4638 *Macromolecules* **2009**, *42*, 4638–4645
DOI: 10.1021/ma9006522

Macromolecules
ARTICLE

Macrocycles from the Photochemical Coupling of Preassociated Terminal Blocks of Block Copolymers

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Received March 26, 2009; Revised Manuscript Received April 26, 2009

ABSTRACT: Cyclization of long polymer chains is difficult because polymer chain ends have a low probability to contact one another and intramolecular cyclization has to compete with interchain coupling. To minimize intermolecular coupling, macrocycles are prepared traditionally under high dilution conditions, which limit the amount of polymer obtainable per volume of solvent. Reported in this paper is a new methodology for synthesizing polymer macrocycles. Instead of using polymers with one pair of reactive groups at the ends of a polymer chain, we use a block copolymer, poly[(2-cinnamoyloxyethyl methacrylate)-*ran*-(2-trifluoroacetoxyethyl methacrylate)]-*block*-poly(solketal methacrylate)-*block*-poly(*tert*-butyl acrylate)-*block*-poly(solketal methacrylate)-*block*-poly[(2-cinnamoyloxyethyl methacrylate)-*ran*-(2-trifluoroacetoxyethyl methacrylate)] or P(CEMA-*r*-TFAEMA)-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-P(CEMA-*r*-TFAEMA), with reactive P(CEMA-*r*-TFAEMA) end blocks to increase the efficiency of end coupling. In our method, a micellar solution is first prepared in a solvent selectively poor for the end CEMA units. This micellar solution is then slowly pumped into a solvent reservoir or reactor under constant stirring and irradiation. In the reactor, where the polymer concentration remains low throughout the preparation for its conversion into macrocycles, the micelles dissociate quickly into end-associated rings or unimolecular micelles, and the rings then get covalently linked photochemically. Since the TFAEMA units in the end blocks are soluble in the solvent used and probably segregate preferentially on the surface of the "balls" formed from the aggregation of the end CEMA units, they help deter the chemical coupling of different macrocycles. Using this methodology, we can prepare large macrocycles in high purity and at high concentrations.

I. Introduction

Polymer physicists have been fascinated by macrocyclic polymers for over half a century for their appealing topology and interesting properties.[1] The lack of chains ends has, for example, been predicted to lead to different chain dynamics in polymer melts and concentrated solutions.[2,3] Such an endless topology leads also to a reduced radius of gyration[1] and intrinsic viscosity[4] for macrocycles relative to their linear counterparts of the same molecular weight. Macrocycles have been of interest also for their biological relevance and the occurrence of cyclic DNA in nature.[5]

Macrocycles have been tantalizing the imagination of synthetic chemists for the immense challenges associated with the preparation of large uniform macrocycles in pure form and in large quantities.[6,7] Intuitively, the most convenient way to macrocycles is to prepare them in one step directly from polymerizing monomers. Condensation polymerization can, for example, be performed at high dilution to make cyclic polymers containing substantial linear chains unless unrealistically low monomer concentrations are used.[8−10] Using a cyclic metathesis catalyst, Grubb's group synthesized from cyclooctene of high-purity large macrocycles in large quantities.[11] The macrocycles prepared from the above approaches are, unfortunately, polydisperse. More importantly, we are unaware of catalysts capable of polymerizing common vinyl monomers such as styrenes and methacrylates into pure macrocycles.

Cyclic polymers can be prepared also from premade linear polymers with reactive end groups. Since such polymers can be fractionated before end cyclization to yield fractions with narrow molecular weight distributions, one can, in principle, obtain macrocycles with uniform sizes this way. The challenge here is to favor the intramolecular cyclization over intermolecular coupling. This is normally done by performing cyclization at high dilutions, which lead to much solvent waste and limit the amount of macrocycles obtainable per unit volume of solvent.[12] Another route to win this intramolecular vs intermolecular reaction competition is to make the intramolecular reaction more efficient. Assuming that the end cyclization is performed in a Θ solvent for a polymer chain with a root-mean-square end-to-end distance of R_n and the reaction volume, within which the end coupling reaction occurs effectively, is v_e, Jacobson and Stockmayer[8] derived that the probability at any given instant for finding chain ends to be within v_e and capable of reaction is

$$P_r = \left(\frac{3}{2\pi}\right)^3 \frac{v_e}{{R_n}^3} \quad (1)$$

Thus, one can increase the efficiency of end cyclization by increasing v_e using more robust reactions such as the click chemistry rather than the traditional less efficient esterification and amidization reactions.[12] This strategy has been demonstrated effective by researchers including Grayson and workers.[13] One can increase v_e also by using a pair of reactive end blocks rather than a pair of reactive end groups. Schappacher and Deffieux,[14] for example, prepared macrocycles from an ABC triblock copolymer using A and C end blocks containing more than one reactive group per block. Alternatively, one can decrease R_n to make the intramolecular reaction more efficient. Tezuka[15] and co-workers, for example, used electrostatic attraction to bring together the ends of oligomer chains to decrease R_n before a ring closure reaction.

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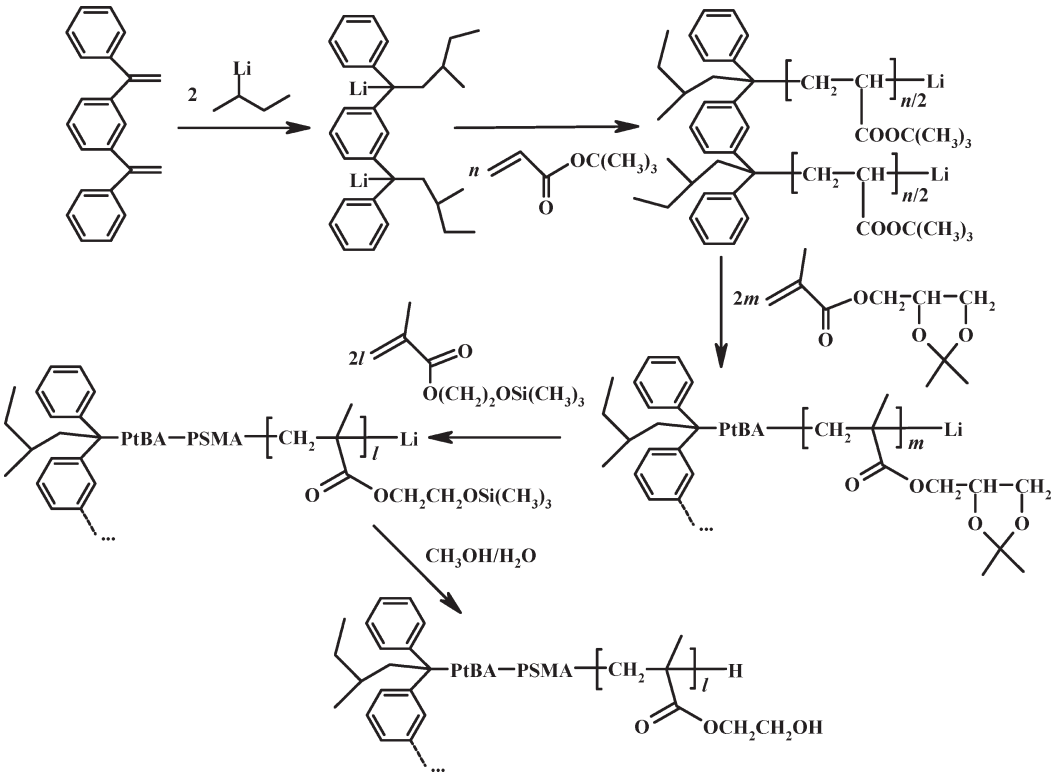
 Published on Web 05/21/2009

Scheme 1. Reactions Involved in the Preparation of PHEMA-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-PHEMA[a]



[a] Starting from line 2, only half of the polymer structure is shown for drawing convenience.

Intermediate between the monomer-direct (one-step) and polymer-first (two-step) syntheses is an approach recently reported by Jerome and co-workers.[16] They prepared macrocycles from the ring-opening polymerization of ε-caprolactone using a cyclic tin alkoxide as the initiator. At the end of polymerization, the ends of a macrocyclic poly(ε-caprolactone) chain were held together by the initiator, which was easy to hydrolyze to yield a linear polymer chain. To prepare permanent macrocycles, they incorporated two short α-(1-acryloxyethyl)-ε-caprolactone blocks between the ends of a poly(ε-caprolactone) chain and the catalyst. A coupling reaction was then performed on these preassociated end blocks.

Aside from the use of isolable polymer precursors in the polymer-first approach, polymers with highly reactive telechelic dianions from anionic polymerization have also been coupled by difunctional agents such as $(CH_3)_2SiCl_2$ to make macrocycles.[7,17−19] Since the anions could easily undergo side reactions with impurities under high dilution conditions, macrocycles prepared at moderate dilution contained large quantities of intermolecularly coupled products and dead linear chains among other impurities.

Reported in this paper is a new methodology for macrocycle preparation. Our methodology combines the advantageous features of the past methodologies and contains new features. As will be discussed in detail later, four separate effective strategies were proposed to attack various issues associated with successful macrocycle synthesis. Using our methodology, we have produced a cyclic block copolymer from a linear precursor with more than 1000 C−C bonds in high purity and at high polymer concentrations, e.g., up to 5 mg/mL. Since the linear precursor was prepared by anionic polymerization, we expected that the cycles had a uniform ring size distribution as well.

II. Experimental Section

PHEMA-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-PHEMA. 1,3-Bis(1-phenylvinyl)benzene, PEB, was prepared following a literature method.[20,21] PEB was reacted with *sec*-butyl lithium at a 1/2 molar ratio for 1.5 h in THF at −78 °C to produce dianions.[19] The dianions were then used to initiate the sequential polymerization of tBA,[22] SMA,[23,24] and HEMA-TMS[24,25] to yield P(HEMA-TMS)-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-P(HEMA-TMS), where P(HEMA-TMS) denotes poly(2-trimethylsiloxyethyl methacrylate). The polymerization time allowed for each monomer was 2 h. The final polymer concentration in THF was 5 wt %. The polymerization was terminated by adding degassed methanol. Stirring such a mixture in THF/methanol/water at volume ratios of 75/24/1 overnight led to the hydrolysis of the TMS protecting groups of P(HEMA-TMS) to yield PHEMA-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-PHEMA, where PHEMA denotes poly(2-hydroxyethyl methacrylate). The reactions for producing the final pentablock copolymer are depicted in Scheme 1.

P(CEMA-*r*-TFAEMA)-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-P(CEMA-*r*-TFAEMA) or P1. The preparation of this copolymer invoked partial cinnamation of the PHEMA blocks by cinnamoyl chloride first. The polymer was then reacted with excess trifluoroacetic anhydride (TFAA) before more cinnamoyl chloride was added. We started with a cinnmation step because the more efficient cinnamation reaction facilitated the better control of the degree of cinnmation *x*. We treated the resultant polymer with more cinnamoyl chloride after polymer reaction with TFAA to minimize the hydroxyl groups in the terminal blocks. The cinnamation reaction has been shown to be quantitative before.[25]

One specific preparation involved dissolving 1.001 g of PHEMA-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-PHEMA in 15 mL of dry pyridine first. To it under vigorous stirring was then added dropwise 0.1535 g of cinnamoyl chloride dissolved in 5 mL of dry pyridine. The reaction mixture was stirred for 15 h before it was cooled in an ice−water bath. To it was added dropwise 4.0 mL of TFAA. The mixture was stirred at room temperature for 10 h. This was followed by the addition of another 2.0 mL of TFAA and the stirring of the mixture for another 6 h. The TFAA addition and reaction procedure was repeated another two times. The reaction mixture was then precipitated in 150 mL

of ice-cooled methanol/water at v/v = 1/1. The precipitate was washed thrice with the above solvent mixture at 20 mL each time and dried under vacuum to yield 1.098 g of crude product.

The prepared polymer was again dissolved in 20 mL of dry pyridine before 0.20 g of cinnamoyl chloride was added, and the reaction mixture was further stirred overnight. The product was precipitated and purified following procedures described above to yield 1.011 g of product.

Macrocycle Preparation. Unless mentioned otherwise, macrocycles were prepared by pumping at 0.15 mL/min of a polymer solution into a solvent reservoir under constant stirring and irradiation. The chloroform (CF)/cyclohexane (CH) mixture used to prepare the polymer solution, and the solvent had the same cyclohexane volume fraction f_{CH}, which was typically 90%. The initial polymer solution and solvent volume used was each at 30 mL. The concentration of the initial polymer solution was 4.0 mg/mL, and that of the final mixture was 2.0 mg/mL. The amount of time required to pump the whole polymer solution into the reactor was ~200 min. To minimize solvent evaporation during photolysis, the reactor temperature was regulated to 20 °C. Also, the reactor and the pumping liquid formed a closed system. After photolysis, solid samples were obtained in quantitative yield after rota-evaporation of solvent.

The pump used for polymer solution addition was a MPP-100 variable flow minipump purchased from VWR. The focused irradiation beam used was from a 500 W mercury lamp in an Oriel 6140 lamp housing powered by an Oriel 6128 power supply. The beam was filtered by a 270 nm cutoff filter to remove short-wavelength light. To facilitate micelle dissociation after a P1 solution was pumped into the reactor, the tip of the polymer addition needle was wrapped by a piece of aluminum foil folded into a trumpet that was 1.5 cm long. The foil blocked the UV beam. Thus, the newly added sample got irradiated only after it had diffused away from the protection of the aluminum foil and into illuminated regions of the reactor. The reactor was cylindrically shaped and had a path length of 15.5 cm and a cross-sectional diameter of 3.4 cm.

CEMA double bond conversion was monitored by following CEMA absorbance decrease at 276 nm.[25] After polymer addition, we normally irradiated the whole sample for another 60 to 120 min to ensure a CEMA double bond conversion of ~40%. The only exception was a P1 sample irradiated at f_{CH} = 65%. After P1 was added, another 4 h irradiation led to only 8% of CEMA double bond conversion.

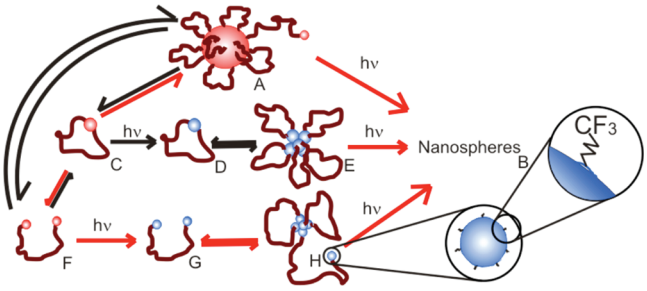
In one case, macrocycles were prepared at f_{CH} = 90% at a final polymer concentration of 5.0 mg/mL. In this case, the initial polymer solution concentration used was 10.0 mg/mL, and the polymer solution and solvent volumes were adjusted 20 mL to reduce polymer consumption.

Macrocycle Purification. To remove high-molecular-weight impurities, macrocycles were redissolved in THF at 10 mg/mL. Methanol/water at v/v = 1/1 was then added to induce cloudiness. The cloudy solution was then equilibrated in a fridge at 8 °C overnight before being centrifuged at 2600*g* for 20 min to settle down the insoluble part. The supernatant was rota-evaporated to remove solvent, and the solid was dried under vacuum.

Size Exclusion Chromatography. Size exclusion chromatograph analyses were performed on a system consisting a 1200 series Agilent isocratic pump, a Wyatt Wish-01 high-pressure injector equipped with a 20 μL loop, a Wyatt DAWN HELLOS-II multiangle laser light scattering or LS detector (658 nm, 120 mW), a Wyatt Optilab rEX refractometer (658 nm), or RI detector. The μ-Styragel columns used were Waters HT 5, HT 4, and 500 Å. The flow rate of eluant THF was 1.00 mL/min. All samples were analyzed at a comparable polymer concentration of 6−8 mg/mL.

Molecular Weight Determination. The weight-average molecular weight M_w of P1 and P1 macrocycles was determined in THF using the Wyatt DAWN HELLOS-II multiangle LS detector in batch mode. To determine the specific refractive index increments dn_r/dc, the refractive index differences Δn_r between a series of P1 or P2 solutions and solvent THF were measured by the Wyatt Optilab rEX refractometer. The Δn_r data were then plotted against polymer concentration c, and the dn_r/dc values were obtained from the slopes of such straight lines. Before LS measurements, the samples were clarified by pushing them through 0.1 μm Whatman poly(tetrafluoroethylene) syringe filters.

Scheme 2. Schematic of Possible Processes Occurring in an Irradiated System[a]



[a] The processes denoted by red arrows should be avoided for macrocycle formation. On the right are some structural details of the pompons from P(CEMA-*r*-TFAEMA). The TFAEMA units should segregate on the surface preferentially.

Viscosity Measurement. A Ubbelohde viscometer was used to measure at 25.0 ± 0.2 °C the flow times of P1 and P1 macrocycles in THF at different concentrations. Before flow time measurements all samples were clarified by filtration through 0.2 μm filters. The relative viscosity η_r was obtained from the ratio of the flow times of a solution and THF. The η_r data were analyzed using the Huggins equation

$$(\eta_r - 1)/c = [\eta] + k_h[\eta]^2 c \qquad (2)$$

to yield the intrinsic viscosity $[\eta]$ and the Huggins constant k_h.

III. Results and Discussion

Experimental Design. According to eq 1, the probability of end cyclization can be increased by increasing the reaction volume v_e of the end groups. We decided to achieve this following Jerome and co-workers[16] and Schappacher and Deffieux[14] using a pair of reactive end blocks rather than only one pair of end groups per linear polymer chain. In principle, we could have used an ABA triblock copolymer for this project. We used an ABCBA pentablock copolymer with photo-cross-linkable terminal A blocks because we wanted to show that this methodology could be used to prepare cyclic block copolymers[19,26] for self-assembly studies.[27,28]

We improved on the Schappacher and Deffieux methodology by performing the cyclization in selectively poor solvents for the end A blocks. In such solvents below the critical micelle concentration (cmc) of the polymer, unimer cycles (C of Scheme 2) formed due to the intramolecular aggregation of the end blocks. This helped decrease the root-mean-square end-to-end distance of the polymer chains.

Obviously, always in equilibrium with the unimer cycles were pompon−coil−pompon unimers or PCPs (F), which possessed end blocks existing presumably as individual pompons. The PCP structure was favored entropically. The driving force for unimer cycle formation from PCP was a reduction in the interfacial energy of the system when two end pompons of a PCP were fused into one in a macrocycle. Provided in the Supporting Information is an analysis on how variations in the end block size and the interfacial tension between the pompons and the solvent phase affect the system's free energy. The effect of variations in the end group association energy on

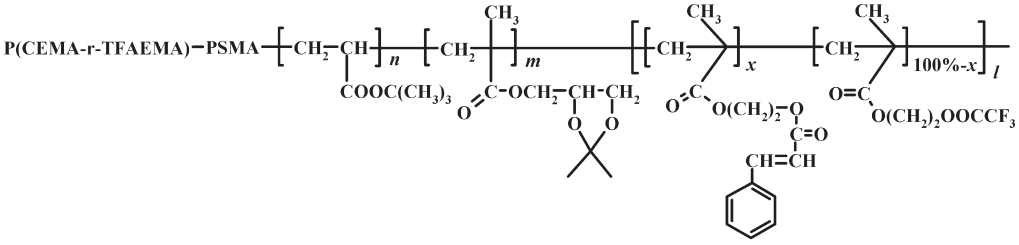
the end-to-end distance distribution function of a polymer chain has been discussed before.[29,30] We ensured that unimer cycles were the dominant species at low polymer concentrations by using a sufficiently poor solvent for the end blocks and using end blocks that were larger than necessary so that the interfacial energy reduction effect prevailed.

Above the cmc, also in equilibrium with the unimer cycles and PCPs were some spherical micelles (A), which were formed from the intermolecular aggregation of the insoluble end A blocks. In the micelles, most of the chains should assume a looped conformation with both end blocks stretching into the core. Occasionally, the entropically favored dangling conformation with one end block in the core and the other stretching into the solvent phase could also occur.[31] We mitigated the micelles by adopting a slow reactant addition strategy, which involved the slow pumping of a concentrated pentablock copolymer solution into a solvent reservoir under constant stirring and irradiation. Since the reactant was added slowly and reagent added before had been converted to macrocycles and other species, reactant concentration remained low throughout the preparation.

Through the channeling of materials from A to C and from F to C, we minimized the population of PCPs and spherical micelles and thus mitigated the photo-cross-linking of the spherical micelles (A→B) and the preparation of permanent PCPs (F→G). The low concentration of cross-linked PCPs in turn made the PCP micellization process (G→H) and micelle photo-cross-linking process (H→B) negligible. Photolysis of such a system should yield, therefore, predominantly macrocycles (C→D).

The macrocycles could still undergo micellization (D→E) as their population increased. The intercycle cross-linking would lead to the undesirable cross-linked micelles or nanospheres (E→B). We further improved on the Schappacher and Deffieux strategy by mitigating this process using A blocks that consisted of a random copolymer rather than a homopolymer. In such an A block, the photo-cross-linkable units were insoluble and segregated out from the solvent phase. The soluble units were inert and segregated presumably preferentially on the surface of the pompons formed by the insoluble part. They acted to prevent the direct contact of photoactive insoluble units in the pompons of different macrocycles and thus the chemical coupling of different pompons.

On the basis of these design considerations, the penta block copolymer or P1 that we used was poly[(2-cinnamoyloxyethyl methacrylate)-*ran*-(2-trifluoroacetoxyethyl methacrylate)]-*block*-poly(solketal methacrylate)-*block*-poly(*tert*-butyl acrylate)-*block*-poly(solketal methacrylate)-*block*-poly[(2-cinnamoyloxyethyl methacrylate)-*ran*-(2-trifluoroacetoxyethyl methacrylate)], P(CEMA-*r*-TFAEMA)-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-P(CEMA-*r*-TFAEMA) or P1. Since the precursor to this pentablock was prepared by anionic polymerization using a dianionic initiator, this polymer had a symmetric structure. Shown below is the polymer with the structures for the repetitive parts omitted.



P(CEMA-*r*-TFAEMA)-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-P(CEMA-*r*-TFAEMA)

The CEMA units were used as the photoreactive end groups because they could undergo photodimerization without the need for any additives.[25] Some TFAEMA units were introduced into the terminal blocks because they were photoinactive and were soluble in the chloroform (CF)/cyclohexane (CH) mixtures, which were used as the cyclization media.

A single brown curve, rather than three joint curves of two colors, was used to depict the PSMA-*b*-PtBA-*b*-PSMA part of each chain in Scheme 2 because the PtBA and PSMA blocks of P1 were all soluble under our experimental conditions and no special distinctive functions were performed by the individual blocks as far as macrocycle preparation was concerned. Aside from the processes depicted in Scheme 2, mixed micelles could also form from a mixture of macrocycles and unimer cycles, for example, and other processes might also occur. These processes were omitted for simplicity.

The two insoluble ends of a polymer chain have been depicted to fuse into a spherical structure in Scheme 2. This is expected in a sufficiently poor solvent for sufficiently large end blocks because spheres have the smallest area/volume ratio and thus the smallest interfacial energy. For the ability of the CEMA units to undergo both interblock and intrablock dimerization,[32,33] such a globular structure should be locked in and be retained even in a good solvent for the un-cross-linked end blocks if the CEMA double conversion is high and the end blocks are sufficiently long. The structure will definitely deviate from the globular structure if these conditions are not met.

Properties of the Polymers. The pentablock copolymer used was meticulously characterized by SEC, ^{1}H NMR, and LS. To obtain the $2l/2m/n$ value with a higher accuracy, we prepared PCEMA-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-PCMEA or P2 from the same PHEMA-*b*-PSMA-*b*-PtBA-*b*-PSMA-*b*-PHEMA precursor and analyzed this sample by ^{1}H NMR. Following peak analysis procedures reported before,[34] we determined $2l/2m/n$ = 1.0/1.1/2.7 (Table 1). The spectrum of P2 was then compared with that of P1 to yield a cinnamation degree x of 70%. The specific refractive index was determined to be 0.092 mL/g for P1. Using our SEC system equipped with both a LS and a RI detector, we obtained a polydispersity index M_w/M_n of 1.09 for this polymer.

In principle, we could have obtained the weight- and number-average molecular weights M_w and M_n for P1 from the SEC system in the online mode. We plotted the molecular weight M_w vs elution time t for P1 and discovered that log M_w did not decrease linearly with t. Rather, log M_w decreased initially with t, went through a minimum, and then increased with t. This suggested that P1 was fractionated not purely by molecular weight but also by chemical composition. For this, we determined M_w of P1 by the LS detector in the batch or off-line mode. This yielded $M_w = 1.13 \times 10^5$ g/mol.

Table 1. Molecular Characteristics of P1

NMR $2l/2m/n$	dn_r/dc (mL/g)	SEC-LS M_w/M_n	LS $10^{-5}M_n$ (g/mol)	l	m	n	x
1.0/1.1/2.7	0.092	1.09	1.13	70	75	375	70%

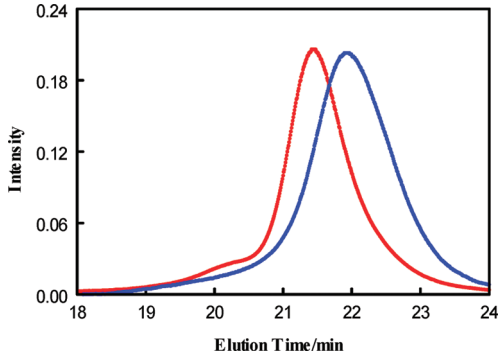


Figure 1. Comparison of SEC traces of P1 (red) and P1 irradiated at a final concentration of 2.0 mg/mL (blue).

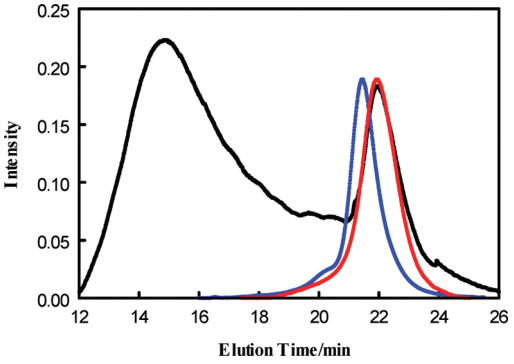


Figure 2. Comparison of SEC traces of P1 (blue) and irradiated P1 samples obtained using the slow reactant addition method (red) and the batch reactor protocol (dark).

Because of the nonlinear relationship between log M_w and t for P1, the M_w/M_n value should be in error. Thus, we calculated only the weight-average l, m, and n values using the LS M_w and NMR $2l/2m/n$ data. These were 70, 75, and 375, respectively.

Our optimization experiments indicated that macrocycles were prepared best in CF/CH at a CH volume fraction f_{CH} of 90%. To know the solubility of different species at this solvent composition, we checked by visual inspection the solubility of the following homopolymers $PSMA_{45}$, $PCEMA_{190}$, and $PTFAEMA_{190}$, where the subscripts denote the repeat unit numbers of the polymers. The results indicated that $PSMA_{45}$ and $PTFAEMA_{190}$ were soluble and $PCEMA_{190}$ were insoluble at $f_{CH} = 90\%$. Our prior results[35] suggest that PtBA should be soluble in this solvent mixture. Thus, our extrapolation was that the PtBA and PSMA blocks and the TFAEMA units of P1 were soluble and the CEMA units were insoluble at $f_{CH} = 90\%$. The conclusions were corroborated by our ^{1}H NMR analysis of P1 and P2 in a mixture of deuterated CF/CH at a deuterated CH volume fraction of 90% (Supporting Information).

We also performed dynamic light scattering analysis of P1 and P2 at different concentrations in CF/CH at $f_{CH} = 90\%$ and determined the critical micellar concentrations for them. They were 0.041 and 0.025 mg/mL for P1 and P2, respectively (Supporting Information).

Macrocycle Formation. Macrocycles were produced by irradiating under constant stirring a CF/CH solvent reservoir, into which was pumped slowly a P1 solution. Figure 1 compares the SEC RI traces of P1 and P1 irradiated at a final concentration of 2.0 mg/mL. The RI traces were compared because the RI signal intensity was directly proportional to the amount of materials present.

We notice the following features about the data. First, the peak maximum of the irradiated sample was shifted by ~0.5 min to the low-molecular-weight side. Second, no cross-linked micellar peak was observed for the irradiated sample despite the fact that the final polymer concentration was 2.0 mg/mL, which was 49 times the cmc value of 0.041 mg/mL for P1. More interestingly, the irradiated sample had a shoulder even smaller than the precursor P1 on the high-molecular-weight side.

The SEC peak shifted to the low-molecular-weight side because macrocycles or cross-linked PCPs were prepared. The sample should have consisted mostly of macrocycles because the peak shift was significant. Quantitatively, the peak molecular weights, based on polystyrene standards, of P1 and the irradiated sample were 6.9×10^4 and 5.2×10^4 Da, respectively. Thus, a 25% reduction in the apparent molecular weight was observed for the irradiated sample. This reduction is comparable to those reported for PS macrocycles with a comparable molecular weight.[7,17]

One can also calculate the volume compaction of the irradiated sample relative to P1. According to theories of SEC universal calibration,[36] polymers of different families with the same retention time possess the same hydrodynamic volume. The hydrodynamic volume V_P of a monodisperse PS sample with molecular weight M_P is

$$V_P = \frac{[\eta]_P M_P}{2.5} \tag{3}$$

where $[\eta]_P$ is the intrinsic viscosity of the hypothetic monodisperse sample. For PS in THF, the SEC eluant, $[\eta]_P$, can be calculated using[37]

$$[\eta]_P = 1.10 \times 10^{-2} M_P^{0.725} \text{ mL/g} \tag{4}$$

The combined use of eqs 3 and 4 and the PS-equivalent peak molecular weights M_P yielded a volume reduction of 39% for the irradiated sample relative to P1. This volume collapse was large and could not have been achieved by cross-linked PCPs because of the relatively short end blocks. This thus again suggests formation of macrocycles as the major product. This claim will be unambiguously proven later when the intrinsic viscosities of the macrocycles and P1 in THF are compared.

Efficacy of the Slow Reactant Addition Strategy. Figure 2 compares the SEC traces of P1 and two irradiated P1 samples. Of the irradiated samples, one was irradiated using the slow pumping protocol as described above. The other was irradiated using the static reactor design, meaning that a solution at 2.0 mg/mL was irradiated directly. For both samples, the final P1 concentration was the same at 2.0 mg/mL. When P1 was added slowly, only a macrocycle peak was observed. Using the static reactor design, the sample exhibited an intense broad cross-linked micelle peak and a macrocycle peak. The results demonstrate the superb robustness of the slow reagent addition protocol and our successful channeling of materials from A of Scheme 1 to C.

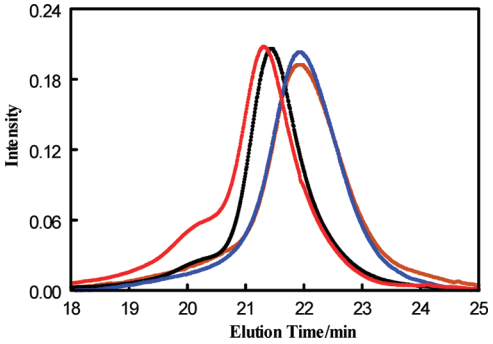


Figure 3. Comparison of SEC traces of P1 (black) and P1 irradiated at f_{CH} = 65% (red), 80% (brown), and 90% (blue).

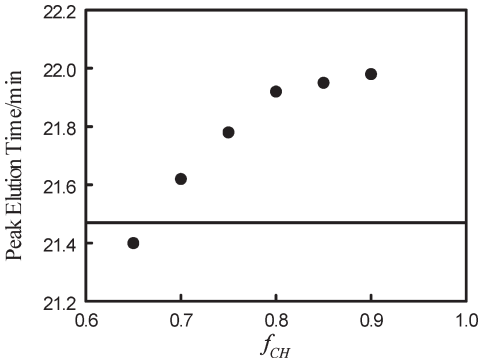


Figure 4. Variation of peak elution time with f_{CH} for P1 samples irradiated at different f_{CH}.

The slow reagent addition strategy is not new. It was first used by Roovers and Toporowski[17] for the preparation of macrocycles from the coupling of the terminal dianions of polystyrene by $Si(CH_3)_2Cl_2$. This strategy has been more recently used by Hawkers and co-workers[38] as well as by Liu and co-workers[39] for the preparation of tadpole molecules, which are diblock copolymers consisting of a cross-linked globular block and a coil block. This strategy has been used to advantage also by Grayson and co-workers[13] in preparing macrocycles. Most recently, an ingenious variation of this slow reagent addition strategy was demonstrated by Ge et al.[40] There the one pair of reactive end groups of the diblock copolymer chains were segregated into the core and corona of micelles and were prevented from reaction. In the unimer form, the polymer chain ends could contact one another and underwent cyclization by click chemistry. The conversion of the unimers into macrocycles decreased the unimer concentration and prompted the dissociation of micelles, which served as a reservoir for unreactive polymers, to maintain the unimer and micelle equilibrium. The reagent was "added" slowly in this case because the rate of polymer chain dissociation from micelles synchronized with that of unimer chain cyclization.

Efficacy of the End Preassociation Strategy. Figure 3 compares SEC traces of P1 and P1 irradiated using the slow P1 addition protocol at different f_{CH}'s. P1 irradiated at f_{CH} = 65% has the largest shoulder on the high-molecular-weight side. The shoulder size decreased from f_{CH} = 65% to 80% and 90%. Also, the peak elution time increased in the same order from 21.40 min to 21.92 and 21.98 min for the irradiated samples.

A more thorough study yielded data of Figure 4, which plots the variation in the SEC peak elution time of irradiated P1 samples as a function of f_{CH}. Also shown in the figure is a straight line indicating the peak elution time of 21.47 min for

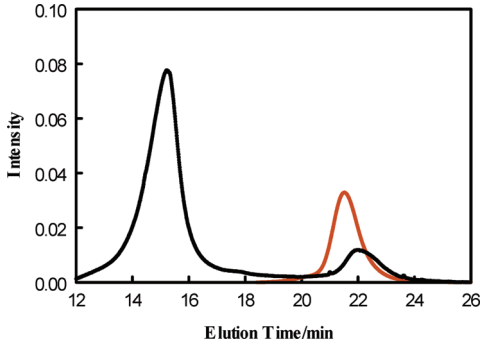


Figure 5. Comparison of SEC traces of P2 (brown) and P2 irradiated at f_{CH} = 90% (black).

P1. The figure shows that only the sample irradiated at f_{CH} = 65% had a peak elution time shorter than 21.47 min. The peak elution time of the other samples increased steeply with f_{CH} initially. Above f_{CH} = 80%, the slope of increase decreased substantially.

A logical explanation for the observed peak elution time variation trend for samples with $f_{CH} \geq 70\%$ is that these samples consisted of a mixture of macrocyles and cross-linked PCPs. As the content of the more compact macrocycles increased with increasing f_{CH}, the peak elution time increased. Above a critical f_{CH} value of ~80%, macrocycles became dominant and thus the macrocycle fraction barely increased with f_{CH}.

The sample irradiated at f_{CH} = 65% behaved uniquely because the P(CEMA-*r*-TFAEMA) blocks were soluble and had not collapsed yet at this solvent composition. An open end block structure facilitated intermoelcular coupling, yielding high molecular weight species responsible for the larger shoulder on the high-molecular-weight side. A mixture of intermolecularly coupled impurities and P1 made the SEC peak to appear lower than 21.47 min.

The open P(CEMA-*r*-TFAEMA) structure also explained why the CEMA units were difficult to cross-link at f_{CH} = 65%. The CEMA double bond conversion was only 8% for this sample despite a longer irradiation time used. For the samples at f_{CH} = 80% and 90%, lower radiation dosages led to CEMA double bond conversions of 38% and 42%, respectively. CEMA dimerization occurred more efficiently at higher CEMA concentrations such as in pompons of Figure 1 because the prerequisite for the reaction was the alignment of the double bonds of two CEMA units within 0.4 nm in the CEMA triplet lifetime.[41]

We could have used such an inefficient reaction for end cyclization because we increased the reaction volume v_e by using reactive end blocks rather than only a pair of end groups and we decreased R_n by end preassociation. Evidently, the F→C process of Scheme 1 became more favorable as f_{CH} and thus the interfacial tension between CEMA and the solvent phase increased in the examined f_{CH} range.

Mitigation of Intermacrocycle Cross-Linking. P1 with P(CEMA-*r*-TFAEMA) end blocks has been shown to undergo controlled cyclization to yield macrocycles in high purity. Figure 5 compares the SEC traces of P2 and P2 irradiated using the slow reagent addition protocol at f_{CH} = 90%. Despite the identical conditions used for P1 macrocycle preparation, this polymer with PCEMA homopolymer terminal blocks yielded a mixture of macrocycles and nanospheres. We further observed that the macrocycle peak eventually disappeared completely after this sample was irradiated for 6 h rather than 2 h after P2 was completely pumped in. This was in blatant contrast to the P1 behavior. Using P1, a negligible SEC peak shape change was observed

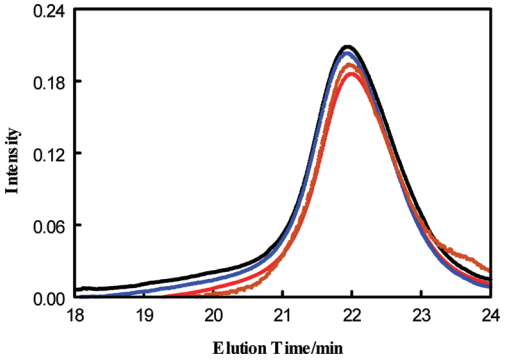


Figure 6. Comparison of SEC traces of P1 macrocycle samples prepared at a final P1 concentration of 2.0 (blue) and 5.0 mg/mL (black). Also shown for comparison are the SEC traces of the sample prepared at 5.0 mg/mL after purification by SEC fractionation (brown) and fractionation precipitation (red).

after further sample irradiation. These data suggest the extreme robustness of our strategy in mitigating process E→B of Scheme 1 using random rather than homopolymer end blocks.

Robustness of Our Methodology. Figure 6 compares SEC traces of P1 and P1 irradiated at $f_{CH} = 90\%$ at the final P1 concentrations of 2.0 and 5.0 mg/mL, respectively. We did not perform macrocycle preparation at higher concentrations for lack of more sample. Even at 5.0 mg/mL, no cross-linked micelle peak was seen. Also, the shoulder at the high-molecular-weight side was expanded only slightly relative to that of the sample prepared at a final concentration of 2.0 mg/mL.

As seen in Figure 1, the macrocycle sample prepared at 2.0 mg had a smaller high-molecular-weight shoulder than its precursor P1. Thus, that sample contained a negligible amount of high-molecular-weight impurities. The SEC trace of the sample prepared at 5.0 mg/mL leveled off or reached baseline on the high-molecular-weight side at 17.2 min. Ratioing the area sandwiched by the black and blue SEC traces of Figure 6 between 17.2 and 21 min over the total area under the black SEC trace, we estimated that the high-molecular-weight impurities should be less than 4% for the sample prepared at 5.0 mg/mL. Thus, the SEC yield of the macrocycles should be 96%. This is in stark contrast to the SEC yield of ~30% for a sample prepared from the coupling of polystyryl dianions with 300 styrene units by 1,4-(bisbromomethyl)benzene[7] or a SEC yield of 23% in coupling polystyryl dianions with 860 styrene units by dimethyldichlorosilane.[17] For the preparation at a final P1 concentration of 5.0 mg/mL, 20 mL of P1 solution at 10.0 mg/mL was pumped at 0.15 mL/min into 20 mL of solvent. The total irradiation time used was 4 h. This thus allowed the production of 200 mg of macrocycles in only 40 mL of solvent in a mere 4 h! This is again in contrast to 3 days spent to achieve the coupling of polymer dianions.[19]

The high-molecular-weight impurities could be removed by fractionation precipitation. Also shown in Figure 6 was the SEC trace for the sample prepared at 5.0 mg/mL and then purified by fractionation precipitation with a final yield of 40%. While the efficacy of the purification method was obvious, sample loss was unfortunately heavy. We also purified a portion of this sample by SEC collecting the fraction between the retention times of 20 and 24 min. The SEC trace was also shown in Figure 6 for comparison. Again, the high-molecular-weight impurities were effectively removed. Unfortunately, this sample contained a small shoulder at the low-molecular-weight side. Since the HT 5 column used in this fractionation failed shortly after this task, our suspicion is that the small-molecular-weight impurity was leached out from the polystyrene column packing material. In this case, the final polymer yield including this small amount of low-molecular-weight impurity was 88%.

Table 2. Comparison of Properties of P1 and P1 Macrocycles

sample	dn_r/dc (mL/g)	$10^{-5}M_w$ (g/mol)	$[\eta]$ (mL/g)	k_h
P1	0.091	1.13	29.3	0.33
cyclic P1	0.081	1.17	18.8	0.31

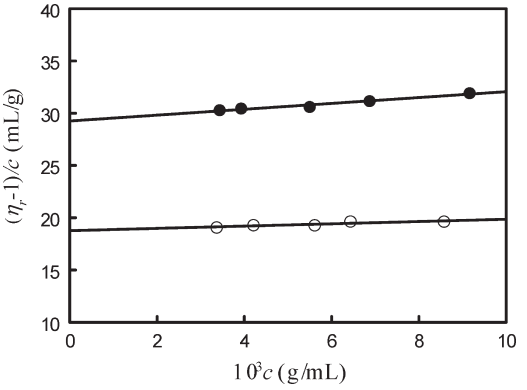


Figure 7. Plot of $(\eta_r - 1)/c$ vs c for P1 (●) and P1 macrocycles (○).

Despite the positive attributes of our methodology, we should point out that the macrocycles from our method are structurally different from the traditional macrocycles, which are sealed by one molecular unit rather than a pompon. As far as applications are concerned, this structural difference may be of no consequence if the length of the end blocks can be reduced below 20 units. We did not minimize the end block size but used end blocks which were larger than necessary because the main objective of this paper was for concept demonstration. As mentioned in the Supporting Information, one can ensure unimer cycle rather than PCP formation not only by increasing the end block size but also by increasing the interfacial tension γ between the insoluble part of the pompons and the solvent phase. Root-mean-square end-to-end distances R_n of hydrophilic polymers have, for example, been shown to decrease in water substantially by only one pair of interacting hydrophobic end groups.[42,43] This occurred most likely for the high γ value between the hydrophobes and water.

One may also be concerned with the residual CEMA units in the macrocycles. They should not be problematic for two reasons. First, we have been working with PCEMA-containing block copolymers since 1995 and have established that these polymers can be stored as solid in amber-colored bottles for years without cross-linking. Second, the TFAEMA units in the macrocycles are most likely to segregate onto the surface of balls of the macrocycles. This should further help deter intercycle fusion.

Properties of the Macrocycles. The sample purified by SEC fractionation as described above was used for molecular weight determination by LS. Using $dn_r/dc = 0.081$ mL/g determined experimentally, we obtained $M_w = 1.17 \times 10^5$ g/mol for the macrocycles (Table 2). This value was in close agreement with $M_w = 1.13 \times 10^5$ g/mol for P1. This result verified thus unambiguously that a molecular configuration change was responsible for the SEC peak position shift between P1 and irradiated P1.

The sample purified by fractionation precipitation was used for viscosity measurements in THF at 25 °C. Figure 7 plots the viscosity data of this sample and that of P1. From the slopes and intercepts of the straight lines and using eq 2,

we obtained the intrinsic viscosities [η] and Huggins constants for the samples with results shown in Table 2. The ratio between the intrinsic viscosities of P1 and P1 macrocycles was 0.64.

Theoretically, the intrinsic viscosity ratio should be 0.66,[4] which is in good agreement with the observed value of 0.64. This again confirmed the preparation of macrocycles by us. The slightly smaller ratio could be due to the structural difference between our macrocycles and the traditional macrocyles or probably due to the fact that we had overdone the fractionation and removed some high-molecular-weight macrocycles during the sample purification process. A comparison of the SEC traces in Figures 1 and 6 revealed that the linear precursor P1 had species with retention time shorter than 19.3 min. On the other hand, the macrocycle sample was free of species shorter than this retention time. Smaller intrinsic viscosity ratios have been reported by others before,[18,44,45] and overfractionation has been cited as the cause for the smaller ratios.

IV. Conclusions

A new methodology has been proposed for the preparation of polymer macrocycles. The key features of this method included the use of reactive end blocks rather than only one pair of reactive end groups for end cyclization, the performance of the cyclization in a selectively poor solvent for the reactive end blocks, the slow addition of the linear precursors into the reaction flask, and the use of end blocks consisting of a random copolymer rather than a homopolymer. The reactive end blocks with many reactive groups in each block were used mainly to increase the chances of end cyclization. The cyclization was done in a poor solvent for the end blocks so that they would aggregate under high dilution conditions to decrease the interfacial energy between the precipitated part of the end blocks and the solvent phase. Reactant was added into the reactor slowly mainly to maintain a consistently low concentration for the linear precursor. End blocks consisting of random copolymers rather than homopolymers were used so that the soluble inert part of the random copolymer could segregate on the surface of a pompon formed by aggregated and then chemically linked end blocks. Such groups prevented the direct contact of the insoluble reactive functional groups of different pompoms. Using all the strategies of this methodology and a pentablock copolymer that was tailor-made and characterized, we prepared macrocycles from a photochemical reaction that would have never been used for its low efficiency in the solution phase. The macrocycles were prepared in high purity and at high final macrocycle concentrations. The macrocycles were large consisting of 520 monomer units excluding the end blocks. The macrocycles should have been quite uniform in size because of the low polydispersity of their linear precursor. The effectiveness of the various strategies proposed for our methodology was demonstrated, and the properties of the macrocycles were studied.

Acknowledgment. NSERC of Canada is thanked for sponsoring this research. The Outstanding Overseas Chinese Scholar Funds of the Chinese Academy of Sciences is thanked for covering J.W.H.'s travel expenses.

Supporting Information Available: Some experimental details and a theoretical analysis of the free energy reduction associated with unimer cycle formation from pompon−coil−pompon monomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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