the mechanism is altered, which is consistent with the strongly reduced activity.

To gain further insight, the obtained results were additionally supported by comparing the adducts of **1** and methanol (as a model alcohol), using density functional calculations (B3LYP/TZVP/PCM)[19] and implicit CH_2Cl_2 solvation (for a detailed description see Supporting Information). The guanidine–methanol interaction can be quantified by the extent of proton transfer within the formed hydrogen bridge. The distance between the basic guanidine nitrogen and the alcohol proton decreases, whereas the bond dissociation energy (BDE) rises with increasing electron density of the guanidines (Table 2). In addition, the gas-phase basicities of **1a**–**1d** were calculated and are in good agreement with empirical determined basicities of related acyclic guanidines.[20] The basicities show the same trend as compared with the adduct formation, which is consistent with the observed activity differences and further verify the impact of the substituents on the basic properties.

Table 2. Computationally Calculated Distances and Bond Dissociation Energy (BDE) for Adducts of 1 and Methanol as well as Gas-Phase Basicities

entry	catalyst	$d_{N-H(OMe)}$ [Å]	BDE [kcal/mol]	GB [kcal/mol]
1	**1a**	1.835	−4.5	241
2	**1b**	1.813	−4.9	245
3	**1c**	1.797	−4.9	248
4	**1d**	1.793	−5.3	252
5	Δ_{max}	0.042	0.8	13

CONCLUSION

In summary, we synthesized new aromatic guanidine-based organocatalysts for the ROP of L-lactide and investigated the influence of electronic effects on their activity. It turned out that the catalytic activity of acyclic guanidines could be retained upon replacing one aliphatic cyclohexyl group with an aromatic phenyl moiety. Importantly, this structural modulation allows for tuning of the catalysts' activity by incorporating electronically active substituents. By introducing strongly electron-donating dimethylamino groups (**1d**), the catalytic activity was enhanced by 2 orders of magnitude as compared to electron-withdrawing trifluoromethyl groups (**1a**). This significant reactivity difference is an important prerequisite to dynamically alter the catalytic activity of guanidines with the aid of photoswitchable systems, which is the subject of current efforts in our research group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.5b02137.

Experimental procedures, characterization data, GPC experiments, and details on DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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