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Molecular Recognition by a Cationic Cage-type Host Bearing Chiral Binding Sites

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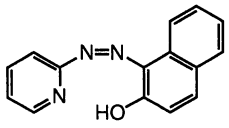
The guest-binding behavior of a novel cage-type host bearing chiral binding sites was examined in aqueous media. The binding constants for inclusion of non-ionic and anionic dyes were in the order of 10^5–10^6 mol^{-1} dm^3, and the circular dichroism was induced on an incorporated achiral guest through its stereochemical interaction with the chiral host cavity.

Various cyclophanes with chiral binding sites have been known to execute diastereomer-selective molecular recognition.[1] However, such chiral internal cavities are not well shielded from external media and/or not large enough to incorporate bulky guest molecules. On these grounds, we became interested in the host–guest chemistry of cyclophanes which provide three-dimensionally extended hydrophobic cavities constructed with rigid macrocyclic skeletons and chiral binding sites.[2] In this context, we report here the effective guest-recognition behavior of a cationic cage-type cyclophane bearing chiral binding sites (**1**) in aqueous media and the observations of induced circular dichroism upon incorporation of achiral guests into the host cavity.

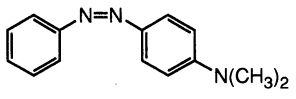
Host **1** was derived from **2**[3] by the reaction with methyl iodide in dry *N*,*N*-dimethylformamide at room temperature over 7 days. Replacement of the counterion from iodide to chloride was performed on a column of Amberlite IRA-401 with methanol as eluant. The product was finally purified by gel-filtration chromatography on a column of Sephadex LH-20 with methanol–chloroform (1:1 v/v) as eluant to afford a pale yellow solid: yield 86%, mp 265–268 °C (decomp); 500 MHz ^{1}H NMR (D_2O, 27 °C, DSS) δ = 0.8 (24H, br s, $CH(C\underline{H}_3)_2$), 1.3 (8H, m, $NCH_2C\underline{H}_2$), 1.9 (4H, m, $C\underline{H}(CH_3)_2$), 3.2 (8H, m, $NC\underline{H}_2CH_2$), 3.5 (12H, m, NCH_3), 3.8 (4H, m, CO-CH), 4.0 (4H, br s, Ar-$C\underline{H}_2$-Ar), 4.5 (16H, m, Ar-$C\underline{H}_2$-N), 7.1 (32H, m, Ar-H), 8.9 (4H, m, Py-H4), 9.3 (4H, m, Py-H2), and 9.5 (4H, m, Py-H6); IR (KBr) 2940 (CH) and 1640 (C=O) cm^{-1}; MS (SIMS) m/z 2104 (M^+). Found: C, 65.12; H, 6.29; N, 10.30%. Calcd for $C_{118}H_{128}N_{16}O_{12}\cdot 4H_2O$: C, 65.15; H, 5.94; N, 10.34%.

The guest-binding behavior of host **1** toward various hydrophobic molecules were examined by electronic absorption spectroscopy in an aqueous 2-[4-(2-hydroxyethyl)piperazinyl]-ethanesulfonate (HEPES) buffer [0.01 mol dm^{-3}, pH 7.0, μ 0.10 (KCl)] at 30.0 °C. The following dyes were adopted as guest molecules: 1-(2-pyridylazo)-2-naphthol (PAN), *N*,*N*-dimethyl-4-(phenylazo)aniline (Methyl Yellow), disodium 7-hydroxy-8-phenylazonaphthalene-1,3-disulfonate (Orange G), disodium 8-hydroxy-5,7-dinitronaphthalene-2-sulfonate (Naphthol Yellow S), 5,5'-

Nonionic guests

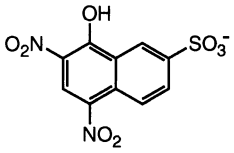


PAN

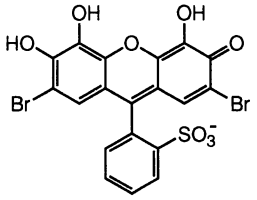


Methyl Yellow

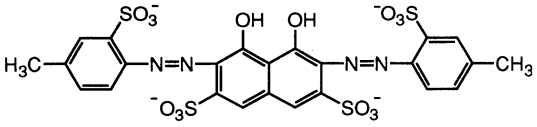
Anionic guests



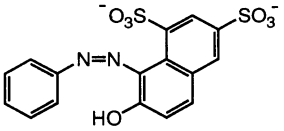
Naphthol Yellow S



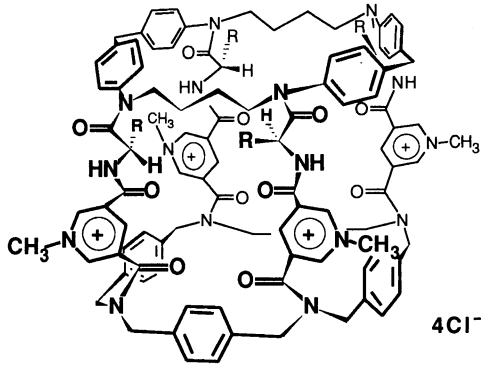
Bromopyrogallol Red



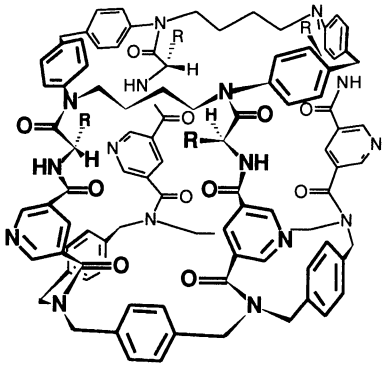
Dimethylsulfonazo III



Orange G



1: R = $CH(CH_3)_2$



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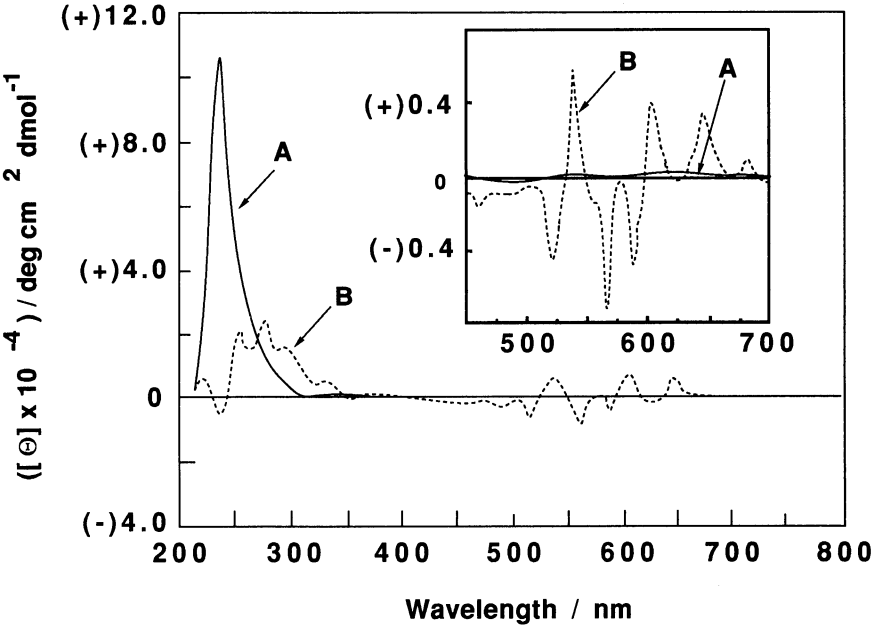

Fig. 1. CD spectra of host **1** (7.0×10^{-5} mol dm^{-3}) in aqueous HEPES buffer (0.01 mol dm^{-3}, pH 7.0, μ 0.10 with KCl) at 30.0 °C: A, without any guest; B, in the presence of Dimethylsulfonazo III (2.1×10^{-4} mol dm^{-3})

dibromopyrogallolsulfonephthalein (Bromopyrogallol Red), and disodium 2,7-bis[(4-methyl-2-sulfophenyl)azo]-1,8-dihydroxynaphthalene-3,6-disulfonate (Dimethylsulfonazo III). An absorption intensity originated from each of the guest molecules decreased along with a concomitant red shift of its absorption maximum upon addition of **1**. The Job's method[4] was applied to combinations of host **1** and hydrophobic guests, Naphthol Yellow S and Bromopyrogallol Red. The spectral measurements were carried out at 420 and 560 nm for the former and the latter guest, respectively, by maintaining the total concentration at 2.0×10^{-5} mol dm^{-3} in an aqueous HEPES buffer [0.01 mol dm^{-3}, pH 7.0, μ 0.10 (KCl)] at 30.0 °C. Host **1** was found to undergo complexation with the guest at a 1:1 molar ratio of host to guest. The binding constants for formation of 1:1 host–guest complexes were evaluated on the basis of Benesi-Hildebrand relationship in a manner as reported previously;[5,6] 1.0×10^6, 6.5×10^5, 3.7×10^5, 3.4×10^5, 2.5×10^5, and 1.2×10^5 mol^{-1} dm^3 for inclusion of PAN, Methyl Yellow, Naphthol Yellow S, Dimethylsulfonazo III, Bromopyrogallol Red, and Orange G, respectively.

We have previously examined chirality-based molecular discrimination performed by host **2** toward some amino acids.[6] In order to clarify such specific guest-binding behavior, we investigated in this work the asymmetric character of host **1**, as provided by its hydrophobic

Table 1. UV-vis absorption bands for various guests and induced CD bands upon complexation with **1** in aqueous HEPES buffer (0.01 mol dm^{-3}, pH 7.0, μ 0.10 with KCl) at 30.0 °C

Guest	λ_{max} / nm	[Θ] / deg cm^2 $dmol^{-1}$[a]
PAN	479	-1.4×10^4
Naphthol Yellow S	379	-2.6×10^3
	401	-5.5×10^2
	417	1.6×10^3
	428	-1.4×10^3
	440	1.8×10^3
	468	-1.2×10^3
Dimethylsulfonazo III	520	-4.4×10^3
	537	5.7×10^3
	567	-7.3×10^3
	587	-4.6×10^3
	600	3.9×10^3
	613	2.0×10^3
	647	3.2×10^3
	682	8.7×10^2
Orange G	458	-2.4×10^3
	499	-1.4×10^3

a) Molecular ellipticity at each absorption band of a guest molecule.

internal cavity, by means of a computer-aided molecular modeling study[7] and circular dichroism (CD) spectroscopy. The result reveals that the four pyridinium moieties bound to the chiral L-valine residues in the bridging components of **1** approach closely to each other and twisted in the same direction. Host **1** (7.0×10^{-5} mol dm^{-3}) shows a CD band at 242.0 nm with molecular ellipticity ([Θ], deg cm^2 $dmol^{-1}$) of 1.04×10^5 in an aqueous HEPES buffer [0.01 mol dm^{-3}, pH 7.0, μ 0.10 (KCl)] at 30.0 °C (Fig. 1A). Upon addition of Dimethylsulfonazo III (2.1×10^{-4} mol dm^{-3}), the CD band intensity originated from the host decreased along with appearance of induced CD bands in the absorption ranges of the guest (Fig. 2B). Similar CD spectral changes were observed with other hydrophobic guests, such as PAN, Naphthol Yellow S, and Orange G (Table 1). The decrease of CD band intensity at 242 nm is attributable to conformational changes around the pyridinium moieties of **1** upon complexation with the guest molecules to form thermodynamically stable complexes. Optimized conformations of the host–guest complexes in the gas phase were examined by molecular mechanics and dynamics calculations.[7] The pyridinium moieties are separated from each other as a guest molecule is incorporated into the internal cavity. As a consequence, the circular dichroism is induced on the incorporated guest molecule through its stereochemical interaction with the chiral host cavity.

In conclusion, the present cage-type host (**1**) furnishes a chiral hydrophobic cavity for inclusion of various guest molecules and is expected to be utilized as a multifunctional receptor model.

References

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