Urea-functionalized Resorcinarenes: Preparation, Self-folding, and Their CD Phenomena Caused by Chiral Urea Termini through Intramolecular Hydrogen Bonding Interactions

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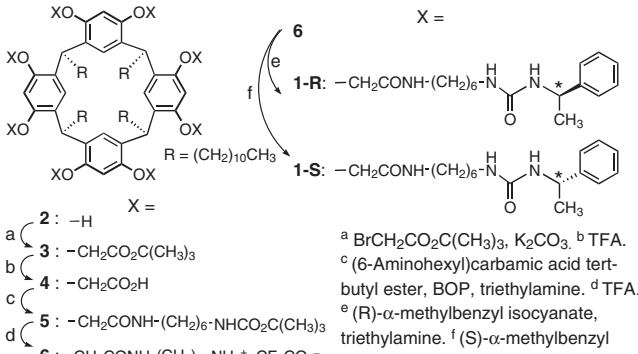
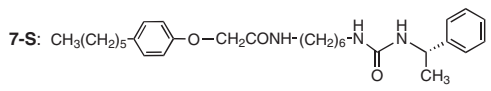
Self-folding resorcinarenes bearing optically active urea moieties showed unique circular dichroism (CD) phenomena on the macrocyclic skeleton, which were caused by their chiral urea termini through intramolecular hydrogen bonding interactions in chloroform. These characteristic CD bands were disappeared upon complexation with anions such as chloride and bromide.

Resorcinarenes[1] such as **2** are starting materials for syntheses of various open-ended cavitands.[2] In particular, resorcinarenes with amide- or urea-functionalized groups have been known to form intramoleclar hydrogen bonding belts and give a self-folding cavitand[3] in apolar organic solvents. However, limited studies have been reported on the development of chiral self-folding cavitands.[4] On these grounds, we became interested in the resorcinarene-besed self-folding cavitands capable of providing an asymmetric internal cavity. Resorcinarene bearing eight optically active urea moieties **1-R** and **1-S** were designed by introducing (*R*)- and (*S*)-methylbenzylurea residues, respectively, onto each OH groups of **2** through an alkyl spacer having amide linkage. In this context, we report preparation and self-folding of **1-R** and **1-S** as well as their unique circular dichroism (CD) phenomena on the macrocycles caused by chiral urea termini through intramolecular hydrogen bonding interactions in chloroform. In addition, their spectral changes were also investigated upon complexation with anion as a guest.



Scheme 1. Preparation of urea-functionalized resorcinarenes.



Resorcinarenes bearing eight (*R*)- and (*S*)-methylbenzylurea residues **1-R** and **1-S** were prepared by following the reaction sequence given in the Scheme 1.[5] We also prepared mono-urea derivative **7-S** having a *S*-configuration by using 4-hexylphenol in place of **2** in a manner similar to that applied to the synthesis of **1-S**. In general, small urea molecules tend to form self-assemblies by hydrogen bonding interactions in apolar organic solvents.[6] First, hydrogen-bonding properties of **1-S** in chloroform solutions (1.3 mM) were evaluated by FT-IR measurements,[7] as compared with those for the mono-urea derivative **7-S** (10 mM) (1 M = 1 mol dm^{-3}). The absorption frequencies originating from N–H deformation band and C=O stretching vibrations of **1-S** shifted to the higher and lower wavenumbers (δ_{N-H}, 1565 and $\nu_{C=O}$, 1658 cm^{-1}, respectively), in comparison with those for **7-S** (δ_{N-H}, 1554 and $\nu_{C=O}$, 1668 cm^{-1}, respectively), indicating the formation of hydrogen bonds[7] for urea and amide residues of **1-S**. Kobayashi and Seki reported similar results for the hydrogen bonding formation of urea derivatives by the identical methods.[7] A similar character in the hydrogen-bonding properties of another macrocyclic urea **1-R** was also confirmed by the identical methods. Combined these results suggest that **1** forms intramolecular hydrogen bonds by bundling the urea and amide residues in a cyclic fashion to give a self-folding cavitand in chloroform, as schematically shown in Figure 1. When all of the urea or amide residues are oriented in the same direction, the cyclic hydrogen bonding belts are formed cooperatively.

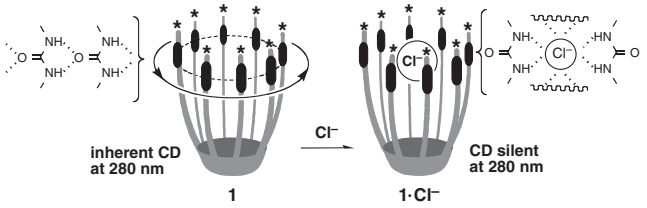


Figure 1. Schematic representations for **1** and the complex of **1** with chloride. Each black oval stands for a urea moiety.

The asymmetric character of the present octa-urea **1-R**/**1-S** was examined by CD spectroscopy at 298 K. A chloroform solution of compound **1-S** showed positive CD bands at 254, 261, and 267 nm as well as a negative band at 280 nm as shown in Figure 2. No concentration-dependency on the CD spectra of **1-S** was observed at least within the concentration range of 15 μM–0.76 mM, indicating that **1-S** exists in a monomeric state.[8] In addition, mono-urea **7-S** shows similar signed CD bands at 255, 261, and 268 nm with ca. 1/8 lessened intensity of **1-S** (Figure 2). These results suggest that the CD bands in a shorter wavelength range are originally attributable to the optically active urea residues. On the other hand, the negative CD band at 280 nm indicates that the originally achiral macrocyclic skeleton of **1-S** gains inherent chirality through the asymmetric

cyclic hydrogen bonding belts around the urea terminus in chloroform. The formation of intramolecular hydrogen bonds of **1-S** is responsible for the unique CD phenomena, because the CD band of **1-S** at 280 nm was weakened to ca. 42% in intensity in chloroform–methanol (92:8 v/v) and completely disappeared in chloroform–methanol (3:97 v/v). Methanol acts as a competitor for the intramolecular hydrogen bonding formations. A similar asymmetric character was observed for **1-R** having inverted CD signs in chloroform (Figure 2).

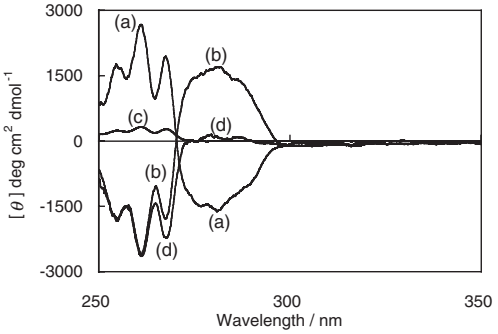


Figure 2. CD spectra of **1-S** (a), **1-R** (b), **7-S** (c), and **1-R** in the presence of chloride (36 equiv.) (d) in chloroform at 298 K.

An intrinsic potential of **1** to act as a host[9] for anion inclusion has been investigated by ^{1}H NMR and CD[10] spectroscopy. Upon addition of chloride (as a tetrabutylammonium salt) to a $CDCl_3$ solution containing **1-S**, the ^{1}H NMR signal due to the urea protons of **1-S** were sharpened and underwent substantial downfield shifts in the presence of chloride, showing a simple saturation behavior for the complexation as shown in Figure 3.

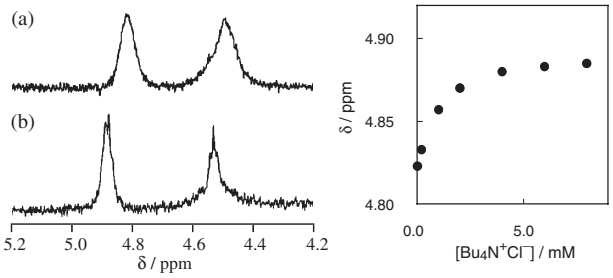


Figure 3. Partial ^{1}H NMR spectra of **1-S** in $CDCl_3$ at 298 K in the absence (a) and presence of chloride (36 equiv.) (b). Inset; the corresponding NMR titration curve.

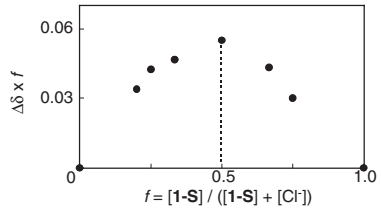


Figure 4. Job plot for a combination of **1-S** and chloride.

The stoichiometry for the complex was confirmed to be 1:1 host–guest[11] by Job plot (Figure 4). These results indicate again that **1** has a self-folding cavity suitable for binding an anion within, as schematically shown in Figure 1. Similar complexation behavior of **1-S** was also confirmed with bromide. The binding constants (K) for 1:1 host–guest complexes were evaluated on the basis of the computer-aided least squares curve fitting methods applied to the NMR data (K; 1000 and 600 M^{-1} for chloride and bromide, respectively). Interestingly, the CD bands of **1-S** at 280 nm was weakened to ca. 70% in intensity in the presence of chloride (3 equiv.) and disappeared in the presence of an excess amount of chloride (36 equiv.) These results suggested that the encapsulated guest anions disrupted the formation of intramolecular hydrogen bonds of **1-S**, as schematically shown in Figure 1, so that the resulting complexes did not show any CD phenomena at 280 nm. Similar complexation behavior of **1-R** with the anions was also confirmed by the identical methods (Figure 2d).

In conclusion, resorcinarene-type hosts bearing eight (*R*)- and (*S*)-methylbenzylurea residues **1-R** and **1-S** form a self-folded conformation originating from the intramolecular hydrogen-bonding interactions and exhibit the unique CD phenomena on the macrocyclic skeleton in chloroform. The guest-binding behavior toward anions such as chloride and bromide were monitored by the changes in CD band intensity as well as ^{1}H NMR spectroscopy. The guest-binding sites of these hosts are close to the chiral residues, so that these hosts are expected to perform chiral recognition toward molecular anions. Further studies are currently in progress along this line.

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References and Notes

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5 **1-R**; 600 MHz ^{1}H NMR ($CDCl_3$, 298 K) δ 0.86, 1.23–1.28, 1.35, 1.75, 2.0, 3.0, 3.2, 4.46, 4.81, 5.7–6.4, 7.15, 7.2. MS (FAB) m/z 3533 $[M + H]^+$. Found: C, 69.68; H, 8.86; N, 8.99%. Calcd for $C_{208}H_{312}N_{24}O_{24}\cdot 3H_2O$: C, 69.55; H, 8.94; N, 9.37%. **1-S**; 600 MHz ^{1}H NMR ($CDCl_3$, 298 K) δ 0.86, 1.23–1.28, 1.35, 1.75, 2.0, 3.0, 3.2, 4.46, 4.81, 5.7–6.4, 7.15, 7.2. MS (FAB) m/z 3533 $[M + H]^+$. Found: C, 69.81; H, 8.80; N, 9.12%. Calcd for $C_{208}H_{312}N_{24}O_{24}\cdot 3H_2O$: C, 69.55; H, 8.94; N, 9.37%.
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