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Hydrophilic Stars, Amphiphilic Star Block Copolymers, and Miktoarm Stars with Degradable Polycarbonate Cores

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ABSTRACT: A facile one-pot synthetic approach toward the realization of star polymers made of degradable carbonate cores is reported. The synthetic strategy involved triethylborane-activated anionic copolymerization of a difunctional epoxide with CO_2 initiated by bis(triphenylphosphine)iminium chloride (PPNCl). Vinyl cyclohexene dioxide (VCD) was, thus, used as a difunctional cross-linker, and core compositions with 80−90% carbonate content were achieved. Poly(ethylene oxide) (PEO) arms were grown from these in-situ generated polycarbonate core anions to build a range of star polymers, including hydrophilic PEO stars and star-shaped block copolymers. Poly(propylene oxide) (PPO) precursors were used in a second approach as macroinitiators to form carbonate cores through the arm-first method; miktoarm stars having a large number of arms, both hydrophilic and hydrophobic, could be derived by this method. The carbonate cores of the synthesized stars were readily degraded through hydrolysis of the core carbonate linkages to yield PEO and PPO chains. Potential applications of these types of systems are manifold, especially for PEG-based drug delivery vehicles.
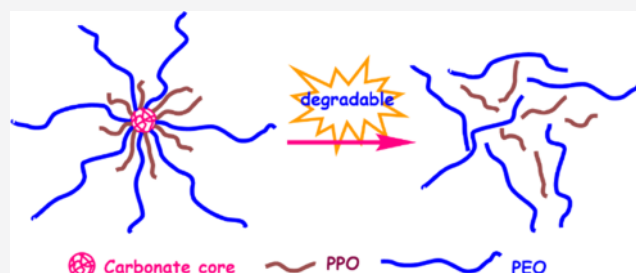
■ INTRODUCTION

Poly(ethylene oxide) (PEO), often referred to as poly-(ethylene glycol), is a widely utilized polymer for the conjugation of biomolecules (PEGylation) for drug delivery due to its unique properties such as chemical stability, hydrophilicity, biocompatibility, and especially "stealth effect".[1−5] PEO samples carrying many terminal functional groups are sometimes preferred to mere linear PEO for they offer better protection to conjugated biomolecules and have much higher loading capacities. Therefore, a great deal of effort has been devoted to synthesizing branched PEOs with starlike, dendrimer-like, and hyperbranched structures[6−10] or linear PEOs with multifunctionalities.[6,11]

In comparison to hyperbranched PEOs, usually characterized by a broad polydispersity and ill-defined structure,[10,12] PEO dendrimers exhibit well-defined structures but necessitate tedious multistep synthesis;[13−19] in contrast PEO-based star polymers have attracted significant attention as their synthetic methodology is relatively easy and cost-effective.[20−29] Generally, star-branched PEO structures are composed of a core and radiating arms. PEO stars can be obtained either by linking a given number of linear chains to a central core following the "arm-first" method or by growing branches from a multifunctional initiator via the "core-first" approach, which was well reviewed by Lapienis.[8] Due to the steric hindrance during the coupling, starlike PEOs synthesized by the "arm-first" method exhibit generally low molar masses; in contrast, PEO stars synthesized by the "core-first" method can be of high molar masses. Although a core that carries a definite number of functional groups affords an accurate number of arms of PEOs, this number of arms is generally very limited by the availability of core molecules of high functionality.[24−26] When synthesizing PEO stars with a higher number of arms by the "core-first" method, the precursors serving subsequently as the star cores are generally generated through anionic polymerization of cross-linkers, such as divinylbenzene,[29] diepoxides, or glycidol.[20−23,27,30] Such PEO stars exhibit special topological features such as a fluctuation in their degree of branching, which can be large, a low solution viscosity, and smaller hydrodynamic volumes compared to their linear analogues.[8,31−33]

As a vehicle for the delivery of biomolecules that requires a long residence time in the body, the hydrodynamic size of conjugates after PEGylation should be above 6−8 nm, which is the threshold for glomerular filtration to avoid renal clearance. However, due to their nondegradability, PEOs with molar mass higher than 40 kg/mol can accumulate in the body.[4,34] A number of synthetic ways have been contemplated toward the preparation of degradable linear PEOs: through modification of commercially available PEOs, by polycondensation of PEG
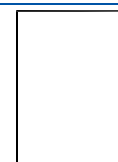
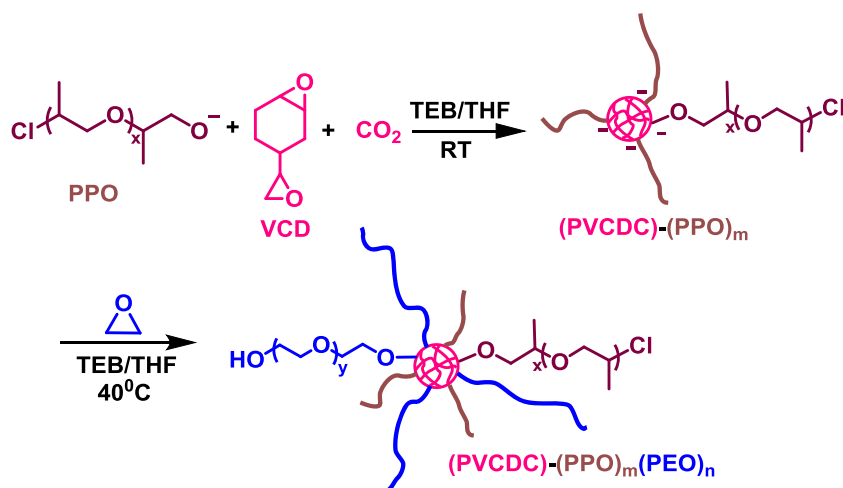**Scheme 1. Synthesis of PEO Stars and PEO-b-PPO Star Block Copolymers with a Degradable PVCDC Carbonate Core by the "Core-First" Method**
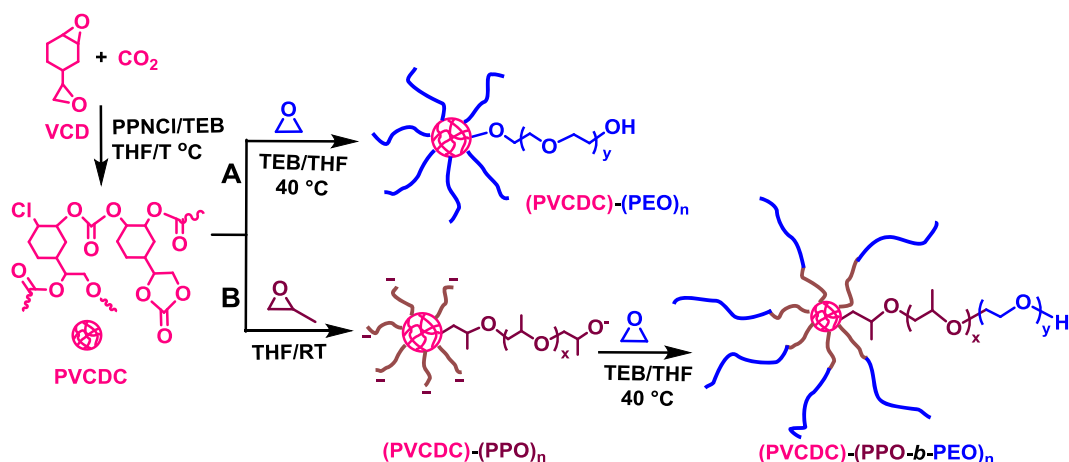
Scheme 2. Synthesis of Miktoarm Stars μ-(PEO)ₘ(PPO)ₙ with Degradable PVCDC Cores

telechelics or anionic copolymerization of EO with other monomers to incorporate cleavable moieties,[35] etc. These attempts were well summarized by Dingels and Frey.[36] As for star or branched PEOs that can undergo degradation under a trigger, the reports of their synthesis are very few. To be compatible with the anionic ring-opening polymerization (AROP) of EO, which occurs under basic conditions, the strategies used have been to incorporate acid-labile ketal linkages within the core or within branching points by the "core-first" methodology. For instance, we previously reported degradable dendrimer-like PEOs using an original ABC-type branching agent featuring a cleavable ketal group, following an iterative divergent approach based on the AROP of ethylene oxide and the "arborization" of PEO chain ends.[14] Tonhauser and co-workers designed acid-labile PEO stars by incorporating acetal moieties into the core structure using an acetal-containing inimer.[37] To avoid incompatibility with the conditions of the AROP of EO, one generally resorts to the "arm-first" methodology for the synthesis of degradable PEO stars. For instance, Matyjaszewski et al. synthesized degradable PEO stars, containing disulfide linkages in their core through "arm-first" atom transfer radical copolymerization (ATRP) of a methacrylated PEO macromonomer with disulfide dimethacrylate as the cross-linker.[38] They also resorted to the "core-

first" method to obtain stars grown from modified tannic acid serving as the core.[39] Johnson and co-workers described the one-pot synthesis of core-photocleavable poly(norbornene)-g-PEO brush-arm stars through ring-opening metathesis polymerization (ROMP) of a norbornene–PEO macromonomer with a photocleavable bis-norbornene cross-linker.[40] This methodology combines graft-through ROMP and "arm-first" cross-linking to introduce degradable linkages within stars during coupling or cross-linking.

Our group recently proposed a new metal-free approach allowing the successful copolymerization of CO_2 and epoxides using triethylborane (TEB)-based ate complexes;[41,42] upon slightly changing the polymerization conditions, the carbonate content (50–96%) in the obtained poly(ether-carbonate)s could be easily tuned. Under the same conditions, epoxides such as ethylene oxide, propylene oxide, or glycidyl azide could be effectively homopolymerized in a "living" manner.[43−45] The above results demonstrate the stability of carbonate linkages in the presence of ate complexes mediating the AROP of epoxides, in contrast to the known incompatibility of ester or carbonate linkages generally observed in the AROP of epoxides under basic conditions:[46] such incompatibility generally ends up in the degradation of the latter linkages during synthesis. This prompted us to synthesize PEO stars where the cores

would be composed of carbonate linkages that remain stable and tolerant toward the growing active species and could, thus, be cleaved after synthesis under hydrolytic conditions. Indeed, degradation investigations have reported that the carbonate linkages could well be hydrolytically degraded in vitro and biodegraded in vivo through surface erosion.[47−50] In this work, we report the synthesis of PEO stars made of degradable cores in one pot through a "core-first" approach, as shown in Scheme 1. The degradable core was first formed through copolymerization of a diepoxide (VCD) with CO_2; the PEO stars (PVCDC)-(PEO)$_n$ were then obtained in the same reactor following addition of EO through AROP in the presence of TEB (Scheme 1A). Based on the above synthesis, hydrophobic stars (PVCDC)-(PPO)$_n$ and amphiphilic star blocks (PVCDC)-(PPO-b-PEO)$_n$ (Scheme 1B) were further derived through the aforementioned "core-first" method. In another way, (PCVDC)-(PPO)$_m$(PEO)$_n$ miktoarm stars were obtained by the "arm-first" and "in-out" methodology (Scheme 2).[51]

■ EXPERIMENTAL SECTION

Materials. All reactions were carried out under a dry and oxygen-free argon atmosphere in a Braun Labmaster glovebox. All chemicals purchased from Aldrich and Acros were used without further purification, unless otherwise specially mentioned. Vinyl cyclohexene dioxide (VCD), propylene oxide (PO), and cyclohexene oxide (CHO) were distilled under reduced pressure over calcium hydride before use. Ethylene oxide (EO) was purified by stirring over CaH_2 for one day and distilled into a flask containing n-BuLi and stirred for a couple of hours followed by a further distillation. Bis-(triphenylphosphoranylidene)ammonium chloride (PPNCl) was recrystallized from a methylene chloride−diethyl ether solvent mixture and dried overnight under vacuum at 50 °C. Triethylborane (TEB, 1 M in THF) was used without further purification. Tetrahydrofuran (THF) was distilled from a sodium/benzophenone mixture before use. CO_2 (99.995%) from Abdullah Hashim Industrial & Gas Co. was further purified by flowing through a purifier of VICI Co.

Characterization. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III-400 Hz instrument and chemical shifts are reported in ppm using tetramethylsilane as the internal standard in $CDCl_3$ solvent. FT-IR spectra were recorded using a Thermoscientific Nicolet iS10 FT-IR spectrometer. The molar mass (M_n) and molar mass distribution ($Đ$) of linear and star polymers were measured on a GPC instrument VISCOTEK VE2001 equipped with Styragel HR2 THF (1 mL/min) as the eluent at 35 °C and a differential refractive index (RI) detector. Polystryrene and PEO standards were used for calibration of the instrument. The absolute molar mass of star polymers was determined by triple-detection GPC (refractometry, light scattering at λ = 670 nm, and viscometry). Refractive index increment (dn/dc) of star samples in THF was measured with a Brookhaven Instruments differential refractometer. Dynamic light scattering (DLS) measurements were performed using a Malvern Zetasizer Nano ZS instrument equipped with a 632.8 nm He−Ne laser. The measurement angle was 173°. For analysis, the polymer sample solution was prepared in DMF solvent and filtered through a 0.25 μm PTFE filter. The cells were temperature-controlled at 20 ± 0.1 °C. MALDI-TOF MS experiments were performed on a Bruker Ultrafex III MALDI-TOF mass spectrometer (Bruker Daltonik, Bremen, Germany) using trans-2-[3-(4-tert-butylphenyl)2-methyl-2-propenylidene]malononitrile (DCTB) as the matrix in THF and NaTFA as the ionizing agent. Typically, 40 mg of DCTB, 10 mg of sample, and 10 mg of NaTFA were dissolved in 1 mL of THF separately and mixed in the ratio of 20:10:5 μL; 1 μL from that mixture was spotted over the plate for measurement.

Synthesis of PEO Stars with Polycarbonate Cores (PVCDC)-(PEO)$_n$. Reactions were carried out in a 100 mL Parr reactor with an in-built charging port, which was dried at 120 °C overnight and then evacuated in a glovebox chamber for 3 h. For illustrating the synthetic procedure, the core sample designated as (PVCDC1)-(EO$_{300}$)$_n$ in entry 1 in Table 2 is taken as a representative. PPNCl (0.057 g, 0.1 mmol) was first added into the reactor, followed by THF (2.5 mL) and TEB (0.1 mL, 1 equiv). To this reaction mixture, vinyl cyclohexene dioxide (64 μL, 0.5 mmol) was introduced, and then the reactor was closed and taken out from the glovebox to charge CO_2 to 10 bar. The polymerization was carried out at 80 °C for 15 h. After cooling the reactor and CO_2 being slowly released, EO (1.3 mL, 30 mmol) and TEB (0.3 mL) in THF (13 mL) were carefully injected into the reactor through the charging port, and polymerization was done at 40 °C for another 4 h. Finally, the reaction mixture was quenched with HCl in methanol (1 mol/L). The obtained crude product was purified through precipitation in diethyl ether and dried in a vacuum oven at 40 °C overnight.

For the characterization of the core formed, the same copolymerization of VCD with CO_2 has to be done as above and then quenched using HCl in methanol (1 mol/L). The obtained crude PVCDC core product was purified through precipitation in methanol and dried under vacuum at 40 °C overnight.

Synthesis of Star Block (PCVDC)-(PPO-b-PEO)$_n$. Entry 1 in Table 3, star block sample (PVCDC1)-(PO$_{87}$-b-EO$_{340}$)$_n$, was taken as an example. Polycarbonate core PVCDC1 was synthesized as illustrated in the synthesis of homostars. To the synthesized PVCDC1 core mixture (0.1 mmol) inside an autoclave, PO (1.3 mL, 8.7 mmol) in THF (2.6 mL) was injected, and the polymerization was carried out at RT under stirring for 6 h. Then, EO (1.7 mL, 34 mmol) and TEB (0.3 mL) in THF (17 mL) were sequentially injected through the charging port and polymerization was continued at 40 °C for another 4 h. At the end of polymerization, the reaction mixture was quenched with HCl in methanol (1 mol/L). The crude product was purified through precipitation in hexane, followed by drying in a vacuum oven at 40 °C overnight.

Synthesis of Miktoarm Star Copolymers (PVCDC)-(PPO)$_m$(PEO)$_n$. A typical synthetic procedure of miktoarm star copolymers is described here by taking entry 3 in Table 4 as an example. The poly(propylene oxide) (PPO, M_n = 4.2 kg/mol) macroinitiator was first synthesized in a 100 mL dried Parr autoclave by stirring PPNCl (34 mg, 0.06 mmol), TEB (60 μL, 0.06 mmol), and PO (0.27 mL, 4.3 mmol) in THF (0.27 mL) at RT for 1 h. After VCD (183 μL, 1.4 mmol) in THF (6 mL) was injected, the reactor was charged with CO_2 to 10 bar, and kept at 50 °C for 17 h under stirring to form the star macroinitiator. The reactor was then cooled and CO_2 was slowly released, EO (1 mL, 20 mmol) and TEB (180 μL, 0.18 mmol) in THF (10 mL) were finally charged, and polymerization was carried out at ambient temperature for another 1 h. The polymerization was quenched with HCl in methanol (1 mol/L). The product was obtained through precipitation in diethyl ether followed by drying in a vacuum oven at 40 °C overnight.

Hydrolytic Degradation of Star Polymers. In a typical hydrolysis reaction, 60 mg of star sample was dissolved in 4 mL of THF, followed by the addition of 2 M KOH in methanol. The hydrolysis reaction was carried out at 50 °C under stirring for 3 days and then the solvent was removed under reduced pressure. Dichloromethane was added to extract the polymer. The hydrolyzed polymer samples were obtained after concentration and drying.

■ RESULTS AND DISCUSSION

Synthesis of PEO Stars with a Degradable Polycarbonate Core. *Synthesis of Polycarbonate Cores.* PEO stars having a degradable core made of carbonate linkages were first prepared by the "core-first" approach, as shown in Scheme 1. VCD was used as the cross-linker (difunctional monomer) to form the degradable polycarbonate core by copolymerization with CO_2 using a boron-based ate complex as the initiator (Scheme 1).[42] VCD contains two types of epoxides, one alicyclic and disubstituted and the other monosubstituted, both known to exhibit different reactivities; however, no clear chemoselectivity was evidenced since macrogel formation was

Table 1. Results of TEB-Activated Copolymerization of VCD with CO_2 under Different Conditions[a]

| entry	samples	[Cl⁻]:[TEB]:[VCD]	T (°C)	conv. (%)[b]	carbonate content (%)[c]	$M_{n(GPC)}$/Đ (kg/mol)[d]	F[e]
1	PVCDC1	1:1:5	80	>99	85	5.9/1.8	4.6
2	PVCDC2	1:1:5	70	>99	88	6.3/1.8	6.3
3	PVCDC3	1:1:5	60	>99	90	8.6/5.6	8.5
4	PVCDC4	1:1:5	50	>99	90	12.0/5.3	20.8
5	PVCDC5	1:1:6	80	>99	90	9.6/3.7	9.2
6	PVCDC6	1:1:7	80	gel			
7	PVCDC7	1:1.5:5	70	>99	88	7.0/4.1	7.7
8	PVCDC8	1:1:6	60	gel			
9[f]	PVCDC9	1:1:5	70	>99	89	6.7/1.9	5.8
10[g]	PVCDC10	1:1:5	80	>99	90	7.5/2.3	11.8

[a]Copolymerization was carried out for 15 h with a VCD/THF (v/v) ratio equal to 1:2.5 using PPNCl as the initiator or as otherwise mentioned. [b]Conversion was measured by ^{1}H NMR of the crude reaction mixture. [c]Determined by ^{1}H NMR. [d]Measured by GPC with THF as the eluent and calibrated using polystyrene standards. [e]The functionality was taken from the arm numbers of PEO stars in Table 2. [f]Volume ratio of VCD/THF was 1:2. [g]Monofunctional CHO was added to the cross-linker in the molar ratio of VCD/CHO = 1:1 and VCD/THF (v/v) = 1:2.5.

observed even at a moderate concentration of VCD. Soluble polycarbonates were, however, reported upon discontinuing the copolymerization of VCD with CO_2 at moderate conversion.[52] To avoid macrogelation when using the "core-first" methodology, low amounts of VCD were used with a ratio of VCD to initiator smaller than 5. The challenge here was indeed to prepare colloidal, submicron size range, cross-linked polycarbonates and, thus, to avoid macrogelation. The parameters that generally play an essential role in the formation of such colloidal, yet reactive, nanogels, which can eventually serve as cores for star synthesis, are the concentration of the reaction medium and the ratios of cross-linker (VCD) to the initiator and to the comonomer. The temperature (T) of the reaction is another parameter to be considered as a very high temperature can favor the formation of cyclic carbonates and, thus, the generation of unproductive intramolecular carbonate linkages, from the cross-linking standpoint. The polymerization conditions and results are listed in Table 1.

As shown previously,[42] the copolymerization behavior of CO_2 with propylene oxide (PO) is different from that of alicyclic cyclohexene oxide (CHO) when using onium salts as an initiator in the presence of TEB. In the case of CHO, only alternating copolymers with CO_2 (polycarbonates) were obtained with 100% selectivity of linear vs cyclic carbonates; in the case of PO, a poly(ether-co-carbonate) was formed, containing about 10% of ether linkages along with some cyclic propylene carbonate side products, whose amount was found to increase with the temperature of polymerization. Unlike poly(ether-co-carbonate)s or linear polycarbonates that do contribute to cross-linking, cyclic carbonates do not participate in cross-linking reactions during the copolymerization of VCD with CO_2. Before adding ethylene oxide, the product of the copolymerization of VCD with CO_2 was sampled out and thoroughly characterized.

As shown in Table 1, a ratio of VCD to initiator equal to 5 leads to soluble polycarbonate cores and results in a complete conversion of VCD. The obtained polycarbonate cores exhibit a broad molar mass distribution, probably due to occurrence of core−core coupling reactions (Figure 1A). As shown in a representative NMR spectrum (Figure 2A), the peaks corresponding to the CHO-type epoxide units (3.2 ppm) of VCD and the PO-type epoxide units (2.5 and 2.7 ppm) of the same cross-linker have all disappeared, indicating the complete reaction of diepoxides. The peaks corresponding to the acyclic
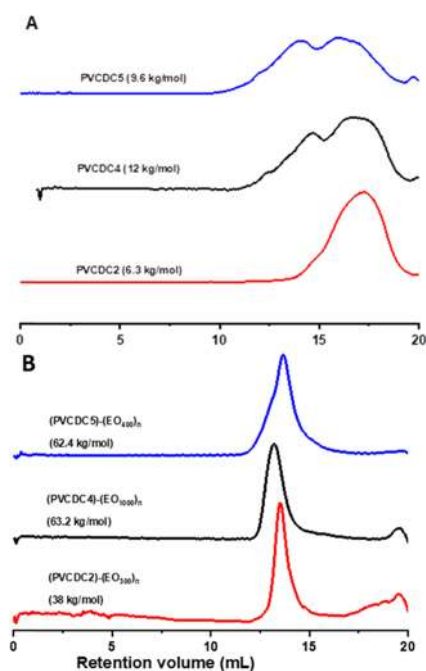
Figure 1. Representative GPC overlay profiles of (A) PVCDC polycarbonate cores and (B) (PVCDC)-(PEO)$_n$ stars.

and cyclic carbonate linkages overlap in the region between 5.0 and 4.0 ppm; their presence can also be clearly detected by IR spectroscopy (Figure S1), with strong absorption peaks at 1800 and 1740 cm^{-1} attributable to the stretching of the carbonyl of cyclic and acyclic carbonates, respectively. The selectivity of acyclic vs cyclic carbonates during core synthesis, as determined by IR analysis, falls typically in the range of 63−68% except for entry 10, which indicates 80% selectivity. Besides carbonate linkages, resonances in the region of 3.3−3.5 ppm (Figure 2A) show also the presence of ether linkages resulting from the homopolymerization of VCD. Based on the ratio of intensities of the peaks located between 4 and 5 ppm to those of the peaks found around 3.5 ppm, the carbonate content of the formed cores could be deduced. As shown in Table 1, the carbonate vs ether content does not change considerably with the temperature and stands at around 90%. In contrast, the apparent molar masses of the obtained cores increase with the decrease of the polymerization temperature. Since the formation of cyclic carbonate linkages does not
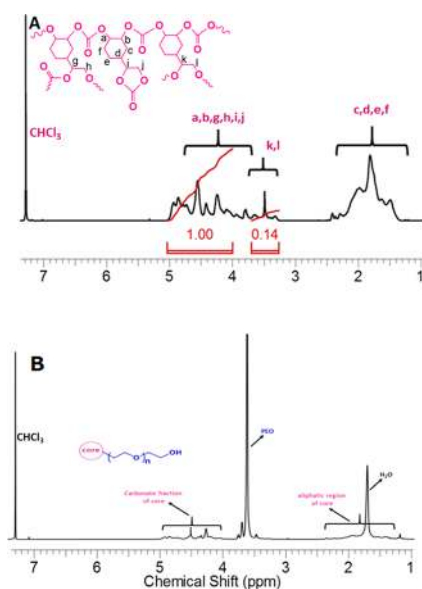
Figure 2. Representative ^1H NMR spectra in $CDCl_3$ of (A) polycarbonate cores (PVCDC) and (B) (PVCDC)-(PEO)$_n$ stars.

315 contribute to cross-linking, lowering the temperature favors the
316 formation of "linear" acyclic carbonate linkages, resulting in a
317 higher degree of cross-linking, and thus higher apparent molar
318 masses and functionality (vide infra) of the synthesized cores.
319 Indeed, the functionality of the cores increases from 4.6 to 20.8
320 when decreasing the temperature of polymerization from 80 to
321 50 °C for a given feeding ratio (entry 1−4, Table 1). To favor
322 the incorporation of the monosubstituted epoxide carried by
323 VCD, attempts to add more TEB to increase the cross-linking
324 density and, in turn, the molar mass and functionality of the
325 core were found successful (entry 7 in Table 1). Utilizing a
326 mono-epoxide (CHO) in addition to VCD and CO_2 was also
327 helpful to enhance the extent of cross-linking without
328 provoking the entire gelation of the reaction medium (entry
329 10 in Table 1). On the other hand, an increase in the amount
330 of VCD generally resulted in the gelation of the medium
331 (entries 6, 8 in Table 1). When the ratio of VCD to initiator
332 was <5, the functionality of the core could, thus, be fine-tuned
333 by varying the polymerization temperature and the amount of

334 TEB used, and through the introduction of a mono-epoxide as
335 a third monomer; of the three options, the first one, which is
336 the variation of the temperature, proved the most effective.

337 *Growth of PEO Arms from "Living" Polycarbonate Cores.*
338 The highly branched polycarbonate cores prepared according
339 to the conditions previously described served to initiate the
340 polymerization of EO and grow PEO arms (Scheme 1A).
341 Ethylene oxide, together with THF solvent, was then injected
342 into the same Parr reactor after CO_2 was gradually released,
343 and the polymerization of ethylene oxide was subsequently
344 carried out at 40 °C under stirring. Depending on the cores
345 utilized as macroinitiators and the amount of EO charged,
346 PEO stars exhibiting different arm numbers and lengths could
347 be obtained.

348 An overlay of FT-IR spectra in Figure S1 clearly shows the
349 presence of the characteristic peaks due to carbonate cores,
350 indicating the integrity of carbonate linkages during the
351 polymerization of EO. Likewise, the NMR characterization
352 shows, in addition to the characteristic peak of PEO at 3.77
353 ppm, peaks in the 4.0−5.0 ppm region attributable to C**H** and
354 C**H**$_2$ protons of carbonate linkages, confirming the formation
355 of PEO stars (Figure 2B). After the formation of the PEO
356 stars, the GPC traces remarkably shift to the high molar mass
357 region and exhibit distributions that are symmetrical and
358 narrower with a dispersion around 1.5 in most cases (Figure
359 1B). To calculate the number of arms of each PEO star
360 formed, the actual or absolute molar masses of PEO stars were,
361 thus, measured using light scattering. Then, the polycarbonate
362 core of the stars was completely hydrolyzed, and the molar
363 masses of linear PEO arms were determined by GPC calibrated
364 with PEO standards. Based on the absolute molar mass values,
365 $M_{w,star(LS)}$, the arm numbers could be estimated using the
366 following formula

$$N_{arm} = M_{w,star(LS)} \times W_{PEO}/M_{n(arm)} \qquad (1)$$

368 where $M_{w,star(LS)}$, $M_{n(arm)}$, and W_{PEO} are the absolute molar
369 mass of PEO stars, the molar mass of each arm determined by
370 GPC analysis, and the weight percentage of PEO in the stars,
371 respectively. In Table 2 are listed some of the parameters that
372 were varied from one experiment to another one, such as the
373 temperature of polymerization, the amount of TEB used, and
374 the ratio of EO to the initiator; under these conditions, PEO

Table 2. Characterization of (PVCDC)-(PEO)$_n$ Star Polymers Synthesized by the "Core-First" Method[a]

entry	star polymer	[EO]:[Cl$^-$]	$M_{n,star}/Đ$[b] (kg/mol)	$M_{w,star(LS)}$[c] (kg/mol)	$M_{n,PEO}$[d] (kg/mol)	N_{arm}[e]
1	(PVCDC1)-(EO$_{300}$)$_n$	300	45.4/1.3	57.2	12.6	4.6
2	(PVCDC2)-(EO$_{300}$)$_n$	300	38/1.1	77.7	12.2	6.1
3	(PVCDC2)-(EO$_{500}$)$_n$	500	41.5/1.1	125	19.0	6.5
4	(PVCDC3)-(EO$_{50}$)$_n$	50	13.0/2.4	nd	2.1	
5	(PVCDC3)-(EO$_{100}$)$_n$	100	23.4/1.6	nd	4.4	
6	(PVCDC3)-(EO$_{400}$)$_n$	400	48.1/1.5	140	15.0	9.3
7	(PVCDC4)-(EO$_{1000}$)$_n$	1000	63.2/1.3	835	40.1	20.8
8	(PVCDC5)-(EO$_{400}$)$_n$	400	62.4/2	151	16.3	9.2
9	(PVCDC7)-(EO$_{500}$)$_n$	500	44.4/1.6	148	19.2	7.7
10	(PVCDC9)-(EO$_{300}$)$_n$	300	38.8/1.4	70.1	12.0	5.8
11	(PVCDC10)-(EO$_{100}$)$_n$	100	24.1/1.6	50.8	4.1	12.3
12	(PVCDC10)-(EO$_{300}$)$_n$	300	34.7/1.5	144	12.8	11.2

[a]Polymerization of EO by the formed PVCDC core anion was carried out by keeping the ratio of TEB to PPNCl as 3:1 and EO in THF (v/v, 1/10) at 40 °C for 4 h, and the conversion was calculated by gravimetry. [b]Determined by GPC with THF as the eluent based on a polystyrene standard. [c]Determined by GPC equipped with multiangle light scattering (GPC-MALLS). [d]PEO arms obtained after degradation were determined by GPC based on a PEO standard. [e]Calculated based on formula 1.

Table 3. Characterization of (PVCDC)(PPO-b-PEO)$_n$ Star Block Polymers Synthesized by the "Core-First" Method[a]

entry	core[b]	[PO]:[EO]:[Cl$^-$]	(PVCDC)-(PPO)$_n$ M_n/Đ[c] (kg/mol)	(PVCDC)-(PPO-b-PEO)$_n$ (kg/mol) M_n/Đ[c]	$M_{w(LS)}$[d]	PPO-b-PEO (kg/mol) M_n[e]	N_{arm}[f]
1	PVCDC1	87/340/1	12.8/1.6	23.9/1.4	114	19.1	5.9
2	PVCDC2	44/340/1	15.7/1.4	31.6/2.5	145	19.6	7.4
3	PVCDC3	87/340/1	12.5/1.3	43.1/2.6	225	21.0	10.7
4	PVCDC4	44/340/1	18.9/1.7	50.0/1.8	380	22.1	17.3
5	PVCDC5	87/340/1	17.4/2.3	40.2/2.1	245	27.2	8.2

[a]Polymerization of PO by PVCDC core anions was carried out by keeping the ratio of TEB to PPNCl as 1:1 and PO in THF (v/v, 1/2) at RT for 6 h; the sequential polymerization of EO was carried out with a ratio of TEB to PPNCl (3:1) and EO in THF (v/v, 1/10) at 40 °C for 4 h. [b]The core was prepared as in Table 1. [c]Determined by GPC with THF as the eluent based on polystyrene standards. [d]Measured by GPC equipped with multiangle laser light scattering (GPC-MALLS). [e]The hydrolyzed linear arm blocks were analyzed by GPC calibrated with PEO standards. [f]Calculated based on formula 1.

Table 4. Characterization of Amphiphilic Miktoarm Stars with Polycarbonate Cores[a]

entry	[VCD]/ [PPO$^-$]	time[b] (h)	$M_{n\ PPO}$[c] (kg/mol)	$M_{n,PEO}$[c] (kg/mol)	wt %[d] PPO	wt %[d] PEO	$M_{w\mu(PPO)_m(PEO)_n}$ (kg/mol)[e]	$M_{w(PPO)_m\ star}$ (kg/mol)[f]	arm number[g] PPO	arm number[g] PEO
1	23	11	3.0	16.8	13	67	231	62.2	10.0	9.3
2	23	17	4.2	13.0	24	52	255	122	14.7	10.0
3	23	28	4.2	12.4	23	53	214	100	12.0	9.2
4	26	12	4.2	14.4	23	51	195	95	10.8	6.9
5	35	14	4.2	15.8	21	47	239	126	12.1	7.1
6	35	18	4.2	14.4	21	48	258	134	12.9	8.6
7	17	20	4.5	26.1	13	77	316	72.6	9.5	9.3

[a]The miktoarm PPO and PEO stars were prepared through the copolymerization of VCD with CO_2 using pre-prepared active PPO chains (10 mM in THF) at 50 °C and then polymerization of EO at RT through sequential addition of EO in THF (v/v = 1:10) and TEB (TEB/PPO$^-$ = 3:1) (see details in the experimental part). [b]Copolymerization time of VCD and CO_2 with active PPO chains. [c]Pre-prepared PPO arm and degraded PEO arm were measured by GPC with THF as the eluent based on PEO standards. [d]Calculated based on the composition of PEO and PPO from NMR data of miktoarm stars, and under the assumption that complete incorporation of VCD and PPO into miktoarm stars occurred and that 80% of epoxides in VCD reacted with CO_2. [e]Measured by GPC equipped with multiangle laser light scattering (GPC-MALLS). [f]$M_{w(PPO)_m\ star}$ was deduced from the molar mass value of miktoarm stars and the weight content of PEO in the stars: $M_{w(PPO)_m\ star} = (1 - wt\ \%\ PEO) \times M_{w\mu(PPO)_m(PEO)_n}$. [g]$N_{PPO} = M_{w\mu(PPO)_m(PEO)_n} \times wt\ \%\ PPO/M_{n,PPO}$; $N_{PEO} = M_{w\mu(PPO)_m(PEO)_n} \times wt\ \%\ PEO/M_{n,PEO}$.

stars carrying 5−20 arms could be prepared with a molar mass of up to 835 kg/mol.

Synthesis of Star Block Copolymers (PVCDC)-(PPO-b-PEO)$_n$ with a Degradable Polycarbonate Core. Some of the polycarbonate cores formed by the core-first method were also utilized to synthesize star block copolymers with arms consisting of PPO-b-PEO chains. For this, PO was initially polymerized from the "living" carbonate cores, followed by polymerization of EO (Scheme 1B). Molecular characterization results of the star blocks prepared by this procedure are shown in Table 3.

The distributions of GPC traces became narrower after the formation of PPO stars with dispersity of molar mass around 1.5 (Figure S2). After polymerization of EO, the GPC traces shifted to the higher molar mass region and the precursor peak vanished, indicating that all the PPO arms efficiently initiated the ROP of EO and brought about the growth of PEO blocks. The absolute molar masses of these star block copolymers could be obtained by MALLS/GPC; for the M_n values of PPO-b-PEO block copolymer arms, they were determined after hydrolysis of the star cores and isolation of the latter arms; these values were subsequently used to determine the actual number of arms in the star structure, which ranged from 5 to 17, values that are close to those obtained for PEO homostars.

Synthesis of Amphiphilic Miktoarm Stars (PVCDC)-(PPO)$_m$(PEO)$_n$. After the successful synthesis of PEO stars and PPO-b-PEO star-shaped block copolymers, we attempted the synthesis of miktoarm stars μ-A$_m$B$_n$, composed of hydrophobic poly(propylene oxide) (PPO) and hydrophilic PEO arms, both of them linked to degradable polycarbonate cores. The synthetic strategy adopted for the synthesis of such miktoarm stars was to generate first "living" PPO arms, then build degradable polycarbonate cores, and finally use the latter to grow PEO arms through in- and -out sequences of reactions. This methodology is similar to the one developed for the synthesis of miktoarm stars via living anionic polymerization,[53] with the difference that VCD was used as a cross-linker instead of divinylbenzene to form the core.

In the in- and -out methodology, the "living" linear macroinitiator PPO served to initiate the polymerization of the cross-linker, VCD, and build the star core whose anionic sites could then be utilized to trigger the growth of arms of a second monomer, here EO (Scheme 2). Theoretically, the number of initiating sites carried by the star cores must be equal to the number of PPO macroinitiator arms that were used to build these cores. The number of branches that could be subsequently initiated and grown by polymerization of another monomer, here EO, must also be more or less equal to the initial number of PPO arms. However, the initiating sites carried by the cores may not be all accessible to the second monomer and, therefore, may vary with the extent of cross-linking of the core, and the steric hindrance due to the PPO

arms already connected to the core. As shown in the subsequent section, the TEB-controlled synthetic method incurs minimum purification steps and offers the major advantage of being versatile enough to afford in one pot the synthesis of miktoarm stars made of hydrophobic carbonate cores and amphiphilic shells composed of both hydrophilic PEO and hydrophobic PPO arms.

In the presence of CO_2, "living" PPO chains with their end-standing alkoxide active sites readily react with the latter monomer and with VCD to eventually give rise to polycarbonate-based cross-linked cores. As in the previously described methodologies, it is vital to precisely control factors such as the dilution of the reaction medium, the arm length, and the amount of cross-linker utilized to avoid macroscopic gelation. (PVDCD)-(PPO)$_m$ stars synthesized under different reaction conditions (Table 4) were thus first characterized. The generated carbonate cores could be easily identified by IR analysis with the characteristic IR absorption due to cyclic carbonates at 1808 cm^{-1} and acyclic carbonates at 1745 cm^{-1}.

The GPC traces of these (PVCDC)-(PPO)$_m$ stars featured a broad distribution of star-shaped species (Figure 3). This
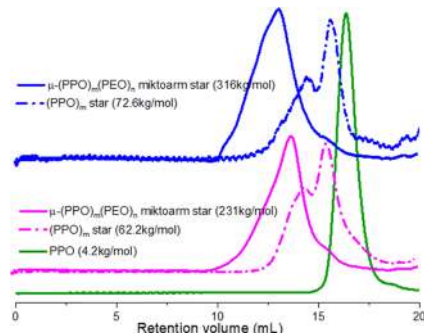

Figure 3. Representative GPC overlay profiles of linear PPO arm, PPO stars, and miktoarm (PPO)$_m$(PEO)$_n$ stars (lower: entry 2, upper: entry 7 in Table 4).

shows that besides reactions contributing to the growth and to the formation of each core, intermolecular star–star couplings also occurred, resulting in the broad distribution of star populations observed. The "bump" seen in GPC traces at lower elution volumes is indicative of such star–star couplings that are the products of reactions between unreacted epoxides carried by a star core and the anionic sites belonging to another star core. On the other hand, none of the GPC traces of these (PVCDC)-(PPO)$_m$ precursor stars indicates the presence of residual PPO macroinitiator, which ascertains that all of them contributed to star core formation. Unlike the case of the core-first methodology, where intermolecular star–star coupling could occur without major interference due to steric hindrance and, thus, could give rise to rather homogeneous cores, the arm-first methodology did not afford a unimodal distribution of star-shaped species because the star–star coupling phenomenon could take place only partially due to the hindrance by the PPO arms. Typically and whatever the experimental conditions used, we observed a bimodal distribution of star-shaped species: the first population at higher elution volumes corresponds to stars obtained directly by the reaction of "living" PPO macroinitiators with VCD and CO_2, and the second at lower elution volumes corresponds to star–star couplings. Upon increasing the reaction time, this second population of star-shaped species grew at the expense

of the first population. Augmenting the concentration of cross-linker to values higher than those indicated in Table 4 generally resulted in the macrogelation of the medium within the dilution generally utilized. Using PPO macroinitiators of small size was beneficial to the formation of homogeneous star-shaped species. It was not attempted to determine the actual molar masses of the star formed and to deduce their number of arms at this stage. It was only after the growth of PEO arms in the subsequent step that the actual molar masses of miktoarm stars were measured and the number of PEO arms and that of PPO arms were deduced.

In a third step, EO was added to grow PEO arms from these active sites carried by the cores to generate miktoarm stars. Upon characterization of the samples eventually obtained by ^{1}H NMR (Figure S3), a new highly intense band corresponding to protons of CH_2CH_2O linkages was visible at 3.5 ppm. The molar mass distributions of the obtained miktoarm stars with their polycarbonate cores all became narrower, although slightly broad (Figure 3). To be sure that no linear contaminants are present in the miktoarm star samples, PPO-b-PCHC-b-PEO triblock terpolymers of approximately the same composition as that of miktoarm stars were synthesized by sequential polymerization of PO, CHO, and EO. Both miktoarm stars and the latter triblock copolymers were characterized by dynamic light scattering (DLS), and the respective distributions of hydrodynamic sizes were compared. Miktoarm polymers exhibit a hydrodynamic size very different from that of the linear block copolymers (d size <2 nm) even after stirring the samples for five days in DMF solvent, confirming the absence of any linear block copolymer contaminant in the miktoarm star samples (Figure S4). The absolute molar masses of miktoarm stars were then determined by light scattering. Given the compositions drawn from the ratio of intensities of NMR peaks due to PPO and PEO blocks in the miktoarm star samples (Figure S3) and the feeding amount of VCD and PPO leading to the formation of (PVCDC)-(PPO)$_m$ stars, the weight fraction of the PEO arms and PPO arms in the miktoarm stars could be obtained, and thus, the molar masses of the PPO star precursors could be deduced. As shown in Table 4, based on the molar mass of PEO arms obtained after hydrolysis of the miktoarm star cores and that of PPO arms present, the average number of PEO arms and PPO arms could be respectively calculated. The presence of slightly more PPO arms than PEO arms in the formed miktoarm stars indicates that some initiating sites were inaccessible to the second monomer.

Hydrolysis of the Star Polycarbonate Cores. The primary objective of this study was to impart degradability to the star cores. Toward this goal, hydrolysis was attempted under basic conditions at 50 °C. The adopted reaction conditions facilitated the degradation of the highly branched core, which is composed of carbonate units, releasing PPO and PEO arms. The product of degradation was then extracted with DCM to isolate PEO and PPO arms, which were further characterized using FT-IR, NMR, GPC, and MALDI-TOF MS.

Characteristic IR absorptions of linear acyclic carbonates and cyclic carbonates (1745 and 1808 cm^{-1}) were absent in the hydrolyzed sample (Figure S5). Besides, the ^{1}H NMR spectrum of the hydrolyzed star sample, (PVCDC)-(PEO)$_n$, after precipitation showed peaks solely of the PEO chains (3.5 ppm) and was devoid of peaks of any carbonate linkages from the core networks, thus confirming the degradation of carbonate cores within the star structure (Figure S6). This

implies the effectiveness of polycarbonate as both a macro-anionic initiator and a degradable core network. These claims were further corroborated by the GPC analysis of the hydrolysis products (in THF using PEO standard) and MALDI-TOF MS characterization. It was observed that homo-PEO stars display a unimodal distribution corresponding to their unhydrolyzed PEG arm chains. Figure 4A reveals
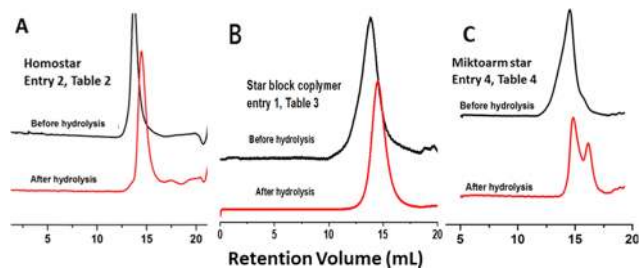

Figure 4. Representative GPC traces of hydrolyzed samples.

the shift of GPC traces of star polymers after hydrolytic degradation, clearly indicative of chain scissions within the carbonate cross-linked networks, which freed PEO arms. Degraded star-shaped block copolymers also exhibited a unimodal distribution arising from their unhydrolyzed PPO-*b*-PEO arms (Figure 4B). On the other hand, miktoarm stars produced upon hydrolysis a bimodal distribution of polymer populations and, thus, revealed the presence of two separate peaks by GPC analysis corresponding to each type of arm species PEO and PPO (Figure 4C). In these amphiphilic stars, apart from PPO and PEO segments, all other moieties consist of carbonate units, which were degraded by hydrolysis. This was further confirmed by the NMR spectrum of degraded star-shaped block copolymers and miktoarm stars (Figures S7 and S8).

In MALDI-TOF MS (Figure S9) of the hydrolyzed samples, populations of peaks with a difference of m/z 44 were observed, which corresponds to hydrolyzed PEO chains separated from the core. Notably, it can be clearly seen that the main population corresponds to PEO chains terminated with hydroxyls at both ends, where two other populations corresponding to PEO chains terminated at one end by hydroxyl groups and the other end by VCD derivatives also exist. All of these positive observations strongly substantiate the formation of star polymers with fully degradable cores.

■ CONCLUSIONS

The advantages of star polymers that contain hydrolyzable cores are manifold for a wide range of applications for PEG-based drug delivery systems. Taking advantage of the chemistry of TEB-activated anionic copolymerization of epoxide with CO_2, we succeeded in incorporating degradable carbonate units within the core structure of star polymers. Polycarbonate macroanions with 80–90% carbonate content were synthesized by a series of reactions through the "core-first" and "arm-first" methodologies and were further used to grow EO arms. These star polymers are proven to be susceptible to selective degradation of their core, allowing the isolation of arm chains. Degradation experiments were carried out under basic conditions, but they could have been undertaken under acidic conditions (pH < 5) as carbonate linkages are known to undergo degradation under both basic and acidic conditions. This boron-based chemistry is versatile

enough not only to build hydrolyzable polycarbonate cores but also to grow polyether arms without affecting the integrity of carbonate linkages. The same chemistry could also be successfully used to assemble other types of hydrolyzable stars, including polystyrene and polydiene stars, through the core-first methodology.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.9b02658.

Characterization data of IR, NMR, GPC, DLS, and MALDI-TOF (PDF)

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Notes

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