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Planar chiral desymmetrization of a two-layered cyclophane and control of dynamic helicity through the arrangement of two nonstereogenic centers

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We designed a planar chiral two-layered cyclophane, which is inherently achiral but desymmetrized by the arrangement of two nonstereogenic centers. We demonstrate the control of dynamic helicity that is generated by the helical twisting of two-layered planes in the cyclophane, where methyl and cyclohexylmethyl groups act as directing groups.

Planar chirality is generated when a plane possesses different arrangements of atoms above and below the chiral plane.¹ Planar chiral molecules undergo racemization through rotation of the chiral plane.^{2,3} The chiroptical properties⁴ of molecules with enantiomers have been investigated to enable their isolation through optical resolution⁵ or enantioselective synthesis,⁶ and such robust chiral scaffolds have been used as building blocks for the construction of chiral architectures,⁷ functional materials,⁸ and asymmetric catalysts.^{1c,9} For most of the reported planar chiral cyclophanes, a chain-length-dependent strategy was used to make the molecule robust and configurationally stable.^{3,4,5a-i,6a-e} Thus, configurational stability can often be achieved by making at least part of a molecule inflexible. This would appear to pose a problem for the design of a planar chiral molecule that can exhibit a range of motion.

We report a planar chiral and configurationally stable cyclophane. The cyclophane is composed of two layers that are stacked in pairs and bridged with four terephthalamide units (Fig. 1). The arrangement of two nonstereogenic centers X and Y on each amide nitrogen in the bridge generates planar chirality (1: X ≠ Y). The two-layered scaffold is inherently achiral (2: X = Y). Since neither plane can rotate, the chirality is assured to be configurationally stable. However, regarding the conformation, the two planes can be allowed to twist in a clockwise or counterclockwise manner in cases where the

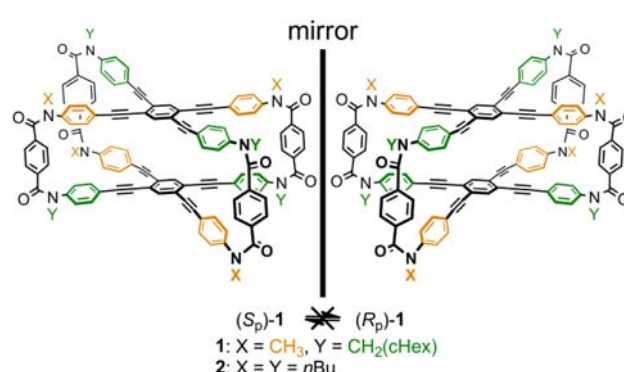


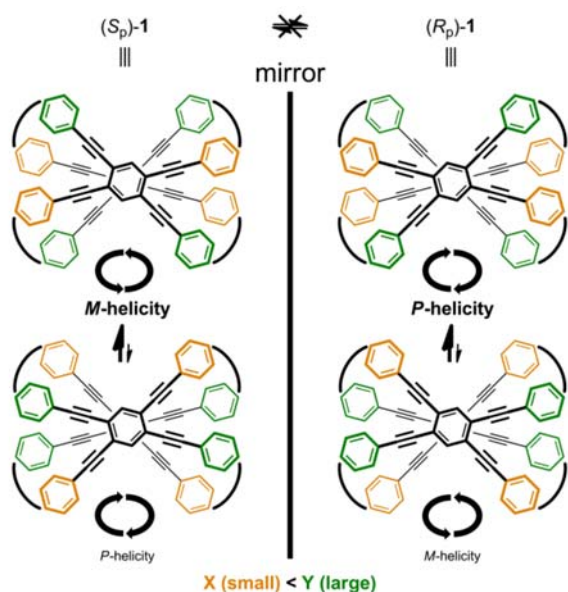
Fig. 1 Chemical structures of cyclophanes **1** and **2**. Planar chiral desymmetrization of **1** through the arrangement of two nonstereogenic centers X and Y (X ≠ Y). Stereochemical notation of planar chiral **1** is conformed to that reported in ref1c.

molecule prefers not to adopt an eclipsed form. If interconversion between two twisted forms in each enantiomer is realized, we would consider such a molecule to be conformationally dynamic.

The two nonstereogenic centers X and Y, which are selected for size to be relatively small and large, can also play another role. In a helically twisted form of the two-layered cyclophane, the two nonstereogenic centers X and Y would act in concert as directing groups to determine the preferred direction of helical twisting: the smaller group should occupy a narrower space and the larger group should occupy a vacant space, which consequently would lead to a preference for a particular sense of dynamic helicity (Scheme 1). Thus, the difference in relative sizes of X and Y can control the screw-sense preference¹⁰ of dynamic helicity even without any transmission of chirality. In each configurationally stable isomer, a single pair of X and Y creates contrary preferences for (*M*)- or (*P*)-helicity. The control of dynamic helicity is a fascinating issue,¹¹ and has been generally achieved through the transmission of some stereogenic element such as point chirality¹² or planar chirality.^{5m,8d} The generation of planar chirality and the unprecedented control of dynamic helicity through the arrangement of two nonstereogenic centers are described below.

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Scheme 1. Control of dynamic helicity through the transmission of a difference in size between two nonstereogenic centers X (small) and Y (large) on each amide nitrogen in the bridge (terephthalamide unit), which is depicted as an arc for clarity.

We synthesized a two-layered cyclophane **1** [X = CH₃, Y = CH₂(cHex)] with a four-fold bridge. Two of the four bridges were used to form an intermediary macrocycle, which was sequentially coupled to aniline derivatives with an X or Y group to give *rac*-**1** as a racemate through a double-ring-closing condensation (Scheme S1).¹³ Both (–)-**1** and (+)-**1** were obtained by HPLC separation with a chiral stationary column ([α]_D = –359 for the first fraction and [α]_D = +365 for the second fraction). We also synthesized an achiral model **2** [X = Y = *n*Bu] as a single species using a similar strategy (Scheme S2). A single-crystal X-ray analysis of **2** revealed that the two planes were forced to adopt an eclipsed form with a slight deformation of the planes to infill the cavity¹⁴ (Fig. 2). Alternatively, a conformational search for model **2'** [X = Y = Me] found a helically twisted form as the most energy-minimized structure, in which a deformation as seen in the crystal seemed to be resolved¹⁴ (Fig. 3). Such a helically twisted form led us to expect the realization of a control of helicity through arrangement of the two nonstereogenic centers X (small) and Y (large) (Scheme 1). There were no signs of an eclipsed form even when the energy window was extended up to 60 kJ mol^{–1}.

Next, we investigated the dynamic structure of **1** in solution. The ¹H and ¹³C NMR spectra of *rac*-**1**, measured in chloroform-

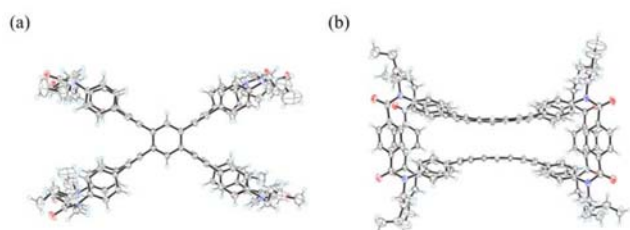


Fig. 2 X-ray structure of **2** [X = Y = *n*Bu]: (a) top view and (b) side view. Solvents are omitted for clarity.

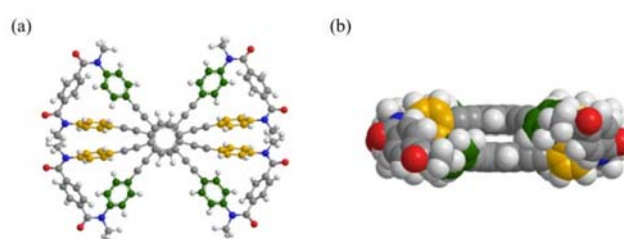


Fig. 3 The most energy-minimized structure for **2'** [X = Y = Me]: (a) top view (ball and stick representation) and (b) side view (space-filling representation), obtained by a conformational search using MacroModel software (v9.9 OPLS_2005, Monte Carlo Multiple Minimum method, non-solvated, 50 000 steps). Only one enantiomeric form with (*M*)-helicity is depicted.

d at room temperature, showed a single set of averaged resonances (Fig. S1), which can be explained if we consider a dynamic interconversion(s) among species involving two diastereomeric forms with (*M*)- or (*P*)-helicity. This was also supported by VT measurements which showed changes in the chemical shift of averaged resonances with temperature (Fig. S2). Notably, a single set of average resonances emerged even when the temperature was lowered to 223 K.

The UV-vis spectrum of two-layered *rac*-**1**, measured in dichloromethane at room temperature, showed that two bands [λ_{max}/nm (log ε) 312 (5.16) and 360 (sh. 4.82)] characteristic of 1,2,4,5-tetrakis(phenylethynyl)benzene [316 (5.14) and 350 (4.68)]¹⁵ were mostly retained in appearance, although the intensity was markedly attenuated and the shape was broadened (Fig. 4b). A slight hypsochromic shift of the former band even with the attachment of an auxochrome and global attenuation of the spectral intensity might be attributed to the reduction of coplanarity due to twisting of the phenylethynyl groups.^{12b} In these absorption regions, we found compositive Cotton effects in the CD spectra of (–)-**1** and (+)-**1**, which were completely mirror-imaged (Fig. 4a). This chiroptical observation indicated that a particular sense of dynamic helicity was preferred in each enantiomer due to the arrangement of methyl and cyclohexylmethyl groups. These Cotton effects were enhanced with a decrease in temperature

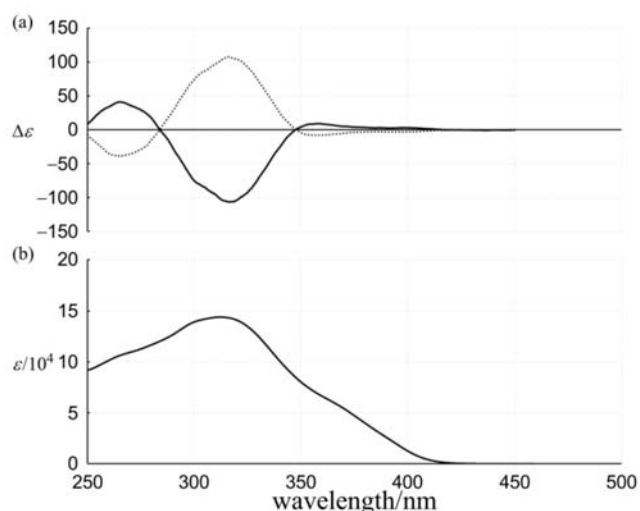


Fig. 4 (a) CD spectra of (–)-**1** (solid line) and (+)-**1** (dashed line), and (b) UV-vis spectrum of *rac*-**1**. All spectra were measured in CH₂Cl₂ at room temperature.

(Fig. S3), which supported the contribution of a dynamic interconversion between two diastereomeric forms with (*M*)- or (*P*)-helicity.

In conclusion, we have demonstrated a successful control of dynamic helicity using two nonstereogenic centers based on a two-layered cyclophane, which is inherently achiral but desymmetrized by the arrangement of two nonstereogenic centers X (small) and Y (large). We used terephthalamide as a four-fold bridging unit, which induced the cyclophane to adopt helically twisted forms with (*M*)- or (*P*)-helicity, and thus dynamic helicity was generated in the configurationally stable cyclophane. Helical twisting of the two planes in the cyclophane created two diastereomeric forms due to the difference in size between X and Y, where methyl and cyclohexylmethyl groups acted as directing groups to determine a preferred sense of dynamic helicity, even though they are not stereogens.

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- During the condensation, an undesired product **3** was formed along with *rac*-**1** in a ratio of 58:42 (*rac*-**1**:**3**) (Scheme S1), and they were separated by HPLC, prior to optical resolution of *rac*-**1**.
- The shortest distance between two carbons in each plane was 3.562(5)  . The corresponding value estimated for a helically twisted form of model **2'** was 3.642  .
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