A binary neodymium catalyst for the polymerization of lactones

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A binary neodymium catalyst for the polymerization of lactones

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Polylactones are widely used in biomedical applications and for drug delivery due to their biocompatibility and biodegradability. Polylactones are produced by the ring-opening polymerization (ROP) of the corresponding lactone monomers using various catalysts. Among other ROP techniques (anionic, cationic, and radical), coordination ROP is less sensitive to substituents in the monomer and exhibits *living* polymerization behavior. Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) and aluminum isopropoxide ($Al(O\text{-}i\text{-}Pr)_3$) are the common catalysts for coordination ROP of ε-caprolactone. Unfortunately, in the presence of ester linkages at the γ-position in ε-caprolactone monomers, $Sn(Oct)_2$ and $Al(O\text{-}i\text{-}Pr)_3$ may react to the ester group which is a major drawback in the polymerization. Herein, we demonstrate the ability of $NdCl_3{\cdot}3TEP$/TIBA catalytic system (TEP = triethylphosphate, TIBA = triisobutylaluminum) to polymerize not only ε-caprolactone, but also γ-functionalized ε-caprolactone monomers with varying linkages at the γ-position of ε-caprolactone. In utilizing the $NdCl_3{\cdot}3TEP$/TIBA catalytic system we were able to make block copolymers of PVL-*b*-PCL (PVL = polyvalerolactone, PCL = polycaprolactone), PBrCL-*b*-PCL (PBrCL = poly(γ-bromo-ε-caprolactone) and the amphiphilic block copolymer, PMEEECL-*b*-PCL (PMEEECL = poly(γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone)). The activation energy for the polymerization of ε-caprolactone with $NdCl_3{\cdot}3TEP$/TIBA catalytic system was determined to be 32.6 kJ mol^{-1}.

Introduction

The biocompatibility and biodegradability of polylactones make them prime candidates for use in biomedical applications and drug delivery.[1, 2] Polylactones are widely produced via ring-opening polymerization (ROP) of the corresponding lactone monomer, i.e. ε-caprolactone (ε-CL), δ-valerolactone (δ-VL), etc. Due to the synthetic versatility, ε-CL is used extensively to generate aliphatic polyesters for drug delivery applications. For example, polymers with prodrugs[3-8] and various stimuli-responsive polymers[9-12] can be obtained with synthetic modifications on the ε-CL ring. ROP of ε-CL can be achieved by anionic, cationic, coordination, or enzymatic polymerization techniques.[13] Backbiting in anionic polymerization, poor control over the polymerization in cationic polymerization, and lower polymer yields and molecular weights obtained in enzymatic polymerization led most researchers to focus on coordination polymerization.[13] Coordination ROP is widely accepted as it provides better control over the polymerization. ROP with organocatalysts have also garnered much attention due to their ability to deliver well-defined polyesters.[14-22]

Organometallic complexes composed of tin, aluminum, and zinc are mainly used as catalysts for coordination ROP.[23-27] Complexes consisting of some of the alkaline-earth metals and rare-earth metals are also used in common for coordination ROP.[28-31] Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$), which is approved by the Food and Drug Administration (FDA), is the most widely used catalyst for the ROP of lactones.[32] $Sn(Oct)_2$ is an efficient catalyst for the polymerization of non-functionalized and functionalized caprolactone monomers, and in some cases *living* polymerization was observed.[33, 34] Polymerization of functionalized ε-CL monomers is challenging in the case where there are interactions between the substituent and the catalyst. Furthermore, the linkage between the ε-CL ring and the substituent (such as an ether, ester, etc.) will have an impact on the polymerization. $Sn(Oct)_2$ has been used to polymerize monomers that contain substituent ester linkage at the γ-position, although with low yields and low molecular weights.[35] In some cases, copolymers were synthesized between ε-CL and functionalized ε-CL monomers to obtain improved molecular weights.[5, 35] In the presence of sterically crowded substituents with an ester linkage at the γ-position, however, the polymerization proceeds, generating polymers with moderate molecular weights.[5]

We recently encountered difficulties using $Sn(Oct)_2$ to polymerize γ-4-phenylbutyrate-ε-caprolactone, a prodrug monomer.[7] In this report, we observed high transesterification into a butyrolactone analog preferentially over the formation of the block copolymer.[7] Various strategies used for the ROP focus mainly on the polymerization of non-functionalized ε-CL and not on functionalized ε-CL monomers. When it comes to actual applications, a catalytic system that can polymerize both functionalized and non-functionalized ε-CL is fundamentally necessary.

Herein, we describe the ability of $NdCl_3{\cdot}3TEP$/TIBA catalytic system (TEP= triethylphosphate, TIBA= triisobutylaluminum) to

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be used for the ROP of not only regular ε-CL but also γ-substituted-ε-caprolactone monomers. Previously we demonstrated the ability of this catalytic system to polymerize dienes, vinyl monomers, and γ-4-phenylbutyrate-ε-caprolactone.[36] The true advantage of this catalytic system is in making copolymers between different classes of monomers. Furthermore, in another article published by our group, we demonstrate the ability of $NdCl_3$·3TEP to polymerize ε-CL with alcohol initiators.[37] However, this system was not that efficient. This article investigates the effect of the co-catalyst ratio, temperature, and kinetic parameters for the polymerization of ε-CL. To demonstrate the versatility of this system, further experiments were carried out for copolymer synthesis and homopolymerization of different functionalized ε-CL monomers.

Experimental

Materials

$NdCl_3·6H_2O$ (99.9%, Aldrich), triethylphosphate (TEP, 99.8%, Aldrich), and TIBA (25 wt% in toluene, Aldrich) were used as received. Toluene (99.9%, Fisher Scientific) was distilled over sodium/benzophenone ketyl before use. All other solvents and chemicals purchased from Fisher Scientific were used without any purification unless otherwise mentioned. ε-Caprolactone (97 %, Aldrich), and δ-valerolactone (99%, Acros Organics) was distilled over calcium hydride and stored over molecular sieves under a nitrogen atmosphere before polymerization. $NdCl_3$·3TEP,[36] γ-benzyl-ε-caprolactone,[38] γ-4-phenylbutyrate-ε-caprolactone,[7] γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone (MEEECL),[9] and 4-hydroxycyclohexanone,[39] were synthesized according to previously published procedures. All monomers were dried over CaH_2 prior to polymerization.

Analysis

Proton and carbon nuclear magnetic resonance (^{1}H, and ^{13}C, NMR respectively) spectra were recorded in $CDCl_3$ or benzene-d_6 on a Bruker AVANCE III™ 500 spectrometer (500 MHz and 125 MHz respectively) at 25 °C. Multiplicities were given as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet), and the chemical shifts are given in ppm. Diffusion ordered NMR spectroscopy (DOSY) experiments were acquired on a Bruker AVANCE III™ 500 spectrometer (500 MHz). The samples recorded in $CDCl_3$ at 27 °C, and a Shigemi tube was used to minimize convection. The pulse sequence used was bipolar pulse pair stimulated echo (Bruker *stebpgp1s*). The gradient strength was 53.5 G/cm at 10 A maximum output of the gradient amplifier. The gradient duration (δ) was 1.7 ms, and the diffusion delay (Δ) was 60 ms. The spectra were collected from 0.5 to 8 ppm in 8 transients and with 4 dummy transients. Size exclusion chromatography (SEC) was carried out on a Viscotek VE 3580 system equipped with Viscotek columns (T6000M), connected to the refractive index (RI), low angle light scattering (LALS), right-angle light scattering (RALS), and viscosity detectors. SEC solvent/sample module (GPCmax) was used with HPLC grade THF as the eluent, and triple point calibration was based on polystyrene standards. Differential scanning calorimetry (DSC) were recorded on a Mettler Toledo TGA/DSC-1 system with a heating and a cooling rate of 10 °C/min and -10 °C/min, respectively under a flow of nitrogen.

Synthesis of Monomers

Synthesis of 4-bromocyclohexanone. Tetrabromomethane (5.6 g, 0.017 mol) was added slowly to a solution of 4-hydroxycyclohexanone (1.0 g, 0.0085 mol) and triphenylphosphine (4.6 g, 0.017 mol) in dichloromethane (10 mL). The reaction was stirred at room temperature for 48 h, and dichloromethane was evaporated under reduced pressure. The resulting liquid was purified by column chromatography using ethyl acetate and hexane at a ratio of 2:3 (Rf = 0.56) to yield a yellow oil (1.3 g, 84 %). 1H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 2.33 (m, 6H), 2.74 (m, 2H) and 4.61 ppm (m, 1H). 13C NMR (25 °C, 125 MHz, $CDCl_3$): δ = 35.89, 38.65, 49.31 and 208.92 ppm.

Synthesis of γ-bromo-ε-caprolactone (BrCL). To a stirring solution of 4-bromocyclohexanone (2.80 g, 0.0158 mol) in dichloromethane (50 mL) at 0 °C, was added a solution of 77 % m-chloroperoxybenzoic acid (mCPBA) (6.03 g, 0.0269 mol) in dichloromethane (50 mL) and the reaction was allowed to reach room temperature. The reaction was monitored by thin-layer chromatography (TLC) until the complete consumption of the starting material, which usually takes about 12 h. Potassium carbonate (2.5 g in 7 mL of water) was added to the reaction mixture and stirred vigorously for 4 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane, (2x20 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. The product was isolated by flash chromatography using gradient elution with hexane and ethyl acetate (hexane/ethyl acetate; 95/5 to 5/95 v/v) to yield a pale yellow oil (2.2 g, 72 %). ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 2.25 (m, 2H), 2.35 (m, 2H), 2.60 (m, 1H), 3.08 (m, 1H), 4.18 (m, 1H), 4.54 (dd, 1H), 4.61 (br.s, 1H). ^{13}C NMR (25 °C, 125 MHz, $CDCl_3$): δ = 30.71, 32.34, 38.80, 51.73, 64.80 and 174.83 ppm.

Synthesis of 4-oxocyclohexyl acetate. 4-(Dimethylamino)pyridine (DMAP) (0.21 g, 1.7 mmol), 4-hydroxycyclohexanone (2.00 g, 0.017 mol), and acetic acid (1.20 g, 0.019 mol), were cooled to 0 °C in a round-bottom flask with dichloromethane (60 mL). A solution of 1-ethyl-3-(3-(dimethylamino)-propyl)carbodiimide hydrochloride (EDCl) (4.04 g, 0.21 mol) in dichloromethane (40 mL) was slowly added to the cooled solution. The reaction was stirred overnight and was washed with a saturated solution of potassium carbonate and with deionized water to remove any water-soluble products. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain the product as a yellow liquid (1.60 g, 60%). ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 2.07 (m, 4H), 2.10 (s, 3H), 2.37 (m, 2H), 2.52 (m, 2H), 5.16 (m, 1H).

Synthesis of γ-acetate-ε-caprolactone. Synthesis and purification of γ-acetate-ε-caprolactone was carried out similar to that of γ-bromo-ε-caprolactone using 4-oxocyclohexyl acetate (1.60 g, 0.010 mol), 77% mCPBA (3.90 g, 0.017 mol) and dichloromethane (100 mL). The product was obtained as a white solid (0.82 g, 46%). ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 1.96 (m, 2H), 2.05 (m, 2H), 2.07 (s, 3H), 2.53 (m, 1H), 2.89 (m, 1H), 4.14 (m, 1H), 4.42 (m, 1H), 5.10 (m, 1H). ^{13}C NMR (25 °C, 125 MHz, $CDCl_3$): δ = 21.32, 27.69, 28.60, 34.13, 63.66, 70.18, 170.06, and 175.06 ppm.

Polymerization Experiments

General procedure for the polymerization of ε-caprolactone with $NdCl_3$·3TEP/TIBA. For a ratio of [ε-caprolactone]:[Nd]:[Al] of 500:1:5, TIBA (0.16 mL 0.175 mmol) and $NdCl_3$·3TEP (0.186 M, 0.19 mL, 0.035 mmol) were added to a Schlenk flask and stirred for 1 min under a nitrogen atmosphere. ε-caprolactone (ε-CL) (2.00 g, 0.018 mol) was added to the catalyst mixture, stirred at the desired temperature for 4 h, and precipitated into methanol. The polymer was washed with methanol several times and dried under vacuum before characterization from ^{1}H, ^{13}C NMR, and SEC. The same procedure was used for the polymerization of all substituted caprolactone monomers and δ-valerolactone.

General procedure for chain extension experiments. Sequential monomer addition experiment was carried out for ε-caprolactone using the ratio of [ε-CL1]:[ε-CL2]:[Nd]:[Al] = 50:100:1:5. TIBA (0.82 mL, 0.88 mmol) and $NdCl_3$·3TEP (0.186 M, 0.94 mL, 0.175 mmol) were added to a Schlenk flask and stirred for 1 min under a nitrogen environment. Toluene (5 mL) was added to the catalyst mixture with ε-caprolactone (1.00 g, 0.0088 mol), and the reaction was carried out at 80 °C. Aliquots were withdrawn at different time intervals and were analyzed with ^{1}H NMR to calculate the monomer conversion. When the conversion of the first monomer portion was ~ 100 %, the second ε-caprolactone portion (2.00 g, 0.0176 mol) was added. After 2 h, the second monomer portion was fully consumed, and the polymer was precipitated into methanol.

Synthesis of poly(δ-valerolactone)-*b*-poly(ε-caprolactone) (PVL-*b*-PCL) with $NdCl_3$·3TEP/TIBA at 80 °C. Block copolymer synthesis between ε-caprolactone and δ-valerolactone was carried out by using the ratio of [δ-VL]:[ε-CL]:[Nd]:[Al] = 50:100:1:5. The same procedure as above was followed by using TIBA (0.93 mL, 1.00 mmol), $NdCl_3$·3TEP (0.186 M, 1.2 mL, 0.20 mmol), δ-valerolactone (1.00 g, 0.01 mol) and ε-caprolactone (2.28 g, 0.02 mol). Toluene (6 mL) was added with δ-valerolactone. ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 1.39 (m, 2H), 1.66 (m, 8H), 2.32 (t, 4H), 4.13 (t, 4H).

Synthesis of poly(ε-caprolactone)-*b*-poly(δ-valerolactone) (PCL-*b*-PVL) with $NdCl_3$·3TEP/TIBA at 80 °C. The ratio of [ε-CL]:[δ-VL]:[Nd]:[Al] = 200:1000:1:5 was used to synthesize PCL-*b*-PVL. The same procedure as above was followed by using TIBA (0.20 mL, 0.20 mmol), $NdCl_3$·3TEP (0.169 M, 0.26 mL, 0.40 mmol), ε-caprolactone (1.00 g, 0.01 mol) and δ-valerolactone (4.40 g, 0.04 mol). Toluene (6 mL) was added with ε-caprolactone. ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 1.36 (m, 2H), 1.66 (m, 8H), 2.32 (t, 4H), 4.07 (t, 4H).

Synthesis of poly(γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone)-*b*-poly(ε-caprolactone) (PMEEECL-*b*-PCL) with $NdCl_3$·3TEP/TIBA at 80 °C. PMEEECL-*b*-PCL was synthesized by using the ratio of [PMEEECL]:[ε-CL]:[Nd]:[Al] = 50:100:1:5. The same procedure as above was followed by using TIBA (0.17 mL, 0.18 mmol), $NdCl_3$·3TEP (0.167 M, 0.22 mL, 0.04 mmol), MEEECL (0.50 g, 1.81 mmol) and ε-caprolactone (0.41 g, 3.62 mmol). Toluene (0.5 mL) were added with MEEECL. ^{1}H NMR (500 MHz, CDCl3) δ: 1.35–1.40 (m, 2H), 1.61–1.68 (m, 4H), 1.73–1.90 (m, 4H), 2.29–2.32 (t, 2H), 2.35–2.43 (m, 2H), 3.37 (s, 3H), 3.44–3.48 (m, 1H), 3.53–3.67 (m, 12H), 4.05–4.07 (t, 2H), 4.14–4.17 (m, 2H).

Synthesis of poly(γ-bromo-ε-caprolactone)-*b*-poly(ε-caprolactone) (PBrCL-*b*-PCL) with $NdCl_3$·3TEP/TIBA at 80 °C. PBrCL-*b*-PCL was synthesized by using the ratio of [PBrCL]:[ε-CL]:[Nd]:[Al]= 50:100:1:5. The same procedure as above was followed by using TIBA (0.24 mL, 0.26 mmol), $NdCl_3$·3TEP (0.167 M, 0.31 mL, 0.05 mmol), BrCL (0.50 g, 2.59 mmol) and ε-caprolactone (0.59 g, 5.17 mmol). Toluene (0.5 mL) were added with BrCL. ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 1.39 (m, 2H), 1.63 (m, 4H), 2.15 (m, 2H), 2.25 (m, 2H), 2.32 (m, 2H), 2.61 (m, 2H), 4.06 (t, 2H), 4.14 (t, 2H), 4.35 (m, 1H).

Synthesis of poly(ε-caprolactone)-*b*-poly(γ-benzyl-ε-caprolactone) (PCL-*b*-PBnCL) with $NdCl_3$·3TEP/TIBA at 80 °C. The ratio of [ε-CL]:[δ-BnCL]:[Nd]:[Al] = 75:25:1:5 was used to synthesize PCL-*b*-PBnCL. The same procedure as above was followed by using TIBA (0.55 mL, 0.60 mmol), $NdCl_3$·3TEP (0.169 M, 0.70 mL, 0.12 mmol), ε-caprolactone (1.00 g, 0.01 mol) and (γ-benzyl-ε-caprolactone (0.64 g, 0.003 mol). Toluene (6 mL) was added with ε-caprolactone. ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$): δ = 1.38 (m, 2H), 1.64 (m, 4H), 1.8 (m, 2H), 1.9 (m, 2H), 2.3 (t, 4H), 3.53 (m, 1H), 4.05 (t, 2H), 4.14 (m, 2H), 4.47 (s, 2H), 7.29 (s, 5H).

Results and Discussion

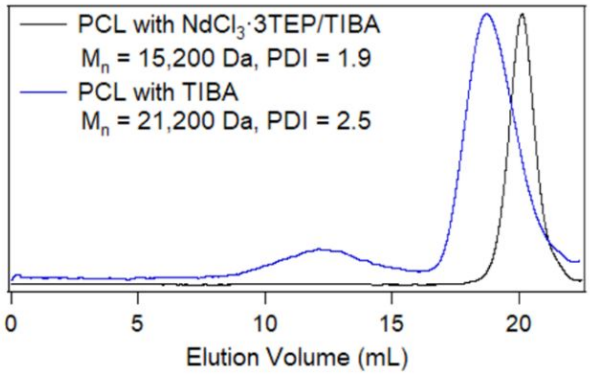


Figure 1. SEC traces for PCL obtained with TIBA and $NdCl_3$·3TEP/TIBA

Table 1. Variation of co-catalyst ratio, monomer ratio, and temperature for the polymerization of ε-CL with $NdCl_3$·3TEP/TIBA catalytic system

Entry	Ratio [ε-CL]:[Nd]:[Al]	Temp. (°C)	Time (h)	% Conversion	$M_n^{Theoretical}$ (Da)[a]	M_n^{SEC} (Da)[b]	PDI
1	500:1:1	40	4	-	-	-	-
2	500:1:5	40	4	25	14,250	20,500	2.11
3	500:1:10	40	4	40	22,800	33,600	1.61
4	500:1:20	40	4	60	34,200	18,000	1.96
5	500:1:30	40	4	57	32,500	15,000	1.85
6	500:1:5	23	4	9	5,130	-	-
7	500:1:5	60	4	45	25,650	43,700	1.51
8	500:1:5	80	4	98	55,860	62,300	1.30
9	400:1:5	80	4	96	45,600	48,800	1.59
10	250:1:5	80	4	99	28,500	32,400	1.56
11	100:1:5	80	4	100	11,400	23,400	1.41

[a] $M_n^{theoretical}$ was calculated by ([ε-CL]:[Nd]) x conversion x (molar mass of ε-CL). [b] M_n was obtained with triple calibration using polystyrene standards

Control experiments for ROP of ε-CL was initially carried out with $NdCl_3$·3TEP and TIBA alone, respectively. The use of $NdCl_3$·3TEP alone did not yield a polymer. TIBA by itself, produced a polymer. However, as seen from the SEC traces (Figure 1) there are two distributions present, which is most likely due to cationic polymerization of ε-CL. As a comparison, we carried out a one-point experiment with $NdCl_3$·3TEP/TIBA catalytic system for ε-CL at a ratio of 500:1:10 between [ε-CL]:[Nd]:[Al] at 40 °C. The ROP carried out with $NdCl_3$·3TEP/TIBA catalytic system was more controlled, and the SEC traces showed only one distribution (Figure 1). After our initial assessment, the ROP of ε-CL was performed to determine the effect of TIBA content.

Effect of the co-catalyst ratio for the polymerization of ε-CL

Polymerization of ε-CL was performed using $NdCl_3$·3TEP/TIBA catalytic system with the variation of [Nd]: [Al] ratio from 1 to 30 (Table 1, entries 1-5). At a ratio of 500:1:1 between [ε-CL]:[Nd]:[Al] with a reaction time of 4 h, a polymer was not obtained (Table 1, entry 1). On the other hand, Stere et al. obtained a polymer when the polymerization was performed with $NdCl_3$·3TBP/TIBA (TBP= tributylphosphate) system at a ratio of 100:1:1 between [ε-CL]:[Nd]:[Al]. However, only 25% of the monomer was converted after 9 h at 45 °C and 30% at 55 °C.[40] This difference in catalytic activity can be attributed to steric effects. In $NdCl_3$.3TBP/TIBA catalytic system, TIBA alkylates $NdCl_3$.3TBP to generate the active species. Consequently, the size of the ligand can impact the accessibility of the active sites on the Nd. Larger ligands may hinder the approach of caprolactone molecules to the active sites, potentially reducing the catalyst's polymerization activity. [41]
Upon increasing the Nd to organoaluminum ratio from 5 to 30, an increase in monomer conversion was observed (Table 1, entries 2-5). The number average molecular weight (M_n) increased at [Nd]:[Al]=1:10 and then decreased with increasing organoaluminum ratio (Table 1, entries 2-5). Shen et al. also observed adecrease in molecular weight with the increase in organoaluminum content for the $Nd(acac)_3·3H_2O$/TEA catalytic system (acac= acetylacetonato, TEA= triethylaluminum).[42] The M_n obtained for the polymer at the ratio [ε-CL]:[Nd]:[Al] = 500:1:5 (Table 1, entry 2) was the closest to the theoretical M_n. Hence, we selected this ratio to perform further optimizations. As seen from the ^1H NMR spectrum of polycaprolactone (Figure S1 (a), See Supporting Information for details), it is evident that one end group of the polymer chain is a hydroxyl group. This was further confirmed by D_2O exchange (Figure S1).

Effect of temperature, [ε-CL]/[Nd] ratio, and kinetic experiments on polymerization of ε-CL

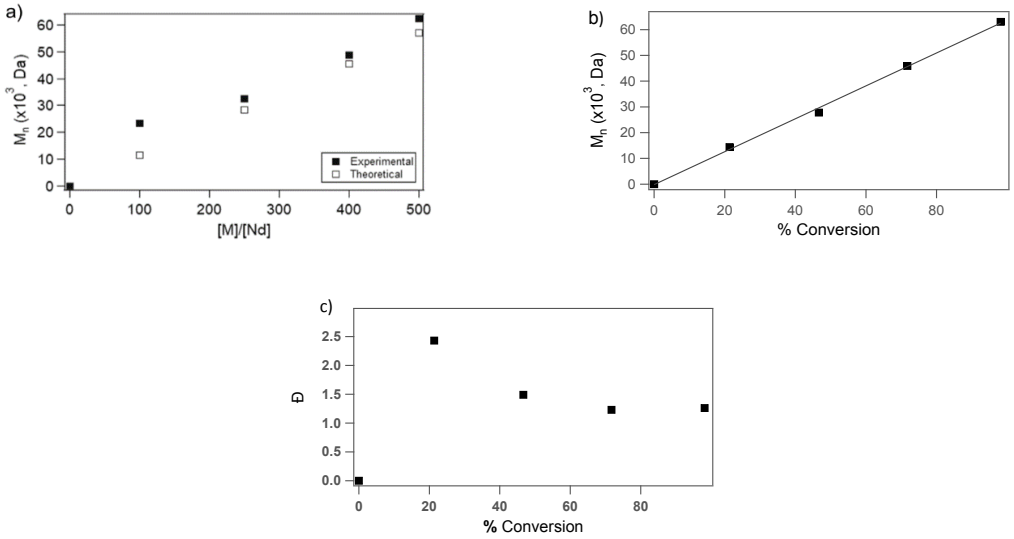


Figure 2. (a) M_n vs [M]/[Nd], (b) M_n vs. conversion at a [ε-CL]:[Nd]:[Al] ratio of 500:1:5, for the polymerization of ε-CL with $NdCl_3$·3TEP/TIBA catalytic system at 80 °C. $M_n^{experimental}$ was obtained using triple calibration, and $M_n^{theoretical}$ was calculated by ([ε-CL]:[Nd]) × conversion × (molar mass of ε-CL)

The temperature of polymerization was varied from room temperature (23 °C), 60 to 80 °C (Table 1, entry 6-8). With the increase in temperature, catalytic activity and M_n increased. The molecular weight of the polymer obtained at 80 °C, was closest to the theoretical M_n and had the lowest Đ (Table 1, entry 8). In order to determine the activation energy (E_a) for the ROP of ε-CL with $NdCl_3$·3TEP/TIBA catalytic system, kinetic studies were carried out at these three temperatures (Figure S2). With the increase in temperature, the rate of polymerization increased (Figure S2 (a), (b), and (c)). The $\ln\{[M]_0/[M]\}$ vs. time plots for all three temperatures followed the same trend (Figure S2 (b) and (c)). All reactions had a slower initiation. However, no evidence of chain termination was found. Due to the presence of slow initiation, E_a was obtained for conversions < 20% (Figure S2 (c)).

In order to determine the effect of [ε-CL]/[Nd] ratio, polymerization experiments were carried out at a constant [Nd]/[Al] ratio of 1:5 and [ε-CL]/[Nd] ratio was varied from 100, 250, 400 and 500 (Table 1, entries 8-11) at 80 °C. A linear increase of the molecular weight as a function of [ε-CL]/[Nd] was observed for ratios above 250 (Table 1, entries 8-10 and Figure 2 (a)). At a ratio of 100:1:5, it deviated from linearity (Table 1, entry 11 and Figure 2 (a)) due to increased transfer reactions with higher catalyst concentrations. All other ratios were closer to the theoretical M_n. It can be speculated that at a higher monomer concentration, the system exhibits a more controlled polymerization. Kinetic experiments carried out at 80 °C at a [ε-CL]:[Nd]:[Al] ratio of 500:1:5 showed the absence of chain termination and transfer (Figure S2 (b), and 2 (b), respectively); however, the initiation was slow.

Sequential monomer addition and block copolymer synthesis

Further analysis of *living* behavior was demonstrated by sequential monomer addition and block copolymer synthesis. Sequential monomer addition was carried out at a [ε-CL1]:[ε-CL2]:[Nd]:[Al] ratio of 50:100:1:5 at 80 °C. At 100% conversion of the first portion, a second portion of ε-CL was introduced. At 100% conversion of the second portion, an increase in molecular weight from 11.5 kDa to 19.6 kDa was observed (Figure S3 (a)). The ability to perform chain extension shows the presence of a living chain end. Block copolymer synthesis between δ-VL and ε-CL, BrCL and ε-CL, and MEEECL and ε-CL, were also performed at a feed ratio of [M]: [ε-CL]:[[Nd]:[Al] = 50:100:1:5 at 80 °C (M = δ-VL, or BrCL or MEEECL). For PVL-*b*-PCL, at 100% conversion of δ-VL, ε-CL was added, and an increase in molecular weight from 5.4 kDa to 12.1 kDa was observed (Scheme S1 (a), Figure S3 (b)). The monomodal distribution of the SEC trace for PVL-*b*-PCL clearly shows the formation of a block copolymer and not a mixture of the two homopolymers. Furthermore, DSC traces for PCL, PVL and PVL-*b*-PCL show the variation of the melting temperature (T_m), cold crystallization (T_c) (Figure 3 (a) and Figure S4, respectively) and the presence of two glass transition temperatures (T_g) (Figure 3 (b)). According to ^{1}H NMR (Figure S5), the polymer composition for δ-VL and ε-CL is 29 and 71 mol%, respectively, which agrees with the feed ratio. Synthesis of PBrCL-*b*-PCL was carried out similar to that of PVL-*b*-PCL, and an increase in molecular weight from 4.6 kDa to 8.1 kDa was observed (Figure S3 (c)). DSC traces show the changes in T_m, T_g, and T_c, where the T_g of both polymers reside at -47.3 °C and exhibit as a single transition (Figure 3). To further confirm the block copolymer synthesis, DOSY experiments were carried out. Accordingly, there is a clear variation in the diffusion coefficients, going from D = 4.52 x 10^{-10} m^2s^{-1}, 1.13 x 10^{-10} m^2 s^{-1} to 2.12 x 10^{-10} m^2s^{-1} for PCL, PBrCL and PBrCL-*b*-PCL respectively (Figure S9). The composition of the polymer, according to ^{1}H NMR (Figure S6) is 27% and 73 mol% for BrCL and ε-CL, respectively. The formation of an amphiphilic block copolymer was achieved by the use of MEEECL, a hydrophilic thermoresponsive caprolactone monomer, and ε-CL, the hydrophobic counterpart (Scheme S1 (c)). Amphiphilic block copolymers are used for drug delivery

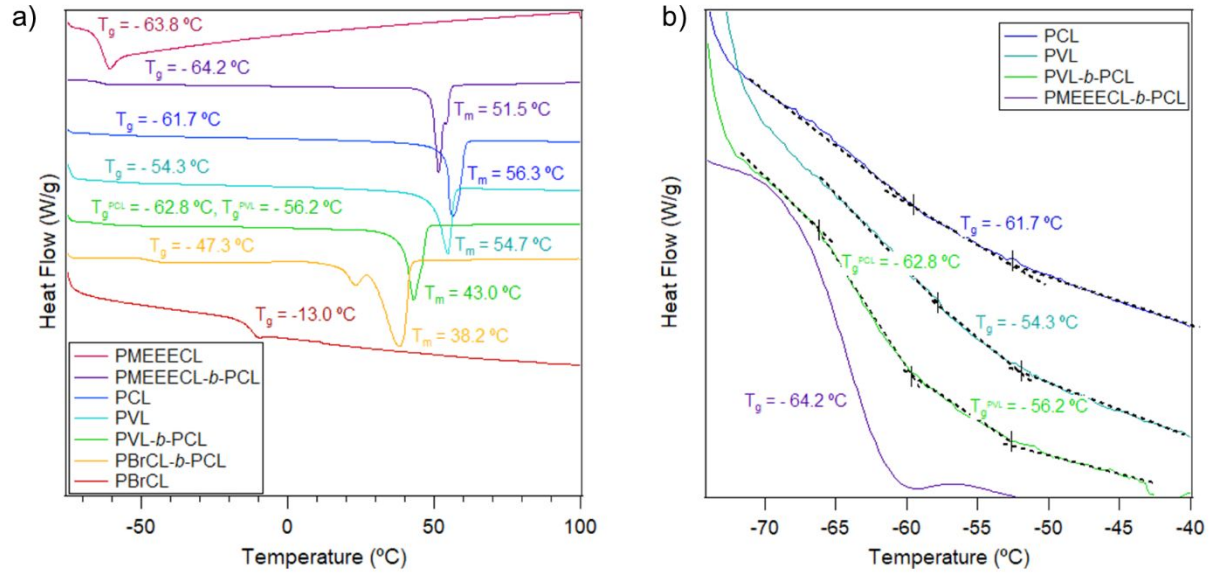


Figure 3. (a) Endothermic DSC traces for PMEEECL, PMEEECL-b-PCL, PCL, PVL, PVL-b-PCL, PBrCL and PBrCL-b-PCL (b) DSC traces for PCL, PVL, PVL-b-PCL, and PMEEECL-b-PCL for the temperature range of -75 °C to -40 °C

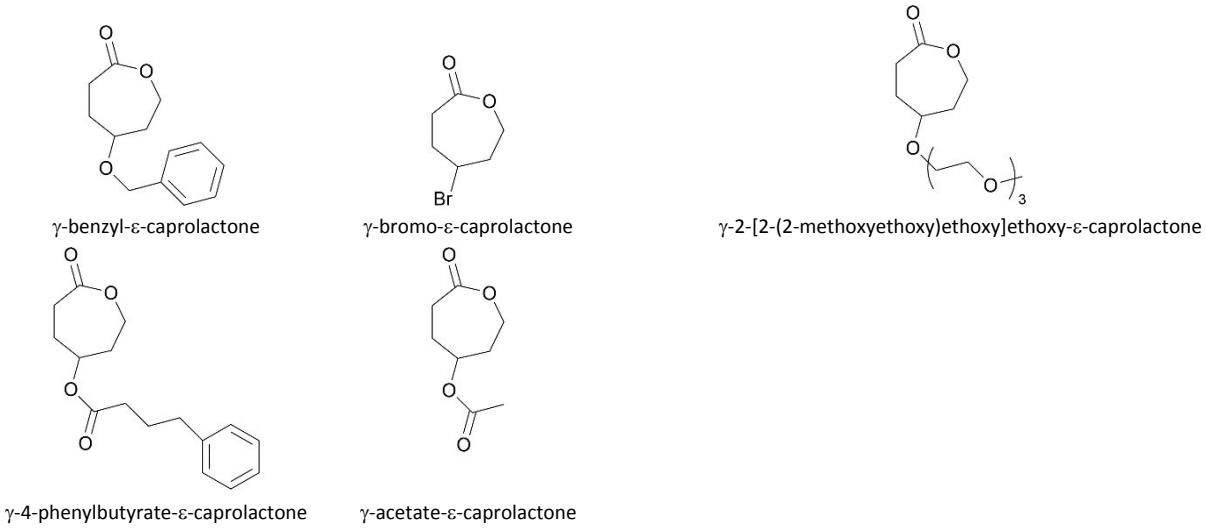


Figure 4. Structures of γ-benzyl-ε-caprolactone , γ-bromo-ε-caprolactone, γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone, γ-4-phenylbutyrate-ε-caprolactone, and γ-acetate-ε-caprolactone

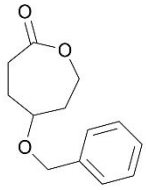
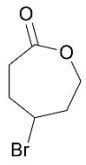
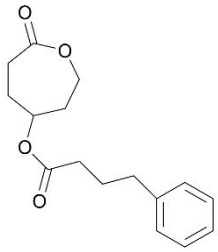
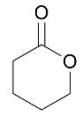
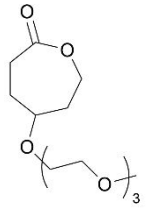
applications to form micelles in aqueous environments.[43, 44] Previously, we have demonstrated the thermoresponsive behavior of amphiphilic polymers obtained with MEEECL.[9, 10, 38] Upon chain extension from PMEEECL to PMEEECL-*b*-PCL, an increase in molecular weight from 7.1 kDa to 12.1 kDa (Figure S3 (d)) was observed. The composition of the polymer obtained from ^{1}H NMR (Figure S10) was 17 mol% of MEEECL and 83 mol% of ε-CL. DSC trace of PMEEECL-*b*-PCL shows the corresponding T_m, T_g, and T_c (Figure 3 (a), (b), and Figure S4, respectively). However, due to the close glass transition temperatures of PMEEECL and PCL, the T_g for PMEEECL-*b*-PCL shows as one single transition (Figure 3 (b)).

For a catalytic system to be effective for the synthesis of block copolymers, it has to demonstrate its ability to do polymerization in both directions. Towards that, we did two chain extension reaction starting with ε-CL monomer. In the first experiment, we choose unsubstituted δ-VL monomer while in the second experiment, we choose a γ-benzyl substituted ε-CL (BnCL) monomer. The chain extension reaction of δ-VL monomer was rapid and complete conversion observed after 2 h. However, in the case BnCL monomer, only 64 % conversion was observed after 2 h and the conversion rate increased to 92 % after 12 h. This demonstrated the successful synthesis of PCL-*b*-PVL and PCL-*b*-PBnCL using the $NdCl_3$·3TEP/TIBA catalytic system in both directions. The SEC analysis of PCL-*b*-PVL and PCL-*b*-PBnCL (Figure S3 (e), Scheme S1 (d) and Figure S3 (f), Scheme S1 (e) respectively) confirmed the formation of block copolymers with a monomodal distribution. Notably, the molecular weight of PCL-*b*-PVL (M_n = 90.1 kDa) highlighted the capability of the $NdCl_3$·3TEP/TIBA catalytic system to generate

copolymers with a high molecular weight (Figure S3 (e)). According to ^{1}H NMR (Figure S7) the polymer composition of PCL-*b*-PVL consisted of 15 mol% ε-CL and 85 mol% δ-VL, which matched the feed ratio of [ε-CL]:[δ-VL]:[Nd]:[Al] = 200:1000:1:5. Similarly, for PCL-*b*-PBnCL, the ^{1}H NMR analysis (Figure S8) indicated a polymer composition of 70 mol% ε-CL and 30 mol% δ-BnCL, corresponding to the feed ratio of [ε-CL]:[δ-BnCL]:[Nd]:[Al] = 75:25:1:5. Additionally, an increase in molecular weight from 8.3 kDa to 16.3 kDa was observed for PCL-*b*-PBnCL (Figure S3 (f)).

All kinetic experiments and chain extension experiments show living characteristics of the $NdCl_3$·3TEP/TIBA catalytic system for the polymerization of ε-CL, however, the system cannot be categorized as a fully living system due to the presence of slow initiation. While many catalysts show living properties, not all of them have the ability to polymerize functionalized ε-CL monomers and the majority of the studies were limited to non-functionalized ε-CL. Hence, we extended our study for the polymerization of γ-substituted-ε-caprolactone monomers as well.

Table 2. Polymerization of γ-benzyl-ε-caprolactone, γ-bromo-ε-caprolactone, γ-4-phenylbutyrate-ε-caprolactone, γ-acetate-ε-caprolactone, δ-VL, and γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone with $NdCl_3$·3TEP/TIBA catalytic system

Monomer	Entry	Ratio [M]:[Nd]:[Al]	Temp. (°C)	Time (h)	% Conv.	M_n ^{SEC} (Da)[a]	Đ
	1	250:1:5	80	2	100	17,600	1.58
	2	250:1:5	80	3	100	23,400	1.84
	3	250:1:5	40	6	64	22,000	1.52
	4	250:1:5	80	2	51	16,300	1.75
	5	250:1:5	40	6	41	11,300	1.30
	6	250:1:5	80	4	96	18,300	1.46
	7	250:1:5	80	6	85	8,300	1.09

[a]M_n was obtained with triple calibration

Polymerization of different lactone monomers

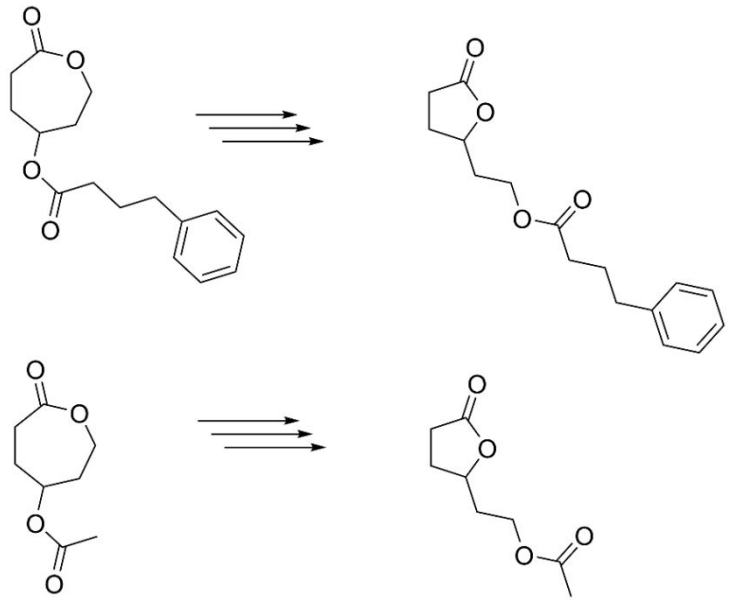


Figure 5. Structures of the transesterified butyrolactone analog of γ-4-phenylbutyrate-ε-caprolactone and γ-acetate-ε-caprolactone

For this study, we selected different substituted monomers based on different linkages to the caprolactone ring. γ-benzyl-ε-caprolactone and γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone, have ether linkages between the caprolactone ring and the substituent; γ-4-phenylbutyrate-ε-caprolactone and γ-acetate-ε-caprolactone have ester linkages; γ-bromo-ε-caprolactone has a Br at the γ-position (Figure 4). All the γ-substituted monomers were synthesized according to the previous publications[7, 38] except for γ-bromo-ε-caprolactone, where the synthetic route was improved than what is currently used. As seen in Scheme S2, pathway II shows the usual route to synthesize γ-bromo-ε-caprolactone,[45] while pathway I show the synthetic route that we employed. By using the Appel reaction on 4-hydroxyclohexanone followed by the Baeyer-Villiger oxidation, γ-bromo-ε-caprolactone was obtained. The new route improved the overall yield of this reaction, decreased the time from 6 days to less than one day, and lowered the cost compared to obtaining the lactone monomer through pathway II. The polymerization of γ-benzyl-ε- caprolactone, where there is an ether linkage at the γ-position, showed increased catalytic activity (Table 2, entry 1), where the polymerization completed in two hours at 80 °C. The same polymerization conditions for ε-CL took almost four hours for the reaction to go to completion (Table 1, entry 10). In the presence of a Br group at the γ-position, the polymerization was faster than that for ε-CL, but slower than γ-benzyl-ε-caprolactone (Table 2, entry 2). For γ-4-phenylbutyrate-ε-caprolactone, we performed the polymerization at two different temperatures, 40 and 80 °C. Due to an additional ester linkage at the γ-position, the use of high temperature causes transesterification, and a butyrolactone analog is produced. This phenomenon was previously reported by our group.[7] The formed byproduct, however, does not participate in the polymerization. Therefore, for γ-acetate-ε-caprolactone, polymerization was carried out at 40 °C. When the polymerization was carried out at 40 °C for γ-4-phenylbutyrate-ε-caprolactone, the polymerization was much slower, where conversion to the polymer was only 64% after 6 h (Table 2, entry 3), and the conversion to the transesterified product was ~11%. Increasing the temperature to 80 °C, 51% of the monomer was converted to the polymer (Table 2, entry 4), but 49% was converted to the transesterified product within 2 h. Therefore, in the presence of an ester linkage at the γ-position, it is preferable to use lower temperatures. Polymerization of γ-acetate-ε-caprolactone followed similar trends to that of γ-4-phenylbutyrate-ε-caprolactone, where the polymerization was slower, and transesterification was present (Table 2, entry 5). A conversion of ~10% was observed for the transesterified product of γ-acetate-ε-caprolactone. The structures of the transesterified butyrolactone analogs of γ-4-phenylbutyrate-ε-caprolactone and γ-acetate-ε-caprolactone are shown in Figure 5. We have previously proven the formation of the butyrolactone product as a consequence of transesterification.[7] Homopolymerization of δ-VL was also carried out using $NdCl_3$·3TEP/TIBA catalytic system, however, the rate of polymerization was somewhat slower than that of ε-CL (Table 2, entry 6), due to the stable 6-membered configuration of δ-VL. The polymerization of γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone monomer resulted in homopolymer with 85% conversion after 6h (Table 2, entry 7). The MEEE substitution at the γ-position decreased the rate of polymerization comparing to ε-CL (Table 2, entry 6).

Conclusions

In conclusion, $NdCl_3$·3TEP/TIBA catalytic system was shown to be effective for the polymerization of ε-CL, functionalized caprolactones with varying γ-substituents and δ-VL. Kinetic studies revealed some living characteristics at higher monomer concentrations. However, the system shows a slower initiation.

$NdCl_3$·3TEP/TIBA catalytic system was successfully utilized to form PVL-*b*-PCL and PBrCL-*b*-PCL block copolymer and the synthesis of an amphiphilic block copolymer, PMEEECL-*b*-PCL. Additionally, this catalytic system demonstrated its ability to synthesize copolymers in both directions, as evidenced by the synthesis of PCL-*b*-PVL and PCL-*b*-PBnCL. The presence of an ester linkage at the γ-position harms the polymerization of caprolactones with the $NdCl_3$·3TEP/TIBA catalytic system, however, it performs better than the conventional $Sn(Oct)_2$ catalyst. Overall, based on this study and our previous work, we have demonstrated that $NdCl_3$·3TEP/TIBA catalytic system is a versatile system that can polymerize not only dienes and vinyl monomers but also non-functionalized and functionalized lactones.

Conflicts of interest

There are no conflicts to declare.

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