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Chirality transcription and amplification by [2]pseudorotaxanes

A chirality transcription and amplification by the forming of chiral [2]pseudorotaxanes by an achiral crown ether having 2',2"-quaterphenyl group and chiral *sec*-ammonium ions are reported. It was revealed that the absolute configurations of the chiral *sec*-ammonium ions can be detected directly from the CD spectra of the chiral [2]pseudorotaxanes.

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Chirality transcription and amplification by the formation of chiral [2]pseudorotaxanes by an achiral crown ether having the 2',2"quaterphenyl group and chiral *sec*-ammonium ions are reported. It was revealed that the absolute configurations of the chiral *sec*ammonium ions can be detected directly from the CD spectra of the chiral [2]pseudorotaxanes.

Chirality recognition in supramolecular interaction plays an important role in many natural systems such as the DNA double helix and secondary  $\alpha$ -helix structure of proteins.<sup>1</sup> Recently various artificial and biomimetic supramolecular systems for chirality recognition have been extensively studied.<sup>1–7</sup> Crown ethers having chiral centers are widely used for chirality recognition of chiral amines, ammonium salts, amino acids, and so on.<sup>8–10</sup>

Chiral crown ethers recognize chiral guests by the difference in stabilities between diastereomeric complexes such as (R)-host-(R)-guest and (R)-host-(S)-guest complexes. When we looked at the recognition system from a different angle, we came up with an idea for a supramolecular system. That is, an achiral crown ether having a functional group which can invert the chirality of an atropisomer depending on the chirality of guests could achieve chirality transcription to the crown ether from the guest. We designed a new benzo-2',2"-quaterphenyl-26-crown-8 ether (1). The 2', 2''-quaterphenyl group can flip like a co-axis rotor blade, and the macrocyclic ring can form [2]pseudorotaxanes<sup>11</sup> with cationic organic guests such as secammonium salts. We expected that information on the chirality of the ammonium salts is transcribed into the 2',2"-quaterphenyl unit of 1 (Fig. 1). Concretely, information on the absolute configurations of sec-ammonium ions would be transcribed

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<sup>†</sup> Electronic supplementary information (ESI) available: Experimental procedures and physicochemical properties, X-ray structures, and molecular calculations. CCDC 914474. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc38758a  $\begin{array}{c} & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ \end{array} \end{array}$ 

Chirality transcription and amplification by

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[2]pseudorotaxanes<sup>+</sup>

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**Fig. 1** Conceptual diagram of the chiral transcription by the formation of [2]pseudorotaxanes.

into the spatial arrangement of two biphenyl chromophores in the 2', 2''-quaterphenyl group. It is well known that the circular dichroism (CD) exciton chirality method provides valuable information on the spatial arrangement of the chromophores.<sup>12-14</sup> Therefore, information on the absolute configuration is detected directly by CD spectroscopy. In addition, information on the chirality would be amplified by the drastic conformational changes of the 2', 2''-quaterphenyl group which has two large electronic transition moments. Recently, some research groups have reported the supramolecular chirality transcription system of amines,<sup>15-18</sup> amino acids,<sup>19-22</sup> and peptides<sup>23</sup> using CD spectroscopy. However, their systems require complicated molecules or need chemical conversion of the target molecules, and it is difficult to obtain the information about their absolute configurations. Here we report chiral transcription and amplification by the formation of [2]pseudorotaxanes.

The new benzo-2',2"-quaterphenyl-26-crown-8 ether (1) was prepared by the reaction of 1,1':3',1'':3'',1'''-quaterphenyl-4',6"-diol<sup>24</sup>

and triethylene glycol ditosylate<sup>25</sup> in 20% yield. Chiral ammonium salts (*R*)- and (*S*)-2(**a** and **b**)-H·PF<sub>6</sub> were prepared from (*R*)- or (*S*)-phenylethylamine and the corresponding aldehyde in good yield. The structures of the chiral ammonium salts were confirmed by <sup>1</sup>H and <sup>13</sup>C NMR, MS, and elemental analysis. Single crystals of (*R*)-2**a**-H·PF<sub>6</sub> were obtained, and X-ray structure was determined. (For further information see ESI.†)

Crown ether 1 was treated with equimolar amounts of (R)-2a-H·PF<sub>6</sub>, (R)-2b-H·PF<sub>6</sub>, (S)-2a-H·PF<sub>6</sub>, and (S)-2b-H·PF<sub>6</sub> to give complexes  $[\mathbf{1} \cdot (R) \cdot 2\mathbf{a} \cdot H] [PF_6], [\mathbf{1} \cdot (R) \cdot 2\mathbf{b} \cdot H] [PF_6], [\mathbf{1} \cdot (S) \cdot 2\mathbf{a} \cdot H] [PF_6],$ and  $[1 \cdot (S) - 2\mathbf{b} - \mathbf{H}][\mathbf{PF}_6]$  in quantitative yield, respectively. The structure of  $[\mathbf{1} \cdot (R) \cdot \mathbf{2a} \cdot \mathbf{H}] [PF_6]$  was confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and NOESY. When equimolar amounts of 1 and (R)-2a-H·PF<sub>6</sub> were mixed in  $CDCl_3$ , the ethyleneoxy protons  $(H_2-H_7)$  of 1 and the methyl protons of (R)-2a-H·PF<sub>6</sub> exhibited peak broadening in the <sup>1</sup>H NMR spectrum, indicative of exchange occurring on the <sup>1</sup>H NMR time scale between the [2]pseudorotaxane and free species (Fig. 2).<sup>26,27</sup>‡ In the <sup>13</sup>C NMR, remarkable chemical shift changes of the ethyleneoxy carbons  $(C_2-C_7)$  were observed (Fig. S12, ESI<sup>+</sup>). In addition, the NOESY spectrum of the mixture exhibits a NOE cross peak between the ethyleneoxy protons  $(H_4 \text{ or } H_5)$  of 1 and the methyl protons  $(H_d)$  of (R)-2a-H<sup>+</sup> (Fig. S13, ESI<sup>+</sup>). From these results, it was confirmed that the combination of the crown ether 1 and the chiral sec-amine salts forms the [2]pseudorotaxanes.

In the Cold Spray Ionization-MS (CSI-MS) of  $[\mathbf{1} \cdot (R) - 2\mathbf{a} - H][PF_6]$ and  $[\mathbf{1} \cdot (R) - 2\mathbf{b} - H][PF_6]$ , fragment ion peaks arising from  $[\mathbf{1} \cdot (R) - 2\mathbf{a} - H]^+$ and  $[\mathbf{1} \cdot (R) - 2\mathbf{b} - H]^+$  were observed at m/z = 888 and 841, respectively (Fig. 3). The CSI-MS measurements of the enantiomers  $[\mathbf{1} \cdot (S) - 2\mathbf{a} - H][PF_6]$  and  $[\mathbf{1} \cdot (S) - 2\mathbf{b} - H][PF_6]$  showed the same fragment ion peaks. The CSI-MS data also support the formation of the [2]pseudorotaxanes.

To investigate the chirality transcription and amplification by the [2]pseudorotaxanes, the UV-vis and CD spectra of the



**Fig. 2** Partial <sup>1</sup>H NMR spectra (400 MHz, CDCl<sub>3</sub>, 298 K, [**1**] = [ammonium salts] = 14 mM) of (*R*)-**2a**-H·PF<sub>6</sub> (a), **1** (b), and [**1**·(*R*)-**2a**-H][PF<sub>6</sub>] (c).



**Fig. 3** CSI-MS (CHCl<sub>3</sub>, 298 K, [1] = [ammonium salts] = 30 mM) of a 1 : 1 mixture of 1 and (*R*)-**2a**-H·PF<sub>6</sub> (a), 1 and (*S*)-**2a**-H·PF<sub>6</sub> (b), 1 and (*R*)-**2b**-H·PF<sub>6</sub> (c), 1 and (*S*)-**2b**-H·PF<sub>6</sub> (d).



**Fig. 4** CD spectra (CHCl<sub>3</sub>, 273 K, [**1**] = [ammonium salts] = 3.0 mM) (a) and UV spectra (CHCl<sub>3</sub>, 293 K, [**1**] = [ammonium salts] = 0.20 mM) (b) of **1** (red), (*R*)-**2a**-H·PF<sub>6</sub> (black), [**1**·(*R*)-**2a**-H][PF<sub>6</sub>] (pink), [**1**·(*S*)-**2a**-H][PF<sub>6</sub>] (purple), [**1**·(*R*)-**2b**-H][PF<sub>6</sub>] (green), and [**1**·(*S*)-**2b**-H][PF<sub>6</sub>] (blue). The preferred conformation of [**1**·(*R*)-**2a**-H][PF<sub>6</sub>] (c). Optimized structure of [**1**·(*R*)-**2a**-H] by *ab initio* B3LYP/6-31G\* (d).

crown ether 1, ammonium salts, and [2]pseudorotaxanes were measured (Fig. 4a and b). Crown ether **1** has a  $\lambda_{max}$  arising from  $\pi$ - $\pi^*$  transition around 260 nm in the UV-vis spectrum. This absorption is due to the polarization along the long axis of the biphenyl chromophore moieties in the 2', 2''-quaterphenyl group. Since 1 is an achiral molecule having a flexible 2', 2''quaterphenyl group, no Cotton effect was observed. Although the chiral ammonium salt (R)-2a-H·PF<sub>6</sub> shows CD Cotton effects around 260 nm (aromatic <sup>1</sup>L<sub>b</sub> band), the amplitude is very weak. On the other hand, the [2]pseudorotaxane  $[\mathbf{1} \cdot (R) \cdot \mathbf{2a} \cdot \mathbf{H}][PF_6]$ exhibits significant CD Cotton effects due to the exciton coupling between the two biphenyl chromophores in the 2',2"-quaterphenyl group;  $\lambda_{\text{ext}}$  = 263.4 nm ( $\theta$  = -8700),  $\lambda_{\text{ext}}$  = 243.1 nm ( $\theta$  = +18700). The negative first and positive second Cotton effects indicate the negative exciton chirality<sup>12-14</sup> between the two chromophores. Therefore, the two long axes of the two chromophores of  $[1 \cdot (R) - 2a - H]$  [PF<sub>6</sub>] constitute a counterclockwise screw sense (Fig. 4c). In contrast, [2]pseudorotaxane  $[\mathbf{1} \cdot (S) \cdot \mathbf{2a} \cdot \mathbf{H}]$ - $[PF_6]$  shows the mirror image of the Cotton effects of  $[1 \cdot (R) - 2a - H]$ -[PF<sub>6</sub>] in the CD spectrum ( $\lambda_{ext}$  = 261.6 nm ( $\theta$  = +12100),  $\lambda_{ext}$  = 242.8 nm ( $\theta = -20\,800$ )). The CD spectra of  $[\mathbf{1} \cdot (R) - 2\mathbf{b} - H][PF_6]$ and  $[1 \cdot (S) - 2b - H][PF_6]$  show the same sign of Cotton effects with



Fig. 5 CD signals at 261.6 nm of  $[1\cdot(R)-2a-H][PF_6]$  and  $[1\cdot(S)-2a-H][PF_6]$  with varying %ee values. [1] = [ammonium salts] = 3.0 mM.

 $[1 \cdot (R)-2a-H][PF_6]$  and  $[1 \cdot (S)-2a-H][PF_6]$ , respectively. This means that the [2]pseudorotaxanes containing the chiral *sec*-ammonium salts with the same absolute configuration show the same Cotton effects in CD spectra.

Because good crystals of the [2]pseudorotaxanes suitable for X-ray crystallography were not obtained, a conformer search using molecular mechanics and then optimization using semiempirical AM1 calculations followed by *ab initio* B3LYP/6-31G\* calculations of  $[(R)-2\mathbf{a}-\mathbf{H}]^+$  were carried out (Fig. 4d). The optimized structure shows that the ammonium salt is incorporated in the crown ether ring, and the two biphenyl moieties constitute a counterclockwise screw sense with the dihedral angle of 84°. The modeling strongly supports the result of CD measurements.

To evaluate the effectiveness of the [2]pseudorotaxane system for quantitative enantiomeric excess (ee) determination of chiral *sec*-ammonium ions, a calibration curve<sup>28-31</sup> was created using (*R*)- and (S)-2**a**-H·PF<sub>6</sub> with varying ee (-100, -80, -60, -40, -20, 0, +20, +40, +60, +80, +100 %ee of (*R*)-2**a**-H·PF<sub>6</sub>). The CD amplitudes at 261.6 nm were plotted *versus* %ee (Fig. 5). The calibration curve shows a linear relationship with  $R^2 = 0.998$ . The result indicates that the system is applicable to quantitative ee determination of chiral *sec*-ammonium ions.

In conclusion, we demonstrated that a combination of 1 and chiral sec-ammonium salts achieves the chiral transcription and amplification by forming [2]pseudorotaxanes. In this system, the crown ether forms complexes with chiral secammonium ions to make [2]pseudorotaxanes, and the chirality of the sec-ammonium ion is transcribed into the crown ether. Since two biphenyl parts in the 2',2"-quaterphenyl group rotate like a co-axial rotor, the chirality of the atropisomers of the crown ether can be inverted depending on the chirality of the guest ions. When the crown ether formed the chiral [2]pseudorotaxane with (R)-sec-ammonium ions, the negative first and positive second Cotton effects indicating a counterclockwise screw sense were observed in the CD spectrum. The chirality transcription and amplification by the formation of the pseudorotaxane would open a new way to determine the absolute configuration and ee of chiral sec-amines.

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#### Notes and references

<sup>‡</sup> The association constant  $K_a$  of  $[1\cdot(R)-2a-H][PF_6]$  was not determined because of the peak broadening in the <sup>1</sup>H NMR spectrum. The  $K_a$  value of  $[1\cdot(R)-2b-H][PF_6]$  is calculated using <sup>1</sup>H NMR titration experiments at 273 K to be 370 M<sup>-1</sup> (Fig. S14, ESI<sup>†</sup>). The value is smaller than the [2]pseudorotaxane of dibenzo[24]crown-8 and dibenzylammonium (27 000 M<sup>-1</sup> at 298 K)<sup>11</sup> and is larger than that of chiral crown ether and benzyl ammonium (3.3 M<sup>-1</sup> at 283 K; Y. Tachibana, N. Kihara, Y. Ohga, T. Takata, *Chem. Lett.*, 2000, **29**, 806).

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