

Folding Construction of a Pentacyclic Quadruply fused Polymer Topology with Tailored *kyklo*-Telechelic Precursors**

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Dedicated to Professor Teiji Tsuruta on the occasion of his 95th birthday

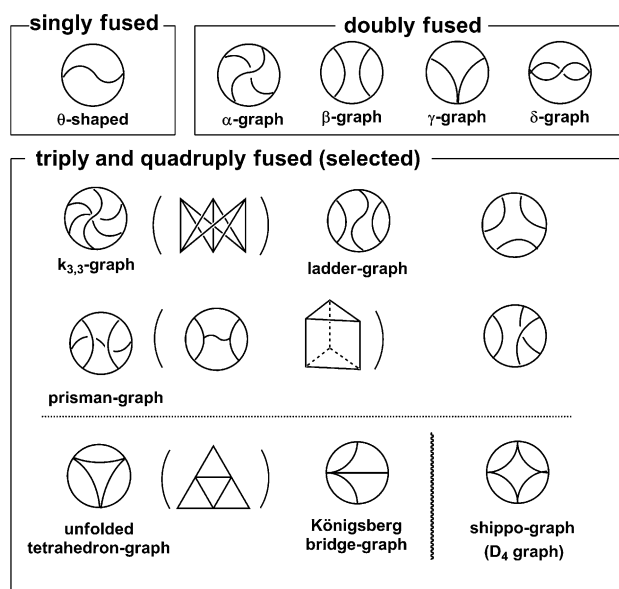
Abstract: A pentacyclic quadruply fused polymer topology has been constructed for the first time through alkyne–azide addition (click) and olefin metathesis (clip) reactions in conjunction with an electrostatic self-assembly and covalent fixation (ESA-CF) process. Thus, a spiro-type, tandem tetracyclic poly(tetrahydrofuran), poly(THF), precursor having two allyloxy groups at the opposite positions of the four ring units was prepared by the click-linking of one unit of an eight-shaped precursor having alkyne groups at the opposite positions with two units of a single-cyclic counterpart having an azide and an alkene group at the opposite positions. Both are obtainable through ESA-CF. The subsequent metathesis clip-folding of the tetracyclic precursor could afford a pentacyclic quadruply fused polymer product, of “shippo” form, in 19 % yield.

The programmed folding of polymer molecules, which is widely observed in diverse biopolymer events including DNA packaging and protein 3D structure formation, has also been highlighted in a variety of cyclic peptides, cyclotides, constructing fused multicyclic structures formed through the intramolecular S–S bridging with cysteine residues, to be crucial for their extraordinary stability and bioactivity.^[1,2] Notably, in particular, a topologically intriguing, prototypical non-planar $K_{3,3}$ -graph construction, which cannot be embedded in the plane in such a way that its edges intersect only at their endpoints, has recently been identified in cyclotides from diverse origins.^[1,3]

The effective and programmed folding by synthetic polymers into designated multicyclic forms, on the other hand, has been an ongoing challenge in polymer chemistry.^[4] We have developed an electrostatic self-assembly and covalent fixation (ESA-CF) method^[5] for the programmed polymer folding in which linear, star, and other branched 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, that is, θ

(fused), 8 (spiro), and manacle (bridged), as well as a trefoil (spiro-tricyclic) construction have been effectively produced through the ESA-CF process.^[5,6]

A class of fused multicyclic polymer topologies, rather than their spiro and bridged counterparts, are particularly attracting not only by their relevance to their programmed folding of cyclotides but also from the significance of topological geometry conjectures^[5,7] (Scheme 1). Thus, a tet-



Scheme 1. Graph presentation of fused multicyclic polymer topologies.

racyclic triply fused macromolecular $K_{3,3}$ -graph has been constructed through the ESA-CF method using a uniform-size dendritic polymer precursor having six cyclic ammonium salt end groups carrying two units of a trifunctional carboxylate counteranions, and subsequent covalent conversion by the ring-opening reaction of cyclic ammonium salt groups at an elevated temperature under dilution.^[8]

Moreover, a tandem alkyne–azide addition (click) and olefin metathesis (clip) reaction in conjunction with the ESA-CF process has been introduced, where a variety of spiro and bridged-type multicyclic polymer precursors (kyklo-telechelics) were employed to afford prepolymers having as large as 300-membered atom ring sizes and having alkyne, azide, and/or olefinic groups at the prescribed positions in their cyclic structures.^[9] Thereby, we have successfully constructed all four forms of doubly fused tricycle topologies (α , β , γ , and δ -

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graph) by means of the ESA-CF method in conjunction with a tandem click and clip reaction.^[10,11] Furthermore, three forms of triply fused tetracyclic constructions including an unfolded tetrahedron-graph (Scheme 1), in addition to a $K_{3,3}$ -graph and a ladder form, have also been realized.^[12]

As part of our continuing efforts to push forward the frontier of constructing complex polymer architectures, we show herein, as the first example of a pentacyclic quadruply fused form, the construction of a polymer topology having a $p4m$ symmetry, named a D_4 graph (Scheme 1).^[13,14] This particular pentacyclic construction is frequently encountered in traditional art design worldwide, including Japan, and is known as a “shippo” form.^[15]

For the construction of a pentacyclic quadruply fused polymer product (**III**), we employed a tandem *spiro*-tetracyclic polymer precursor having two allyloxy groups at the opposite positions of the four ring units (**II**), obtainable by the click linking process of single-cyclic and dicyclic telechelic precursors (*kyklo*-telechelics) having tailored functional groups at the designated positions of cyclic and dicyclic units (Scheme 2). Thus first, a single cyclic poly(THF) having an azide and allyloxy groups (**1a**) and an 8-shaped poly(THF) having two alkyne groups at the opposite positions (**1b**) were prepared by the ESA-CF procedure and subjected to the click reaction in an equimolar azide/alkyne ratio. The progress of the reaction was followed by SEC and exhibited noticeable peak-shift toward the higher molecular weight region (Figure 1, **II**, broken line). The peak molecular weight for **II** ($M_p = 9.7$ kDa) was nearly equal to the sum of those of the precursors, that is, two units of **1a** and one unit of **1b** ($2 \times$

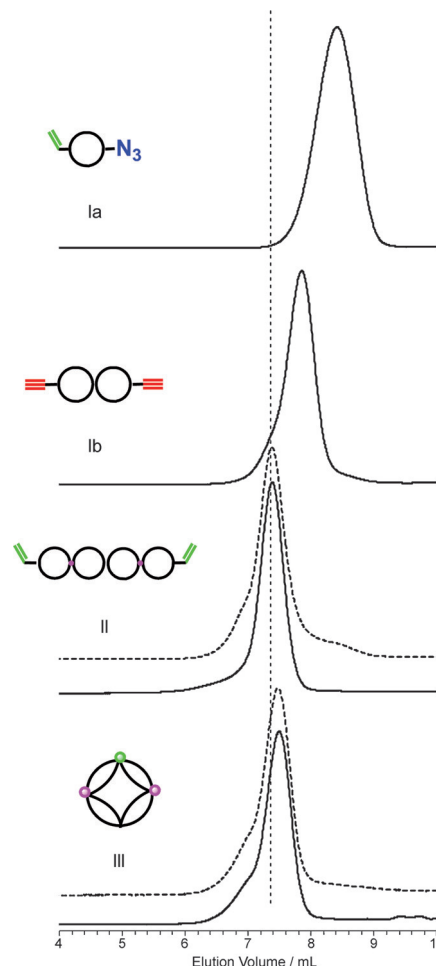
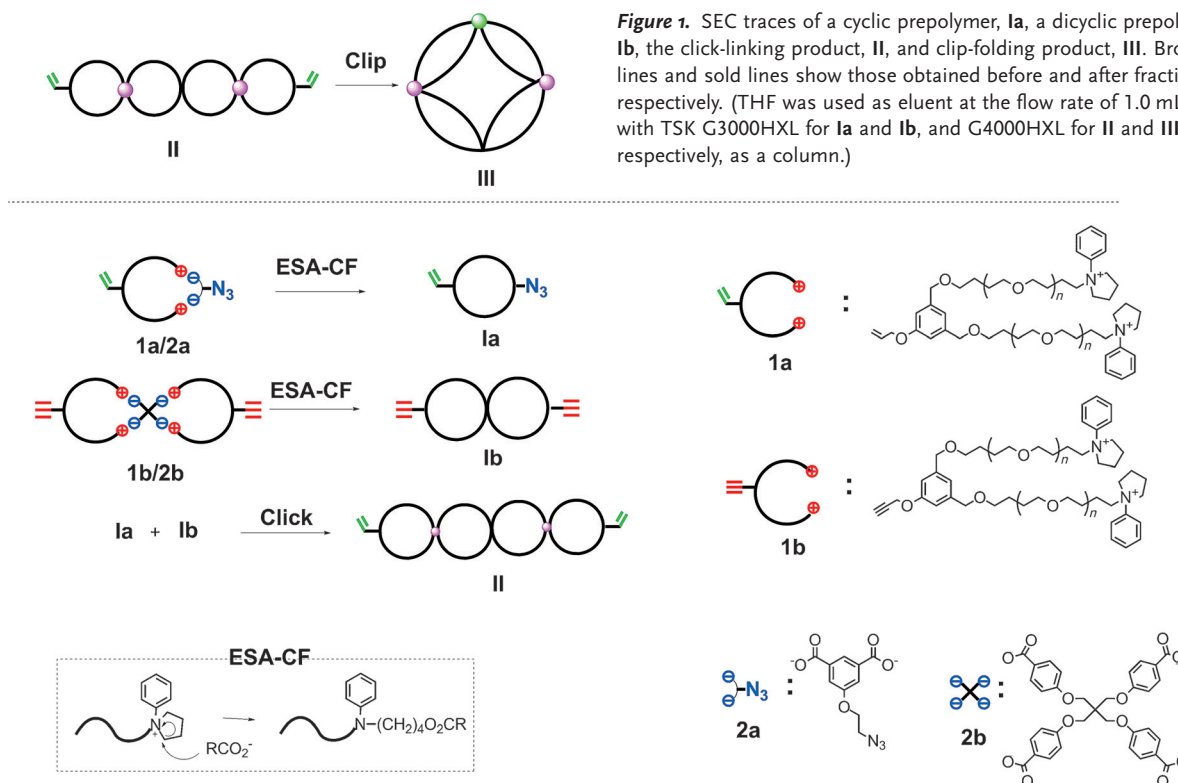


Figure 1. SEC traces of a cyclic prepolymer, **1a**, a dicyclic prepolymer, **1b**, the click-linking product, **II**, and clip-folding product, **III**. Broken lines and solid lines show those obtained before and after fractionation, respectively. (THF was used as eluent at the flow rate of 1.0 mL min^{-1} , with TSK G3000HXL for **1a** and **1b**, and G4000HXL for **II** and **III**, respectively, as a column.)



Scheme 2. Construction of a pentacyclic quadruply fused polymer topology by click-linking and clip-folding using *kyklo* telechelic precursors obtained by the ESA-CF process.

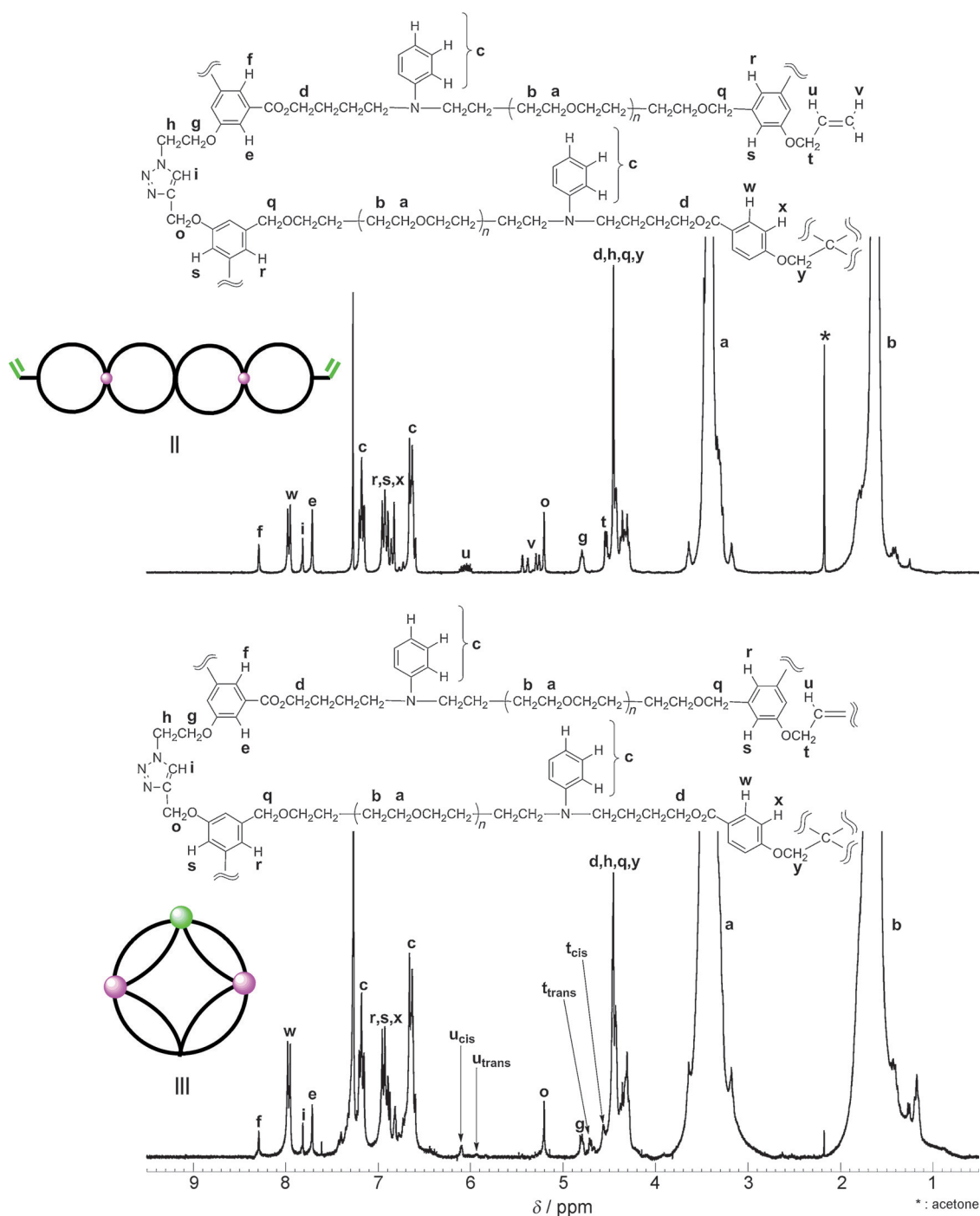


Figure 2. ^1H NMR (300 MHz) spectra of a spiro-tetracyclic prepolymer having allyl groups at the opposite positions of four ring units, **II**, and the clip-folding product, **III** (CDCl_3 , 40°C).

2.6 kDa + 5.2 kDa = 10 kDa). After the subsequent preparative SEC fractionation, **II** was recovered in 50 % yield (Figure 1, **II**, solid line).

The ^1H NMR spectroscopic analysis of **II** (Figure 2, top), in comparison with its prepolymers **Ia** and **Ib** (Supporting Information, Figure S1, top and bottom, respectively), showed the signals for the triazole proton signal at 7.82 ppm in **II**, replacing the ethynyl protons at 2.54 ppm in **Ib** and that of the azidomethylene protons at 3.64 ppm in **Ia** shifted to

4.23–4.45 ppm, confirming the effective click reaction. The signals for the allyloxy units at 5.24–5.48 and 5.96–6.15 ppm in **II** are visible intact during the click process. By comparing the signal intensities of the main-chain protons with the linking group protons, $M_n(\text{NMR})$ of **II** was determined to be 16 kDa.

The MALDI-TOF mass spectrum of the isolated species **II** showed a uniform series of peaks with an interval of 72 mass units for the repeating THF monomer units, and each peak exactly matched the total molar mass of **II** (Figure 3,

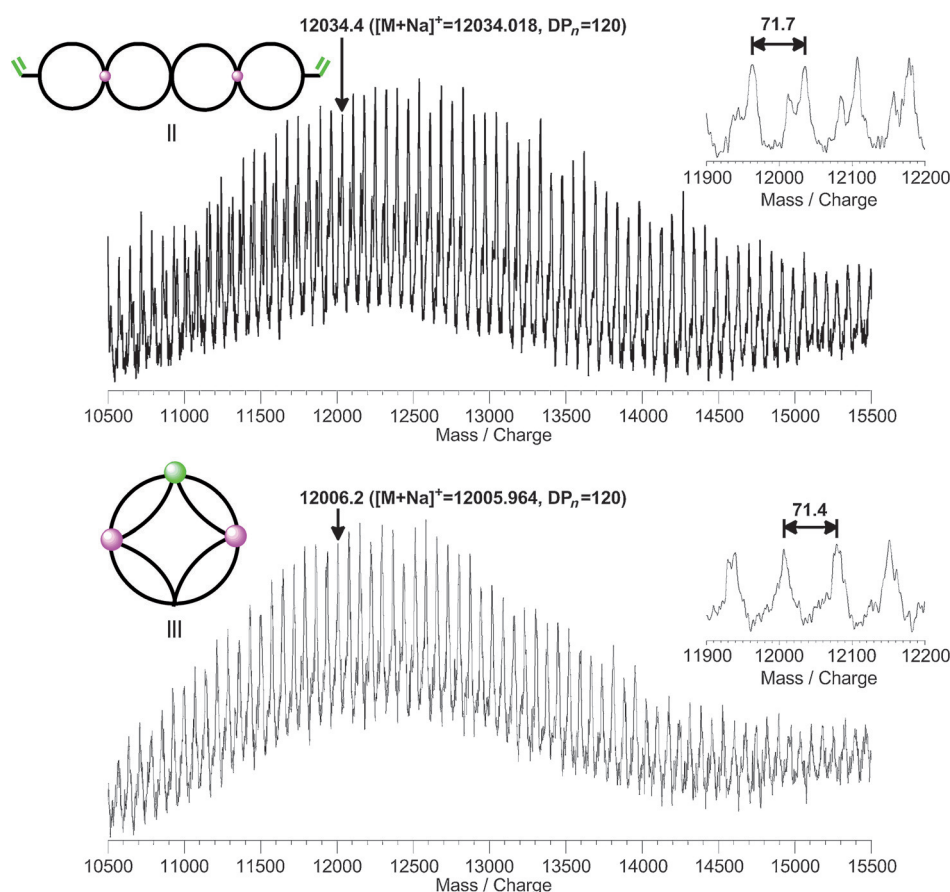


Figure 3. MALDI-TOF mass spectra of a spiro-tetracyclic prepolymer having allyl groups at the opposite positions of four ring units, **II**, and the clip-folding product, **III**. Linear mode, matrix: dithranol with sodium trifluoroacetate. DP_n denotes the number of monomer units in the products.

top). Thus, the peak at $m/z = 12034.4$, which was assumed to be the adduct with Na^+ , corresponds to the expected chemical structure with a DP_n of 120; $(C_4H_8O) \times 120 + C_{201}H_{234}N_{14}O_{32}$ plus Na^+ equals 12034.018. Furthermore, the sum of twice the molar mass of **Ia** with a DP_n of 30 ($2 \times (3033.8 - [Na^+]) = 6021.6$) plus the molar mass of **Ib** with a DP_n of 60 ($6012.2 - [Na^+] = 5989.2$) is 12010.8, in agreement with the molar mass of **II** with a DP_n of 120 ($12034.4 - [Na^+] = 12011.0$) given above (Supporting Information, Figure S2, top and bottom, respectively for MALDI-TOF mass spectra of **Ia** and **Ib**).

The subsequent clip folding, that is, intramolecular olefin metathesis reaction, of **II** was conducted under dilution (0.2 g L^{-1}) by repeated addition of a Grubbs catalyst first generation into the reaction solution to produce a pentacyclic quadruply fused polymer product **III** (Scheme 2). SEC showed that the crude reaction product retained unimodal profile with a noticeable peak shift toward the smaller 3D size, to agree with the formation of an intramolecular condensation product (Figure 1, **III**, broken line). Finally, the product **III** was isolated by means of the preparative SEC fractionation technique (Figure 1, **III**, solid line), after the column chromatography work-up with silica gel and alumina. The yield of isolated product of **III** was 19%.

The 1H NMR spectroscopic comparison of isolated **III** with its precursor **II** (Figure 2) showed that the signals for the

allyloxy units are completely replaced by those of the inner olefinic units at 6.07–6.16 (*cis*) and 5.90–5.98 (*trans*) ppm, indicative of the effective metathesis condensation reaction even under applied dilution.

MALDI-TOF mass comparison of **III** with its precursor **II** (Figure 3, top and bottom, respectively) further substantiated the successful construction of a pentacyclic quadruply fused polymer topology. Thus, the peak at $m/z = 12006.2$ in **III**, which is assumed to be the adduct with Na^+ , corresponds to the expected product with a DP_n of 120; $(C_4H_8O) \times 120 + C_{199}H_{230}N_{14}O_{32} + Na^+ = 12005.964$. Furthermore, the decrease of 28 mass units in the respective peaks of **III** from **II** corresponds to the elimination of an ethylene molecule along with the clip folding process.

The extent of the contraction of the 3D size for the pentacyclic **III** from the tetracyclic **II** was quantitatively estimated after the SEC fractionation by their $M_p(\text{SEC})/M_n(\text{NMR})$ ratios, which showed noticeable reduction from 0.61 to 0.54. The

observed degree of the contraction in 3D size was more significant in comparison with a singly fused θ -shaped (0.63)^[5b,6] as well as doubly fused δ -graph (0.61)^[10] and γ -graph (0.60)^[11] constructions, but comparable with a triply fused unfolded tetrahedron graph (0.52)^[12] and with a $K_{3,3}$ graph (0.49)^[8] construction. Accordingly, the programmed polymer folding could produce unusually compact polymer conformation in their 3D structures.

Keywords: click reactions · multicyclic polymers · olefin metathesis · polymer folding · topological polymer chemistry

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- [1] a) D. J. Craik, *Science* **2006**, *311*, 1563–1564; b) D. J. Craik, *Trends Plant Sci.* **2009**, *14*, 328–335; c) K. Jagadish, J. A. Camarero, *Pept. Sci.* **2010**, *94*, 611–616; d) J. A. Camarero, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 10025–10026; e) T. L. Aboye, J. A. Camarero, *J. Biol. Chem.* **2012**, *287*, 27026–27032; f) D. J. Craik, *Nat. Chem.* **2012**, *4*, 600–602.
- [2] a) A. Alon, I. Grossman, Y. Gat, V. K. Kodali, F. DiMaio, T. Mehlman, G. Haran, D. Baker, C. Thorpe, D. Fass, *Nature* **2012**, *488*, 414–418; b) C. Wu, J.-C. Leroux, M. A. Gauthier, *Nat. Chem.* **2012**, *4*, 1044–1049; c) S. Yang, Y. Xiao, D. Kang, J. Liu,

- Y. Li, E. A. B. Undheim, J. K. Klint, M. Rong, R. Lai, G. F. King, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 17534–17539; d) Z. Dekan, M. Mobli, M. W. Pennington, E. Fung, E. Nemeth, P. F. Alewood, *Angew. Chem. Int. Ed.* **2014**, *53*, 2931–2934; *Angew. Chem.* **2014**, *126*, 2975–2978; e) A. D. de Araujo, M. Mobli, G. F. King, P. F. Alewood, *Angew. Chem. Int. Ed.* **2012**, *51*, 10298–10302; *Angew. Chem.* **2012**, *124*, 10444–10448; f) H.-K. Cui, Y. Guo, Y. He, F.-L. Wang, H.-N. Chang, Y.-J. Wang, F.-M. Wu, C.-L. Tian, L. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 9558–9562; *Angew. Chem.* **2013**, *125*, 9737–9741.
- [3] a) S. P. Puttamadappa, K. Jagadish, A. Shekhtman, J. A. Camarero, *Angew. Chem. Int. Ed.* **2010**, *49*, 7030–7034; *Angew. Chem.* **2010**, *122*, 7184–7188; b) K. Jagadish, R. Borra, V. Lacey, S. Majumder, A. Shekhtman, L. Wang, J. A. Camarero, *Angew. Chem. Int. Ed.* **2013**, *52*, 3126–3131; *Angew. Chem.* **2013**, *125*, 3208–3213; c) Y. Ji, S. Majumder, M. Millard, R. Borra, T. Bi, A. Y. Elnagar, N. Neamati, A. Shekhtman, J. A. Camarero, *J. Am. Chem. Soc.* **2013**, *135*, 11623–11633.
- [4] For reviews, see: a) O. Altintas, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2012**, *33*, 958–971; b) M. Ouchi, N. Badi, J.-F. Lutz, M. Sawamoto, *Nat. Chem.* **2011**, *3*, 917–924; c) S. Perrier, *Nat. Chem.* **2011**, *3*, 194–196; For polymer folding by intramolecular cross-linking process, see: d) O. Altintas, P. Krolla-Sidenstein, H. Gliemann, C. Barner-Kowollik, *Macromolecules* **2014**, *47*, 5877–5888; e) B. V. K. J. Schmidt, N. Fechner, J. Falkenhagen, J.-F. Lutz, *Nat. Chem.* **2011**, *3*, 234–238; f) O. Shishkan, M. Zamfir, M. A. Gauthier, H. G. Börner, J.-F. Lutz, *Chem. Commun.* **2014**, *50*, 1570–1572; g) E. Harth, B. Van Horn, V. Y. Lee, D. S. Germack, C. P. Gonzales, R. D. Miller, C. J. Hawker, *J. Am. Chem. Soc.* **2002**, *124*, 8653–8660; h) E. J. Foster, E. B. Berda, W. W. Meijer, *J. Am. Chem. Soc.* **2009**, *131*, 6964–6966; i) K. Zhang, M. A. Lackey, J. Cui, G. N. Tew, *J. Am. Chem. Soc.* **2011**, *133*, 4140–4148; j) S. Mavila, C. E. Diesendruck, S. Linde, L. Amir, R. Shikler, N. G. Lemcoff, *Angew. Chem. Int. Ed.* **2013**, *52*, 5767–5770; *Angew. Chem.* **2013**, *125*, 5879–5882; k) E. Huerta, P. J. M. Stals, E. W. Meijer, A. R. A. Palmans, *Angew. Chem. Int. Ed.* **2013**, *52*, 2906–2910; *Angew. Chem.* **2013**, *125*, 2978–2982.
- [5] a) *Topological Polymer Chemistry: Progress of cyclic polymers in syntheses, properties and functions* (Ed.: Y. Tezuka), World Scientific, Singapore, **2013**; b) H. Oike, H. Imaizumi, T. Mouri, Y. Yoshioka, A. Uchibori, Y. Tezuka, *J. Am. Chem. Soc.* **2000**, *122*, 9592–9599.
- [6] Y. Tezuka, A. Tsuchitani, Y. Yoshioka, H. Oike, *Macromolecules* **2003**, *36*, 65–70.
- [7] Y. Tezuka, H. Oike, *J. Am. Chem. Soc.* **2001**, *123*, 11570–11576.
- [8] T. Suzuki, T. Yamamoto, Y. Tezuka, *J. Am. Chem. Soc.* **2014**, *136*, 10148–10155.
- [9] a) N. Sugai, H. Heguri, K. Ohta, Q. Meng, T. Yamamoto, Y. Tezuka, *J. Am. Chem. Soc.* **2010**, *132*, 14790–14802; For click construction of multicyclic polymer topologies, see also: b) Z. Jia, M. J. Monteiro, *J. Polym. Sci. Part A* **2012**, *50*, 2085–2097; c) M. D. Hossain, Z. Jia, M. Monteiro, *Macromolecules* **2014**, *47*, 4955–4970; d) M. D. Hossain, D. Lu, Z. Jia, M. J. Monteiro, *ACS Macro Lett.* **2014**, *3*, 1254–1257; e) Y. Tomikawa, H. Fukata, Y. S. Ko, T. Yamamoto, Y. Tezuka, *Macromolecules* **2014**, *47*, 8214–8223.
- [10] Y. Tezuka, K. Fujiyama, *J. Am. Chem. Soc.* **2005**, *127*, 6266–6270.
- [11] M. Igari, H. Heguri, T. Yamamoto, Y. Tezuka, *Macromolecules* **2013**, *46*, 7303–7315.
- [12] N. Sugai, H. Heguri, T. Yamamoto, Y. Tezuka, *J. Am. Chem. Soc.* **2011**, *133*, 19694–19697.
- [13] K. Taniyama, A. Yasuhara, *Topol. Appl.* **2001**, *112*, 87–109.
- [14] The present pentacyclic quaruply fused graph is expressed as $V_8(0,4)[0^{a,d}.0^{a,b}.0^{b,c}.0^{c,d}]$, according to the systematic notation (see Ref. [7]).
- [15] Some examples of traditional art designs of “shippo” form are shown in the Supporting Information, Figure S3.

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