

## Intramolecular Chirality Transfer in *trans*-5,6-Diaryl-5,6-dihydro-1,10-phenanthroline-5,6-diols: Solvato- and Halochromic Responses by Circular Dichroism

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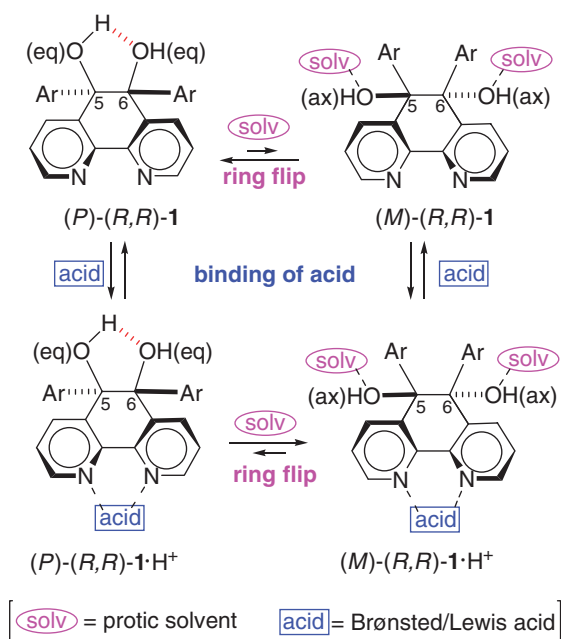
Not only the configuration at the C5 and C6 stereocenters but also the intra/intermolecular hydrogen-bonding mode are determinant for the sense of mobile helicity of the dihydrophenanthroline unit in the title diols in solution. Thus, drastic changes in chiroptical signals are induced through conformational switching of **1** upon addition of protic solvent and/or acid.

Numerous diastereo- and enantioselective procedures have paved the way toward the efficient generation of stereogenic centers in organic compounds, whereas atropselective synthesis of axially chiral molecules, e.g., chiral biaryls, is still under significant advance.<sup>1</sup> In the bridged biaryls, the chiral element is defined as helicity, which is more difficult to arrange stereoselectively.<sup>2</sup> The optically active helical molecules have been attracting increasing recent attention,<sup>3</sup> and transmission of point chirality to helicity is a promising method in obtaining enantioenriched helicenes.<sup>2,4</sup>

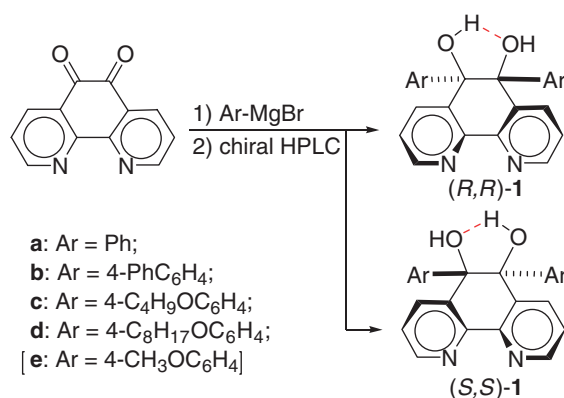
The dihydrophenanthroline<sup>5</sup> and -phenanthrene skeletons are among the smallest frameworks of helical  $\pi$ -systems, whose energy barrier for helicity inversion is only 5 kcal mol<sup>-1</sup>.<sup>6</sup> By using such "mobile" helicity, successful construction of novel chirality-sensing<sup>7</sup> and chiroptical-response systems were realized.<sup>8</sup> At the same time, these skeletons provide unique opportunity to scrutinize the detailed mechanism for intramolecular transmission of point chirality to helicity.<sup>9</sup> In our continuing efforts to develop novel chiroptical response systems,<sup>8,10</sup> we have become interested in the chiroptical properties of the title diols **1**, whose helical conformation would be modified by solvation or salt formation. Here we report their solvato- and halochromic behavior by the drastic changes in the circular dichroism (CD) spectrum.

As shown in Scheme 1, diols **1** with *R,R*-configuration for C5 and C6 adopt *P*-helical geometry for the dihydrophenanthroline unit when the hydroxy groups at the stereogenic centers occupy the pseudoequatorial positions, which is suitable for intramolecular hydrogen bonding (H-bond).<sup>5,9f</sup> In contrast, aryl groups at C5 and C6 would be placed at the equatorial positions by ring flip when the intramolecular H-bond is broken upon addition of protic solvent, thus increasing *M*-helicity preference of the (*R,R*)-diols.<sup>11</sup> Protonation or complexation with a metal ion at the bidentate N-ligand would induce not only bathochromic shift of UV but also affect helicity preference, so that the halochromic response by CD<sup>12</sup> is also expected upon addition of Brønsted/Lewis acid (Scheme 1). These are the central points of our design for a chiroptical switching system based on the title diols **1**.

Phenyl (**1a**) and biphenyl-4-yl (**1b**) derivatives were obtained by the reactions of phenanthroline-5,6-dione and



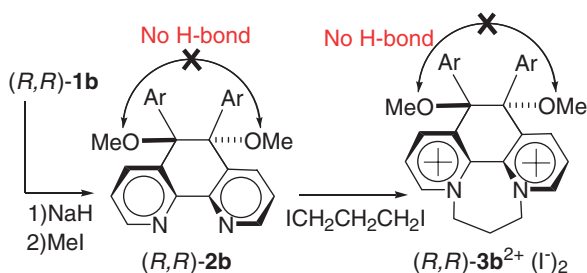
Scheme 1.



Scheme 2.

PhMgBr or 4-PhC<sub>6</sub>H<sub>4</sub>MgBr as described recently.<sup>13</sup> By using 4-C<sub>4</sub>H<sub>9</sub>OC<sub>6</sub>H<sub>4</sub>MgBr or 4-C<sub>8</sub>H<sub>17</sub>OC<sub>6</sub>H<sub>4</sub>MgBr, alkoxy phenyl derivatives **1c**<sup>14</sup> and **1d**<sup>14</sup> were newly prepared in respective yield of 35 and 23% (Scheme 2). Although methoxy derivative **1e** was obtained by a similar reaction (y. 35%), further studies of **1e** were hampered due to its very low solubility.

Optical resolution of diols **1a–1d** was conducted by using chiral HPLC (Sumichiral OA-2000, CH<sub>2</sub>Cl<sub>2</sub>, recycled). In all

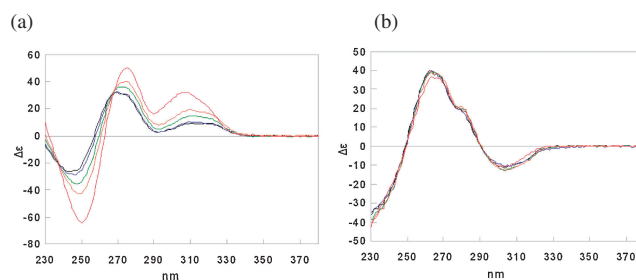


Scheme 3.

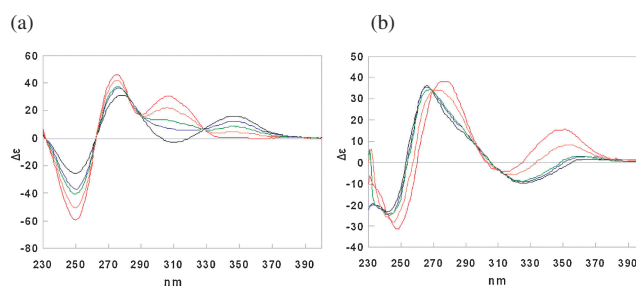
cases, the first fractions are dextrorotatory  $[+]-\mathbf{1}$ ,<sup>14,15</sup> and their circular dichroism (CD) spectra are similar to each other in the sense that they exhibit positive Cotton effects for the first band (300–310 nm) in  $\text{CH}_2\text{Cl}_2$  (Figure S1).<sup>14,16</sup> Their configurations at C5 and C6 are determined to be *R,R* by derivatization of  $(+)-\mathbf{1b}$  into dimethoxydiazepinophenanthroline diiodide  $(R,R)-(+)-\mathbf{3b}^{2+}(\text{I}^-)_2$  (Scheme 3), which was analyzed carefully by X-ray<sup>17</sup> at a low temperature considering anomalous dispersion [Flack parameter  $\chi = -0.02(3)$ ] (Figure S2).<sup>14</sup> Crystallographic study was also conducted for  $(R,R)-(+)-\mathbf{1c}$  ( $P1$ ,  $Z = 4$ ),<sup>17</sup> which adopts *P*-helical geometry for the dihydrophenanthroline unit (Figure S3) as in the cases of  $(R,R)-(+)-\mathbf{1a}$  and  $-\mathbf{1b}$  crystals determined previously.<sup>13</sup>

According to a conformational search on  $(R,R)-\mathbf{1b}$  by using the Conflex program,<sup>18</sup> the *P*-helical structure is found as the energy-minimized conformer, for which several variants exist within a narrow range of energy (0.1 kcal mol<sup>-1</sup>).<sup>19</sup> The TD-DFT calculations indicated that they all exhibit positive Cotton effects for the first band (300–310 nm) (Figure S4),<sup>14</sup> showing that  $(R,R)-\mathbf{1b}$  in  $\text{CH}_2\text{Cl}_2$  adopts *P*-helicity primarily. Intramolecular H-bonding in  $(R,R)-\mathbf{1b}$  would be the important factor for the observed conformational preference since a similar calculation on the dimethoxy derivative  $(R,R)-\mathbf{2b}$  showed that the *M*-helical structure is dominant, for which the negative Cotton effect was calculated for the first band (Figure S5).<sup>14</sup> This prediction is in accord with the experimental CD spectrum of  $(R,R)-\mathbf{2b}$  ( $\lambda_{\text{ext}} = 303$  nm,  $\Delta\epsilon = -11.0$  in  $\text{CH}_2\text{Cl}_2$ ). The above results show that *O*-methylation of  $(R,R)-\mathbf{1b}$  induces conformational switching from *P*- to *M*-helicity by prohibiting the intramolecular H-bond in  $(R,R)-\mathbf{2b}$ , which is accompanied by the change in the sign of Cotton effects from positive to negative at the 300–310 nm region.

Not only the chemical modification of hydroxy groups but also simple addition of protic solvent could cleave the intramolecular H-bond (Scheme 1), which is evidenced by the CD spectra of  $(R,R)-\mathbf{1b}$  measured in a series of  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{OH}$  mixed solvent with a different ratio (Figure 1a). Thus, an increase in  $\text{CH}_3\text{OH}$  proportion weakened the positive ellipticity for the first band (300–310 nm), suggesting that some portion of  $(R,R)-\mathbf{1b}$  changed its helicity from *P* to *M* to give a mixture of (*P*)- and (*M*)- $(R,R)-\mathbf{1b}$  with *P*-helicity in major. Similar behavior was also observed in other diols  $(R,R)-\mathbf{1a}$ ,  $-\mathbf{1c}$ , and  $-\mathbf{1d}$  (Figure S6),<sup>14</sup> but the spectrum of dimethoxy derivative  $(R,R)-\mathbf{2b}$  remained unchanged irrespective of  $\text{CH}_3\text{OH}$  proportion in  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{OH}$  (Figure 1b). Since the spectrum of  $(R,R)-\mathbf{1b}$  measured in  $\text{CH}_3\text{CN}$  is identical to that in  $\text{CH}_2\text{Cl}_2$ , the decisive factor for switching the helicity is not the polarizability of



**Figure 1.** CD spectra of (a)  $(R,R)-\mathbf{1b}$  ( $1.5 \times 10^{-5}$  M) and (b)  $(R,R)-\mathbf{2b}$  ( $2.0 \times 10^{-5}$  M) in a series of  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{OH}$  mixed solvent with a different ratio ( $\text{CH}_3\text{OH}$  v/v %: red 0, orange 25, green 50, blue 75, and black 90).

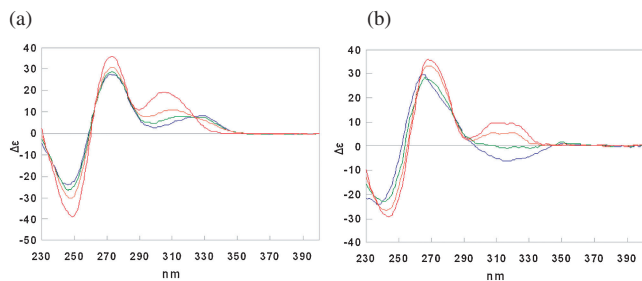


**Figure 2.** (a) CD spectral changes of  $(R,R)-\mathbf{1b}$  ( $2.3 \times 10^{-5}$  M) upon addition of TsOH in  $\text{CH}_2\text{Cl}_2$  (TsOH equiv: red 0, orange 0.25, green 0.50, blue 0.75, and black 1.0). (b) CD spectral changes of  $(R,R)-\mathbf{1b}\cdot\text{H}^+$  ( $\mathbf{1b}$ :  $2.2 \times 10^{-5}$  M; TsOH:  $8.8 \times 10^{-5}$  M) in a series of  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{OH}$  mixed solvent with a different ratio ( $\text{CH}_3\text{OH}$  v/v %: red 0, orange 1, green 5, blue 10, and black 25).

solvent but the formation of intermolecular H-bonds between protic solvent and the hydroxy groups in  $\mathbf{1}$ .

Halochromic response was then studied by salt formation of diol  $(R,R)-\mathbf{1b}$  at the dihydrophenanthroline unit with Brønsted/Lewis acid. According to NMR analysis, monoprotonation occurs exclusively at the dihydrophenanthroline unit upon gradual addition of TsOH in  $\text{CDCl}_3$  (Figure S7).<sup>14</sup> Similar addition to a  $\text{CH}_2\text{Cl}_2$  solution of  $(R,R)-\mathbf{1b}$  caused a red-shift of the first band from 300–310 to 330 nm in the UV spectrum (Figure S8).<sup>14</sup> Protonation also induced a red-shift of ellipticity in the CD spectrum without changing the sign of Cotton effects (Figure 2a), indicating that *P*-helicity is still preferred for  $(R,R)-\mathbf{1b}\cdot\text{H}^+$  in  $\text{CH}_2\text{Cl}_2$ .

The protic solvent also affects the helicity preference of  $(R,R)-\mathbf{1b}\cdot\text{H}^+$  as shown in Figure 2b. A much smaller amount of  $\text{CH}_3\text{OH}$  is sufficient (5%) to induce the maximum effect, and the proportion of *M*-conformer is larger than the unprotonated  $(R,R)-\mathbf{1b}$  as evidenced by the negative sign of the Cotton effect for the first band. Such observation suggests that cleavage of intramolecular H-bond by  $\text{CH}_3\text{OH}$  is facilitated by protonation of the dihydrophenanthroline unit, which can be accounted for by considering planarization of the helical  $\pi$ -system upon protonation.<sup>21</sup> That is, larger separation between two equatorial hydroxy groups at C5 and C6 is expected in (*P*)- $(R,R)-\mathbf{1b}\cdot\text{H}^+$  than in unprotonated (*P*)- $(R,R)-\mathbf{1b}$ , which would be responsible for weakening the intramolecular H-bond between hydroxy groups upon protonation at the N-ligand.



**Figure 3.** CD spectral changes of (*R,R*)-**1b** upon addition of (a) CuI in CH<sub>3</sub>CN ( $2.6 \times 10^{-5}$  M) and (b) Cu(OTf)<sub>2</sub> in CH<sub>3</sub>OH ( $1.3 \times 10^{-5}$  M) (salt equiv: red 0, orange 0.25, green 0.50, and blue 1.0).

Since the above halochromic response was observed not only with Brønsted acid but also with Lewis acid [CuI in CH<sub>3</sub>CN and Cu(OTf)<sub>2</sub> in CH<sub>3</sub>OH] (Figure 3), the present diol **1** can serve as a promising motif for developing multiinput (protic solvent, acid) and multioutput (UV, CD) response systems.

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- Not only the intermolecular H-bond with solvent but also the solvophobic effects in polar media are favored for the latter conformation since two aryl groups at the equatorial positions can stay in proximity with  $\pi$ - $\pi$  stacking.
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- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.
- $[\alpha]_D^{23-25}$  (CHCl<sub>3</sub>): +424 ( $c = 0.26$ ) for (*R,R*)-**1a**, +340 ( $c = 0.06$ ) for (*R,R*)-**1b**, +361 ( $c = 0.135$ ) for (*R,R*)-**1c**, +242 ( $c = 0.136$ ) for (*R,R*)-**1d**. The values for **1c** and **1d** were proven concentration-independent over the  $c$  range of 0.02–0.14, showing no aggregation of **1** into the supramolecular rod-like structures that were commonly found in the crystal structure of **1** (Refs. 13 and 14).
- CD (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{ext}}/\text{nm}$  ( $\Delta\epsilon$ ): 259 (+44.1), 292 (+4.71), 308 (+9.49) for (*R,R*)-**1a**, 250 (−64.0), 275 (+50.2), 290 (+16.4), 306 (+32.1) for (*R,R*)-**1b**, 235 (−34.6), 268 (+39.4), 291 (+0.148), 312 (+21.5) for (*R,R*)-**1c**, 234 (−31.1), 268 (+35.8), 292 (+0.358), 313 (+19.3) for (*R,R*)-**1d**.
- Selected crystal data are as follows (*R,R*)-(+)-**1c**: C<sub>32</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>,  $M_r = 500.55$ , triclinic,  $P1$ ,  $a = 13.792(19)$ ,  $b = 14.103(18)$ ,  $c = 14.947(19)$  Å,  $\alpha = 91.059(19)$ ,  $\beta = 101.98(2)$ ,  $\gamma = 109.86(2)^\circ$ ,  $V = 2662(6)$  Å<sup>3</sup>,  $Z = 4$  (four independent molecules), CCDC 764385. **3b**<sup>2+</sup>(I<sup>−</sup>)<sub>2</sub>(MeCN): C<sub>43</sub>H<sub>39</sub>I<sub>2</sub>N<sub>3</sub>O<sub>2</sub>,  $M_r = 883.61$ , monoclinic,  $P2_1$ ,  $a = 12.316(1)$ ,  $b = 7.1700(8)$ ,  $c = 24.511(2)$  Å,  $\beta = 101.846(2)^\circ$ ,  $V = 2118.4(4)$  Å<sup>3</sup>,  $Z = 2$ , CCDC 764386.
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- The structural variations are related to the different twisting direction (axial chirality) of the biphenyl units at C5 and C6 [e.g., (*R*<sub>ax</sub>,*R*<sub>ax</sub>), (*R*<sub>ax</sub>,*S*<sub>ax</sub>), (*S*<sub>ax</sub>,*S*<sub>ax</sub>)]. In the calculated CD spectra for these conformers, the ellipticity at 260–280 nm is more positive for (*R*<sub>ax</sub>,*R*<sub>ax</sub>) and less positive (or negative) for (*S*<sub>ax</sub>,*S*<sub>ax</sub>) forms, which is in accord with the addition of biphenyl-based components expected from the Mislow's helicity rules (Ref. 20).
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- When the acid treatment was conducted in CH<sub>3</sub>OH, UV spectral changes were observed that resemble those in CH<sub>2</sub>Cl<sub>2</sub>. However, the sign of Cotton effect also changed for the first band in the CD spectrum (Figure S9),<sup>14</sup> showing that a mixture of (*P*)/(*M*)-(*R,R*)-**1b** in CH<sub>3</sub>OH is protonated to give (*M*)-(*R,R*)-**1b**·H<sup>+</sup> as the major component.