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Cubic Azaparacyclophane†

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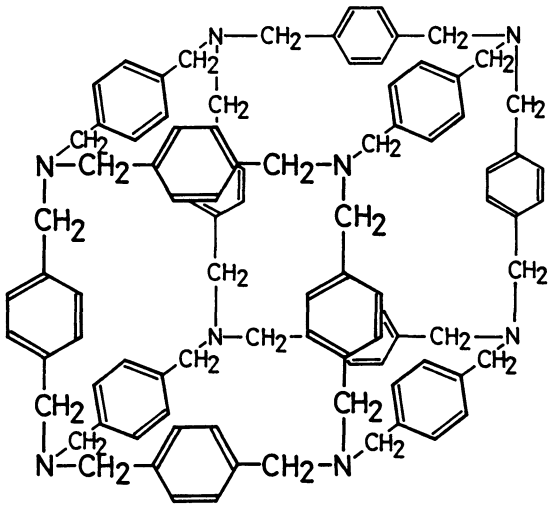
A cubic macrocycle, each face being constructed with the 2,-11,20,29-tetraaza[3.3.3.3]paracyclophane ring, was prepared as a novel host molecule which provides a relatively rigid and hydrophobic three-dimensional cavity, and its guest-binding behavior was examined in acidic aqueous media.

Cyclophanes with a sizable internal cavity behave as artificial host molecules capable of exhibiting molecular discrimination.[1,2] In view of the current interest in host-guest interactions in aqueous media, we have prepared various water-soluble cyclophane derivatives.[2] Recently, we developed octopus[3] and capped[4] azaparacyclophanes, each of which provides a sterically adjustable three-dimensional space for incorporation of guest molecules of various bulkiness. These host molecules strongly bind hydrophobic guests through the induced-fit mechanism, and the microenvironments around the incorporated guest molecules are highly apolar and viscous. We now designed a cubic cyclophane (**1**) which provides a relatively rigid and large hydrophobic cavity surrounded by six faces, each being constructed with the 2,11,20,29-tetraaza[3.3.3.3]paracyclophane ring. In this communication, we report the synthesis of **1** and its guest-binding behavior in aqueous media.



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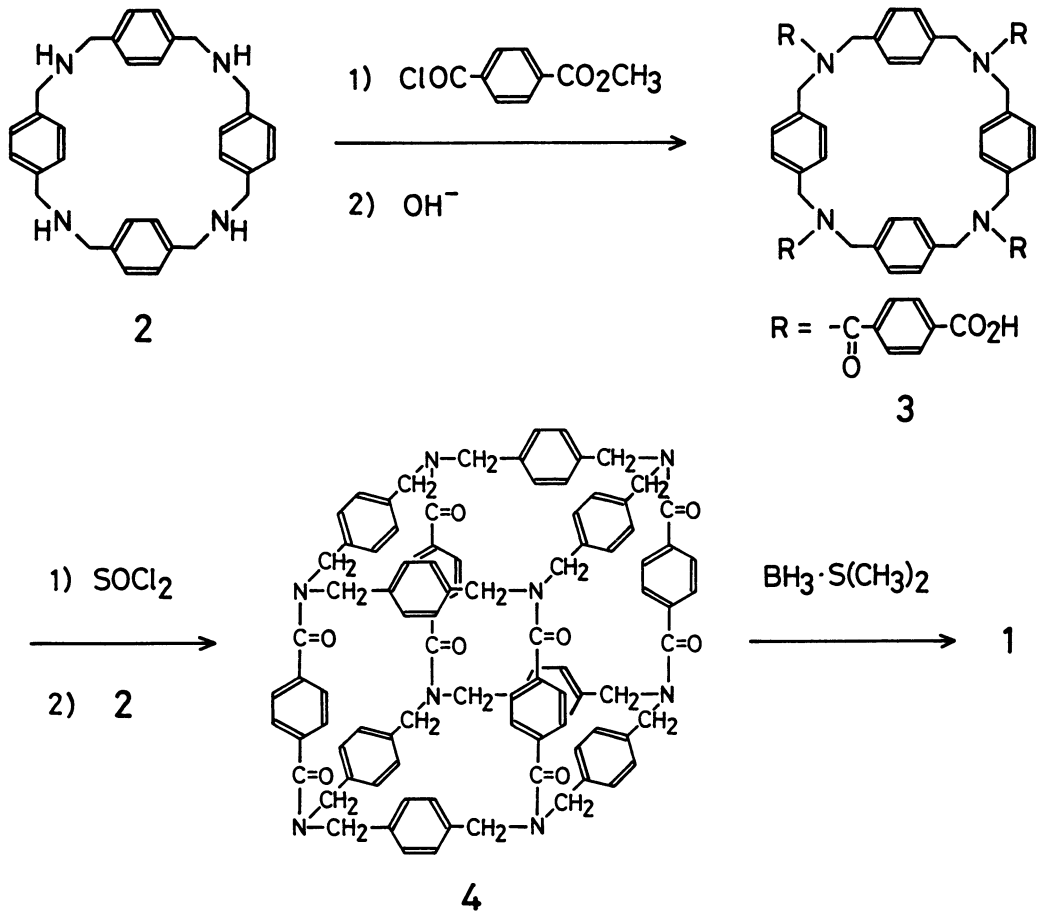
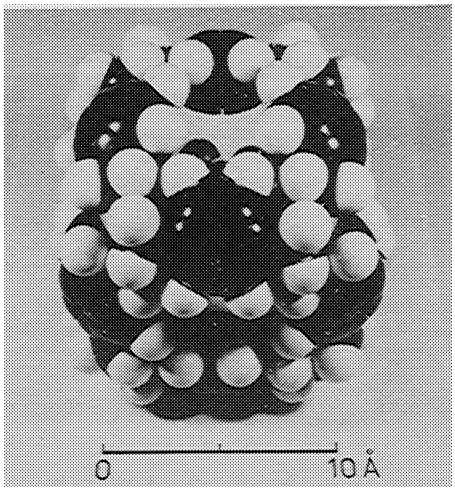
† Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



Scheme 1.

The host (**1**) was prepared according to the reaction steps given in Scheme 1. 2,11,20,29-Tetraaza[3.3.3.3]paracyclophane (**2**) was chosen as the basic macrocyclic skeleton. This compound was obtained by the coupling reaction of 1,4-bis(chloromethyl)benzene with p-toluenesulfonamide in N,N-dimethylformamide in the presence of sodium hydride, followed by removal of the tosyl groups of N,N',N'',N'''-tetratosyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane with sodium/liquid ammonia, in a manner similar to that reported by Inazu et al.[5] Condensation of **2** with methyl 4-chloroformylbenzoate in dry dichloromethane and the subsequent alkaline hydrolysis gave N,N',N'',N'''-tetrakis(4-carboxybenzoyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (**3**); yield, 66%.[6] This product was converted into the corresponding acid chloride and then reacted with **2** in dry dichloromethane—benzene (150:7 v/v) under high dilution conditions to give the 1:1 adduct (**4**), which was purified by gel filtration chromatography on a column of Sephadex LH-20 with chloroform—methanol (1:1 v/v) as an eluant; yield, 43%.[7] Reduction of **4** by borane—dimethyl sulfide[8] in dry dichloromethane and the subsequent acid hydrolysis afforded **1** as the octahydrochloride salt, which was purified by gel filtration chromatography on a column of Sephadex LH-20 with methanol—water (1:1 v/v) as an eluant; yield, 39%.[9]

In the light of the CPK molecular model, **1** provides a relatively large and globular hydrophobic cavity with the maximum inner diameter of ca. 9 Å (Fig. 1),



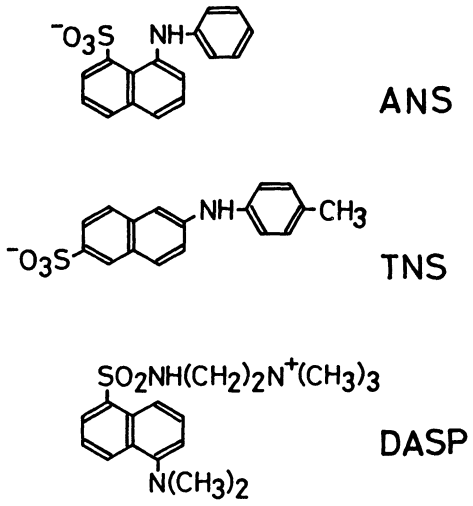


Fig. 1. CPK molecular model of **1**.

and only guest molecules capable of passing through the 2,11,20,29-tetraaza[3.3.3.-3]paracyclophane ring (hole size, 5.5—7 Å[10]) can be incorporated into the inner cavity of the present host molecule. The guest-binding behavior of **1** was examined by fluorescence spectroscopy in an aqueous acetate buffer [0.01 mol dm^{-3}, pH 3.0, μ 0.10 (KCl)] at 30.0 °C. The fluorescence intensities originated from anionic guest molecules increased upon addition of **1**, and the binding constants evaluated on the basis of the Benesi-Hildebrand equation in a manner similar to that reported previously[11] were found to be relatively large; 3.0 x 10^4 and 1.0 x 10^4 dm^3 mol^{-1} for 6-p-toluidinylnaphthalene-2-sulfonate (TNS) and 8-anilinonaphthalene-1-sulfonate (ANS), respectively. The fluorescence maximum observed for ANS in water (λ_{max} 515 nm) was significantly shifted to a lower wavelength region upon complex formation with **1** (λ_{max} 480 nm). Thus, the microscopic polarity of the guest-binding site provided by **1** is nearly equivalent to that of methanol [λ_{max} 482 nm; $E_T(30)$[12] 55.5 kcal mol^{-1}]. On the other hand, N,N,N',N',N",N",N''',N'''-octamethyl-2,11,-20,29-tetraazonia[3.3.3.3]paracyclophane tetrafluoroborate (**5**), a cyclophane analog with a single ring, provides a polar microenvironment, more or less, for ANS (λ_{max} 510 nm).[10] The microscopic polarity around the TNS molecule incorporated into **1** was found to be comparable [λ_{max} 450 nm; $E_T(30)$ 56.5 kcal mol^{-1}] to that for ANS. Moreover, tight molecular associations between **1** and the present guest molecules resulted in marked repression of the molecular motion of the incorporated guests as reflected on the fluorescence polarization parameters (P);[3,4] 0.15 for both ANS and TNS, whereas the P values in methanol are 0.006 and 0.008 for ANS and TNS, respectively. The result strongly indicates that **1** incorporates these anionic guests into its hydrophobic interior cavity. On the other hand, **1** exhibited no capacity of binding the cationic 1-dimethylaminonaphthalene-5-sulfonamidoethyltrimethylammonium species (DASP).

In conclusion, it became apparent that the cubic azaparacyclophane (**1**) provides a relatively hydrophobic binding site for anionic guest molecules in acidic aqueous media, where the amino nitrogens are protonated, and the molecular motion of incorporated guest molecules are markedly repressed. Although desolvation of

the guest molecules in the hydrophobic cavity of **1** is less efficient than that in the cavities of octopus and capped azacyclophanes[3,4] because **1** bears poor allowance for molecular flexibility, the present cubic cyclophane is expected to discriminate guest molecules through the biomimetic lock-and-key mechanism. Further studies are currently in progress along this line.

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6) Found: C, 69.53; H, 4.99; N, 4.98%. Calcd for $C_{64}H_{52}N_4O_{12}\cdot 2H_2O$: C, 69.56; H, 5.11; N, 5.07%.

7) Found: C, 74.74; H, 5.57; N, 7.14%. Calcd for $C_{96}H_{80}N_8O_8\cdot 4H_2O$: C, 74.59; H, 5.73; N, 7.24%.

8) H. C. Brown, Y. M. Choi, and S. Narasimhan, J. Org. Chem., 47, 3153 (1982).

9) Found: C, 61.02; H, 6.53; N, 6.15%. Calcd for $C_{96}H_{96}N_8\cdot 8HCl\cdot 13H_2O$: C, 61.08; H, 6.94; N, 5.94%. A molecular weight determined for the free base form by osmometry in chloroform is consistent with formation of an inclusion complex of **1** with two solvent molecules (found, 1620; calcd for $\mathbf{1}\cdot 2CHCl_3$, 1601), and such inclusion behavior was evidenced by IR spectroscopy.

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12) A polarity scale established by Dimroth and Reichardt: C. Reichardt, "Solvent Effects in Organic Chemistry," Verlag Chemie, Weinheim (1979), pp. 270—272; 1 kcal = 4.184 kJ.

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