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A Simple and Facile Approach to Aliphatic *N*-Substituted Functional Eight-Membered Cyclic Carbonates and Their Organocatalytic Polymerization

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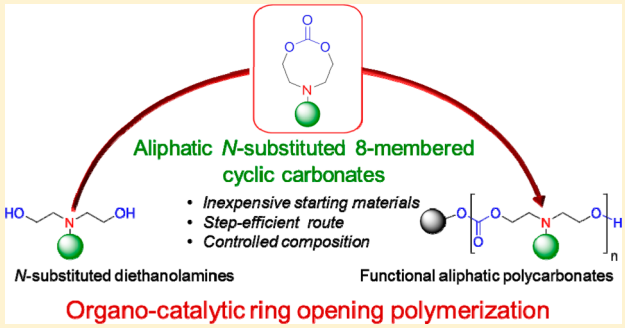
Supporting Information

ABSTRACT: Aliphatic *N*-substituted functional eight-membered cyclic carbonates were synthesized from *N*-substituted diethanolamines by intramolecular cyclization. On the basis of the *N*-substituent, three major subclasses of carbonate monomers were synthesized (*N*-aryl, *N*-alkyl and *N*-carbamate). Organocatalytic ring opening polymerization (ROP) of eight-membered cyclic carbonates was explored as a route to access narrowly dispersed polymers of predictable molecular weights. Polymerization kinetics was highly dependent on the substituent on the nitrogen atom and the catalyst used for the reaction. The use of triazabicyclodecene (TBD), instead of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), as the catalyst for the *N*-alkyl substituted monomers significantly enhanced the rate of polymerizations. Computational studies were performed to rationalize the observed trends for TBD catalyzed polymerizations. With the optimal organocatalyst all monomers could be polymerized generating well-defined polymers within a timespan of ≤2 h with relatively high monomer conversion (≥80%) and low molar-mass dispersity ($Đ_M \leq 1.3$). Both the glass transition temperatures (T_g) and onset of degradation temperatures (T_{onset}) of these polymers were found to be *N*-substituent dependent and were in the range of about −45 to 35 °C and 230 to 333 °C, respectively. The copolymerization of the eight membered monomers with 6-membered cyclic comonomers including commercially available L-lactide and trimethylene carbonate produced novel copolymers. The combination of inexpensive starting materials, ease of ring-closure and subsequent polymerization makes this an attractive route to functional polycarbontes.



INTRODUCTION

The development of facile synthetic approaches to access well-defined degradable polymers with diverse functional groups remains a challenge in contrast to well-established synthetic techniques for the formation of nondegradable synthetic polymers (e.g., acrylates) or natural polymers (e.g., proteins). The ring opening polymerization (ROP) of functional cyclic precursors is a promising strategy to synthesize well-defined degradable materials with excellent control over numerous parameters,[1] which could potentially suit various biomedical applications. Tremendous progress has recently been made in the development of various classes of degradable and, in some cases, functional polymers[2] such as polyesters,[3] polyphosphoesters,[4] polycarbonates,[5] and polypeptides.[6] In spite of these advances, many synthetic approaches suffer from challenges arising from multistep routes for the synthesis of monomers or the postfunctionalization of reactive polymers, often requiring relatively expensive reagents or starting materials. Efficient and straightforward access to degradable polymers from readily available and inexpensive precursors will have implications for the synthesis of next generation biocompatible and eco-friendly materials.

Aliphatic cyclic carbonates are an important class of materials[7] owing to their biodegradability, low toxicity, biocompatibility and potential biomedical applications.[8] Critically, the successful application of aliphatic polycarbonates in the biomedical field stems from unprecedented ease in which many desired functionalities can be introduced.[5,8] Significant effort has been devoted to develop facile strategies to incorporate functionality at both the monomer level[5,8−28] and postpolymerization[16−23,26,29] by judicious combination of

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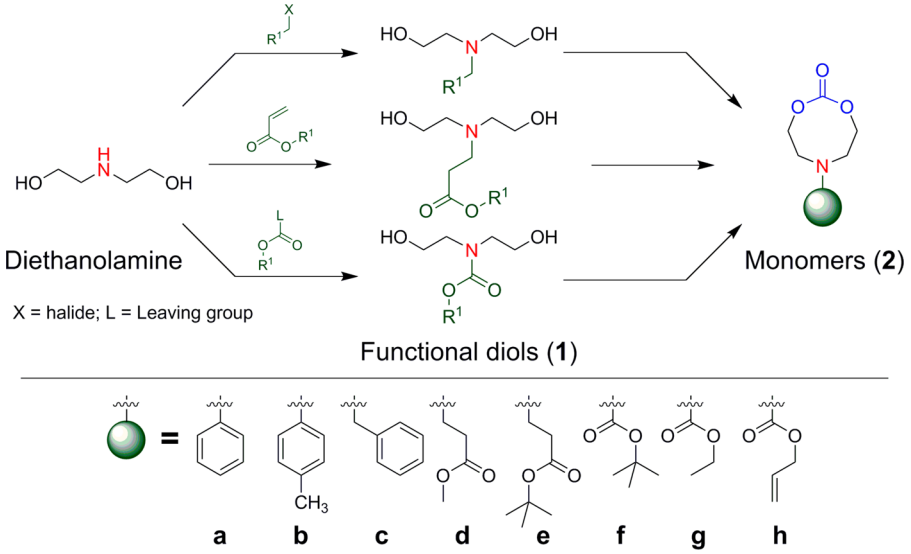
Scheme 1. Two-Step Approach to Access Well-Defined Aliphatic Functional Cyclic Carbonate Monomers by Starting from Inexpensive Diethanolamine via (1) Chemoselective Derivatization of the Secondary Amine, Followed by (2) Intramolecular Cyclization to Access 8-Membered Aliphatic *N*-Substituted Cyclic Carbonate Monomers



orthogonal coupling chemistries. Ease of functional group installation coupled with functional group tolerant organocatalysts[30] has enabled the synthesis of well-defined polycarbonates that have impacted the medical field.

In our continued efforts towards the development of functional carbonate monomers, we have explored the use of *N*-substituted diethanolamines (DEAs) as inexpensive and readily available[31] starting materials[32] for the synthesis and subsequent polymerization of aliphatic *N*-substituted eight-membered cyclic carbonate monomers. Functional 8-membered cyclic carbonates were synthesized via intramolecular cyclization of the 1,5-diol of *N*-substituted DEAs and subsequently polymerized via organocatalytic ROP to access new functional aliphatic *N*-substituted polycarbonates. The nucleophilic secondary amine of DEA can be used as a reactive handle to chemoselectively introduce desired physicochemical functionalities without selective protection and deprotection of the hydroxyl groups. More importantly, this approach will offer a direct route to the synthesis of medium size functional cyclic carbonates, effectively expanding the range of accessible polycarbonates.

RESULTS AND DISCUSSION

Monomer Design and Synthesis. In general for ROP processes, the size of the monomer ring dictates ROP behavior and importantly offers a unique opportunity to precisely engineer the presentation of functional groups and their spacing. For example, it has been demonstrated that the spacing of pendant functional groups in peptides influenced numerous properties including their biodegradability.[13] To date, functional aliphatic polycarbonates have been synthesized from five- to seven-membered cyclic carbonates.[8] Except for a few reports, functional eight-membered cyclic carbonates are essentially unexplored.[33−35] Earlier it was reported that cyclizing *N*-methyl diethanolamine to an 8-membered cyclic carbonate was not feasible, however synthesis of 16-membered cyclic carbonate monomer was possible via thermal depolymerization of low molecular weight oligomers. These large ring carbonates were shown to undergo enzymatic polymerization.[8,36] Yamada and co-workers reported the synthesis of a number of *N*-aryl substituted eight-membered cyclic carbonates in the 1980s;[33,34] to the best of our knowledge, the ROP of these substrates has not been explored. Recently, we reported the antimicrobial gels from 8-membered mono- and dicyclic carbonate monomers derived from *N*-methyl diethanolamine and *N*,*N*,*N*′,*N*′-tetrakis-(2-hydroxyethyl)ethylenediamine, respectively.[35] In order to access a wide variety of eight-membered cyclic carbonates, we envisioned a simple two-step approach starting from DEA (Scheme 1). To demonstrate the feasibility of this approach, we chose a set of diols (**1**) that are either commercially available (**1a**, **b** and **f**) or can be readily synthesized from DEA via alkylation (**1c** with benzyl bromide), Michael-addition (**1d** and **1e** with acrylates) or by reactions with other commercially available reagents (**1g** and **1h**). These diols were successfully cyclized by reacting with either ethylchloroformate or triphosgene in the presence of a base to yield corresponding carbonate monomers (**2a**−**h**, Scheme 1, Figure S1−S8) in overall isolated yields of ∼21−53%. As the formation of medium size rings is known to be synthetically challenging,[37] these yields are remarkable considering that no special conditions such as high dilution were necessary. Collectively, these monomer examples demonstrate that innumerable functional groups can be reliably introduced at the nitrogen site, including aryl- and alkyl-substituents as well as carbamates, providing access to novel classes of eight-membered *N*-heterocyclic carbonates. It should be noted that latent reactive groups [such as the protected carboxylic acid (**2e**), the protected secondary amine (**2f**) and the allyl group (**2h**)] may serve as versatile handles for further chemical manipulation. The ability to access these functional cyclic monomers with reasonable yield in a step-efficient route from inexpensive and commercially available precursors is a significant advance.

Kinetics of Polymerization. Since 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) has been demonstrated as an effective organocatalyst (OC) for the ROP of different classes of cyclic monomers, we decided to explore DBU as a catalyst to polymerize these cyclic carbonates.[30] The polymerization of selected monomers **2a**, **2c** and **2g** with benzyl alcohol (Bn−

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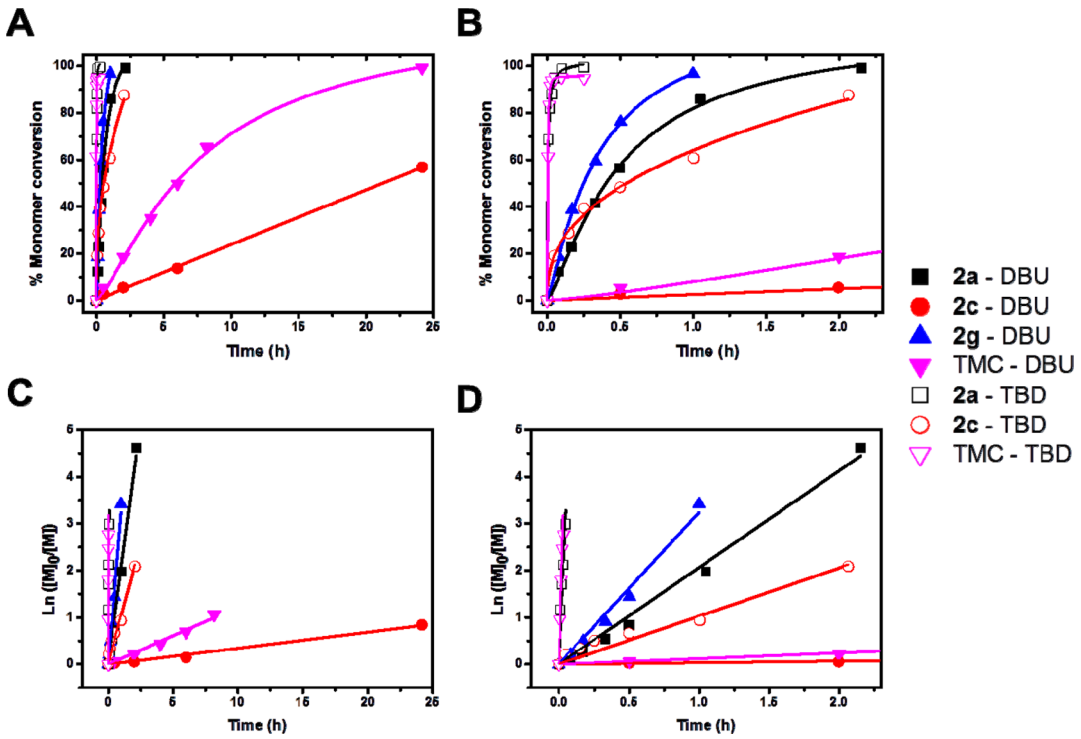

Figure 1. Kinetics of OC-ROP of representative functional 8-membered cyclic carbonates **2a** (squares), **2c** (circles) and **2g** (triangles) compared to that of **TMC** (inverted triangles) for DBU (closed symbols) or TBD (open symbols) as the catalyst: (A) monomer conversion versus time plot with (B) zoom in showing the earlier time points; (C) semilogarithmic kinetic plot with (D) zoom in showing the earlier time points. Conditions: $[M]_0$ = 0.483 M; $[Bn{-}OH]_0$:$[M]_0$:[Catalyst] = 1.0:20:1.0; DCM = 1.0 mL.

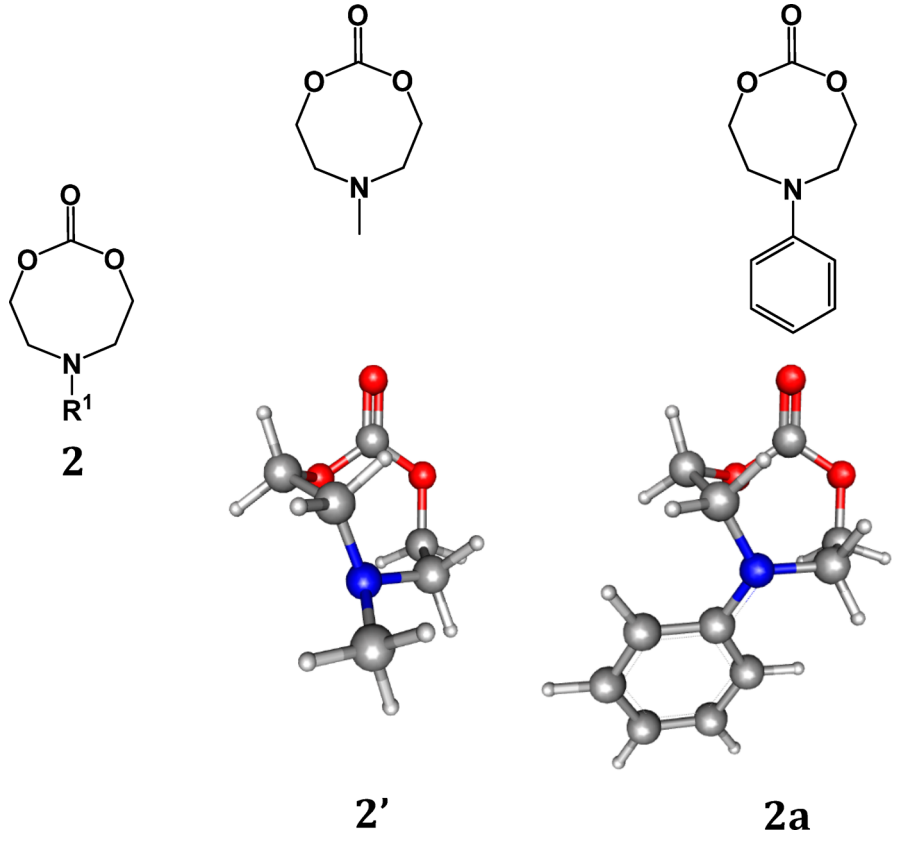

Figure 2. Lowest energy conformers of the 8-membered cyclic amino carbonates **2′** and **2a**, in which R^1 = CH_3 present in **2′** represents a computational model for the functional R^1 groups in **2c**, **2d** and **2e**.

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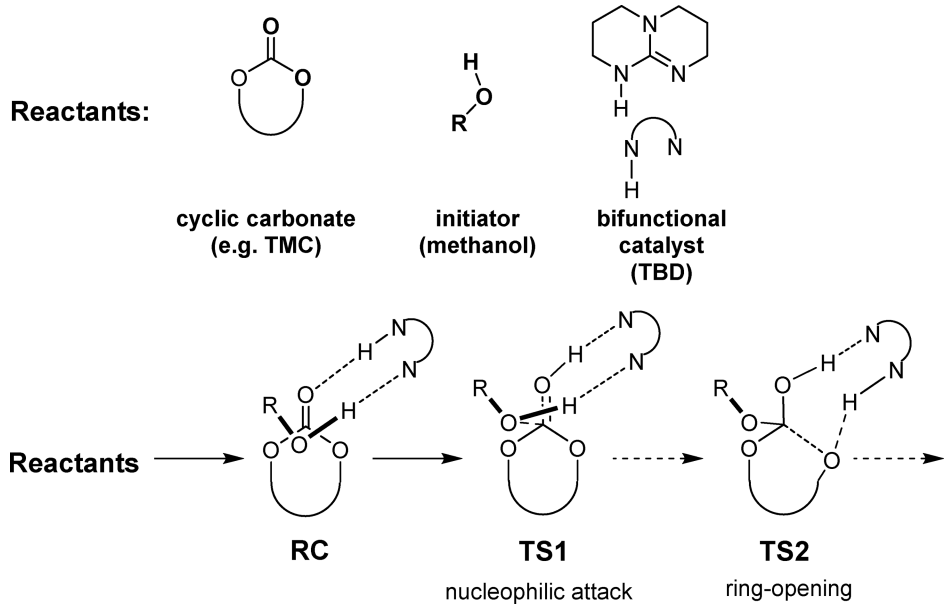

Figure 3. Steps of the preferred ROP reaction pathway between a cyclic carbonate, an initiator and the bifunctional organocatalyst TBD; for the ROP of L-lactide, TS1 is the rate-limiting step,[39] while for other cyclic esters, both TS1 and TS2 possess comparable barrier heights.[42]

OH) as the initiator in the presence of DBU catalyst was studied at room temperature in dichloromethane (DCM) solvent (1.0 mL) (($[M]_0$ = 0.483 M Ratio: $[Bn-OH]_0$:[DBU]:$[M]_0$ = 1.0:1.0:20). These monomers were chosen to represent three major subclasses of *N*-substituents (*N*-aryl; *N*-alkyl and *N*-carbamate). The kinetics of polymerization of these monomers was compared to that of trimethylene carbonate (TMC), a commercially available 6-membered cyclic carbonate monomer. Dramatic difference in the rate of polymerization between the monomers was observed (Figure 1A,B, closed symbols). Near quantitative conversion of monomer **2a** and **2g** was observed in ∼2 h, whereas only ∼55% conversion was observed for **2c** even after 24 h and almost quantitative monomer conversion for TMC in ∼24 h. The semilogarithmic kinetic plot for all the monomers was found to be linear (Figure 1C,D, closed symbols; Figure S9), indicating that the rate of polymerization was first-order in monomer. On the basis of the kinetic plot, the following trend was observed for DBU: $k_{obs}^{(DBU)}$: **2g** > **2a** > **TMC** > **2c**.

As TBD has been known to dramatically improve the rates of ROP by serving as an efficient catalyst,[38] the influence of TBD on the polymerization of **2a**, **2c** and **TMC** was investigated under conditions similar to those of DBU ($[M]_0$ = 0.483 M; $[Bn-OH]_0$:[TBD]:$[M]_0$ = 1.0:1.0:20; DCM 1.0 mL). Faster polymerization rates were observed for all the monomers (Figure 1A,B, open symbols). Near quantitative conversion of monomer **2a** and **TMC** was observed in <10 min, whereas ∼85% conversion was observed for **2c** after 2 h. The semilogarithmic kinetic plot for all the monomers was found to be linear (Figure 1C,D, open symbols; Figure S9). On the basis of the kinetic plot, the following trend was observed for TBD: $k_{obs}^{(TBD)}$: **TMC** ∼ **2a** > **2c**. These results suggest that the OC-ROP of these functional 8-membered cyclic carbonates occurs in a controlled fashion, resulting in polymers with predictable molecular weights. In addition to the observed dependence on the catalyst for the rates of these reactions (TBD > DBU), the rate was also found to be highly dependent on the nature of the *N*-substituent; carbonates with *N*-aryl substituents were observed to polymerize more rapidly than those with *N*-alkyl substituents.

Computational Studies. Computational studies were performed in order to understand the basis for the striking difference in the polymerization kinetics using the computational protocol outlined in the accompanying Supporting Information. The conformational space of the 8-membered cyclic monomer **2** (with the nitrogen atom substituted with a CH_3 group as a model for **2c**−**e**) was surveyed first. Only low-lying conformers were considered in our nonexhaustive search. One would expect that 8-membered cyclic carbonates possess more conformations than corresponding 6-membered carbonates. In addition, inversion of the nitrogen atom in the ring will increase the number of possible conformations, although these are expected to be limited by the presence of the rigid carbonate groups. In all, six conformers were considered (see Figure S10, Supporting Information). The twisted conformer **2′** (Figure 2) possesses the lowest free energy (by $\Delta G \geq 3.5$ kcal/mol) and thus subsequent studies were limited to this conformer. The lowest conformer found for **2a** is also shown in Figure 2.

A complete computational study of possible ROP mechanisms would involve comparison of the energies and structures for reactions used in experiments involving the various initiators, monomers and catalysts. Such a study would be computationally costly and fall beyond the scope of the present study and was consequently not done. Instead, based on insights from previous studies on organocatalytic ring-opening polymerizations[39−41] (which revealed the general reaction pathway shown in Figure 3), we restricted our attention to key stationary points of the mechanism using CH_3OH as a computational model for Bn−OH, TBD as catalyst and 8-membered carbonates **2** and **2′**.

As illustrated in Figure 3, the ROP reaction starts with the formation of a reactant complex (**RC**) in which the alcohol and carbonate are both activated by the TBD catalyst via bifunctional activation. If the transition state for nucleophilic attack (**TS1**) is the rate-limiting step of the ROP, studying the

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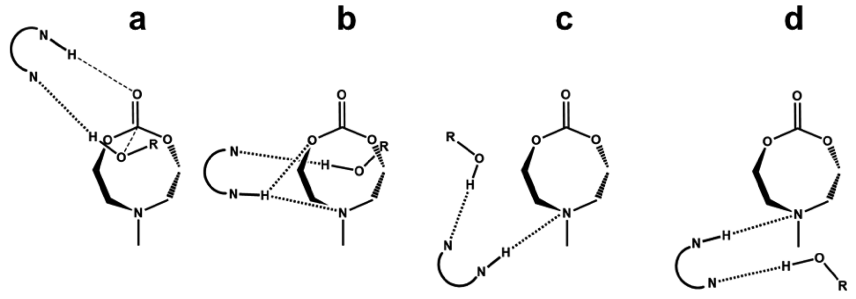

Figure 4. Low-lying complexes formed between TBD, **2′** and CH_3OH (for 3-dimensional structures see Figure S11, Supporting Information). Free energies and relative free energies are shown in kcal/mol.

RC might give insights into structural and electronic effects influencing the observed reactivity trends.

The nitrogen atom present in the 8-membered carbonates is capable of forming a hydrogen bond with the N−H of TBD, and may thereby disrupt binding of TBD with the alcohol and the carbonyl group of the carbonate. Hydrogen-bonding should be especially pronounced when the amine is aliphatic as in **2′** and related analogues. Through a nonexhaustive conformational search of complexes formed by TBD, **2′** and CH_3OH we found several complexes that do not lie on the preferred pathway for ROP. One of these complexes include the low-lying complex **RC$_d$** which is more stable than other predicted reactant complexes **RC$_a$**, **RC$_b$**, **RC$_c$** (Figure 4; 3-dimensional structures are shown in Figure S11, Supporting Information). Although the differences in free energy between these adducts are small ($\Delta\Delta G \leq 1.3$ kcal/mol), to the extent that the TBD catalyst speciates as intermediates **RC$_b$**, **RC$_c$**, and **RC$_d$**, this would reduce the concentration of the active TBD catalyst and thereby inhibit the rate of ROP of *N*-alkyl substituted monomers (such as **2c**).

In contrast to the *N*-alkyl substituted 8-membered carbonates, the N-aryl substituted 8-membered carbonates such as **2a** should be less capable of accepting H-bonds from TBD since the lone pairs on the nitrogen atoms are delocalized. The delocalization of the nitrogen lone pair can be assessed from the out-of-plane (oop) dihedral angles formed by the three C−N bonds involving the nitrogen atoms for **2a** and **2′** relative to those for prototypical sp^3 and sp^2 hybridized nitrogen atoms (Table 1). The rather small oop dihedral angle for **2a** is due to resonance between the lone pair on nitrogen and the directly attached aromatic substituent.

If the rate-limiting step of the ROP was the opening of the ring (**TS2**, Figure 3) as observed in other systems,[43] then the differences in the enthalpy of ring-opening may also manifest in the activation energy for ring-opening and account for observed differences in reactivity between the different 8-membered amino carbonates (e.g., **2′** (a surrogate for **2c**) vs **2a**) and 6-membered carbonates (e.g., TMC). To this end, we computed isodesmic measures for the enthalpies of ring-opening[44,45] for (**2′**) and (**2a**)[32,46] and compared them with that of TMC. An exhaustive conformer search for the products of the isodesmic reactions (see Figures S13 and S14, Supporting Information)[46] was not attempted, instead structures were simply reoptimized.[46] These calculations reveal that the calculated enthalpy of ring-opening (ΔH_{ro}) for the three cyclic carbonates differ significantly (Table 1): ΔH_{ro} = −6.6 kcal/mol (TMC), −10.0 kcal/mol (**2′**) and −12.5 kcal/mol (**2a**). The comparatively more negative enthalpy of ring-opening for the *N*-aryl substituted carbonate **2a** relative to *N*-alkylated carbonate **2′** is likely due to the relaxed conformations of the ring-opened structure which allows the nitrogen to planarize and the N lone pairs to delocalize into the aromatic ring (Figure S14c, see Supporting Information).[47] Similar trends in the enthalpy of ring-opening was observed for the *N*-aryl and *N*-alkyl morpholinones obtained from diethanolamines.[32] For the 8-membered ring DEA carbonates, the relative magnitudes for the enthalpies of ring-opening of the carbonates **2a** (−12.5 kcal/mol) > **2′** (−10.0 kcal/mol) correlate with the faster rate of polymerization of *N*-aryl **2a** relative to *N*-alkyl **2c.**

Table 1. Out-of-Plane Dihedral Angles (oop) Formed by the C−N Bonds Involving the Nitrogen Atom in the Carbonate Ring as an Indicator of Hydrogen Bond Acceptor Strength[a]

	oop [deg]	ΔH_{ro} [kcal/mol]
sp^3 (ideal tetrahedron)	55	
(**2′**)	52	−10.0
(**2a**)	19	−12.5
sp^2	0	

[a]For the definition of the oop angle, see Figure S12.

Exploration of Polymerization Conditions. The ROP behavior of these monomers was explored in a systematic fashion by using different organocatalysts (Scheme 2, Table 2). A targeted degree of polymerization (*DP*) of ∼20 was chosen for the catalyst screening to compare different classes of monomers. These experiments were carried out to assess the relative polymerizability of different subclasses of monomers, under comparable conditions. For monomer **2a**, well-defined polymers of different DP_n were readily accessed in 2 h with 5.0 mol % of DBU as catalyst and benzyl alcohol as the initiator (in relation to monomer; entries 1−3 in Table 2). By changing the catalyst from DBU to a combination of DBU/TU or TBD, no major change in the polymerization behavior was observed, except for an increase in the $Đ_M$ for the TBD catalyst (entries 2, 4 and 5). Considering that TBD polymerizes **2a** at a faster rate than both the DBU or DBU/TU catalysts, well-defined polymers could be obtained in ∼3 min (entry 6). Polymerization can also be initiated with both small molecule initiators

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Scheme 2. Organocatalytic ROP of Functional Eight-Membered Cyclic Carbonate Monomers

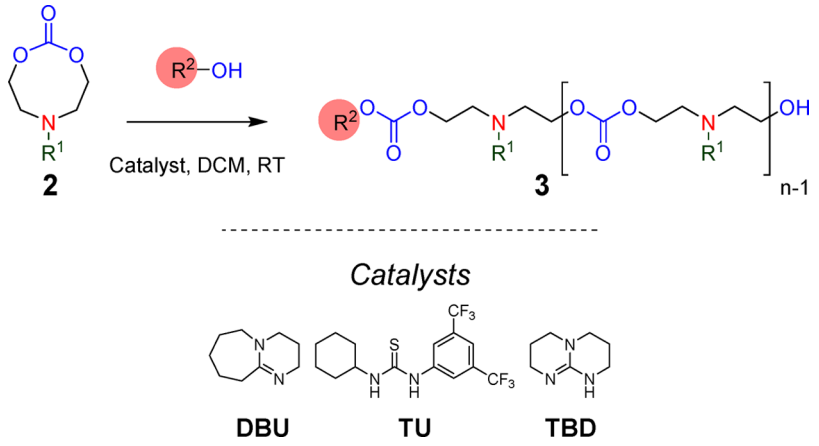

Table 2. Exploration of Reaction Conditions for the Organocatalyzed ROP of Aliphatic Functional *N*-Substituted Eight-Membered Cyclic Carbonates

entry[a]	initiator (I)	monomer (M)	cat. (C)	$[I]_0$:$[M]_0$:$[C]$[b]	time	% conv.[c]	M_n^{SEC} (Da)[d]	$Đ_M$[d]
1	Bn−OH	**2a** (R^1 = Ph)	DBU	1:10:0.5	2 h	86	2220	1.07
2	Bn−OH	**2a** (R^1 = Ph)	DBU	1:20:1	2 h	97	4220	1.09
3	Bn−OH	**2a** (R^1 = Ph)	DBU	1:40:2	2 h	99	7470	1.12
4	Bn−OH	**2a** (R^1 = Ph)	DBU:TU	1:20:1: 1	2 h	95	3930	1.10
5	Bn−OH	**2a** (R^1 = Ph)	TBD	1:20:1	2 h	99	2540	1.83
6	Bn−OH	**2a** (R^1 = Ph)	TBD	1:20:1	3 min	95	2830	1.24
7	[e]mPEG−OH	**2a** (R^1 = Ph)	DBU	1:20:1	2 h	92	10290	1.14
8	Bn−OH	**2b** (R^1 = Tol)	DBU	1:20:1	2 h	82	3970	1.15
9	Bn−OH	**2c** (R^1 = Bn)	DBU	1:20:1	2 h	5	700	1.08
10	Bn−OH	**2c** (R^1 = Bn)	DBU	1:20:1	24 h	57	2340	1.21
11	Bn−OH	**2c** (R^1 = Bn)	TBD	1:20:1	2 h	87	3310	1.21
12	Bn−OH	**2d** (R^1 = $(CH_2)_2CO_2Me$)	TBD	1:20:1	2 h	69	1950	1.19
13	Bn−OH	**2e** (R^1 = $(CH_2)_2CO_2{}^tBu$)	TBD	1:20:1	2 h	71	2840	1.33
14	Bn−OH	**2e** (R^1 = $(CH_2)_2CO_2{}^tBu$)	DBU	1:20:1	48 h	48	2900	1.21
15	Bn−OH	**2f** (R^1 = ^{t}BOC)	DBU	1:20:1	2 h	96	4790	1.14
16	Bn−OH	**2g** (R^1 = EtOC)	DBU	1:20:1	2 h	98	4270	1.13
17	Bn−OH	**2h** (R^1 = AllOC)	DBU	1:20:1	2 h	97	4330	1.12
18	Bn−OH	**TMC**	DBU	1:20:1	2 h	19	640	1.23
19	Bn−OH	**TMC**	DBU	1:20:1	8 h	65	1950	1.19
20	Bn−OH	**TMC**	TBD	1:20:1	2 h	96	2010	2.09
21	Bn−OH	**TMC**	TBD	1:20:1	2 min	94	2830	1.19

[a]All reactions were conducted in DCM (1.0 mL), corresponding to $[M]_0$ = 0.483 M, except for entries 1 and 3 where $[M]_0$ = 0.242 and 0.966 M, respectively, and the polymers were not purified for additional characterization. [b]Initiator to monomer ratio rounded off to an integer. [c]As determined by ^{1}H NMR spectroscopy. [d]Based on crude sample, uncorrected polystyrene equivalent molar mass (M_n^{SEC}) and molar-mass dispersity ($Đ_M$) as determined by SEC with THF as eluent. [e]M_n = 5.0 kDa

(Bn−OH) and macroinitiators such as poly(ethylene glycol) monomethyl ether (entries 2 and 7, respectively). In general, monomer **2a** could be polymerized in the presence of DBU catalyst, exhibiting moderately high to high monomer conversion (~86−99%) within 2h; $Đ_M$ were typically below 1.3. Monomer **2b** could also be polymerized under similar conditions (entry 8). DBU polymerizes monomers **2c−e** well, however the rate of polymerization was significantly slower in comparison to **2a** (entries 9, 10 and 14). TBD catalyzes the ROP of these monomers more efficiently, and at a significantly faster rate (entries 11−13). For instance, monomer **2e** could be polymerized with TBD achieving 71% monomer conversion at 2 h, while only 48% monomer conversion was observed for the reaction involving DBU after 48 h with similar catalysts loading (entries 13 and 14). As for monomers **2f−h**, the polymerization proceeded well with DBU as the catalyst, with monomer conversion values reaching 95−98% after 2 h (entries 15−17); these results are consistent with the kinetics study. Representative examples showcasing the polymerization of **TMC** with both DBU and TBD are also listed for comparison (entries 18−21). These results demonstrate that with the optimal catalyst and polymerization time, the organocatalyzed ROP of eight-membered cyclic carbonate occurs in a controlled fashion, yielding high conversion in ≤2 h, while maintaining relatively low $Đ_M$ (<1.3).

Preparative experiments targeting a range of molecular weights to generate materials for detailed characterization are shown in Table 3 (Figure S15−S36). Polymers with *DP* from 20 to 200 were targeted, by using an initial monomer concentration of $[M]_0$ = 0.483 M or $[M]_0$ = 0.966 M, benzyl alcohol as the initiator and 5 mol % (relative to monomer) of DBU or TBD as the catalyst. These conditions afforded

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Table 3. Sythesis and Characterization of *N*-Substituted Diethanolamine-Based Aliphatic Polycarbonates

entry	monomer (M)	polym.	cat. (C)	$[I]_0$:$[M]_0$:$[C]_0$[a]	$[M]_0$ conc. (M)[b]	conv. (%)[c]	M_n^{Theo} (Da)[d]	M_n^{NMR} (Da)[e]	M_n^{SEC} (Da)[f]	$Đ_M$[f]	T_g (°C)[g]	T_{onset} (°C)[h]	T_{max} (°C)[h]
1	**2a**	**3a-1**	DBU	1:40:2	0.483	88	7400	7320	6250	1.12	31.7	333	363
2	**2a**	**3a-2**	DBU	1:100:5	0.483	95	19790	19630	5350	1.13	30.8	–	–
3	**2a**	**3a-3**	DBU	1:200:10	0.483	94	39070	35520	4890	1.18	31.7	–	–
4	**2a**	**3a-4**	DBU	1:100:5	0.966	97	20210	17870	10440	1.25	35.1	–	–
5	**2b**	**3b-1**	DBU	1:20:1	0.483	78	3560	3580	3700	1.09	23.0	–	–
6	**2b**	**3b-2**	DBU	1:40:2	0.483	70	6300	5790	5150	1.12	26.0	328	357
7	**2b**	**3b-3**	DBU	1:100:5	0.966	94	20900	20090	11550	1.17	–	–	–
8	**2c**	**3c**	TBD	1:40:2	0.966	67	6040	5880	2740	1.28	−30.4	278	308
9	**2d**	**3d**	TBD	1:40:2	0.966	75	6620	6970	2930	1.41	−45.6	230	258
10	**2e**	**3e**	TBD	1:40:2	0.966	56	5920	6020	4320	1.41	−37.2	260	275
11	**2f**	**3f-1**	DBU	1:40:2	0.483	90	8430	8220	7090	1.12	10.2	232	245
12	**2f**	**3f-2**	DBU	1:100:5	0.966	98	22770	22650	13600	1.17	8.5	–	–
13	**2g**	**3g**	DBU	1:100:5	0.483	>99	20220	19720	4360	1.16	−8.6	262	285
14	**2h**	**3h**	DBU	1:100:5	0.483	>99	21410	19410	5010	1.23	–	249	275

[a]All reactions were conducted with benzyl alcohol as the initiator for 2 h and the initiator to monomer ratio rounded off to an integer. [b]All reactions conducted in DCM at the specified initial monomer concentration. [c]As determined by ^{1}H NMR spectroscopy. [d]M_n^{Theo} was calculated on the basis of monomer conversion. [e]Determined by comparing the relative integral values of intensities from the initiator (benzyl alcohol) and that of polymer by ^{1}H NMR spectroscopy. [f]Uncorrected polystyrene equivalent molar mass (M_n^{SEC}) and molar-mass dispersity ($Đ_M$) as determined by SEC with THF as eluent. [g]Glass transition temperature as determined by DSC based on second heating cycle. [h]The initial temperature at which the polymer starts to degrade (T_{onset}) and the temperature at maximum degradation rate (T_{max}) were determined by TGA; – = not determined.

monomer conversions ranging from 56−99% after 2 h at room temperature. The polycarbonates obtained from monomers **2a**, **2b** and **2f** polymerized with DBU at an initial monomer concentration of $[M]_0$ = 0.966 M exhibited molecular weights of M_n^{SEC} = 10−13.5 kDa with $Đ_M$ = 1.17−1.25 (entries 4, 7 and 12, Table 3). For these samples, the molecular weights calculated by ^{1}H NMR end group analysis were comparable with that predicted from the conversion and ratio of $[M]_0/[I]_0$. However, the M_n^{SEC} values were lower relative to those determined by end group analysis (M_n^{NMR}), which could be partly a consequence of the different hydrodynamic volumes of the polycarbonates relative to the polystyrene standards. The SEC for these polymers (entries 4, 7 and 12, Table 3, corresponding to Figure S33, S35 and S36 respectively) exhibit bimodal traces. In contrast, the polycarbonates obtained at lower $[M]_0$ = 0.483 M exhibited molecular weights of M_n^{SEC} = 4−5 kDa with $Đ_M$ = 1.13−1.23 (entries 2, 3, 13 and 14, Table 3). These molecular weight data are much lower than those calculated by end group analysis (M_n^{NMR}) or those predicted from the conversion and ratio of $[M]_0/[I]_0$. The SEC traces for these polymers exhibit a unimodal peak (Figure S28, S30, S31 and S32). Collectively these data suggest that there are competitive pathways for enchainment that become evident at $[M]_0/[I]_0$ ratios ≥40 and this process is also dependent on the initial monomer concentration, $[M]_0$. On the basis of our previous studies, it is likely that at $[M]_0/[I]_0$ ratios ≥40, when the concentration of the alcohol initiator $[I]_0 \leq 0.01$ M, the DBU catalyst can mediate the ring-opening polymerization by two competitive mechanisms to afford a mixture of linear and cyclic chains.[48] DBU and other amidines have been shown to mediate the zwitterionic polymerization of lactones in the absence of alcohol initiators to yield cyclic polymers.[48−50] The lower molecular weights observed by SEC (M_n^{SEC}) at lower monomer and initiator concentrations are consistent with the formation of a mixture of linear and cyclic chains. In these cases, the ^{1}H NMR end group analysis overestimates the molecular weights (M_n^{NMR}) since only a fraction of the chains are linear with benzyl alcohol end groups.

The results of Table 3 indicate that for the generation of higher molecular weight polycarbonates, higher monomer concentrations are optimal. Nevertheless, for many biomedical applications, higher molecular weights are not always advantageous, as higher molecular weight polymers are less readily cleared. For instance, markedly reduced renal clearance was observed for polymers of molecular weights higher than 20 kDa (for PEG),[51] suggesting that the molecular weights that can be accessed with the ROP of these aliphatic functional *N*-substituted eight-membered cyclic carbonates could still be well utilized for nanomedicine.

Degradable cationic polymers find applications as antimicrobials and also for therapeutics delivery. Polymers derived from the protected secondary amine containing monomer (**2f**) would serve as a platform to acess well-defined polycations. In order to explore the feasibility of deprotecting the ^{t}Boc groups, a representative polymer (**3f**) was subjected to acidic conditions for 1h (∼20 x molar excess per ^{t}Boc group 90 vol % solution in DCM) and over 95% of the ^{t}Boc groups were found to be deprotected (Figure S37). As per ^{1}H NMR, no obvious degradation of the polymer was observed and this might be due to the fact that the deprotection is carried out under acidic conditions where the deprotected amines get immediately protonated, mitigating the nucleophilicity of the amino residues. We have observed similar phenomenon with the deprotection of pendant primary amine containing polycarbonates.[9]

Evaluation of Thermal Properties. Differential scanning calorimetry (DSC) was conducted to evaluate the thermal properties of these *N*-substituted diethanolamine-based aliphatic polycarbonates (Table 3, Figure S38−S49). The glass transition temperatures (T_g) of these polymers ranged from ∼−46 to +35 °C. The *N*-aryl substituted polymers demonstrated relatively higher T_g compared to the *N*-carbamate and *N*-alkyl class of polymers. *N*-alkyl series demonstrated a relatively low T_g values (∼−46 to −30 °C). It is interesting to note that in spite of the monomers being structural isomers the T_g values of polymers **3b** and **3c** are at least 50 °C apart, underscoring the ability to engineer the physicochemical

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properties of materials through the design of functional monomers. Thermogravimetric analysis (TGA) was conducted on representative samples to evaluate their thermal stabilities by heating the polymeric sample from room temperature to 500 °C at 10 °C/min under N_2 atmosphere. The initial decomposition temperature or the temperature at which the material started to degrade (T_{onset}) is an important measure of thermal stability of polymer. T_{onset} was found to be in the range of 230−333 °C (Figure 5 and Table 3), depending on *N*-substitution. A trend similar to T_{onset} was observed for temperature at maximum degradation rate (T_{max}, in the range of ∼245−363 °C) (Figure S50 and Table 3). T_{onset} data for most of the polymers are comparable to that of reported PTMC values (∼240−260 °C). It is noteworthy that the *N*-aryl substituted class of polymers demonstrated significantly higher thermal stability (T_{onset} ∼ 330 °C).[22,52] Also, in comparison to poly(pentamethylene carbonate) (PPMC, T_{onset} = ∼331 °C; T_{max} = 358 °C),[53] an all-carbon analogue of these *N*-substituted diethanolamine-based aliphatic polycarbonates, most of the polymers demonstrate a relatively lower T_{onset} and T_{max} values, suggesting that the presence of nitrogen atom in the backbone could be contributing toward lower thermal stabilities.

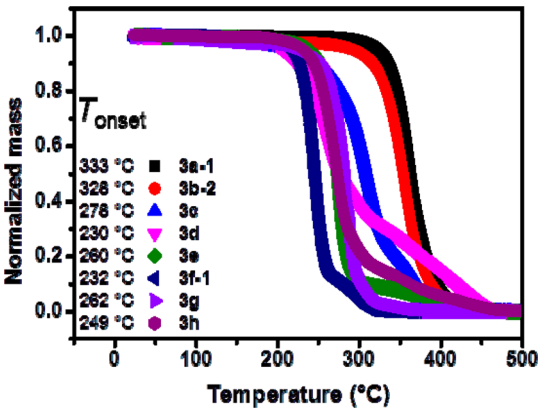

Figure 5. Overlaid thermolytic profiles of diethanolamine-based aliphatic *N*-substituted polycarbonates.

Exploration of Copolymerization. Copolymerization behaviors of selected monomers were also explored to demonstrate the feasibility of integrating the new class of monomers with some of the existing classes of six-membered cyclic esters and carbonates (Figure 6, Table 4). Monomer **2a** was found to copolymerize well with L-lactide (LLA), MTC-OBn, and TMC-NH^{t}Boc with relatively high and almost comparable monomer conversion, while maintaining a low $Đ_M$ (entries 1, 3, and 4 in Table 4). When the monomer conversion was monitored for the copolymerization of **2a** and LLA, it was evident that the LLA polymerized at a faster rate than **2a** (conversion for LLA and **2a** at 42 s = 70 and 8%; at 67 min = 85 and 76% respectively). These data may indicate that gradient polymers could be made, but further studies are necessary to characterize the sequence distributions of these copolymers. The copolymerization of monomer **2a** with TMC (entry 2) and eight-membered cyclic carbonates **2e** (entry 5) proceeded with extremely different polymerization kinetics, resulting in ∼4 times higher incorporation of monomer **2a** as compared to the comonomer **2e**.[54] Collectively these copolymerization results highlight the possibilities of not only accessing unique polymers with well-defined compositions and low molecular weight distributions to tailor the physicochemical properties (such as melting point, glass transition temperature, rate of degradation, etc.) but also engineering the polymer microstructure (such as pseudoblock copolymer, gradient copolymer,[54] random copolymer, etc.).

CONCLUSION

In summary, we have reported a straightforward route to access functional eight-membered aliphatic cyclic carbonates by starting from DEA-based precursors. Commercial availability of numerous *N*-substituted derivatives of DEA and straightforward chemoselective derivatization of DEA with readily available reagents including alkyl halide and acrylates, renders this approach attractive for the facile development of novel functional monomers. Organocatalytic ring opening polymerization of these carbonate monomers proceeded with excellent control, paving access to well-defined functional polymers with predictable molecular weights and low molar-mass dispersity. Depending upon the nature of *N*-substitution, polymerization kinetics of these monomers was found to vary from ∼2 h to >48 h. Through computation, we rationalized the reactivity trend for the organocatalytic ROP of the *N*-substituted cyclic monomers with TBD. ROP is promoted by the ability of TBD to form H-bonding interactions with the alcohol and the carbonyl group on the monomer. Aromatic substituents disrupt competing H-bonding interactions involving the amine in the ring, while aliphatic substituents do not. The glass transition temperatures and thermolytic behavior of these polymers were found to be tunable with the choice of *N*-substituent. These monomers can also be copolymerized with other classes of monomers, including commercially available L-lactide and trimethylene carbonates. Facile synthesis and the degradable nature of these materials render them attractive for applications in the biomedical field.

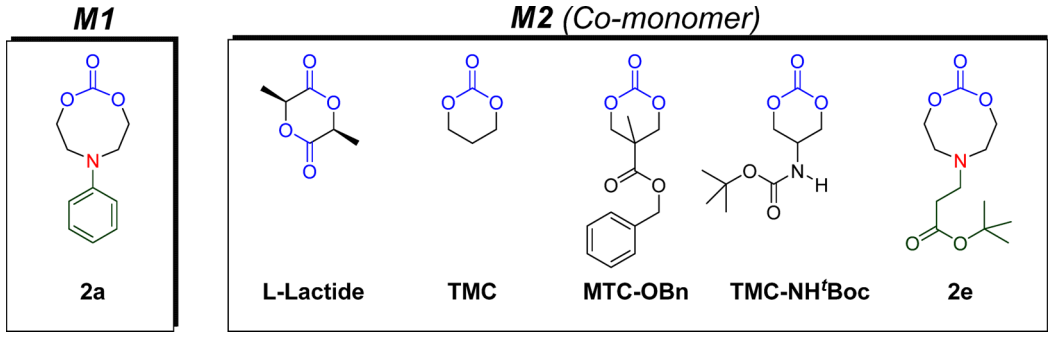

Figure 6. Structure of selected cyclic monomers used for copolymerization with **2a**.

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Table 4. Copolymerization of Selected Cyclic Monomers with 2a to Access Functional Copolymers

entry[a]	initiator (I)	monomer (M1)	monomer (M2)	cat. (C)	$[I]_0:[M1]_0:[M2]_0:[C]$[b]	time	% conv. (M1)[c]	% conv. (M2)[c]	$M_n^{(SEC)}$[d]	$Đ_M$[d]
1	Bn−OH	**2a** (R^1 = Ph)	L-Lactide	DBU	1:10:10:1.0	2 h	95	82	3890	1.29
2	Bn−OH	**2a** (R^1 = Ph)	TMC	DBU	1:10:10:1.0	2 h	>99	14	2800	1.08
3	Bn−OH	**2a** (R^1 = Ph)	MTC-OBn	DBU	1:10:10:1.0	2 h	95	96	4530	1.14
4	Bn−OH	**2a** (R^1 = Ph)	TMC-NH^{t}Boc	DBU	1:10:10:1.0	2 h	97	>99	3650	1.27
5	Bn−OH	**2a** (R^1 = Ph)	**2e**	DBU	1:10:10:1.0	2 h	81	20	2850	1.11

[a]All reactions were conducted in DCM (1.0 mL), $[M]_0 = [M1]_0 + [M2]_0 = 0.483$ M, and the polymers were not purified for additional characterization. [b]Initiator to monomer ratio rounded to integer. [c]As determined by ^{1}H NMR spectroscopy. [d]Based on crude sample, uncorrected polystyrene equivalent molar mass (M_n^{SEC}) and molar-mass dispersity ($Đ_M$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06355.

Experimental details, computational details, FTIR, ^{1}H and ^{13}C NMR spectra of all monomers and representative polymers, representative SEC chromatograms, processed TGA and DSC curves. (PDF)

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Notes

The authors declare no competing financial interest.

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