Enantioselective Discrimination by Cage-Type Cyclophanes Bearing Chiral Binding Sites in Aqueous Media

Yukito Murakami,* Osamu Hayashida, and Yasuyuki Nagai

Department of Chemical Science and Technology
Faculty of Engineering, Kyushu University
Fukuoka 812, Japan

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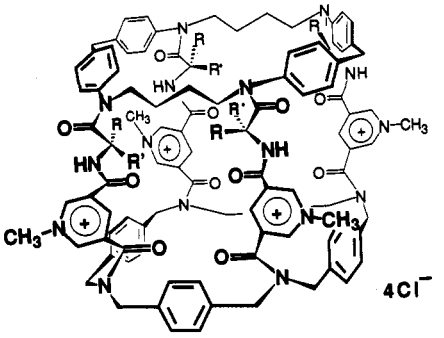
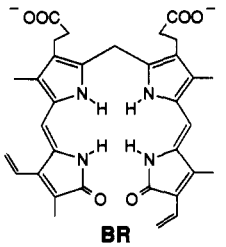
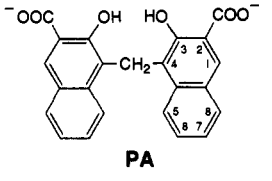
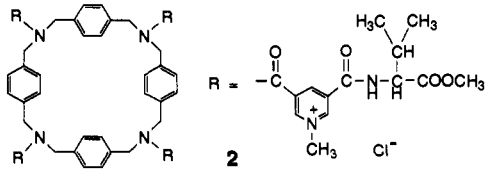
The development of artificial hosts capable of performing chiral recognition toward guest molecules in aqueous media is of great importance for creating supramolecules which exercise functional simulation of cell-surface receptors.[1] We have previously prepared water-soluble cage-type cyclophanes bearing chiral binding sites provided by L- and D-valine residues [(+)-**1** and (−)-**1**, respectively][1-4] and clarified that each host furnishes a three-dimensionally extended and helically twisted internal cavity, the helical twisting being caused by the chiral valine residues introduced into the bridging segments.[3,4] The twisted directions of the bridging components in (+)-**1** and (−)-**1** were concluded to be opposite to each other on the basis of molecular mechanics and dynamics calculations.[4] Both of the chiral hosts show circular dichroism (CD) bands in aqueous carbonate buffer (0.02 M, pH 10.0, μ 0.10 with KCl), reflecting the asymmetric character of their internal cavities; [θ], 1.2×10^5 and -1.3×10^5 deg cm^2 dmol^{-1} at 237 and 236 nm (respective CD peak wavelengths) for (+)-**1** and (−)-**1**, respectively, at 28.0 °C (Figure 1a). In this communication, we report on the chirality-based molecular discrimination ability of the cage-type cyclophanes toward anionic guests, (4*Z*,15*Z*)-bilirubin IXα (BR) and 4,4′-methylenebis(3-hydroxy-2-naphthalenecarboxylic acid) (pamoic acid; PA).



(+)-**1** { R = CH(CH$_3$)$_2$, R′ = H } (−)-**1** { R = H, R′ = CH(CH$_3$)$_2$ }







The cytotoxic yellow-orange bile pigment of jaundice, BR, consists of two dipyrrinone moieties conjoined by a methylene group and places the propionic acid group of one dipyrrinone moiety in a location suitable for intramolecular hydrogen bonding with the pyrrole and lactam residues of the other dipyrrinone. The bile pigment is folded into either of two ridge-tile-shaped enantiomers stabilized by intramolecular hydrogen-bonding interactions (Figure 2)[5] and undergoes rapid interconversion between those conformational enantiomers without showing any detectable CD bands over a relatively wide wavelength range in the aqueous carbonate buffer. Upon addition of (+)-**1** to the carbonate buffer containing BR, an electronic absorption intensity originating from BR (ϵ = 47 000 M^{-1} cm^{-1} at 436 nm; 30.0 °C) decreased, reflecting formation of the corresponding host–guest complex. Moreover, when BR was added to the carbonate buffer containing (+)-**1**, the CD band originating from (+)-**1** was weakened in intensity along with appearance of negatively and positively signed CD bands, which are due to the exciton coupling between two proximal dipyrrinone chromophores within the incorporated guest molecule, in a longer wavelength range at 28.0 °C; [θ], -2.3×10^4 and 1.8×10^4 deg cm^2 dmol^{-1} at 464 and 404 nm, respectively (Figure 1b). The decrease in CD band intensity originating from the host is attributable to conformational

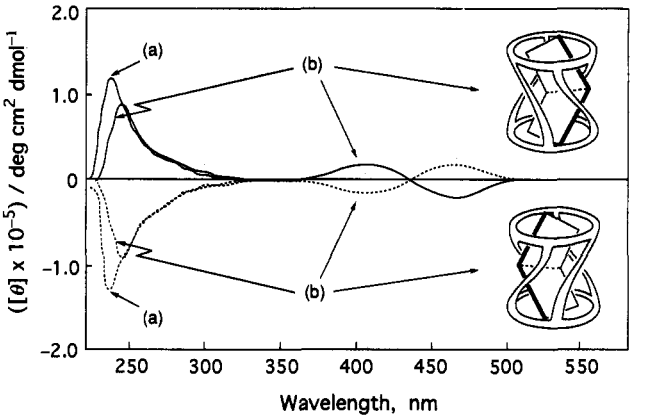


Figure 1. Circular dichroism spectra of (+)-**1** (3.0×10^{-5} M) and (−)-**1** (3.0×10^{-5} M) (solid and dashed lines, respectively) in aqueous carbonate buffer (0.02 M, pH 10.0, μ 0.10 with KCl) at 28.0 °C: (a) without any guest; (b) in the presence of BR (3.0×10^{-5} M).

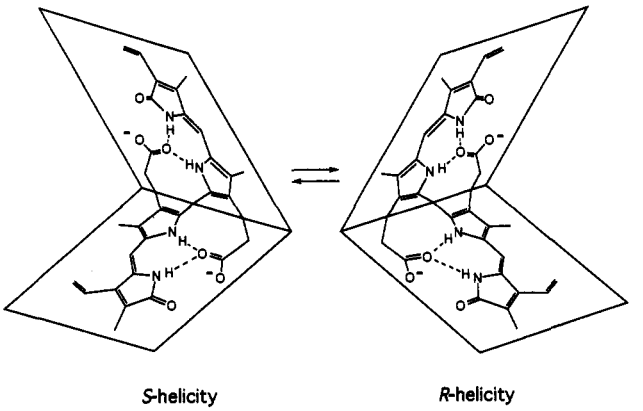


Figure 2. Three-dimensional representations for two conformational enantiomers of BR stabilized by intramolecular hydrogen bonding, which undergo rapid interconversion in aqueous media.

* To whom correspondence should be addressed.

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changes around the pyridinium moieties of (+)-1 upon complexation with the guest in a manner as predicted for the complexation of the identical host with 1-hydroxy-2,4-dinitronaphthalene-7-sulfonate.[4] The bisignate Cotton effects indicate that the BR molecule selectively assumes a conformational enantiomer of *S*-helicity upon complexation with (+)-1 on the basis of an exciton-coupling theory,[6] in a manner similar to that performed by cyclodextrins.[7,8] On the other hand, bisignate CD bands with inverted signs were observed for BR at 28.0 °C in the presence of (−)-1; $[\theta]$, 1.8×10^4 and -1.6×10^4 deg cm^2 dmol^{-1} at 463 and 406 nm, respectively (Figure 1b). This means that the *R*-helicity enantiomer of BR is incorporated into (−)-1, in preference to the *S*-helicity enantiomer, in aqueous media. The stoichiometry for the complexes formed with the cage-type hosts and BR was investigated by means of the molar ratio method.[9] The result reveals that the present hosts tend to form complexes with BR in a 1:1 molar ratio of host to guest. Binding constants (K) for the 1:1 host–guest complexes were calculated on the basis of CD spectroscopic data obtained at various concentrations of the hosts in a manner as described previously;[1] 6.4×10^5 and 6.9×10^5 M^{-1} for the BR complexes of (+)-1 and (−)-1, respectively, at 28.0 °C.

A similar enantioselective inclusion by the cage-type hosts was observed toward PA, which assumes two conformational enantiomers in aqueous solution.[10] Upon addition of (+)-1 to the carbonate buffer containing PA, bisignate CD bands due to two exciton transitions within the incorporated guest molecule appeared in a somewhat shorter wavelength range relative to BR at 30.0 °C ($[\theta]$, -2.4×10^3 and 1.2×10^3 deg cm^2 dmol^{-1} at 379 and 339 nm, respectively), indicating that the PA molecule bound to (+)-1 selectively assumes an *S*-helicity conformation. On the other hand, PA bound to (−)-1 exhibited similar bisignate Cotton effects with inverted CD signs ($[\theta]$, 2.8×10^3 and -1.0×10^3 deg cm^2 dmol^{-1} at 379 and 339 nm, respectively), verifying that the incorporated PA molecule is present as the *R*-helicity conformer in the chiral internal cavity of (−)-1. Both hosts, (+)-1 and (−)-1, moderately bind the identical guest in the aqueous carbonate buffer with binding constants of 1.7×10^3 and 1.6×10^3 M^{-1}, respectively, at 30.0 °C as evaluated by fluorescence spectroscopy. The inclusion interaction of (−)-1 with PA was investigated by means of ^{1}H NMR spectroscopy in D_2O (pD 10.3)/$(CD_3)_2SO$ (4:1 v/v) at 303 K. Upon addition of (−)-1 to the solution of PA, all ^{1}H NMR signals due to the guest were subjected to substantial upfield shifts. The evaluated complexation-induced shifts (CIS)[11] were −0.04, −0.08, −0.07, −0.11, and −0.07 ppm for H-1, H-5, H-6, H-7, and H-8, respectively. Therefore, the PA molecule seems to be incorporated into the three-dimensional cavity provided intramolecularly by the two macrocyclic skeletons and the four bridging components, in a manner similar to that performed by the host toward steroid hormones.[4] Although noncage host **2**, a peptide cyclophane bearing four flexible branches,[12] also binds the identical guests, BR and PA (K = 5.5×10^3 and 6.7×10^3 M^{-1}, respectively, at 30.0 °C in the aqueous carbonate buffer), no CD signal was observed in the absorption ranges of the guests. This indicates that the guests are incorporated into the host cavity without chirality-based molecular discrimination in aqueous media.

In conclusion, the helically twisted and three-dimensionally extended hydrophobic cavities of the cage-type hosts furnish conformationally forced microenvironments for chiral recognition toward enantiomeric guests which otherwise undergo rapid interconversion between respective conformational enantiomers in aqueous media.

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