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Triazabicyclodecene: A Simple Bifunctional Organocatalyst for Acyl Transfer and Ring-Opening Polymerization of Cyclic Esters

Russell C. Pratt,[†] Bas G. G. Lohmeijer,[†] David A. Long,[‡] Robert M. Waymouth,*[,§] and James L. Hedrick*[,†]

IBM Almaden Research Center, 650 Harry Road, San Jose, California 95120, Kenyon College, Gambier, Ohio 43022, and Department of Chemistry, Stanford University, Stanford, California 95032

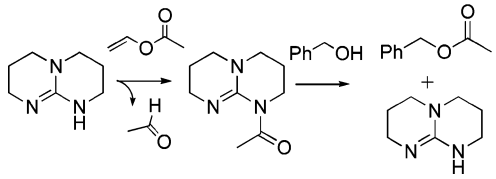
Received February 3, 2006; E-mail: waymouth@stanford.edu; hedrick@almaden.ibm.com

To harness the ability of macromolecules to generate interesting and functional microstructures, it is of utmost importance to have control over the size and distribution of the different polymer segments. For applications in microelectronics and in living systems, the resulting polymers should be free of any metal residues. These requirements have motivated the development of novel chemistry, such as the controlled radical polymerizations mediated by nitroxide and dithioester intermediates.[1,2] Our own work has focused on the development of metal-free organocatalytic ring-opening polymerizations (ROPs) of cyclic esters and has led us to investigate the reactivity of known transesterification agents such as 4-(dimethylamino)pyridine[3] and phosphines[4] as well as the more recently developed *N*-heterocyclic carbenes[5] (NHCs) and bifunctional amino-thioureas.[6]

We have proposed a monomer-activated mechanism for NHCs wherein the highly nucleophilic NHC attacks the carbonyl group to accelerate transesterification.[5] Alternatively, the strongly basic NHC could activate the alcohol for transesterification through formation of a hydrogen bond.[7] The bifunctional amino-thiourea catalysts were proposed to simultaneously activate the alcohol of the initiating/propagating species and the carbonyl of the monomer through hydrogen bonding.[6] Interesting parallels exist between the chemistry of these catalysts and another strongly basic organic molecule, the commercially available guanidine 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD). First, the pK_a values of the conjugate acid of TBD in organic solvents such as THF and MeCN[8a] are close to those determined experimentally and computationally for those of the NHCs (pK_a = 26 vs 17−26).[8b] TBD has been applied as a strongly basic catalyst for a variety of reactions, including Michael additions,[9] Wittig reactions,[10] Henry reactions,[11] and transesterification reactions.[12] More importantly, Corey has shown that bicyclic guanidine catalysts exhibit bifunctional hydrogen-bonding capabilities in the enantioselective Strecker synthesis of α-aminonitriles and α-amino acids,[13] and TBD was shown to react with malonate esters via nucleophilic attack of both disubstituted nitrogens at the carbonyl groups to form betaine-like structures.[14] This prompted us to study the chemistry of TBD with respect to transesterification and ROP.

In initial studies, we found the reaction of TBD with vinyl acetate to be especially revealing. Combination of the reagents in 1:1 stoichiometry as monitored by ^{1}H NMR spectroscopy results in rapid, quantitative formation of acetaldehyde and *N*-acetylTBD as a stable, neutral compound (Scheme 1). Addition of benzyl alcohol to *N*-acetylTBD results in the rapid quantitative formation of benzyl acetate and regenerates TBD, completing a single TBD-catalyzed transesterification turnover. The acylation of TBD and subsequent

Scheme 1. Acyl Transfer Reactions[a]



[a] Conditions: (i) vinyl acetate, Bz, room temperature, 10 min; (ii) $PhCH_2OH$, Bz, 10 min.

esterification indicate that guanidines such as TBD might function not merely as general base catalysts. These results may suggest a novel catalytic role for guanidines, a substructure common to many bioactive natural products.[15]

Having found TBD to be an efficient acyl-transfer and transesterification catalyst, we explored its activity for the ROP of cyclic esters. Polymerization of L-lactide (LLA) in CH_2Cl_2 with TBD at only 0.1% relative to monomer with 1% of 4-pyrenebutanol added as an initiator (targeted degree of polymerization (DP) = 100) generated poly(LLA) in seconds at room temperature, activity rivaling that of the most active metal catalysts.[16] The resulting polymer had a molecular weight of M_n = 24 200 g mol^{-1} and a narrow polydispersity (PDI = M_w/M_n = 1.19). Different molecular weights could be achieved by varying the concentration of initiator (Table 1). Simultaneous refractive index and UV absorbance monitoring by gel permeation chromatography (GPC), together with ^{1}H NMR spectroscopy, shows that the UV-active 4-pyrenebutanol initiator is fully incorporated into the polymer in all cases, demonstrating end-group fidelity (Figure 1, inset). Quenched aliquots taken during TBD-catalyzed polymerizations show a linear increase of M_n with conversion (Figure 1). A slight decrease in PDI from ∼1.25 to ∼1.20 as conversion approaches 90% suggests that broadening of the molecular weight distribution occurs during the initial stages of polymerization, due to the high activity of the catalyst. If reaction mixtures are left to stand, TBD-catalyzed transesterification of the poly(LLA) leads to increased PDIs, but TBD can be quenched at short reaction times simply by addition of benzoic acid.

Encouraged by TBD's high activity for lactide polymerization, we examined its ability to catalyze the ROP of δ-valerolactone (VL) and ϵ-caprolactone (CL). Polymerization of VL proceeded more slowly than that of LLA; nevertheless, a 1.75 M benzene solution of VL was polymerized with 0.5% TBD to >90% conversion within 30 min (Figures 1 and S1). The longer reaction time allows greater control of the PDI: the poly(VL) had an M_n of 14 500 g/mol and PDI = 1.09. ROP of CL is complicated by the onset of transesterification and broadening of the PDI, reflecting the high tendency of poly(CL) chain ends to transesterify.[17] Still, at $[M]_0/[I]_0$ ratios of 50 and 100, the polymerizations reached ∼75% conversions in

[†] IBM Almaden Research Center.
[‡] Kenyon College.
[§] Stanford University.

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Table 1. Results for Base-Catalyzed ROP of Cyclic Esters

monomer[a]	catalyst (%)[b]	$[M]_o/[I]_o$	time	conversion (%)[c]	M_n (g mol^{-1})[d]	PDI[d]
LLA	0.1	100	20 s	99	24 200	1.19
LLA	0.1	500	1 min	95	62 600	1.11
δ-VL	0.5	25	0.2 h	90	3 800	1.06
δ-VL	0.5	50	0.25 h	88	7 000	1.05
δ-VL	0.5	100	0.5 h	91	14 500	1.09
δ-VL	0.3	200	0.5 h	77	16 500	1.12
ϵ-CL	0.5	50	5 h	76	8 200	1.10
ϵ-CL	0.5	100	8 h	72	16 900	1.16
ϵ-CL	0.5	200	8 h	52	20 800	1.16

[a] Solvent for LLA was CH_2Cl_2; for δ-VL and ϵ-CL, C_6D_6 was used. [b] Percentage relative to monomer. [c] Measured by ^{1}H NMR. [d] Measured by GPC in THF.

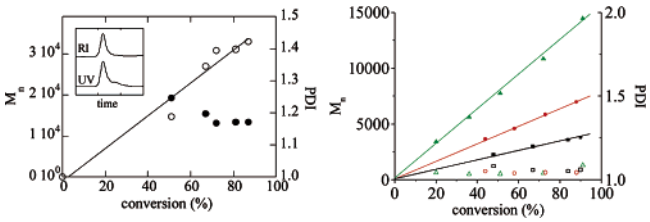
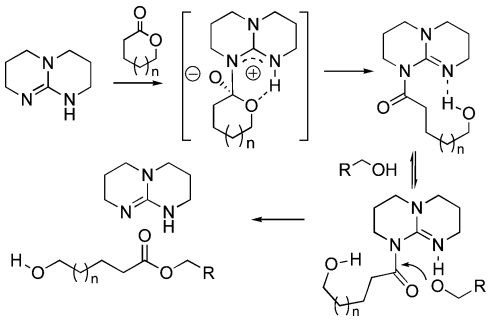


Figure 1. (Left) M_n (○) and PDI (●) versus conversion for ROP of LLA catalyzed by TBD. (Inset) Overlay of signals from refractive index (RI) and UV absorbance GPC detectors showing incorporation of UV-active initiator into poly(LLA). (Right) M_n (filled symbols) and PDI (open symbols) versus conversion for ROP of VL catalyzed by TBD.

5 and 8 h, respectively, at 0.5% TBD loading while retaining low PDIs (1.10−1.16). Reactions targeting high-molecular-weight poly(CL) yielded polymers with higher molecular weight distributions, up to 1.16 after conversions of ∼50% (Figure S2). The ROP of β-butyrolactone (BL) with TBD was unsuccessful; at 25 °C no polymer was observed, and at 50 °C only oligomers were obtained. The versatility of TBD as a catalyst for the preparation of block copolymers is further demonstrated by using monohydroxyl-functionalized macroinitiators such as poly(ethylene oxide) and polystyrene. Clean chain extensions were observed for *rac*-LA, VL, and CL, with excellent polydispersities and short reaction times for *rac*-LA (Table S1). Remarkably, TBD shows high selectivity in copolymerizations of the cyclic esters. At room temperature, the fastest propagating monomer is ring-opened first to >95% conversion, before competition between transesterification of the so-formed polymer backbone and ring-opening of the second monomer starts taking place. Hence, block copolyesters could be prepared by first polymerizing the slower propagating monomer to high conversion and subsequently adding in the second monomer (Table S2).

The strong basicity of TBD and its wide use as a general base catalyst for a variety of transformations would suggest that TBD functions by deprotonating or activating the alcohol for nucleophilic ring-opening of the lactone monomers by a pseudo-anionic mechanism. However, the *N*-methyl derivative of TBD (MTBD) is much less active than TBD for the polymerization of lactide (30 min to reach 92% conversion at 1% MTBD vs 20 s to reach 99% conversion at 0.1% TBD for a targeted DP of 100), despite its similar basicity (pK_a = 25.5).[8] Moreover, higher polymerization rates were observed in benzene and CH_2Cl_2 in contrast to those in THF and DMF, which is the opposite of what would be expected for an anionic mechanism. These results and our mechanistic investigations with vinyl acetate (Scheme 1) suggest another mechanistic possibility, a bifunctional nucleophilic mechanism (Scheme 2). Nucleophilic attack of the imine nitrogen at the carbonyl would generate an intermediate where the adjacent protonated nitrogen is ideally suited for proton transfer to the

Scheme 2. Dual Activation of Monomer and Initiator by TBD



incipient alkoxide to generate the TBD amide. Hydrogen-bond activation of the incoming alcohol should facilitate esterification, liberating the ester and regenerating TBD. By this mechanism, TBD functions as a deceptively simple bifunctional transesterification catalyst, analogous to the amino-thioureas we have used previously.[6]

In summary, we have found TBD to be a very active catalyst for ROP of LLA, VL, and CL, providing polymers of controlled molecular weight and polydispersity. While pseudo-anionic mechanisms are plausible, TBD appears to be uniquely capable of activating both monomer and initiator, which may explain its heightened reactivity. The ready commercial availability, ease of use, and controlled high activity of TBD make it a highly accessible catalyst for solution-phase ROP of cyclic esters.

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Supporting Information Available: Full experimental details, tables, and figures of polymerization. This material is available free of charge via the Internet at http://pubs.acs.org.

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