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Modular Construction of Macrocycle-based Topological Polymers *via* High-Efficient Thiol Chemistry†

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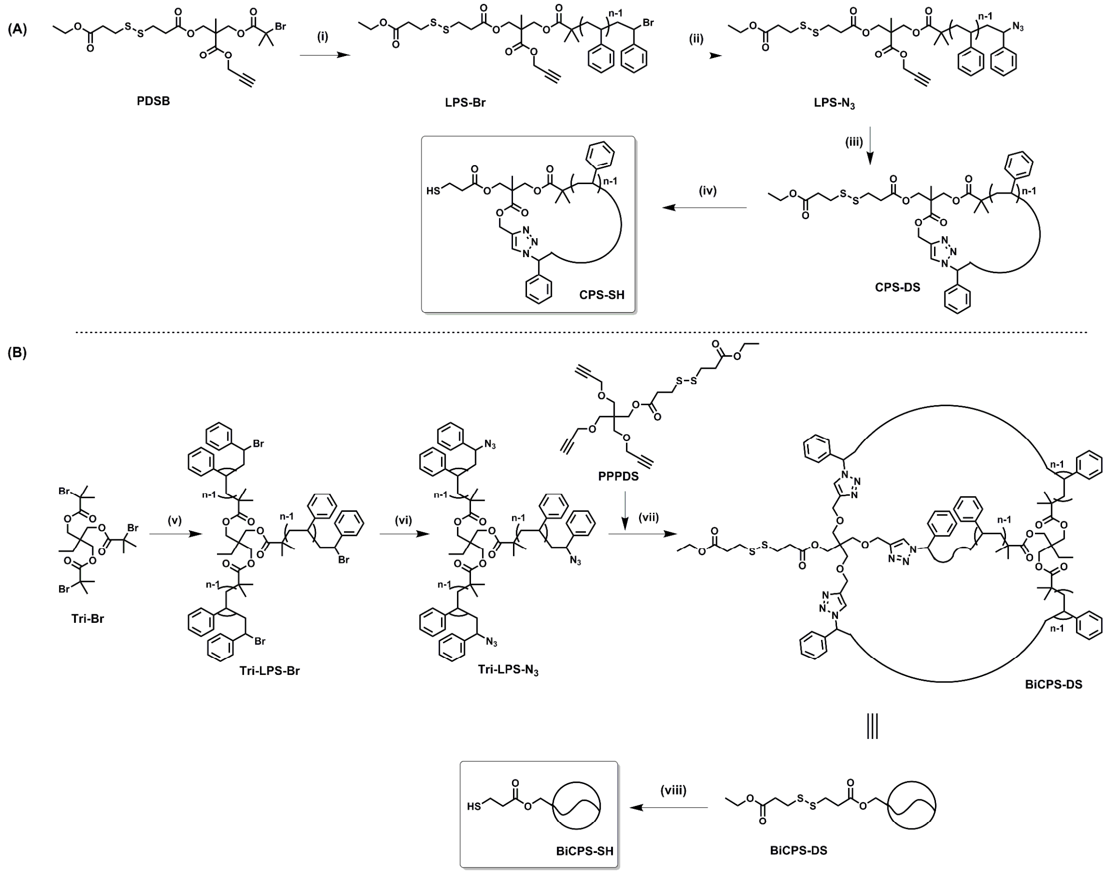
Modular and precise constructions of topological polymers with structural complexity is a prerequisite to understand the structure-property relationships of functional non-linear macromolecules. In this article, several examples of well-defined topological polymers are prepared by using two kinds of functionalized cyclic polymeric precursors via different high-efficient thiol-related chemistries. Firstly, multifunctional ATRP initiators bearing alkyne and disulfide groups were elaborately prepared. Well-defined thiol-containing monocyclic and fused-bicyclic polymers via atom transfer radical polymerization (ATRP) and Cu-catalyzed azide-alkyne cycloaddition (CuAAC) ring closure were then synthesized. Finally, by utilization of thiol-containing monocyclic or fused-dicyclic polymers as building blocks, several kinds of macromolecules with tadpole-, spiro-shaped, fused-dicyclic tadpole and other topologies were successfully constructed via a modular mode. This study expands the scope of available macrocycle-based topological polymers and facilitates further diverse development of even more complex non-linear macromolecules *via* modular synthetic methodology.

Introduction

Natural polymers generated by sophisticatedly biological mechanisms, such as DNA, proteins and peptides, are known to possess precisely controlled structures, enabling these polymers with accurate and unique functions[1]. For the synthetic polymers, in order to obtain predicable properties, the precision synthesis of polymers with well-controlled architecture is a prerequisite. Many chemists start to learn from nature for seeking efficient synthetic methodology to prepare polymers with precisely controlled architectures. Modular synthesis from prefabricated building blocks, an important lesson from nature, has been employed for the synthesis of artificial proteins[2], bioconjugate polymers[3], and various synthetic macromolecules with well-defined topologies[3b, 4]. Among diverse of well-defined topological synthetic polymers, cyclic polymer[5] without chain terminals, usually displays unique physical properties including a smaller hydrodynamic volume, less chain entanglement, higher glass transition temperature, unique thermal phase transition as well as a different diffusion mode[6,7]. Moreover, due to the topological effects, functional cyclic polymers usually show more interesting functions with respect to their linear precursors.[8] For example, cyclic poly((2-dimethylamino) ethylmethacrylate) was found to be less cytotoxicity and could self-assembly into more compact particles when complexed with plasmid DNA[9]. Cyclic poly(caprolactone)s exhibit a delay in the molecular weight loss during acid-catalyzed degradation as compared to their linear analogs[10]. Inspired by these interesting results, the construction of more complex topological polymers based on macrocycles might bring unexpected macromolecular properties and functions. People have made tremendous efforts on this, and many exquisite such polymers have been fabricated based on high-efficient chemical reactions, such as "click" chemistry[11]. "Click" chemistry like Cu-catalyzed azide-alkyne cycloaddition (CuAAC) reaction[12] offers a toolbox for synthesizing many multi-component cyclic polymers with complicated architectures, such as β-graph, γ-graph, δ-graph[13], θ-shape (fused-) polymers[14]. Spiro- and bridged-polymers[11a, 15] have also been constructed *via* combination of CuAAC with electrostatic self-assembly and covalent fixation. Tadpole-shaped[16], sun-shaped[17], and bicyclic polymers[18], tricyclic polymers or more[11b, 19] were also fabricated from tandem atom transfer radical polymerization (ATRP) and CuAAC. In addition, polymers with dumbbell-shaped and pinwheel-shaped topologies were reported *via* reversible addition-fragmentation chain transfer (RAFT) polymerization and CuAAC[20]. For the development of cyclic-based topological polymers, CuAAC "click" reaction is usually utilized for both ring closure reaction to afford monocyclic polymer and chemical connections between monocyclic polymer chain and another motifis[11b, 16, 20-21]. In order to build up diverse macrocycle-based topological polymers, chemical connections between monocyclic polymer chain and another polymer chain are very critical due to the demanding for high designability of polymer topologies, small amount of available monocyclic polymers and low efficiency of polymeric reactions[11b]. Besides CuAAC, thiol-X "click" chemistry, as another important member of "click" chemistry toolbox, has also provided an alternative and effective tool for polymer synthesis[4c, 22] and functional materials functionalization[23] under mild conditions.[24] Notably, the thiol-X "click" chemistry involves various chemical reactions, including radical-induced thiol-ene addition, thiol-yne addition, and nucleophilic-based reactions (*i.e.*, thiol-epoxy ring opening reaction, thiol-isocyanate reaction, thiol-halogen substitution and thiol-Michael addition[22c]). Especially, the thiol-Michael addition has been widely used for the polymer synthesis and modifications due to its modular nature, highly efficient process, and "green" catalyst.[23a, 25] Moreover, reversible formation of disulfide and thiol under oxidation-reduction atmosphere is another kind of fascinated and useful approaches for many interesting applications.[26] Thiol group is also known for its strong bonding with gold, and the sulfur-gold bond has been popularly used for manufacturing functional materials/devices[27]. Therefore, the thiol-funtionalized cyclic polymer is an ideal and versatile building block for the facile and efficient synthesis of macrocycle-based topological polymers in a modular manner, which is expected to enrich the topological constructions of cyclic polymers, and endow uncommon significance for further studies and applications.

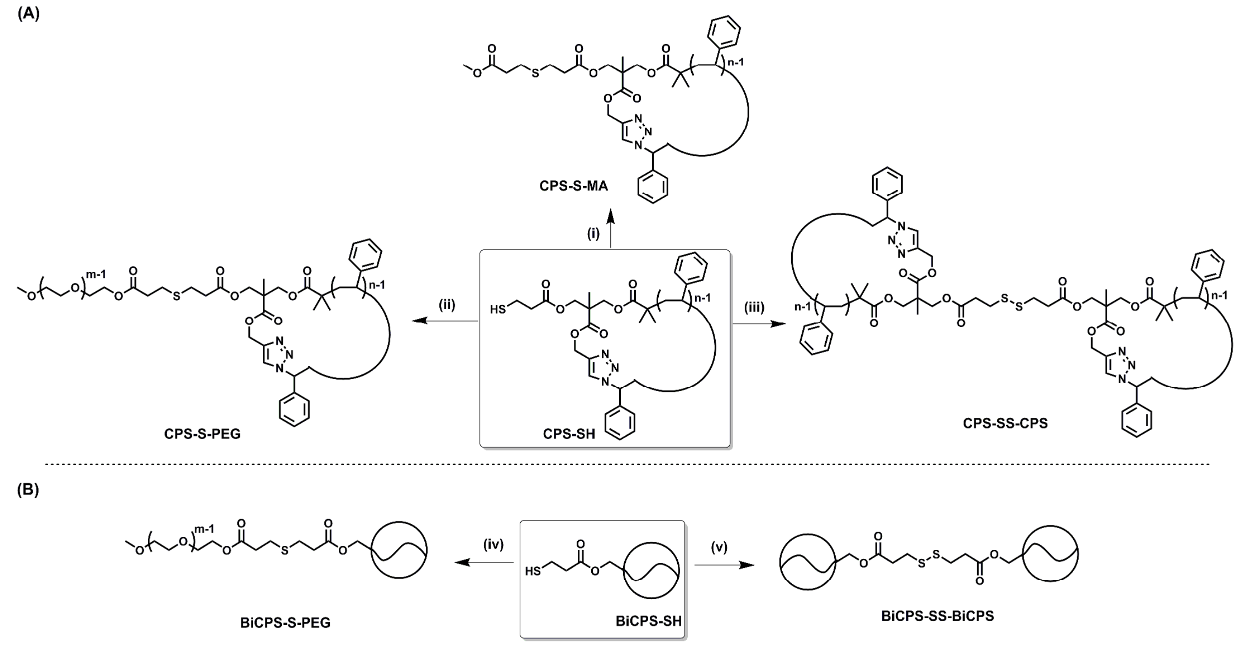
Herein, several examples of modular synthesis of macrocycle-based topological polymers with thiol-containing cyclic polymer as building block are illustrated. Firstly, novel multifunctional ATRP initiators with alkyne and disulfide moieties were elaborately designed and used for ATRP. After facile substitution of chain end halogen by azide group, well-defined monocyclic and fused-bicyclic polymers *via* CuAAC ring closure were then synthesized. Finally, tadpole-, spiro-shaped, fused-dicyclic tadpole and other topological polymers from the thiol-monocyclic and fused-bicyclic polymers as building blocks were successfully constructed and fully characterized. The general synthetic routes are illustrated in **Schemes** 1&2.

Scheme 1. Synthetic Routes for the Thiol-functionalized Macrocycle Building Blocks *via* ATRP and CuAAC[a]



[a] Reaction conditions: (i) St, CuBr$_2$, AsAc, PMDETA, toluene, 75 °C, 27%; (ii) NaN$_3$, DMF, 25 °C, 89%; (iii) CuBr, PMDETA, toluene, 60 °C, 70%; (iv) Zn, HOAc, THF, 40°C, 87%; (v) St, CuBr$_2$, AsAc, PMDETA, toluene, 110°C, 34%; (vi) NaN$_3$, DMF, 25 °C, 90%; (vii) PPPDS, CuBr, PMDETA, toluene, 60 °C, 65%; (viii) Zn, HOAc, THF, 40°C, 86%.

Scheme 2. Synthetic Routes for Constructing Macrocycle-based Topological Polymers from Building Blocks *via* Thiol Chemistry[b]



[b] Reaction conditions. (i) MA, DBU, THF, 30°C, 80%; (ii) mPEG-AA, DBU, THF, 30°C, 83%; (iii) $FeCl_3$, DMF, 60°C, 80%; (iv) mPEG-AA, DBU, THF, 30°C, 80%; (v) $FeCl_3$, DMF, 60°C, 81%.

Experimental section

Chemicals and Solvents. Styrene (St, Sinopharm Chemical Reagent, China, 99%), methyl acrylate (MA, ≥ 98.5%) were purified by distillation from calcium hydride under reduced pressure prior to use. Cuprous bromide (CuBr, Aldrich, 98%) was freshly purified by stirring in acetic acid overnight, washed with acetone, and dried in vacuum. *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA, Energy Chemical, 99%), sodium azide (NaN_3, Sigma-Aldrich, ≥ 99.5%), Zinc powder (Zn, Aladdin Co., 99.99%), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, TCI, > 98%), poly(ethylene glycol) methyl ether acrylate (mPEG-AA, Sigma-Aldrich, average $M_n = 480$) were used as received. *N, N'*-Dicyclo-hexylcarbodimide (DCC, 99%), 4-dimethylaminopyridine (DMAP, > 99%), copper(II) bromide ($CuBr_2$, 98.5%), ascorbic acid (AsAc, 99.9%), acetic acid (HOAc, > 99.5%), iron(III) chloride anhydrous ($FeCl_3$, > 97.0%), tetrahydrofuran (THF), *N, N*-dimethylformamide (DMF), toluene, hexane, ethanol, methol and all other chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd. without any further purification.

Characterization. The number-average molecular weight (M_n) and polydispersity ($Đ = M_w/M_n$) of the polymers were determined by a TOSOH HLC-8320 size exclusion chromatography (SEC) equipped with refractive-index and UV detectors using two TSKgel Super Mutipore HZ-N (4.6×150 mm, 3 µm beads size) columns arranged in series, and it can separate polymers in the molecular weight range from 500 ~ 1.9×10^5 g/mol. THF was used as the eluent at a flow rate of 0.35 mL/min at 40 °C. Data acquisition was performed using EcoSEC software, and molecular weights were calculated with polystyrene (PS) standards.

In order to purify the crude polymers, an Agilent PL-50 preparative SEC system equipped with a manual injector and differential refractive index detector was used. Flow rate was maintained at 3 mL/min and THF was used as the eluent. Separations were achieved using a PLgel 10 µm MIXED-D, 300×25 mm preparative SEC column held at 40 °C. The dried crude polymer was dissolved in THF at 15-20 mg/mL concentration and filtered through a 0.45 µm PTFE syringe filter prior to inject. Different fractions were collected manually, and the composition of each was determined using the TOSOH HLC-8320 SEC equipped with refractive-index and UV detectors as described above.

Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectra were acquired on a UltrafleXtreme MALDI TOF mass spectrometer equipped with a 1 kHz smart beam-II laser. The instrument was calibrated prior to each measurement with external PMMA at the molecular weight under consideration. The compound trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]-malononitrile (DCTB, Aldrich, > 98 %) served as matrix and was prepared in $CHCl_3$ at a concentration of 20 mg/mL. The cationizing agent sodium trifluoroacetate was prepared in ethanol at a concentration of 10 mg/mL. The matrix and cationizing salt solutions were mixed in a ratio of 10/1 (v/v). All samples were dissolved in THF at a concentration of 10 mg/mL. After sample preparation and solvent evaporation, the plate was inserted into the MALDI mass spectrometer. The attenuation of the laser was adjusted to minimize undesired polymer fragmentation and to maximize the sensitivity.

All ^{1}H NMR, ^{13}C NMR spectra were collected using a Bruker nuclear magnetic resonance instrument (300-MHz) using tetramethylsilane (TMS) as the internal standard at room temperature, NMR samples were prepared with concentration of 10-20 mg/mL in $CDCl_3$ or DMSO-d_6 for ^{1}H NMR or 80-100 mg/mL for ^{13}C NMR. The ^{1}H NMR spectra were referenced to δ 7.26 ppm in $CDCl_3$ or δ 2.50 ppm in DMSO-d_6, and ^{13}C NMR spectra were referenced to δ 77.00 ppm in $CDCl_3$.

Infrared spectra were obtained on a Bruker TENSOR-27 FT-IR spectrometer by mixing polymer with KBr (10 mg/g) as tablets.

Synthetic Procedures.

Linear polystyrene with bromine at the end (LPS-Br). $CuBr_2$ (97.2 mg, 0.435 mmol), AsAc (153.1 mg, 0.870 mmol), freshly distilled St (10 mL, 87.0 mmol) and toluene (15 mL) were added into a 50 mL Schlenk flask. The mixture was degassed using three freeze/pump/thaw cycles, followed by adding initiator prop-2-yn-1-yl 3-((2-bromo-2-methylpropanoyl)oxy)-2-(((3-((3-ethoxy-3-oxopropyl)disulfanyl)propanoyl)oxy)methyl)-2-methylpropanoate **(PDSB)** (469.8 mg, 0.870 mmol) and PMDETA (96.4 mg, 0.557 mmol) under argon protection. After one further freeze/pump/thaw cycle, the reaction mixture was placed in a preheated 75 °C oil bath and allowed to stir under argon for seven hours. The crude mixture was then cooled to room temperature, diluted with THF and transferred onto a short neutral alumina column to remove copper salts, after the solvent was removed, the concentrated product was precipitated from an excess of methanol twice, collected by vacuum filtration, and dried *in vacuo* at 25 °C to afford the product as a white powder (2.44 g; Conversion: 27%). $M_{n,NMR}$ = 4000 g/mol. SEC results: $M_{n,SEC}$ = 3900 g/mol, $M_{w,SEC}$ = 4430 g/mol, ***Đ*** = 1.13.

LPS-N$_3$. A 25 mL round bottomed flask was filled with **LPS-Br** (1.80 g, 0.45 mmol), NaN_3 (0.58 g, 9.0 mmol), and DMF (12 mL). The solution was allowed to stir at room temperature for 24 h, collected by filtration to remove residual sodium salts before purification by precipitation into methanol and followed by filtrating and drying *in vacuo* at 25 °C to give a white solid (1.6 g; Yield: 89%). $M_{n,NMR}$ = 4000 g/mol. SEC results: $M_{n,SEC}$ = 4090 g/mol, $M_{w,SEC}$ = 4610 g/mol, ***Đ*** = 1.13.

Cyclic polystyrene with disulfide bond in the side chain (CPS-DS). In a 1000 mL three-necked round-bottom flask equipped with a magnetic stirrer, toluene (800 mL) was added. The whole system was deoxygenated by bubbling with argon at room temperature for several hours. After that, PMDETA (785.8 μL, 3.75 mmol) and CuBr (0.36 g, 2.50 mmol) were added into the flask under protection of argon flow in order. At the same time, the solution of linear polymer **LPS-N$_3$** (0.20 g, 0.05 mmol) in 20 mL toluene was degassed *via* three freeze/pump/thaw cycles and added slowly into the 1000 mL flask (thermostat at 60 °C) *via* a peristaltic pump at a rate of 0.6 mL/h under the protection of argon flow. After the addition of polymer solution to the catalyst solution, the reaction was carried out at 60 °C for an additional 24 h before cooling to room temperature. The mixture was transferred directly onto a short column of silica gel, when toluene run out, the column was eluted by THF to remove copper salts and get the crude mixture, after the solvent was removed, the product was precipitated from an excess of methanol twice, filtered, and dried in a vacuum oven at 25 °C for 24 h to give a white solid (0.14 g, yield: 70%), The crude product was purified by preparative SEC (yield: 75%) (**Figure S4†**). $M_{n,NMR}$ = 4000 g/mol. SEC results: $M_{n,SEC}$ = 3240 g/mol, $M_{w,SEC}$ = 3500 g/mol, ***Đ*** = 1.08.

CPS-SH. In a 5 mL reaction tube equipped with a magnetic stirrer, a solution of HOAc (0.6 mL) and Zn (30 mg) was added to a solution of **CPS-DS** (30 mg) in THF (0.9 mL). The mixture was degassed using three freeze/pump/thaw cycles and stirred under argon at 40 °C for 6 h. The mixture was then passed through basic aluminum oxide to remove residual Zn, and precipitated in methanol, filtered, and dried overnight in a vacuum oven at 25 °C to get a white solid (25 mg, yield: 87%). $M_{n,NMR}$ = 4200 g/mol. SEC results: $M_{n,SEC}$ = 3220 g/mol, $M_{w,SEC}$ = 3470 g/mol, ***Đ*** = 1.08.

CPS-S-MA. In a 5 mL reaction tube equipped with a magnetic stirrer, a drop of DBU and MA (100 μL) was added to a solution of **CPS-SH** (15 mg) in THF (1.0 mL). The mixture was degassed using three freeze/pump/thaw cycles and stirred under argon at 30 °C for 6 h. The mixture was then directly precipitated in methanol, filtered, and dried overnight in a vacuum oven at 25 °C to get a white solid (12 mg, yield: 80%). $M_{n,NMR}$ = 4300 g/mol. SEC results: $M_{n,SEC}$ = 3500 g/mol, $M_{w,SEC}$ = 3710 g/mol, ***Đ*** = 1.06.

CPS-S-PEG. In a 5 mL reaction tube equipped with a magnetic stirrer, a drop of DBU and mPEG-AA (100 μL) was added to a solution of **CPS-SH** (15 mg) in THF (1.0 mL). The mixture was degassed using three freeze/pump/thaw cycles and stirred under argon at 30 °C for 6 h. The mixture was then directly precipitated in methanol, filtered, and dried overnight in a vacuum oven at 25 °C to get a white solid (14 mg, yield: 83%). $M_{n,NMR}$ = 4800 g/mol. SEC results: $M_{n,SEC}$ = 3760 g/mol, $M_{w,SEC}$ = 4000 g/mol, ***Đ*** = 1.06.

CPS-SS-CPS. In a 5 mL reaction tube equipped with a magnetic stirrer, $FeCl_3$ (47 mg, 284.0 mmol) was added to a solution of **CPS-SH** (30 mg, 7.1 mmol) in DMF (1.5 mL). The reaction mixture was stirred in air atmosphere at 60 °C for 72 h. The resultant polymer was then passed through basic aluminum oxide to remove ferric salts, precipitated in an excess of methanol, filtered, and dried in a vacuum oven overnight at 25 °C to get a white solid (24 mg, yield: 80%). The crude product was purified by preparative SEC (yield: 95%) (**Figure S4†**). $M_{n,NMR}$ = 7900 g/mol. SEC results: $M_{n,SEC}$ = 6170 g/mol, $M_{w,SEC}$ = 6430 g/mol, ***Đ*** = 1.04.

Tri-LPS-Br. $CuBr_2$ (0.146 g, 0.653 mmol), AsAc (0.229 g, 1.305 mmol), freshly distilled St (15 mL, 130.5 mmol) and toluene (60 mL) were added into a 100 mL Schlenk flask, followed by adding 1,1,1-tris(2-bromo isobutyryloxymethyl)propane (3Bri-Pr[28], 1.135 g, 1.958 mmol) and PMDETA (0.226 g, 1.305 mmol). The mixture was degassed using three freeze/pump/thaw cycles, and then the reaction mixture was placed in a preheated 110 °C oil bath and allowed to stir under argon for three hours. The crude mixture was then cooled to room temperature, diluted with THF and transferred onto a short neutral alumina column to remove copper salts, after the solvent was removed, the concentrated product was precipitated from an excess of methanol twice, collected by vacuum filtration, and dried *in vacuo* at 25 °C to afford the product as a white powder (4.65 g; Conversion: 34%). $M_{n,NMR}$ = 3400 g/mol. SEC results: $M_{n,SEC}$ = 3200 g/mol, $M_{w,SEC}$ = 3530 g/mol, ***Đ*** = 1.10.

Tri-LPS-N$_3$. Similar with **LPS-N$_3$**. $M_{n,NMR}$ = 3500 g/mol. SEC results: $M_{n,SEC}$ = 3280 g/mol, $M_{w,SEC}$ = 3590 g/mol, ***Đ*** = 1.09.

BiCPS-DS. In a 1000 mL three-necked round-bottom flask equipped with a magnetic stirrer, toluene (800 mL) was added. The whole system was deoxygenated by bubbling with argon at room temperature for several hours. After that, PMDETA (1.08 mL, 5.14 mmol) and CuBr (0.37 g, 2.57 mmol) were added into the flask under protection of argon flow in order. At the same time, the solution of linear polymer **Tri-LPS-N$_3$** (0.10 g, 0.029 mmol) and compound ethyl 3-((3-oxo-3-(3-(prop-2-yn-1-yloxy)-2,2-bis((prop-2-yn-1-yloxy)methyl)propoxy)propyl) disulfanyl)propanoate **(PPPDS)** (26.86 mg, 0.057 mmol) (It was found that if the molar feed of a star telechelics and an end-linking reagent was chosen as 1/1 or 1/1.2, the infrared absorption peak at 2100 cm^{-1} arising from azido did not disppear completely due to incomplete CuAAC reaction) in 20 mL toluene was degassed *via* three freeze/pump/thaw cycles and added slowly into the 1000 mL flask (thermostat at 60 °C) *via* a peristaltic pump at a rate of 1.0 mL/h under the protection of argon flow. After the addition of polymer solution to the catalyst solution, the reaction was carried out at 60 °C for an additional 24 h before cooling to room temperature. The mixture was transferred directly onto a short column of silica gel, when toluene run out, the column was eluted by THF to remove copper salts and get the crude mixture, after the solvent was removed, the product was precipitated from an excess of methanol twice, filtered, and dried in a vacuum oven at 25 °C for 24 h to give a white solid (74 mg, yield: 65%). The crude product was purified by preparative SEC (yield: 50%) (**Figure 5**). $M_{n,NMR}$ = 4000 g/mol. SEC results: $M_{n,SEC}$ = 3180 g/mol, $M_{w,SEC}$ = 3370 g/mol, $Đ$ = 1.06.

BiCPS-SH, BiCPS-S-PEG, BiCPS-SS-BiCPS. Operating step was similar to **CPS-SH, CPS-S-PEG, CPS-SS-CPS. BiCPS-SH**, $M_{n,NMR}$ = 4000 g/mol. SEC results: $M_{n,SEC}$ = 3130 g/mol, $M_{w,SEC}$ = 3390 g/mol, $Đ$ = 1.08. **BiCPS-S-PEG**, $M_{n,NMR}$ = 4600 g/mol. SEC results: $M_{n,SEC}$ = 3680 g/mol, $M_{w,SEC}$ = 3940 g/mol, $Đ$ = 1.07. **BiCPS-SS-BiCPS** (**Figure S8†**), $M_{n,NMR}$ = 8400 g/mol. SEC results: $M_{n,SEC}$ = 6140 g/mol, $M_{w,SEC}$ = 6360 g/mol, $Đ$ = 1.03.

Results and Discussions

Synthesis of disulfide-containing linear PS precursor. The synthetic route outlined in **Scheme 1** was quite straightforward. The most widely used tandem ATRP and CuAAC "click" reaction[5d,12a, 29] were employed to prepare the disulfide-functionalized macrocycle polymers. After reduction of disulfide groups, the thiol-containing macrocycle polymers were used as the prefabricated building blocks for subsequent constructions based on the versatile and high-efficiency thiol chemistry. As shown in **Scheme 1A**, in order to synthesize the linear PS precursor, an initiator (PDSB) containing alkyne, disulfide and bromine group was specifically designed and synthesized. The structure of PDSB was distinctly confirmed by ^{1}H NMR and ^{13}C NMR (**Figure S1†**).

Linear polymer LPS-Br with protected thiol group (disulfide) was synthesized by Activators Generated by Electron Transfer (AGET) ATRP[30] for its well-controlled nature and tolerance of functional groups. The polymerization stopped at about 30% conversion to get high degree of chain end fidelity. The number average molecular weight ($M_{n,SEC}$) was 3900 g/mol ($Đ$ = 1.13) with unimodal and symmetric distribution as shown in **Figure S2†**. It's bromo chain end functionality was determined by comparing the methyne protons at the ω-chain end ("t") to methylene protons near the alkynyl at initiator part of the polymer ("b") by using ^{1}H NMR spectroscopy (~95%) [18] (**Figure 2A**). And then the bromo chain end groups of the precursor were completely transformed into azido groups by nucleophilic substitution reaction (**Figure 2A&2B, Figure S3†**). From ^{1}H NMR spectra (**Figure 2A&2B**) and MALDI-TOF mass spectra (**Figure 3A&3B**), the disulfide was found to be quite stable under these conditions, ensuring the successes of the following procedures.

Synthesis of CPS-DS with disulfide *via* CuAAC "click" chemistry. The ring-closure method usually involves the intramolecular ring-closure of α,ω-heterodifunctional polymers[5d, 6] and intermolecular ring-closure between α,ω-homodifunctional polymer and α,ω-homodifunctional polymer (or small molecules)[6, 18, 31]. In this work, unimolecular heterodifunctional approach, *i.e.*, CuAAC intramolecular cyclization reaction between azido and alkyne groups was performed to get the typical cyclic PS under highly dilute condition (0.25 mg/mL).[5d] Over the expected period of time, LPS-N$_3$ in toluene solution was slowly added into 800 mL warm toluene containing PMDETA and CuBr *via* syringe pump. After stirring for additional 24 h, the reaction was completed and the crude product was conveniently obtained by elution with flash column chromatography on silica gel. Monteiro *et al.* elegantly utilized log normalized Gaussian distribution to simulate the purities of cyclic or other topological polymers[16c, 32]. In this work, after purifying by preparative SEC (**Figure S4†**), the evaluations of the purities of macrocycle-based topological polymers were based on the deliberate analysis of FT-IR, ^{1}H NMR and MALDI-TOF mass spectra. In the FT-IR spectrum (**Figure S3†**), the characteristic vibrational bands of alkyne group around 3300 cm^{-1} and azide group around 2100 cm^{-1} disappeared completely. Because the cyclization leaded to a reduced hydrodynamic volume, the cyclic polymers exhibited a longer size exclusion retention time than the linear precursor[5d, 6] (**Figure 1**). The <G> values, defined as the ratio of the apparent peak molecular weight of the cyclic product and linear precursor (<G> = M_{pc}/M_{pl}), was 0.75, agreeing well with the literatures.[33]

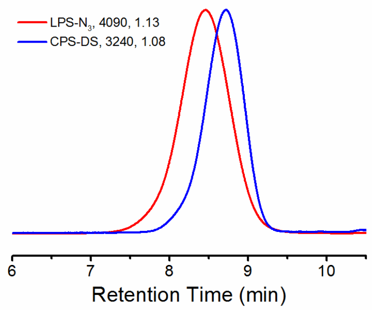


Figure 1. SEC RI traces of LPS-N$_3$ (M_p = 4320), CPS-DS (purified by prep SEC, M_p = 3250). THF was used as the eluent, and PS standards were used for the calibration. All SEC traces were normalized to height.

The ^{1}H NMR spectra of CPS-DS together with the PS precursor LPS-N$_3$ were shown in **Figure 2B** and **2C**, respectively.

As a result of high efficiency “click” reaction, the peak for methine proton ("t") of the precursor polymer shifted to 5.07 ppm (original at 3.95 ppm), the peaks at 2.70-2.94 ppm were divided into four peaks. The peak for methylene protons near the triazole unit ("b") shifted from 4.66 ppm to 4.03 ppm and the alkynyl proton at 2.43 ppm ("a") disappeared due to cyclization reaction.

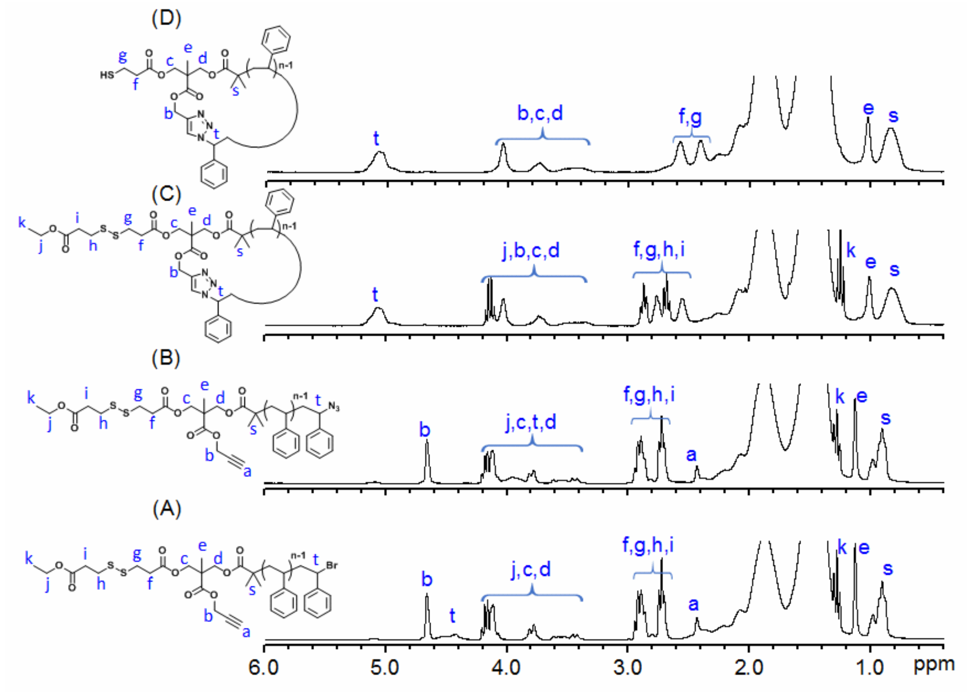


Figure 2. 300 MHz ^{1}H NMR spectra in $CDCl_3$ of (A) LPS-Br, (B) LPS-N_3, (C) CPS-DS (purified by prep SEC), (D) CPS-SH.

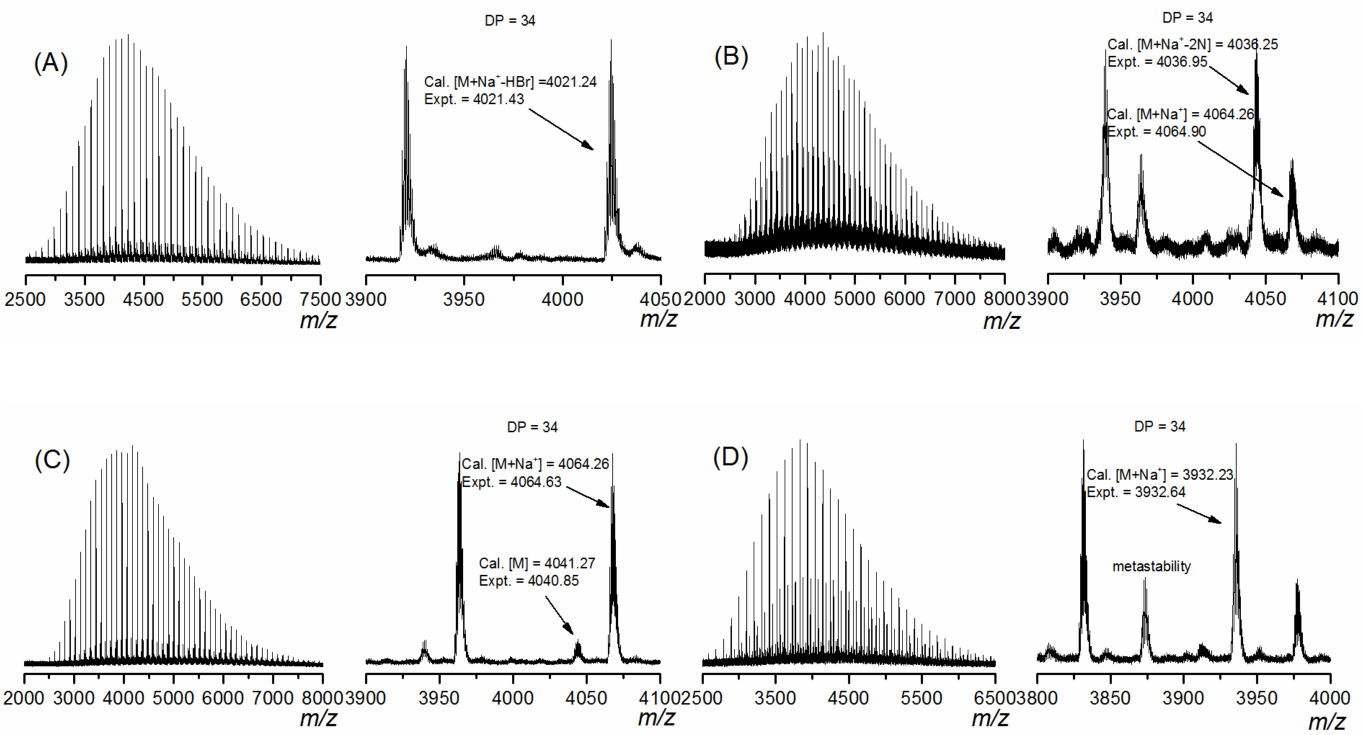


Figure 3. MALDI-TOF mass spectrum using Na salt as cationization agent and DCTB matrix. (A) LPS-Br, (B) LPS-N_3, (C) CPS-DS (purified by prep SEC), and (D) CPS-SH, acquired in reflectron mode. Left: Full spectra and Right: magnified views of the spectra within a specific mass range.

The structure of CPS-DS was further confirmed by the MALDI-TOF mass spectroscopy (**Figure 3C**). The full spectrum of CPS-DS exhibits only one symmetric distribution. And a representative peak *m/z* value of 3960.61 g/mol corresponding to 33-

mer of CPS-DS with a sodium was in good agreement with the calculated mass ($[M_{33}+Na]^+$, cal. 3960.20 g/mol). Therefore, all the obtained results strongly supported the molecular structures and uniformity of the resulting cyclic PS.

Synthesis of BiCPS-DS with disulfide *via* CuAAC "click" chemistry. The preparation of fused-bicyclic polymer *via* ATRP and CuAAC bimolecular coupling was reported by Chang and Paik *et al.*.[18] However, the reported fused-bicyclic PS did not contain the potential thiol group and could not be used as building block for constructing more complex topological macrocycle-based polymers. As shown in **Scheme 1B**, linear 3-arm star PS precursor (Tri-LPS-Br) was synthesized by AGET ATRP using the trifunctional initiator (3Bri-Pr), and the polymerization was stopped close to 35% conversion with $M_{n,SEC}$ of 3200 g/mol ($Đ$ = 1.10) (**Figure S5**†). It's bromo chain end functionality was determined by comparing the methyne protons at the ω-chain end ("e") to methyl protons at initiator part of the polymer ("a") using ^{1}H NMR spectroscopy (~91%)[18] (**Figure 4A**). Then, the bromo chain end groups of the precursor were completely transformed into azido groups by nucleophilic substitution reaction as confirmed by ^{1}H NMR (**Figure 4A&4B**), MALDI-TOF mass spectroscopy (**Figure 6A&6B**) and FT-IR (**Figure S6**†). CuAAC "click" chemistry has also been utilized for the intermolecular ring-closure of homobifunctional polymers[6, 18, 31]. Usually, to minimize the side reactions during bimolecular cyclizations between bifunctional polymer and complementary bifunctional linking reagent, the concentration of polymer was kept at very low degree (0.25 mg/mL)[34] by feeding with a syringe pump. The bimolecular cyclization of multi terminal-functionalized polymers (three or more) was prone to produce more byproducts. In the current work, the synthesis of the target bicyclic PS was conducted in even low polymer concentration (0.125 mg/mL) during CuAAC intermolecular cyclization between three-arm PS (Tri-LPS-N_3) and coupling agent with three terminal alkyne groups, PPPDS (NMR characterization results, **Figure S7**†). After the reaction, the absorbance band of azido group at around 2100 cm^{-1} in FT-IR fully disappeared, indicating the complete chemical transformation (**Figure S6**†). However, due to the incomplete bromo-terminated chain end degree (~91%), and thus the imperfect azido termination, the generation of some branched polymers cannot be completely avoided[18]. The multimodal distribution of SEC chromatogram (**Figure 5**) demonstrated the high content of branched polymers (~50%). After being purified by preparative SEC with the yield of 50%, the target cyclic polymer was obtained with a longer size exclusion retention time than the linear precursor (**Figure 5**).

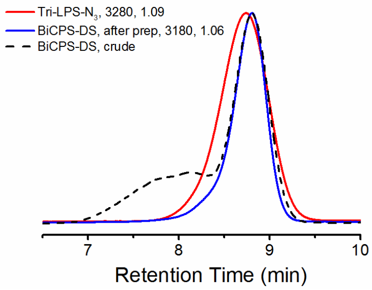


Figure 5. SEC RI traces of Tri-LPS-N_3 (M_p = 3380), BiCPS-DS (purified by prep SEC with 50% yield, M_p = 3060). THF was used as the eluent, and PS standards were used for the calibration. All SEC traces were normalized to height.

The ^{1}H NMR spectra of purified BiCPS-DS together with the PS precursor Tri-LPS-N_3 are shown in **Figure 4B** and **4C**. As a result of intermolecular cyclization, the signals for methyne proton of the precursor polymer shifted from 3.94 ppm to 5.10 ppm, the signals of methylene protons of initiator shifted from 3.26 ppm to 3.39 ppm, and signals of 2.45-2.89 ppm and 1.20-1.25 ppm appeared due to the incorporation of coupling agent PPPDS after intermolecular cyclization.

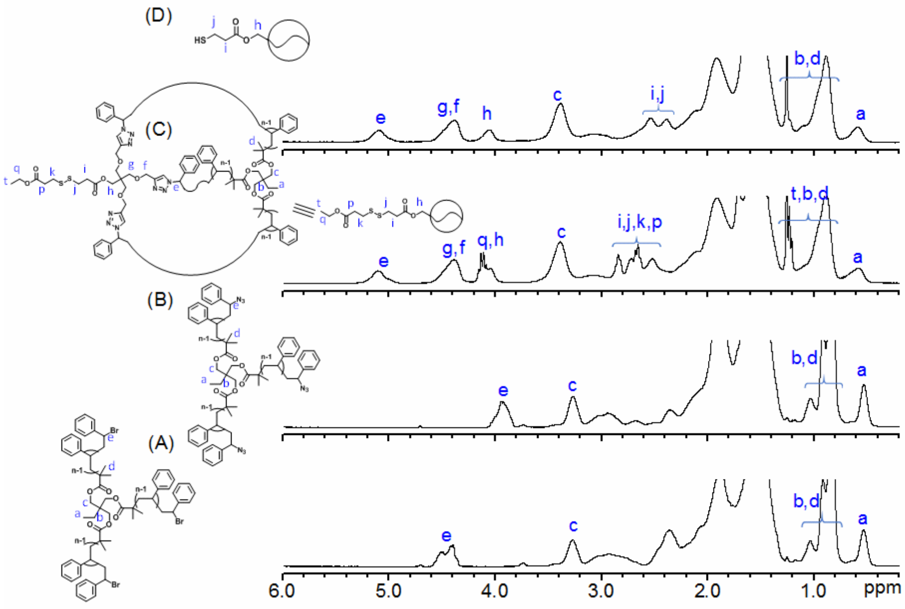


Figure 4. 300 MHz ^{1}H NMR spectra in $CDCl_3$ of (A) Tri-LPS-Br, (B) Tri-LPS-N_3, (C) BiCPS-DS (purified by prep SEC), (D) BiCPS-SH.

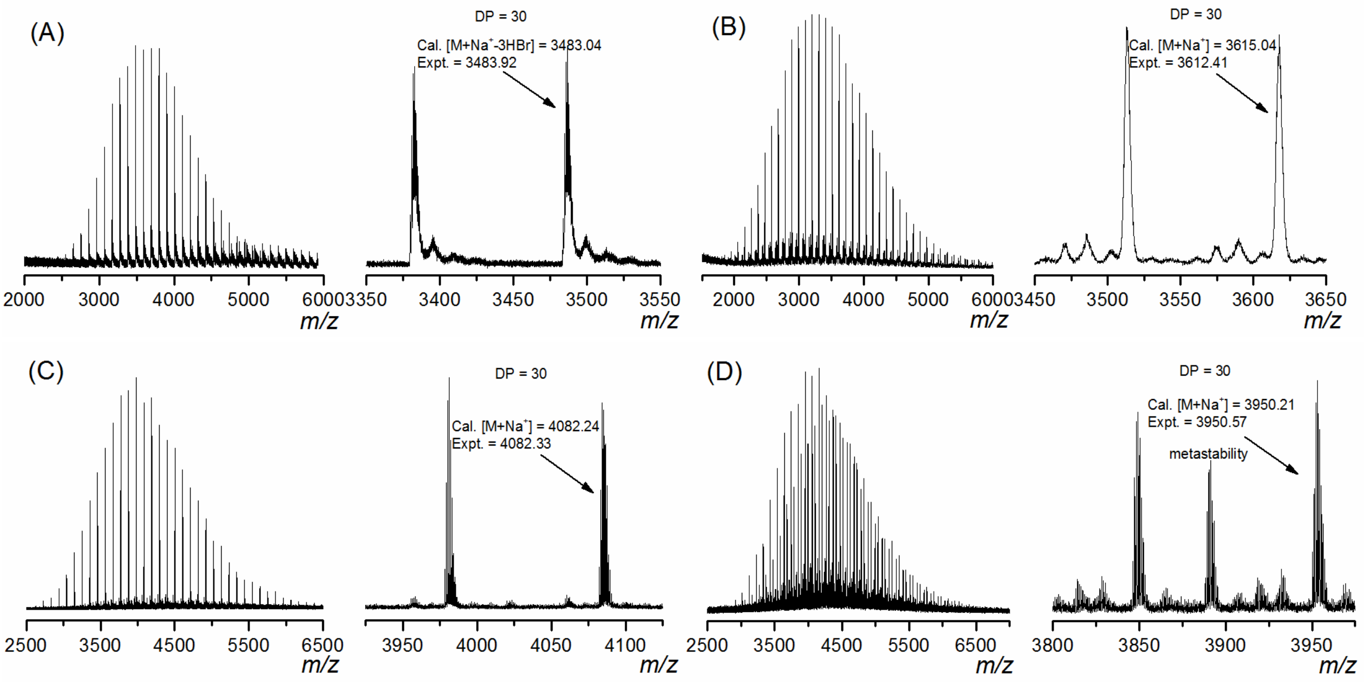


Figure 6. MALDI-TOF mass spectrum using Na salt as cationization agent and DCTB matrix. (A) Tri-LPS-Br, (C) BiCPS-DS (purified by prep SEC), (D) BiCPS-SH, acquired in reflection mode, (B) Tri-LPS-N_3, acquired in linear mode. Left: Full spectra and Right: magnified views of the spectra within a specific mass range.

The structure of BiCPS-DS was further confirmed by MALDI-TOF mass spectroscopy (**Figure 6C**). A typical main peak *m/z* value of 4082.33 g/mol corresponding to 30-mer of BiCPS-DS with a sodium was close to the calculated mass ($[M_{30}+Na]^+$, cal. 4082.24 g/mol). Therefore, it can be concluded that BiCPS-DS has been successfully synthesized. As well illustrated by Chang and Paik *et al.*[18], the fused-dicyclic PS by using three-armed PS with larger DP (M_n = 6250 and Đ = 1.06) can also been constructed with the same procedure, and the larger DP apparently did not affect the bimolecular "Click" efficiency between three-armed PS and trifunctional alkyne linking reagent.

Reduction of disulfide bond and chain-end modification. The reversible transformation between disulfide and thiol group produced many interesting applications in biomedical devices, drug delivery, degradable materials, *etc.*[26]. In order to convert the disulfide group into thiol group, many reducing agents have been utilized, such as hydrazine hydrate[35], tributylphosphine[35b, 36], sodium borohydride[37], dithiothreitol[38], Zn together with acetic acid (HOAc)[39] and so on. Zn/HOAc can exclusively cleavage the disulfide under mild conditions in an efficient way. In this work, in order to get the building block (CPS-SH), reductive degradation of CPS-DS was carried out with excess Zn/HOAc in THF under an inert atmosphere at 40 °C. SEC curve showed unobvious change after the reaction contrasting with CPS-DS (**Figure S2**†). From the ^{1}H NMR spectra (**Figure 2C&2D**), the peaks at 4.18 ppm ("j") and 1.27 ppm ("k") assigned to the methylene protons and methyl protons at the distal end of the cyclic polymer disappeared, and the peaks of four methylenes protons near the disulfide unit at 2.55-2.90 ppm turned into the peaks at 2.60 ppm and 2.41 ppm ("f" and "g") due to the complete degradation of disulfide (**Figure 2C&2D**). The MALDI-TOF mass spectroscopy further confirmed the successful reduction, a typical peak *m/z* value of 3932.64 g/mol corresponding to 34-mer of CPS-SH with a sodium fitted well with the calculated mass ($[M_{34}+Na]^+$, cal. 3932.23 g/mol), and the other series of peak was metastable species under the test condition[40] (**Figure 3D**).

In order to set up a model for the subsequent constructions as well as to confirm the activity of thiol group, a representative thiol-Michael addition reaction was carried out[22c, 23a]. Methyl acrylate (MA) was used to react with the fresh thiol group on the cyclic polymer CPS-SH. Small amount of weak organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), was added, and the mixture was stirred at 30 °C for a predetermined time. After the Michael addition reaction, the SEC curve of CPS-S-MA remained unimodal and symmetric distribution (**Figure 7**). In ^{1}H NMR spectra, the peak at 3.66 ppm ("j") ascribed to the methyl protons of MA species appeared (**Figure 8A**), and two peaks at 2.60 ppm ("f") and 2.41 ppm ("g") near the sulfur changed its splitting mode due to the attach of MA moiety (**Figure 2D&8A**). The MALDI-TOF mass spectrum showed a peak *m/z* value of 4018.29 g/mol corresponding to 34-mer of CPS-S-MA with a sodium ion matched well with the calculated mass ($[M_{34}+Na]^+$, cal. 4018.27 g/mol), and the metastable signals existed in the mass spectrum of precursor CPS-SH disappeared (**Figure 9A**). All these convincing data suggested the successful thiol-Michael addition reaction, which confirmed the high activity of the thiol groups and guaranteed the following constructions.

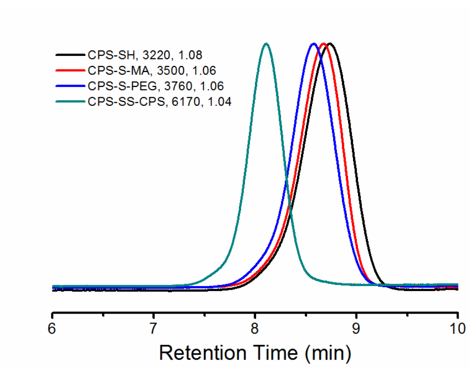


Figure 7. SEC RI traces of CPS-SH (M_p = 3190), CPS-S-MA (M_p = 3420), CPS-S-PEG (M_p = 3780), CPS-SS-CPS (purified by prep SEC, M_p = 6190). THF was used as the eluent, and PS standards were used for the calibration. All SEC traces were normalized to height.

Similar reductive degradation was carried out to get the other building block, *i.e.*, the thiol-functionalized fused-bicyclic (BiCPS-SH). The polymer was also successfully constructed as supported by SEC (**Figure S5**†), ^{1}H NMR (**Figure 4D**) and MALDI-TOF MS (**Figure 6D**) results.

Synthesize tadpole-shaped polymer from CPS-SH building block. The synthetic routes for the constructions of macrocycle-based topological polymers are illustrated in **Scheme 2**. The thiol-Michael addition “click” reaction between CPS-SH and acrylate-terminated PEG (mPEG-AA, M_n = 480) was performed toward a tadpole-shaped polymer (CPS-S-PEG) (**Scheme 2A**). Notably, the excess mPEG-AA can be fully removed by precipitating into methanol. In SEC traces (**Figure 7**), the increased molecular weight was due to the incorporation of PEG segment onto CPS-SH. From ^{1}H NMR spectrum (**Figure 8B**), it was found that the peaks at 4.25 ppm ("k") , 3.64 ppm ("p", "q") and 3.56 ppm ("w") corresponded to the methylene protons of PEG repeat units appeared and 3.38 ppm ("j") belonged to methyl protons at the distal end of the cyclic polymer was also observed. Almost all of the pieces of the peaks in MALDI-TOF MS could be assigned to their calculated ones (**Figure 9B**).

Synthesize spiro-bicyclic polymer from CPS-SH building block. Due to the reversible feature, the conversion of thiols to disulfides under oxidizing condition is frequently used to prepared mutliblock polymers and many other useful polymeric matericals.[41] $FeCl_3$ has been proved to be an efficient oxidation agent in the presence of air.[39a] In this work, the synthesis of spiro-bicyclic polymer (with only one disulfide linkage) from CPS-SH was carried out by using $FeCl_3$ as an oxidation agent under air atmosphere (**Scheme 2A**). The reaction mixture was stirred for 72 h in the presence of 40 equiv of $FeCl_3$. The crude products were then purified by preparative SEC (**Figure S4**†) to remove the tiny amount of by-products during oxidation.[39a] After oxidation, the molecular weight was found to be doubled, from 3220 to 6170 (see the SEC curves in **Figure 7**), implying the successful oxidation. The ^{1}H NMR spectra of CPS-SS-CPS (**Figure 8C**) was almost the same as that of CPS-SH (**Figure 2D**). MALDI-TOF mass spectrum showed the convinced evidence of the formation of CPS-SS-CPS, a main peak *m/z* value of 7846.96 g/mol corresponding to 68-mer of CPS-SS-CPS with a sodium was close to the calculated mass ($[M_{68}+Na]^+$, cal. 7846.13 g/mol) (**Figure 9C**). Therefore, the CPS-SS-CPS was successfully obtained based on all these confirmed results.

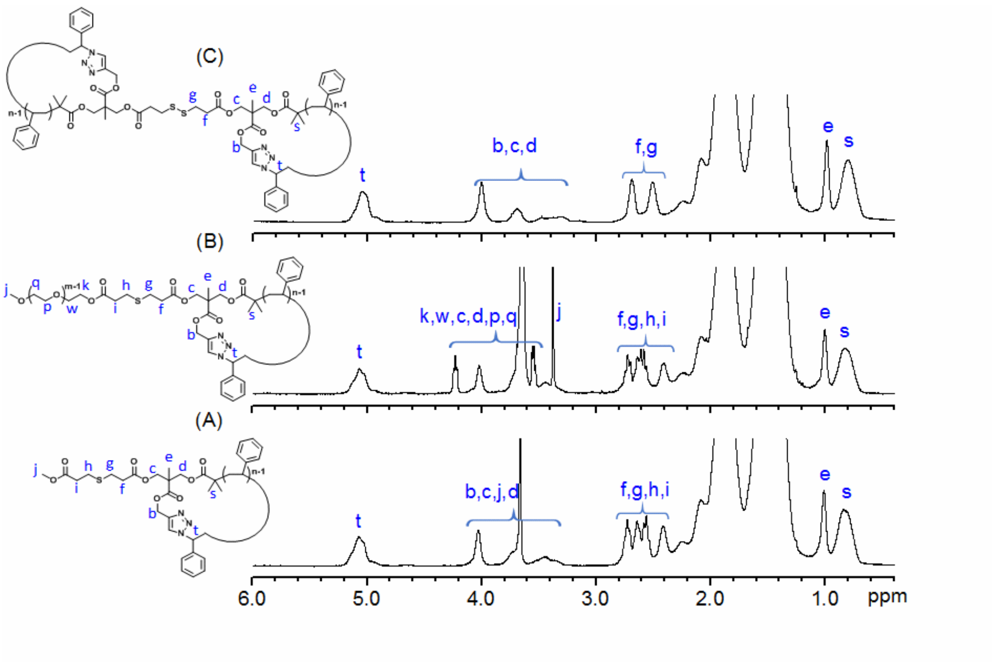


Figure 8. 300 MHz ^{1}H NMR spectra in $CDCl_3$ of (A) CPS-S-MA, (B) CPS-S-PEG, (C) CPS-SS-CPS (purified by prep SEC).

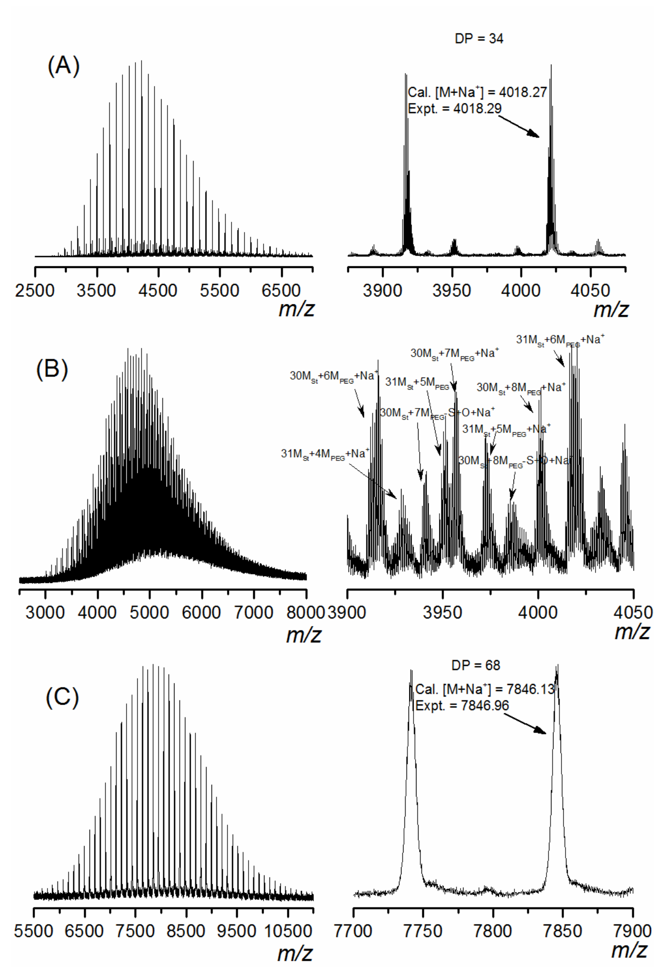


Figure 9. MALDI-TOF mass spectrum using Na salt as cationization agent and DCTB matrix. (A) CPS-S-MA, and (B) CPS-S-PEG, acquired in reflection mode, (C) CPS-SS-CPS (purified by prep SEC), acquired in linear mode. Left: Full spectra and Right: magnified views of the spectra within a specific mass range.

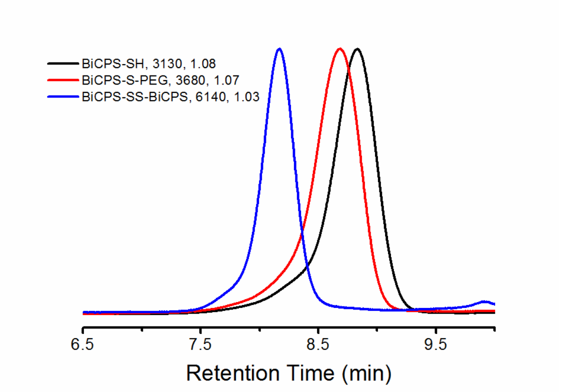


Figure 10. SEC RI traces of BiCPS-SH (M_p = 2980), BiCPS-S-PEG (M_p = 3530), BiCPS-SS-BiCPS (purified by prep SEC, M_p = 6080). THF was used as the eluent, and PS standards were used for the calibration. All SEC traces were normalized to height.

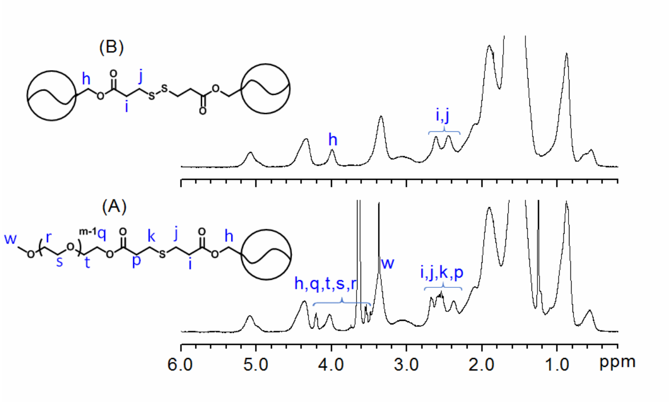


Figure 11. 300 MHz ^{1}H NMR spectra in $CDCl_3$ of (A) BiCPS-S-PEG, (B) BiCPS-SS-BiCPS (purified by prep SEC).

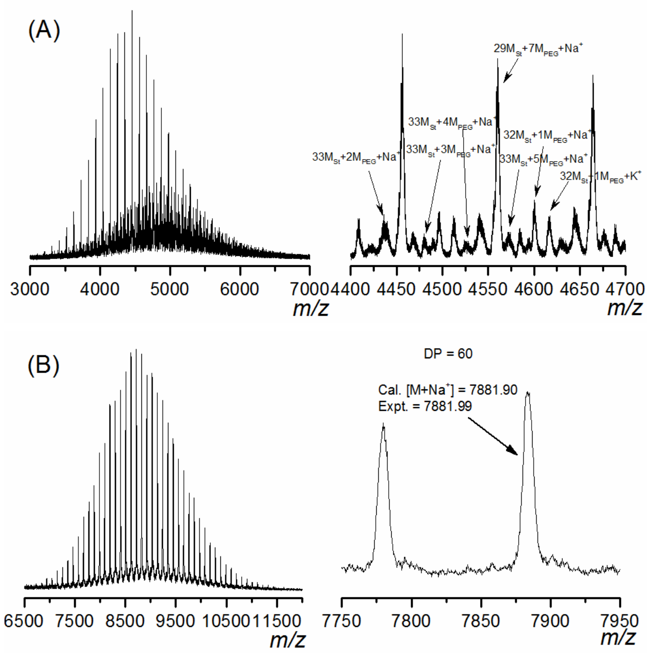


Figure 12. MALDI-TOF mass spectrum using Na salt as cationization agent and DCTB matrix. (A) BiCPS-S-PEG, acquired in reflection mode, (B) BiCPS-SS-BiCPS (purified by prep SEC), acquired in linear mode. Left: Full spectra and Right: magnified views of the spectra within a specific mass range.

On the other hand, using BiCPS-SH as building block, fused-dicyclic tadpole (BiCPS-S-PEG) and fused-dicyclic spiro (BiCPS-SS-BiCPS) polymers were also successfully constructed (**Scheme 2B**) as supported by SEC (**Figure 10**), ^{1}H NMR (**Figure 11**) and MALDI-TOF mass spectrum (**Figure 12**) results.

All the molecular characterizations were shown in **Table 1**, and the results demonstrated that the CPS-SH and BiCPS-SH are versatile building blocks for constructing various cyclic-based topological polymers. Based on a variety of high-efficient thiol chemistry reactions, it is expected that these building blocks could be used for developing many other topological polymers as well as polymeric materials with unique functions. In fact, related work on elucidating the structure-property relationship and self-assembly behaviours of these unique non-linear macromolecules are currently underway in our laboratory.

Table 1. Summary of Molecular Characterizations.

Sample	Representative Molecular Formula[a]	M_{Calcd} (g/mol)[a]	M_{Observed} (g/mol)[a]	$M_{\text{n,NMR}}$[b] (g/mol)	$M_{\text{n,SEC}}$[c] (g/mol)	$M_{\text{w,SEC}}$[c] (g/mol)	$M_{\text{p,SEC}}$[c] (g/mol)	Đ[c]
LPS-Br	$C_{292}H_{300}NaO_8S_2$	4021.24	4021.43	4000	3900	4430	4290	1.13
LPS-N_3	$C_{292}H_{301}N_3NaO_8S_2$ / $C_{292}H_{301}NNaO_8S_2$	4064.26 /4036.25	4064.90 /4036.95	4000	4090	4610	4320	1.13
CPS-DS	$C_{292}H_{301}N_3NaO_8S_2$	4064.26	4064.63	4000	3240	3500	3250	1.08
CPS-SH	$C_{287}H_{293}N_3NaO_6S$	3932.23	3932.64	4200	3220	3470	3190	1.08
CPS-S-MA	$C_{291}H_{299}N_3NaO_8S$	4018.27	4018.29	4300	3500	3710	3420	1.06
CPS-S-PEG	-	-	-	4800	3760	4000	3780	1.06
CPS-SS-CPS	$C_{574}H_{584}N_6NaO_{12}S_2$	7846.13	7846.96	7900	6170	6430	6190	1.04
Tri-LPS-Br	$C_{258}H_{266}NaO_6$	3483.04	3483.92	3400	3200	3530	3310	1.10
Tri-LPS-N_3	$C_{258}H_{269}N_9NaO_6$	3615.04	3612.41	3500	3280	3590	3380	1.09
BiCPS-DS	$C_{280}H_{299}N_9NaO_{13}S_2$	4082.24	4082.33	4000	3180	3370	3070	1.06
BiCPS-SH	$C_{275}H_{291}N_9NaO_{11}S$	3950.21	3950.57	4000	3130	3390	2980	1.08
BiCPS-S-PEG	-	-	-	4600	3680	3940	3530	1.07
BiCPS-SS-BiCPS	$C_{550}H_{580}N_{18}NaO_{22}S_2$	7881.90	7881.99	8400	6140	6360	6080	1.03

[a] These data are based with a sodium ion ($[M \cdot Na]^+$). [b] These data are calculated based on ^1H NMR spectra. [c] These data are obtained from SEC measurements. $Đ = M_{\text{w,SEC}}/M_{\text{n,SEC}}$.

Conclusion

In summary, thiol-functionalized monocyclic and fused-bicyclic polymers have been successfully synthesized using a combination of ATRP and CuAAC cyclization reaction. By utilization of those cyclic polymers as building blocks, several tadpole-, spiro-shaped topological polymers were facilely constructed via modular approach. Taking advantage of the versatile thiol chemistry, this work offered a modular methodology for the facile and precise construction of cyclic-based topological polymers with thiol-functionalized cyclic polymer as building block. Many other complex cyclic polymers with different topologies and compositions as well as cyclic polymer-related bioconjugates and materials can be potentially fabricated *via* similar approaches.

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Notes and references

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