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A Programmed Polymer Folding: *Click* and *Clip* Construction of Doubly *Fused* Tricyclic and Triply *Fused* Tetracyclic Polymer Topologies

Naoto Sugai, Hiroyuki Heguri, Takuya Yamamoto, and Yasuyuki Tezuka*

Department of Organic and Polymeric Materials, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8552, Japan

Supporting Information

ABSTRACT: A tandem alkyne−azide addition, i.e., *click*, and an olefin metathesis condensation, i.e., *clip*, reactions in conjunction with an *electrostatic self-assembly and covalent fixation* (ESA-CF) process, have been demonstrated as effective means to produce constructions of programmed folding of polymers having doubly fused tricyclic and triply fused tetracyclic topologies. Thus, a series of cyclic poly(tetrahydrofuran), poly(THF), precursors having an allyloxy group and an alkyne group (**Ia**), an allyloxy group and an azide group (**Ib**), and two alkyne groups (**Ic**) at the opposite positions was prepared by means of the ESA-CF method. The subsequent click reactions of **Ia** with a linear telechelic poly(THF) precursor having azide end groups (**Id**) and of **Ib** with **Ic** afforded a *bridged* dicyclic polymer (**IIa**) and a tandem *spiro* tricyclic precursor (**IIb**), respectively, both having two allyloxy groups at the opposite positions of the ring units. Finally, the intramolecular metathesis condensation reaction of **IIa** and of **IIb** in the presence of a Grubbs catalyst was performed to construct effectively a doubly *fused* tricyclic and a triply fused tetracyclic polymer topologies (**III** and **IV**), respectively.

Programmed folding of polymer molecules plays crucial roles in diverse events in biopolymer systems such as DNA packaging and protein three-dimensional (3D) structure formation.[1] Moreover, a set of cyclic proteins, *cyclotides*, is increasingly gaining attention by their extraordinary stability and bioactivity ascribed to their *fused* multicyclic structures formed through the covalent folding by the intramolecular S−S linkage with cysteine residues.[2] On the other hand, the effective and programmed polymer folding by synthetic polymers into even primitive cyclic forms has been a formidable synthetic challenge until recently.[3] Remarkable progress has now been ongoing to produce a wide variety of *single* cyclic polymers based on (1) newly developed end-to-end prepolymer folding processes[4] and (2) alternative ring-expansion polymerization.[5] By making use of newly prepared cyclic polymers having prescribed chemical structures, a wide variety of topology effects by cyclic polymers have now been unequivocally demonstrated.[6]

For a synthetic approach to *multicyclic* polymer topologies consisting of the three subclasses of *fused*, *spiro*, and *bridged* forms[7] we have developed an *electrostatic self-assembly and covalent fixation* (ESA-CF) protocol,[8] in which linear and star telechelic precursors having cyclic ammonium salt groups carrying plurifunctional carboxylate counteranions were employed to form polymeric self-assemblies as key intermediates. The three forms of dicyclic constructions, i.e., θ-shaped (*fused*), 8-shaped (*spiro*), and manacle-shaped (*bridged*), as well as a trefoil (*spiro* tricyclic) construction have been effectively produced through the covalent conversion of the electrostatic polymer self-assemblies.[9] A variety of unprecedented *spiro*- and *bridged*-type tricyclic and tetracyclic polymer topologies have been constructed through an alkyne−azide *click* reaction by employing tailored single cyclic and dicyclic polymer precursors (*kyklo*-telechelics) obtainable also by the ESA-CF protocol, affording prepolymers having atom ring sizes as large as 300 members and having alkyne and/or azide groups at the prescribed positions in their cyclic structures.[10]

A class of *fused* multicyclic polymer topologies, in contrast to their *spiro* and *bridged* counterparts, is considered particularly intriguing in the context of programmed polymer folding. However, the production of *fused* multicyclic constructions with synthetic polymers has so far been limited to a few, including doubly *fused* tricycle topologies (δ-graph) through the metathesis condensation with an 8-shaped precursor having allyl groups at the opposite positions of the two ring units obtainable by the ESA-CF protocol.[11] To extend the current frontier of synthetic polymer chemistry, the construction of topologically significant polymers such as an α-graph (doubly *fused* tricyclic), a $K_{3,3}$ graph[12] (triply *fused* tetracyclic), and a prisman graph (triply *fused* tetracyclic) has still been an ongoing challenge (Scheme 1).

Herein we report a tandem alkyne−azide addition, i.e., *click* reaction, and an olefin metathesis, i.e., *clip* reaction, in conjunction with the ESA-CF process as an effective means for producing constructions of programmed folding of polymers having well-defined and unprecedented *fused* multicyclic topologies, namely γ-graph (doubly *fused* tricyclic) and an unfolded tetrahedron graph (triply *fused* tetracyclic) constructions.[13] Notably, the combination of the *click* and *clip* reactions has also been successfully applied to produce a *catenated* multicyclic polymer of charm bracelet and daisy-chain architectures.[14]

A series of single cyclic prepolymers (*kyklo*-telechelics) of symmetric and asymmetric functionalities at the opposite positions of the ring unit were prepared by the ESA-CF process by using a set of *N*-phenylpyrrolidinium-terminated poly(THF) prepolymers having an alkene group (**1a**) or an alkyne group (**1b**) at the center position of the chain, and carrying dicarboxylate counteranions having an alkyne (**2a**) or an azide (**2b**) group (Scheme 2). Thus, cyclic poly(THF) precursors having an allyloxy group and an alkyne group (**Ia**) and having an allyloxy group and an azide group (**Ib**), were synthesized, together with one having two alkyne groups (**Ic**). In addition, a linear poly(THF) having

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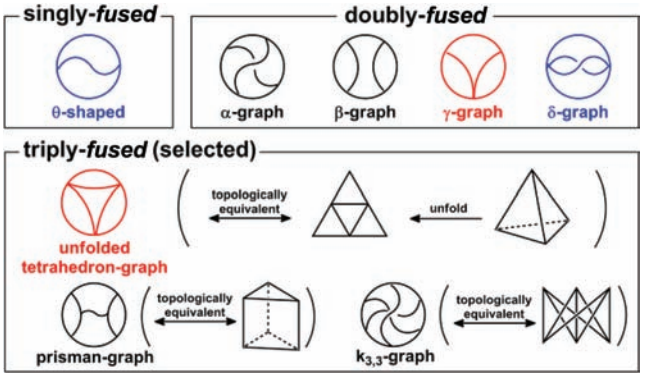
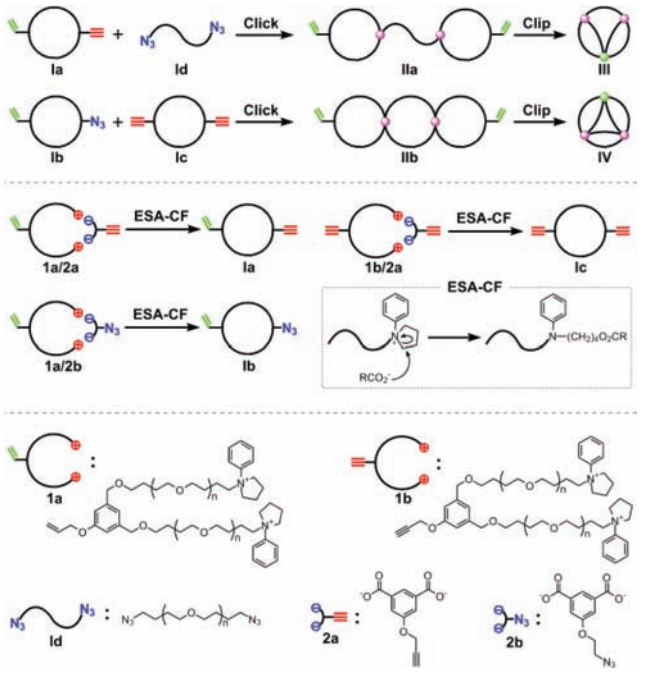
Scheme 1. Graph Presentation of *Fused* Multicyclic Polymer Topologies



Scheme 2. *Click* and *Clip* Construction of Doubly and Triply *Fused* Multicyclic Polymer Topologies using a Series of *Kyklo*-Telechelic Precursors Obtainable by the ESA-CF Process



azide end groups (**Id**) was prepared by simply terminating a living polymerization of THF with tetrabutylammonium azide. (See Supporting Information (SI) for the preparation details.)

The subsequent click reaction[10] was performed in the presence of copper sulfate and sodium ascorbate by employing complementary sets of polymer precursors, namely cyclic (**Ia**)/linear (**Id**) and cyclic (**Ib**)/cyclic (**Ic**) combinations with a slight excess (5−10%) of the former precursors to produce a *bridged* dicyclic (manacle) polymer precursor (**IIa**) and a tandem *spiro* tricyclic counterpart (**IIb**), respectively, both having two allyloxy groups at the opposite positions of the ring units. These products, **IIa** and **IIb**, were finally isolated by preparative SEC in 63% and in 64% yield, respectively. The progress of the reaction and the subsequent purification process were monitored by SEC (Figure 1). In both systems, the SEC traces of both click

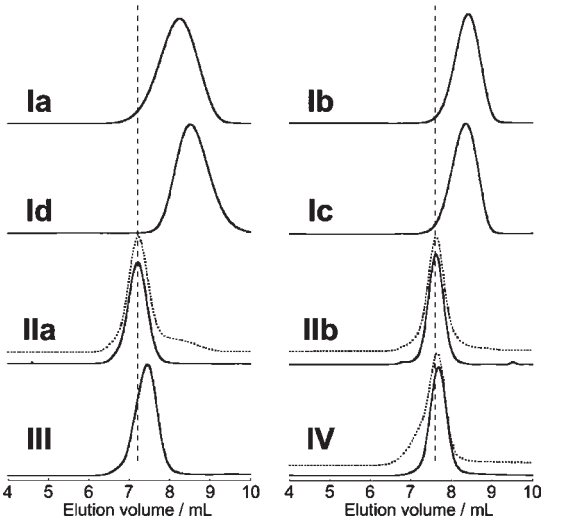


Figure 1. SEC traces of prepolymers, **Ia**, **Ib**, **Ic**, and **Id**, the click products, **IIa** and **IIb**, and the *fused*-type multicyclic polymer products, **III** and **IV**. Broken lines and solid lines show those obtained before and after fractionation, respectively. (THF was used as eluent at late flow 1.0 mL/min, with TSK G3000HXL for **Ia**, **Id**, **IIa**, and **III**, with TSK G4000HXL for **Ib**, **Ic**, **IIb**, and **IV**).

products shifted toward the higher molecular weight region with only traces at the lower molecular weight region due to the precursors charged slightly in excess (Figure 1, **IIa** and **IIb**, broken lines). After the purification by preparative SEC fractionation, the precursor fraction was completely eliminated as seen in Figure 1 (**IIa** and **IIb**, solid lines). The extent of the contraction of the 3D size for dicyclic **IIa** and tricyclic **IIb** was estimated by their M_p(SEC)/M_n(NMR) ratios of 0.82 and 0.63, respectively, with reasonable agreements with the previously reported values for the relevant polymers.[10,11]

^{1}H NMR spectra of **IIa** and **IIb** together with their polymer precursors (**Ia**/**Id** and **Ib**/**Ic**, respectively) are shown in Figure S1 in SI and in Figure 2, respectively. It is shown that the signals for the ethynyl protons (2.53 ppm in **Ia** and 2.54 and 2.55 ppm in **Ic**) and those of the azidomethylene protons (3.30 ppm in **Id** and 3.64 ppm in **Ib**) were replaced by the triazole proton signals at 7.65 ppm in **IIa** and 7.79−7.88 ppm in **IIb**, respectively, to confirm the effective click reaction. The signals for the allyloxy units (5.26−5.44 and 5.99−6.12 ppm in **IIa** and 5.23−5.47 and 5.96−6.15 ppm in **IIb**) are visibly intact during the click process. By comparison of the signal intensities of the main-chain protons with the linking-group protons, M_n's (NMR) were determined to be 10 kDa and 11 kDa for **IIa** and **IIb**, respectively.

MALDI-TOF mass spectra of **IIa** and **IIb** together with those of their polymer precursors (**Ia**/**Id** and **Ib**/**Ic**, respectively) are shown in Figure S3 in SI and in Figure 3, respectively. A uniform series of peaks with an interval of 72 mass units (corresponding to the repeating THF units) were observed for all samples; moreover, each peak exactly matched the molar mass calculated from the chemical structure of the product. Thus, for **IIa**, the peak at m/z = 7926.4, which is assumed to be the adduct with Na^+, corresponds to **IIa** possessing the expected chemical structure with the degree of polymerization, DP_n, of 85; $(C_4H_8O) \times 85 + C_{104}H_{128}N_{10}O_{16}$, plus Na^+ = 7926.332. For **IIb**, the peak at m/z = 9023.5, assumed to be the adduct with Na^+, corresponds to **IIb** possessing the expected chemical structure with a DP_n of 90; $(C_4H_8O) \times 90 + C_{148}H_{180}N_{12}O_{24}$, plus Na^+ = 9023.524.

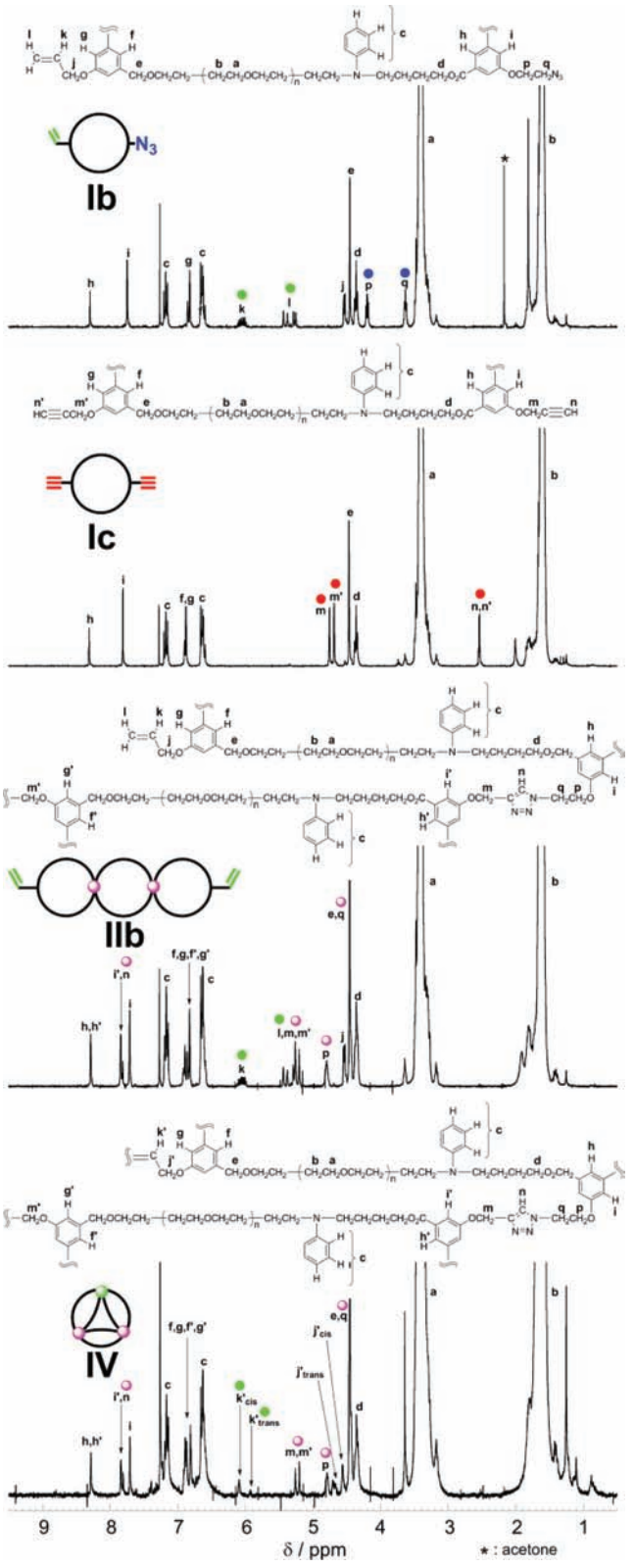


Figure 2. ^{1}H NMR (300 MHz) spectra of the *kyklo*-telechelic prepolymers, **Ib** and **Ic**, the click product, **IIb**, and the triply *fused* tetracyclic polymer product, **IV**. ($CDCl_3$, 40 °C. The samples **IIb** and **IV** after the purification by means of the fractionation with preparative SEC.)

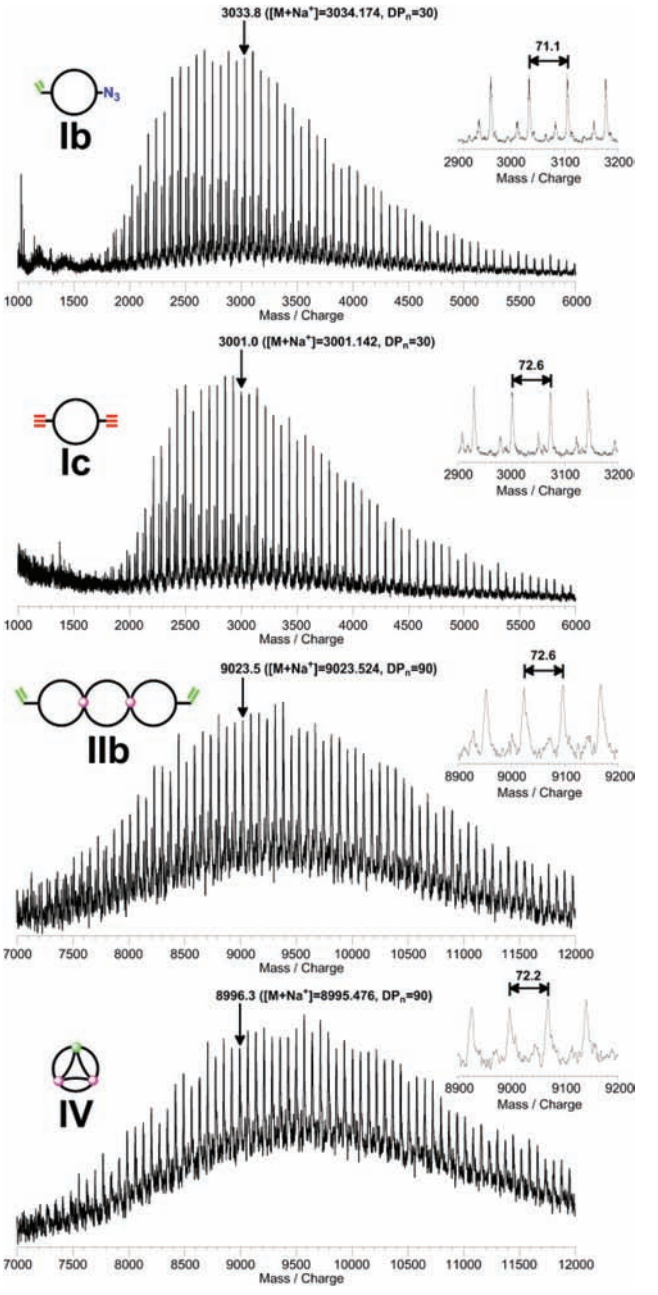


Figure 3. MALDI-TOF mass spectra of *kyklo*-telechelic prepolymers, **Ib** and **Ic**, the click product, **IIb**, and the triply *fused* tetracyclic polymer product, **IV**. (Linear mode, matrix: dithranol with sodium trifluoroacetate. DP_n denotes the number of monomer units in the product.)

The subsequent intramolecular olefin metathesis reaction of **IIa** and **IIb**, possessing *bridged* dicyclic and tandem *spiro* tricyclic topologies and having allyloxy groups at the opposite positions of the ring units, were conducted under dilution (0.2 g/L) by repeated addition of a first-generation Grubbs catalyst into the reaction solution.[15] SEC showed that the crude reaction products contained a noticeable portion of the intermolecular condensation products as seen by broken lines in SEC (Figure 1, **IV**, broken line). Hence, the product **IV** was first recovered by a column chromatography with silica gel, and finally isolated by the purification with preparative SEC fractionation technique (Figure 1, **IV**, solid line). The isolated yields of **III** and **IV** were 28% and 55%, respectively.

^{1}H NMR spectra of the isolated **III** and **IV** are compared with their precursors **IIa** and **IIb** in Figure S2 in SI and in Figure 2,

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respectively. It is shown that the signals for the allyloxy units in **IIa** and in **IIb** are completely replaced by those of the inner olefinic units at 6.07−6.12 (cis) and 5.90−5.95 (trans) ppm in **III** and at 6.04−6.15 (cis) and 5.90−5.96 (trans) ppm in **IV**. It is indicative of the metathesis condensation reaction proceeding effectively in both cases even under applied dilution.

MALDI-TOF mass spectra of **III** and **IV** are compared with their precursors **IIa** and **IIb** in Figure S3 in SI and in Figure 3, respectively, to confirm the successful construction of a doubly *fused* tricyclic and a triply *fused* tetracyclic polymer topologies. Those of **III** and **IV** showed a uniform series of peaks as in **IIa** and **IIb**. Thus, for **III** the peak at m/z = 7898.3, which is assumed to be the adduct with Na^+, corresponds to **III** possessing the expected chemical structure with a DP_n of 85; $(C_4H_8O) \times 85 + C_{102}H_{124}N_{10}O_{16}$, plus Na^+ equals 7898.278. For **IV**, the peak at m/z = 8996.3, which is assumed to be the adduct with Na^+, corresponds to **IV** possessing the expected chemical structure with a DP_n of 90; $(C_4H_8O) \times 90 + C_{146}H_{176}N_{12}O_{24}$, plus Na^+ equals 8995.476. Since **III** and **IV** are produced from **IIa** and **IIb** by the elimination of an ethylene molecule, their molecular weights differ by 28 mass units. This was confirmed by the two sets of mass spectra as shown in Figure S3 in SI and in Figure 3.

The extent of the contraction of the 3D size for tricyclic **III** from dicyclic **IIa** and for tetracyclic **IV** from tricyclic **IIb** was estimated after the SEC fractionation by their M_p(SEC)/M_n-(NMR) ratios, which showed noticeable reduction from 0.82 to 0.60 for **III** and from 0.63 to 0.52 for **IV**. Accordingly, the programmed polymer folding could produce unusually compact polymer conformation in their 3D structures.

In summary, a tandem alkyne−azide addition (i.e., a *click* reaction) and an olefin metathesis condensation (i.e., a *clip* reaction) in conjunction with an *electrostatic self-assembly and covalent fixation* (ESA-CF) process have been demonstrated upon the combination of NMR, SEC, and MALDI-TOF techniques as an effective means for producing constructions of programmed folding of polymers such as doubly *fused* tricyclic and triply *fused* tetracyclic polymer topologies.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for the synthesis, ^{1}H NMR spectra, MALDI-TOF MS spectra, and IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
ytezuka@o.cc.titech.ac.jp

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■ REFERENCES

(1) For DNA packaging, see: (a) Osada, K.; Oshima, H.; Kobayashi, D.; Doi, M.; Enoki, M.; Yamasaki, Y.; Kataoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 12343–12348. For protein 3D structures:(b) Dobson, C. M. *Nature* **2003**, *426*, 884–890. (c) Sosnick, T. R.; Hinshaw, J. R. *Science* **2011**, *334*, 464–465.

(2) (a) Craik, D. *J. Science* **2006**, *311*, 1563–1564. (b) Craik, D. J. *Trends Plant Sci.* **2009**, *14*, 328–335.

(3) For recent developments in polymer folding with synthetic polymers, see: (a) Perrier, S. *Nature Chem.* **2011**, *3*, 194–196. (b) Schmidt, B. V. K. J.; Fechler, N.; Falkenhagen, J.; Lutz, J.-F. *Nature Chem.* **2011**, *3*, 234–238. For polymer folding into helix structures, see:(c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4012. (d) Yashima, E.; Maeda, K.; Iida, H.; Furusho, Y.; Nagai, K. *Chem. Rev.* **2009**, *109*, 6102–6211. (e) Gan, Q.; Ferrand, Y.; Bao, C.; Kauffmann, B.; Grélard, A.; Jiang, H.; Huc, I. *Science* **2011**, *331*, 1172–1175. For polymer folding by intramolecular cross-linking process, see:(f) Harth, E.; Van Horn, B.; Lee, V. Y.; Germack, D. S.; Gonzales, C. P.; Miller, R. D.; Hawker, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 8653–8660. (g) Foster, E. J.; Berda, E. B.; Meijer, E. W. *J. Am. Chem. Soc.* **2009**, *131*, 6964–6966. (h) Zhang, K.; Lackey, M. A.; Cui, J.; Tew, G. N. *J. Am. Chem. Soc.* **2011**, *133*, 4140–4148.

(4) (a) Yamamoto, T.; Tezuka, Y. In *Complex Macromolecular Architectures: Synthesis, Characterization, and Self-Assembly*; Hadjichristidis, N., Hirao, A., Tezuka, Y., Du Prez, F., Eds.; Wiley: Singapore, 2011; pp 3−19. (b) Laurent, B. A.; Grayson, S. M. *Chem. Soc. Rev.* **2009**, *38*, 2202–2213. (c) Yamamoto, T.; Tezuka, Y. *Eur. Polym. J.* **2011**, *47*, 535–541.

(5) (a) Xia, Y.; Boydston, A. J.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5882–5885. (b) Shin, E. J.; Brown, H. A.; Gonzalez, S.; Jeong, W.; Hedrick, J. L.; Waymouth, R. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6388–6391.

(6) For recent developments in functional cyclic polymers, see: (a) Endo, K. *Adv. Polym. Sci.* **2008**, *217*, 121–183. (b) Yamamoto, T.; Tezuka, Y. *Polym. Chem.* **2011**, *2*, 1930–1941. (c) Deffieux, A.; Schappacher, M. *Cell. Mol. Life Sci.* **2009**, *66*, 2599–2602.

(7) Tezuka, Y.; Oike, H. *J. Am. Chem. Soc.* **2001**, *123*, 11570–11576.

(8) (a) Oike, H.; Imaizumi, H.; Mouri, T.; Yoshioka, Y.; Uchibori, A.; Tezuka, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9592–9599.

(9) Tezuka, Y.; Tsuchitani, A.; Yoshioka, Y.; Oike, H. *Macromolecules* **2003**, *36*, 65–70.

(10) Sugai, N.; Heguri, H.; Ohta, K.; Meng, Q.; Yamamoto, T.; Tezuka, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14790–14802.

(11) Tezuka, Y.; Fujiyama, K. *J. Am. Chem. Soc.* **2005**, *127*, 6266–6270.

(12) For the $K_{3,3}$ graph, see: Chen, C.-T.; Gantzel, P.; Siegel, J. S.; Baldridge, K. K.; English, R. B.; Ho, D. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2657–2660.

(13) The doubly *fused* tricyclic (**III**) and triply *fused* tetracyclic (**IV**) topologies constructed in this study are expressed as $III_5(0,3)[0^{a,b}\text{-}0^{a}\text{-}0^{b}]$ and $IV_6(0,3)[0^{a,c}\text{-}0^{a,b}\text{-}0^{b,c}]$, respectively, according to the systematic notation (ref 7) .

(14) (a) Clark, P. G.; Guidry, E. N.; Chan, W. Y.; Steinmetz, W. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 3405–3412. (b) Clark, P. G.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 13631–13633.

(15) To optimize the process, four Ru catalysts, i.e., first- and second-generation Grubbs catalysts and first- and second-generation Hoveyda−Grubbs catalysts, were examined by using linear telechelic poly(THF)s, having two allyloxy or two butenoxy end groups. As a result, Hoveyda−Grubbs catalysts were not effective for allyloxy and butenoxy groups. However, both first- and second-generation Grubbs catalysts were reactive with allyloxy groups, rather than with butenoxy counterparts. Moreover, with a first-generation Grubbs catalyst, side reactions were suppressed better than with a second-generation Grubbs catalyst.