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Dynamic Molecular Propeller: Supramolecular Chirality Sensing by Enhanced Chiroptical Response through the Transmission of Point Chirality to Mobile Helicity

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Abstract: The secondary terephthalamide host **1a-H** attached to four aryl blades was prepared from tetrabromide **2a** by Suzuki−Miyaura coupling and undergoes a conformational change from a nonpropeller anti-form to a propeller-shaped syn-form upon complexation with ditopic guests such as *p*-xylylenediammonium derivatives (*R*,*R*)/(*S*,*S*)-**3** (chirality generation). Through transmission of the point chiralities attached on the nitrogens in the chiral guests to the mobile helicity in **1a-H**, the propeller-shaped host in the complex is biased to prefer a particular handedness (chirality biasing). While chiral guests with simple point chiralities such as (*R*,*R*)/(*S*,*S*)-**3** exhibit only very weak CD activity, complexation with the dynamic propeller host **1a-H** results in much stronger chiroptical signals (chiroptical enhancement). The chirality generation−chirality biasing protocol was successfully applied to a neurotransmitter, (−)-phenylephrine **4**, acting as a chiral ditopic guest. When the chiral auxiliaries are attached to the host as in (*R*,*R*)-**1b-H**, complexation with (*S*,*S*)-**3** causes CD enhancement but not with (*R*,*R*)-**3**, due to chiral recognition.

Introduction

Supramolecular Chirality Transfer Based on Dynamic Helicity. Supramolecular chirality emerges as a result of intermolecular chirality transfer,[1] which is an important area of fundamental chemistry that has been shown to have several applications based on molecular recognition in terms of asymmetric catalysts,[2] memory materials,[3] polymer science,[4] and so on. When intermolecular chirality transfer is studied in a supramolecular assembly such as host−guest complexes,[5] detailed mechanistic approaches become available through a variety of spectroscopic measures such as NMR, UV−vis, or circular dichroism (CD). Helical molecules have often been used as an excellent motif for intermolecular chirality transfer, where the helical sense is successfully controlled by external asymmetric information, such as chiral guest molecules.[6] Thus, in some linear oligomeric/polymeric long-chained hosts that adopts a folded helical geometry, the population of (*P*)/(*M*)-helices is biased to prefer a particular handedness upon complexation with chiral guests through encapsulation at the cavity or binding at the side groups. In more dynamic systems, the substance exists as a random coil before the addition of chiral guests, and the helical structure is formed only upon the admixture of a chiral additive through unidirectional folding (Scheme 1a).[7] These rare examples have successfully demonstrated chirality generation−chirality biasing protocol, which is more advanced response by inducing all-or-nothing-type chiroptical outputs.

In addition to helices of long-chained molecules, propeller-shaped compounds[8] are also attractive since they possess a similar dynamic helicity. Hexaphenylbenzene adopts a propeller-shaped geometry in a crystal phase[9] with all of the phenyl groups tilted in a conrotatory manner. Thus, persubstituted benzenes can be considered to be another class of attractive motif for studying supramolecular chirality transfer to dynamic helicity (Scheme 1b). Since the molecules can adopt a variety of conformations other than a propeller, control of the geometry to enforce the propeller structure (chirality generation) is an important concern in addition to control of the helical sense (chirality biasing). In this context, our approach using the

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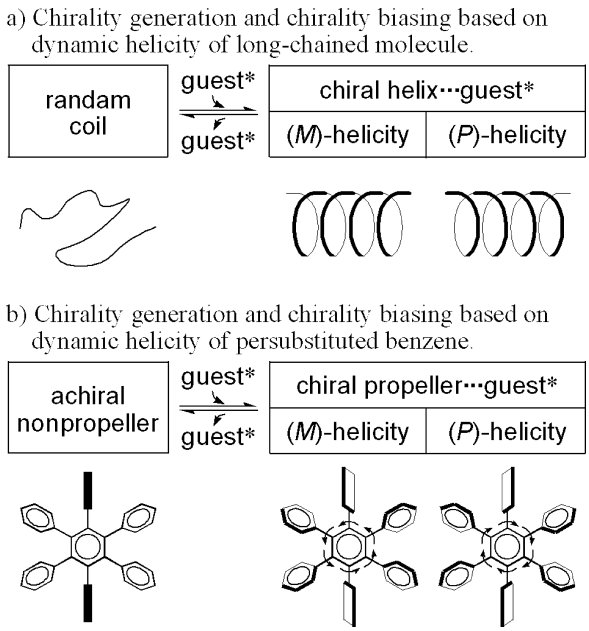
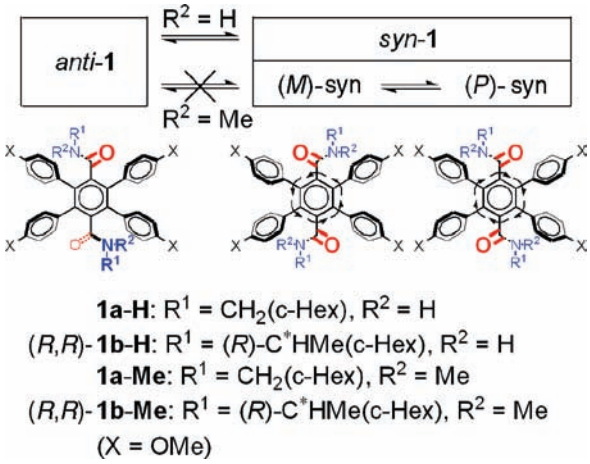
Scheme 1



Scheme 2



directing effect of amide dipoles is interesting, and induces the conrotatory tilting of substituents in *syn*-2,3,5,6-tetraarylterephthalamides, as shown below.

Transfer of Supramolecular Chirality Based on Terephthalamide-Based Molecular Propellers. We recently found that terephthalamide derivatives **1** with four aryl blades are sterically hindered molecules in which all six substituents are largely twisted toward the central benzene core. Consequently, there are two rotational isomers (syn and anti) in terms of the direction of the two amide groups at the 1,4-positions (Scheme 2), which can be isolated as noninterconvertible atropisomers in the case of tertiary amides **1a/b-Me** [R^1 = CH_2(c-Hex)/C*HMe(c-Hex); R^2 = Me]. The substituents are skewed toward either direction to give numerous conformations. Due to the directing effects of the amide dipoles to reduce electrostatic repulsion, the anti-isomer adopts a (pseudo)centrosymmetric structure, whereas the syn-isomer preferably exists as a chiral propeller for which the helicity interconverts very rapidly (mobile helicity). Two enantiomeric propellers with (*P*) and (*M*)-helicity are present in equal amounts for *syn*-**1a-Me** [R^1 = CH_2(c-Hex); R^2 = Me], which has no asymmetric elements other than the mobile helicity. When chiral auxiliaries are attached to the tertiary amide nitrogens as in *syn*-(*R*,*R*)-**1b-Me** [*N*-R^1 = (*R*)-*N*-C*HMe(c-Hex); R^2 = Me], the point chiralities would be intramolecularly transmitted to the mobile helicity[10] of the propeller structure to prefer a particular handedness. This is indeed the case, and the chiroptical properties ascribed to the propeller geometry for *syn*-(*R*,*R*)-**1b-Me** (CD: $\Delta\varepsilon = -7.7$ at 291 nm) were more than 10-fold greater than those for the quasi-centrosymmetric *anti*-(*R*,*R*)-**1b-Me** with a nonpropeller structure ($\Delta\varepsilon = -0.61$ at 291 nm), despite the fact that they have identical chiral auxiliaries.[11]

These characteristics give us the opportunity to construct a supramolecular chiral sensing system with enhanced chiroptical output based on our dynamic molecular propeller, which was designed as described below. Both the syn- and anti-forms of tetraarylterephthalamides **1a/b-H** can act as host molecules at the amide carbonyls for hydrogen-bond-donating guests with ammonium and/or phenol moieties.[12,13d,14] In contrast to the tertiary amides **1a/b-Me**, the syn- and anti-forms of secondary amides **1a/b-H** [R^1 = CH_2(c-Hex)/C*HMe(c-Hex); R^2 = H] would easily interconvert in solution. In the absence of any guest molecules, the anti-form of **1a/b-H** should be predominant in the equilibrated mixture due to the complete cancellation of amide-dipole repulsion. Alternatively, the syn-form of **1a/b-H** would be far more suitable for capturing a ditopic guest by forming supramolecular complexes with a hover-overed cyclophane-structure (Scheme 3).

Thus, the achiral secondary amide host **1a-H** would exist as the anti-form with an achiral nonpropeller geometry in guest-free conditions, and might be converted to the propeller-shaped chiral syn-form upon complexation with a ditopic guest such as *p*-xylylenediammonium derivatives **3** (chirality generation). This system can be considered to be a new example of dynamic molecular recognition,[7,13,14] where the host structure is drastically changed upon complexation. When the point chiralities attached to the ditopic guest as in (*R*,*R*)/(*S*,*S*)-**3** are successfully transmitted intermolecularly to the host, the helicity of the *syn*-**1a-H** unit in the supramolecular complexes should be biased to favor a particular handedness (chirality biasing). Although simple point chiralities on the guest generally produce only minor CD activity, successful transmission to the helical

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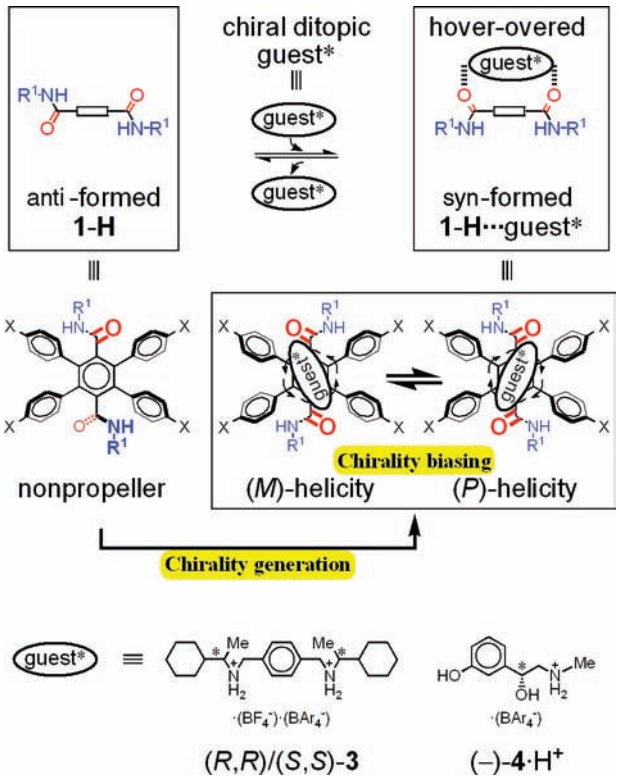
Scheme 3



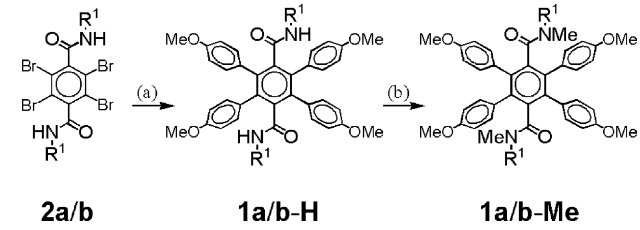
preference of the host induces CD enhancement at the longer-wavelength region of the propeller-shaped host molecules, which makes it easier to detect the guest. These are the central points of our design concept for supramolecular chirality sensing with chiroptical enhancement through the transmission of point chirality to mobile helicity. The successful supramolecular detection of a neurotransmitter, (−)-phenylephrine **4**, by the host **1a**-**H** is also demonstrated.

Cooperative binding at the two carbonyl groups of the terephthalamide host also enables us to distinguish the targeted ditopic guests from the corresponding monotopic guests because the latter cannot induce CD enhancement due to the lack of a change in the structure of the host from the anti- to syn-form upon complexation. Thus, even when they have the same point chirality, monotopic and ditopic guests can be distinguished by their CD spectra. When **1b**-**H** with chiral auxiliaries is used as a host, combination with a chiral guest would form diastereomeric complexes in which chiral auxiliaries on the host and the guest work cooperatively (matched)/uncooperatively (mismatched) to control the helical sense. Thus, these diastereomeric complexes would adopt different structures from each other, and the chiral sense of the enantiomeric guests could be easily distinguished by CD spectroscopy.[14,15] This is the case for the combination of (*R*,*R*)-**1b**-**H** with (*S*,*S*)/(*R*,*R*)-**3**. We describe here the full details of these supramolecular chirality-transfer events by using dynamic hosts **1a/b**-**H** with a propeller-shaped mobile helicity.

Results and Discussion

Molecular Design and Preparation. The achiral cyclohexylmethyl (**a**) or chiral 1-cyclohexylethyl (**b**) group is attached to each of the amide nitrogens in the 2,3,5,6-tetrakis(*p*-methoxyphenyl)terephthalamide hosts **1** (Scheme 2). The latter acts as a chiral handle to bias the direction of skewing of the amide groups in a propeller-shaped syn-conformation. The lack of strong absorption of the chiral auxiliary in the UV region is favorable for studying the chiroptical properties of the hosts **1** in the presence/absence of guest molecules by CD spectroscopy.

Scheme 4. Reagents (a) 4-MeO-C_6H_4-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3 aq., DME, Toluene (y. 89% for **a** and 91% for **b**); (b) NaH, MeI, THF (y. 26% for *syn*-**a**, 52% for *anti*-**a** and 42% for *syn*-**b**, 12% for *anti*-**b**)



The secondary terephthalamide hosts **1a/b**-**H** were prepared by Suzuki−Miyaura coupling[16] of 2,3,5,6-tetrabromoterephthalamide derivatives **2a/b**[11] and 4-methoxyphenylboronic acid (Scheme 4), which were obtained as mixtures of easily interconvertible syn- and anti-forms (vide infra). A methoxy group attached to the aryl blades can simplify the aryl region of ^{1}H NMR spectra to facilitate the analysis of complexation. The tertiary terephthalamides **1a/b**-**Me** were prepared by *N*-methylation of the corresponding secondary amides **1a/b**-**H**, and obtained as a mixture of two atropisomers in terms of the relative direction of the amide groups. Due to the high rotational barrier about the $C_{central}-C_{amide}$ bonds, the syn- and anti-isomers of **1a/b**-**Me** were easily separated by column chromatography. These atropisomers are not interconvertible at all even at an elevated temperature, and thus we can use *syn*- and *anti*-**1a/b**-**Me** separately for control experiments.[11]

As ditopic guest molecules (Scheme 3), *p*-xylylenediammonium derivatives **3** and (−)-phenylephrine salt **4**·H^+ were selected, and these are expected to form hover-overed complexes through binding at the two carbonyl groups of the hosts **1**. The (*R*)/(*S*)-1-cyclohexylethyl group is again used as a chiral auxiliary in the guests (*R*,*R*)/(*S*,*S*)-**3** to study the chiral recognition properties upon the formation of **1a/b**-**H**·(*R*,*R*)/(*S*,*S*)-**3** complexes. The chiral ditopic guests (*R*,*R*)/(*S*,*S*)-**3** were prepared from terephthalaldehyde and (*R*)/(*S*)-1-cyclohexylethylamine. The chiral monotopic guest (*R*)-BnN^+H_2C*HMe(c-Hex) [(*R*)-**5**] was also prepared as a reference in a similar manner from benzaldehyde and obtained as a tetrafluoroborate salt.

Conformational Analysis of Secondary Terephthalamides 1a/b-H. In contrast to tertiary amides **1a/b**-**Me**, the achiral secondary host **1a**-**H** was obtained as a mixture of syn- and anti-forms, which rapidly interconvert due to the very low rotational barrier about $C_{central}-C_{amide}$ bonds. As expected, only two sets of resonances were observed for anisyl protons in the ^{1}H NMR spectrum of **1a**-**H** in $CDCl_3$ at room temperature (Figure S1a of the Supporting Information). Conformational searches with MacroModel software[17] indicated that both the syn- and anti-forms have energy-minimized

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(17) MacroModel v6.5, Schrödinger Inc., 1998, and the GB/SA solvation model for chloroform through 5000-step Monte Carlo simulations using the Amber* force field, and the PRCG minimization algorithm.

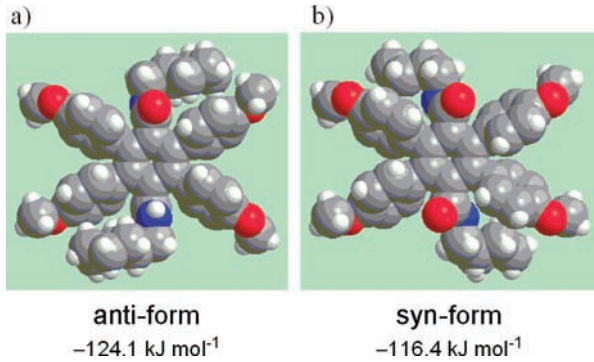

Figure 1. Energy-minimized structures of **1a-H** adopting (a) anti-form (achiral nonpropeller geometry) and (b) syn-form (chiral propeller geometry) according to Monte Carlo simulations in $CHCl_3$. The anti-form preference over syn-forms is also the case for the *N,N′*-dimethyl derivative (anti: −108.0 kJ mol^{-1}; syn: −104.9 kJ mol^{-1}) where the methyl groups are replaced for the cyclohexylmethyl groups, thus the bulkiness of cyclohexyl group does nothing to do with the anti-preference in **1a-H**.

structures, with the latter more stable than the former by 7.7 kJ mol^{-1}, as is commonly observed with 1,4-arylenedicarboxamide derivatives.[18] Preference for the anti-form of **1a-H** can be explained based on electrostatic interaction, and the energy-minimized geometry for the anti-form is a nonpropeller geometry, in which the amide dipole interactions are completely canceled (Figure 1a).

However, the syn-form was predicted to adopt a propeller-shaped conformation, in which the two amide groups are skewed in a conrotatory manner to reduce the repulsion of dipoles to some extent (Figure 1b). These considerations are consistent with the results in our preliminary communication[11] for the preferred geometries of tertiary amides *syn*-**1a/b-Me** (propeller-shaped) and *anti*-**1a/b-Me** (nonpropeller-shaped), which were isolated from each other and then analyzed crystallographically.

Even when we attach the chiral auxiliary to the nitrogens, the chiral secondary amide host (*R,R*)-**1b-H** seems to prefer a quasi-centrosymmetric anti-form, which is shown by the fact that the CD spectrum of (*R,R*)-**1b-H** is similar to that of noninterconvertible atropisomeric tertiary amide *anti*-(*R,R*)-**1b-Me** but not to that of *syn*-(*R,R*)-**1b-Me** in CH_2Cl_2 at room temperature (Figure 2). Thus, the Cotton effect of (*R,R*)-**1b-H** is rather weak due to the nonpropeller geometry in the guest-free state since the strong Cotton effect around 290 nm in *syn*-(*R,R*)-**1b-Me** is due to its propeller-shaped geometry where the helicity is biased due to the intramolecular transmission of point chirality (*R*-configuration) on each amide nitrogen to the mobile helicity (preferred *M*-configuration).[19]

In this way, the secondary amide hosts **1a/b-H** were shown to prefer the anti-form (Scheme 5). However, only the syn-form can bind with a ditopic guest molecule at the two carbonyl groups to form 1:1 complexes with a hover-overed supramolecular cyclophane geometry.

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(19) The weaker Cotton effect around 255 nm commonly observed for (*R,R*)-**1b-H** and both atropisomers of (*R,R*)-**1b-Me** is also present in the tetrabromide precursor (*R,R*)-**2b** or *syn/anti*-(*R,R*)-*N,N′*-bis(1-cyclohexylethyl)-*N,N′*-dimethyl-2,3,5,6-tetrabromoterephthalamides derived by the *N*-methylation of (*R,R*)-**2b** ($\Delta\varepsilon = -2$ to -4). Thus, the shorter-wavelength region is not associated with the propeller/nonpropeller conformation.

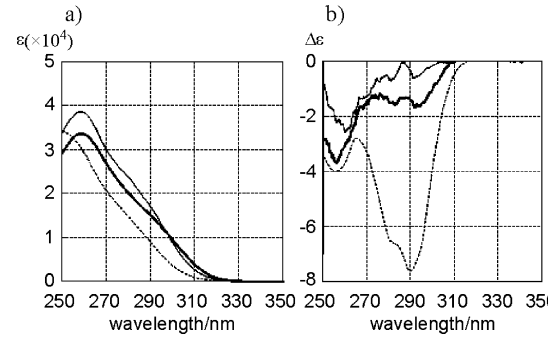
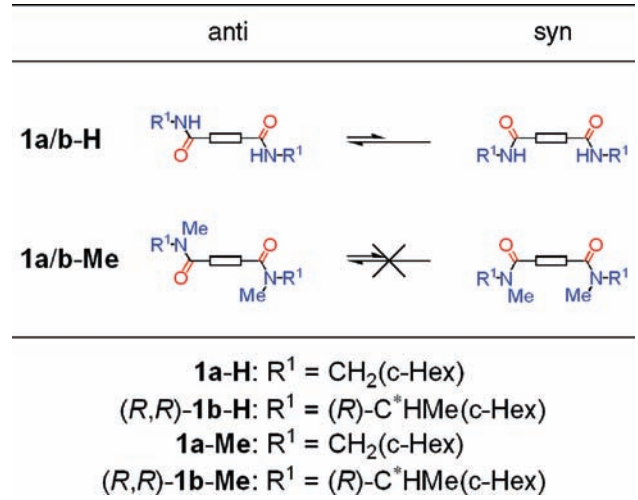


Figure 2. (a) UV and (b) CD spectra of (*R,R*)-**1b-H** (bold line), *anti*-(*R,R*)-**1b-Me** (thin line), and *syn*-(*R,R*)-**1b-Me** (dashed line) measured in CH_2Cl_2 at room temperature.

Scheme 5



Complexation of Achiral Dynamic Host 1a-H with Chiral Ditopic Guests (R,R)/(S,S)-3. The complexation of **1a-H** with (*R,R*)/(*S,S*)-**3** would induce a dynamic change in the structure of the host from the anti- to syn-form, and stronger chiroptical signals might be produced when the helical sense of the propeller-shaped host is biased by intermolecular transmission of the point chiralities on the guests (*R,R*)/(*S,S*)-**3**, which will be demonstrated as follows.

The complexation behavior of **1a-H** with (*R,R*)-**3** was first investigated by ^1H NMR spectroscopy in $CDCl_3$ at room temperature (Figure 3). Upon the gradual addition of (*R,R*)-**3** to the solution of **1a-H** (∼10 mM), a significant downfield shift from δ 5.09 (0 equiv.) to 5.70 (1.5 equiv.) ppm was induced for the NH^C proton of the host. The C_{2h} symmetric methylene proton (H^E) of the achiral host, as seen in the spectrum (a), changed to a complicated pattern of C_2 symmetry due to the lack of a mirror plane in the complex **1a-H**·(*R,R*)-**3**. Also, the remarkable upfield shift was observed for the anisyl protons (H^A).[20] These results can be accounted for by a change in the conformation of the host from the anti- to syn-form through complexation with two carbonyl groups. When the monotopic guest (*R*)-**5** was added, no change in chemical shifts was induced other than a downfield shift for NH^C, which indicated the formation of hydrogen bonds at carbonyl groups but was not

(20) The corresponding protons (H^a and H^b) in the atropisomers *anti*-**1a-Me** and *syn*-**1a-Me** are centered at 7.10 and 6.98 ppm (Figure S1, parts c and e of the Supporting Information), respectively.

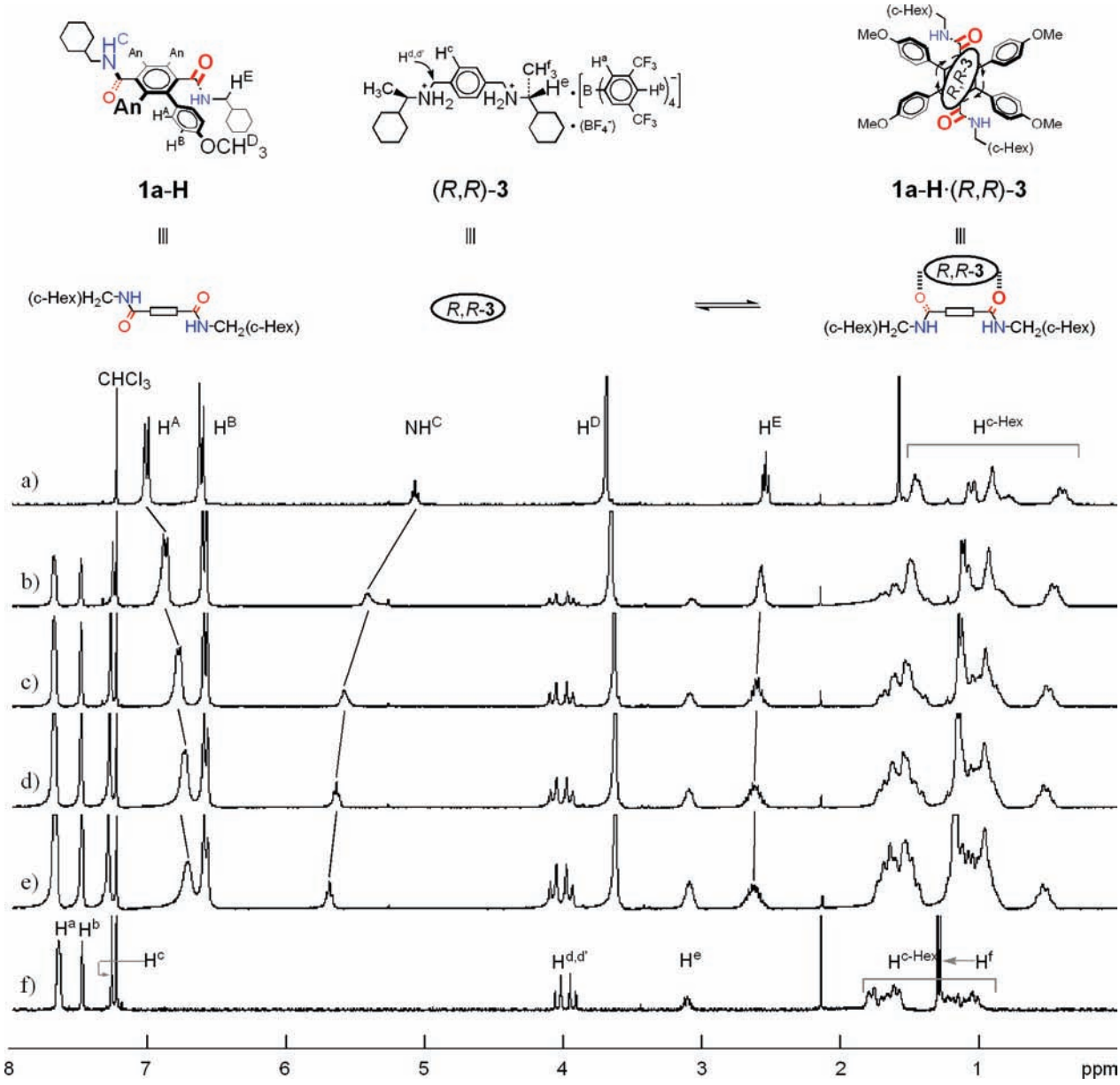
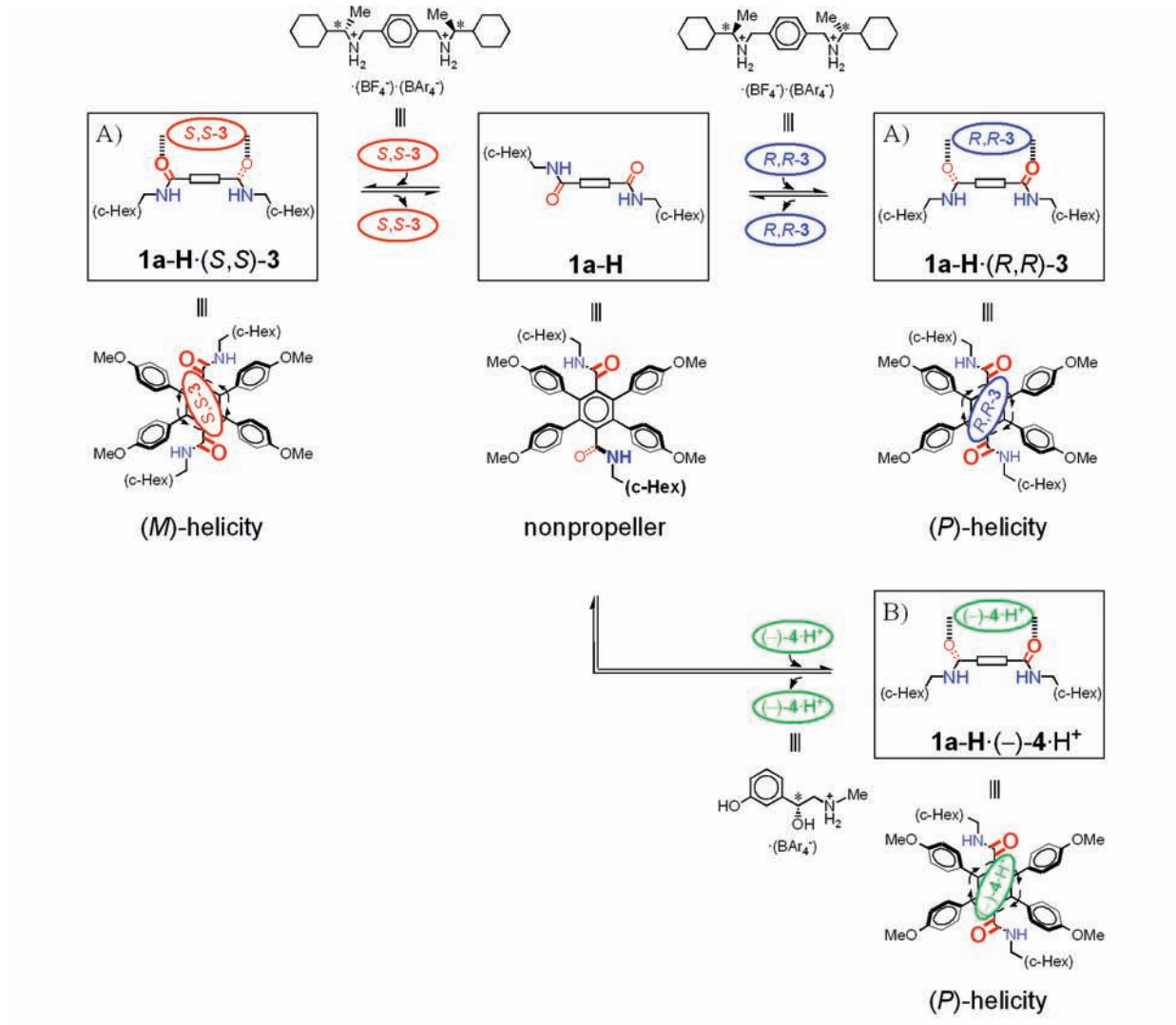


Figure 3. Spectral change in ^{1}H NMR (300 MHz) upon complexation of **1a**-**H** with (*R*,*R*)-**3**; (a) 0 equiv. (**1a**-**H** only), (b) 0.41 equiv., (c) 0.82 equiv., (d) 1.16 equiv., (e) 1.50 equiv., and (f) ^{1}H NMR spectrum of (*R*,*R*)-**3**, measured in $CDCl_3$ at room temperature.

accompanied by a change in geometry from anti to syn (Figure S2A of the Supporting Information).

Continuous changes in the CD spectrum were observed upon complexation of the achiral dynamic secondary host with the chiral ditopic guest in CH_2Cl_2 at room temperature (Figure 4A). When the achiral host **1a**-**H** (4.2×10^{-4} M) was mixed with the chiral guest (*R*,*R*)-**3** (0 to 4 equiv.), a positive Cotton effect was induced in the absorption region of **1a**-**H** ($\lambda_{ext} \approx 300$ nm). The addition of enantiomeric guest (*S*,*S*)-**3** (0 to 4 equiv.) to **1a**-**H** induced a negative Cotton effect, as expected. The observed ellipticity is different from that of chiral guests (*R*,*R*)/(*S*,*S*)-**3** themselves, and is shifted to a longer-wavelength region with a much stronger intensity, thus demonstrating successful chiroptical enhancement. The shape and sign of the induced Cotton effect for the complex **1a**-**H**·(*S*,*S*)-**3** are similar to those for uncomplexed tertiary amide *syn*-(*R*,*R*)-**1b**-**Me** (Figure 2b). Since the negative Cotton effect of the latter was previously shown to correspond to the (*M*)-helicity of the propeller,[11] the helical sense of the propeller conformation in complex **1a**-**H**·(*S*,*S*)-**3** was biased to (*M*)-helicity (negative Cotton effect around 300 nm) whereas that in **1a**-**H**·(*R*,*R*)-**3** was biased to (*P*)-helicity (positive Cotton effect around 300 nm) through the transfer of supramolecular chirality from the chiral auxiliaries of the ditopic guest to the mobile helicity of the host.

A change in the conformation of the host **1a**-**H** from the anti- to syn-form upon complexation must be the key to realizing a transfer of supramolecular chirality, since no Cotton effect was induced around the absorption region of noninterconvertible atropisomer *anti*-**1a**-**Me** upon the addition of chiral guest (*R*,*R*)-**3** under similar conditions (Figure S3D of the Supporting Information). This idea is further supported by the strong CD signal induced upon the complexation of *syn*-**1a**-**Me** with chiral guest (*R*,*R*)-**3** (Figure S3A of the Supporting Information). Although noninterconvertible atropisomer achiral *syn*-**1a**-**Me** adopts a chiral propeller-shaped geometry and exists as a 1:1 mixture of (*P*)- and (*M*)-helicity in the guest-free state, complexation with



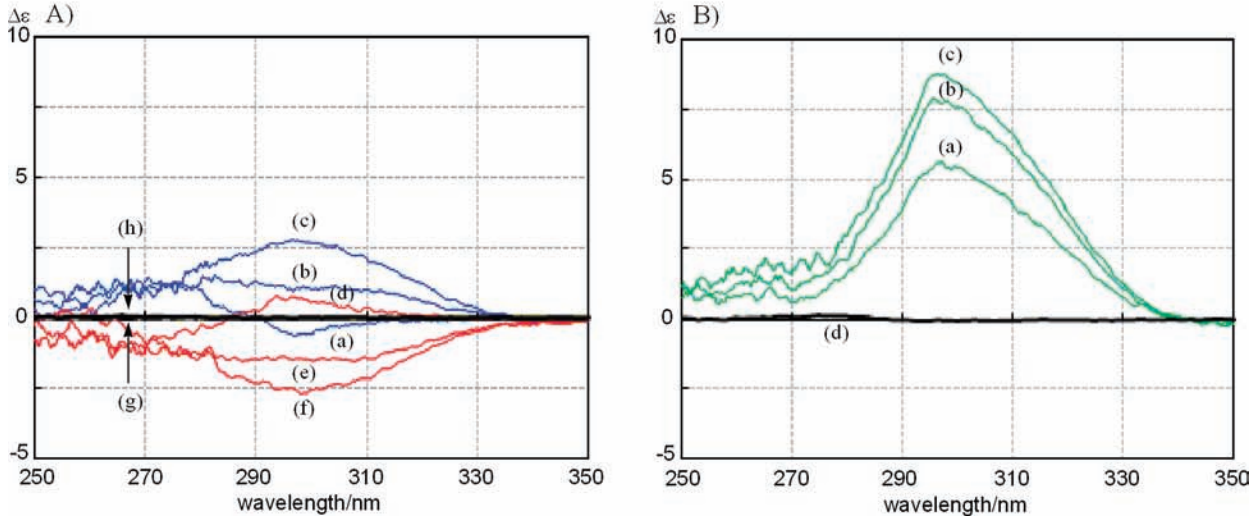


Figure 4. (A) Continuous changes in the CD spectrum upon complexation of achiral host **1a**-**H** (4.2×10^{-4} M) with (*R*,*R*)/(*S*,*S*)-**3**; (a) 1 equiv. (4.2×10^{-4} M), (b) 2 equiv. (8.3×10^{-4} M), (c) 4 equiv. (1.7×10^{-3} M) of (*R*,*R*)-**3** (blue line), (d) 1 equiv. (4.2×10^{-4} M), (e) 2 equiv. (8.3×10^{-4} M), (f) 4 equiv. (1.7×10^{-3} M) of (*S*,*S*)-**3** (red line), and CD spectra of (g) (*R*,*R*)-**3** (black line; 2.7×10^{-4} M), and (h) (*S*,*S*)-**3** (black line; 2.5×10^{-4} M): (B) Continuous changes in the CD spectrum upon complexation of **1a**-**H** (2.8×10^{-4} M) with (−)-phenylephrine **4**·$HBAr_4$; (a) 1 equiv. (2.8×10^{-4} M), (b) 2 equiv. (5.5×10^{-4} M), (c) 4 equiv. (1.1×10^{-3} M) (green line), and (d) CD spectrum of **4**·$HBAr_4$ (black line; 1.8×10^{-4} M). All spectra were measured in CH_2Cl_2 at room temperature.

(*R*,*R*)-**3** biased the preferred sense of helicity to (*P*), as indicated by the positive sign of the Cotton effect around 300 nm. The hover-overed bridging geometry is necessary for the complex to realize the supramolecular chirality transfer since the corre-

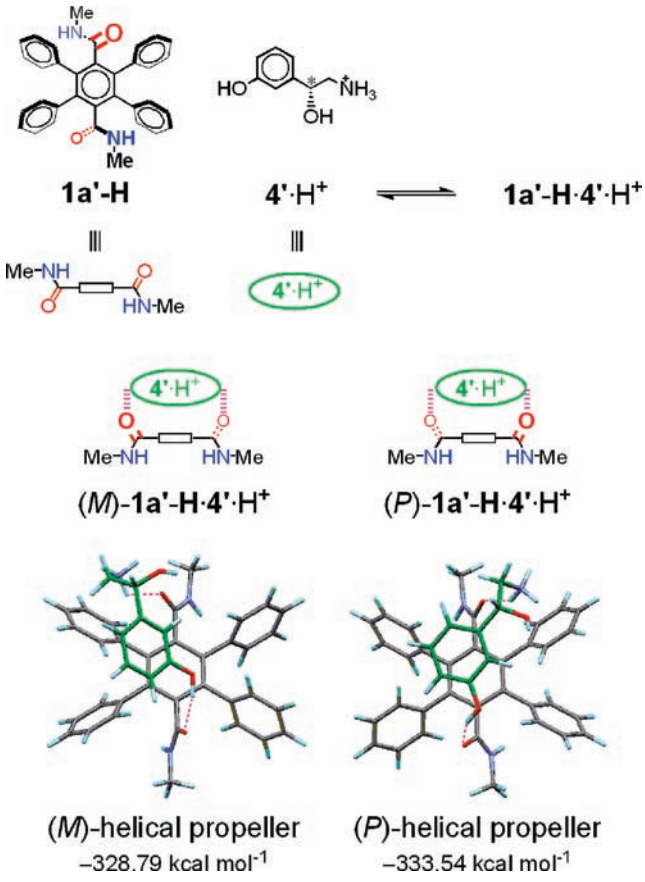
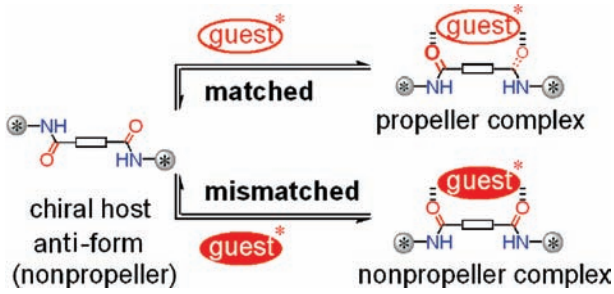


Figure 5. Energy-minimized structures for the hover-overed complexes of **1a′-H** and (−)-norphenylephrine (**4′**)·H^+ obtained by Monte Carlo simulation: (left) (*M*)-helical propeller of **1a′-H** and (right) (*P*)-helical propeller of **1a′-H**.

Scheme 6



sponding monotopic guest (*R*)-**5** cannot induce any CD signal around 300 nm upon complexation with propeller-shaped *syn*-**1a-Me** (Figure S3C of the Supporting Information).

Complexation of Achiral Dynamic Host 1a-H with a Neurotransmitter, (−)-Phenylephrine(4)·HBAr$_4$. Similar to catecholamine derivatives, (−)-phenylephrine (**4**) is an α_1-adrenergic receptor agonist. Since this chiral neurotransmitter has two hydrogen-bonding sites that are suitably separated to bind at the carbonyl groups of terephthalamide-type host molecules,[13d] its complexation with the present host molecules were also examined. We were particularly interested if the point chirality in **4** could be recognized by the host to enable its detection by using CD spectra through supramolecular chirality transfer. Chiral recognition for **4** should be more difficult than that in

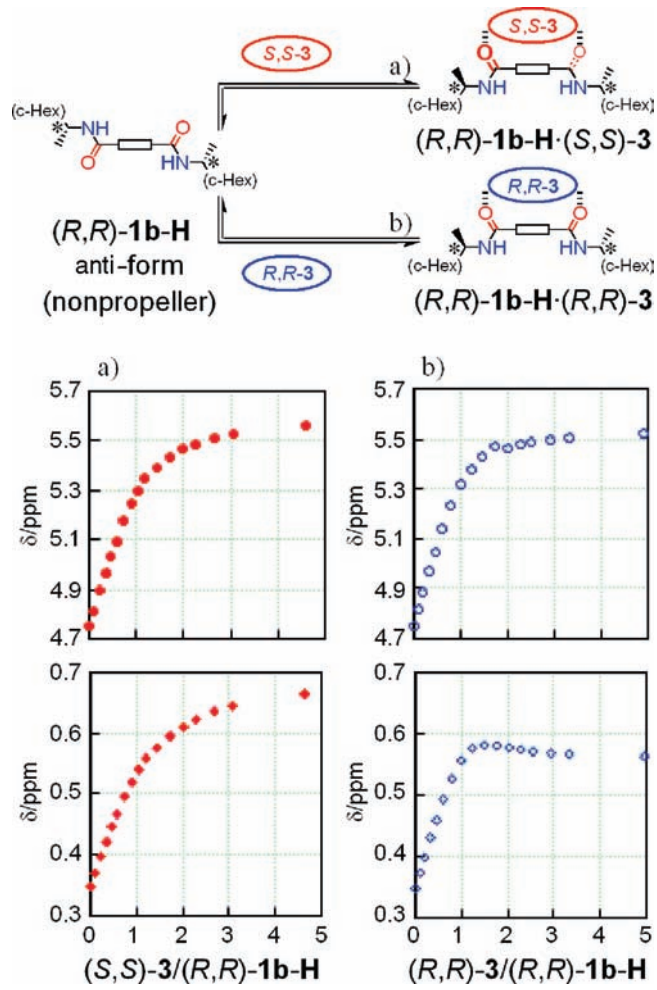


Figure 6. NMR titration curves for complexation of (*R*,*R*)-**1b-H** (2 mM) with (a) (*S*,*S*)-**3** (0−9 mM) (● amide proton NH^C, ♦ methyl proton H^F), and (b) (*R*,*R*)-**3** (0−10 mM) (○ amide proton NH^C, ◇ methyl proton H^F), measured in $CDCl_3$ at 298 K.

the case of **3** since the binding site is not adjacent to the asymmetric center but is separated by another methylene unit in **4**.

First, complexation with achiral host **1a-H** was studied by NMR spectroscopy with the protonated form of **4** (**4**·H^+) (Figure S2B of the Supporting Information). Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate salt was used to attain high solubility in $CDCl_3$. Upon admixing, a significant downfield shift ($\Delta\delta$ 3.3 ppm) for the phenolic OH proton as well as an upfield shift for one of four aromatic protons in the guest **4**·HBAr$_4$ were observed, indicating the hover-overed complexation of **4**·HBAr$_4$ at the two carbonyl groups of **1a-H** through hydrogen bonds, which is accompanied by a change in the conformation of the host from the anti- to syn-form, as in the case of **1a-H**·(*R*,*R*)/(*S*,*S*)-**3** complexes.

In the CD spectra, a large positive Cotton effect was induced when the dynamic host **1a-H** was mixed with (−)-phenylephrine salt **4**·HBAr$_4$ (λ_{ext} = 297 nm, $\Delta\varepsilon$ = +8.8, 4 equiv.) (Figure 4B). If we consider that the noninterconvertible atropisomeric tertiary amide *syn*-**1a-Me** caused a similar positive Cotton effect, whereas *anti*-**1a-Me** failed to induce any CD signals upon combination with **4**·HBAr$_4$ (Figures S3B and S3E of the Supporting Information), the dynamic host **1a-H** changed its

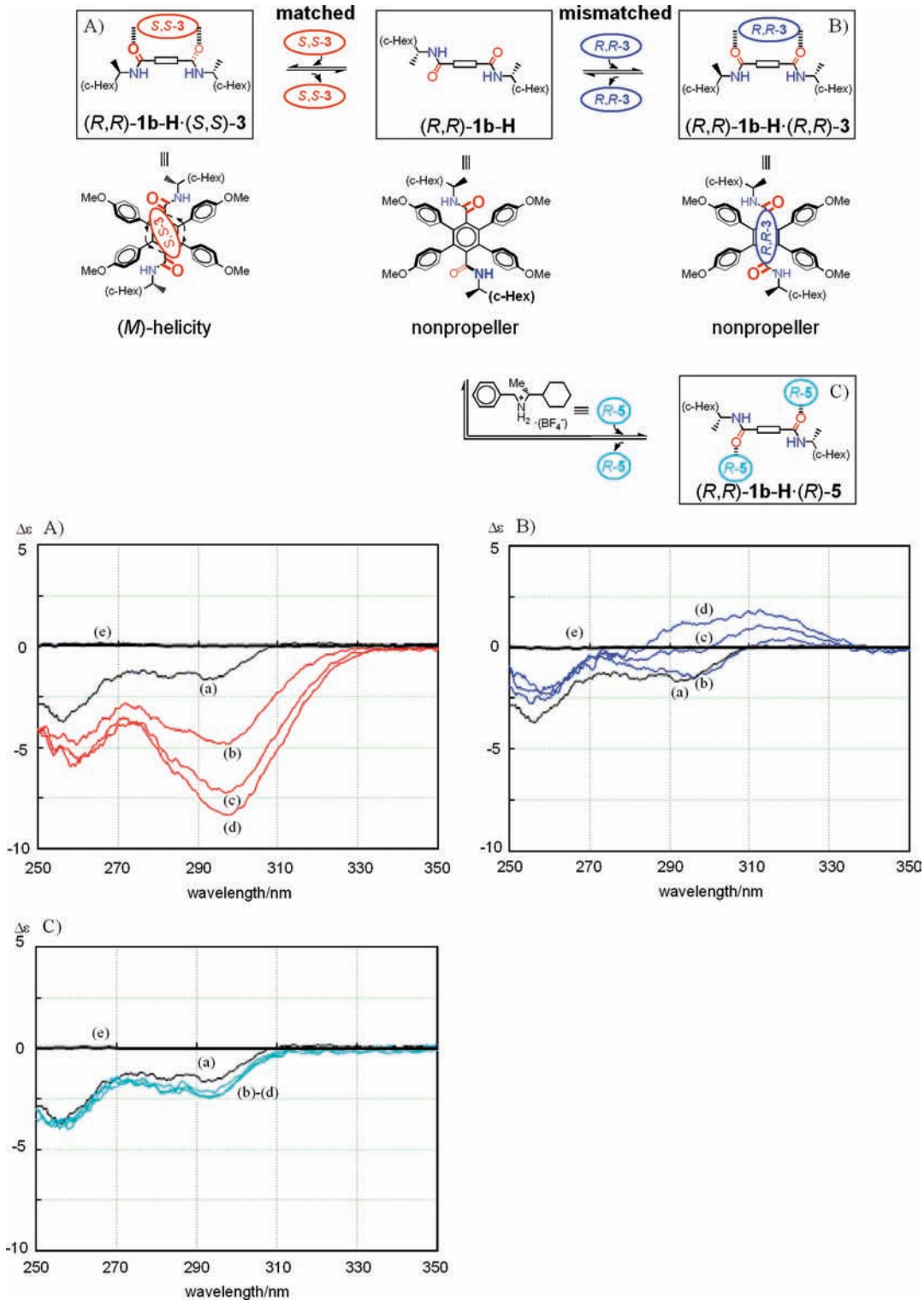


Figure 7. (A) Continuous changes in the CD spectrum upon complexation of chiral host (*R*,*R*)-**1b**-**H** (3.0×10^{-4} M) with (*S*,*S*)-**3**; (a) 0 equiv. ((*R*,*R*)-**1b**-**H** only (thin black line)), (b) 1 equiv. (3.0×10^{-4} M), (c) 2 equiv. (6.0×10^{-4} M), (d) 4 equiv. (1.2×10^{-3} M) (red line), and (e) CD spectrum of (*S*,*S*)-**3** (bold black line; 2.5×10^{-4} M): (B) Continuous changes in the CD spectrum upon complexation of (*R*,*R*)-**1b**-**H** (3.0×10^{-4} M) with (*R*,*R*)-**3**; (a) 0 equiv. ((*R*,*R*)-**1b**-**H** only (thin black line)), (b) 1 equiv. (3.0×10^{-4} M), (c) 2 equiv. (6.0×10^{-4} M), (d) 4 equiv. (1.2×10^{-3} M) (blue line), and (e) CD spectrum of (*R*,*R*)-**3** (bold black line; 2.7×10^{-4} M): (C) Continuous changes in the CD spectrum upon complexation of (*R*,*R*)-**1b**-**H** (3.2×10^{-4} M) with (*R*)-**5**; (a) 0 equiv. ((*R*,*R*)-**1b**-**H** only (thin black line)), (b) 1 equiv. (3.2×10^{-4} M), (c) 2 equiv. (6.5×10^{-4} M), (d) 4 equiv. (1.3×10^{-3} M) (sky blue line), and (e) CD spectrum of (*R*)-**5** (bold black line; 3.5×10^{-3} M). All spectra were measured in CH_2Cl_2 at room temperature.

conformation from anti to syn during complexation with biasing of the propeller-geometry of **1a**-**H** to (*P*)-helicity. On the basis of a Monte Carlo simulation for the energy-minimized geometry of modeled complex of host **1a′**-**H** (R^1 = Me; R^2 = H) with norphenylephrine **4′**·H^+, the hover-overed geometry with a (*P*)-helical propeller structure ($\Delta H_f = -333.54$ kcal mol^{-1}) was more stable than that with (*M*)-helicity (-328.79 kcal mol^{-1}) (Figure 5). The predicted preference for the (*P*)-helicity

is consistent with what was indicated by the positive sign of experimental Cotton effect observed around 300 nm.

If we consider that the CD signal from (−)-phenylephrine(**4**)·$HBAr_4$ itself is very small ($\Delta\varepsilon < 0.2$), then the dynamic host enables chiroptical enhancement through the transfer of supramolecular chirality from the point chirality in the neurotransmitter to the mobile helicity of **1a**-**H**. There are two important points of this success: (1) the change in the conformation of the host from the nonpropeller in anti-form to propeller-shaped geometry in syn-form (chirality generation); and (2) the helicity sense in favor of (*P*) by transmission of the point chirality in the guest thanks to the hover-overed geometry (chirality biasing).

Complexation of Chiral Dynamic Host 1b-H with Chiral Ditopic Guests (R,R)/(S,S)-3. The chiral terephthalamide host (*R*,*R*)-**1b**-**H** with a chiral auxiliary on each of the amide nitrogens would exhibit a preference for the sense of dynamic helicity[7c,21] when it adopts the syn-form with a propeller geometry. In fact, noninterconvertible atropisomer *syn*-(*R*,*R*)-**1b**-**Me** exists predominantly as an (*M*)-propeller which shows a negative Cotton effect around 290 nm.[11] Alternatively, chiral guests of (*R*,*R*)/(*S*,*S*)-**3** have their own preference for the propeller helicity of the host [(*P*) and (*M*), respectively] when they form complexes with achiral host **1a**-**H/Me** with a hover-overed geometry. Thus, we can expect chiral-recognizing events to occur upon the complexation of chiral dynamic host (*R*,*R*)-**1b**-**H** with chiral ditopic guests (*R*,*R*)/(*S*,*S*)-**3** (Scheme 6).

First, diastereomeric complexation of the chiral host (*R*,*R*)-**1b**-**H** with chiral guests (*R*,*R*)/(*S*,*S*)-**3** was investigated by ^{1}H NMR spectroscopy. When a solution of (*S*,*S*)-**3** (∼10 mM) was added to the host solution (2 mM) in $CDCl_3$ at 298 K, the typical upfield shift was induced again for the anisyl protons (H^A), which indicated a change in the conformation from the anti- to syn-form upon complexation (matched pair; Figure S4A of the Supporting Information). The titration curves using amide protons and methyl protons on the stereogenic center are shown in Figure 6. We assumed a 1:1 ratio for the (*R*,*R*)-**1b**-**H**·(*S*,*S*)-**3** complex, and then curve-fitted the observed data to give a binding constant K_a of 2×10^3 M^{-1} (Figure 6a). However, an inflection point is present in the titration curves beyond the addition of 1 equiv. of (*R*,*R*)-**3** to the host (mismatched pair; Figures 6b, S4B of the Supporting Information). This anomaly suggests that several species are involved in the equilibrium for the complexation of (*R*,*R*)-**1b**-**H** with (*R*,*R*)-**3**.

Complexation of the chiral dynamic host (*R*,*R*)-**1b**-**H** with (*R*,*R*)/(*S*,*S*)-**3** was further investigated by a CD spectral method (Figure 7). Upon the addition of (*S*,*S*)-**3** to the solution of (*R*,*R*)-**1b**-**H** in CH_2Cl_2 at room temperature, a negative Cotton effect at around 300 nm gradually increased, as in the case of **1a**-**H**·(*S*,*S*)-**3** (Figure 4a), which indicates that the less CD active *anti*-form of (*R*,*R*)-**1b**-**H** is transformed into the propeller-shaped *syn*-form, and is biased toward the (*M*)-sense by the cooperative influence of the internal and external auxiliaries on the helical sense in the complex (matched pair). However, almost no change was observed upon the addition of (*R*,*R*)-**3** up to 1 equiv. Thus, the mismatched pair does not induce CD modification, though NMR titration suggests a similar binding constant ($K = \sim 10^3$ M^{-1}) for (*R*,*R*)-**1b**-**H**·(*R*,*R*)-**3**. Upon the further addition of (*R*,*R*)-**3** up to 4 equiv., marginal changes occurred to give a positive Cotton effect, the sign of which is consistent with the preference for (*R*,*R*)-**3**. Gradual changes of CD spectra with a rise around 320 nm suggest the formation of complexes with different shapes. The absence of CD spectral changes upon complexation with the monotopic guest (*R*)-**5** is also noteworthy. The quite different behavior of (*R*,*R*)-**1b**-**H** toward (*R*,*R*)/(*S*,*S*)-**3** and (*R*)-**5** can be considered a new, rare example of stereospecific chiroptical modulation.[14,22]

Conclusions

One of the characteristic features of the secondary terephthalamide hosts **1a/b**-**H** is that the helical propeller structure is attained only when they adopt a syn-conformation (chirality generation), which is realized upon complexation with a suitable ditopic guest (Scheme 1b). Although the resulting complexes could not be isolated to conduct crystallographic study, the spectroscopic analyses by NMR and CD provided compelling evidence for the following characteristics of complexation. The sense of the helicity for *syn*-**1a**-**H** is biased by the point chiralities of (*R*,*R*)/(*S*,*S*)-**3** or (−)-phenylephrine **4**, which are effectively transferred due to the hover-overed supramolecular-cyclophane structure of the complexes (chirality biasing). Alternatively, the dynamic host (*R*,*R*)-**1b**-**H** with asymmetric centers on amide nitrogens has its own preferred helicity when adopting the syn-form, and thus it exhibits chiral recognition properties toward (*R*,*R*)/(*S*,*S*)-**3**.

In summary, the newly designed secondary amides **1a/b**-**H** can serve as a new class of dynamic hosts that induce strong CD signaling upon complexation with chiral ditopic guests which exhibit only weak chiroptical output before complexation (chiroptical enhancement). Since only cooperative binding with ditopic guests induces the change in the conformation of the hosts from the anti- to syn-form accompanied by biasing of the sense of helicity, the signaling hosts do not exhibit an enhancement of the CD signal by a monotopic guest (*R*)-**5**, which endows the present system with additional recognition properties. This work has demonstrated chirality generation−chirality biasing protocol, for which only a few examples of long-chain oligomer/polymer have been shown to achieve. Our well-designed molecular propellers are another class of compounds for further exploiting the field of less well-developed supramolecular chirality.

Acknowledgment. The authors express their sincere gratitude to Prof. Nobuhiko Yui (JAIST) for his continuing encouragement.

Supporting Information Available: Experimental details (synthetic procedures and spectral data of new compounds), and figures (Figures S1−S5). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Montgomery, C. P.; New, E. J.; Parker, D.; Peacock, R. D. *Chem. Commun.* **2008**, 4261–4263. (b) Preston, A. J.; Gallucci, J. C.; Parquette, J. R. *Org. Lett.* **2006**, *8*, 5259–5262. (c) Miyake, H.; Sugimoto, H.; Tamiaki, H.; Tsukube, H. *Chem. Commun.* **2005**, 4291–4293.

(22) The sensing of chirality with configurationally-stable tertiary amide *syn*-(*R*,*R*)-**1b**-**Me** was also examined (Figure S5 of the Supporting Information),[23] where the matched pair of *syn*-(*R*,*R*)-**1b**-**Me** and (*S*,*S*)-**3** gave strong chiroptical output from the cooperative preference for (*M*)-helicity, as expected. Mismatched enantiomeric guest (*R*,*R*)-**3** had much smaller effects on the CD spectrum. The monotopic guest (*R*)-**5** failed to modify the CD spectrum, as in the combination of *syn*-**1a**-**Me** and (*R*)-**5**.

(23) As shown by the lack of induction of a Cotton effect upon the mixing of conformationally stable *anti*-**1a**-**Me** and chiral guest (*R*,*R*)-**3**, the chiral amide *anti*-**1b**-**Me** does not act as a host for the ditopic guests (*R*,*R*)/(*S*,*S*)-**3**.