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Dynamic or undynamic chirality generated by helical arrangement of a shape-persistent ring and rod doubly bridged in a molecule

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We synthesized molecular assemblies of a ring and rod that were covalently bound in a molecule. The bridged components were helically arranged in a threaded or unthreaded form to show unique chiroptical properties based on shape-persistent *m*-phenylacetylene rings with six, five and four units and phenylene-ethynylene rods.

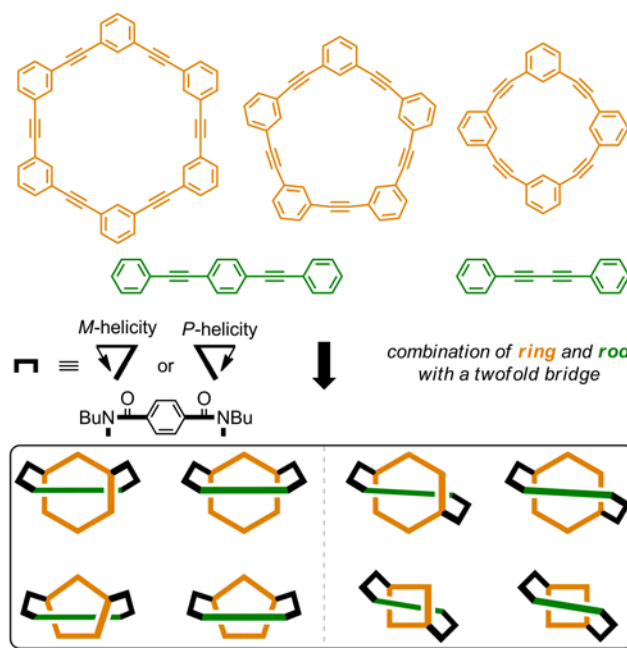
A variety of shape-persistent macrocycles (SPMs) have been shown to exhibit unique properties,^{1,2} especially supramolecular assembly through intermolecular interactions in solution³⁻⁵ as well as on a solid substrate.^{6,7} In host-guest systems,⁸⁻¹⁰ the internal cavity of a robust macrocycle can act as a host that is suitable for capturing a specific guest through the arrangement of functional groups.^{9,10} Despite numerous reports on the above issues, there are still only a few reported examples of chirality-related molecules based on SPMs.¹¹ Regarding this point, here we report the synthesis and chiroptical properties of molecular assemblies using SPMs.

We assumed a molecular assembly of a ring and rod that are covalently bound to each other (Scheme 1). The doubly bridged ring and rod can be helically arranged [(*M,M*) or (*P,P*)], and the molecule can be chiral in either of two cases. In one case, the ring is threaded onto the rod (threaded form).^{10,12} In the other case, the ring and rod are simply bridged (unthreaded form). This difference arises from the relative location of the two bridges on the ring. When the ring is doubly bridged at diametrical locations, chiral forms with a double helical arrangement of (*M,M*) or (*P,P*) are favorable in an unthreaded form compared to a threaded form. Alternatively, two bridges located elsewhere on the circumference of the ring leads to the preference of double helical arrangements in a threaded form. In either case, the threaded and unthreaded forms are

Scheme 1. Ensemble of ring and rod based on phenylene-ethynylene scaffolds through

double covalent bridging.

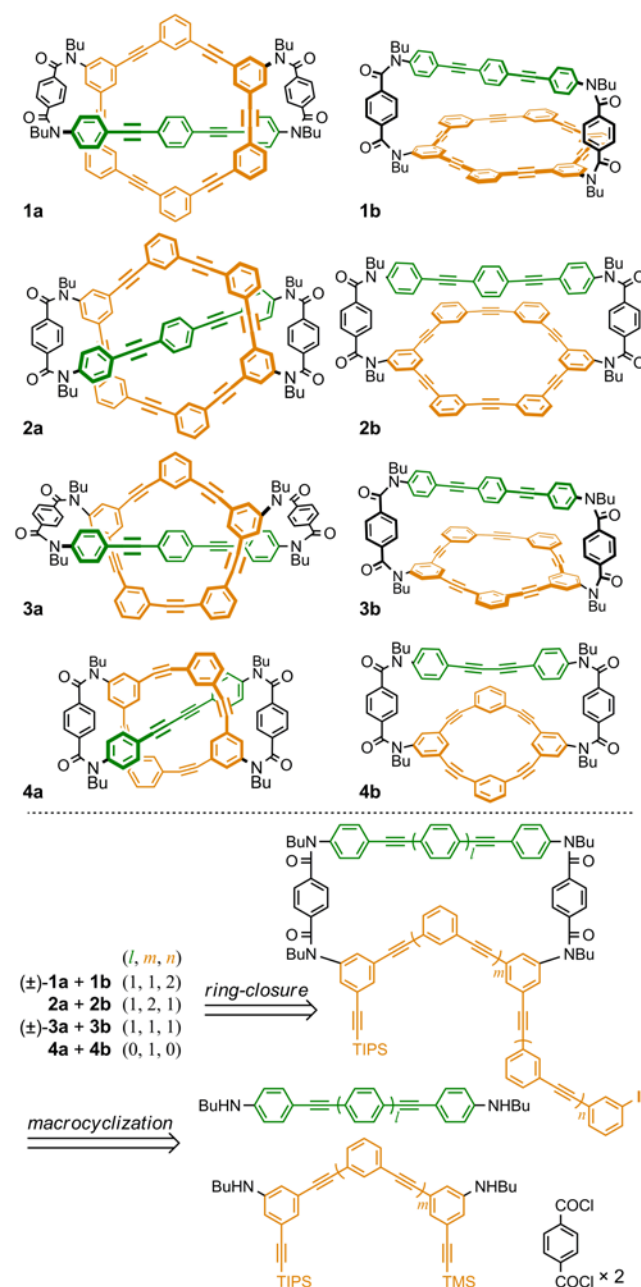
considered to be a set of conformational (rotational) isomers.^{12b-d} If the barrier to rotation could be raised enough to suppress interconversion between the threaded and unthreaded forms, which is brought about through mechanical inversion of a helical sense at one of the two bridges, each form can be considered to be an atropisomer and could be



isolated. If this could be achieved, the stereochemistry of the helical arrangement generated in a threaded form is assured. Alternatively, two enantiomeric conformations with (*M,M*) or (*P,P*) generated in an unthreaded form could dynamically interconvert to each other. Through a supramolecular transmission of chirality, e.g., at bridges in an unthreaded form, a conformational preference for a particular helical sense of (*M,M*) or (*P,P*) could be induced. We envisioned that such an increased barrier to rotation could be attained due to

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Scheme 2. Chemical structures and strategy for the synthesis of 1-4.

appropriate shape-persistency of the components, not only with respect to the ring, but also to the rod and bridges. Thus, we used hexakis-, pentakis- and tetrakis(*m*-phenylacetylene)macrocycles ([6], [5] and [4]PAMs)^{13,14} as a ring, phenylene-ethynylene scaffolds as a rod (long or short), and terephthalamide as a two-fold covalent bridge to synthesize four pairs (**1-4**) of threaded (**a**) and unthreaded (**b**) forms (Scheme 2).

We planned a stepwise strategy for the synthesis of **1a/b-4a/b**. Two amide groups in a terephthalamide unit can be independently modified, and we could assume an intermediary macrocycle, in which a defective part of the ring and rod are covalently assembled. Ring closure on the intermediate would give a pair of threaded and unthreaded

forms simultaneously (Scheme 2). We demonstrate mirror-imaged Cotton effects

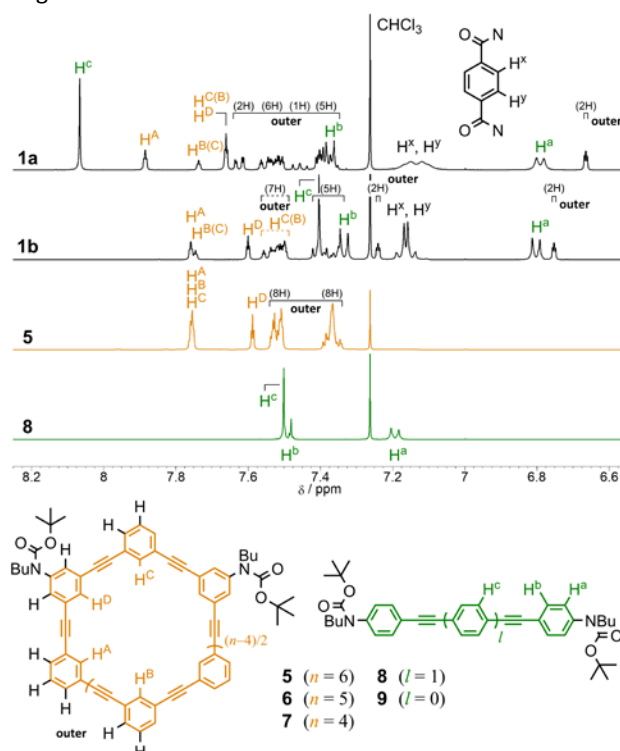


Fig. 1 Partial ¹H NMR spectra (400 MHz) of **1a**, **1b**, **5** and **8**, measured in chloroform-*d* at room temperature, and chemical structures of rings **5** ([6]PAM), **6** ([5]PAM) and **7** ([4]PAM), and rods **8** (long) and **9** (short).

from (–)-**1a** and (+)-**1a**, and (–)-**3a** and (+)-**3a**, respectively, which were successfully separated through chiral HPLC. We also observed induced Cotton effects from **2b/4b** in the presence of a chiral guest molecule, which was bound at the bridges through the formation of hydrogen bonds. The details are described below.

All pairs of threaded and unthreaded forms **1a/b-4a/b** were obtained as a mixture through an intramolecular Sonogashira coupling reaction¹⁵ (45%, *rac*-**1a:1b** = 1:1.2; 30%, **2a:2b** = 1.8:1; 78%, *rac*-**3a:3b** = 1:5.5; 5%, **4a:4b** = 1.6:1) (Scheme S1-S3). Initially, we were not sure which was which based solely on the results of NMR or mass spectra due to similarities in the patterns for **1a** and **1b**. Fortunately, three fractions were obtained by HPLC with a chiral stationary phase. Two of the three fractions exhibited identical NMR spectra, and were considered to be a pair of enantiomers ($[\alpha]_D^{25} = -400$ and $+411$ for the first and second fractions of **1a**). We did not assign the absolute stereochemistry for these enantiomers. There was no sign of any interconversion among the separated isomers, e.g. the ¹H NMR spectra of **1a** and **1b** remained unchanged over a long period of time.

The ¹H NMR spectra of **1a** (C₂) and **1b** (C_{2v}) showed a similar pattern as mentioned above, but their chemical shifts were significantly different from each other (Fig. 1 and Fig. S1). The central phenylene protons (H^c, 4H) of the rod in **1a** were observed as a singlet, which supported free rotation of the corresponding phenylene ring in the interior space of

[6]PAM,¹⁶ where the chemical shift was drastically shifted toward a lower field ($\delta = 8.07$ ppm for **1a**, Cf. 7.40 ppm for **1b** and 7.50 ppm for

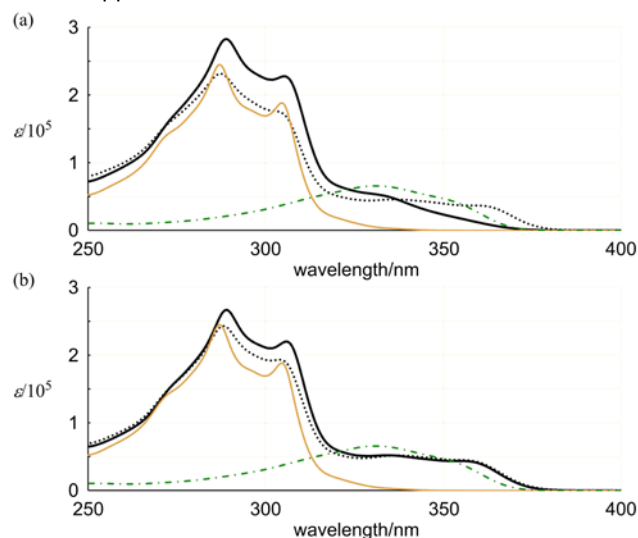


Fig. 2 UV spectra of (a) **1a**, **1b**, **5** and **8**, and (b) **2a**, **2b**, **5** and **8**. Black solid line: threaded form **a**, black dashed line: unthreaded form **b**, orange solid line: ring, and green dashed line: rod. All spectra were measured in dichloromethane at room temperature.

8). Several protons assigned to [6]PAM in **1a** and **1b** were uniquely scattered over a wider range compared to the original positions shown by **5**. Especially, the chemical shift for interior protons (H^A) of [6]PAM in **1a** was shifted toward a lower field. These results reflected the presence of magnetic deshielding from each of the ring and rod.^{14c,17} A 2D ROESY measurement showed NOE correlations between the central phenylene protons (H^C) of the rod and several interior protons (H^A , H^B and H^C) of the ring, which also ensured a threaded form in **1a** (Fig. S2). Similar results were observed with other pairs of **2a/2b** and **3a/3b** (Fig. S1b and Fig. S2). Only one of the two spectra (**a** and **b**) showed downfield shifts for both the central phenylene protons (H^C) of the rod and the interior protons (H^A) of the ring, which helped us to assign it to the threaded form **a**. Notably, the central phenylene protons (H^C) of the rod in **3a** were again observed as a singlet, and the corresponding phenylene ring was allowed to rotate freely even in a narrower interior space of [5]PAM. The threaded form of **4a** was assigned by the appearance of downfield shifts for diyne carbons of the short rod in ¹³C NMR, instead of the central phenylene protons (H^C) in **1a-3a**, in addition to those for interior protons (H^A and H^B) of the ring (Fig. S1b). In threaded forms, a smaller ring showed greater shifts for interior protons of the ring (Table S1).

The UV spectrum of the threaded form **1a** showed two-sectional absorptions [$\lambda_{\max}$ ($\log \epsilon$) = 289 (5.45) and 305 (5.36), and $\lambda_{\max}$ ($\log \epsilon$) = 333 (shoulder 4.72) nm]. The former was attributed to the ring and the latter to the rod, since each substructure showed similar absorptions at 287 (5.39) and 305 (5.27) from **5**, and at 331 (4.82) and 350 (sh. 4.67) nm from **8** (Fig. 2a). Some absorptions for the rod in **1a** seemed to be weakened, while the corresponding absorptions in the

unthreaded form **1b** showed a slight bathochromic shift [$\lambda_{\max}$ ($\log \epsilon$) = 337 (sh. 4.66) and 362 (sh. 4.56) nm]. The spectra of **2a** and **2b** showed almost intact absorptions from the ring and rod substructures, and this resulted in quite similar absorptions for

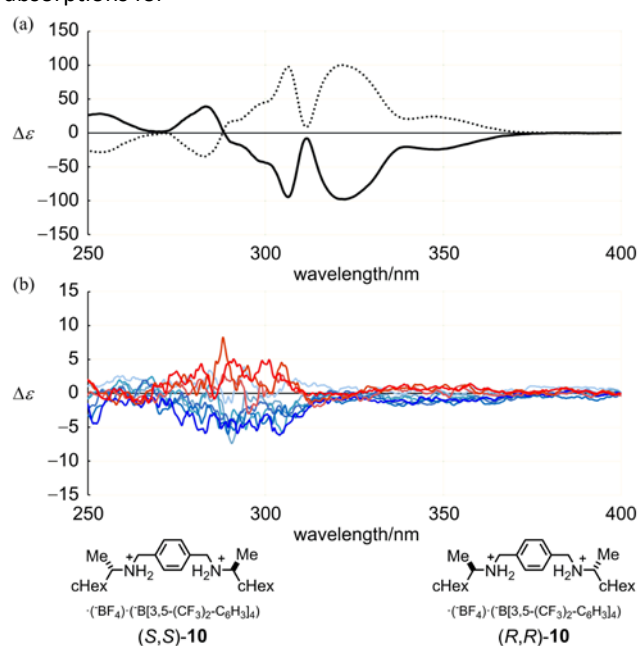


Fig. 3 CD spectra of (a) $(-)-\mathbf{1a}$ (solid line, first fraction) and $(+)-\mathbf{1a}$ (dashed line, second fraction), measured at 293 K; (b) CD spectra of **2b** ($[\mathbf{2b}] = 7.65 \times 10^{-5}$ M) in the presence of chiral guests $(R,R)\text{-}\mathbf{10}$ (1, 2, 4, 6, 8, and 10 equiv. blue lines) or $(S,S)\text{-}\mathbf{10}$ (2, 4, and 8 equiv. red lines), measured at 263 K. All spectra were measured in dichloromethane. Chemical structures of chiral ditopic guests $(S,S)\text{-}\mathbf{10}$ and $(R,R)\text{-}\mathbf{10}$.

2a and **2b** (Fig. 2b). For other pairs of **3a/3b** and **4a/4b**, the spectra were characterized by the additivity of the corresponding ring and rod substructures (Fig. S3), similarly to **2a/2b**.

Optically-resolved enantiomers $(+)\text{-}\mathbf{1a}/(-)\text{-}\mathbf{1a}$ and $(+)\text{-}\mathbf{3a}/(-)\text{-}\mathbf{3a}$ showed uniquely complete mirror-images of Cotton effects in the absorption region of them in CD spectroscopy (Fig. 3a and Fig. S4a).¹⁸ Based on the successive emergence of extremal signs and values, chiral molecules **1a** and **3a** seemed to have similar spectra.

To examine the complexation of **2b** with a chiral hydrogen-bonding guest $(R,R)\text{-}\mathbf{10}$,²⁰ we monitored a change in the UV spectrum of **2b** with the concentration of added **10** in dichloromethane (Fig. S5a). A titration experiment showed that they formed a complex ($K = 2 \times 10^4 \text{ M}^{-1}$, estimated by a curve-fitting method). In the CD spectrum of **2b** in the presence of a chiral guest, several Cotton effects were slightly induced in the absorption region of **2b** (Fig. 3b). Mirror-imaged Cotton effects were induced by mixing with an antipodal guest. These results showed that a conformational preference was induced for a particular sense of dynamic helicity in response to the external chirality. Similar results were obtained in the case of **4b** (Fig. S4b and Fig. S5b).²¹

We have demonstrated the synthesis and chiroptical properties of molecular assemblies with a helical arrangement of a ring and rod that were both based on shape-persistent

phenylacetylene scaffolds, including not only [6]PAM, but also smaller [5] and [4]PAMs as a ring component. In the stepwise synthesis, the final ring-closing reaction gave a mixture of threaded and unthreaded forms. Each species was successfully isolated through chromatographic separation. ^1H NMR spectroscopy revealed that the threading central phenylene ring of the rod can rotate freely in the interior space of [6]PAM in **1a**, as well as in the narrower space of [5]PAM in **3a**. Significant downfield shifts for interior protons of the ring were characteristic of a threaded form due to deshielding from each phenylene-ethynylene component. UV absorption of these assemblies was a result of the sum of absorptions from the corresponding ring and rod substructures. Cycloenantiomerism in **1a** and **3a** with a threaded form (undynamic chirality) was uniquely evidenced by complete mirror-images of strong Cotton effects in CD spectroscopy. Also, in an unthreaded form of **2b/4b** (dynamic chirality), complexation-induced Cotton effects emerged, although the intensity was not very great.

Conflicts of interest

There are no conflicts to declare.

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- 21 Based on the results of conformational searches using MacroModel software (Fig. S6), we considered that the small induced Cotton effects for a complex of **2b/4b** might be attributed to a conformational preference for the local non helicity in the bridging unit, and it seemed hard to differentiate between the conformational energies of

diastereomeric complexes [e.g., (*M,M*)-**2b**·(*R,R*)-**10** and (*P,P*)-**2b**·(*R,R*)-**10**].