# Novel Cage-type Azaparacyclophane bearing Chiral Binding Sites

**Yukito Murakami,* Teruhisa Ohno, Osamu Hayashida and Yoshio Hisaeda**

*Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan*

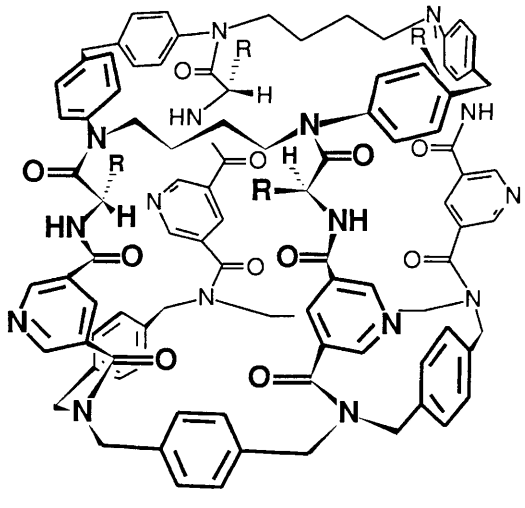
The guest-binding behaviour of a novel cage-type azaparacyclophane, which has been prepared by the reaction of *N,N',N'',N'''*-tetravalyl-1,6,20,25-tetraaza[6.1.6.1]paracyclophane with *N,N',N'',N'''*-tetrakis(5-carboxynicotinoyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane, was examined in aqueous media and evaluated by a computer-aided molecular modelling study on the basis of molecular mechanics (MM2 and MMP2) and molecular dynamics (AMBER and CHARMM) conformational search.

Molecular recognition behaviour of host molecules is very dependent on the hydrophobic character of the host cavity in aqueous media because other non-covalent host–guest interactions become effective in well-desolvated and hydrophobic microenvironments. We have investigated various cage-type cyclophanes that provide three-dimensional hydrophobic cavities and incorporate substrates of various shapes, sizes and hydrophobicity in aqueous media.[1] Recently, attention has been focused on chiral recognition of guest molecules by macrocyclic hosts.[2]

In this context, we now report the preparation and unique guest recognition ability of a novel cage-type cyclophane **1** bearing chiral binding sites and its inclusion ability toward hydrophobic guest molecules in aqueous media. The present host molecule is constructed with two rigid macrocyclic skeletons, tetraaza[6.1.6.1]paracyclophane[3] **2** as the large macrocyclic ring and tetraaza[3.3.3.3]paracyclophane[4] **4** as the smaller one, and four bridging components that connect the macrocycles. The bridging component is composed of a pyridine-3,5-dicarbonyl moiety and an L-valine residue.

The host **1** was synthesized by condensation of *N,N',N'',N'''*-tetravalyl-1,6,20,25-tetraaza[6.1.6.1]paracyclophane **3**† with *N,N',N'',N'''*-tetrakis(5-carboxynicotinoyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane **5**† in the presence of diethyl cyanophosphonate (DECP) under high dilution conditions in dry *N,N*-dimethylformamide at 0 °C by following the reaction sequence given in Scheme 1. The product was purified by gel-filtration chromatography on columns of Sephadex LH-20 and Toyopearl HW-40 Fine in this sequence with methanol–chloroform (1 : 1 v/v) as eluent. Evaporation of the solvent under reduced pressure gave a colourless solid [yield 26%; m.p. 306–308 °C (decomp.)], which was identified by mass spectroscopy and elemental analysis.†‡

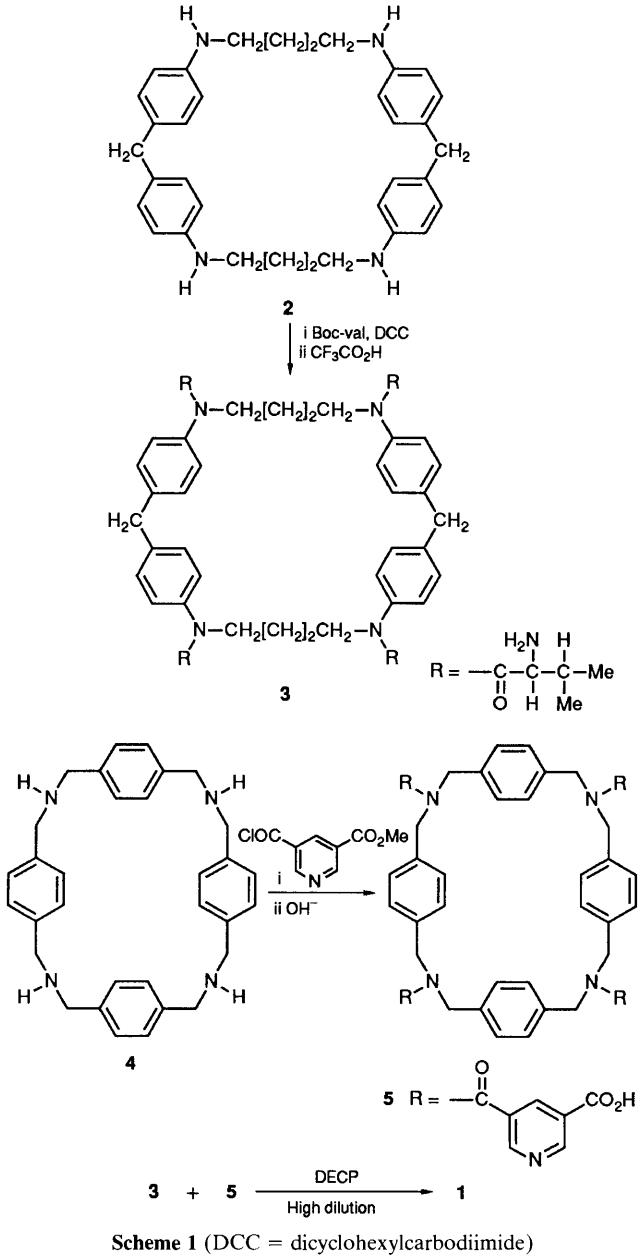
Low energy conformations of host **1** in the gas phase were examined on the basis of molecular mechanics (BIOGRAPH, MM2[5] and MMP2[6]) and molecular dynamics (BIOGRAPH, AMBER[7] and CHARMM[8]) calculations on an IRIS-4D/



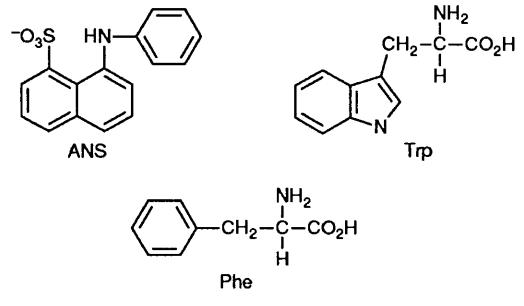
**1**; R = $CHMe_2$

† Satisfactory elemental analyses were obtained.

‡ *Mass spectroscopy data*; *m/z* (SIMS), 1903 ($M^+ + 1$), M 1902. (SIMS = secondary ion mass spectrometry.)




**Scheme 1** (DCC = dicyclohexylcarbodiimide)




220GTX workstation (Silicon Graphics). The result reveals that host **1** provides a globular hydrophobic cavity with a maximum inner diameter of *ca.* 10 Å. In addition, the four L-valine residues in the bridging components are twisted in the same direction so that the host molecule furnishes a chiral internal cavity. This is reflected in circular dichroism (CD) spectra; **1** shows a CD band at 251.6 nm with molecular ellipticity ([Θ], deg $cm^2$ $dmol^{-1}$) of $8.4 \times 10^4$ in methanol–chloroform (1 : 1 v/v) at 30 °C, while **3** and the tetra(methyl ester) form of **5** do not show any detectable CD bands in a relatively wide wavelength range. Thus, hydrophobic molecules, which can fit the three-dimensional cavity in their shapes and sizes, are eligible candidates as guests.

**Table 1** Formation constants ($K$), total molecular energies ($E$) and hydrogen-bonding energies ($E_{hb}$) for host–guest complexes of **1** with amino acids

| Guest | $K^a$/$dm^3$ $mol^{-1}$ | $E^b$/kJ $mol^{-1}$ | $E^b_{hb}$/kJ $mol^{-1}$ |
|---|---|---|---|
| L-Phe | $8.0 \times 10^2$ | 1701.46 | −51.79 |
| D-Phe | —[c] | 1752.53 | −25.76 |
| L-Trp | —[c] | 1732.09 | −57.46 |
| D-Trp | $7.0 \times 10^2$ | 1663.18 | −80.32 |

[a] Measured in aqueous acetate buffer [0.01 mol $dm^{-3}$, pH 4.1, μ 0.10 (KCl)] at 30 °C with concentrations: ANS, $7.5 \times 10^{-7}$ mol $dm^{-3}$; **1**, $7.5 \times 10^{-6}$–$3.7 \times 10^{-5}$ mol $dm^{-3}$; amino acids, $5.0 \times 10^{-4}$ mol $dm^{-3}$. [b] Refer to eqn. (1)§ for computational basis. [c] The formation constant is too weak to be evaluated by the competition method.

The inclusion interaction of host **1** with a hydrophobic guest molecule in aqueous media was investigated by NMR spectroscopy. $^1$H NMR 500 MHz signals of 8-anilinonaphthalene-1-sulphonate (ANS; 0.3 mmol $dm^{-3}$) in $D_2O$–[$^2H_6$]DMSO (7 : 3 v/v) showed significant up-field shifts upon addition of an equimolar amount of **1**. A 41% fraction of the total amount of ANS undergoes complexation with **1** on the basis of the binding constant ($K$) evaluated under the identical medium conditions; $K = 4.3 \times 10^3$ $dm^3$ $mol^{-1}$. The complexation-induced shifts (CIS),[9] the shifts of NMR signals for the guest upon 100% complexation, are −0.16, −0.10, −0.081, −0.073, −0.066, −0.046, −0.029, −0.029 and −0.027 ppm for H-5, H-4, H-3, H-6, H-7, H-4′, H-3′, H-2′ and H-2, respectively. Therefore, the ANS molecule is definitely incorporated into the three-dimensional host cavity provided intramolecularly by the macrocyclic rings and the bridging components.

The guest-binding behaviour of host **1** toward a hydrophobic molecule was examined by fluorescence spectroscopy in an aqueous acetate buffer [0.01 mol $dm^{-3}$, pH 4.1, μ 0.10 (KCl)] at 30 °C. The fluorescence intensity originated from an anionic guest, ANS, increased along with a concomitant blue shift of the fluorescence maximum upon addition of **1**. The binding constant for inclusion of ANS at a 1 : 1 molar ratio of host to guest was evaluated on the basis of the Benesi–Hildebrand relationship in a manner as reported previously;[10,11] $K = 2.8 \times 10^4$ $dm^3$ $mol^{-1}$. The microenvironmental polarity parameter, $E_T^N$,[12] was also evaluated from the maximum emission wavelength due to the fluorescent probe in a manner as reported previously;[11] 0.23 for ANS and comparable to the value of ethyl acetate (0.228). Moreover, the tight association between **1** and the guest molecule resulted in the marked motional repression of the entrapped guest as reflected in the fluorescence polarization parameter ($P$);[11] 0.40 for ANS while those values in methanol and ethyl acetate are 0.006 and 0.025 for ANS, respectively.

We investigated chirality-based molecular discrimination toward the following guest molecules because the host furnishes a chiral cavity as mentioned above; L-phenylalanine (L-Phe), D-phenylalanine (D-Phe), L-tryptophan (L-Trp) and D-tryptophan (D-Trp). For these non-fluorescent guests, $K$ values were evaluated on the basis of their binding behaviour

§ The total molecular energy ($E$) is expressed as an energy sum of bonded and nonbonded interactions, and an enantiomer complex with a lower energy value is regarded to be more stable relative to the other; [see eqn. (1)].

$$E = E_b + E_\theta + E_\varphi + E_i + E_{vdw} + E_{el} + E_{hb} \quad (1)$$

The bonded interactions consist of bond stretching ($E_b$), bond angle bending ($E_\theta$), dihedral angle torsion ($E_\varphi$) and inversion ($E_i$) terms, while the non-bonded interactions are composed of van der Waals ($E_{vdw}$), electrostatic ($E_{el}$) and hydrogen bond ($E_{hb}$) terms.

in competition with ANS after the method of Diederich and Dick,[13] as summarized in Table 1. Optimized conformations of the host–guest complexes in the gas phase were examined by molecular mechanics and dynamics calculations§ on an IRIS-4D/220GTX workstation. It became apparent that the indole moiety of tryptophan is located in the vicinity of the tetraaza[6.1.6.1]paracyclophane skeleton while the benzene moiety of phenylalanine is placed in the neighbourhood of the tetraaza[3.3.3.3]paracyclophane ring. The hydrogen-bonding interaction between the guest and the chiral valine residues of host **1** seems to be quite efficient for L-Phe and D-Trp relative to their enantiomers (see Table 1), and this effect must cause apparent differences in inclusion behaviour.

In conclusion, the present cage-type cyclophane furnishes a hydrophobic internal cavity for inclusion of guest molecules and exercises marked chiral discrimination toward selected amino acids in aqueous media. In addition, the molecular motion of entrapped guest molecules are remarkably repressed.

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