COMMUNICATION

Controlled helical senses of twisting in two-, three- and four-layer cyclophanes with planar chirality

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We synthesized planar chiral cyclophanes with multiple pairs of helical conformations that were generated by twisting at the interlayer. Three- and four-layer cyclophanes preferred a homochiral form with a single sense of twisting through intramolecular transmission of planar chirality. Alternatively, a heterochiral form was dominant in a two-layer cyclophane consisting of two achiral planes that were stacked orthogonally.

When achiral components, such as a plane and/or rod, are stacked one above the other, twisting of one component with respect to the other would lead to a pair of conformations with helical chirality (M- or P-helicity) (Scheme 1). A conformational preference for a particular sense of chirality could almost always be presented by some intramolecular transmission of chirality,[1,2] which would be valid for more complicated molecules with such a two- or three-fold pair of helical conformations, where multiple conformations would be generated between three- or four-layered components by twisting. The point is how demonstrating the induction of a helical-sense preference in each pair, especially for a system where conformational interconversions occur too rapid to quantitatively determine the populations of multiple conformers. We were interested in chiral molecules that consist of multiple pairs of helical conformations and designed multilayer cyclophanes[3-8] with planar chirality[5,6] (Fig. 1). As achiral components, we used a rectangular and anisotropic plane of 1,2,4,5-tetrakis(phenylethynyl)benzene and a linear rod of 1,4-bis(phenylethynyl)benzene. These achiral components were stacked one above the other and covalently bridged at each corner of the plane and/or at each end of the rod. As substituent groups on the terephthaloyl bridge, we used methyl (X = CH_3) and cyclohexylmethyl [Y = CH_2(cHex)]. These

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Scheme 1 Conformational interconversion between two chiral forms created by twisting.

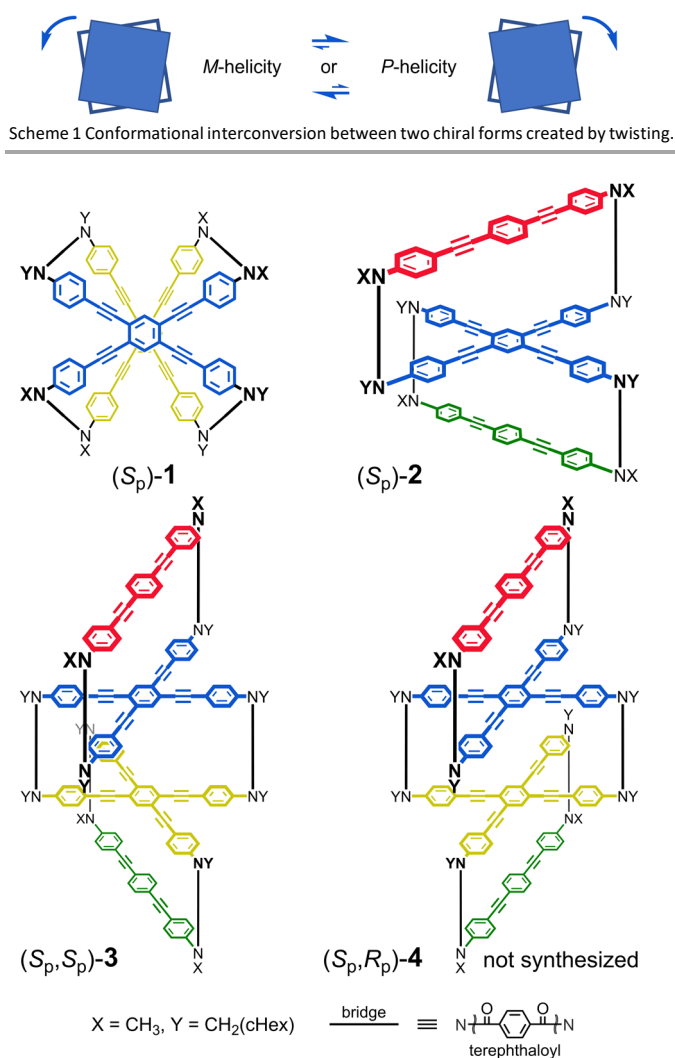X = CH_3, Y = CH_2(cHex)   bridge ≡ terephthaloyl

Fig. 1 Chemical structures of multilayer cyclophanes, two-layer **1**, three-layer **2**, and four-layer **3** and **4**. Only one enantiomer is depicted for planar chiral cyclophanes.

achiral substituents are nonstereogenic and have no preference for a particular sense of helical conformation, when the plane
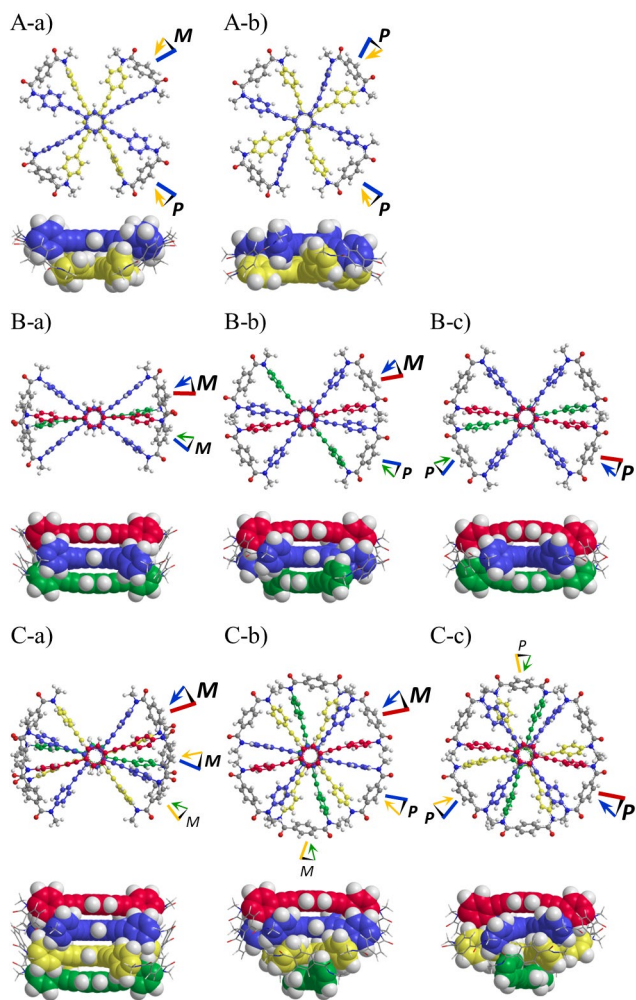
Fig. 2 Energy-minimized structures for model cyclophanes **1'**, (S_p)-**2'** and (S_p,S_p)-**3'** (X = Y = CH$_3$): (A) (a) *MP*-**1'** (rel. 0 kJ mol^{-1}) and (b) *PP*-**1'** (+22.8 kJ mol^{-1}); (B) (a) *MM*-**2'** (rel. 0 kJ mol^{-1}), (b) *MP*-**2'** (+38.9 kJ mol^{-1}) and (c) *PP*-**2'** (+33.6 kJ mol^{-1}); (C) (a) *MMM*-**3'** (rel. 0 kJ mol^{-1}), (b) *MPM*-**3'** (+33.9 kJ mol^{-1}) and (c) *PPP*-**3'** (+37.4 kJ mol^{-1}), obtained by conformational searches using MacroModel software (v9.9 OPLS_2005, Monte Carlo Multiple Minimum method, non-solvated for **1'**,[7] and v11.8 OPLS3e, Low-frequency-mode search, non-solvated for **2'** and **3'**). Top view (ball and stick representation) and side view (space-filling representation for planes and rods, and stick representation for bridges).

and/or rod are twisted. In two-layer **1**, planar chirality was generated by the arrangement of two different achiral groups (X ≠ Y).[7,9] Alternatively, in three-layer **2** and four-layer **3**, planar chirality was constitutionally generated according to the bridging positions on the plane,[5,6] and there is no need to differentiate X and Y. Indeed, for some reasons, a smaller substituent group X was associated with the side of the bridge close to the rod, and a larger Y was on the side close to the plane. These planar chiral cyclophanes were synthesized as racemates (Schemes S1-S3) and optically resolved (Chart S1). The configuration with regard to the planar chirality was assured to be stable during conformational interconversions through twisting. The absolute stereochemistry remains undecided.

First, in two-layer **1**, the two anisotropic planes were stacked orthogonally and bridged quadruply.[7] We could find a two-fold pair of twisted conformations with partial helicity (*M* or *P*) that

was inherently generated between two bridged phenylethynyl groups. These two pairs are nonequivalent due to different X and Y (X ≠ Y). Only at a particular pair with X or Y, additional twisting is allowed to adopt another form through the inversion of partial helicity. In either form, the two bridges paired across the central benzene rings of the planes are equivalent, and we designated this by a single *M* or *P* for each pair with partial helicity when describing different conformations as global helicity *MM*, *MP* and *PP* in **1**. We have revealed a conformational preference for the heterochiral form (*MP*) in planar chiral **1** based on a consideration of the origin of the Cotton effects induced for an enantiomer of **1**.

Next, a conformational preference for a homochiral form was discussed with three-layer **2** and four-layer **3**. We considered several conformations of each cyclophane with a two- or three-fold pair based on the results of conformational searches, and observed a conformational equilibrium in each solution by VT-NMR and VT-CD spectroscopy. Four-layer **3** should be discriminated from an isomeric form **4** with a difference in the stacking manner between the two planes.[7,8] Although there could be several pairs of helical conformations, as in **3**, by twisting of each component in four-layer **4**, it cannot be optically-active by itself due to the presence of a mirror. Indeed, we fortunately achieved the selective synthesis of four-layer **3**, in a precise sense; the selective synthesis of a precursor, which precluded the generation of **4**. The regioselectivity might be due to larger Y groups located close to the plane. Alternatively, planar chiral **1** and **2** were obtained as a mixture of racemic (desired) and optically-inactive (undesired) isomers, respectively. Details of the synthesis are described in the ESI.

Conformational searches were implemented with model cyclophanes: two-layer **1'**, three-layer (S_p)-**2'** and four-layer (S_p,S_p)-**3'** (X = Y = CH$_3$) (Fig. 2). A search for **1'** found that the conformational energy of a heterochiral form (*MP*) was lower than that of a homochiral form (*PP*), as reported previously.[7] Note that *MM* and *PP* of (S_p)-**2'**, and *MMM* and *PPP* of (S_p,S_p)-**3'** are diastereomers, although the designation is apparently enantiomeric. For (S_p)-**2'**, *MM*, one of the two homochiral forms, was found to be the most energy-minimized, and the other diastereomeric forms *PP* and *MP* were at relatively higher energy levels. For (S_p,S_p)-**3'**, conformational energies increased from *MMM* to *MPM*, *PPP*, and others (Fig. S3) with an increase in the number of *P*. These results with model cyclophanes (X = Y = CH$_3$) predicted an inherent nature for each cyclophane, and indicated that the pluralistic control of helical-sense preferences could be feasible. According to the anisotropy of the plane, there is a larger space between two phenylethynyl groups at the 1- and 5-positions than between two phenylethynyl groups at the 1- and 2-positions. In cyclophanes **2** and **3** [X = CH$_3$ and Y = CH$_2$(cHex)], a larger substituent would be keen to occupy a larger space, accompanied by the arrangement of a smaller substituent in a narrower space. Thus, these two nonstereogenic substituent groups would assist the induction of helical-sense preferences as directing groups. The greatest number of larger substituents arranged in a larger space, all out of four in **2** and four out of eight in **3**, could be
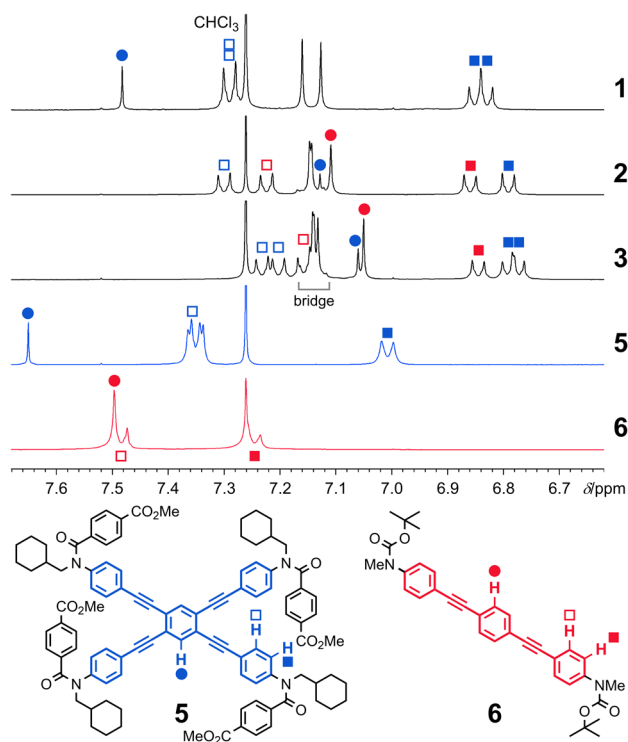
Fig. 3 Partial ^{1}H NMR spectra of cyclophanes **1**, **2** and **3**, and achiral components **5** and **6**, measured in chloroform-*d* at room temperature. In the spectrum of **5**, one of the doublet signals assigned to the terephthaloyl bridge overlapped one of the doublet signals assigned to the peripheral benzene rings (blue □).
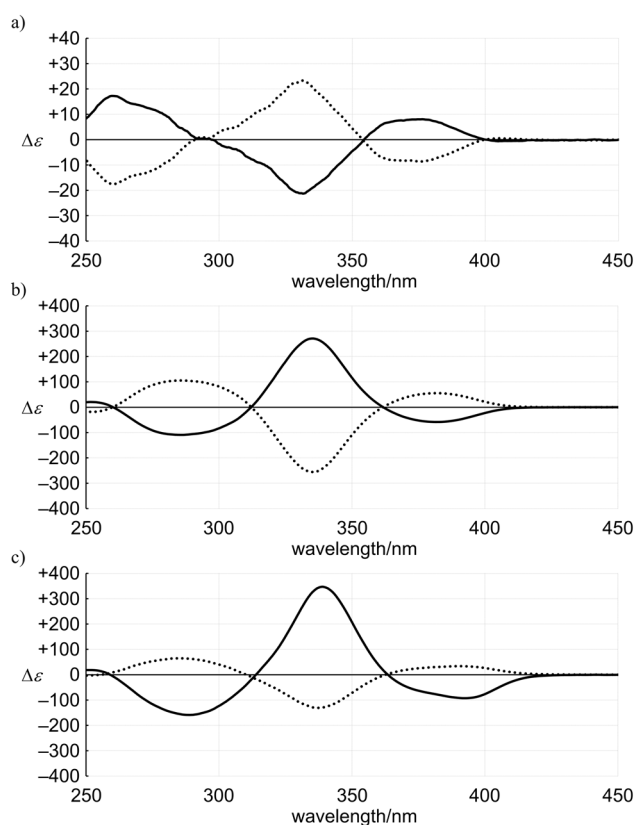

Fig. 4 CD spectra of planar chiral cyclophanes (a) (−)-**1** (solid line) and (+)-**1** (dashed line), (b) (+)-**2** (solid line) and (−)-**2** (dashed line), and (c) (+)-**3** (solid line) and a later eluted fraction containing (−)-**3** (dashed line). All spectra were measured in dichloromethane at 293 K.

attained in *MM* of (S_p)-**2** and *MMM* of (S_p,S_p)-**3**. Notably, the lowest energy was predicted for *MPP*, not *MMM*, of a model for isomeric cyclophane **4'** (X = Y = CH$_3$) (Fig. S3). In either conformation, the central benzene rings of both the plane and rod were highly planar and stacked orderly, while the peripheral benzene rings were tilted with respect to the central benzene ring of each plane or rod.

The ^{1}H NMR spectra of **1**, **2** and **3**, measured at room temperature, showed only a single set of averaged resonances due to rapid interconversions among global and/or local conformations (Fig. 3 and Fig. S1). A significant upfield shift was induced for the aromatic protons (blue ●) of the central benzene ring of the plane, compared to the chemical shift of the corresponding protons in a single plane **5**. The degrees were greater for three-layer **2** and four-layer **3** than for two-layer **1**, since the plane(s) in **2** and **3** were sandwiched between the other components. A more significant upfield shift was induced for the central phenylene protons (red ●) of the rod, compared to the chemical shift of the corresponding protons in a single rod **6**. The chemical shifts were smaller than those for the aromatic protons of the central benzene ring of the plane, which might be related to the rotatability of the central benzene ring in the rod. Doublet signals for the peripheral phenylene protons (blue and red □), which are closer to the central benzene ring of both the plane and rod, were shifted upfield, which indicated that the peripheral benzene rings were densely congested at the interlayer. Regarding the counterpart signals of the doublet (blue and red ▪), similar values of the chemical

shift were recorded with either cyclophane, which was due to deshielding from the central benzene ring of the terephthaloyl bridge.

Even at lower temperatures, the spectra remained to show only a single set (Fig. S2). Average values of the chemical shift for planes and rods changed with temperature greater than those for bridges. These results revealed that several different conformations were included in an equilibrium; they interconverted more rapidly than the NMR time-scale, and the populations changed with temperature. Notably, in the spectra of four-layer **3**, measured at 223-323 K, the changes in the chemical shift of the central phenylene protons of the rod (red ●) were considerably smaller than those of the aromatic protons (blue ●) of the central benzene ring of the plane. This result showed that the arrangement of the rod with respect to the plane seemed to be stable; different conformations were generated according to the sense of twisting between the two planes and they were conformationally interconvertible (e.g., *MMM* and *MPM*).

In the UV spectra of cyclophanes, some characteristics of each component[10,11] were perturbed (Fig. S4). The maximum absorption emerged at a shorter wavelength region, and the intensity was remarkably attenuated, which was smaller than what was expected based on the numbers of the component(s) [323 nm (ε 1.48×10^5) for **1**, 318 nm (1.62×10^5) for **2** and 326 nm (2.57×10^5) for **3**]. Regarding shoulder absorptions at a longer

wavelength region, the intensity was still attenuated. These perturbations were considered to be a result of reduction of the coplanarity of the peripheral benzene rings with respect to the central benzene ring in the plane and rod in cyclophanes.

The CD spectrum of two-layer **1** showed several bisignated Cotton effects (Fig. 4a), which were distinct in shape and intensity from those of an isomeric two-layer cyclophane[9] (Fig. S5) with the two identical achiral planes that were stacked in parallel[12] and twisted helically. To consider the origin of the Cotton effects induced in **1**, we performed complexation experiments with an external chiral element. Since the cyclophane was expected to adopt different conformations, *MP*, *MM* and *PP*, we could see the origin with or without a change in the inherent Cotton effects upon complexation with either of the enantiomeric guests (Fig. S6, details are described in ESI). Based on the results of a stereospecific change on complexation with either of the enantiomeric guests, we concluded that the observed Cotton effects were not due to a biased preference of helical conformations (*MM* and *PP*), but to the *MP* conformation, which is inherently achiral. Thus, in two-layer **1**, a particular pair of partial helicity could induce the neighboring pair to prefer the opposite sense through cooperative cancellation. The CD spectra of three-layer **2** and four-layer **3** were similar to each other, except that unique Cotton effects emerged at a longer wavelength region in the spectrum of **3** (Fig. 4b and 4c). The greater Cotton effects common to these two cyclophanes were due to an arrangement of the rod above and below the plane. The smaller Cotton effects unique to four-layer **3** were considered to be related to a biased preference of helical conformations that were generated by twisting of the two planes, since the rod had no absorption in this region. Thus, the patterns of dissymmetry ($\Delta\varepsilon/\varepsilon$) were different from each other in this region (Fig. S7). VT-CD measurements showed that the intensity of the Cotton effects slightly changed with temperature (increased at lower temperatures) (Fig. S8), although the configuration of the planar chirality was assured. These results elucidated changes in the populations of helical conformations. If we considered the invariant appearance with only a few isosbestic points, a small number of species might be present at equilibrium, although many conformations could have been assumed for multilayer cyclophanes.

In conclusion, we have demonstrated the induction of helical-sense preferences in a particular global conformation among many conformations. In two-layer **1**, a heterochiral conformation was dominantly induced through the cooperative cancellation of several senses of partial helicity, which was concluded from the observation of the Cotton effects based on an achiral framework. This conformational control was attained without a transmission of chirality, although the planar chirality was generated by the arrangement of different achiral groups on purpose to be CD active. Stacking of achiral planes and rods one above the other induced a preference for either of the two homochiral conformations with a single sense of twisting throughout the entire molecule (three-layer **2** and four-layer **3**). The identical preferences for a single sense can be considered to be the result of an intramolecular transmission of planar

chirality, which is generated constitutionally in the multilayered cyclophanes according to the bridging positions.

There are no conflicts to declare.

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