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NOTE

# Acyclic Guanidines as Organic Catalysts for Living Polymerization of Lactide

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ABSTRACT: We describe a facile route to structurally diverse guanidinium organic catalysts by reaction of carbodiimides with secondary amines. The efficacy of these catalysts for the living ring-opening polymerization (ROP) of lactide was demonstrated including predictable molecular weights and end-group fidelity. Theoretical studies indicate that the acyclic guanidines are less basic than 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), but as for the more active TBD, they catalyze ring opening by activation of the alcohol and by stabilizing the resultant tetrahedral intermediates through hydrogen bonding. These results demonstrate that weak secondary interactions are an important concept for controlled polymerization.

Ring-opening polymerization (ROP) of cyclic esters, such as lactide and lactones, is a powerful method for generating polyesters with controlled molecular weight and end-group functionality; several reviews of the elegant organometallic catalytic routes to such materials have appeared.[1] In addition to polymerization techniques that give predictable molecular weights, narrow molecular weight distributions, and end-group fidelity, many advanced applications require the removal of undesired contaminants such as heavy metal ions from catalysts. Toward this goal, new methods based on organocatalytic ring-opening polymerization have been developed.[2−9] Examples of successful organocatalysts for the ROP of cyclic esters, carbonates, and siloxanes include 4-dimethylaminopyridine,[3] phosphines,[4] N-heterocyclic carbenes (NHC),[5] acids,[6] bifunctional aminothioureas,[7] phosphazene bases,[8] amidines, and guanidines.[9,10]

The bicyclic guanidine moiety is a substructure common to many biologically active natural products and the catalytic role in natural products has received considerable attention.[11] Guanidines and chiral guanidines have been used in several asymmetric transformations,[12] but the synthesis of the catalysts, particularly the chiral bicyclic guanidine's is very demanding.[13,14] Along these lines, 1,5,7- triazabicyclo[4.4.0]dec-5-ene ($TBDH^+$, $pK_a = 26$ in acetonitrile)[15] drew our attention as a ROP catalyst for cyclic esters since it is commercially available and easily handled with reported use as a transesterification catalyst.[16] For example, in a ROP of lactide in the presence of TBD in a 1000:1:10 monomer/catalyst/initiator monomer conversion was complete in 2 min, rivaling the NHC catalysts in turnover frequency.[17] As TBD is a strong base, our initial hypothesis was that it deprotonates the alcohol and propagates by an anionic mechanism. However, solvent effects on the polymerization with TBD were inconsistent with a purely anionic mechanism. For the TBD-catalyzed ROP of lactide, the reaction was fastest in $CH_2Cl_2$ (>90% conversion in 2 min), slightly slower in THF (60% conversion in 2 min), and much slower in DMF (0% conversion in 2 min), the opposite of what would be expected for a conventional anionic polymerization.

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These observations and the fact that the much faster rate of TBD relative to other organic catalysts such as 1,8-diazabicyclo-[5.4.0]undec-7-ene ($DBUH^+$, $pK_a = 24$) was not entirely consistent with their relative basicities suggested to us the intriguing possibility that TBD is not functioning merely as a base, but as a novel bifunctional acylation catalyst; acylation of TBD generates an activated acyl intermediate with an adjacent imine that functions as a general base to activate the alcohol for nucleophilic attack (Scheme 1A). Although mechanistic studies implied that TBD can function both as a base and a nucleophilic acylating agent, subsequent theoretical studies indicated that a nucleophilic mechanism had a considerably higher barrier than an alternative hydrogen-bond-mediated mechanism for transesterification reactions (Scheme 1B).[18] The bifunctional hydrogen-bonding capabilities of bicyclic guanidine catalysts were also reported by Corey[19] in the enantioselective Strecker reaction of α-aminonitriles and α-amino acids. Moreover, TBD was shown to react with malonate esters via nucleophilic attack of both disubstituted nitrogens at the carbonyl groups to form betaine-like structures.[20] In this communication, we describe a facile route to structurally diverse acyclic guanidines together with their viability as catalysts for the ROP of lactide. The activity and mechanism of these new catalysts are compared to the cyclic guanidines previously reported.[9,17]

The synthesis of the acyclic guanidines was accomplished by reaction of carbodiimides with secondary amines according to literature procedures (Scheme 2).[21] Three secondary amines were surveyed, pyrrolidine, TBD, and diphenyl[(2S)-2-pyrrolidine]-methanol. Pyrrolidine is readily available and is expected to generate a sterically unencumbered guanidine, **1**, whereas diphenyl[(2S)-2-pyrrolidine]methanol generates a bulky chiral guanidine, **3**, that is likely to have important ramifications in stereoselective polymerizations. The addition of TBD to dicyclohexylcarbodiimide (DCC) generates a biguanidine **2** that is considerably more basic than TBD alone and has been shown to be a potent catalyst for the transesterification of vegetable oils to generate biofuels.[10] DCC was reacted neat at elevated temperature with either pyrrolidine, TBD, or diphenyl[(2S)-2-pyrrolidine]methanol. Once the DCC melted, a homogeneous solution was formed, and the reaction was allowed to proceed overnight to

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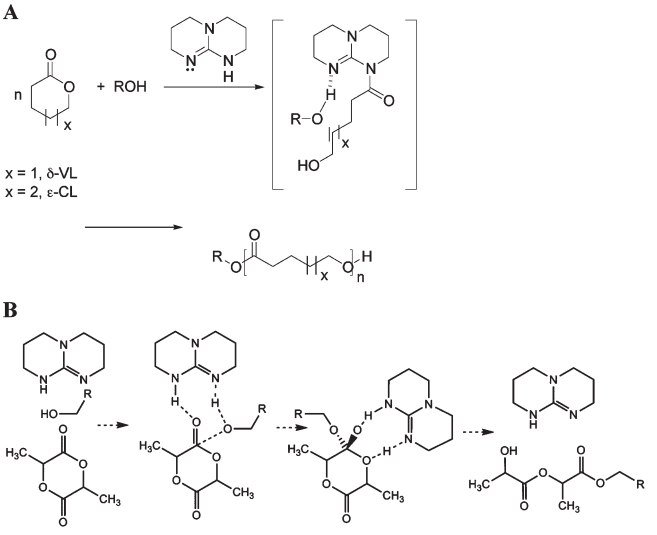
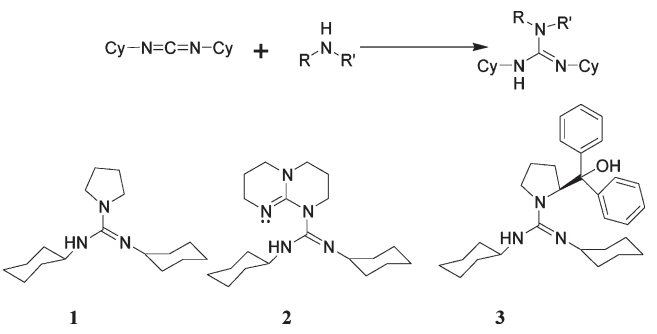
**Scheme 1. ROP of Cyclic Esters through Dual Activation by TBD[a]**

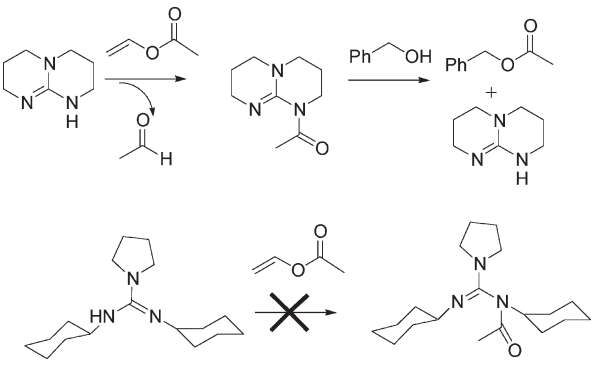



[a] (A) acyl mechanism and (B) hydrogen bonding mechanism.

**Scheme 2. Synthesis of Acyclic Guanidines**




**Scheme 3. Acyl Transfer Reactions with TBD and 1**



generate a viscous oil/gel. GC/MS results showed that quantitative conversion of starting material was accomplished in ~12 h. Compounds **1** and **2** were purified by Kugelrohr distillation and **3** was purified by column chromatography.

The catalytic activity and mechanism of synthesized acyclic guanidines were studied and compared with that of TBD. While theoretical studies implicate an alcohol activation mechanism,[10] in a model reaction it was shown that TBD could be acylated by reaction with vinyl acetate followed by removal of the low-boiling acetaldehyde (Scheme 3). Subsequent addition of excess benzyl alcohol completed the cycle by the formation of methyl benzoate, releasing the TBD-catalyst.[10] In contrast, none of the acyclic guanidines reacted with vinyl acetate to give acylated products.

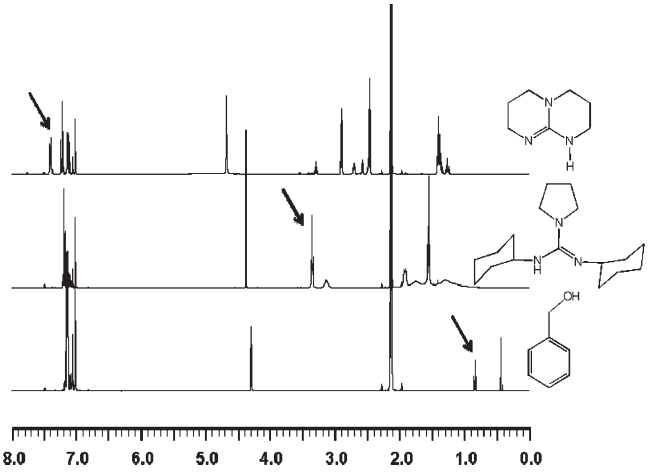
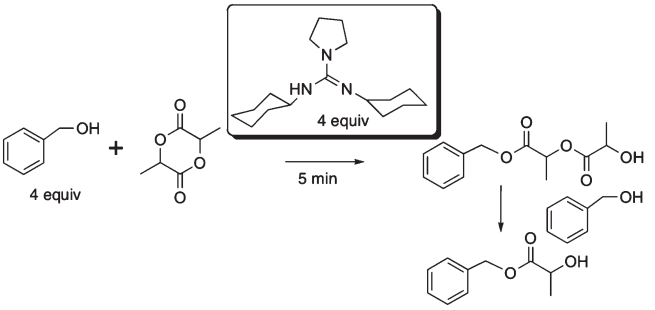



**Figure 1.** $^1$H NMR study. Hydroxy group of benzyl alcohol (bottom spectrum) shift downfield with the addition of noncyclic guanidine, **1** (middle spectrum), and TBD (top spectrum).

**Scheme 4. Single Turnover Reaction of Lactide with Alcohol Using Noncyclic Guanidine Catalyst 1**




However, vinyl acetate reacts with benzyl alcohol giving benzyl acetate over the course of 12 h in the presence of **1,** which is similar to that observed for DBU.[9] As for TBD, the addition of **1** to benzyl alcohol in toluene shifts the alcohol-proton from 0.85 to 3.45 ppm; minor shifts for the α-methylene protons of benzyl alcohol are also observed, indicating a strongly hydrogen bonded complex.

To determine if the acyclic guanidines could mediate the ring-opening of lactide, a single turnover experiment was carried out where an excess of benzyl alcohol was treated with lactide in the presence of guanidine **1** in toluene-$d_8$ (Scheme 4). An aliquot removed upon mixing revealed the formation of the benzyl dilactate; after two days, further transesterification to benzyl lactate was observed.

Having demonstrated that **1** ring-opens lactide in the presence of stoichiometric benzyl alcohol, each of the guanidines **1**−**3** was surveyed for the catalytic ROP of lactide. Polymerization of L-lactide in $CH_2Cl_2$ (2 M) with 1 mol % of **1** relative to monomer (with 1 mol % of pyrenebutanol relative to monomer as the initiator) generated polylactide in approximately 40 min with near quantitative conversion of monomer to polymer (~99%). The resulting polymer had a number average molecular weight $M_n$ = 17 600 with a PDI (PDI = $M_w/M_n$) of 1.06. Concurrent monitoring of both the refractive index and UV absorbance by gel permeation chromatography (GPC) (Figure 2A) together with $^1$H NMR spectroscopy (Figure 2B) shows that the UV-active pyrenebutanol initiator is fully incorporated into the polymer, demonstrating end-group fidelity and supports the initiation of the polymerization by pyrenebutanol. Aliquots taken during the polymerization with benzyl alcohol show a linear increase in molecular weight with conversion, a trend that

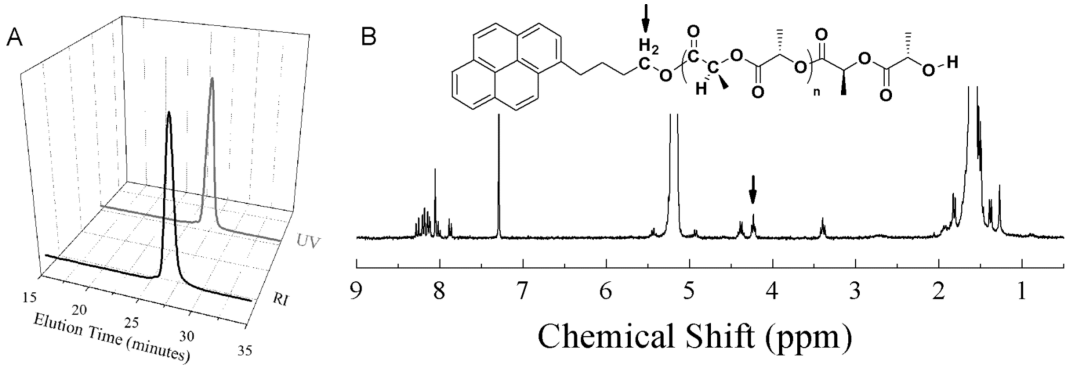



**Figure 2.** (A) Overlay of signals from refractive index (RI) and UV absorbance GPC detectors, (B) NMR spectrum of synthesized PLLA with α H peak of pyrenebutanol marked. (PLLA with $M_n$ of 17 600 and PDI of 1.06 was prepared using catalyst 1 with L-LA/catalyst **1**/pyrenebutanol = 100:1:1).

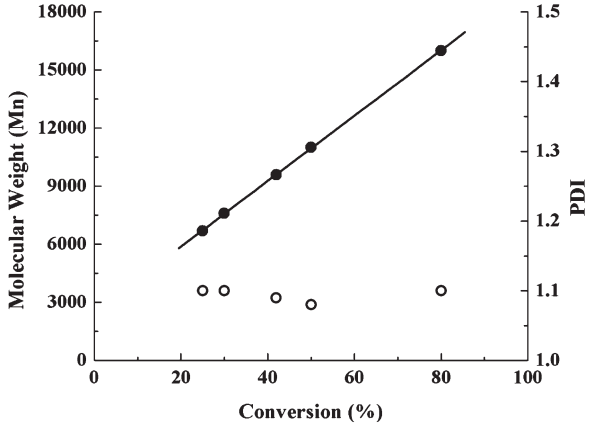



**Figure 3.** Mn (●) and PDI (○) versus conversion for ROP of L-LA catalyzed by noncyclic guanidine catalyst **1** in $CH_2Cl_2$. (L-LA/catalyst **1**/benzyl alcohol = 100:1:1). Molecular weight from GPC using polystyrene standards.

is typically associated with a living polymerization (Figure 3). The PDIs remain narrow throughout the polymerization (< 1.15). Higher targeted degrees of polymerization (DPs), 200 and 400, gave molecular weights of 28 000 g/mol (PDI = 1.13) and 37 000 g/mol (PDI = 1.14), respectively. The differences of the three acyclic guanidines in activity and selectivity were revealed by comparing the three catalysts in a one-to-one ratio of catalyst to benzyl alcohol initiator in $CH_2Cl_2$ (2 M) with targeted polylactide DPs of 100. A quenched aliquot (20 min polymerization time) showed quantitative conversion of monomer to polymer ($M_n$ = 37 000 g/mol, PDI = 1.49) for catalyst **2**, whereas polymers generated from catalysts **1** and **3** showed conversions of 50 and 70% ($M_n$ = 18 000 and 33 000 g/mol and PDIs of 1.13 and 1.04, respectively). The higher activity of **2** is accompanied by the loss in selectivity and control; presumably this catalyst is more active both for ring-opening and for transesterification of the resulting polymer, leading to broader polydispersities. Catalyst **3** shows both high activity and selectivity, but little stereoselectivity for the ROP of rac-lactide ($P_i$, the probability of forming a new *i* dyad, = 0.56) at room temperature and at 0 °C ($P_i$ = 0.62), which we attribute to the remote position of the stereogenic center.

To gain an understanding of the catalytic activity of this new class of guanidines we compared the structures of **1** and its adduct with methanol with the corresponding structures for TBD, using B3LYP/aug-cc-pVTZ//B3LYP/6-31+G*[22] density functional calculations[23] in the presence of a continuum dielectric $\varepsilon = 2.379$ (toluene) using IEF-cPCM[24] as implemented in GAMESS-US.[25]

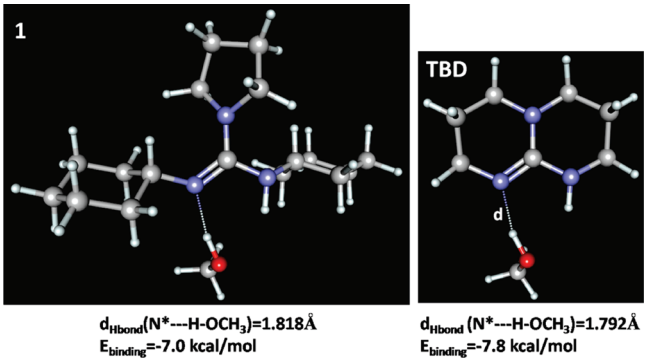



**Figure 4.** Comparison of the adduct of **1** and TBD with methanol; binding energies and hydrogen bond lengths relevant for the catalytic activation of the alcohol initiating the ROP.

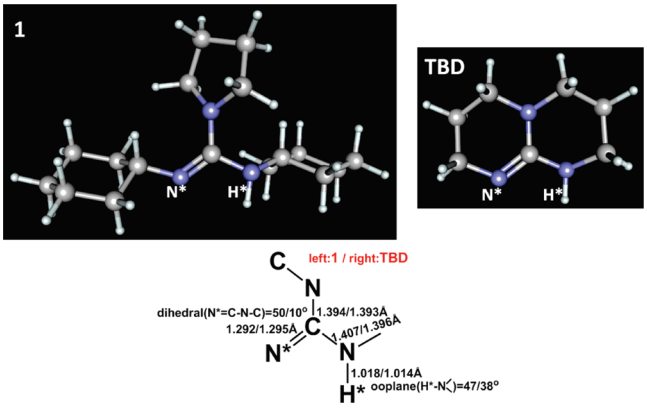



**Figure 5.** Structural comparison of the new guanidine catalyst (**1**) and TBD.

Catalyst **1** forms a more weakly bound adduct with methanol than TBD, as apparent in the binding energy (−7.0 kcal/mol (**1**) versus −7.8 kcal/mol (TBD)) as well as the N*----H−OCH3 hydrogen bond distance (1.818 Å (**1**) vs 1.792 Å (TBD)), indicating **1** to be a weaker base than TBD (see Figure 4). These trends correlate with the observed shifts in 1H resonances of the hydroxyl H for benzyl alcohol upon binding to the guanidine: $\Delta\delta$ = 2.26 ppm (**1**) versus ~7.0 ppm (TBD).

We attribute the lower basicity of **1** (relative to TBD) to the observation that the five-membered pyrrolidine ring in **1** is rotated out-of-plane (dihedral angle 50°(**1**) vs 10°(TBD), Figure 5) due to nonbonding interactions between the pyrrolidine ring and the

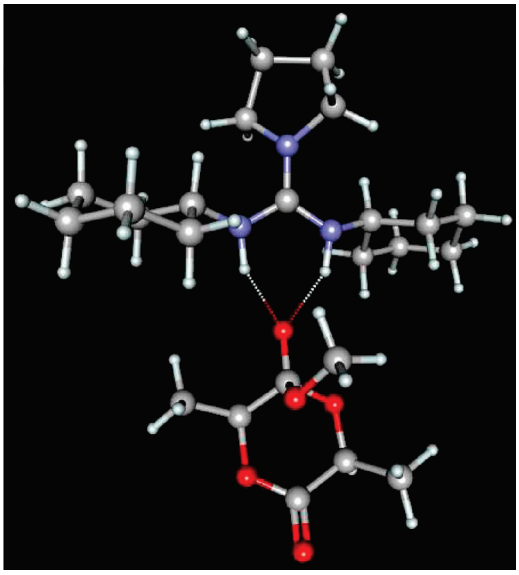


**Figure 6.** Tetrahedral intermediate resulting from the reaction of **1** with methanol and L-lactide.

cyclohexyl groups, thereby attenuating the conjugation between the three guanidine nitrogens.

Investigation of Scheme 1B indicates that **1** stabilizes the structure of the tetrahedral intermediate through hydrogen bonding in an analogous manner to that for TBD[18] (see Figure 6).

The efficacy of acyclic guanidines for the ROP of lactide with predictable molecular weights, narrow polydispersities, and end-group fidelity was demonstrated. Despite the exceptional control of these ring-opening reactions, the rate of ring-opening of lactide with the acyclic guanidines are considerably less than that observed for the bicyclic TBD.[11] Theoretical studies are consistent with a mechanism that involves activation of the alcohol by the guanidine and by stabilization of the resultant tetrahedral intermediates through hydrogen-bonding. NMR studies, combined with theoretical calculations, indicate that the acyclic guanidines are less basic than TBD but are also hydrogen bond donors, which suggests that cooperative effects of weak secondary interactions are important for active and selective catalysis.

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