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Organocatalytic Ring-Opening Copolymerization of Trimethylene Carbonate and Dithiolane Trimethylene Carbonate: Impact of Organocatalysts on Copolymerization Kinetics and Copolymer Microstructures

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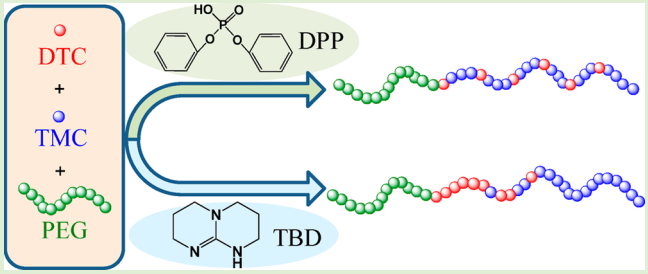
Supporting Information

ABSTRACT: The ring opening copolymerization of trimethylene carbonate (TMC) and dithiolane trimethylene carbonate (DTC) using acidic and basic organocatalysts, i.e., diphenyl phosphate (DPP) and triazabicyclo[4.4.0]dec-5-ene (TBD), was systemically investigated. Interestingly, DPP and TBD gave rise to completely different polymerization kinetics and copolymer sequences. The copolymerization of TMC and DTC using methoxy poly(ethylene glycol) (mPEG−OH) as an initiator and DPP as a catalyst proceeded in a first-order manner and to near completion in 72 h for both monomers, yielding well-controlled copolymers with random sequences, predictable molar mass, and low dispersity (M_w/M_n = 1.09−1.19). By contrast, TBD brought about much faster copolymerization of TMC and DTC under similar conditions (high monomer conversion achieved in 2−4 h), to furnish copolymers with controlled molar mass and moderate dispersity (M_w/M_n = 1.27−1.80). Moreover, polymerization kinetics revealed that DTC was preferentially polymerized followed by first-order polymerization of TMC, leading to blocky copolymers. These results signify that type of organocatalysts has a critical influence on polymerization kinetics of cyclic carbonates, copolymer sequence, and molar mass control.



1. INTRODUCTION

Biodegradable polymers, e.g. polyesters and polycarbonates as key synthetic biomaterials are widely applied in biomedical engineering.[1] In recent years, polycarbonates and copolymers have attracted growing attention for drug delivery and tissue engineering.[2,3] In contrast to polyesters such as poly(lactide-*co*-glycolide) that are prone to hydrolytic degradation and give acidic degradation byproducts,[4−6] polycarbonates like poly(trimethylene carbonate) (PTMC) are stable against hydrolysis and eroded by enzymes, and do not generate acids.[7,8] Moreover, functional polycarbonates with varying functionalities such as acrylate, vinyl sulfone, carboxyl, epoxy, and iodine can be easily prepared to suit different applications.[9−19] Recently, we have invented a functional cyclic carbonate monomer, dithiolane trimethylene carbonate (DTC), on which we have based the developmen of a series of tumor-targeted and reduction-sensitive multifunctional drug nanocarriers including micelles and polymersomes.[20−22] The pendant dithiolane ring in DTC is analogous to that of the lipoic acid, a natural antioxidant in human being.[23−25] We have shown previously that lipoic acid-cross-linked nanoparticles can elegantly resolve the stability and intracellular drug release dilemma of nanomedicines.[26,27] Interestingly, nanosystems made of PDTC and copolymers were found self-cross-linked, i.e., without using dithiothreitol catalyst, during the workup process. The nanopolymersomes based on trimethylene carbonate (TMC) and DTC copolymers showed efficient delivery of doxorubicin hydrochloride and siRNA to the tumor xenografts in nude mice.[28−31]

Polycarbonates and copolymers are usually synthesized by ring-opening polymerization.[18,32−35] Organocatalysts with higher reactivity and better control of polymerization over metal catalysts such as stannous octoate have recently generated great interests for the synthesis of polycarbonates and copolymers.[9,36,37] For example, acidic organocatalysts like diphenyl phosphate (DPP), and basic organocatalysts like triazabicyclo[4.4.0]dec-5-ene (TBD) and diazabicycloundecene (DBU) have been investigated for ring-opening polymerization of cyclic carbonates yielding polycarbonates with well-defined structure.[15,38−41] Employing DBU as a catalyst, Waymouth et al. prepared dynamic and covalent materials from TMC derivatives containing pendant 1,2-dithiolane functionalities.[42]

The aim of the present study is to investigate the ring opening copolymerization behaviors of TMC and DTC using

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Table 1. TMC and DTC Copolymerization Using DPP as a Catalyst ($[R-OH]_0/[DPP]_0 = 1/10$)[a]

entry	copolymer	initiator	$[M]_0$ (mol/L)	time (h)	conv. (%) TMC	conv. (%) DTC	f_{DTC}	F_{DTC}	M_n (kg/mol) theory	M_n (kg/mol) ^{1}H NMR	M_n (kg/mol) SEC	M_w/M_n
1	PEG-P(TMC_{37}-DTC_5)	PEG	1	24	98	99	0.11	0.12	9.9	9.8	15.2	1.13
2	PEG-P(TMC_{38}-DTC_{10})	PEG	1	24	97	98	0.20	0.21	10.8	10.8	16.2	1.09
3	PEG-P(TMC_{35}-DTC_{15})	PEG	1	24	100	98	0.28	0.30	11.9	11.4	16.9	1.10
4	PEG-P(TMC_{95}-DTC_{10})	PEG	2	48	100	100	0.09	0.10	17.0	16.6	18.6	1.09
5	PEG-P(TMC_{142}-DTC_{10})	PEG	2	72	100	100	0.06	0.07	22.0	21.4	33.5	1.10
6	PEG-P(TMC_{233}-DTC_{10})	PEG	2	72	100	100	0.04	0.04	32.0	30.7	38.4	1.11
7	Mal-PEG-P(TMC_{154}-DTC_{11})	Mal-PEG	2	72	96	100	0.06	0.07	23.9	25.4	35.3	1.10
8	NHS-PEG-P(TMC_{156}-DTC_{12})	NHS-PEG	2	72	-	-	0.06	0.07		25.7	44.4	1.12
9	Bn-P(TMC_{21}-DTC_5)	BnOH	1	6	51	52	0.20	0.19	3.2	3.2	6.3	1.19

[a]Note: $[M]_0$ (mol/L) is the total monomer concentration. M_n (theory) was calculated from M_w(initiator) + M_w(TMC) × $[TMC]_0/[I]_0$ × Conv.(TMC) + M_w(DTC) × $[DTC]_0/[I]_0$ × Conv.(DTC). M_n (^{1}H NMR) and M_n (SEC) are determined via ^{1}H NMR and SEC (poly(methyl methacrylate) as standards), respectively. M_w/M_n is the dispersity determined by SEC. f_{DTC} and F_{DTC} refer to the molar content of DTC monomer in the feed and DTC unit in the final copolymer, respectively.

Table 2. TMC and DTC Copolymerization Using TBD as a Catalyst and mPEG−OH as an Initiator ($[mPEG-OH]_0/[TBD]_0 = 1/1$)[a]

entry	copolymer	$[M]_0$ (mol/L)	time (h)	conv. (%) TMC	conv. (%) DTC	f_{DTC}	F_{DTC}	M_n (kg/mol) theory	M_n (kg/mol) ^{1}H NMR	M_n (kg/mol) SEC	M_w/M_n
1	PEG-P(TMC_{37}-DTC_4)	0.5	2	97	98	0.11	0.10	9.9	9.7	16.2	1.30
2	PEG-P(TMC_{38}-DTC_9)	0.5	2	97	98	0.20	0.19	10.8	10.6	20.4	1.27
3	PEG-P(TMC_{38}-DTC_{12})	0.5	2	97	96	0.28	0.24	11.8	11.2	21.0	1.29
4	PEG-P(TMC_{90}-DTC_8)	1	4	100	97	0.09	0.08	16.9	15.8	27.3	1.45
5	PEG-P(TMC_{157}-DTC_{10})	1	4	100	98	0.06	0.06	21.9	21.8	30.9	1.50
6	PEG-P(TMC_{304}-DTC_{11})	1	4	100	96	0.04	0.03	31.9	38.1	45.7	1.80

[a]Note: $[M]_0$ (mol/L) is the total monomer concentration. M_n (theory) was calculated from M_w(initiator) + M_w(TMC) × $[TMC]_0/[I]_0$ × Conv.(TMC) + M_w(DTC) × $[DTC]_0/[I]_0$ × Conv.(DTC). M_n (^{1}H NMR) and M_n (SEC) are determined via ^{1}H NMR and SEC (poly(methyl methacrylate) as standards), respectively. M_w/M_n is the dispersity determined by SEC. f_{DTC} and F_{DTC} refer to the molar content of DTC monomer in the feed and DTC unit in the final copolymer, respectively.

acidic and basic organocatalysts. Surprisingly, acidic DPP and basic TBD gave rise to completely different polymerization kinetics and copolymer sequences. Such a "switch" in polymer sequence depending on the catalyst used is not very common. There are a couple of reports on tuning polyester sequences from lactones by using different catalyst systems.[34,43] None is, however, reported on controlling the microstructures of polycarbonates through changing the catalyst.

2. EXPERIMENTAL SECTION

2.1. Ring-Opening Copolymerization of DTC and TMC Catalyzed by DPP. All polymerizations were carried out in a nitrogen atmosphere. In a representative example (Table 1, Entry 2), to a 25 mL Schlenk bottle equipped with a magnetic stir bar, mPEG−OH macroinitiator (M_n = 5 kg/mol, 100 mg, 20 μmol), TMC (80 mg, 784 μmol), DTC (40 mg, 208 μmol) and 1.0 mL DCM were charged. To the stirred solution, DPP (50 mg, 200 μmol) was added (TMC/DTC/OH/DPP molar ratio of 40/10/1/10, monomer concentration = 1.0 M). The bottle was thermostated at 40 °C under continuous stirring. After 24 h, triethylamine (3 equiv to OH) was added to terminate the reaction, and one aliquot was taken out and evaporated to dryness for ^{1}H NMR measurement. The rest was precipitated into 30- fold cold diethyl ether twice, filtrated, and dried under vacuum for 2 d. Yield: 84.6%. ^{1}H NMR (600 MHz, $CDCl_3$, ppm): PEG: δ 3.64 (−$\underline{CH_2CH_2}$O−) and 3.37 (3H, $\underline{CH_3}$O−); TMC moiety: δ 4.24 (−OCO$\underline{CH_2}CH_2\underline{CH_2}$OCO−) and 2.06 (−OCOCH$_2\underline{CH_2}CH_2$OCO−); DTC moiety: δ 4.19 (−OCO$\underline{CH_2}$−C(CH$_2$SSCH$_2$)-$\underline{CH_2}$OCO−) and 3.02 (−C($\underline{CH_2}$SS$\underline{CH_2}$)−). M_n (^{1}H NMR) = 10.8 kg/mol. M_n (SEC) = 16.2 kg/mol, M_w/M_n = 1.09. ^{13}C NMR (150 MHz, $CDCl_3$, ppm): PEG: δ 70.53 (−$\underline{CH_2CH_2}$O−); TMC moiety: δ 154.86 (−O$\underline{CO}$CH$_2$CH$_2$CH$_2\underline{OC}$O−), 64.24 (−OCO$\underline{CH_2}$CH$_2\underline{CH_2}$OCO−) and 28.00 (−OCOCH$_2\underline{CH_2}$CH$_2$OCO−); DTC moiety: δ 154.55 (−O$\underline{CO}$CH$_2$−C(CH$_2$SSCH$_2$)−CH$_2\underline{OC}$O−), 68.02 (−OCO$\underline{CH_2}$−C-(CH$_2$SSCH$_2$)−$\underline{CH_2}$OCO−), 54.36 (−OCOCH$_2$ $\underline{C}$(CH$_2$SSCH$_2$)−CH$_2$OCO−) and 44.23 (−C($\underline{CH_2}$SS$\underline{CH_2}$)−).

The copolymerization using different initiators like *N*-hydroxysuccinimide ester functionalized PEG (NHS−PEG−OH, M_n = 7.5 kg/mol), maleimide functionalized PEG (Mal−PEG−OH, M_n = 7.5 kg/mol) and benzyl alcohol (Bn) was carried out in a similar way. ^{1}H NMR (600 MHz, ppm): NHS: δ 2.83 (4H, (OC$\underline{CH_2CH_2}$CO)N−OCO−, DMSO-d_6), yield: 92.6%; Mal: δ 6.69 (2H, (OC$\underline{CH{=}\!=CH}$CO)N−CH$_2$−, $CDCl_3$), yield: 90.8%; Bn moiety: δ 7.37−7.39 (ph, $CDCl_3$) and 5.13−5.16 (ph$\underline{CH_2}$OCO−, $CDCl_3$), yield: 40.6%.

2.2. Determination of Polymerization Kinetics of DTC and TMC Catalyzed by DPP. In a nitrogen atmosphere, to a 25 mL Schlenk bottle equipped with a magnetic stir bar, mPEG−OH (M_n = 5 kg/mol, 250 mg, 50 μmol), TMC (750 mg, 7.4 mmol), DTC (100 mg, 0.52 mmol), DCM (4.0 mL), and DPP (125 mg, 500 μmol) were added in that order (TMC/DTC/OH/DPP molar ratio of 147/10/1/10, monomer concentration = 2.0 M). The reaction proceeded under continuous stirring at 40 °C. At predetermined time intervals, ca. 0.5 mL reaction mixture was withdrawn from the bottle under N_2 and directly injected into a DCM solution containing triethylamine (3 equiv. to OH). One aliquot was taken out for determination of monomer conversion. The rest was purified as described above to determine the evolution of molar mass and dispersity by ^{1}H NMR spectroscopy and SEC, respectively. For determination of DTC conversion, the integral ratio of peak at δ 3.07 (dithiolane ring) of DTC to that of PDTC at δ 3.02 was compared. For TMC conversion determination, the integral ratio of peak at δ 2.14 (methylene) of TMC to that of PTMC at δ 2.06 was applied.

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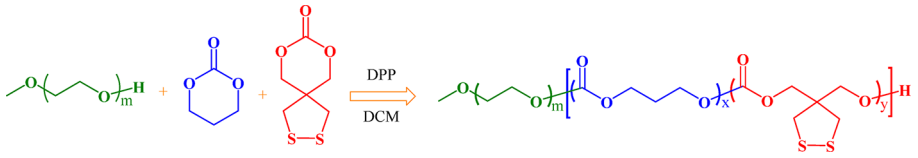
Scheme 1. Ring-Opening Copolymerization of TMC and DTC Using DPP as a Catalyst and mPEG−OH as an Initiator



2.3. ROP of DTC and TMC Catalyzed by TBD. TMC and DTC could be copolymerized using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a catalyst and MeO-PEG−OH (M_n = 5 kg/mol) as a macroinitiator. In a representative example (Table 2, Entry 2), to a 25 mL Schlenk bottle equipped with a magnetic stir bar, mPEG−OH macroinitiator (M_n = 5 kg/mol, 100 mg, 20 μmol), TMC (80 mg, 784 μmol), DTC (40 mg, 208 μmol), and 2.0 mL DCM were charged. To the stirred solution, TBD (2.8 mg, 20 μmol) was added (TMC/DTC/OH/TBD molar ratio of 40/10/1/1, monomer concentration = 0.5 M). The reaction proceeded under continuous stirring at 25 °C. After 2 h, acetic acid (3 equiv. to OH) was added to terminate the reaction, and one aliquot was taken for ^{1}H NMR measurement. The rest was precipitated into 30-fold cold diethyl ether twice, filtrated, and dried under vacuum for 2 days. Yield: 78%. ^{1}H NMR (600 MHz, DMSO-d_6, ppm): PEG: δ 3.51 (−$\underline{CH_2CH_2}$O−) and 3.06 (3H, $\underline{CH_3}$O−); TMC moiety: δ 4.13 (−OCO$\underline{CH_2}$CH$_2$$\underline{CH_2}$OCO−) and 1.97 (−OCOCH$_2$$\underline{CH_2}CH_2$OCO−); DTC moiety: δ 4.17 (−OCO$\underline{CH_2}$−C(CH$_2$SSCH$_2$)−$\underline{CH_2}$OCO−) and 3.07 (−C($\underline{CH_2}$SS$\underline{CH_2}$)−). M_n (^{1}H NMR) = 10.6 kg/mol. M_n (SEC) = 20.4 kg/mol, M_w/M_n = 1.27. ^{13}C NMR (150 MHz, DMF-d_7, ppm): PEG: δ 70.31 (−$\underline{CH_2CH_2}$O−); TMC moiety: δ 154.87 (−O$\underline{CO}$CH$_2$CH$_2$CH$_2$$\underline{OC}$O−), 64.46 (−OCO$\underline{CH_2}CH_2$$\underline{CH_2}$OCO−) and 27.95 (−OCOCH$_2$$\underline{CH_2}CH_2$OCO−); DTC moiety: δ 154.61 (−O$\underline{CO}$CH$_2$−C(CH$_2$SSCH$_2$)−CH$_2$$\underline{OC}$O−), 68.29 (−OCO$\underline{CH_2}$−C(CH$_2$SSCH$_2$)−$\underline{CH_2}$OCO−), 54.35 (−OCOCH$_2$ $\underline{C}$(CH$_2$SSCH$_2$)−CH$_2$OCO−) and 43.85 (−C($\underline{CH_2}$SS$\underline{CH_2}$)−). The determination of polymerization kinetics of DTC and TMC catalyzed by TBD was similar to that by DPP.

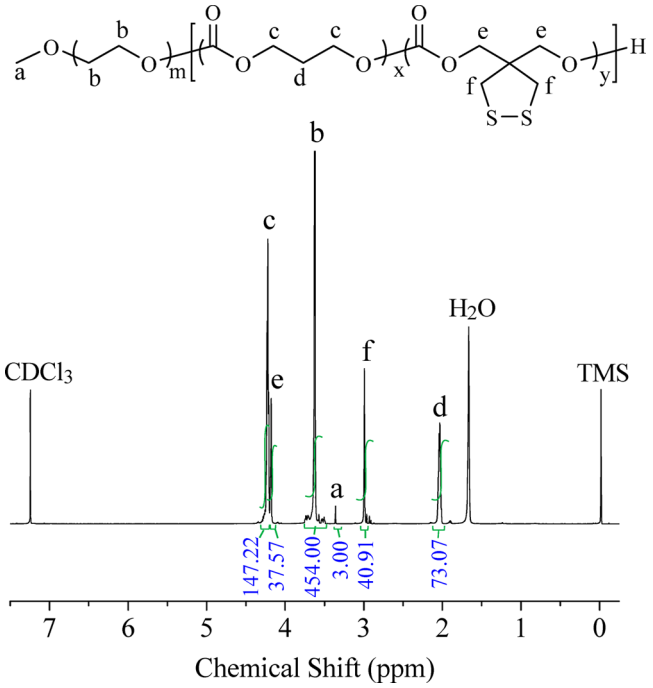


Figure 1. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of PEG-P(TMC$_{38}$-DTC$_{10}$) (Table 1, Entry 2).

3. RESULTS AND DISCUSSION

3.1. Organocatalytic Ring-Opening Copolymerization of TMC and DTC. The ring-opening copolymerization of TMC and DTC was conducted in dry DCM at 40 °C using mPEG−OH as an initiator and DPP as an organocatalyst at a fixed [mPEG−OH]$_0$/[DPP]$_0$ molar ratio of 1/10 (Scheme 1). The polymerization results are summarized in Table 1. The resulting copolymers were denoted as PEG-P(TMC$_x$-DTC$_y$) in which x and y are the number of repeating units of TMC and DTC, respectively. At relatively low monomer-to-initiator ratios (Table 1, Entries 1−3), both TMC and DTC achieved a high conversion in 24 h, as shown by ^{1}H NMR analyses. Figure 1 gives a typical ^{1}H NMR spectrum of thus prepared PEG-P(TMC-DTC) copolymer (PEG-P(TMC$_{38}$-DTC$_{10}$), Table 1, Entry 2). The ratios of TMC and DTC in P(TMC-DTC) could be determined by comparing signals of TMC moieties at δ 2.06 and DTC moieties at δ 3.02, revealing excellent control of copolymer compositions. The M_n values of PEG-P(TMC-DTC) calculated from δ 2.06 and 3.02 with respect to the methylene protons of PEG at δ 3.64, respectively, were close to the design. SEC displayed that all polymers had low dispersity (M_w/M_n = 1.09−1.13) (Figure S1). The M_n determined by SEC, though deviated from the theoretical value due to the fact that polymethacrylate was used as standards, increased in parallel with that calculated from ^{1}H NMR. Excellent control of copolymerization was also achieved at higher monomer-to-initiator molar ratios from 110/1 to 260/1, though a higher monomer concentration of 2 M and longer polymerization time of 48 or 72 h were needed (Table 1, Entries 4−6, Figures S2−6). Moreover, copolymerization of TMC and DTC using Mal−PEG−OH or NHS−PEG−OH as a macroinitiator yielded also well-defined copolymers with controlled composition and M_n, low M_w/M_n of 1.10−1.12, and intact functional groups, as revealed by ^{1}HNMR (Table 1, Entries 7, 8, Figures S7−8). Hence, DPP is a versatile organocatalyst for controlled copolymerization of TMC and DTC, as previously reported for (co)polymerization of TMC.[40,44−46] This excellent control of copolymer composition and molar mass is critical for their clinical translation. DSC revealed that PEG-P(TMC-DTC) copolymers had a T_m of ca. 50.5−51.1 °C due to PEG block and a single T_g ranging from −15.3 to −7.8 °C depending on copolymer molar mass and compositions (Figure S9), supporting that they have a random structure.

To gain more insight to the polymerization mechanism and clear analyses of end groups, P(TMC-DTC) was prepared using BnOH as a model initiator. BnOH has been frequently employed in ring-opening polymerization studies, because both end groups can easily be discerned.[39,47−49] The polymerization was allowed to proceed for 6 h. ^{1}H NMR of the crude polymerization mixture showed conversion of 51% and 52% for TMC and DTC, respectively. ^{1}H NMR of purified P(TMC-DTC) copolymer revealed similar composition to the comonomer feed ratio and an M_n of 3.2 kg/mol, close to the theoretical value (Table 1, Entry 9). MALDI−ToF MS measurement confirmed that P(TMC-DTC) had a narrow dispersity and an M_n of 3.3 kg/mol (Figure 2A). The mass differences between two peaks were 101.99 and 192.54,

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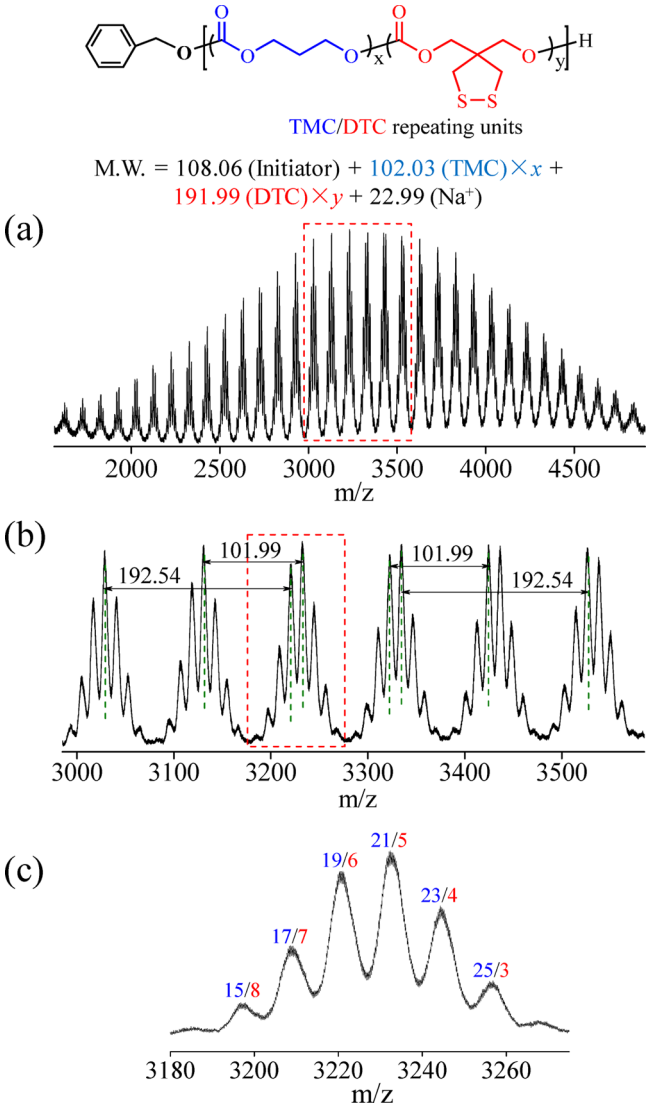

Figure 2. (A) MALDI−ToF MS spectrum of Bn-P(TMC_{21}-DTC_5) (Table 1, Entry 9); (B) Magnified region (m/z from 3000 to 3600); and (C) Magnified one group region (m/z from 3180 to 3280).

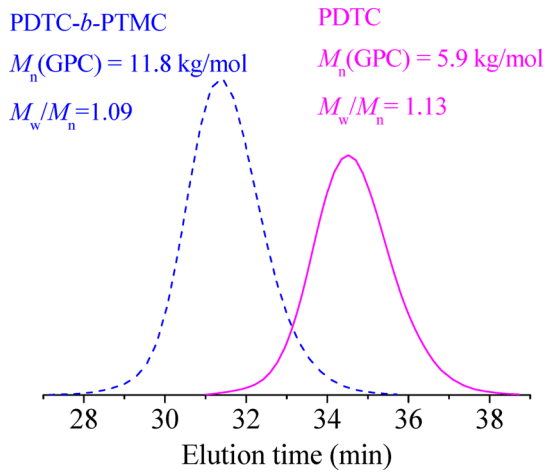

Figure 4. SEC curves of PDTC and PDTC-*b*-PTMC copolymers obtained at a $[DTC]_0/[BnOH]_0$ molar ratio of 10/1 for 24 h followed by adding 40 equiv of TMC and polymerization for another 24 h.

corresponding to TMC and DTC repeating units, respectively (Figure 2B). Notably, all peaks in the spectrum corresponded to adducts of 108.06 + 102.03x + 191.99y + 22.99, in which 108.06 and 22.99 are the masses of benzyl alcohol and sodium ion, respectively. By further analyzing a specific signal-group, the composition of the corresponding molecules could be determined. For example, the signal group at m/z = 3231 had a distribution of TMC/DTC ranging from 15/8, 17/7, 19/6, 21/5, 23/4 to 25/3 (Figure 2C). These results confirm that copolymerization of TMC and DTC is initiated by BnOH and proceeds most likely through an activated monomer mechanism, similar to report by Kakuchi et al. for polymerization of TMC,[40] to produce P(TMC-DTC) copolymers with benzyloxy and hydroxyl terminal groups. These results further imply that DPP catalyzed copolymerization of TMC and DTC proceeds in a living manner without obvious side reactions such as backbiting, decarboxylation, and transesterification reactions.

The copolymerization of TMC and DTC using TBD as a catalyst was performed at 25 °C at a fixed $[mPEG-OH]_0/[TBD]_0$ molar ratio of 1/1. Notably, polymerization was

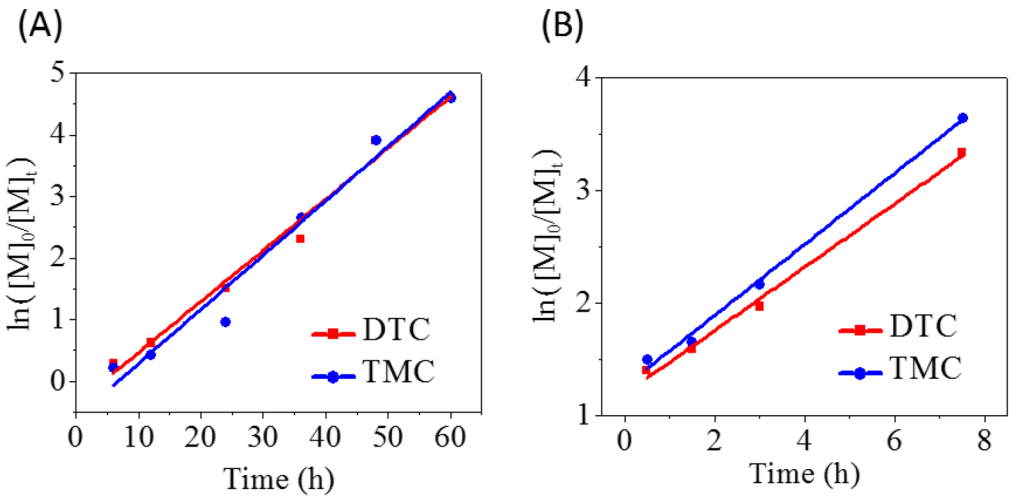

Figure 3. Polymerization kinetics of TMC and DTC using DPP as catalyst and PEG (A) or BnOH (B) as an initiator in DCM. For A, $[TMC]_0+[DTC]_0$ = 2.0 M, and $[TMC]_0/[DTC]_0/[mPEG-OH]_0/[DPP]_0$ = 147/10/1/10. For B, $[TMC]_0+[DTC]_0$ = 1.0 M, and $[TMC]_0/[DTC]_0/[BnOH]_0/[DPP]_0$ = 40/10/1/10.

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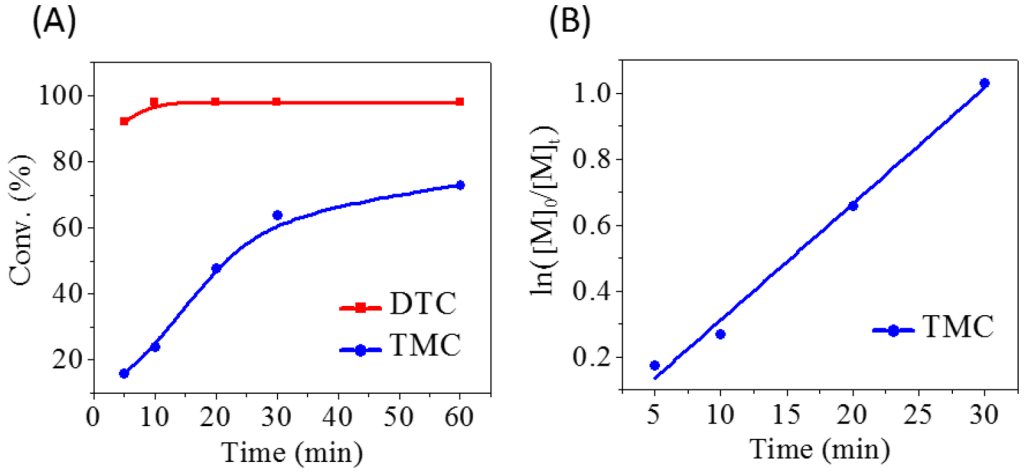

Figure 5. (A) Conversion of TMC and DTC as a function of time using TBD as catalyst and PEG as an initiator in DCM. (B) First order polymerization kinetics plot for TMC monomer. Conditions: $[TMC]_0+[DTC]_0$ = 1.0 M, $[TMC]_0/[DTC]_0/[mPEG-OH]_0/[TBD]_0$ = 230/10/1/0.5.

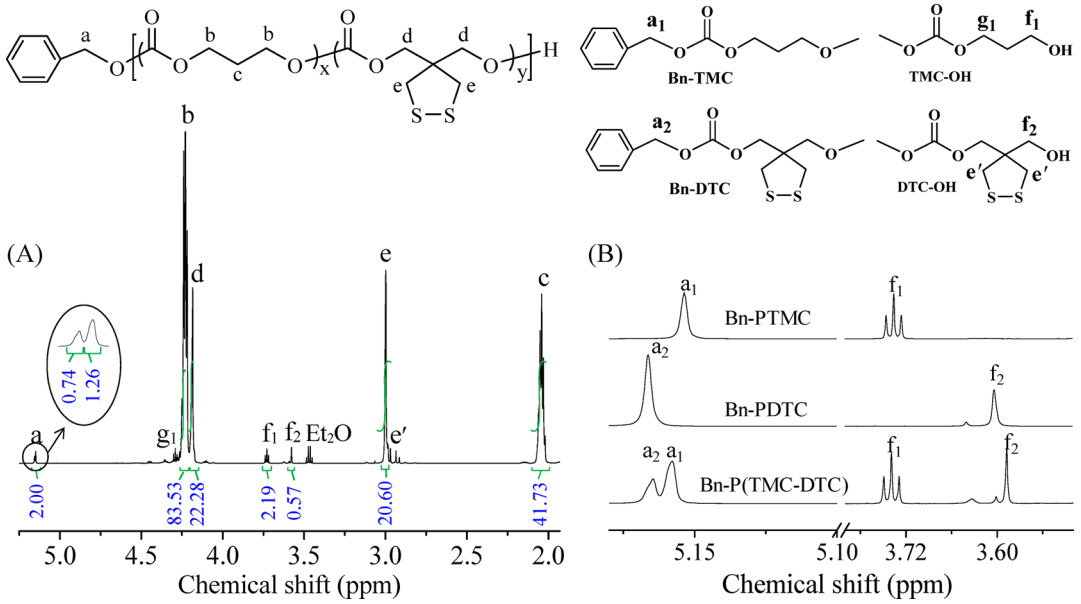

Figure 6. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of P(TMC-DTC) from DPP system (Bn-P(TMC_{21}-DTC_5), Table 1, Entry 9) (A) and magnified methylene regions (B).

completed within 2−4 h even at a lower monomer concentration of 0.5−1.0 M (Table 2), which was significantly faster than that using DPP. ^{1}H NMR analyses revealed that PEG-P(TMC-DTC) copolymers were obtained with well-controlled compositions and M_n. (Figure S10−13) The M_n could be nicely tailored by monomer-to-initiator ratios. However, SEC results showed that thus prepared PEG-P(TMC-DTC) copolymers had moderate dispersity (M_w/M_n = 1.27−1.80), indicating less control over copolymerization than DPP. Furthermore, attempts to copolymerize TMC and DTC using functional PEG such as Mal−PEG−OH and NHS−PEG−OH as a macroinitiator to generate functional block copolymers failed. The results showed that no polymerization took place, and both Mal and NHS groups disappeared after the reaction.

3.2. Influence of Organocatalysts on Copolymerization Kinetics of TMC and DTC. To further unveil their copolymerization behavior, polymerization kinetics of TMC and DTC using DPP and TBD were investigated. The results displayed that using DPP as a catalyst, polymerization of both TMC and DTC monomers proceeded in a first-order manner and slowly to nearly complete conversion, no matter using mPEG−OH or benzyl alcohol as an initiator (Figure 3), indicating that TMC and DTC have a similar reactivity. The M_n of both PEG-P(TMC-DTC) and P(TMC-DTC) increased linearly with increasing monomer conversions (Figure 3). The dispersity remained low throughout the whole polymerization process (M_w/M_n = 1.09−1.19). Hence, DPP presents excellent control over copolymerization of TMC and DTC, yielding most likely random copolymers. To confirm that DPP catalyzes a controlled/living polymerization, sequential polymerization of DTC and TMC was carried out in DCM at a $[DTC]_0/[BnOH]_0$ molar ratio of 10/1 for 24 h with nearly complete DTC conversion, which was followed by adding 40 equiv. TMC and polymerization for another 24 h. SEC curves showed a unimodal and narrow distribution of PDTC-*b*-PTMC block

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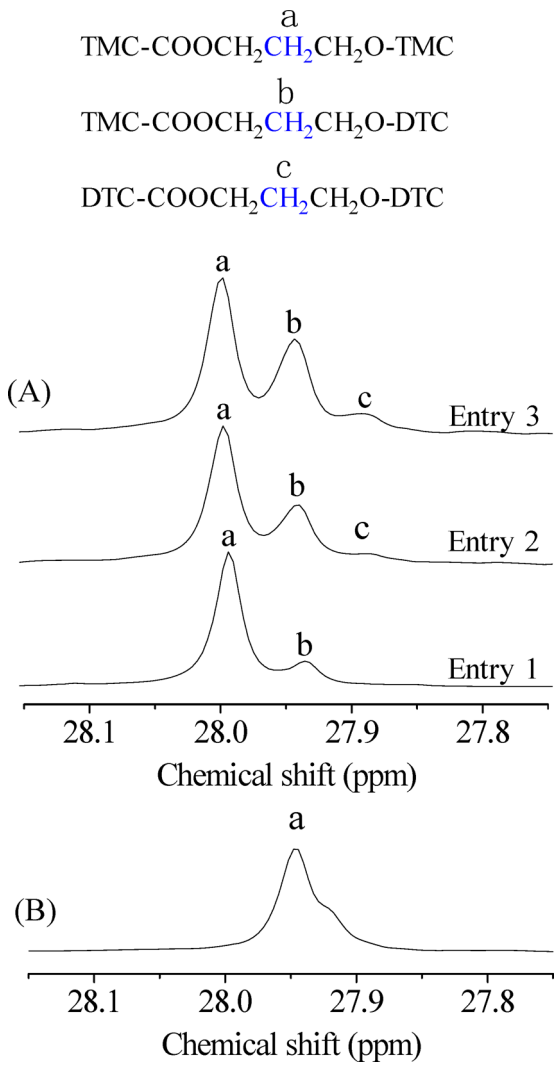

Figure 7. ^{13}C NMR spectra (150 MHz) of a magnified region of PEG-P(TMC-DTC). (A) PEG-P(TMC$_{37}$-DTC$_5$), PEG-P(TMC$_{38}$-DTC$_{10}$), PEG-P(TMC$_{35}$-DTC$_{15}$) from the DPP system in $CDCl_3$ (Table 1, Entries 1−3); (B) PEG-P(TMC$_{37}$-DTC$_4$) from the TBD system in DMF-d_7 (Table 2, Entry 1).

copolymer and clear shift of M_n to a higher value following polymerization of TMC (Figure 4). It is clear, therefore, that DPP-catalyzed copolymerization of TMC and DTC proceeds in a living nature.

In sharp contrast, TBD-catalyzed copolymerization of TMC and DTC proceeded in a completely different manner, in which DTC was consumed very quickly (within 10 min) while TMC reached ca. 70% conversion in 60 min (Figure 5A). The plot of $\ln(M_0/M_t)$ versus time revealed a first-order polymerization kinetics for TMC (Figure 5B). These results indicate that TBD gives most likely a blocky copolymer of TMC and DTC. DSC measurements showed that in contrast to copolymers obtained with DPP, copolymers with the TBD system exhibited pronounced cold crystallization of PEG at −24.8 to −3.0 °C (Figure S9), which renders it difficult to discern the T_g of P(TMC-DTC). The different thermal behaviors signify that PEG-P(TMC-DTC) copolymers obtained with DPP and TBD have a different microstructure.

3.3. Influence of Organocatalysts on the Microstructure of P(TMC-DTC) Copolymers. The microstructures of P(TMC-DTC) copolymers obtained with DPP and TBD catalysts were further analyzed using ^{1}H NMR and ^{13}C NMR, which have been applied for study of different copolymer microstructures.[34,39,47,50−52] ^{1}H NMR of P(TMC-DTC) from DPP system (Table 1, Entry 9) displayed two sets of signals attributable to the methylene protons in benzyloxy terminal groups (a_1 and a_2) and those next to hydroxyl terminal groups (f_1 and f_2), respectively (Figure 6). The ratio of f_1/f_2 (3.84) was close to the feed ratio (4/1), supporting random distribution of TMC and DTC units throughout the P(TMC-DTC) copolymer chain.

^{13}C NMR of PEG-P(DTC-TMC) obtained with DPP in $CDCl_3$ showed characteristic peaks of PEG (δ 70.53), PTMC (δ 154.86, 64.24 and 28.00) and PDTC (δ 154.55, 68.02, 54.36 and 44.23) (Figure S14). It is noteworthy that the middle methylene peaks of TMC unit (−CH_2−$\underline{\boldsymbol{CH_2}}$−$CH_2$−) were split due to different linkages (Figure 7). The signals at δ 28.00, 27.94, and 27.88 were assignable to TMC−***TMC***−TMC, TMC−***TMC***−DTC and DTC−***TMC***−DTC, respectively. As shown in Figure 7A, signals of TMC−***TMC***−DTC and DTC−***TMC***−DTC increased with increasing DTC contents in PEG-P(TMC-DTC). However, unlike other carbonate copolymers showing different carbonate linkages,[19,53] here only two carbonate signals were seen, probably due to the similar chemical environment of carbonate groups in TMC and DTC and/or low DTC content in the copolymer. These data, together with the kinetics study and end group analysis, point to a random copolymerization of TMC and DTC.

The microstructure of copolymers of DTC and TMC obtained using TBD as the catalyst and BnOH as the initiator was studied using NMR analyses as well. Using DMF-d_7 as solvent, ^{1}H NMR spectra displayed that the majority of BnOH first initiated DTC, giving a characteristic peak at δ 5.16 (methylene protons of benzyloxy group linked to DTC) and hardly any peak at δ 5.13 due to methylene protons of benzyloxy group linked to DTC. Meanwhile, much more TMC ends (f_2, δ 3.54) compared to DTC ends (a_2, δ 3.56) were observed (molar ratio: 1.63/0.15). Moreover, ^{13}C NMR analyses (Figure 7B, Figure S15) of P(TMC-DTC) from TBD system revealed that, in contrast to P(TMC-DTC) from the DPP system, no clear split of the middle methylene peaks of TMC unit was observed. These results further confirm the blocky nature of P(TMC-DTC) copolymers prepared using the TBD system.

The monomer sequence of the copolymers is crucial to their properties. For instance, unlike the random PEG-P(TMC-DTC) from the DPP system, which could be easily dissolved in DMSO, DCM, or $CHCl_3$, the solubility of the blocky PEG-P(TMC-DTC) from the TBD system in $CHCl_3$ or DMSO became very low, similar to PEG−PDTC diblock copolymer. These two different types of PEG-P(TMC-DTC) copolymers would likely lead to core-cross-linked and interfacially cross-linked micellar nanoparticles, respectively, which might afford different drug release behaviors and drug efficacy.

4. CONCLUSION

We have demonstrated that acidic and basic organocatalysts bring about vastly different ring-opening copolymerization behaviors of TMC and DTC, leading to copolymers with random and blocky microstructures, respectively. Using DPP as catalyst, both TMC and DTC are polymerized in a first-order kinetics and living manner, affording P(TMC-DTC) random copolymers with predetermined compositions and molar mass

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as well as narrow dispersity (M_w/M_n < 1.19). Notably, DPP is tolerant to different functional groups, including *N*-hydroxysuccinimide ester (NHS) and maleimide (Mal), which render it interesting for preparation of functional block copolymers. By contrast, with TBD as a catalyst, DTC is preferentially polymerized followed by first-order polymerization of TMC, furnishing P(TMC-DTC) blocky copolymers with controlled molar mass but moderate dispersity (M_w/M_n = 1.27−1.80). Moreover, TBD cannot tolerate functional groups like NHS and Mal. Under similar conditions, TBD catalyzes much faster copolymerization of TMC and DTC than DPP.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.biomac.8b00415.

Materials, characterization, SEC curves, DSC traces, and ^{1}H and ^{13}C NMR spectra of PEG-P(TMC-DTC) using DPP or TBD as a catalyst (PDF)

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Notes

The authors declare no competing financial interest.

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