Guanidine and Amidine Organocatalysts for Ring-Opening Polymerization of Cyclic Esters

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ABSTRACT: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD), *N*-methyl-TBD (MTBD), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) are effective organocatalysts for the ring-opening polymerization (ROP) of cyclic esters such as lactide (LA), δ-valerolactone (VL), and ϵ-caprolactone (CL). TBD is shown to polymerize LA, VL, and CL in a fast and controlled manner, whereas MTBD and DBU polymerized LA and addition of a thiourea cocatalyst led to the ROP of VL and CL being achieved. Each of the catalysts produced polymers displaying high end group fidelity, good correlation between theoretical and observed molecular weight, and linear relationships between conversion and molecular weight. The enhanced activity of TBD relative to MTBD and DBU is attributed to its bifunctionality, enabling the simultaneous activation of both the cyclic ester monomer and the alcohol group of the initiator/propagating species. Temperature-dependent NMR studies generated individual association constants for MTBD with benzyl alcohol and thiourea with VL. In combination with temperature-dependent ROP of VL in the presence of benzyl alcohol, MTBD, and thiourea, these data have led to the derivation of the activation energy for the ROP (49 ± 3 kJ mol^{-1}). The simplicity of the reaction conditions, the ready availability of the catalysts, the variety of polymerizable cyclic ester monomers, and the exquisite control over the polymerization are demonstrated.

Introduction

Aliphatic polyesters are an important class of polymers, which, as a result of their outstanding materials properties and facile degradation, have many applications ranging from textiles and packaging to microelectronics and drug delivery.[1] However, for advanced applications, polymerization techniques that give predictable molecular weights, low polydispersity indices, and high end group fidelity are a necessity, and strategies employing the ring-opening polymerization (ROP) of cyclic esters meet these requirements. Organometallic catalytic polymerization reactions have commonly been employed in the preparation of polylactide and polylactones.[2] Nevertheless, heavy metal contaminants from the catalyst residues in the polymer can have detrimental effects on the performance of the final polymers, especially in microelectronics and drug delivery. We have therefore initiated a research program on synthetic approaches to ROP of cyclic esters that are metal-free (organocatalytic). Among the successful organocatalysts discovered in our laboratories are tertiary amines such as 4-(dimethylamino)pyridine (DMAP), phosphines, and *N*-heterocyclic carbenes (NHCs).[3] For these potent organocatalysts we have proposed monomer activated mechanisms. Recently, we have developed an alternative pathway for the ROP of cyclic esters through bifunctional organocatalysis, using thiourea−tertiary amines.[4] The carbonyl group of a lactide monomer is activated toward electrophilic attack by the thiourea via hydrogen bonding, and the initiating/propagating alcohols are activated as nucleophiles by the tertiary amine (Scheme 1). Moreover, we demonstrated that the thiourea and the tertiary amine functionality are not required to be linked in the same molecule, and using (−)-sparteine as the activating agent for the alcohol enabled shorter reaction times while maintaining excellent control over the polymerization (~40-fold increase in polymerization rate).[5] Although adverse transesterification of the polymer backbone is essentially absent, even at high monomer conversions, the thiourea−tertiary amine systems studied so far are limited to ROP of lactide only. By increasing the basicity of the activating agent for the alcohol, we were hoping to even further increase the polymerization rates for lactide. Indeed, by application of the strong guanidine base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) ($pK_a = 26.0$ in acetonitrile for TBD[6] vs $pK_a = 17.5$ or 21.66 for (−)-sparteine[7]), the ROP of lactide in the absence of thiourea cocatalyst is completed within seconds for a degree of polymerization (DP) of 100: interestingly, bifunctional activation is still present. In a recent communication, we have shown that TBD is uniquely capable of inserting into the ester of the cyclic ester monomer, and subsequent hydrogen bonding of the adjacent nitrogen to an incoming alcohol completes a transesterification cycle to form the polyester (Scheme 2). Furthermore, this powerful organocatalyst is also able to readily polymerize δ-valerolactone and ϵ-caprolactone.[8] While TBD shows high selectivity toward ring opening of the monomer over transesterification of the polymer backbone, at high conversions broadening of the polydispersity indices (PDIs) is observed, an indication that TBD will eventually transesterify the polymer backbone leading to poor end group fidelity and broad molecular weight distributions.

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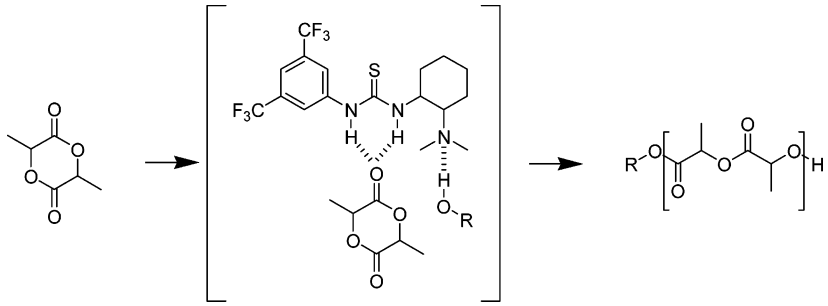
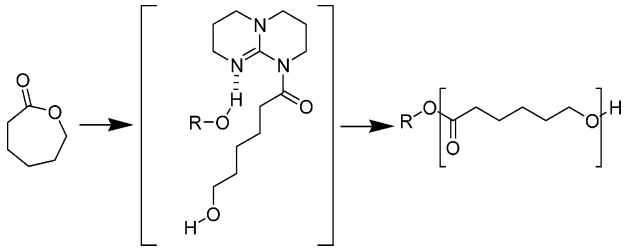
Scheme 1. Ring-Opening Polymerization of Lactide through Dual Activation by a Thiourea−Tertiary Amine Catalyst



Scheme 2. Ring-Opening Polymerization of Caprolactone through Dual Activation by TBD



Other structurally similar guanidine and amidine bases such as N-methylated TBD (MTBD) and 1,8-diaza[5.4.0]bicycloundec-7-ene (DBU) were also found to be active in the ROP of lactide. Bifunctional activation of monomer and initiator may again be accomplished by the use of a thiourea cocatalyst leading to polymerization of cyclic ester monomers with lower ring strain. In this paper we will present the results of our studies of using amidine and guanidine bases for the ring-opening polymerization of several cyclic esters.

Experimental Section

L-Lactide and DL-lactide (Purac) were recrystallized three times from toluene and dried in a vacuum prior to use. Dry toluene and methylene chloride were obtained from drying columns using a setup from Innovative Systems. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (98%), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (98%), δ-valerolactone (VL) (technical), ϵ-caprolactone (CL) (>99%), and β-butyrolactone (BL) (>98%) were received from Aldrich and distilled twice from CaH_2. 1,5,7-Triazabicyclo-[4.4.0]dec-5-ene (TBD) (98%) was used as received (Aldrich). Benzene-d_6 and methylene-d_2 chloride (99.6%, anhydrous) were stored over molecular sieves (3 Å). Chloroform-d was freshly distilled from CaH_2 and stored over molecular sieves (3 Å) for no longer than 2 weeks. 4-Pyrenebutanol (99%, Aldrich) and the thiourea−cocatalyst[4,5] were dissolved in THF, stirred overnight over CaH_2, filtered, and recovered by evaporation of the solvent before use in polymerizations. Monohydroxy-functional macroinitiators PEO_{120}−OH, PS_{60}−OH, and $PDMA_{40}$−OH were dried by azeotropic distillation of toluene (3×). PEO−OH was received from Fluka; PS−OH and PDMA−OH were synthesized by nitroxide-mediated polymerization according to literature procedures.[9] Storage of compounds and reaction assembly were performed in an inert atmosphere glovebox. ^{1}H NMR spectra were obtained on a Bruker Avance 400 instrument at 400 MHz; conversion was measured by the ratio of the integrations of the NMR signals of the α-methylene or methine protons of the monomer vs those of the polymers. Gel permeation chromatography was performed in THF using a Waters chromatograph equipped with four 5 μm Waters columns (300 mm × 7.7 mm) connected in series with increasing pore size (10, 100, 1000, 10^5, 10^6 Å), a Waters 410 differential refractometer, and a 996 photodiode array detector, calibrated with polystyrene standards ($750-2 \times 10^6$ g mol^{-1}).

Polymerization of L-LA Using TBD. L-LA (100 mg, 0.7 mmol) was dissolved in CH_2Cl_2 and added to a solution of 4-pyrenebutanol (1%) and TBD (0.1%) in CH_2Cl_2 (1 mL). Stirring was continued for 15 s, benzoic acid was added to quench the reaction, and the solvent was evaporated to yield a glassy solid. ^{1}H NMR ($CDCl_3$): 8.21−7.72 (m, 9H, aromatic), 5.20−5.06, (m, CH PLA backbone) 4.33 (t, 2H, C(=O)OCH_2), 4.24−4.14 (m, 2H, C*H*−O*H*), 3.21 (t, 2H, pyrene-CH_2), 1.61−1.41 (m, CH_3 PLA backbone, CH_2CH_2 PB). GPC (RI): M_n (PDI) = 24 200 g mol^{-1} (1.19).

Polymerization of L-LA Using MTBD. L-LA (100 mg, 0.7 mmol) and 4-pyrenebutanol (1.9 mg, 7 μmol) were dissolved in $CDCl_3$ (1 mL). The solution was then transferred to a vial containing MTBD (1 μL, 1 mg, 7 μmol) to initiate the polymerization. The polymerization was quenched after 1 h by addition of benzoic acid (5 mg). The polymer was analyzed after evaporation of the solvent or after precipitation into methanol and filtration. GPC (RI): M_n (PDI) = 17 900 g mol^{-1} (1.05).

Polymerization of L-LA Using DBU. L-LA (100 mg, 0.7 mmol) and 4-pyrenebutanol (1.9 mg, 7 μmol) were dissolved in $CDCl_3$ (1 mL). The solution was then transferred to a vial containing DBU (1 μL, 1 mg, 7 μmol) to initiate the polymerization. The polymerization was quenched after 1 h by addition of benzoic acid (5 mg). The polymer was analyzed after evaporation of the solvent or after precipitation into methanol and filtration. GPC (RI): M_n (PDI) = 21 000 g mol^{-1} (1.05).

Polymerization of δ-VL Using TBD. VL (100 mg, 1.0 mmol) was added to a solution of TBD (0.7 mg, 5 μmol) and 4-pyrenebutanol (5.5 mg, 20 μmol) in benzene-d_6 (0.5 mL). The solution was stirred for 15 min and then quenched by addition of benzoic acid (5 mg), and the solvent evaporated to yield a glassy solid. ^{1}H NMR ($CDCl_3$): δ 8.25−7.77 (m, 9H, aromatic), 4.50 (bs, 1H, OH), 4.20 (t, 2H, PB−C(=O)OCH_2), 4.10 (m, 90H, C(=O)OCH_2 PVL backbone), 3.45 (t, 2H, CH_2OH), 3.22 (t, 2H, PB−CH_2), 2.36 (m, 90H, CH_2C(=O)O PVL backbone), 1.70 (m, 184H, CH_2CH_2 PVL backbone, CH_2CH_2 PB); GPC (RI): M_n (PDI) = 7000 g mol^{-1} (1.05).

Polymerization of δ-VL Using MTBD and TU. VL (100 mg, 1.0 mmol) was added to a solution of MTBD (7.9 mg, 50 μmol), thiourea (18.5 mg, 50 μmol), and 4-pyrenebutanol (2.7 mg, 10 μmol) in benzene-d_6 (0.5 mL). The solution was stirred for 4 h and then quenched by addition of benzoic acid (5 mg), and the solvent evaporated. GPC (RI): M_n (PDI) = 12 100 g mol^{-1} (1.06).

Polymerization of δ-VL Using DBU and TU. VL (100 mg, 1.0 mmol) was added to a solution of DBU (7.9 mg, 50 μmol), thiourea (18.5 mg, 50 μmol), and 4-pyrenebutanol (5.5 mg, 20 μmol) in benzene-d_6 (0.5 mL). The solution was stirred for 3 h and then quenched by addition of benzoic acid (5 mg), and the solvent evaporated. GPC (RI): M_n (PDI) = 4100 g mol^{-1} (1.06).

Polymerization of ϵ-CL Using TBD. ϵ-CL (113 mg, 1.0 mmol) was added to a solution of TBD (0.7 mg, 5 μmol) and pyrenebutanol (5.5 mg, 20 μmol) in benzene-d_6 (0.5 mL). The solution was stirred for 5 h and quenched by addition of benzoic acid, and the solvent evaporated yielding a glassy solid.^{1}H NMR ($CDCl_3$): δ 8.25−7.77 (m, 9H, aromatic), 4.50 (bs, 1H, OH), 4.18 (t, 2H, PB−C(=O)-OCH_2), 4.06 (m, 90H, C(=O)OCH_2 PCL backbone), 3.42 (t, 2H, CH_2OH), 3.22 (t, 2H, PB−CH_2), 2.31 (m, 80H, CH_2C(=O)O PCL backbone), 1.64 (m, 160H, CH_2CH_2CH_2 PCL backbone), 1.38 (m, 84H, CH_2CH_2CH_2 PCL backbone, CH_2CH_2 PB). GPC (RI): M_n (PDI) = 8200 g mol^{-1} (1.10).

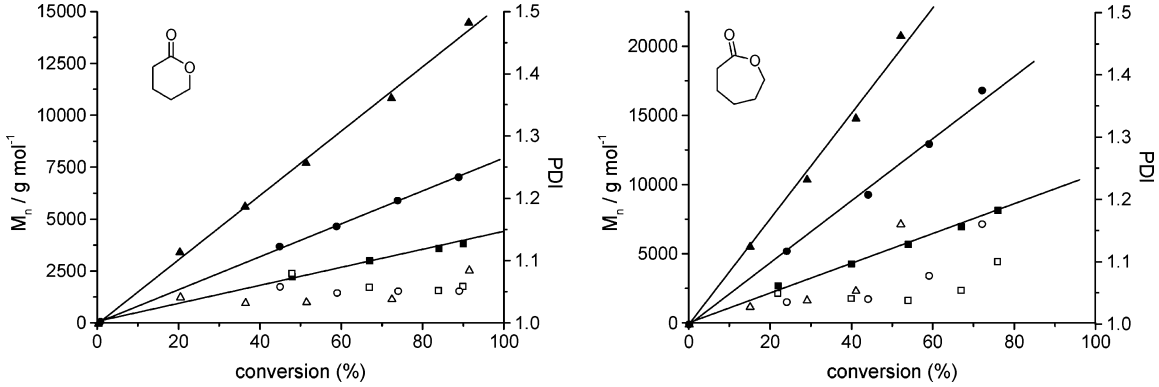


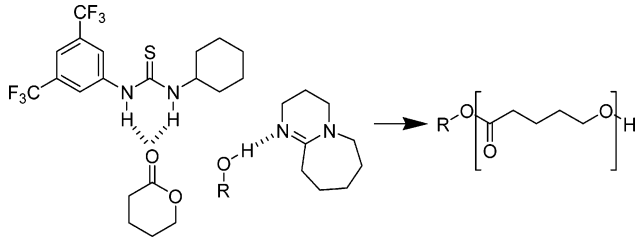
Figure 1. Ring-opening polymerization of valerolactone (left) and caprolactone (right) using TBD and pyrenebutanol as initiator. For VL the targeted degrees of polymerization were 25 (squares), 50 (circles), and 100 (triangles); for CL they were 50 (squares), 100 (circles), and 200 (triangles). The open symbols represent the polydispersities.

Table 1. Results of ROP of Cyclic Esters LA, VL, CL, and BL Using DBU, MTBD, TBD, and Combinations with TU

catalyst	monomer	catalyst (%)[a]	$[M]_0/[I]_0$	solvent	time (h)	conv (%)[b]	M_n (g mol^{-1})[c]	PDI[c]
TBD	L-LA	0.1	100	CH_2Cl_2	20 s	99	24 200	1.19
	L-LA	0.1	500	CH_2Cl_2	1 min	95	62 600	1.11
	δ-VL	0.5	25	C_6D_6	0.2	90	3 800	1.06
	δ-VL	0.5	50	C_6D_6	0.25	88	7 000	1.05
	δ-VL	0.5	100	C_6D_6	0.5	91	14 500	1.09
	δ-VL	0.3	200	C_6D_6	0.5	77	16 500	1.12
	ϵ-CL	0.5	50	C_6D_6	5	76	8 200	1.10
	ϵ-CL	0.5	100	C_6D_6	8	72	16 900	1.16
	ϵ-CL	0.5	200	C_6D_6	8	52	20 800	1.16
	β-BL	10	100	C_6D_6	72	0		
MTBD	L-LA	1	100	$CDCl_3$	0.5	92	17 900	1.05
	L-LA	0.5	500	CD_2Cl_2	0.5	99	55 300	1.10
	δ-VL	5	100	C_6D_6	72	0		
	δ-VL[d]	5	100	C_6D_6	4	92	12 100	1.06
	ϵ-CL	5	100	C_6D_6	72	0		
	ϵ-CL[d]	5	100	C_6D_6	120	78	7 700	1.05
	β-BL	5	100	C_6D_6	72	0		
	β-BL[d]	5	100	C_6D_6	72	0		
DBU	L-LA	1	100	$CDCl_3$	1	99	21 000	1.05
	L-LA	1	500	$CDCl_3$	2	98	85 000	1.08
	δ-VL	5	100	C_6D_6	72	0		
	δ-VL[d]	5	50	C_6D_6	3	95	4 100	1.06
	δ-VL[d]	5	100	C_6D_6	4	95	8 300	1.05
	δ-VL[d]	5	200	C_6D_6	6	95	16 200	1.05
	ϵ-CL[d]	5	100	C_6D_6	120	78	8 100	1.04
	β-BL[d]	5	100	C_6D_6	72	0		

[a] Percentage relative to monomer. [b] Measured by ^{1}H NMR. [c] Measured by GPC in THF. [d] 5 mol % TU added relative to monomer.

Scheme 3. Ring-Opening Polymerization of Valerolactone through Dual Activation by DBU and Thiourea



Polymerization of ϵ-CL Using MTBD and TU. ϵ-CL (113 mg, 1.0 mmol) was added to a solution of MTBD (7.9 mg, 50 μmol), thiourea (18.5 mg, 50 μmol), and pyrenebutanol (5.5 mg, 20 μmol) in benzene-d_6 (0.5 mL). The solution was stirred for 120 h and quenched by addition of benzoic acid, and the solvent evaporated yielding a glassy solid. GPC (RI): M_n (PDI) = 7700 g mol^{-1} (1.05).

Polymerization of ϵ-CL Using DBU and TU. ϵ-CL (113 mg, 1.0 mmol) was added to a solution of DBU (7.9 mg, 50 μmol), thiourea (18.5 mg, 50 μmol), and pyrenebutanol (5.5 mg, 20 μmol) in benzene-d_6 (0.5 mL). The solution was stirred for 120 h and quenched by addition of benzoic acid, and the solvent evaporated yielding a glassy solid. GPC (RI): M_n (PDI) = 8100 g mol^{-1} (1.04).

Block Copolymer Synthesis Using Macroinitiators. DL-LA (250 mg, 1.7 mmol) was added to a solution of TBD (0.3 mg, 2 μmol) and PEO_{110}−OH (100 mg, 20 μmol) in CH_2Cl_2 (4 mL). The solution was stirred for 15 s and quenched by addition of benzoic acid (5 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR ($CDCl_3$): 5.20−5.06 (m, ∼170H, C*H*$CH_{3\ PLA}$), 4.33−4.16 (m, 2H, C*H*$_2$OC(=O)), 3.92−3.48 (m, ∼450H, OC*H*$_{2\ PEO}$) 3.37 (s, 3H, OC*H*$_3$), 1.61−1.41 (m, ∼510H, CHC*H*$_{3\ PLA}$). GPC (RI): M_n (PDI) = 19 000 g mol^{-1} (1.05).

DL-LA (250 mg, 1.7 mmol) was added to a solution of TBD (0.3 mg, 2 μmol) and PS_{55}−OH (240 mg, 40 μmol) in CH_2Cl_2 (3 mL). The solution was stirred for 25 s and quenched by addition of benzoic acid (5 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR ($CDCl_3$): 7.37−6.57 (m, ∼285H; $H_{aromatic}$, C_6H_5 PS), 5.23−5.06 (m, ∼190H; C*H*$_{PLA}$, *H*C−ON, PhOC*H*$_2$), 4.40−4.22 (b, 2H; C*H*−OH, ON−C*H*), 3.16−0.51 (m, ∼750H; C*H*$_{2\ PS}$, C*H*$_{PS}$, C*H*$_{3\ PLA}$, C*H*$_{3\ ini}$, CH_3CHCH_3, C(C*H*$_3$)$_3$), C*H*$_3$CHCH$_3$, CH_3CHCH_3). GPC (RI): M_n (PDI) = 22 900 g mol^{-1} (1.07).

DL-LA (250 mg, 1.7 mmol) was added to a solution of TBD (0.3 mg, 2 μmol) and $PDMA_{40}$−OH (80 mg, 20 μmol) in CH_2Cl_2 (4 mL). The solution was stirred for 25 s and quenched by addition of benzoic acid (5 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR ($CDCl_3$): 7.27−7.08 (m, 9H; $H_{aromatic}$), 5.21−5.08 (m, ∼200H; C*H*$_{PLA}$, *H*C−ON, PhOC*H*$_2$), 4.38−4.18 (b, 2H; C*H*−OH, ON−C*H*), 3.22−0.48 (m, ∼1050H; N(C*H*$_3$)$_{2\ PDMAA}$, C*H*$_{2\ PDMAA}$, C*H*$_{PDMAA}$, ON−C*H*, C*H*$_{3\ PLA}$, C*H*$_{3\ initiating\ fragment}$, CH_3CHCH_3, C(C*H*$_3$)$_3$), C*H*$_3$CHCH$_3$, CH_3CHCH_3). GPC (RI): M_n (PDI) = 27 700 g mol^{-1} (1.06).

VL (2.0 g, 20 mmol) was added to a solution of TBD (13.9 mg, 100 μmol) and PEO_{110}−OH (2.0 g, 400 μmol) in toluene (25 mL). The solution was stirred for 15 min and quenched by addition of benzoic acid (35 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR ($CDCl_3$): 4.50 (b, 1H, OH), 4.20 (m, 2H, OCH_2CH_2-OC(=O)), 4.10 (m, 60H, CH_2OC(=O)$_{PVL}$), 3.84−3.48 (m, 440 H, OC$H_{2\ PEO}$), 3.37 (s, 3H, OCH_3), 2.25 (m, 60H, OC(=O)C$H_{2\ PVL}$), 1.62 (m, 120H, CH_2C$H_{2\ PVL}$). GPC (RI): M_n (PDI) = 11 000 g mol^{-1} (1.04).

VL (100 mg, 1 mmol) was added to a solution of TBD (0.7 mg, 5 μmol) and PS_{55}−OH (120 mg, 20 μmol) in toluene (1 mL). The solution was stirred for 15 min and quenched by addition of benzoic acid (5 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR ($CDCl_3$): 7.41−6.63 (m, ∼285H; $H_{aromatic}$, C_6H_5 PS), 4.72 (b, 2H, PhCH_2), 4.50 (b, 1H, *H*C−ON), 4.10 (m, 40H, CH_2OC-(=O)$_{PVL}$), 3.22−0.44 (m, ∼300H; C$H_{2\ PS}$, CH_{PS}, OC(=O)-CH_2CH_2C$H_{2\ PVL}$, C$H_{3\ ini}$, CH_3CHCH_3, C(CH_3)$_3$), CH_3CHCH$_3$, CH_3CHCH_3). GPC (RI): M_n (PDI) = 12 200 g mol^{-1} (1.12).

VL (100 mg, 1 mmol) was added to a solution of TBD (0.7 mg, 5 μmol) and $PDMA_{40}$−OH (100 mg, 25 μmol) in toluene (1 mL). The solution was stirred for 15 min and quenched by addition of benzoic acid (5 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR ($CDCl_3$): 7.24−7.06 (m, 9H; $H_{aromatic}$), 4.81 (b, 2H, PhCH_2), 4.62 (b, 1H, *H*C−ON), 4.10 (m, 50H, CH_2OC(=

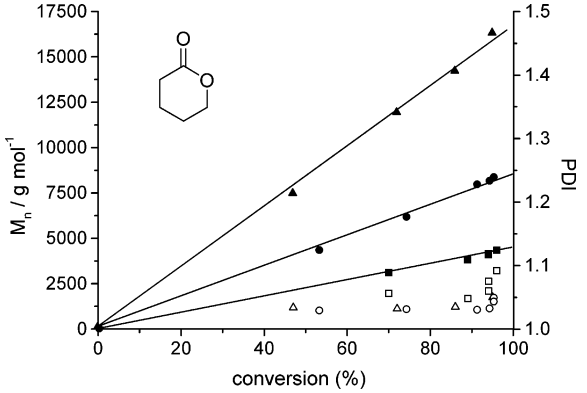


Figure 2. Ring-opening polymerization of valerolactone using DBU and thiourea as catalyst and pyrenebutanol as initiator. The targeted degrees of polymerization were 50 (squares), 100 (circles), and 200 (triangles). The open symbols represent the polydispersities.

O)$_{PVL}$), 3.22−0.50 (m, ∼650H; N(C*H*$_3$)$_2$ $_{PDMAA}$, C*H*$_2$ $_{PDMAA}$, C*H*$_{P\text{-}DMAA}$, ON−C*H*, C*H*$_3$ $_{initiating\ fragment}$, OC(═O)C*H*$_2$C*H*$_2$C*H*$_2$ $_{PVL}$ CH$_3$C*H*CH$_3$, C(C*H*$_3$)$_3$), C*H*$_3$CHCH$_3$, CH$_3$CHC*H*$_3$). GPC (RI): M_n (PDI) = 11 100 g mol^{-1} (1.17).

CL (2.3 g, 20 mmol) was added to a solution of TBD (13.9 mg, 100 μmol) and PEO$_{110}$−OH (2.0 g, 400 μmol) in toluene (25 mL). The solution was stirred for 3 h and quenched by addition of benzoic acid (35 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR (CDCl$_3$): 4.53 (b, 1H, OH), 4.16 (m, 2H, OCH$_2$C*H*$_2$OC(═O)), 4.07 (m, 60H, OCH$_2$C*H*$_2$OC(═O)$_{PCL}$), 3.71−3.48 (m, 440H, C*H*$_2$O$_{PEO}$), 3.37 (s, 3H, OC*H*$_3$), 2.30 (m, 60H, OC(═O)CH$_2$ $_{PCL}$), 1.64 (m, 120H, C*H*$_2$CH$_2$C*H*$_2$ $_{PCL}$), 1.41 (m, 60H, CH$_2$C*H*$_2$CH$_2$ $_{PCL}$). GPC (RI): M_n (PDI) = 11 100 g mol^{-1} (1.03).

CL (113 mg, 1 mmol) was added to a solution of TBD (0.7 mg, 5 μmol) and PS−OH (120 mg, 20 μmol) in toluene (1 mL). The solution was stirred for 3 h and quenched by addition of benzoic acid (5 mg). The solvent was evaporated yielding a glassy solid. ^{1}H NMR (CDCl$_3$): 7.38−6.55 (m, ∼285H; H$_{aromatic}$, C$_6$*H*$_5$ $_{PS}$), 4.81 (b, 2H, PhC*H*$_2$), 4.53 (b, 1H, *H*C−ON), 4.17 (m, 2H, OCH$_2$C*H*$_2$-OC(═O)$_{PCL}$), 4.07 (m, 160H, OCH$_2$C*H*$_2$OC(═O)$_{PCL}$), 3.33−0.53 (m, ∼825H; C*H*$_2$ $_{PS}$, C*H*$_{PS}$, OC(═O)C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$ $_{PCL}$, C*H*$_3$ $_{ini}$, CH$_3$C*H*CH$_3$, ON−C*H*, C(C*H*$_3$)$_3$, C*H*$_3$CHCH$_3$, CH$_3$CHC*H*$_3$). GPC (RI): M_n (PDI) = 23 400 g mol^{-1} (1.11).

Synthesis of Block Copolyesters. VL (115 mg, 1.2 mmol) was added to a solution of 4-pyrenebutanol (5.2 mg, 19 μmol) and TBD (1.1 mg, 8 μmol) in CH$_2$Cl$_2$ (2.5 mL). The reaction mixture was stirred for 12 min, after which a sample was withdrawn and quenched with benzoic acid (2.5 mg) for analysis of conversion, molecular weight, and polydispersity. GPC (RI): M_n (PDI) = 4000 g mol^{-1} (1.05). A solution of DL-lactide (200 mg, 1.4 mmol) in CH$_2$Cl$_2$ (2.5 mL) was added to the polymerization mixture. The reaction mixture was quenched by the addition of benzoic acid (5 mg) after 15 s. ^{1}H NMR (CDCl): δ = 8.25−7.77 (m, 9H, aromatic), 5.20−5.06, (m, 200H, C*H*$_{PLA\ backbone}$), 4.20 (t, 2H, PB−C(═O)-OCH$_2$), 4.10 (m, 40H, C(═O)OCH$_2$ $_{PVL\ backbone}$), 3.45 (t, 2H, CH$_2$-OH), 3.22 (t, 2H, PB−CH$_2$), 2.36 (m, 40H, CH$_2$C(═O)O$_{PVL\ backbone}$), 1.70−1.40 (m, 684H, CH$_2$CH$_2$ $_{PVL\ backbone}$, CH$_2$CH$_2$ PB, CH$_3$ $_{PLA\ backbone}$, CH$_2$CH$_2$ PB). GPC (RI): M_n (PDI) = 23 300 g mol^{-1} (1.21).

CL (113 mg, 1 mmol) was added to a solution of 4-pyrenebutanol (5.5 mg, 20 μmol) and TBD (1.4 mg, 1 μmol) in toluene (1.3 mL). The reaction mixture was stirred for 7 h, after which a sample was withdrawn and quenched with benzoic acid (2.5 mg) for analysis of conversion, molecular weight, and polydispersity. ^{1}H NMR (C$_6$D$_6$): δ = 8.26−7.77 (m, 9H, H$_{aromatic}$), 4.20 (t, 2H, pyC(═O)-OCH$_2$), 4.04 (m, 130H, C(═O)OC*H*$_2$ $_{backbone}$), 3.68 (t, 2H, C*H*$_2$-OH), 3.21 (t, 2H, pyC*H*$_2$), 2.16 (m, 130H, CH$_2$C(═O)), 1.63−1.24 (m, 390H, CH$_2$ $_{backbone}$). GPC (RI): M_n (PDI) = 7900 g mol^{-1} (1.10). The solution was divided into two equivolumetric parts. A solution of DL-lactide (75 mg, 0.5 mmol) in CH$_2$Cl$_2$ (2.7 mL) was added to one part of the polymerization mixture. This reaction mixture was subsequently quenched by the addition of benzoic acid (5 mg) after 30 s. ^{1}H NMR (CDCl$_3$): δ = 8.26−7.77 (m, 9H, H$_{aromatic}$), 5.20−5.06, (m, 200H, C*H*$_{PLA\ backbone}$), 4.20 (t, 2H, pyC-(═O)OCH$_2$), 4.12 (m, 130H, C(═O)OC*H*$_2$ $_{backbone}$), 3.68 (t, 2H, C*H*$_2$-OH), 3.21 (t, 2H, pyC*H*$_2$), 2.16 (m, 130H, CH$_2$C(═O)), 1.63−1.24 (m, ∼1000H, CH$_2$, CH$_3$ $_{backbone}$). GPC (RI): M_n (PDI) = 26 700 g mol^{-1} (1.17). To the other part a solution of VL (60 mg, 0.6 mmol) in toluene (2.5 mL) was added. This reaction mixture was stirred for another 16 h and then quenched by the addition of benzoic acid (5 mg). ^{1}H NMR (C$_6$D$_6$): δ = 8.26−7.77 (m, 9H, H$_{aromatic}$), 4.20 (t, 2H, pyC(═O)OCH$_2$), 4.04 (m, 330H, C(═O)OC*H*$_2$ $_{backbone}$), 3.55 (t, 2H, C*H*$_2$OH), 3.21 (t, 2H, pyC*H*$_2$), 2.16 (m, 330H, CH$_2$C-(═O)), 1.63−1.24 (m, ∼1000H, CH$_2$ $_{backbone}$). GPC (RI): M_n (PDI) = 20 600 g mol^{-1} (1.09).

^{1}H NMR Titration Experiments of TU and VL. Stock solutions of thiourea and of VL were prepared in C$_6$D$_6$. Ratios of VL:TU of 0.25 to 40 were targeted at concentrations ranging from ∼0.01 to ∼0.002 M by mixing the appropriate aliquots of both stock solutions and C$_6$D$_6$. In total, 13 different solutions were

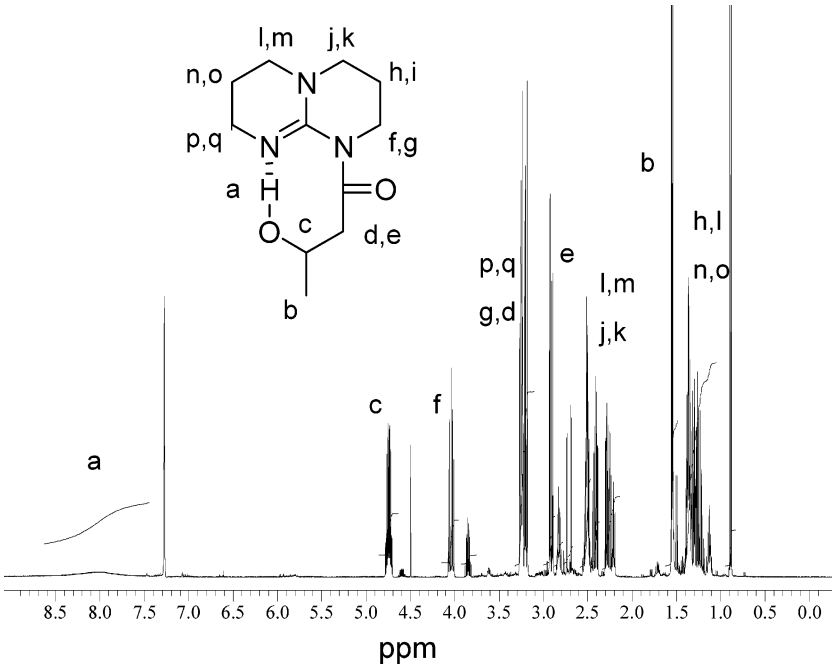


Figure 3. Assigned ^{1}H NMR spectrum of the adduct of TBD and BL at 0.05 M in C$_6$D$_6$.

prepared, transferred to NMR tubes, and sealed. NMR spectra of these samples were recorded (64 scans) at five different temperatures on a Bruker Avance 300 instrument at 300 MHz with VT setup. As a reference experiment, a concentration series of thiourea in C_6D_6 was prepared: the chemical shift of the NH protons was found to be independent of concentration.

^{1}H NMR Dilution Experiments of MTBD and Benzyl Alcohol. A stock solution of benzyl alcohol in C_6D_6 was added to a stock solution of MTBD in C_6D_6 to obtain a 1:1 molar ratio of the two components at a ~0.2 M concentration. This stock solution was diluted with aliquots of C_6D_6, giving in total 15 different solutions spanning a concentration range of ~0.2 to ~0.001 M. They were transferred to NMR tubes and sealed. NMR spectra of these samples were recorded (64 scans) at four different temperatures on a Bruker Avance 300 instrument at 300 MHz with VT setup. As a reference experiment, a concentration series of benzyl alcohol in C_6D_6 was prepared: the chemical shift of the OH proton was found to shift slightly, 0.27 ppm over the concentration range. However, implementing these data into the determination of the associant constant does not affect its value significantly.

Results and Discussion

ROP of LA. TBD is an effective organocatalyst for the ring-opening polymerization of L-lactide.[8] At a loading of 0.1%, L-lactide is quantitatively converted into polymer in less than 1 min. A typical setup requires 0.5 mg of TBD (3.6 μmol) to polymerize 500 mg of LA (3.6 mmol), initiated from 9.5 mg of 4-pyrenebutanol (36 μmol) in 5 mL of methylene chloride while targeting a degree of polymerization of 100. After 1 min P(L-LA) with a molecular weight of 23 600 g/mol and a polydispersity of 1.06 is obtained by GPC using polystyrene standards. To prevent adverse transesterification of the backbone, the catalyst was neutralized by benzoic acid, but even if TBD was not quenched after 7.5 min, the polydispersity had only increased from 1.06 to 1.23, contrasting other highly active organocatalysts such as N-heterocyclic carbenes.[10] Excellent agreement between the targeted and experimentally found molecular weight was observed, and linear relationships between conversion and molecular weight indicated well-controlled polymerizations. Furthermore, minimal epimerization of the monomer is observed by ^{1}H NMR during polymerization of L-lactide. Interestingly, polymerization of *rac*-lactide shows a slight isotactic enhancement with a P_i value of 0.58, comparable to that obtained by other organic catalysts at room temperature.[11] Application of MTBD or DBU (catalyst loading of 1 mol % vs monomer) for a targeted DP of 100 in the presence of an alcoholic initiator can be achieved in ~60 min. While slower and requiring higher catalysts loadings than TBD, both MTBD and DBU provided exquisite control over the polymerization of lactide, producing polymers with DP's approaching 500 predictably with narrow molecular weight distributions (PDI $\leq$ 1.1), even at high monomer conversions (Table 1). The onset of polymer transesterification is mitigated in comparison to TBD, providing sufficient time to monitor and quench the polymerization with benzoic acid upon full monomer conversion. No significant differences in selectivity of stereochemistry in the polymerization of *rac*-LA were found between TBD, DBU, and MTBD (P_i value of 0.58−0.60).

Polymerization of δ-Valero- and ϵ-Caprolactone. The polymerization of δ-valerolactone (VL) and ϵ-caprolactone (CL) has been studied with the organic catalysts DBU, MTBD, and TBD. Low loadings of TBD (0.5% with respect to monomer) polymerized VL and CL to near quantitative conversions, yielding polymers with predictable molecular weights up to DP's of 200, end group fidelity, and low polydispersities (<1.16) (Figure 1). In the presence of an alcoholic initiator neither DBU nor MTBD polymerized any of these monomers with loadings up to 20 mol % vs monomer. We surmised that the addition of 5 mol % of a thiourea cocatalyst (TU) together with either DBU or MTBD would enable VL and CL polymerizations (Scheme 3). Table 1 shows that the polymerization of VL and CL by either DBU or MTBD in the presence of TU cocatalyst proceeded to high conversions with predictable molecular weights up to DPs of 200, end group fidelity, and low polydispersity. Figure 2 shows the linear relationships of molecular weight with conversion of VL for different targeted DP's. The similar polymerization rates of VL in the case of DBU/TU and MTBD/TU vs TBD can be explained by the different catalyst loadings. In comparison to TBD, these catalyst mixtures polymerize with exceptional control as judged from the narrow polydispersities (minimal adverse transesterification during polymerization). However, even with relatively high loadings of DBU/TU or MTBD/TU, polymerization of CL is retarded compared to catalysis by TBD, requiring 5 days for a DP of 100 to reach 80% conversion. In this case, transesterification is more noticeable than in lactide polymerization. Broadening of the molecular weight distribution is observed

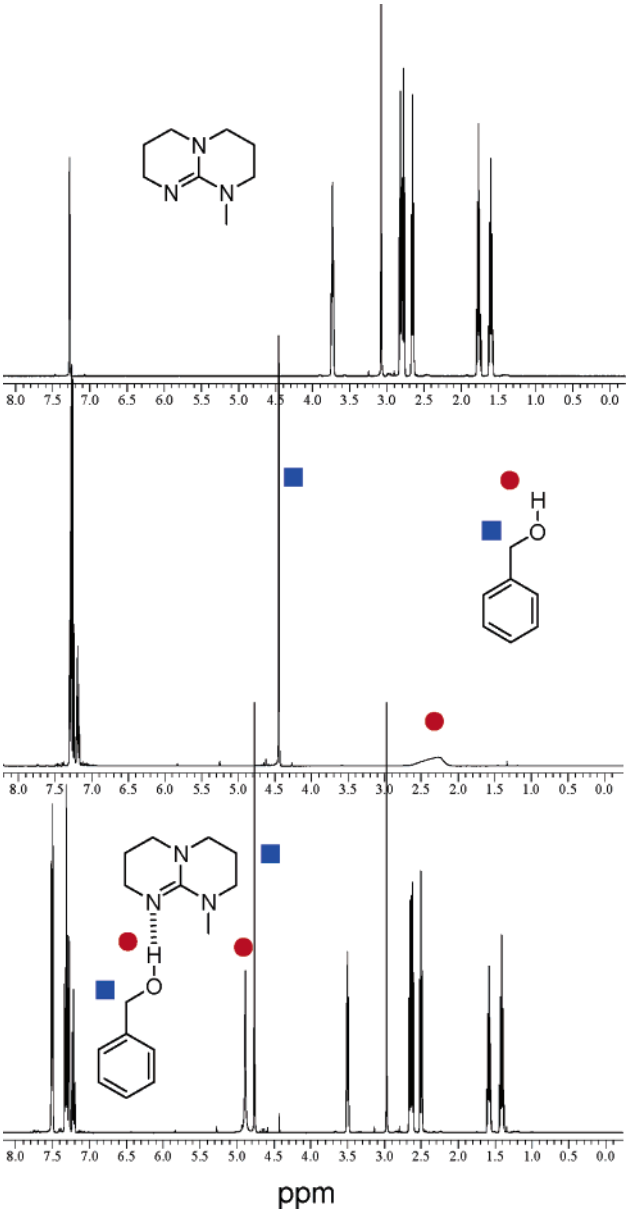


Figure 4. ^{1}H NMR spectrum of benzyl alcohol, MTBD and their 1:1 complex at 0.1 M in C_6D_6 at RT.

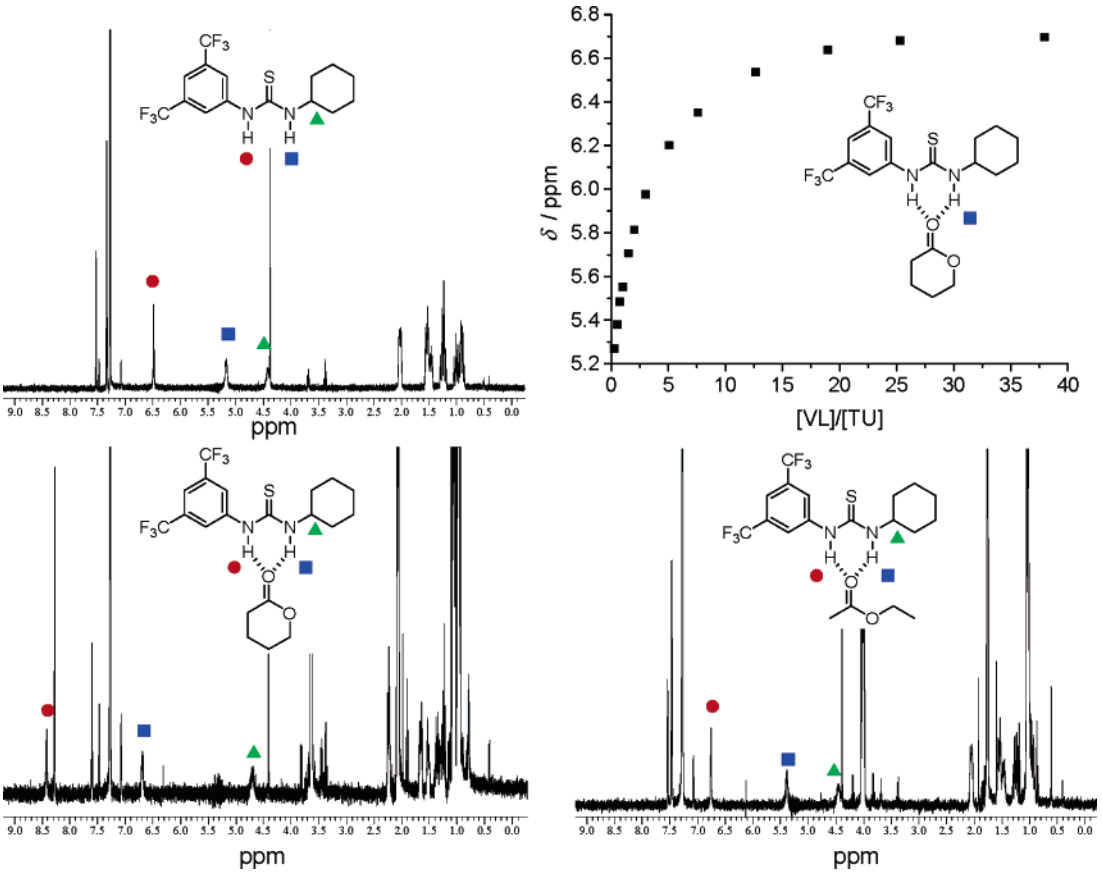


Figure 5. ^{1}H NMR spectrum of the thiourea catalyst at 8.11 mM in C_6D_6 (top left), with 38 equiv of valerolactone at 2.32 mM TU concentration in C_6D_6 at the end point of the titration (bottom left) and with 38 equiv of ethyl acetate for comparison of the shifts of the NH protons at 2.32 mM TU concentration (bottom right). The top right figure shows the chemical shift of one of the NH protons as a function of the ratio of VL vs TU, and this figure was used for subsequent curve-fitting to derive the association constant.

upon standing of the reaction mixture in the presence of the organocatalysts. Nevertheless, since this is a relatively slow process in comparison with the actual polymerization, this can easily be prevented by quenching the polymerization. Interestingly, these catalysts (TBD as well as DBU/TU and MTBD/TU) also work in bulk monomer at 50 °C: CL required 1 h for a DP of 100 to reach 85% conversion, whereas polymerization of VL was completed within 5 min. Although slightly broader polydispersity indices were observed (PDI = 1.15 for both PCL and PVL), the polymerization is still well-behaved.

Polymerization of β-Butyrolactone. Although we have tried several combinations of the catalysts described previously, we have been unable to polymerize BL in a controlled fashion. A titration of BL to thiourea revealed a weakened binding (K_{ass} < 10), indicating that hydrogen bond activation of the carbonyl of BL may not be as strong. Moreover, when using TBD, closer inspection by ^{1}H NMR in C_6D_6 revealed that an adduct is formed between TBD and BL. A 1:1 mixture of both reactants showed the formation of the acyl intermediate (Figure 3), and all peaks could be assigned. Using HMBC 2D-NMR techniques, it could unambiguously be shown that the acyl group of the ring-opened BL is connected to TBD through one of its nitrogen atoms. Interestingly, the alcoholic proton of the intermediate is significantly shifted downfield to 8.3 ppm (at 0.05 M), which suggests strong hydrogen bonding of this proton to the adjacent nitrogen atom in TBD. We propose that formation of an eight-membered ring effectively competes for hydrogen bond formation of an incoming alcohol of an initiator, thereby precluding polymerization. Heating the reaction mixture to 50 °C to disrupt this hydrogen bonding gave low molecular weight oligomers as detected by GPC, with crotonate formed as byproducts through competing α-hydrogen abstraction and a subsequent elimination, leading to uncontrolled polymerizations.[12] Polymerization of BL with either DBU or MTBD with TU did not give any polymer at room temperature, and at elevated temperatures the formation of undesirable crotonates were again observed. Nevertheless, the observation of an adduct of BL and TBD suggests that acyl intermediates may be involved in the ROP of CL, LA, and VL using TBD.

Mechanistic Aspects. TBD can be acylated by reaction with vinyl acetate and removal of the low-boiling acetaldehyde byproduct. Subsequent addition of excess benzyl alcohol completed the cycle by the formation of benzyl acetate and regenerating the TBD catalyst.[8] Neither MTBD nor DBU reacted with vinyl acetate to give acylated products, although both bases have been reported to be efficient transesterification agents when there is alcohol present, presumably by direct transfer of the acyl group between alcohols.[13] In contrast to TBD, if acylation takes place, DBU and MTBD would be expected to form zwitterionic intermediates: the existence of this zwitterion has so far not been proven.[14] Fully protonated MTBD, through reaction with e.g. benzoic acid, shows a singlet at 11.5 ppm at 0.05 M. Figure 4 shows the ^{1}H NMR spectrum of a 0.05 M solution of benzyl alcohol and MTBD in C_6D_6, mixed in a 1:1 ratio. A clear shift of the alcohol proton from 2.0 to 4.9 ppm can be observed and is attributed to the hydrogen bonding of the alcohol proton to the tertiary amine of MTBD. In fact, minor shifts can also be observed for the α-methylene protons of benzyl alcohol (from 4.42 to 4.77 ppm), for the adjacent aromatic protons in the 2- and 6-positions (from 7.20 to 7.52 ppm), and for the methylene protons of MTBD, indicating a hydrogen-bonded complex. DBU and TBD also show upfield

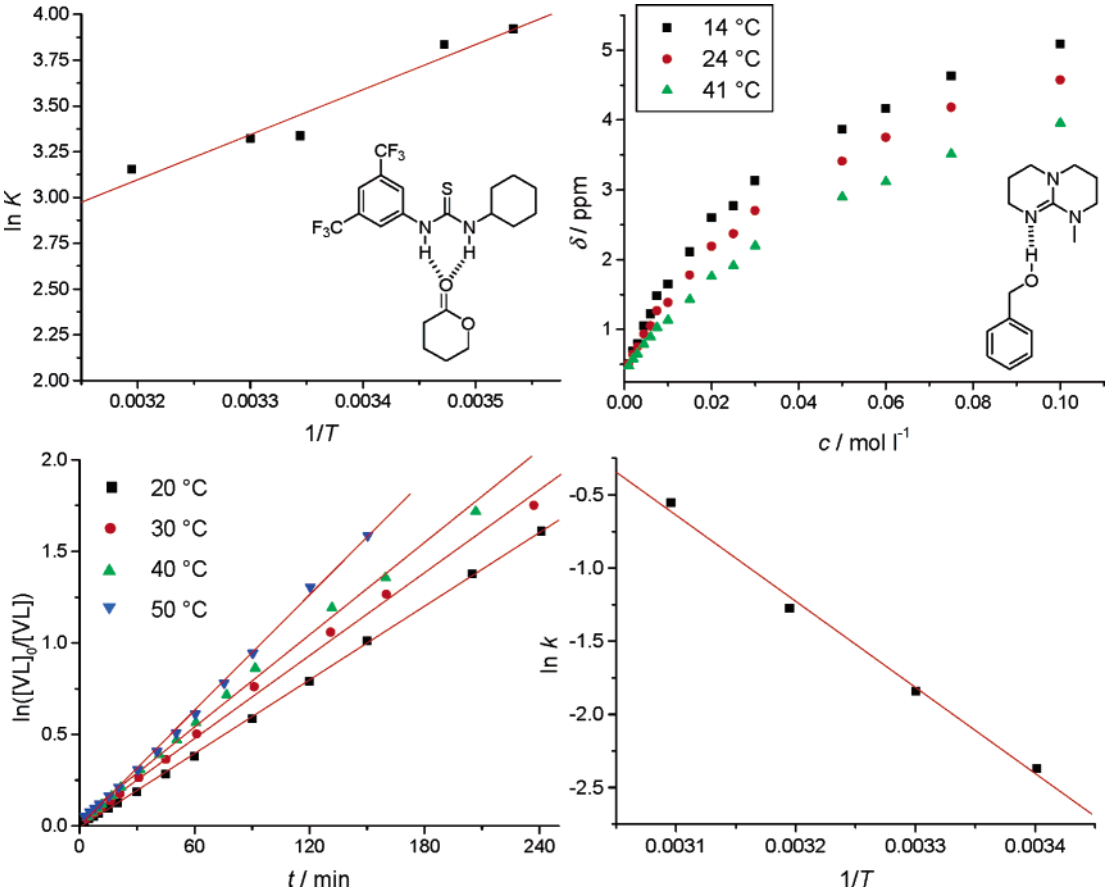


Figure 6. Temperature dependency of the association constant of VL and TU by plotting ln *K* as a function of 1/*T* (top left). Chemical shift of the OH proton in benzyl alcohol as a function of the concentration in the presence of an equimolar amount of MTBD at three different temperatures (top right). First-order linear fits of the kinetic data for the polymerization of VL in the presence of TU and MTBD with benzyl alcohol as initiator (bottom left). The obtained slope gives a propagation rate constant that in an Arrhenius plot of ln *k* vs 1/*T* finally leads to a value for the activation energy (bottom right).

shifts of the alcohol proton, to 6.8 and 6.7 ppm, respectively, although it must be noted that TBD is well-known to self-associate. Comparable shifts are observed for the three bases in CD_2Cl_2, a typical polymerization solvent for LA (lactide is insoluble in C_6D_6 at RT). Although hydrogen bonding takes place in this solvent, extended reaction times (>4 h at room temperature) lead to solvent decomposition (also observed in $CDCl_3$).[15] In the presence of an alcoholic initiator, only TBD produced the ring-opened products for all of these monomers LA, VL, CL, and BL. DBU and MTBD showed ring-opened products for lactide, but only starting materials in the case of BL, VL, and CL. TBD therefore appears to be the most versatile catalyst for the ROP of cyclic esters. It is also noticeable that DBU and MTBD, having nearly identical pK_a values of 24.3 and 25.5 in acetonitrile, respectively,[6] polymerize lactide with comparable rates. We surmise that alcohol activation is sufficient to effect the polymerization of LA by a quasi-anionic polymerization mechanism for LA. Although MTBD and DBU are efficient bases for alcohol activation, this alone is insufficient activation to effect small molecule transesterification or ROP of VL and CL: simultaneous activation of the monomer by TU is required to effect these transformations. To gain further understanding of the polymerization of lactones by supramolecular activation using organic catalysts, we have studied the hydrogen-bonding capabilities of TU with VL and CL using ^{1}H NMR: typically, a titration of a solution of VL to a solution of TU in C_6D_6 shifted the two NH signals of TU from 5.19 to 6.71 ppm and 6.48 to 8.42 ppm, respectively, by saturation of the TU binding site with VL (Figure 5). This process enables calculation of association constants of VL and CL with TU at room temperature (21 °C), found to be 39 ± 5 and 42 ± 5 M^{-1}, respectively, by literature procedures:[16,17] the values are in good agreement with data previously obtained for lactones and ureas.[16] Titration of a linear ester, such as ethyl acetate, into a solution of TU in C_6D_6, keeping all other conditions such as concentration, solvent, and temperature constant, results in negligible shifts of the NH protons of the TU being observed, indicating a markedly lower binding affinity (Figure 5). This observation clearly demonstrates that electrophilic activation of the linear ester toward nucleophilic attack is minimized and may be rationalized by the cisoid conformation of the cyclic ester vs the transoid conformation in the linear ester. More importantly, these NMR results provide a rationale for the very slow rate of transesterification of the linear polyester compared to the ring opening of the cylic ester. Only after polymerization, when monomer is depleted, does transesterification of the polymer backbone become significant, albeit at a slower rate than the ring opening. NMR titrations performed at different temperatures (from 10 to 45 °C) enabled the determination of $\Delta H°$ and $\Delta S°$ for the binding of VL to TU ($\Delta H° = -21 \pm 3$ kJ mol^{-1}, $\Delta S° = -41 \pm 8$ J mol^{-1} (Figure 6)). The negative enthalpic term is in correspondence with literature values for hydrogen bonding,[18] and the negative entropy term shows that at higher temperatures the bimolecular association will be less favored, as expected. Similarly, we have conducted a dilution experiment of a 1:1 mixture of benzyl alcohol and MTBD (from 14 to 40 °C) (Figure 6).[17] The K_{ass} value of 14 ± 2 M^{-1} at 25 °C is within the same order of magnitude as for the TU/VL pair. This may have implications for further optimizing catalyst loadings. The $\Delta H°$ and $\Delta S°$ for binding were again calculated

by temperature-dependent NMR studies and found to be -16 ± 1 kJ mol^{-1} and -30 ± 1 J mol^{-1}. In further investigations, the polymerization of VL with a targeted degree of polymerization of 50 with MTBD and TU as catalysts and benzyl alcohol as initiator was carried out at different temperatures (20, 30, 40, and 50 °C). Samples were withdrawn at regular time intervals, and conversion was determined by NMR through integration of the $CH_2OC(=O)$ signal in the polymer and monomer. The polymerization rate constant at these temperatures was then obtained from fitting the first-order kinetic data according to the following formula:

$$\ln\left(\frac{[VL]_0}{[VL]}\right) = kK_1K_2[MTBD]_0[TU]_0[ROH]_0t$$

where k is the polymerization rate constant, K_1 the equilibrium constant for VL and TU, K_2 the equilibrium constant for MTBD and benzyl alcohol, and $[TU]_0$, $[MTBD]_0$, and $[ROH]_0$ the concentrations at $t = 0$ min. It is assumed that the equilibrium constant K_2 for MTBD and benzyl alcohol is the same as for MTBD with the propagating alcohol and that the alcohol concentration remains constant throughout the polymerization. The plots can be well-fitted by first-order kinetics at conversions below 70%, where viscosity and undesired side reactions are unlikely to have an effect (Figure 6). Moreover, the GPC analyses at the different temperatures give comparable molecular weights and polydispersities at the same conversions, showing that adverse side reactions such as transesterification are not taking place. An Arrhenius plot of ln k as a function of $1/T$ yields a straight line and allows the derivation of the activation energy for the polymerization, determined as 49 ± 3 kJ mol^{-1} (Figure 6). Since the association constants for VL and CL with TU are more or less the same but the polymerization rate is much slower for CL while all other parameters in the kinetic expression are kept the same, the activation energy for ROP of CL is expected to be much higher using MTBD and TU as cocatalysts. A lower propagation rate constant is commonly observed for CL as compared to VL.[19]

Copolymerizations. Copolyesters of lactide and lactones are of interest in biomedical applications for fine-tuning of the T_g and hydrolysis rate.[1] Typically, these copolyesters have been prepared by random copolymerizations of these monomers in the presence of organometallic promoters at temperatures between 100 and 150 °C.[20] We studied the copolymerization of CL, VL, and LA using TBD or MTBD/TU and DBU/TU. Remarkably, the catalyst systems show high selectivity in copolymerizations of the cyclic esters. At room temperature, the fastest propagating monomer (k(LA) ≫ k(VL) > k(CL)) is ring-opened first to >95% conversion, before competition between transesterification of the so-formed polymer backbone and ring opening of the second monomer begins. Figure 7 shows the ^{1}H NMR of a copolymerization attempt of VL and CL using MTBD and the thiourea cocatalyst (DP = ([VL] + [CL])/[I] = 300). Initially, VL was polymerized to PVL, while little CL was converted (<5% conversion); after 3 h, 98% of VL had been converted, and the resulting polymer had a molecular weight of 17 800 g/mol with PDI of 1.05. Thereafter, CL was slowly consumed (65% conversion after 5 days), and GPC analysis revealed a modest increase in molecular weight with concurrent broadening of the PDI (M_n = 22 500 g/mol, PDI = 1.39). The high selectivity of the catalyst for one monomer over the other strongly contrasts the fairly nonselective nature of metal catalysts that follow a true coordination−insertion mechanism[19] and can likely be attributed to a much lower activation energy of VL using these catalysts. Interestingly, in copolymerization attempts of LA with either CL or VL using TBD as the catalyst, the lactone was not found to be incorporated into the polymer backbone, and only transesterification of the PLA backbone after full consumption of LA took place (M_n = 8700 g/mol, PDI = 1.09 to M_n = 10 600 g/mol, PDI = 1.33). Block copolyesters could be prepared in a controlled manner by first polymerizing the slower propagating monomer to high conversion and subsequently adding in the second monomer (Table 2). The versatility of TBD, MTBD/TU, and DBU/TU as catalysts for the preparation of block copolymers is further demonstrated by using monohydroxyl-functionalized macroinitiators such as poly(ethylene oxide), polystyrene, and poly(*N*,*N*-dimethylacrylamide).[9] Clean chain extensions were observed for *rac*-LA, VL, and CL, with excellent polydispersities (Table 3). Preparation of block copolymers containing a LA block of DP = 100 using 0.1% TBD required only 30 s.

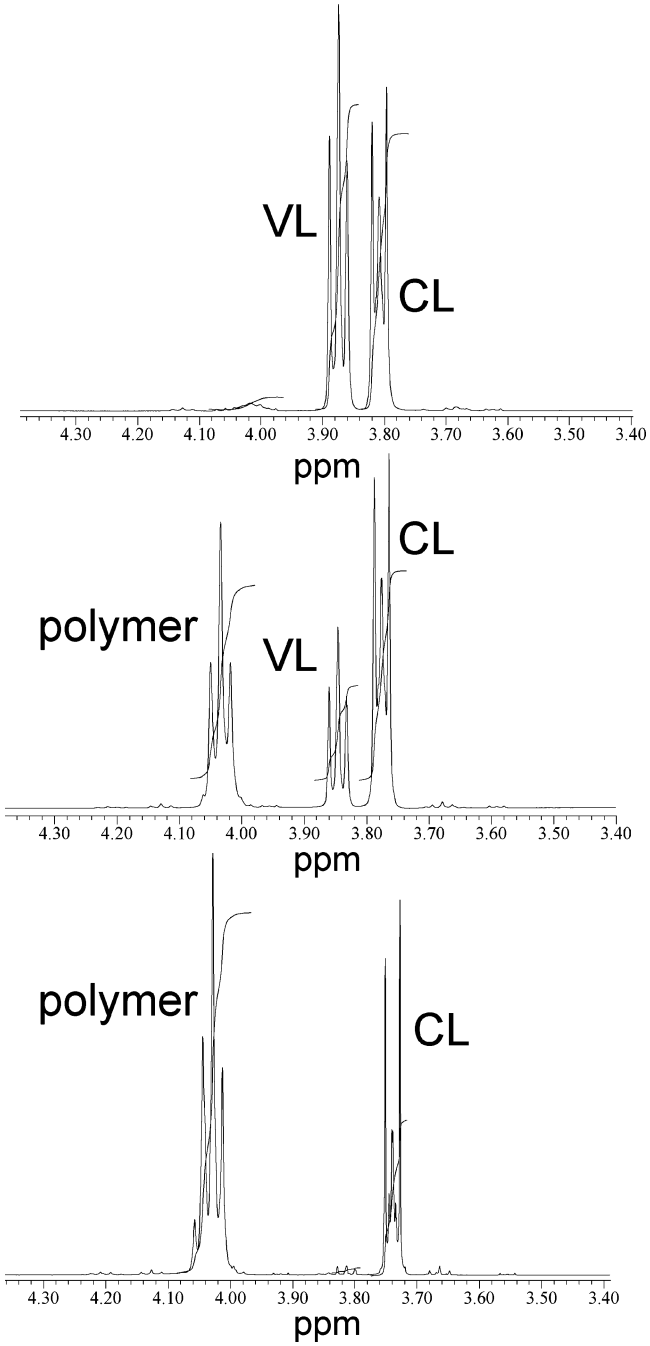


Figure 7. ^{1}H NMR spectra in C_6D_6 of the polymerization of CL and VL using MTBD and TU.

Table 2. One-Pot Synthesis of Block Copolyesters by Sequential Monomer Addition

monomer 1	DP_{th}[a]	time	conv[b] (%)	M_n (PDI)[c]	monomer 2	DP_{th}	time	conv[b,d] (%)	M_n (PDI)[c]
VL	100	12 min	50	4000 (1.05)	DL-LA	100	15 s	99	23 300 (1.21)
CL	100	7 h	70	7900 (1.10)	DL-LA	100	30 s	99	26 700 (1.17)
CL	100	7 h	70	7900 (1.10)	VL	100	16 h	95	20 600 (1.09)

[a] Initiator was 4-pyrenebutanol. [b] Determined by ^{1}H NMR. [c] Determined by GPC in THF equipped with an RI detector. [d] Conversion of monomer 2: integration of NMR signal of the α-CH_2 from left-over monomer 1 does not change during the course of polymerization of monomer 2.

Table 3. Block Copolymers from Macroinitiators Using TBD

macroinitiator	monomer	DP_{th}	time	conv[a] (%)	M_n (PDI)[b]
PEO_{120}−OH	DL-LA	100	15 s	85	19 000 (1.05)
	VL	50	15 min	55	11 000 (1.04)
	CL	50	3 h	50	11 100 (1.03)
PS_{55}−OH[c]	DL-LA	50	15 s	95	22 900 (1.07)
	VL	25	15 min	90	12 200 (1.12)
	CL	150	3 h	60	23 400 (1.11)
$PDMA_{40}$−OH[c]	DL-LA	100	25 s	99	27 700 (1.06)
	VL	25	15 min	99	11 100 (1.17)

[a] Determined by ^{1}H NMR. [b] Determined by GPC in THF equipped with an RI detector. [c] Synthesized by nitroxide-mediated polymerization.[9]

Conclusions

We have shown the efficacy of TBD, MTBD, and DBU for the ring-opening polymerization of cyclic esters with excellent control over molecular weight and polydispersity. TBD is uniquely capable of a bifunctional activation of both monomer and the alcohol, whereas DBU and MTBD only activate the alcohol. This is sufficient activation to efficiently polymerize of LA; however, polymerization of VL and CL requires the addition of the organic Lewis acid thiourea. NMR experiments demonstrated the hydrogen-bonding interactions between the tertiary amines and the alcohol, between TU and VL or CL, and the relatively weak interactions between TU and linear esters, providing a rationale for the excellent control these catalysts display for ROP. Further investigation of the polymerization mechanism by temperature-dependent NMR experiments allowed derivation of the activation energy for ROP of VL using MTBD/TU as the catalyst. BL is not polymerized by these organocatalysts in a controlled fashion at room temperature due to (a) the formation of a stable hydrogen-bonded intermediate in the case of TBD and (b) insufficient activity in the case of DBU/TU and MTBD/TU. Increasing the temperature gives rise to side reactions and loss of control. In copolymerization experiments, guanidine and amidine catalysts are extremely selective, making them most suitable for synthesis of copolyesters with blocky architectures. Block copolymers could also be easily prepared from hydroxyl-functionalized macroinitiators. The ready availability of the catalysts, the mild conditions of polymerization, and the metal-free nature of the polymerization process make these catalysts attractive candidates for the synthesis of polyesters for both biomedical and microelectronic applications.

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References and Notes

(1) (a) Ree, M.; Yoon, J.; Heo, K. *J. Mater. Chem.* **2006**, *16*, 685−697. (b) Li, M.; Coenjarts, C. A.; Ober, C. K. *Adv. Polym. Sci.* **2005**, *190*, 183−226. (c) Ueda, H.; Tabata, Y. *Adv. Drug Delivery Rev.* **2003**, *55*, 501−518. (d) Amass, W.; Amass, A.; Tighe, B. *Polym. Int.* **1998**, *47*, 89−144. (e) Scheirs, J.; Long, T. E. In *Modern Polyesters: chemistry and technology of polyesters and copolyesters*; John Wiley and Sons Ltd.: Chichester, 2003.

(2) Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. *Chem. Rev.* **2004**, *104*, 6147−6176.

(3) (a) Nederberg, F.; Connor, E. F.; Glausser, T.; Hedrick, J. L. *Chem. Commun.* **2001**, 2066−2067. (b) Nederberg, F.; Connor, E. F.; Moeller, M.; Glausser, T.; Hedrick, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2712−2715. (c) Myers, M.; Connor, E. F.; Glausser, T.; Moeck, A.; Nyce, G. W.; Hedrick, J. L. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 844−851. (d) Connor, E. F.; Nyce, G. W.; Myers, M.; Moeck, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914−915. (e) Nyce, G. W.; Glausser, T.; Connor, E. F.; Moeck, A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 3046−3056. (f) Nyce, G. W.; Csihony, S.; Waymouth, R. M.; Hedrick, J. L. *Chem.−Eur. J.* **2004**, *10*, 4073−4079. (g) Coulembier, O.; Dove, A. P.; Pratt, R. C.; Sentman, A. C.; Culkin, D. A.; Mespouille, L.; Dubois, P.; Waymouth, R. M.; Hedrick, J. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4964−4968. (h) Coulembier, O.; Lohmeijer, B. G. G.; Dove, A. P.; Pratt, R. C.; Culkin, D. A.; Benight, S. J.; Mespouille, L.; Dubois, P.; Waymouth, R. M.; Hedrick, J. L. *Macromolecules* **2006**, *39*, 5617−5628.

(4) Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 13798−13799.

(5) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Dove, A. P.; Li, H.; Waymouth, R. M.; Hedrick, J. L. *Macromolecules*, in press.

(6) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019−1028.

(7) (a) Boczon, W.; Jasiewicz, B. *Collect. Czech. Chem. Commun.* **2003**, *68*, 696−710. (b) Toom, L.; Kütt, A.; Kaljurand, I.; Leito, I.; Ottosson, H.; Grennberg, H.; Gogoll, A. *J. Org. Chem.*, in press.

(8) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556−4557.

(9) Bosman, A. W.; Vestberg, R.; Heumann, A.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715−728.

(10) Culkin, D. A.; Waymouth, R. M., unpublished results.

(11) (a) Ovitt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1316−1326. (b) Chamberlain, B. M.; Cheng, M.; Moore, D. R.; Ovitt, T. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 3229−3238. (c) Jensen, T. R.; Breyfogle, L. E.; Hillmyer, M. A.; Tolman, W. B. *Chem. Commun.* **2004**, 2504−2505. (d) Chisholm, M. H.; Iyer, S. S.; McCollum, D. G.; Pagel, M.; Werner, Zwanziger, U. *Macromolecules* **1999**, *32*, 963−973. (e) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Lindgren, T. A.; Doscotch, M. A.; Siepmann, J. I.; Munson, E. J. *Macromolecules* **1997**, *30*, 2422−2428. (f) Thakur, K. A. M.; Kean, R. T.; Zell, M. T.; Padden, B. E.; Munson, E. J. *Chem. Commun.* **1998**, 1913−1914. (g) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Munson, E. J. *Macromolecules* **1998**, *31*, 1487−1494.

(12) (a) Schreck, K. M.; Hillmyer, M. A. *Tetrahedron* **2004**, *34*, 7177−7185. (b) Hori, Y.; Hagiwara, T. *Int. J. Biol. Macromol.* **1999**, *25*, 237−245. (c) Dubois, P.; Jerome, R. *Polym. Int.* **1996**, *41*, 479−485. (d) Zhang, Y.; Gross, R. A.; Lenz, R. W. *Macromolecules* **1990**, *23*, 3206−3212. (e) Kemnitzer, J. E.; McCarthy, S. P.; Gross, R. A. *Macromolecules* **1992**, *25*, 5927−5934. (f) Kricheldorf, H. R.; Scharnagl, N.; Jedlinski, Z. *Polymer* **1996**, *37*, 1405−1411. (g) Borgne, A. L.; Spassky, N. *Polymer* **1989**, *30*, 2312−2319. (h) Rieth, L. R.; Moore, D. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 15239−15248. (i) Jedlinski, Z.; Kurcok, P.; Lenz, R. *Macromolecules*, **1998**, *31*, 6718−6720.

(13) See for example: (a) Green, M. UK Patent 955 232, 1984. (b) Schuchardt, U. F.; Vargas, R. M.; Gelbard, G. *J. Mol. Catal. A* **1995**, *99*, 65−70. (c) LePerchec, P.; Baudry, R.; Alvarez, F. US Patent 6 646 103 B1, 2003. (d) Bensa, D.; Rodriguez, J. *Synth. Commun.* **2004**, *34*, 1515−1533.

(14) Heldebrandt, D. J.; Jessop, P. G.; Thomas, C. A.; Eckerdt, C. A.; Liotta, C. L. *J. Org. Chem.* **2005**, *70*, 5335−5338.

(15) Aggarwal, V. K.; Mereu, A. *J. Org. Chem.* **2000**, *65*, 7211−7212.

(16) (a) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080. (b) Horman, I.; Dreux, B. *Anal. Chem.* **1983**, *55*, 1219−1221.

(17) The following formula was used for titration of VL to TU (see also ref 15a): $\delta = \alpha(\delta_{max} - \delta_0) + \delta_0$, where $\alpha = \{K_1[TU] + K_1[VL] + 1 - (K_1^2[TU]^2 - 2K_1^2[TU][VL] + 2K_1[TU] + K_1^2[VL]^2 + 2K_1[VL] + 1)^{1/2}\}/2K_1[TU]$. The preceding equation reduces to $\alpha = \{2K_2c + 1 - (4K_2c + 1)^{1/2}\}/2K_2c$ for the 1:1 dilution experiments, where $[TU] = [VL] = c$. A Levenberg−Marquardt nonlinear least-squares fitting

procedure, implemented in the Matlab programming environment, was used to obtain the best-fit values for K_1 or K_2, δ_{max}, and δ_0.

(18) (a) Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 8, 8891−8896. (b) Bühlmann, P.; Nishizawa, S.; Xiao, K. P.; Umezawa, Y. *Tetrahedron* **1997**, *53*, 1647−1654. (c) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217−220.

(19) (a) Duda, A.; Kowalski, A.; Penczek, S.; Uyama, H.; Kobayashi, S. *Macromolecules* **2002**, *35*, 4266−4270. (b) van der Mee, L.; Helmich, F.; Vekemans, J. A. J. M.; Palmans, A. R. A.; Meijer, E. W. *Macromolecules* **2006**, *39*, 5021−5027.

(20) (a) Kurcok, P.; Penczek, J.; Franek, J.; Jedlinski, Z. *Macromolecules* **1992**, *25*, 2285−2289. (b) Bero, M.; Kasperczyk, J. *Macromol. Chem. Phys.* **1996**, *197*, 3251−3258. (c) In't Veld, P. J. A.; Velner, E. M.; Van de Witte, P.; Hamhuis, J.; Dijkstra, P. J.; Feijen, J. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 219−226. (d) Parrish, B.; Quansah, J. K.; Emrick, T. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1983−1990. (e) Wahlberg, J.; Persson, P. V.; Olsson, T.; Hedenström, E.; Iversen, T. *Biomacromolecules* **2003**, *4*, 1068−1071. (f) Mosnáček, J.; Duda, A.; Libiszowski, J.; Penczek, S. *Macromolecules* **2005**, *38*, 2027−2029. (g) Stassin, F.; Jérôme, R. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 2777−2789. (h) Kricheldorf, H. R.; Bornhorst, K.; Hachmann-Thiessen, H. *Macromolecules* **2005**, *38*, 5017−5024.

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