Synthesis of Cyclic Polyelectrolyte via Direct Copper(I)-Catalyzed Click Cyclization

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INTRODUCTION Polyelectrolyte has received extensive attention due to its promising applications in various fields.[1] As the properties of polyelectrolyte are generally determined by its conformation,[2] cyclic polyelectrolyte is expected to exhibit some unique properties in comparison with the linear one.[3] However, due to the challenge in synthesis of cyclic polyelectrolyte, the experimental studies on such special polymer are rarely reported.[4] A feasible method to synthesize cyclic polyelectrolyte should be based on the ionization of its neutral precursor as the electrostatic repulsion would prevent the direct cyclization of the linear polyelectrolyte chain.[5]

On the other hand, although a number of attempts have been devoted to the synthesis of cyclic polymer,[6–9] design and development of new synthetic methods are still the important subjects in this area.[8] Currently, the ring-closure reaction of linear precursor with two complementary reactive terminal groups in dilute solution has been extensively used to synthesize cyclic polymer.[9–13] Huisgen 1,3-dipolar cycloaddition reaction of organic azide and alkyne proves to be efficient in the cyclization of linear polymer due to the high reactivity between such two groups and the low susceptibility to side reactions.[11,14,15] The linear precursor is usually prepared by atom transfer radical polymerization (ATRP), because the terminal Br group can be readily converted into azide with a reasonable yield.[16–18] The alkynyl-containing initiator is generally protected with tetramethylsilane (TMS) or triisopropylsilane (TIPS) so that the side reactions in the following polymerization are eliminated, especially in the synthesis of cyclic poly(*tert*-butyl acrylate) (P*t*BA).[18,19] TMS or TIPS is usually removed using tetrabutylammonium fluoride (TBAF) for the next click cyclization. However, the azide groups are often detached from the ends of polymer chains in the deprotection process, which would prevent the next click cyclization.

Recently, Cuevas et al.[20] developed a direct click reaction of azide with TMS-protected alkyne group by using copper (I) bromide/triethylamine (CuBr/TEA) as the catalyst complex. Such direct copper(I)-catalyzed click reaction without any deprotection steps is expected to be more convenient and efficient than the traditional method in the synthesis of cyclic polymer. However, to the best of our knowledge, this reaction has not been used in polymer synthesis yet. In the present work, we have successfully prepared cyclic poly(acrylic acid) (PAA) from its neutral precursor (i.e., cyclic P*t*BA), which is synthesized directly via the copper(I)-catalyzed click cyclization with azide and TMS-protected alkyne groups at the ends of linear P*t*BA.

RESULTS AND DISCUSSION

Synthesis of Linear P*t*BA

When propargyl 2-bromoisobutyrate (H—C≡C—Br) was used to initiate the polymerization of *t*-BA with CuBr and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) as the catalyst, the product will have a small amount of undesirable large molecular weight polymer due to the radical polymerization of alkyne. To eliminate the side reactions, TMS-protected initiator (TMS—C≡C—Br) was used. The well-defined P*t*BA with TMS-protected alkyne group was obtained via ATRP with CuBr/PMDETA as the catalyst in acetone at 60 °C.[21] The characterization of the polymers is listed in Table 1.

The bromine groups at the ends of linear P*t*BA chains were converted into azide groups via nucleophilic substitution in dimethylformamide (DMF) in the presence of an excess of NaN_3 (Scheme 1). After the reaction, the solution was passed through neutral alumina to remove the excessive sodium azide (NaN_3). Gel permeation chromatograph (GPC) traces in Figure 1(a) show that the elution peak of TMS—C≡C—P*t*BA—N_3 is almost the same as that of TMS—C≡C—

Additional Supporting Information may be found in the online version of this article.

TABLE 1 Characterization of Linear and Cyclic PtBA

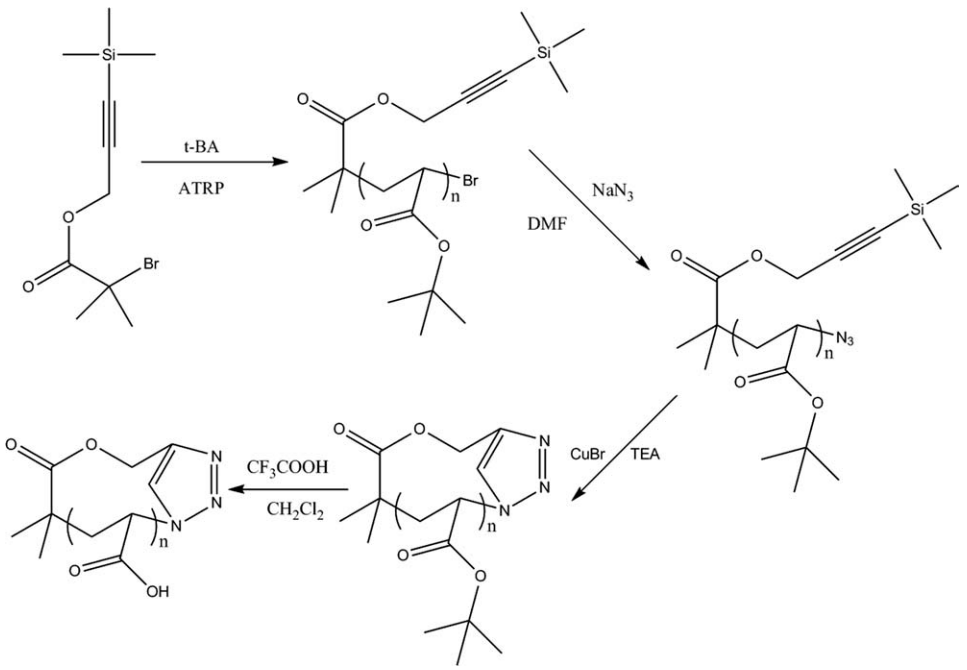
Sample[a]	Polymerization Time (h)	M_n[b] (g/mol)		M_w/M_n[b]	
		Linear	Cyclic	Linear	Cyclic
PtBA1	5	6300	4700	1.07	1.06
PtBA2	3	4200	3500	1.08	1.09
PtBA3	1	1700	1600	1.02	1.01

[a] The polymerizations were carried out at 60 °C with the feed molar ratio of $[Initiator]_0/[CuBr]_0/[PMDETA]_0/[Monomer]_0 = 1:1:1:60$.
[b] Determined by GPC.

P*t*BA—Br. ^{1}H NMR spectra of TMS—C≡C—P*t*BA—Br and TMS—C≡C—P*t*BA—N_3 are shown in Figure 1(b). For TMS—C≡C—P*t*BA—Br, the peak *a* at 4.65 ppm is ascribed to methylene protons (2H) of propargyl residues, and the peak *b* at 4.10 ppm is ascribed to methine proton (1H) adjacent to the terminal bromide. For TMS—C≡C—P*t*BA—N_3, a new peak at 3.64 ppm (*b*′) corresponding to the methine proton adjacent to the terminal azide group comes out and the peak *b* disappears. The integration ratio of *a*′:*b*′ is nearly 2:1, which is consistent with the structure of TMS—C≡C—P*t*BA—N_3. The facts indicate that the terminal bromine groups are completely converted into azides. FTIR in Figure 1(c) shows TMS—C≡C—P*t*BA—N_3 has a new band at 2109 cm^{-1} compared with TMS—C≡C—P*t*BA—Br, further indicating the existence of terminal azide groups. It is worth noting that we have also tried the TMS deprotection before the azidation reaction.[11] However, this reaction sequence requires to precipitate P*t*BA in the mixture of CH_3OH/H_2O several times to remove the unreacted TBAF and the detached TMS during purification, which will result in a low yield of linear precursor.

Intramolecular Cyclization of Linear P*t*BA

As the click reaction favors the intramolecular cyclization when the polymer concentration is below 0.1 mmol L^{-1},[16] the TMS—C≡C—P*t*BA—N_3/DMF mixture was added dropwise to a DMF solution containing CuBr and TEA (ligand) using a microliter syringe (Scheme 1). The molar ratio of the catalyst to the reactive end group was about 100 so that the click reaction was complete. GPC measurements demonstrate that cyclic P*t*BA has a higher elution time than the linear one as the cyclic polymer has a more compact structure with a smaller hydrodynamic volume [Fig. 1(a)]. In Figure 1(b), in comparison with the linear precursor, peaks *a*′ and *b*′ initially at 4.65 and 3.64 ppm disappear and new peaks at 5.18 ppm (*a*″ + *b*″) and 7.74 ppm (*c*″) appear in the ^{1}H NMR spectrum of cyclic P*t*BA after the click cyclization, implying that the cyclization of linear P*t*BA is successful, because the new peaks are attributed to the triazole ring. The intramolecular end-to-end click cyclization was also confirmed by FTIR. Figure 1(c) shows the disappearance of characteristic azide absorbance peak at 2109 cm^{-1} and the appearance of characteristic 1,2,3-triazole absorbance peak at 3300 cm^{-1} in the spectrum of cyclic P*t*BA, indicating that all the azides participate into the formation of triazole ring with TMS-protected alkyne groups. Clearly, well-defined cyclic P*t*BA was successfully synthesized by the direct copper(I)-catalyzed click cyclization without any deprotection steps. Note that if the cyclic P*t*BA was synthesized using the traditional method, the azide groups were often detached from the ends of P*t*BA chains in the deprotection process, which would prevent the next click cyclization (see Fig. S1 in Supporting Information). In addition, Table 1 shows that the narrowly distributed cyclic P*t*BA with different molecular weights can be prepared using the same method (also see Fig. S2 in



SCHEME 1 Strategy of synthesis of cyclic PAA.

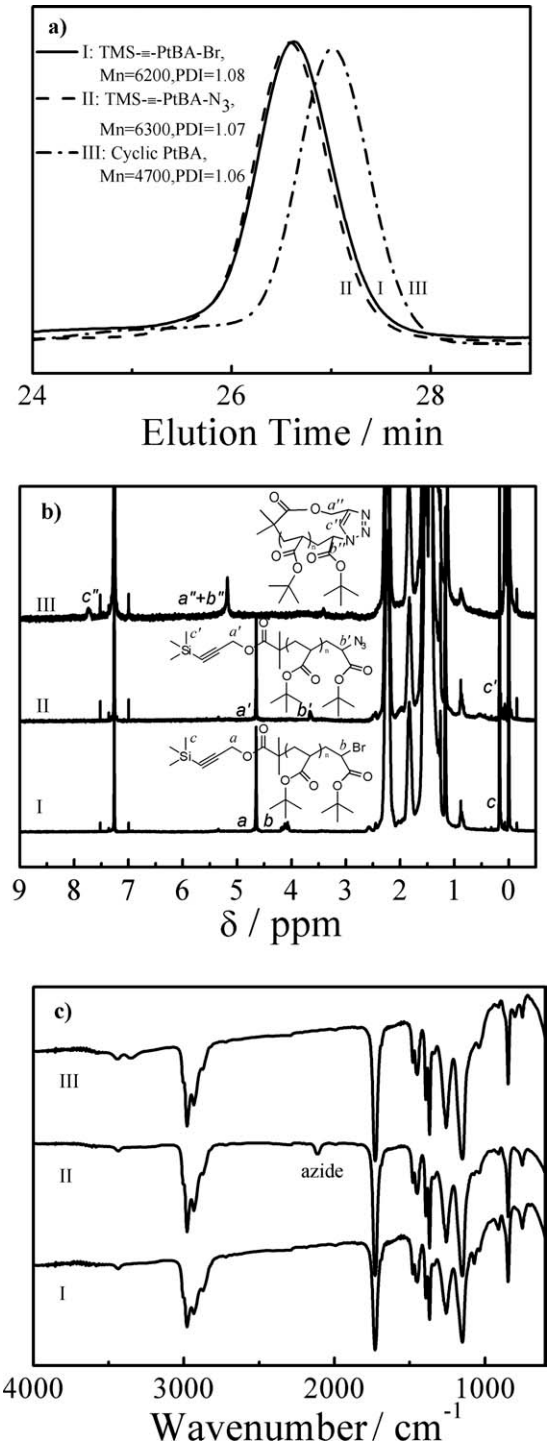


FIGURE 1 Characterization of linear and cyclic P*t*BA. (a) GPC traces of (I) TMS—C≡C—P*t*BA-Br, (II) TMS—C≡C—P*t*BA—N_3, and (III) cyclic P*t*BA; (b) ^{1}H NMR spectra of (I) TMS—C≡C—P*t*BA—Br, (II) TMS—C≡C—P*t*BA—N_3, and (III) cyclic P*t*BA; (c) FTIR spectra of (I) TMS—C≡C—P*t*BA—Br, (II) TMS—C≡C—P*t*BA—N_3, and (III) cyclic P*t*BA.

Supporting Information). Actually, for the linear precursor with relatively low molecular weights, the cyclic polymer chain can be successfully prepared without the undesirable high molecular weight byproducts, which is due to the high reactivity between azide and alkyne groups and the low susceptibility to side reactions. Besides, the low concentration (below 0.1 mmol L^{-1}) of the linear precursor used in the click reaction also favors the intramolecular cyclization. However, for the linear precursor with larger molecular weight (e.g., 7200 g mol^{-1}), an undesirable high molecular weight byproduct was produced during the cyclization (see Fig. S2 in Supporting Information).

Hydrolysis of Cyclic P*t*BA

The hydrolysis of cyclic P*t*BA was carried out in the solution of trifluoroacetic acid (TFA)/CH_2Cl_2 at room temperature.[22] Conversion of cyclic P*t*BA into cyclic PAA was ascertained by ^{1}H NMR and FTIR (Fig. 2). As can be seen from Figure 2(a), the peak (*f*) at 1.44 ppm originating from *tert*-butyl groups of P*t*BA disappears in the ^{1}H NMR spectrum of cyclic PAA, indicating the complete hydrolysis of such groups. Figure 2(b) shows the characteristic peak of carbonyl of ester group at 1732 cm^{-1} in cyclic P*t*BA shifts to 1716 cm^{-1}, which is

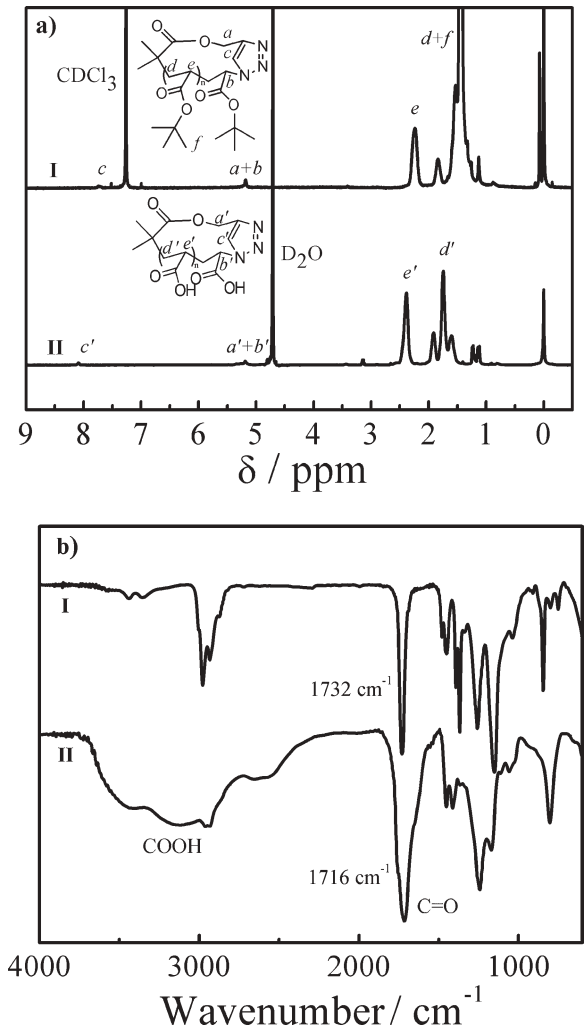


FIGURE 2 Characterization of cyclic P*t*BA and cyclic PAA. (a) ^{1}H NMR spectra of (I) cyclic P*t*BA and (II) cyclic PAA; (b) FTIR spectra of (I) cyclic P*t*BA and (II) cyclic PAA.

ascribed to the carbonyl of carboxyl group. In addition, a broad peak from 2500 to 3300 cm^{-1} is attributed to hydroxyl from the carboxyl group. All the aforementioned results indicate that the cyclic P*t*BA is completely converted into cyclic PAA. Additionally, our preliminary experiments demonstrate that the cyclic PAA chains actually exhibit quite different properties compared with the linear ones. For example, the intrinsic viscosities for the cyclic ($M_n \sim 3200$ g mol^{-1}) and linear ($M_n \sim 4000$ g mol^{-1}) PAA are ~0.10 and ~0.16 dL g^{-1}, respectively, at room temperature. The GPC measurements show that the cyclic PAA chain has a smaller hydrodynamic radius than that of the linear PAA chain with the same degree of polymerization, because the former has a higher elution time (see Fig. S3 in Supporting Information). In addition, quartz crystal microbalance experiments demonstrate that the multilayer formed by the cyclic PAA is quite different from that of linear PAA (see Fig. S4 in Supporting Information).

EXPERIMENTAL

Materials

Chlorotrimethyl silane (TMS-Cl) was distilled over CaH_2 under reduced pressure prior to use. *Tert*-butyl acrylate (*t*-BA, Aldrich) was passed through a column of alumina to remove inhibitor, and then distilled over CaH_2 under reduced pressure prior to use. CuBr (AR grade) was stirred in glacial acetic acid, washed with ethanol, and then dried in a vacuum oven. Triethylamine (TEA) was stirred with KOH for 12 h at room temperature, refluxed with toluene-4-sulfonylchloride, and distilled before use. Tetrahydrofuran (THF) was refluxed in the presence of Na wire, and then distilled prior to use. DMF was dried with anhydrous $MgSO_4$ and distilled under reduced pressure prior to use. Acetone was refluxed in the presence of a small amount of $KMnO_4$ and then distilled from a purple sodium ketyl solution. Dichloromethane (CH_2Cl_2) was distilled under nitrogen over CaH_2. PMDETA (Aldrich), butyl lithium (BuLi, 1.6 M in hexane), 2-bromoisobutyryl bromide (Aldrich), and sodium azide (NaN_3; Acros) were used as received. The water used was purified by filtration through Millipore Gradient system after distillation, giving a resistivity of 18.2 MΩ cm.

Synthesis of 3-Trimethylsilyl-2 propynyl-2-bromo-2-methylpropanoate (TMS—C≡C—Br)

3-Trimethylsilyl-2-propyn-1-ol was synthesized as follows. A solution of propargyl alcohol (1.2 mL, 20.0 mmol) in THF (150.0 mL) was cooled down to −78 °C, and BuLi (1.6 M in hexane, 27.5 mL, 44.0 mmol) was added dropwise within 60 min. Then, TMS-Cl (5.8 mL, 45.0 mmol) was added dropwise to the mixture. The mixture was heated to room temperature and stirred for another 2 h. A total of 50 mL of hydrochloric acid solution (2.0 M) was introduced, and then the reaction was stirred for another 1 h. The aqueous layer was washed with diethyl ether twice and the combined organic layers were washed with $NaHCO_3$ and brine and dried over Na_2SO_4. The crude product was isolated as yellow oil and used without further purification.

3-Trimethylsilyl-2-propynyl 2-bromo-2-methylpropanoate was synthesized as follows. 2-Bromoisobutyryl bromide (3.0 mL, 2.0 mmol) in CH_2Cl_2 (10.0 mL) was added dropwise to a solution of 3-trimethylsilyl-2-propyn-1-ol (2.6 g, 20 mmol) and TEA (3.5 mL, 2.4 mmol) in THF (30.0 mL) at 0 °C. Afterward, the mixture was allowed to stir for 24 h at room temperature. The resulted triethylammonium salts were filtrated out, and the solvent was removed by rotary evaporation. The crude product was dissolved in CH_2Cl_2 and washed twice with saturated NH_4Cl solution and twice with water. The organic layer was dried using anhydrous $MgSO_4$, and the solvent was removed *in vacuo*, yielding dark brown oil. The crude product was passed through a silica-gel column using hexane/ethyl acetate (95:5) mixture as the eluent. The final product was isolated as colorless oil and dried under vacuum.

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.76 (*s*, 2H, —CH_2—O_2C), 1.97 (*s*, 6H, O_2C—C(CH_3)$_2$Br), 0.18 (*s*, 9H, (CH_3)$_3$Si); ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 171.23 (O—C(=O)), 93.14, 98.50 ((CH_3)$_3$Si—C≡C—CH_2), 55.50 (O_2C—C(CH_3)$_2$—Br), 54.60 (≡—CH_2—O_2C), 31.02 (O_2C—C(CH_3)$_2$—Br).

Synthesis of Br-Terminated P*t*BA (TMS—C≡C—P*t*BA—Br)

TMS—C≡C—Br (277 mg, 1.0 mmol), *t*-BA (8.7 mL, 60.0 mmol), PMDETA (208 μL, 1.0 mmol), CuBr (143 mg, 1.0 mmol), and acetone (2.2 mL) were added into a 25 mL glass tube. After three freeze–vacuum–thaw cycles, the tube was sealed under vacuum and then immersed in an oil bath thermostated at 60 °C. After a certain time, the polymerization was quenched by rapidly cooling the mixture to room temperature and exposing it to air. The mixture was filtered through neutral alumina to remove the catalyst using THF as the eluent. The polymer was precipitated by pouring the solution into the mixture of CH_3OH and H_2O (1:1/v:v). The product was dried under vacuum at 40 °C.

Synthesis of Azide End-Functionalized P*t*BA (TMS—C≡C—P*t*BA—N_3)

TMS—C≡C—P*t*BA-Br (0.2 mmol), NaN_3 (130 mg, 2.0 mmol), and DMF (5.0 mL) were added into a 25-mL round-bottomed flask with a magnetic stirrer, and the mixture was stirred at room temperature for 24 h. Afterward, the mixture was diluted with CH_2Cl_2 and washed four times with water. The solution was concentrated in vacuum, and polymer was precipitated by pouring the solution into the mixture of CH_3OH and H_2O (1:1/v:v). The product was dried under vacuum at 40 °C.

Synthesis of Cyclic P*t*BA

DMF (200 mL) was added into a 250-mL round-bottomed flask and degassed by three freeze–pump–thaw cycles. After the flask was evacuated and refilled with N_2, 287 mg of CuBr (2.0 mmol) and 576 mg of TEA (2.0 mmol) were introduced. The linear precursor (TMS—C≡C—P*t*BA—N_3) (0.02 mmol) in 10.0 mL of DMF was degassed by three freeze–pump–thaw cycles. Then this solution was added to CuBr/TEA mixture at 100 °C via syringe pump at a rate of 0.5 mL/h. After the addition of polymer solution, the reaction was allowed to proceed for another 6 h. The mixture was then cooled to room temperature, concentrated *in vacuo*, and diluted with CH_2Cl_2 (100.0 mL). The organic layer was washed twice using saturated $NaHSO_4$ solution, dried over anhydrous $MgSO_4$, filtered through neutral alumina to

remove the catalyst, and concentrated under vacuum. The cyclic polymer was obtained by precipitation in the mixture of CH_3OH and H_2O (1:1/v:v).

Synthesis of Cyclic PAA

Trifluoroacetic acid (TFA; 4.0 mL, 54.0 mmol) in 10.0 mL of CH_2Cl_2 was added dropwise to a solution of cyclic P*t*BA (500 mg) in 20.0 mL of CH_2Cl_2. The mixture was allowed to stir at room temperature for 24 h. Then, the CH_2Cl_2 and excess TFA were removed *in vacuo*. The obtained solid was dissolved in water and dialyzed against water for 3 days. Afterward, the cyclic PAA solution was lyophilized to give a white powder.

Characterization

All proton nuclear magnetic resonance (NMR) spectra were determined on a Bruker DMX-400 instrument with $CDCl_3$ or D_2O as solvent and TMS as internal standard. Fourier transform infrared (FTIR) spectra were recorded on a Bruker VECTOR-22 IR spectrometer. The number-average molecular weight (M_n) and polydispersity index (M_w/M_n) were determined by GPC (Waters 1515) using monodisperse polystyrene as the standard and THF as the eluent with a flow rate of 1.0 mL min^{-1}.

CONCLUSIONS

On the basis of the direct copper(I)-catalyzed click cyclization without any deprotection steps, we have successfully synthesized well-defined cyclic P*t*BA and PAA. The cyclic P*t*BA and PAA are confirmed by the GPC, NMR, and FTIR measurements. The present synthetic strategy provides a convenient and efficient method to synthesize cyclic polyelectrolyte and can be applied to other polymer systems.

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