

## PAPER

View Article Online  
View Journal | View Issue



Cite this: *Org. Biomol. Chem.*, 2023, **21**, 2562

# An attempt to consider cooperativity in helical-sense preferences induced in fused macrocycles†

Ryo Katoono, \* Takaaki Kudo and Shunsuke Kawai

We synthesized bis and tris(macrocycle)s in which a two- or three-fold macrocycle was fused and each adopted twisted forms with *M*- or *P*-helicity. According to the sense of twisting in each element, diverse conformations can be generated in a molecule. We present two types of conformational preferences. One is the innate preference for a helical form with an identical sense of twisting throughout the entire molecule. The other is the helical-sense preference for a particular sense of twisting. We were interested in the relationship between  $K_n$  and  $(K_1)^n$ , where  $K_n$  is an equilibrium constant for the conformational inter-conversion between two helical forms (*MM* and *PP*, *MMM* and *PPP*) and  $n$  is the number of elements, since we considered that the relationship could be a metric to see the interinfluence among these macrocyclic elements in a single molecule. Through VT measurements in  $^1\text{H}$  NMR and CD spectroscopy, we attempted to quantify the helical-sense preferences induced in the fused macrocycles ( $n = 2$  and  $3$ ) to compare  $K_n$  and  $(K_1)^n$ .

Received 3rd February 2023,  
Accepted 23rd February 2023

DOI: 10.1039/d3ob00171g

rsc.li/obc

## Introduction

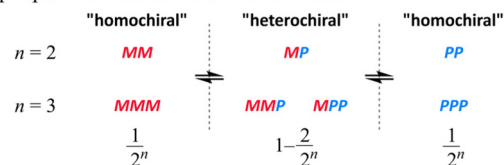
The pair of enantiomers in a racemate that conformationally interconvert with each other have the ability to change the ratio of enantiomers according to circumstances.<sup>1</sup> When several such racemic elements are assembled into a single molecule,<sup>2</sup> diverse conformations can be generated according to the chiral sense in each element (Scheme 1). These conformers with an identical or different sense of chirality would be statistically populated in solution if each element has no preference for a particular sense. Since there are always two forms where all elements prefer the same sense throughout the entire molecule (for descriptive purposes we term this a "homochiral" situation in a molecule), the populations of the homochiral conformers decrease with an increase in the number of elements ( $n$ ). If the molecule is designed to reduce the chance to adopt "heterochiral" conformation(s) where different senses of chirality coexist in a molecule,<sup>3</sup> we could consider the ratio of enantiomers (*MM* and *PP*, *MMM* and *PPP* etc.) of a molecule with several elements as like a simple case of *M* and *P* ( $n = 1$ ) (Scheme 2).

When an imbalance in the populations with *M*- or *P*-helicity is induced in the monomeric element ( $n = 1$ ) through some

(a) a pair of enantiomers in a racemate

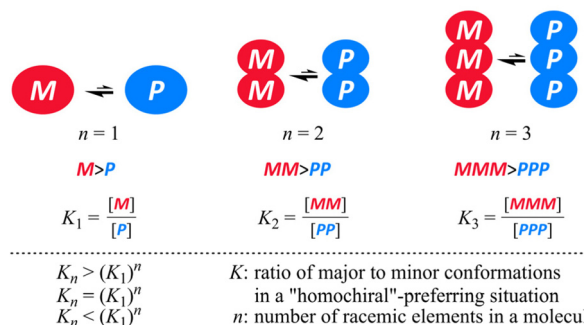


(b) multiple pairs of enantiomers in a racemate



that conformationally interconvert to each other

**Scheme 1** (a) Conformational interconversion between enantiomers in a racemate and (b) conformational diversity in a molecule with multiple pairs of enantiomers in a racemate.

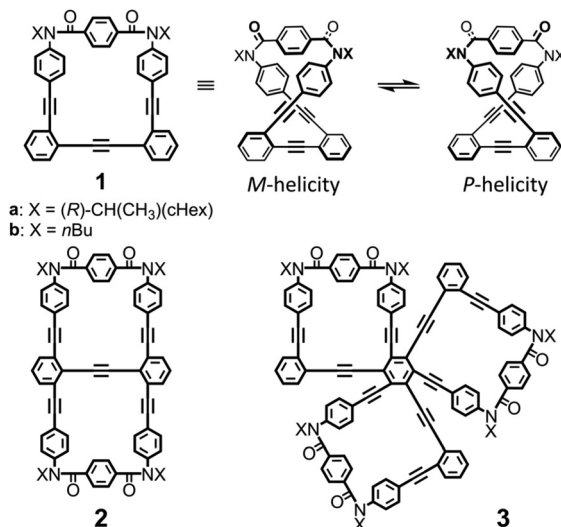


**Scheme 2** Types of relationships between  $K_n$  and  $(K_1)^n$ .

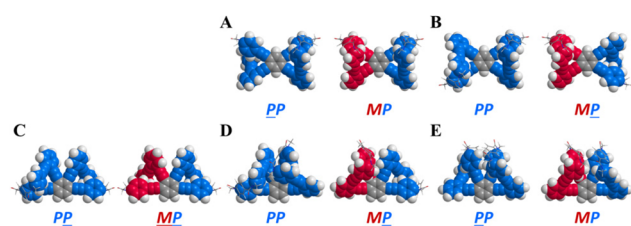
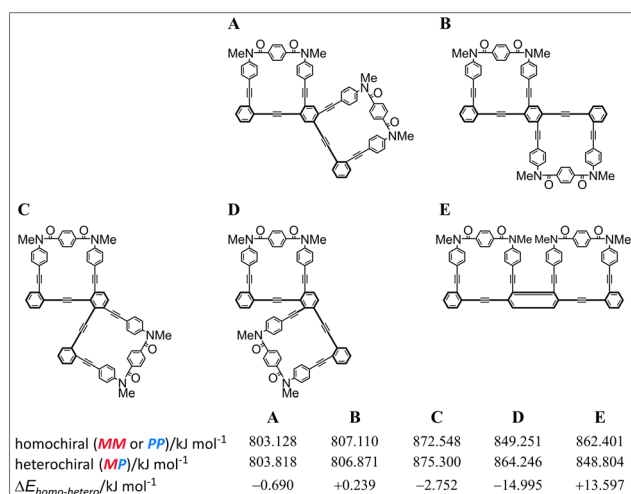
Department of Chemistry, Faculty of Science, Hokkaido University,  
Sapporo 060-0810, Japan. E-mail: katoono@sci.hokudai.ac.jp; Tel: +81 11 706-4616

† Electronic supplementary information (ESI) available: NMR, UV and CD spectroscopic data, and titration experiments (Fig. S1–S7), experimental details of new compound syntheses, and copies of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and MS spectra. See DOI: <https://doi.org/10.1039/d3ob00171g>



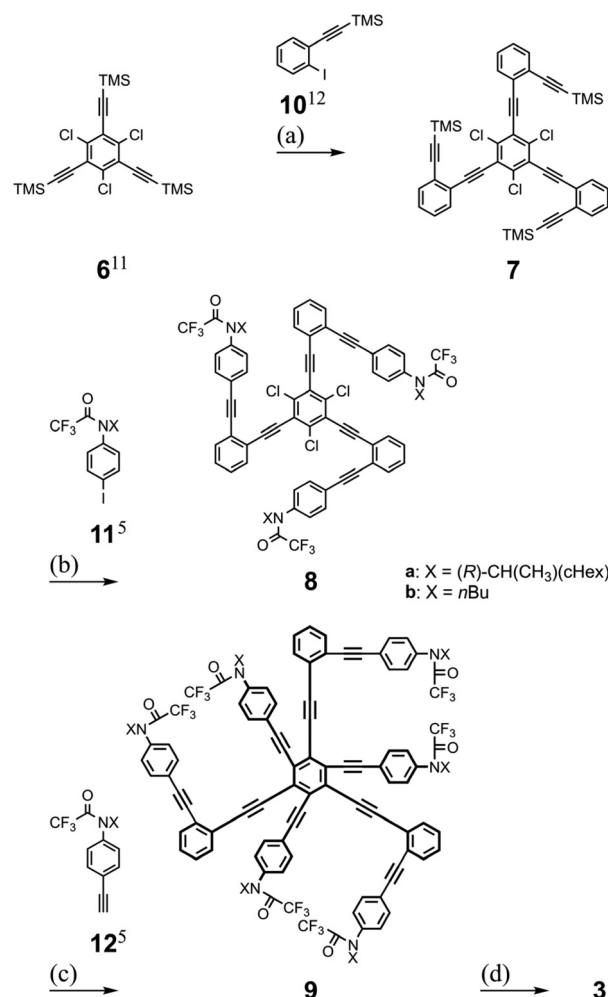


**Fig. 1** Chemical structures of monomeric macrocycle **1**, bis(macrocycle) **2** and tris(macrocycle) **3**.

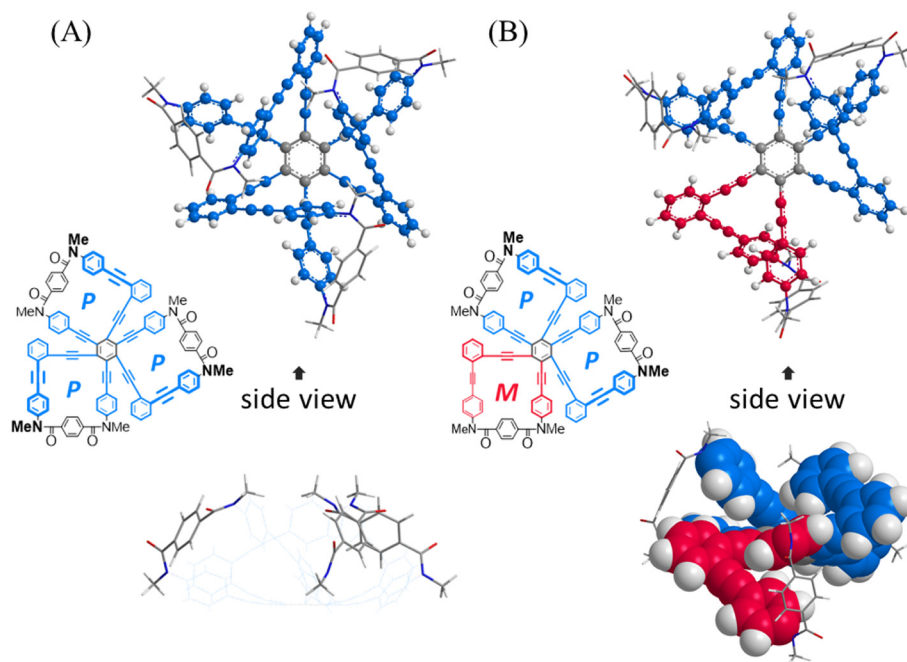


**Fig. 2** Energy-minimized structures for model bis(macrocycles) A–E: PP-A (rel. 0 kJ mmol<sup>-1</sup>) and MP-A (+0.690 kJ mol<sup>-1</sup>); PP-B (+0.239 kJ mol<sup>-1</sup>) and MP-B (rel. 0 kJ mol<sup>-1</sup>); PP-C (rel. 0 kJ mmol<sup>-1</sup>) and MP-C (+2.752 kJ mol<sup>-1</sup>); PP-D (rel. 0 kJ mol<sup>-1</sup>) and MP-D (+14.995 kJ mol<sup>-1</sup>); PP-E (+13.597 kJ mol<sup>-1</sup>) and MP-E (rel. 0 kJ mol<sup>-1</sup>), obtained by conformational searches using MacroModel software (v11.8 OPLS3e, MCMM, non-solvated). Space-filling representation for phenylene ethynylenes and stick representation for terephthaloyl bridges. An underlined code denotes the sense of the macrocycle located below the TPEB plane.

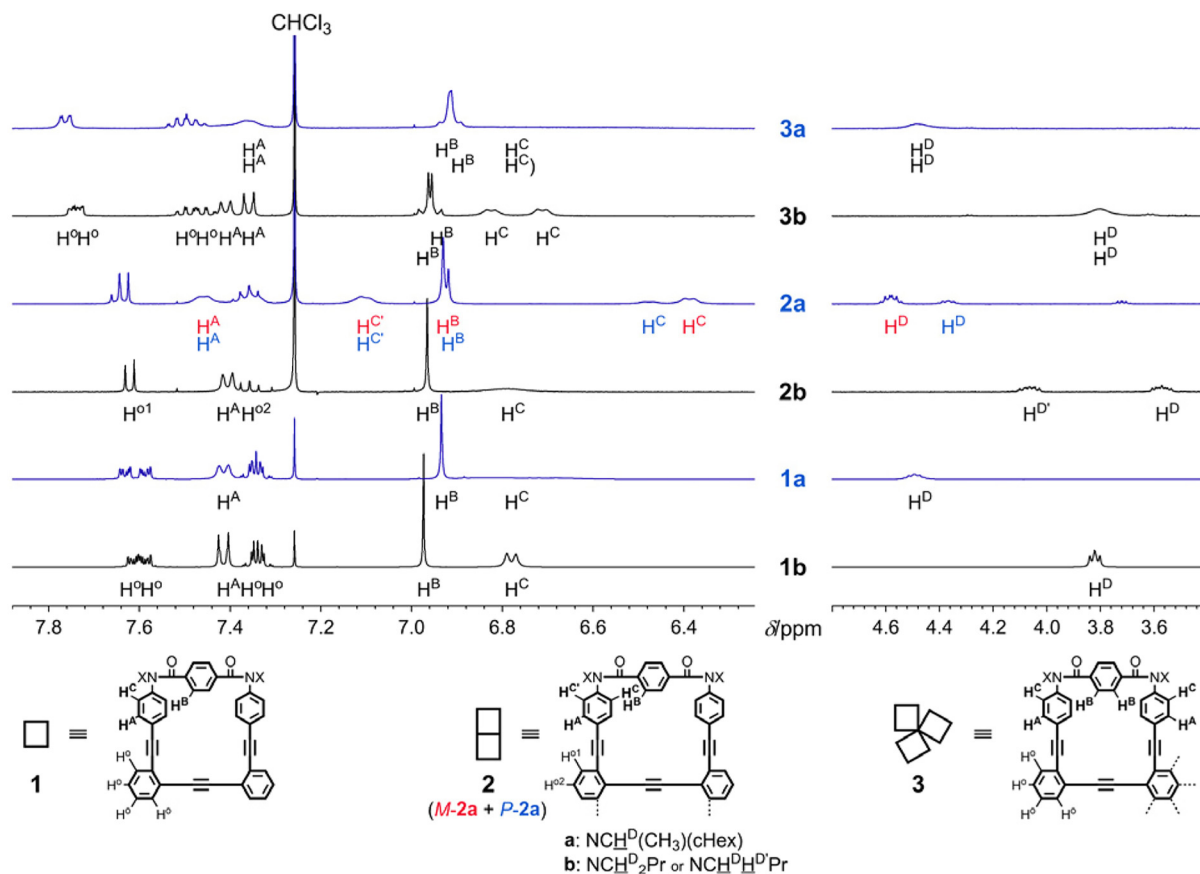
transmission of chirality,  $K_n$  would increase with an increase in the number of elements and be equal to  $(K_1)^n$ , where  $K_1$  is defined as the ratio of the major to minor conformation ( $K_1 > 1$ ). Alternatively,  $K_n$  might be smaller or larger than  $(K_1)^n$  as a result of some perturbation. We were interested in the relationship between  $K_n$  and  $(K_1)^n$ , since the relationship would be a metric to see the interinfluence between elements in a molecule. A conformational search would be valid to explore candidate molecules that could energetically disfavor heterochiral conformations. NMR spectroscopy would be an effective tool for estimating a ratio of diastereomers,<sup>4</sup> though there could be a limit to integrate precisely both major and minor peaks, especially for a case where the ratio could be greatly biased to prefer a particular form. Since uncertainty based on integration could not be excluded absolutely, we proposed that measurements could be implemented at several temperatures



**Scheme 3** Synthesis of tris(macrocycle)s **3a** and **3b**. Reagents and yields: (a) (i) K<sub>2</sub>CO<sub>3</sub>, MeOH, THF (94%), (ii) **10**,<sup>12</sup> Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, THF, <sup>1</sup>Pr<sub>2</sub>NH (54%); (b) **11a/b**,<sup>5</sup> Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, tetra-*n*-butylammonium fluoride (TBAF), THF, Et<sub>3</sub>N (85% for **8a** and 83% for **8b**); (c) **12a/b**,<sup>5</sup> PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, X-Phos,<sup>13</sup> dioxane, <sup>1</sup>Pr<sub>2</sub>NH (63% for **9a** and 69% for **9b**); (d) (i) NaH, MeOH, THF (85% for **9a'** and 99% for **9b'**), (ii) terephthaloyl chloride, Et<sub>3</sub>N, toluene (27% for **3a** and 42% for **3b**).



**Fig. 3** Energy-minimized structures for a model tris(macrocycle) **3c** ( $X = \text{CH}_3$ ): (A) *PPP* (rel.  $0 \text{ kJ mol}^{-1}$ ) and (B) *MPP* ( $+33.5 \text{ kJ mol}^{-1}$ ), obtained by conformational searches using MacroModel software (v11.8 OPLS3e, first: MCMM to find two structures, and second: mixed torsional/low-mode sampling for each structure, non-solvated). Ball and stick representation for phenylene ethynylenes and stick representation for terephthaloyl bridges (side view: wire-frame or space-filling representation for phenylene ethynylenes and stick representation for terephthaloyl bridges).



**Fig. 4** Partial  $^1\text{H}$  NMR spectra [400 MHz; left: aromatic protons and right: methine (a) or methylene (b) protons] of **1a**, **1b**, **2a**, **2b**, **3a** and **3b**, measured in chloroform-*d* at room temperature. Nonequivalent protons (four  $\text{H}^{\text{O}}$  in **1**, and four  $\text{H}^{\text{O}}$  and two  $\text{H}^{\text{A}}$ ,  $\text{H}^{\text{B}}$  and  $\text{H}^{\text{C}}$  in **3**) were not assigned.



to obtain a linear extrapolation such as a least-squares estimation. The barrier for interconversion between two enantiomeric or diastereomeric forms should be imposed moderately to observe both major and minor peaks within an NMR time-scale. It is also important for these two peaks to stand separately for better integration.

In consideration of these requisites, we used macrocycle **1** ( $n = 1$ ),<sup>5</sup> which can adopt chiral forms with *M*- or *P*-helicity by twisting; these diastereomeric (**a**: X = 1-cyclohexylethyl) or enantiomeric (**b**: X = butyl) forms are conformationally interconvertible (Fig. 1). The imbalance in the populations of twisted forms with *M*- or *P*-helicity could be realized by transmission of internal (**a**) and external (**b**) chirality.<sup>6</sup> Thus, we designed bis and tris(macrocycle)s **2** ( $n = 2$ )<sup>7</sup> and **3** ( $n = 3$ ) (Fig. 1), where two or three macrocyclic elements were assembled by fusion of **1**. Here we demonstrate that there was an innate preference for the homochiral forms over heterochiral forms in **2** and **3** by using the MacroModel software and by observing two sets of resonances assigned to two diastereomeric forms with *M*- or *P*-helicity in the NMR spectra measured at low temperatures. Once a ratio was estimated by NMR spectroscopy, we could see a ratio at different temperatures from the intensity of the Cotton effects in CD spectroscopy, since the intensity is related to enantiomeric or diastereomeric excess (ee or de =  $K_n - 1/K_n + 1$ , where  $K_n$  is experimentally estimated as the ratio of major to minor conformations). Based on this, we explored a diastereomeric ratio induced in a complexed state by CD spectroscopy. The details of synthesis and attempts to compare  $K_1$  and  $(K_1)^n$  through intramolecular or intermolecular transmission of chirality are described below.

## Results and discussion

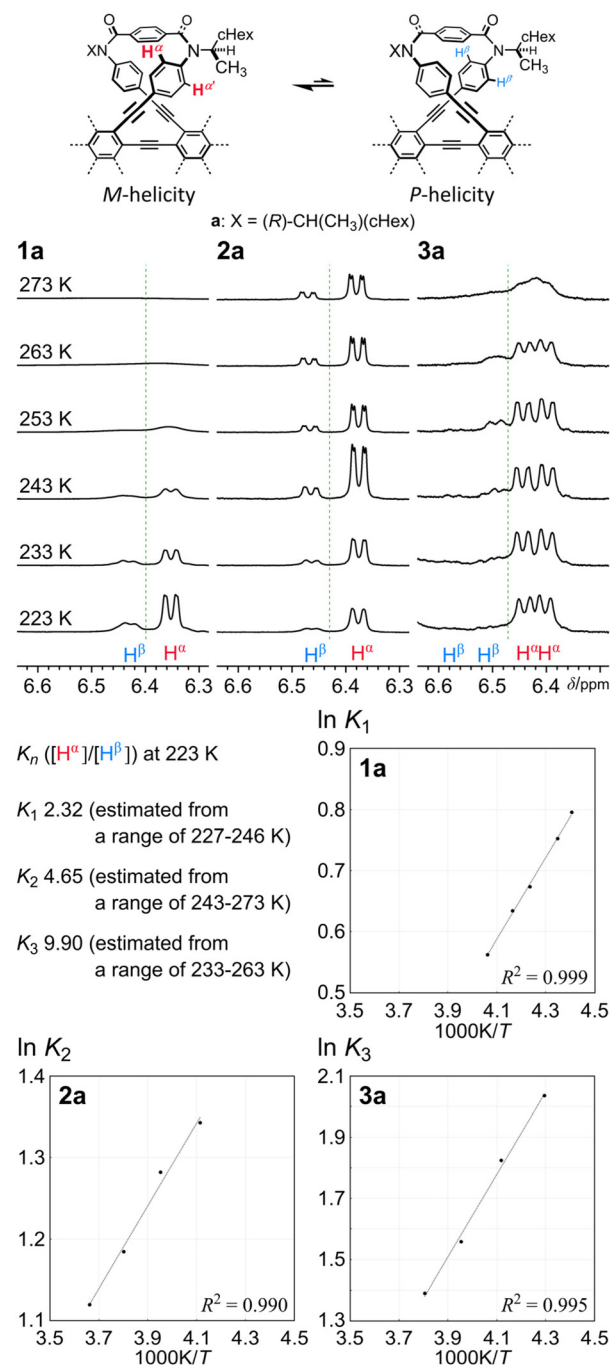
### Conformational searches

First, we investigated whether or not an innate preference for a homochiral form could be induced according to the arrangement of a two-fold macrocycle by using conformational searches with model bis(macrocycle)s **A–E** (Fig. 2). As the substituent group on the nitrogen, we used a methyl group, which has no preference for any sense of twisting. We assumed that no preference would be generated when there was no difference in the conformation energy between homochiral and heterochiral forms ( $\Delta E_{\text{homo-hetero}}$ ). In such a molecule, each macrocyclic element would be independent of the helical sense in a neighboring macrocycle. Alternatively, a difference in the conformation energy would be considered to be a result of the influence of either element in establishing its own sense according to the sense of a neighboring macrocycle. The results showed that the difference was small for **A** and **B**, which were based on 1,2,4,5-tetrakis(phenylethynyl)benzene (TPEB), while relatively large differences were predicted for **C**, **D** and **E**,<sup>8</sup> which were based on 1,2,3,4-TPEB. Especially for **D**, the difference was significant and we expected that either macrocycle could prefer the same sense as that of the neighboring macrocycle, which is a substructure of the tris(macro-

cycle) **3**. Next, we implemented a similar search for a model tris(macrocycle) **3c** (X = CH<sub>3</sub>). As expected, a homochiral form was found to be the most energy-minimized (Fig. 3).

### Synthesis of tris(macrocycle)s **3**

Tris(macrocycle)s **3** are 1,3,5-/2,4,6-differentiated hexakis(phenylethynyl)benzenes (HPEBs)<sup>10</sup> and we started with 1,3,5-tri-



**Fig. 5** Partial VT-<sup>1</sup>H NMR spectra (400 MHz) of **1a**, **2a** and **3a**, measured in chloroform-*d* at 223–273 K, and plots of  $\ln K_n$  versus  $1/T$  for the conformational interconversion between two diastereomeric forms with *M*- or *P*-helicity in a solution of **1a**, **2a** or **3a**.  $K_n = [\alpha (\text{major})]/[\beta (\text{minor})]$ .



chloro-2,4,6-tris(2-trimethylsilyl ethynyl)benzene **6**.<sup>11</sup> Stepwise Sonogashira coupling reactions of aryl iodides (**10**<sup>12</sup> and **11**<sup>5</sup>) with desilylated acetylenes on **6** and on the resulting **7** gave trichloro-intermediates **8**. The third Sonogashira coupling of aryl acetylenes (**12**<sup>5</sup>) with the chlorides<sup>13</sup> on **8** furnished HPEB **9**, a threefold ring-closing precursor. Finally, the three macrocycles were accomplished by a threefold condensation reaction with terephthaloyl chloride (Scheme 3). According to the results of the conformational searches (Fig. 2), bis(macrocycle) **D** seemed to be a proper analyte. However, we rejected it due to the nonequivalency of 1,3-/2,4-differentiation on 1,2,3,4-TPEB, which was not suitable for <sup>1</sup>H NMR analysis. Instead, we used bis(macrocycle)s **2** as analogs.

### Estimation of $K_n$ and $(K_1)^n$ based on <sup>1</sup>H NMR spectroscopy

In the <sup>1</sup>H NMR spectra of **1**, **2** and **3**, measured at room temperature or above, the macrocycles were observed as single species (Fig. 4). Through VT-measurements, we demonstrated (i) a conformational preference for the homochiral form with the series of **b** compounds (Fig. S1†) and (ii) a conformational preference for either of the two homochiral forms with the series of **a** compounds (Fig. 5 and Fig. S2†).

In the VT-<sup>1</sup>H NMR spectra of **1b** (X = *n*Bu) (Fig. S1A†),<sup>5</sup> measured at 223–323 K, there was no change in the chemical shift for *p*-phenylene protons (H<sup>A</sup>, H<sup>B</sup> and H<sup>C</sup>) throughout the entire range of temperature, although signals were broadened and split due to the slower rotation of *p*-phenylene rings than the NMR timescale at lower temperatures, since there was no form available other than an enantiomeric pair of twisted forms with *M*- or *P*-helicity. Also for **2b** (Fig. S1B†),<sup>7</sup> no change in the chemical shift was induced with a change in temperature, which showed that either of the two chiral forms (homochiral *MM*/*PP* and heterochiral *MP*) continued to exist alone in solution, and could not be assigned based solely on this measurement due to similarities in the patterns of averaged resonances for the homochiral and heterochiral conformations. For **3b** (Fig. S1C†), only a slight change in the chemical shift was induced, which reflected a slight change in popu-

lations with different conformations. Ultimately, only a single set of resonances emerged in the spectrum measured at 223 K, which suggested that the dominant conformation could be assigned to the homochiral form of **3b** based on the molecular symmetry.

The <sup>1</sup>H NMR spectra of **1a**,<sup>5</sup> **2a**<sup>7</sup> and **3a** [X = (*R*)-CH(CH<sub>3</sub>)(cHex)], measured at low temperatures, showed that two diastereomeric forms with *M*- or *P*-helicity coexisted and the ratio of the major (α) to minor (β) conformations gradually increased with a decrease in temperature (Fig. 5 and Fig. S2†). During VT measurements, there were several coa-

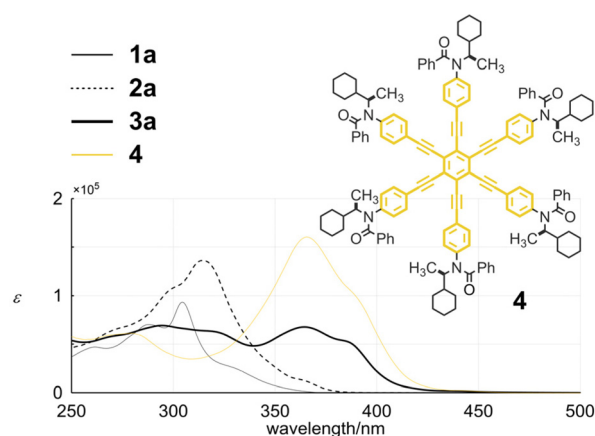


Fig. 6 UV spectra of **1a**, **2a**, **3a** and **4**, measured in dichloromethane at room temperature.

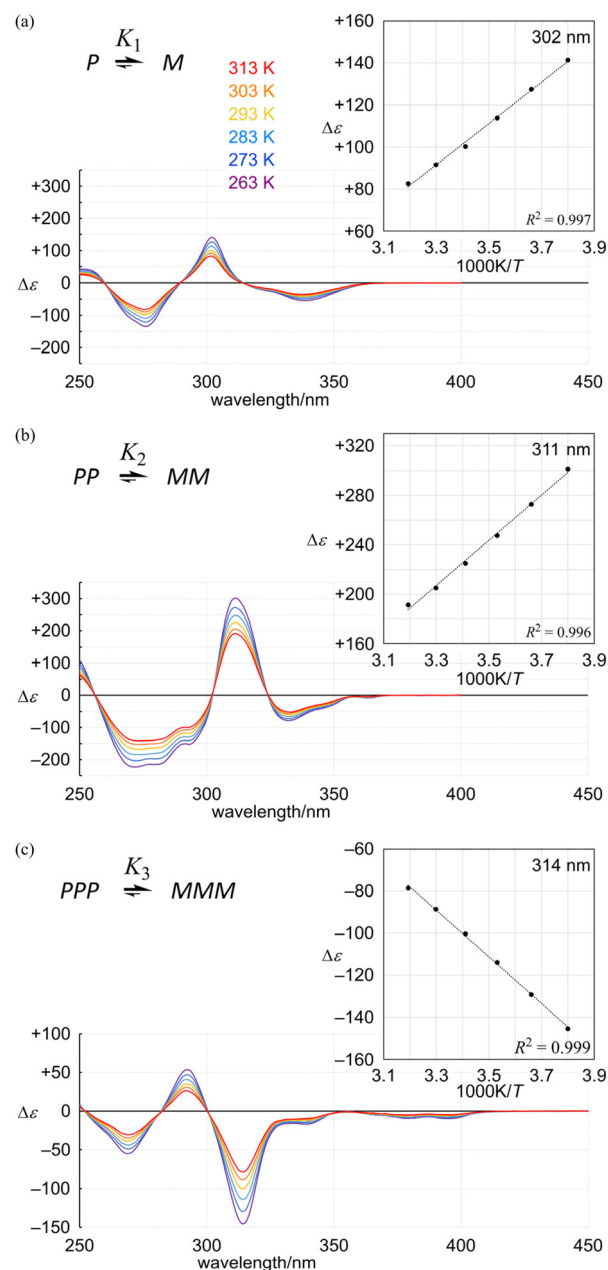


Fig. 7 VT-CD spectra of (a) **1a**, (b) **2a** and (c) **3a**, measured in dichloromethane at 263–313 K. Inset: plots of  $\Delta\epsilon$  (at 302 nm for **1a**, 311 nm for **2a** and 314 nm for **3a**) versus  $1/T$ .



lescings processes. One was related to local interconversions through rotation of *p*-phenylene rings ( $H^B$ ,  $H^A$  and  $H^C$ ), as seen for **b**. The other was attributed to the global interconversion between the two diastereomeric forms with *M*- or *P*-helicity. These processes were observed at different temperatures according to the difference in the chemical shifts between the two chemically exchanging protons. If we considered that the populations of the diastereomers with *M*- or *P*-helicity in the spectra of **2a** were differentiated, either conformation of **2b** that had existed alone throughout the entire range of temperature could also be assigned to the homochiral forms (*MM* and *PP*), since the differentiation cannot occur in the heterochiral form (*MP*) of **2**. Based on the values of the integral for  $H^A$  and  $H^B$  measured at several temperatures, we obtained a regression line and estimated the equilibrium constants at 223 K to be  $K_1 = 2.3$  (de 40%),  $K_2 = 4.7$  (65%) and  $K_3 = 9.9$  (82%). These values were not significantly different from squared  $(K_1)^2$  and cubed  $(K_1)^3$  values, calculated to be 5.4 (69%) and 13 (85%), respectively. These results might indicate that the original preference induced in **1a** through the intramolecular transmission of point chirality (*R*) seemed almost intact or slightly attenuated in each macrocycle in **2a** and **3a**. The preferred sense was consist-

ent,<sup>6</sup> as shown by similarities in the chemical shift for  $H^A$  or  $H^B$  in each solution of **1a**, **2a** and **3a**.

### Estimation of $K_n$ and $(K_1)^n$ based on CD spectroscopy

Tris(macrocycle) **3a** showed two regions of absorption (Fig. 6). One was observed for the minimum chromophore of diphenylacetylene at 250–300 nm. The other was seen in a longer wavelength region, which was characteristic of HPEB.<sup>14</sup> Regarding the absorption of HPEB, the intensity was significantly attenuated compared to that of an analogous HPEB **4**<sup>15</sup> (**3a**:  $\epsilon$   $6.77 \times 10^4$  at 364.5 nm and **4**:  $1.60 \times 10^5$  at 365.5 nm), which indicated that some dihedral angles of peripheral phenylene rings with respect to the central benzene ring of HPEB were perturbed in **3a**. These spectral features were not altered in **3b** by replacing the chiral auxiliary (*R*) with a butyl group on the nitrogen in the terephthaloyl bridge (Fig. S3†).

The spectral pattern of the Cotton effects in the shorter wavelength region (below 300 nm for **3a**) was similar to those seen in the spectra of **1a**<sup>5</sup> and **2a**,<sup>7</sup> although each extreme (292 and 269 nm) was different from the corresponding extreme for **1a** (302 and 276 nm) and **2a** (311 and 273 nm) due to a difference in the effective conjugation length in each framework (Fig. 7).

**Table 1** Calculated values of  $\Delta\epsilon_{223\text{ K}}$ ,  $|\Delta\epsilon_{\text{max}}|$ ,  $K_n$  and de, based on the results of VT-CD measurements for the conformational interconversion between two diastereomeric forms with *M*- or *P*-helicity in a solution of **1a**, **2a** or **3a**, measured in dichloromethane at 263–313 K

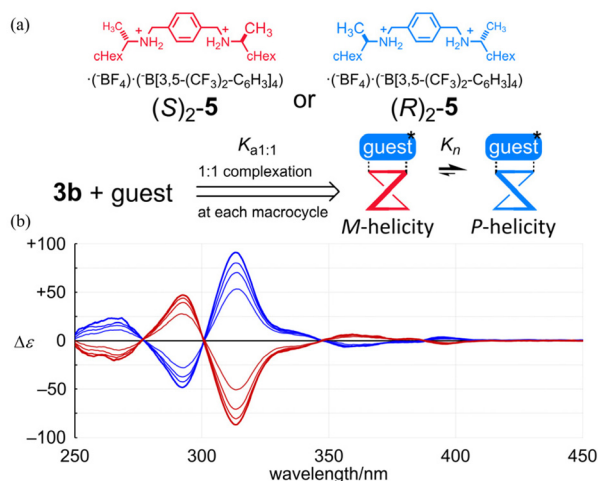
1a					
Temperature	$\Delta\epsilon$ measured at 302 nm		$K_1$	de	
313 K	+82.61		1.38	16%	
303 K	+91.59		1.43	18%	
293 K	+100.3		1.48	19%	
283 K	+113.9		1.56	22%	
273 K	+127.5		1.65	24%	
263 K	+141.3		1.74	27%	
223 K	$\Delta\epsilon_{223\text{ K}}$	+207	2.32 (H <sup><math>\alpha</math></sup> /H <sup><math>\beta</math></sup> )	40%	
	$ \Delta\epsilon_{\text{max}} $	521			
2a					
Temperature	$\Delta\epsilon$ measured at 311 nm		$K_2$	de	$(K_1)^2$
313 K	+191.3		1.82	29%	1.90
303 K	+205.2		1.91	31%	2.03
293 K	+224.9		2.04	34%	2.18
283 K	+247.4		2.21	38%	2.43
273 K	+272.7		2.42	42%	2.72
263 K	+301.3		2.70	46%	3.04
223 K	$\Delta\epsilon_{223\text{ K}}$	+424	4.65 (H <sup><math>\alpha</math></sup> /H <sup><math>\beta</math></sup> )	65%	5.40
	$ \Delta\epsilon_{\text{max}} $	656			
3a					
Temperature	$\Delta\epsilon$ measured at 314 nm		$K_3$	de	$(K_1)^3$
313 K	−78.56		1.82	29%	2.61
303 K	−88.67		1.98	33%	2.90
293 K	−100.3		2.18	37%	3.22
283 K	−114.0		2.46	42%	3.79
273 K	−129.3		2.84	48%	4.47
263 K	−145.5		3.34	54%	5.31
223 K	$\Delta\epsilon_{223\text{ K}}$	−220	9.90 (H <sup><math>\alpha</math></sup> /H <sup><math>\beta</math></sup> )	82%	12.5
	$ \Delta\epsilon_{\text{max}} $	270			



In the VT-CD spectra of **1a**, **2a** and **3a**, measured at 263–313 K, the intensities of several Cotton effects changed with temperature, while the spectral appearance was maintained. The presence of several isosbestic points showed that only two conformers were involved in the equilibrium and the populations of these two conformers changed with temperature through interconversion in each solution. Plotting several values of  $\Delta\epsilon$  with the greatest intensity (302 nm for **1a**, 311 nm for **2a** and 314 nm for **3a**) versus  $1/T$  led to a linear relationship (Fig. 7, inset). Based on this relationship, we estimated the value of  $\Delta\epsilon$  at 223 K (Table 1). Since the equilibrium constant  $K_n$  at 223 K was estimated by NMR spectroscopy (Fig. 5), we calculated  $|\Delta\epsilon_{\text{max}}|$  to convert measured values of  $\Delta\epsilon$  at several temperatures to  $K_n$  (Table 1).<sup>16</sup> The results indicated that  $K_n$  seemed to be comparable or smaller than  $(K_1)^n$  in either solution of **2a** and **3a**, similarly to the results obtained from NMR spectroscopy measured at low temperatures.

Next, we investigated whether or not a conformational preference for a particular sense of twisted forms with *M*- or *P*-helicity could be influenced in the bis and tris(macrocycle)s

when chiral information was imposed externally. As an external chiral source, we used a chiral guest (*S*)<sub>2</sub>-**5** or (*R*)<sub>2</sub>-**5** (Fig. 8),<sup>5,7</sup> since we have found that the guest molecule could form a 1 : 1 or 1 : 2 complex with **1b** or **2b** at the terephthaloyl bridge to control the twisting sense of each macrocycle. For **3b**, first we examined the complexation with the guest by NMR spectroscopy (Fig. S4†). Based on complexation-induced changes in the chemical shifts on the addition of the guest, we confirmed that the guest (*H*<sup>a</sup>, upfield shift) was captured at the terephthaloyl bridge (*H*<sup>b</sup>, upfield shift). The complexation ratio was estimated to be 1 : 2 (Job plots), measured in 3 vol% acetonitrile-*d*<sub>3</sub>/chloroform-*d*. Complexation-induced changes in the chemical shifts for aromatic protons (*H*<sup>A</sup> and *H*<sup>C</sup>) were smaller than that for *H*<sup>B</sup>, which was in the binding site and underwent an upfield shift due to the proximity of the guest. This result showed that there was almost no change in the populations of the conformers involved in the equilibrium before and after complexation. A similar consideration was supported by the UV spectra of **3b**, measured in the absence or presence of the guest (Fig. S5†). There was almost no change in absorption in the shorter wavelength region on complexation, as in the complexation of **1b** or **2b**, while absorptions were slightly attenuated in the region regarding HPEB. A pair of mirrored Cotton effects were induced in the CD spectra of **3b** in the presence of each chiral guest (Fig. 8). The spectral appearance of the complexation-induced Cotton effects remarkably resembled that of **3a**, although there was a slight difference in profile in the absorption region of HPEB. Since the association constant  $K_{a1:1}$  could be different in each solution,<sup>17</sup>  $K_n$  induced in a complexed state should be compared as an imaginary ratio when all of the molecules of the host were assumed to be in a complexed state. We performed titration experiments based on plots of complexation-induced molar CDs ( $\Delta\epsilon$ ) at an extreme wavelength (301 nm for **1b**, 310 nm for **2b** and 313.5 nm for **3b**) versus the equivalents of the guest added to each solution (Fig. 8 and Fig. S6†) to estimate an imaginary value of  $|\Delta\epsilon_{100\% \text{ complex}}|$  through a curve-fitting method<sup>18</sup> (Table 2). The value of  $|\Delta\epsilon_{100\% \text{ complex}}|$  was converted to  $K_n$ . The estimated value of  $K_2$  was comparable to  $(K_1)^2$  and  $K_3$  was larger than  $(K_1)^3$ , even though the association constant was lowered in **3b**.



**Fig. 8** (a) Chemical structures of (*S*)<sub>2</sub>-**5** and (*R*)<sub>2</sub>-**5**, and (b) CD spectra of **3b** (**[3b]** =  $1.3 \times 10^{-4}$  M) in the presence of (*S*)<sub>2</sub>-**5** (red lines) or (*R*)<sub>2</sub>-**5** (blue lines) (3, 6, 9 and 12 equiv.).

**Table 2** Calculated values of  $|\Delta\epsilon_{100\% \text{ complex}}|$ ,  $K_n$  and ee, based on the results of titration experiments for the complexation of **1b**, **2b** or **3b** with (*R*)<sub>2</sub>-**5**, measured in dichloromethane at 293 K

<b>1b</b>		<b>2b</b>		<b>3b</b>	
$K_{a1:1}$	$2.16 \times 10^4 \pm 5.61 \times 10^3 \text{ M}^{-1}$	$K_{a1:1}$	$1.45 \times 10^4 \pm 3.57 \times 10^3 \text{ M}^{-1}$	$K_{a1:1}$	$4.80 \times 10^3 \pm 1.10 \times 10^3 \text{ M}^{-1}$
Equiv.		Equiv.		Equiv.	
0.5	−12.8	0.5	−30.5	1	+53.3
1	−26.8	1	−63.0	2	+70.3
2	−32.7	2	−75.7	3	+80.1
3	−35.1	3	−85.4	4	+91.0
4	−38.0	4	−91.0		
$ \Delta\epsilon_{100\% \text{ complex}} $	$39.35 \pm 1.32$	$ \Delta\epsilon_{100\% \text{ complex}} $	$96.46 \pm 3.51$	$ \Delta\epsilon_{100\% \text{ complex}} $	$102.9 \pm 5.0$
$K_1$	$1.16 \pm 0.005$	$K_2$	$1.34 \pm 0.02$	$K_3$	$2.23 \pm 0.1$
ee	$7.6 \pm 0.3\%$	ee	$15 \pm 0.5\%$	ee	$38 \pm 2\%$
		$(K_1)^2$	$1.35 \pm 0.02$	$(K_1)^3$	$1.57 \pm 0.03$
		ee	$15 \pm 0.5\%$	ee	$22 \pm 0.7\%$



## Conclusions

We have demonstrated a conformational preference for a homochiral form of bis and tris(macrocyclic)s, where an identical sense of twisting was induced throughout the entire molecule. Toward a comprehension of the interinfluence of several chiral elements in a single molecule, we attempted to explore the relationship between  $K_n$  and  $(K_1)^n$ . Due to uncertainty based on integration in NMR spectroscopy, we could not find a significant difference. Regarding intramolecular transmission, the preference in the bis or tris(macrocyclic) seemed comparable to or less than the original preference induced in the monomeric macrocycle. Alternatively, the preference might be enhanced in the tris(macrocyclic) in a complexed state through the intermolecular transmission of chirality. The results may present a new form of cooperativity, which would be a driving force to enhance a helical-sense preference with an increase in the number of elements, since such enhancement could be considered to be a type of sergeant-and-soldiers<sup>19</sup> in a single molecule.

## Conflicts of interest

There are no conflicts to declare.

## References

- Ö. Demir and İ. Doğan, *Chirality*, 2003, **15**, 242; Y. Liu, S. A. Vignon, X. Zhang, K. N. Houk and J. F. Stoddart, *Chem. Commun.*, 2005, 3927; S. Cantekin, D. W. R. Balkenende, M. M. J. Smulders, A. R. A. Palmans and E. W. Meijer, *Nat. Chem.*, 2011, **3**, 42; V. Diemer, J. Maury, B. A. F. L. Bailly, S. J. Webb and J. Clayden, *Chem. Commun.*, 2017, **53**, 10768.
- D. Casarini, L. Lunazzi, A. Mazzanti and E. Foresti, *J. Org. Chem.*, 1998, **63**, 4991; I. R. Lahoz, A. Navarro-Vázquez, A. L. Llamas-Saiz, J. L. Alonso-Gómez and M. M. Cid, *Chem. – Eur. J.*, 2012, **18**, 13836; H. Bock, S. Huet, P. Dechambenoit, E. A. Hillard and F. Durola, *Eur. J. Org. Chem.*, 2015, 1033; M. Ball, B. Fowler, P. Li, L. A. Joyce, F. Li, T. Liu, D. Paley, Y. Zhong, H. Li, S. Xiao, F. Ng, M. L. Steigerwald and C. Nuckolls, *J. Am. Chem. Soc.*, 2015, **137**, 9982; Z. J. Kinney, V. C. Kirinda and C. S. Hartley, *Chem. Sci.*, 2019, **10**, 9057; K. K. Kartha, A. Takai, Z. Futera, J. Labuta and M. Takeuchi, *Angew. Chem., Int. Ed.*, 2021, **60**, 16466.
- S. E. Penty, M. A. Zwiijnenburg, G. R. F. Orton, P. Stachelek, R. Pal, Y. Xie, S. L. Griffin and T. A. Barendt, *J. Am. Chem. Soc.*, 2022, **144**, 12290.
- A. D. Bain, *Prog. Nucl. Magn. Reson. Spectrosc.*, 2003, **43**, 63.
- R. Katoono, Y. Tanaka, K. Kusaka, K. Fujiwara and T. Suzuki, *J. Org. Chem.*, 2015, **80**, 7613.
- A preferred sense was assigned to *M*-helicity upon the intramolecular transmission of point chirality (*R*) on the nitrogen (ref. 5).
- R. Katoono, S. Kawai, K. Fujiwara and T. Suzuki, *Chem. Sci.*, 2015, **6**, 6592.
- A tris(macrocyclic) relative to the structure **C** in fact adopted both heterochiral ( $C_2$ -symmetry) and homochiral ( $D_3$ -symmetry) forms.<sup>9</sup> Regarding the structure **E**, either macrocycle would prefer the opposite sense to what was induced in a neighboring macrocycle.
- R. Katoono, K. Sakamoto and T. Suzuki, *Chem. Commun.*, 2019, **55**, 5503.
- J. E. Anthony, S. I. Khan and Y. Rubin, *Tetrahedron Lett.*, 1997, **38**, 3499; M. Sonoda, A. Inaba, K. Itahashi and Y. Tobe, *Org. Lett.*, 2001, **3**, 2419; Y. Li, L. Xu, S. L.-F. Chan, Y. Li, R. Jiang, H. Liu and C.-M. Che, *Chem. – Asian J.*, 2014, **9**, 2842.
- Y. Tobe, N. Nakagawa, J. Kishi, M. Sonoda, K. Naemura, T. Wakabayashi, T. Shida and Y. Achiba, *Tetrahedron*, 2001, **57**, 3629.
- H. Kinoshita, N. Hirai and K. Miura, *J. Org. Chem.*, 2014, **79**, 8171.
- P. Ehlers, A. Neubauer, S. Lochbrunner, A. Villinger and P. Langer, *Org. Lett.*, 2011, **13**, 1618.
- K. Kondo, S. Yasuda, T. Sakaguchi and M. Miya, *J. Chem. Soc., Chem. Commun.*, 1995, 55.
- R. Katoono, K. Kusaka, S. Kawai, Y. Tanaka, K. Hanada, T. Nehira, K. Fujiwara and T. Suzuki, *Org. Biomol. Chem.*, 2014, **12**, 9532.
- An imaginary value of  $|\Delta\epsilon_{\max}|$  is related to measured values of  $\Delta\epsilon$  and ee or de according to the following equation: ee or de =  $\Delta\epsilon/|\Delta\epsilon_{\max}|$ .
- P. Thordarson, *Chem. Soc. Rev.*, 2011, **40**, 1305.
- S. Akine, *TitrationFit, program for analyses of host-guest complexation*, Kanazawa University, Kanazawa, Japan, 2013.
- N. J. V. Zee, M. F. J. Mabesoone, B. Adelizzi, A. R. A. Palmans and E. W. Meijer, *J. Am. Chem. Soc.*, 2020, **142**, 20191; T. Ikai, R. Ishidate, K. Inoue, K. Kaygisiz, K. Maeda and E. Yashima, *Macromolecules*, 2020, **53**, 973.

