Polymer Folding

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 significanse of topological geometry conjectures[5,7] (Scheme 1). Thus, a tet-
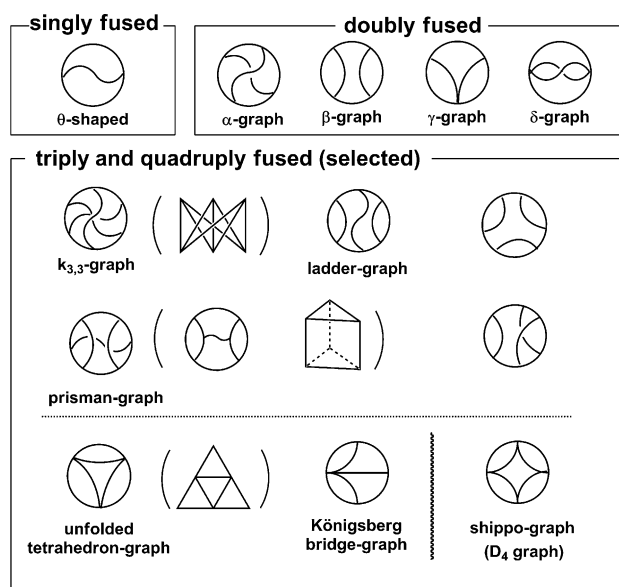
Scheme 1. Graph presentation of fused muticyclic polymer topologies.

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 (**Ia**) and an 8-shaped poly(THF) having two alkyne groups at the opposite positions (**Ib**) 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 **Ia** and one unit of **Ib** ($2 \times$
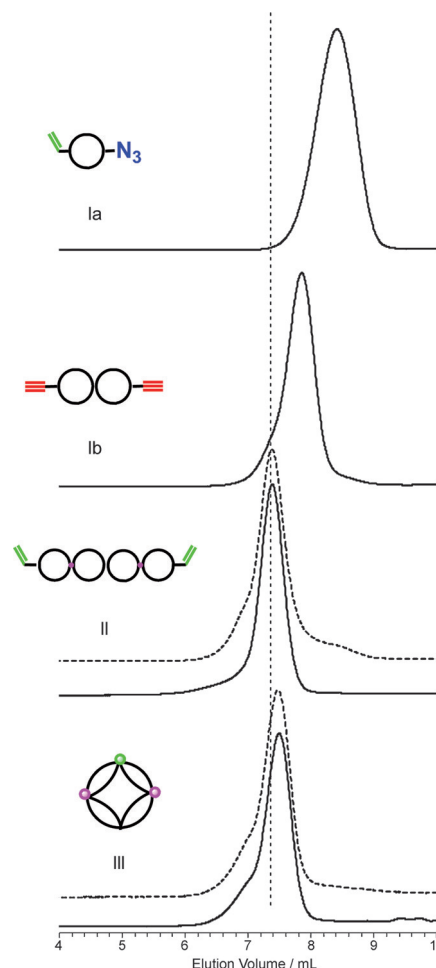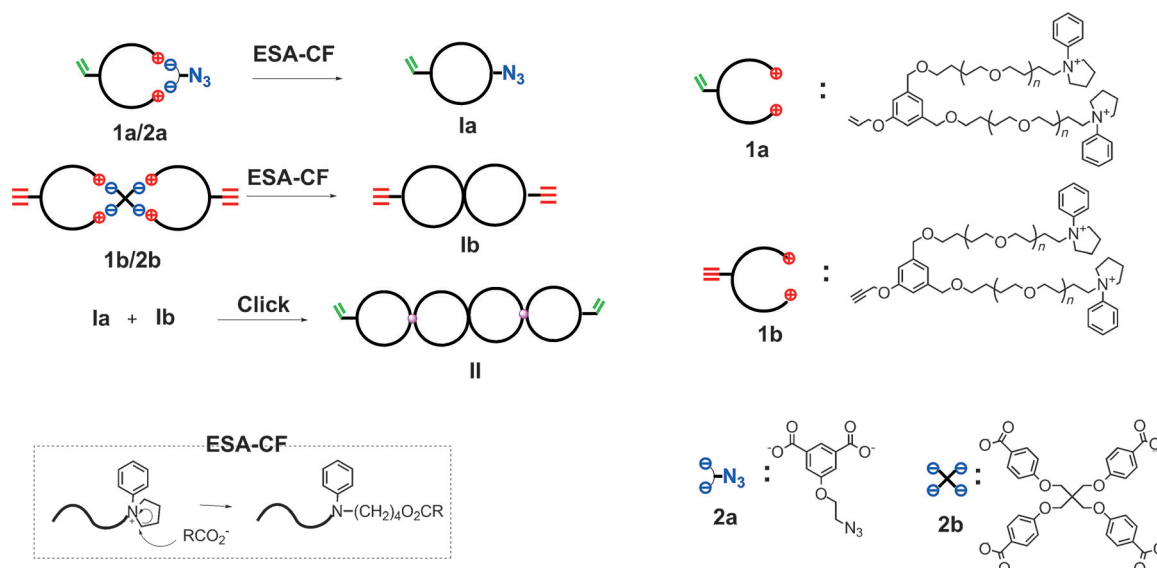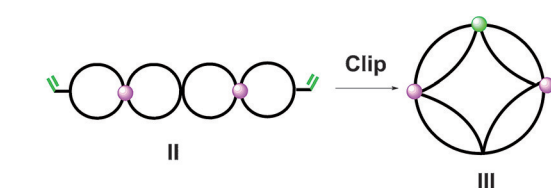

Figure 1. SEC traces of a cyclic prepolymer, **Ia**, a dicyclic prepolymer, **Ib**, the click-linking product, **II**, and clip-folding product, **III**. Broken lines and sold lines show those obtained before and after fractionation, respectively. (THF was used as eluent at the flow rate of 1.0 mLmin^{-1}, with TSK G3000HXL for **Ia** and **Ib**, 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.
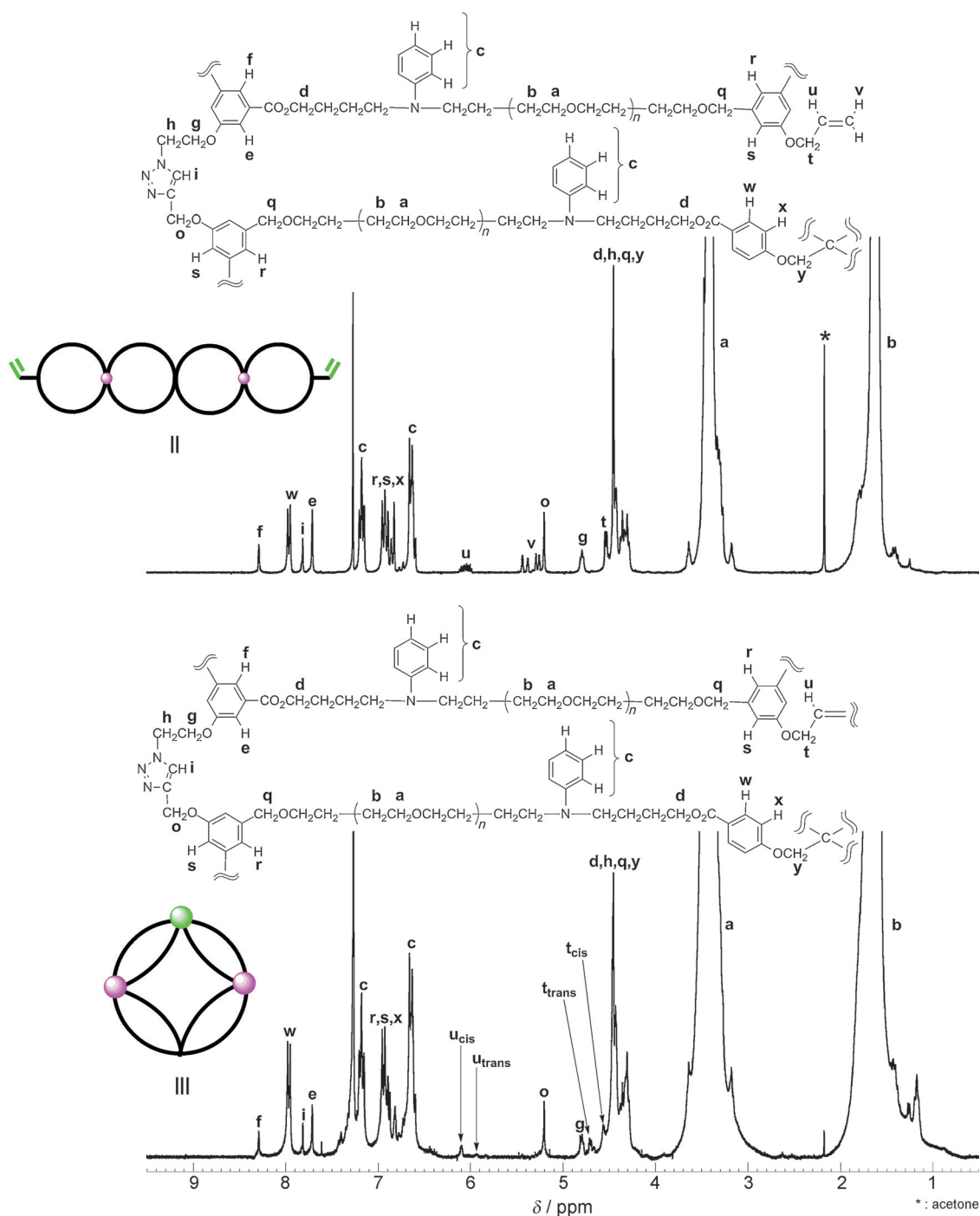
Figure 2. ¹H NMR (300 MHz) spectra of a spiro-tetracyclic prepolymer having allyl groups at the opposite positions of four ring units, **II**, and the clip-folding product, **III** (CDCl₃, 40 °C).

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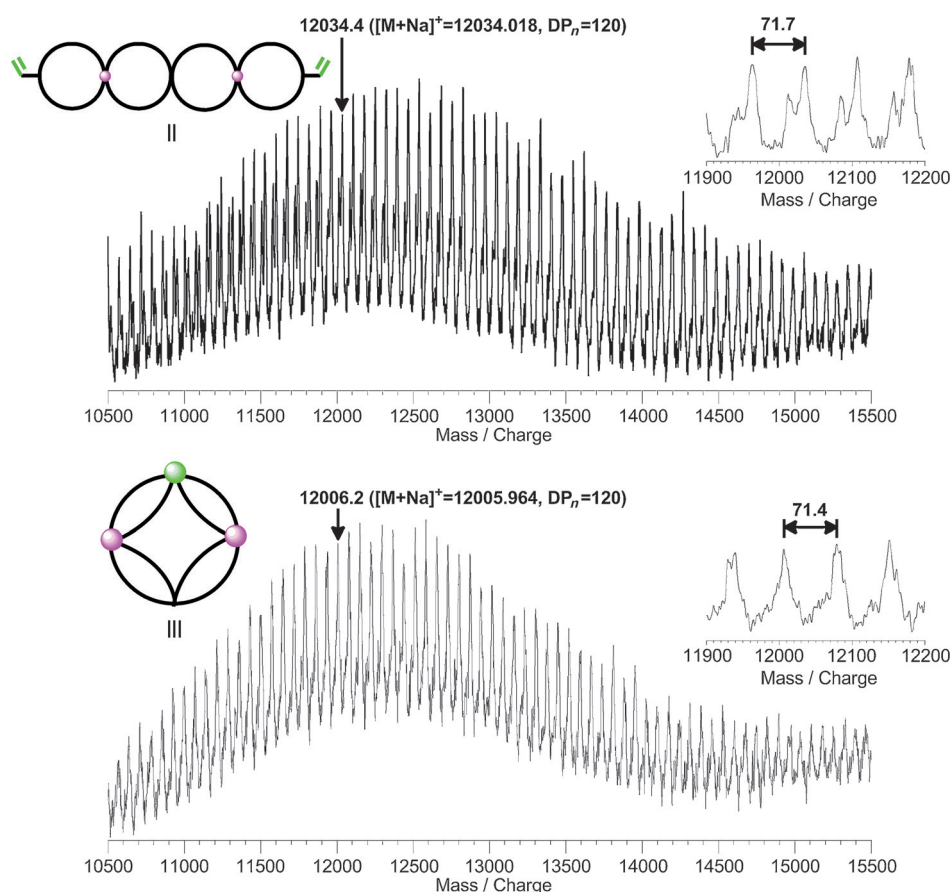
Figure 3. MALDI-TOF mass spectra of a spiro-tetracyclic prepolymer having allyl groups at the opposite positions of four ring units, **II**, and the clip-folding product, **III**. Linear mode, matrix: dithranol with sodium trifluoroacetate. DP_n denotes the number of monomer units in the products.

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 ^{1}H 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 $M_p(SEC)/M_n(NMR)$ 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.

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[14] The present pentacyclic quaruply fused graph is expressed as $V_8(0,4)[0^{a,d}\text{-}0^{a,b}\text{-}0^{b,c}\text{-}0^{c,d}]$, 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.