

The Role of Hydrogen Bonding in the Formation and Dynamics of Two Distinct Types of Cyclic Supramolecular Polymers

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Abstract: Cyclic polymers are attractive synthetic targets in both polymer chemistry and supramolecular polymer chemistry; however, there is a gap between these two research fields in terms of the synthetic strategies involved, and achieving a commonality remains elusive. Herein, we describe the formation of two distinct types of cyclic supramolecular polymers (SPs) from structurally similar rosette-shaped molecules. The first SP (Type I) is characterized by a uniform diameter and circularity, whereas the other (Type II) has properties reminiscent of flexible cyclic covalent polymers. Remarkably, the only difference in the structures of the two monomers that form these completely distinct cyclic SPs is the absence (Type I) or presence (Type II) of hydrogen-bonding moieties. An all-atom molecular-dynamics simulation suggested that the Type II SP can adopt various ‘conformations’ due to the dynamic nature of its hydrogen bonds, thereby behaving like a flexible covalent polymer. Real-time high-speed atomic-force microscopy confirmed the presence of flexibility in the chains of the Type II SP on the observation timescale (several tens of seconds). Our results therefore highlight an example of a similarity between a covalent polymer and a noncovalent SP that should help to bridge the gap between these polymers, leading to new advanced materials.

Introduction

Over the past several decades, cyclic structures have attracted a considerable amount of attention from both supramolecular and polymer chemists. It appears, however, that the respective research directions of these two groups of chemists have stemmed from their distinct perspectives. Supramolecular chemists see cyclic structures as building blocks for host molecules (e.g., cyclophanes)^[1] or mechanically interlocked molecules (e.g., catenanes, rotaxanes, etc.),^[2,3] or they associate them with naturally occurring supramolecular entities such as photosynthetic reaction centers.^[4–7] On the other hand, polymer chemists compare cyclic structures with their common linear counterparts in terms of the absence of termini, expecting unusual mechanical properties and new applications.^[8–16]

The difference in these research directions is reflected in the corresponding strategies for synthesizing cyclic structures. In supramolecular chemistry, cyclic structures should ideally have a well-defined size. An effective method for achieving this goal involves designing molecular components that spontaneously assemble to form a thermodynamically stable cyclic structure. A seminal work by Fujita^[17] reported the quantitative formation of macrocyclic metal complexes under thermodynamic control. Later, Hunter^[4] and Kobuke,^[5] for example, produced porphyrin-molecule-based

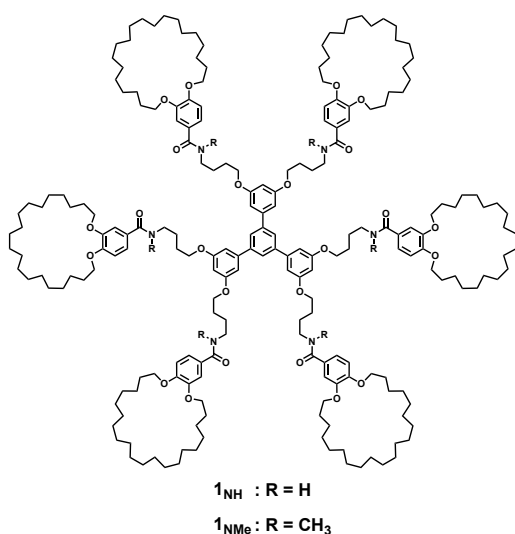
macrocycles as light-harvesting antenna mimics. Another powerful method for synthesizing cyclic entities is template-directed synthesis, as illustrated by the synthesis of various classic cyclic molecules such as crown ethers.^[18] Recently, Anderson and co-workers^[6,7,19,20] made an elegant leap forward by adopting a Vernier template approach that permits the synthesis of much larger macrocycles of well-defined sizes.

On the other hand, the synthesis of cyclic covalent polymers involves difficulties inherent in the structural properties of polymers.^[8–12] Thus, the two ends of a polymer are far apart and are tethered by a flexible chain. Consequently, intrapolymer cyclization competes with interpolymer reactions and, accordingly, requires highly dilute reaction conditions. To address this issue, ring-expansion metathesis polymerization (REMP) and electrostatic self-assembly and covalent fixation (ESA-CF) strategies have been developed by Grubbs^[13] and Tezuka,^[14] respectively. Moreover, specialized experimental tools, such as customized glassware^[15] and tailored column chromatography techniques,^[16] have been developed to permit the scalable production of cyclic covalent polymers.

At the border between these two research fields, cyclic supramolecular polymers (SPs) have emerged in the last decade, although only a handful of examples have been reported to date.^[21–33] Representative examples of cyclic SPs are those reported by the Yagai group.^[21–26] These cyclic SPs are formed from rosette-shaped monomers consisting of π -conjugated molecules, and they are characterized by having a uniform diameter, attributed to the ‘intrinsic curvature’ of the SP. Such curvature is encoded in the molecular components (i.e., rosette) and generated by a well-defined stacking displacement between adjacent rosettes.^[21,22] As such, this cyclization mechanism is reminiscent of that of the above-mentioned supramolecular cyclic metal complexes.^[4,5,17] Remarkably, the Yagai group has even produced multiply interlocked cyclic SPs,^[34] and their studies have raised the concept of cyclic structures in the supramolecular domain to the next level of hierarchy.

Here, we report two distinct types of cyclic SPs: the first type resembles Yagai’s cyclic SPs (type I), whereas the other is much more akin to cyclic covalent polymers (type II). Intriguingly, these completely distinct cyclic SPs were obtained from structurally similar monomers without (type I) or with (type II) hydrogen-bonding moieties (**1**_{NMe} and **1**_{NH}, respectively; Scheme 1). It should be noted that Matsubara and Tamiaki^[27] recently reported a cyclic SP that could seemingly be classified as type II, although the authors’ principal interest lay elsewhere. In this study, we compared the two distinct types of cyclic

SPs by using high-speed atomic-force microscopy (AFM) in real time. We found that the type II cyclic SP is, indeed, akin to a cyclic covalent polymer in terms of both its appearance and its cyclization mechanism. An all-atom molecular-dynamics simulation corroborated this observation. Our two distinct types of cyclic SPs formed from very similar monomers would thus appear to link the respective perspectives of supramolecular chemists and polymer chemists.



Scheme 1.

Results and Discussion

The syntheses of $\mathbf{1_{NMe}}$ and $\mathbf{1_{NH}}$ are described in the Supporting Information (SI). Similar C_3 -symmetric monomers based on a 1,3,5-trisubstituted benzene core have been reported previously.^[35,36] We introduced alkylene loops ($-\text{C}_{20}\text{H}_{40}-$) as solubilizing groups at the periphery of the monomers. The difference between the alkylene loops and the alkyl chains, such as a dodecyl chain ($-\text{C}_{12}\text{H}_{25}$), that are commonly used for this purpose in supramolecular polymerization is intriguing; however, this is beyond the scope of this manuscript and will be reported in due course.^[37] The amide groups in $\mathbf{1_{NMe}}$ are methylated, preventing them from participating in hydrogen bonding. $\mathbf{1_{NMe}}$ and $\mathbf{1_{NH}}$ exhibited markedly different melting points (79 and 174 °C, respectively), as determined by differential scanning calorimetry (SI, Figure S19), briefly indicating the impact of hydrogen bonding.

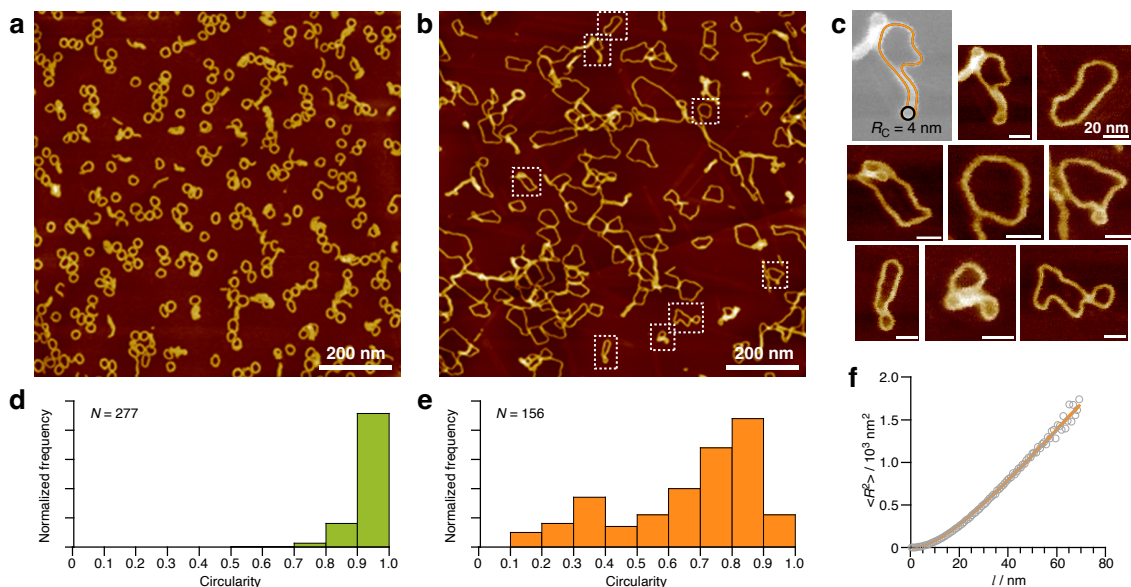


Figure 1. (a–c) AFM images of cyclic SPs from **1_{NMe}** (a) and **1_{NH}** (b,c). In (c), some of the cyclic SPs from **1_{NH}** [highlighted in (b)] are displayed to show its flexibility. (d,e) Histograms of circularity of cyclic SPs consisting of **1_{NMe}** (d) and **1_{NH}** (e). (f) End-to-end distance plots ($\langle R^2 \rangle$) as a function of the contour length of the cyclic SPs from **1_{NH}**. Note that cyclic SPs do not have ends, and their contours are restricted by the cyclized structure; therefore, we segmented the cyclic SPs and analyzed as linear SPs (see SI, Figure S27). A least-squares fit, shown by the orange line, indicates a persistence length of 10.3 ± 0.1 nm.

First, we investigated the supramolecular polymerization of **1_{NMe}** and **1_{NH}**. The monomers were dissolved in methylcyclohexane (MCH) at a concentration of 10 μM in a glass vial by heating using a heat gun, and the solutions were then left at 20 $^\circ\text{C}$. The resulting solutions were spin-coated onto highly oriented pyrolytic graphite (HOPG) and examined by atomic-force microscopy (AFM). Remarkably, both monomers formed cyclic SPs; however, they displayed distinct appearances (Figure 1a,b). The heights of these cyclic SPs, as determined by AFM, were c.a. 3 nm (SI, Figure S20), suggesting that the SP chains consisted of unimolecular stacks of rosette-shaped monomers. Not surprisingly, the concentration of the monomers was the critical factor, and 1D wavy SPs prevailed at higher concentrations ($\sim 50 \mu\text{M}$), where one-dimensional polymerization occurred in preference to intrapolymer cyclization (SI, Figure S21).

Figure 1d,e show the histogram of the circularity (C), which signifies the similarity of the shape to that of a mathematically perfect circle, of the cyclic SPs consisting of **1_{NMe}** and **1_{NH}**, respectively (SI, Figure S22). The cyclic SPs of **1_{NMe}** exhibited a C value close to 1, with a small deviation: 0.93 ± 0.05 (Figure 1d), indicating their well-defined curvature. Furthermore, the ratio of weight to number averages of the perimeter (i.e., dispersity of size: $\bar{D} = P_w/P_n$) of the cyclic SP of **1_{NMe}** was close to unity (1.01) (Figure S23, Table S1). On the other hand, the cyclic SPs of **1_{NH}** exhibited the values of C and $\bar{D}$ of 0.66 ± 0.21 (Figure 1e) and 1.32 (Figure S23), respectively. These results indicate that the structure of the cyclic SPs of **1_{NMe}** is well defined, whereas that of **1_{NH}** is not. Dynamic-light-scattering measurements confirmed the presence of the corresponding structures in solution, with hydrodynamic radii consistent with the values determined by AFM (SI, Figure S24). We therefore infer that **1_{NMe}** forms similar cyclic SPs to those that form from Yagai's rosette monomers (type I), whereas **1_{NH}** forms cyclic SPs resembling covalent cyclic polymers (type II).

Some of cyclic SPs of **1_{NH}** (type II) were deflated, having a hairpin curve with a radius of curvature (R_C) as small as 4 nm while remaining seamlessly connected (Figure 1c), suggesting that SPs of **1_{NH}** have considerable flexibility. Such structures should be stabilized by hydrogen bonding of the amide groups. IR spectral measurements for solution samples indeed confirmed the presence of hydrogen bonding between the amide groups although a higher concentration was required for this measurement because of the lower sensitivity of the technique (SI, Figure S25). In addition, temperature-dependent absorption spectral changes suggest that the cyclic SPs of **1_{NH}** are more thermally stable than those of **1_{NMe}**. Specifically, thermal depolymerization of **1_{NH}** was not observed even at 60°C, whereas SPs formed from **1_{NMe}** fully depolymerized at 35 °C under identical conditions (10 μ M in MCH; see SI, Figure S26). From the AFM images, by using *Easyworm* software, we determined the persistence length of SPs of **1_{NH}** to be 10.3 ± 0.1 nm (Figure 1f, see SI, Figure S27 for more detail).^[38–40] Thus, if one considers the SP of **1_{NH}** as a worm-like chain, the number average perimeter ($P_n = 174$ nm, Table S1) is much larger than its Kuhn length. Previously, we have reported a linear SP consisting of a monomer resembling **1_{NH}**, but based on a rigid, flat triphenylene core.^[41] The persistence length of this polymer was 4.19 ± 0.15 μ m, significantly greater than that of **1_{NH}** (SI, Figure S28). We therefore attribute the short persistence length of SPs of **1_{NH}** to the triphenylbenzene core that can adopt a variety of conformation due to its rotational freedom.

We were intrigued by the factors that drove SPs of **1_{NH}** to cyclize without an “intrinsic curvature”. To investigate the flexibility of the cyclic SP consisting of **1_{NH}**, we conducted an all-atom molecular dynamics (MD) simulation using *Gromacs 2016.6* (see the SI for the detailed settings).^[42] The atomic charges of SP and MCH were determined at the B3LYP/6-31G(d,p) level, and the force-field parameters were assigned in the manner of a second-generation general amber force field (GAFF2).^[43–45] Cyclic SPs cannot be simulated as such because of the practical problem of the system-size limitation associated with a full atomistic model. As an alternative, in the MD cell, 32 monomer units of **1_{NH}** were periodically stacked at intervals of 0.35–0.45 nm in the presence of 12,800 solvent molecules (MCH). Note that the periodic boundary condition permits the evaluation of the structural flexibility of an SP chain that is much longer than its persistence length (Figures 2a and 2b). Upon equilibration, the distance between the triphenylbenzene cores settled at around 0.4 nm (Figure 2c), indicating that interaction between the neighboring aromatic rings is weak.^[46] Hence, the main driving force for supramolecular polymerization of **1_{NH}** should be hydrogen bonding between amide groups. Intriguingly, however, some of the amide groups were found not to participate in hydrogen bonding (as highlighted in Figure 2b). The average value of the number of N–H groups involved in hydrogen bonding per monomer (where the maximum value is 6) was 4.8 (Figure 2f), and this value fluctuated over time (Figure 2g), suggesting a dynamic nature of the SP chains consisting of **1_{NH}**. Dihedral angles within the triphenylbenzene core ranged from 26.3° to 57.1° (mean value $\pm$ 2s; see Figure 2d), confirming its rotational freedom. We also estimated the tilt angle between the neighboring triphenylbenzene cores, and we found that various angles are possible (Figure 2e). On taking these results into consideration, it becomes apparent that the SP chain consisting of **1_{NH}** can adopt many different ‘conformations’, thereby behaving more like a flexible polymer chain rather than a stiff crystalline structure. We infer that the reversible dissociation and association of the hydrogen bonds plays a key role in relaxing the stress generated within the SP chain (Figure 2g).

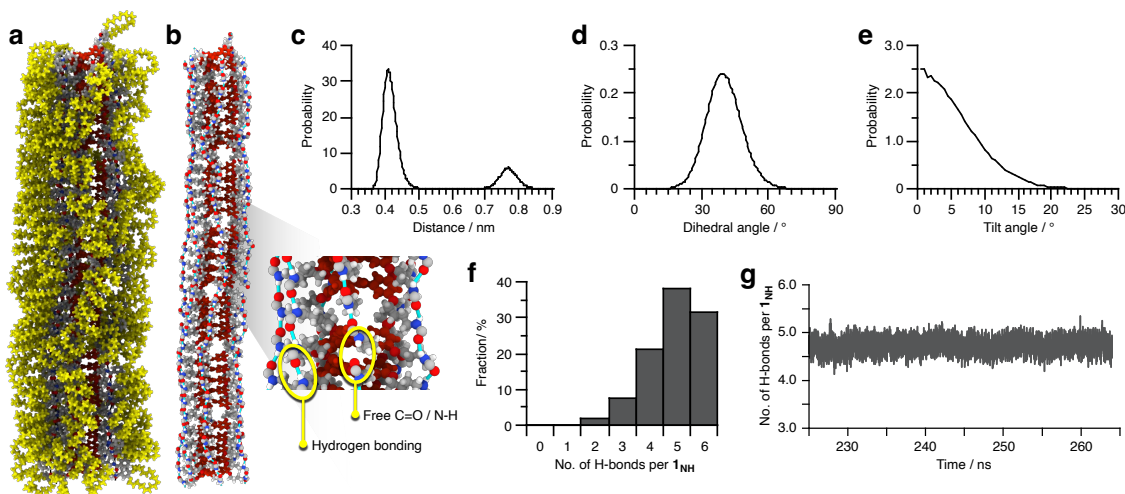


Figure 2. (a) Snapshot of the SP structure of **1**_{NH} and (b) a partial view around the hydrogen-bonding groups and triphenylbenzene cores from the all-atom MD simulations. The side loops ($-\text{C}_{20}\text{H}_{40}-$) are depicted in yellow in (a), and are omitted from (b). Atoms of C, O, N and H are colored gray, red, blue, and white, respectively, and the hydrogen bonding is depicted as black stick. The triphenylbenzene cores are rendered in dark red. (c–e) Probability distributions for the distance between neighboring triphenylbenzene cores (c), for the dihedral angle defined by the biphenyl groups in a triphenylbenzene core (d), and for the tilt angle between neighboring triphenylbenzene cores (e). (f) Fraction of **1**_{NH} with respect to the number of hydrogen-bonded NH groups. (g) Time course of the number of hydrogen-bonded NH groups in **1**_{NH}.

The dynamic nature of cyclic SPs formed from **1**_{NMe} and **1**_{NH} were investigated using high-speed AFM, which has an extraordinary spatiotemporal resolution (1 nm and sub-100 ms).^[47–53] By mixing the two SPs in a sample chamber, we successfully captured both cyclic SPs in a single frame (Figure 3a and SI, Supplementary Movie 1), which permitted a comparison of the structural dynamics of these distinct cyclic SPs under identical experimental conditions (temperature, set-point amplitude, etc.). Figures 3b and 3c show the time courses of the correlation coefficients and circularity, respectively, as determined from successive images of three selected cyclic SPs consisting of **1**_{NMe} and **1**_{NH} (see also SI, Figure S29).^[48] In brief, fluctuations of these values over time indicate the structural flexibility on the observation time scale (2 frames/s). Obviously, the cyclic SPs of **1**_{NMe}

retained their shape (see also Figure 3d; SI, Supplementary Movie 2). It should be noted that these structures tended to diffuse on the substrate while retaining their shape (SI, Figure S30); we therefore rule out the possibility that the circularity C is maintained by the interactions between the cyclic SPs and the substrate. In contrast, the shapes of the cyclic SPs of $\mathbf{1}_{\text{NH}}$ significantly fluctuated (Figures 3e and SI, Supplementary Movie 3), suggesting that the SP chains of $\mathbf{1}_{\text{NH}}$ is dynamic.

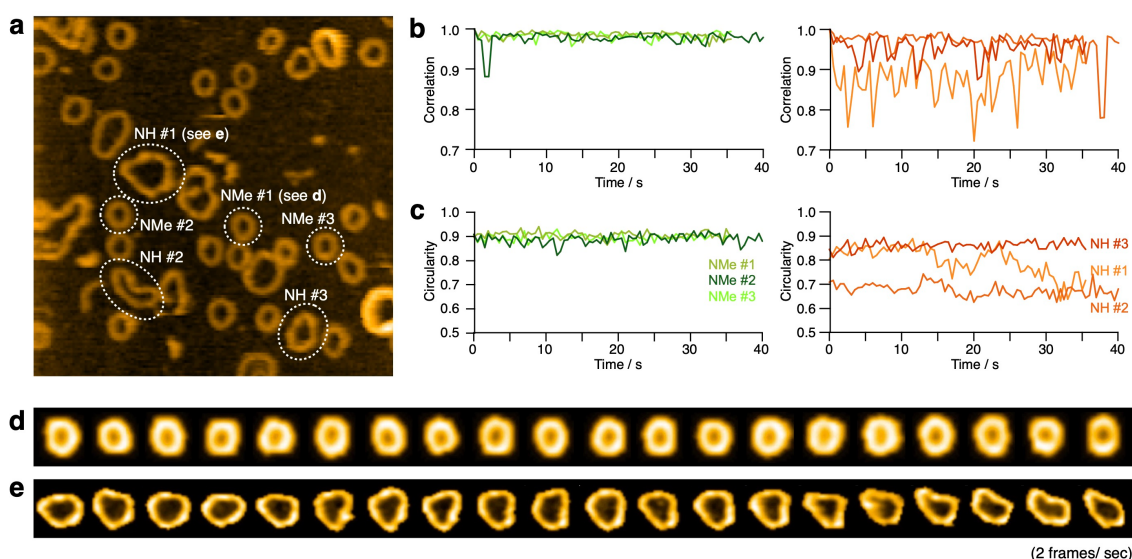


Figure 3. (a) High-speed AFM image in which both cyclic SPs consisting of $\mathbf{1}_{\text{NMe}}$ and $\mathbf{1}_{\text{NH}}$ are captured in the same frame. (b,c) Time courses of the correlation coefficients (b) and circularities (c) of $\mathbf{1}_{\text{NMe}}$ (left, green) and $\mathbf{1}_{\text{NH}}$ (right, orange) obtained from successive images. The results of three selected cyclic SPs [highlighted in (a)] are shown for each structure. (d,e) Successive AFM images for an individual cyclic SP consisting of $\mathbf{1}_{\text{NMe}}$ [d: NMe#1 in (a)] and $\mathbf{1}_{\text{NH}}$ [e: NH#1 in (a)]. The successive images shown in (d) and (e) can be seen as video in Supplementary Movies 2 and 3, respectively.

To gain a deeper insight into the structural changes in the cyclic SPs, each SP was observed separately. When zoomed in, cyclic SPs consisting of $\mathbf{1}_{\text{NMe}}$ collapsed abruptly, probably as a result of increased mechanical perturbation from the AFM probe; subsequently, the SP depolymerized from its termini (Figure 4a; SI, Supplementary Movie 4). This observation suggests that molecules of $\mathbf{1}_{\text{NMe}}$ are weakly assembled

through van der Waals interactions, and that cyclic SPs of $\mathbf{1}_{\text{NMe}}$ are topologically stabilized due to the absence of termini as in the case of Yagai's rosette.^[26]

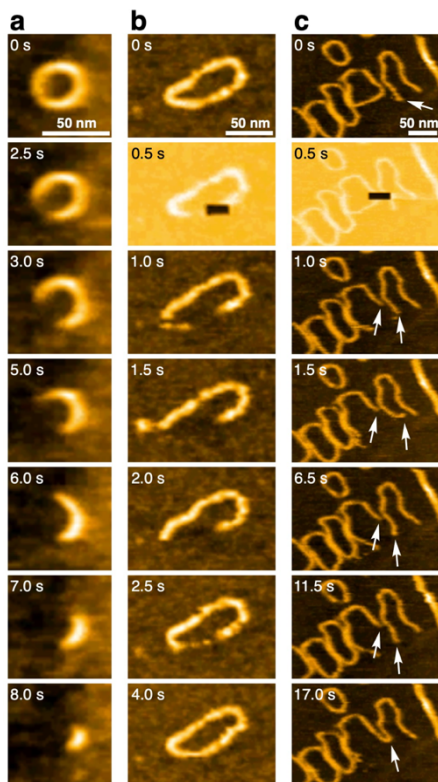


Figure 4. (a,b) Successive high-speed AFM images of cyclic SPs consisting of $\mathbf{1}_{\text{NMe}}$ (a) and $\mathbf{1}_{\text{NH}}$. (b) In (b), the cyclic SP was cut by the AFM probe at 0.5 s, and then spontaneously “repaired” over time. (c) Successive high-speed AFM images capturing a process in which two adjacent cyclic SPs of $\mathbf{1}_{\text{NH}}$ were cut and the ends of the two SPs then coalesced, as indicated by the white arrows. These successive images shown in (a) to (c) can be seen as video in Supplementary Movies 4 to 6, respectively.

On the other hand, cyclic SPs of $\mathbf{1}_{\text{NH}}$ were robust and did not collapse under the measurement conditions, due to the presence of multiple hydrogen bonds along the SP chain, being endowed with a greater resistance to mechanical force. To investigate the stability of cyclic SPs of $\mathbf{1}_{\text{NH}}$, we intentionally cut the cyclic SP consisting of $\mathbf{1}_{\text{NH}}$ by increasing the tapping force (more than 100 pN) in a specific area by decreasing the set-point amplitude (c.a. 10%) of the cantilever for feedback control.^[49] To our surprise, the opened SP of $\mathbf{1}_{\text{NH}}$ bent and then rejoined to form the original closed cyclic structure (Figure 4b, SI, Supplementary Movie 5). From the AFM snapshots, by using *Easyworm*

software, we estimate the persistence length of the SPs of **1_{NH}** to be 17.6 ± 3.8 nm (SI, Figure S31), which is comparable with the value determined under dry conditions (see above).

We also captured another intriguing dynamic behavior of **1_{NH}**. When two adjacent cyclic SPs consisting of **1_{NH}** were cut, the chain ends of the two SPs became connected (Figure 4c; SI, Supplementary Movie 6). Although the supramolecular polymerizations, in equilibrium with a monomer, have previously been visualized by high-speed AFM,^[49–53] to the best of our knowledge, this is the first real-time observation of the connection of two ends of SPs. Taking all the observations into consideration, we infer that the SP of **1_{NH}** has short persistence length and highly ‘reactive’ chain ends, which in turn permits the intrapolymer cyclization. Importantly, these characteristics are consistent with the prerequisites for the formation of cyclic covalent polymers, which was also applied to the ring closure of other 1D materials such as single-walled carbon nanotubes.^[54]

N-Methylated amide or urea analogs of a monomer are often used as capping reagents to inhibit supramolecular polymerization.^[55–58] We thus sought to investigate supramolecular copolymerization of **1_{NMe}** and **1_{NH}**. A mixture of **1_{NMe}** and **1_{NH}** did not form cyclic SPs, but resulted in short 1D SPs. (SI, Figure S32). In addition, when a cyclic SP of **1_{NH}** was mechanically opened by the high-speed AFM probe in the presence of **1_{NMe}** (i.e., under the same condition for the measurement shown in Figure 3a), it no longer rejoined (SI, Figure S33 and Supplementary Movie 7). These results show that structurally similar **1_{NMe}** and **1_{NH}** can copolymerize or that **1_{NMe}** can endcap an SP of **1_{NH}**; however, the monomers are incompatible for forming cyclic SPs. This observation further suggests that **1_{NMe}** and **1_{NH}** have different cyclization mechanisms.

Conclusion

In conclusion, we have shown that two distinct types of cyclic SPs are obtained from monomers that are structurally similar apart from their hydrogen-bonding capacity. The finding provides a new insight into the monomer design principle for achieving cyclic SPs. The first type of SP, characterized by a uniform diameter and circularity, is probably formed through the mechanism proposed by Yagai and co-workers.^[21,22] The other type of cyclic SP, although still rare,^[27] is akin to a covalent cyclic polymer, not only in its appearance, but also in its cyclization mechanism, in which the short persistence length and ‘reactive’ termini play a pivotal role. This study, therefore, has identified an example of a similarity between covalent and noncovalent (supramolecular) polymers that might

provide a clue toward the synthesis of supramolecular polymers with unique topologies.

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Keywords: supramolecular polymers • cyclic polymers • high-speed AFM

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