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Host–Guest Interactions of Cage-type Cyclophanes Bearing Chiral Binding Sites Provided by Dipeptide Residues

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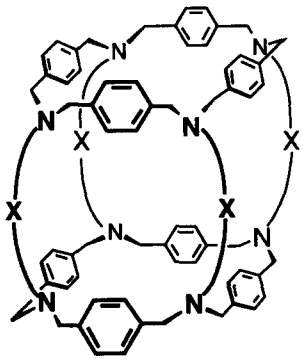
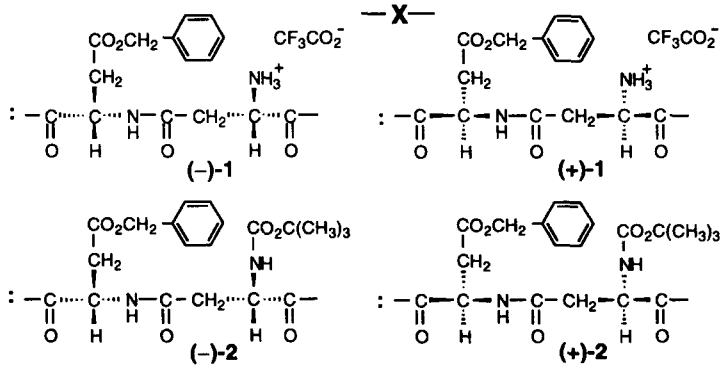
Abstract: Novel cage-type cyclophanes, which are constructed with two rigid macrocyclic skeletons, tetraaza[3.3.3.3]paracyclophanes, and four bridging segments composed of β-L-aspartyl-L-aspartyl residues and β-D-aspartyl-D-aspartyl residues individually, were prepared. Chiral host–guest interactions between the hosts and a hydrophobic guest, pamoic acid, were examined by circular dichroism spectroscopy in aqueous media.

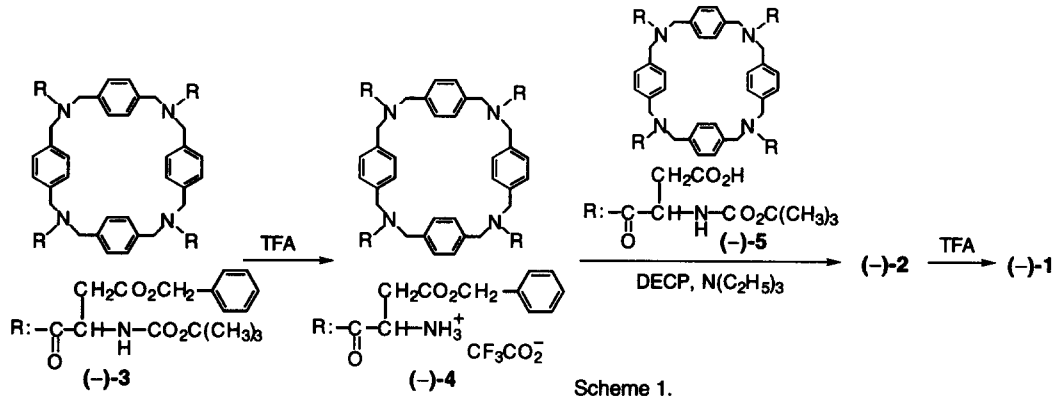
The development of artificial receptors capable of performing enantioselective or diastereoselective molecular recognition is very important to mimic specific molecular functions performed by naturally occurring receptors in aqueous media.[1] We have previously prepared various cage-type cyclophanes having leucine, valine, and alanine residues in their bridging segments and examined their chiral recognition behavior toward hydrophobic guests in aqueous media.[2] We now designed cage-type cyclophanes, which are constructed with two rigid macrocyclic skeletons, tetraaza[3.3.3.3]paracyclophanes, and four bridging segments composed of β-L-aspartyl-L-aspartyl residues and β-D-aspartyl-D-aspartyl residues individually [**(–)-1** and **(+)-1**, respectively]. In this communication, we report on the preparation, asymmetric character, and unique guest-recognition behavior of the cage-type hosts, with emphasis on chiral host–guest interactions between the cage-type hosts and a hydrophobic guest, pamoic acid (PA), in aqueous media.





A cage-type cyclophane bearing β-L-aspartyl-L-aspartyl residues, **(–)-1**, was synthesized by following a reaction sequence shown in Scheme 1. A peptide cyclophane bearing L-aspartic acid moieties **(–)-4** was

prepared from *N,N',N'',N'''*-tetrakis[(*tert*-butoxycarbonyl)-β-benzyl-L-asparty]-2,11,20,29-tetraaza[3.3.3.3]-paracyclophane, (−)-**3**,[3] by a reaction with trifluoroacetic acid (TFA). Cage-type cyclophane (−)-**2** was synthesized by condensation of (−)-**4** with *N,N',N'',N'''*-tetrakis[(*tert*-butoxycarbonyl)-L-asparty]-2,11,20,29-tetraaza[3.3.3.3]paracyclophane, (−)-**5**, in the presence of diethyl cyanophosphonate (DECP) under high dilution conditions at 0 °C. Cage-type cyclophane (−)-**1** with solubility in aqueous media was prepared by deprotection of the α-amino group of (−)-**2**. The use of *N,N',N'',N'''*-tetrakis[(*tert*-butoxy-carbonyl)-β-benzyl-D-asparty]-2,11,20,29-tetraaza[3.3.3.3]paracyclophane and *N,N',N'', N'''*-tetrakis[(*tert*-butoxycarbonyl)-D-asparty]-2,11,20,29-tetraaza[3.3.3.3]paracyclophane in place of (−)-**3** and (−)-**5**, respectively, resulted in formation of a cage-type cyclophane bearing β-D-aspartyl-D-aspartyl moieties, (+)-**1**. All the novel products were purified by gel-filtration chromatography and identified by ^{1}H NMR , ESI-MS, and IR spectroscopy as well as by elemental analyses.[4]



Scheme 1.

First, we evaluated asymmetric character of the present hosts by means of circular dichroism (CD) spectroscopy. Cage-type hosts (−)-**1** and (+)-**1** show CD bands opposite to each other in aqueous acetate buffer (0.01 mol dm^{-3}, pH 5.5, μ 0.1 with KCl) at 30 °C, reflecting the asymmetric character of their internal cavities: [θ] −2.0 x 10^5 and −1.3 x 10^5 deg cm^2 dmol^{-1} for (−)-**1** at their respective CD peak wavelengths of 209 and 225 nm, respectively; +1.8 x 10^5 and +1.4 x 10^5 deg cm^2 dmol^{-1} for (+)-**1** at their respective CD peak wavelengths of 207 and 225 nm, respectively (Fig. 1). On the other hand, peptide cyclophanes (−)-**4** and (+)-**4** show relatively weak CD bands as compared with those of the cage-type hosts: [θ] +2.8 x 10^4 and −8.1 x 10^4 deg cm^2 dmol^{-1} for (−)-**4** at their respective CD peak wavelengths of 203 and 227 nm, respectively; −3.0 x 10^4 and +8.0 x 10^4 deg cm^2 dmol^{-1} for (+)-**4** at their respective CD peak wavelengths of 203 and 227 nm, respectively. These results suggest that conformational flexibility of the cage framework of (−)-**1** and (+)-**1** is diminished relative to those of the non-cage hosts. Such conformationally restricted internal cavities provided by the cage-type hosts seem to be suitable for chiral recognition toward hydrophobic guests in aqueous media.

The guest-binding behavior of cage-type hosts (−)-**1** and (+)-**1** toward an anionic guest, PA, was examined by fluorescence spectroscopy in aqueous acetate buffer (0.01 mol dm^{-3}, pH 5.5, μ 0.1 with KCl) at 30 °C. Upon addition of the hosts to the acetate buffer containing PA (1.0 x 10^6 mol dm^{-3}), a fluorescence intensity originating from the guest increased along with a concomitant blue shift of the fluorescence maximum, reflecting formation of the corresponding host–guest complexes.[5] Stoichiometry for the complexes formed with the hosts and PA was investigated by the Job's continuous variation method.[6] The

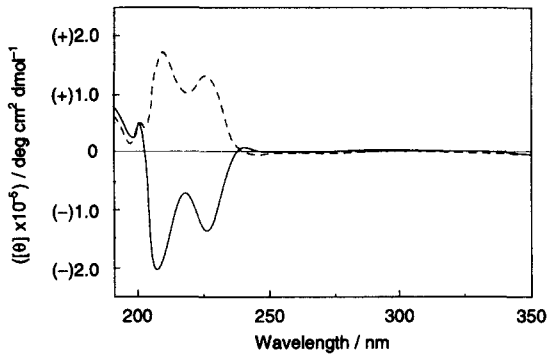
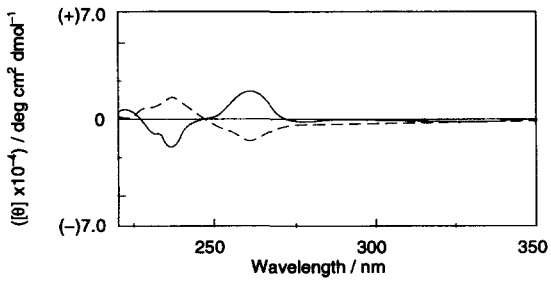
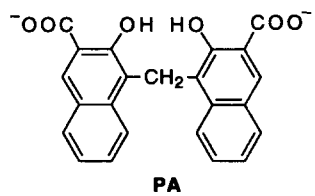


Fig. 1 CD spectra of (−)-**1** (1.0 x 10^{-5} mol dm^{-3}) and (+)-**1** (1.0 x 10^{-5} mol dm^{-3}) (solid and dashed lines, respectively) in aqueous acetate buffer (0.01 mol dm^{-3}, pH 5.5, μ 0.1 with KCl) at 30 °C

result revealed that the present hosts underwent complex formation with the guest in a 1:1 molar ratio of host to guest. Binding constants (*K*) of (−)-**1** and (+)-**1** toward PA were evaluated on the basis of Benesi-Hildebrand relationship for 1:1 host–guest interaction in a manner as described previously.[3] *K* values for (−)-**1** and (+)-**1** with PA were 7.2 x 10^5 and 7.1 x 10^5 dm^3 mol^{-1}, respectively. On the other hand, both peptide cyclophanes (−)-**4** and (+)-**4** showed no capacity of binding PA by means of fluorescence spectroscopy.

The formation of such inclusion complexes of the cage-type hosts with the guest was also detected by CD spectroscopy. Upon addition of PA to an aqueous acetate buffer (0.01 mol dm^{-3}, pH 5.5, μ 0.10 with KCl) containing (−)-**1**, bisignate CD bands originated from the incorporated guest appeared in a longer wavelength range ([θ], −1.9 x 10^4 and +1.9 x 10^4 deg cm^2 $dmol^{-1}$ at 237 and 261 nm, respectively) (Fig. 2). This result reveals that the PA molecule specifically assumes a *P*-helicity conformation upon complexation with (−)-**1** in a manner similar to that observed with other cage-type cyclophanes having three L-valine residues.[7] On the other hand, bisignate CD bands with inverted signs were observed for PA incorporated into (+)-**1**; [θ], +1.5 x 10^4 and −1.0 x 10^4 deg cm^2 $dmol^{-1}$ at 236 and 259 nm, respectively (Fig. 2), indicating that the PA molecule bound to (+)-**1** selectively assumes a *M*-helicity conformation. On the other hand, such induced CD bands were not observed upon addition of PA to (−)-**4** and (+)-**4** under the same conditions. As a consequence, the CD phenomena apparently come from the incorporated guest through its stereochemical interaction with the chiral host cavity.





PA

Fig. 2 CD spectra of PA (2.0 x 10^{-5} mol dm^{-3}) in the presence of (−)-**1** (1.0 x 10^{-5} mol dm^{-3}) and (+)-**1** (1.0 x 10^{-5} mol dm^{-3}) (solid and dashed lines, respectively) in aqueous acetate buffer (0.01 mol dm^{-3}, pH 5.5, μ 0.1 with KCl) at 30 °C

In conclusion, the present cage-type cyclophanes having dipeptide moieties are capable of providing chiral internal cavities that exhibit induced CD phenomena due to an incorporated guest molecule. Chirality-based molecular recognition of the cage-type hosts toward various chiral guest molecules in aqueous media is under investigation in our laboratories.

REFERENCES AND NOTE

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4. (–)-**4**: mp 123–125 °C; ^{1}H NMR [500MHz, $(CD_3)_2SO$, 373 K] δ = 2.9–3.0 [dd, J_{vic} 7.0 Hz and J_{gem} 17.0 Hz, 4H, CH_2CO_2 (nonequivalent); dd, J_{vic} 5.0 Hz and J_{gem} 17.0 Hz, 4H, CH_2CO_2 (non-equivalent)], 4.3–4.6 [m, 16H, CH_2Ar], 4.7 [m, 4H, NHC*H*CO], 5.1 [s, 8H, OCH_2Ar], 6.9 [m, 16H, NCH_2ArH], 7.3 [m, 20H, OCH_2ArH]; IR (KBr) 1660 (amide C=O) and 1730 (ester C=O) cm^{-1}; Found: C, 56.59; H, 4.73; N, 6.10%. Calcd for $C_{84}H_{84}F_{12}N_8O_{20}$•3/2$H_2O$: C, 56.66; H, 4.92; N, 6.29%. ESI-MS *m/z* 1297 (M – 2CF_3CO_2H – 2$CF_3CO_2^-$)$^{2+}$, 649 (M – 2CF_3CO_2H – 2$CF_3CO_2^-$)$^{3+}$; Calcd M for $C_{84}H_{84}F_{12}N_8O_{20}$, 1754. (–)-**2**: mp 281–284 °C (dec.); ^{1}H NMR [500MHz, $(CD_3)_2SO$, 373 K] δ = 1.3–1.4 [m, 36H, C(CH_3)$_3$], 2.5–3.1 [m, 16H, CHCH_2CO_2 and CHCH_2CON], 3.3–5.5 [m, 32H, ArCH_2N], 5.1–5.2 [m, 8H, ArCH_2O], 5.2 and 5.6 [m, 8H, C*H*CH_2CO_2 and C*H*NHCO_2], 6.3–6.9 [m, 32H, Ar*H*CH_2N], 7.2–7.4 [m, 20H, Ar*H*CH_2O]; IR (KBr) 1650 (amide C=O), 1720 (urethane C=O), and 1740 (ester C=O) cm^{-1}; Found: C, 65.44; H, 6.28; N, 8.55%. Calcd for $C_{144}H_{160}N_{16}O_{28}$•4$H_2O$: C, 65.64; H, 6.43; N, 8.51%. (–)-**1**: mp 237–240 °C (dec.); ^{1}H NMR [500MHz, $(CD_3)_2SO$, 373 K] δ = 2.5–3.2 [m, 16H, CHCH_2CO_2 and CHCH_2CON], 3.3–5.6 [m, 32H, ArCH_2N], 4.8 [m, 4H, C*H*CH_2CO_2], 5.2 [m, 8H, ArCH_2O], 4.8 and 5.6 [m, 8H, C*H*CH_2CO_2 and C*H*NH_3], 6.3–6.9 [m, 32H, Ar*H*CH_2N], 7.0–7.4 [m, 20H, Ar*H*CH_2O]; IR (KBr) 1650 (amide C=O) and 1740 (ester C=O) cm^{-1}; Found: C, 60.57; H, 5.41; N, 8.79%. Calcd for $C_{132}H_{132}F_{12}N_{16}O_{28}$: C, 60.55; H, 5.08; N, 8.56%. ESI-MS *m/z* 1082 (M – 2CF_3CO_2H – 2$CF_3CO_2^-$)$^{2+}$, 721 (M – CF_3CO_2H – 3$CF_3CO_2^-$)$^{3+}$; Calcd M for $C_{132}H_{132}F_{12}N_{16}O_{28}$, 2619.
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