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Molecular Discrimination by Water-soluble Cubic Azaparacyclophane

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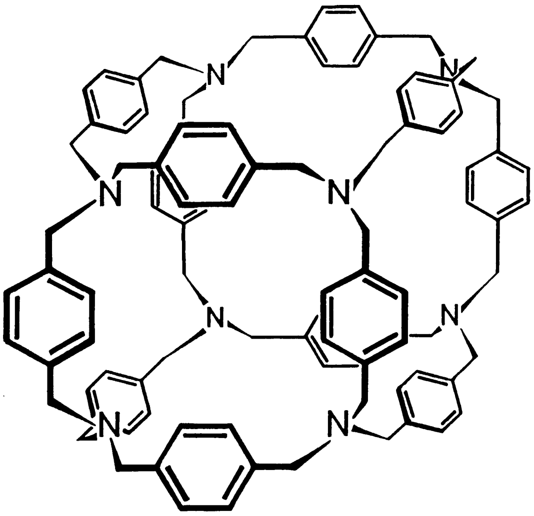
A cubic cyclophane surrounded by six faces, each being constructed with the [3.3.3.3]azaparacyclophane ring, behaved as a polycationic host in acidic aqueous media and exhibited size-sensitive and regioselective molecular discrimination that originates from rigid geometry of its hydrophobic cavity.

Molecular recognition by cyclophanes having a sizable hydrophobic cavity is currently attracting much attention in the field of host-guest chemistry.1) Although moderate guest discrimination has been exercised by various cyclophanes composed of a single macrocyclic skeleton, more specific molecular recognition can be achieved by modified cyclophane hosts capable of providing a three-dimensionally extended internal cavity. Recently, we have prepared a cubic azaparacyclophane (**1**) composed of six faces, each being constructed with the 2,11,20,29-tetraaza[3.3.3.3]paracyclophane ring, as a novel host which provides a relatively rigid and hydrophobic three-dimensional cavity.2) In this communication, we report on marked guest-discrimination ability of **1** in acidic aqueous media as exercised through an ingenious lock-and-key mechanism.

Rigidity of the molecular framework of the cubic azaparacyclophane is reflected on its broad ^1H NMR (400 MHz) signals. In $DCON(CD_3)_2$ at 25 °C, both phenyl and methylene proton signals appeared as broad singlets at δ=7.28 and 3.40 ppm with half bandwidths ($\Delta\nu_{1/2}$) of 160 and 176 Hz, respectively. These signals were little changed in their broadness even at high temperatures; $\Delta\nu_{1/2}$ values are 144 and 128 Hz for the phenyl and methylene signals at 125 °C, respectively. Since such signal-broadening was not observed for the corresponding single macrocycle, N,N',N'',N'''-tetramethyl-2,11,20,29-tetraaza-



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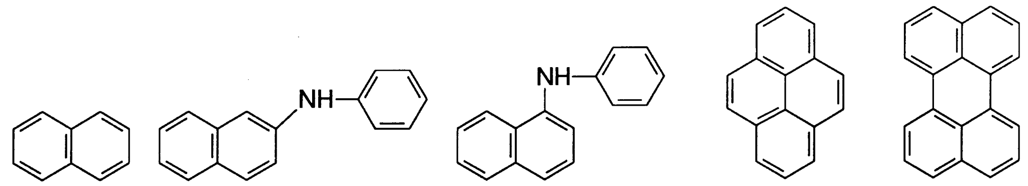
[3.3.3.3]paracyclophane,$^{3)}$ the conformational motion of **1** is highly restricted in solution due to the cubic framework. Broad ^{1}H NMR signals were also observed for **1** in cationic molecular forms in aqueous media. In a pD region below 2.5 in D_2O, broad singlet signals were observed at δ=7.47 and 4.39 ppm for the phenyl and methylene protons, respectively, indicating that all the amino nitrogens are completely protonated. On the other hand, proton signals of the methylene moieties were separated at pD 4.0 into two broad singlets with identical peak areas at δ= 3.53 and 4.39 ppm. This means that the cubic cyclophane mainly exists as a tetracationic species with four tertiary amino moieties protonated in a tetrahedral arrangement, and that the intramolecular proton migration is extremely sluggish under such conditions. On these grounds, we examined guest recognition ability of **1** in an aqueous acetate buffer (0.01 mol dm^{-3}, μ 0.10 with KCl) at 30.0 °C by fluorescence spectroscopy with primary emphasis on substrate selectivity.$^{4)}$

First, we investigated size-selective molecular discrimination by the tetracationic host formed at pH 4.0 toward the following nonionic fluorescent guests of various bulkiness; naphthalene, N-phenyl-2-naphthylamine (β-PNA), N-phenyl-1-naphthylamine (α-PNA), pyrene, and perylene. The fluorescence intensity of each guest molecule increased significantly upon addition of **1**, indicating the host-guest complexation. Incorporation of guest molecules into the hydrophobic interior cavity provided by **1** was reflected on the microscopic polarity experienced by the guests, as evaluated from the maximum emission wavelengths (λ_{max}) for the guests bound to the host: e.g., $E_T(30)^{5)}$ 34 kcal mol^{-1}, λ_{max} 406 nm for α-PNA; $E_T(30)$ 41 kcal mol^{-1}, λ_{max} 400 nm for β-PNA. In order to avoid possible formation of excimers and to assure formation of the host-guest complexes at 1:1 molar ratio, excess amounts of **1** were used over amounts of the guests for determination of the binding constants. Then, the binding constants (K) were evaluated on the basis of the Benesi-Hildebrand relationship$^{6)}$ for the 1:1 host-guest interaction, and good linear correlations with respect to double-reciprocal plots of the extent of fluorescence intensity change upon addition of the host against the total concentration of the host$^{7)}$ were obtained with the above five guest compounds. In the light of the binding constants given in Chart 1, α-PNA fits the host cavity most tightly among the guest molecules examined here, even though pyrene and perylene are more hydrophobic than α-PNA. The CPK molecular model study gives us apparent evidence for such size-selective molecular discrimination. The host-guest interaction of the octacationic host formed at pH 2.5 with the above nonionic guests was extremely weak, and the complex formation was not detected by fluorescence spectroscopy.

Second, we employed naphthalenesulfonate derivatives as anionic guests for the



K / dm^3 mol^{-1} 3000 69000 88000 5600 710

Chart 1.

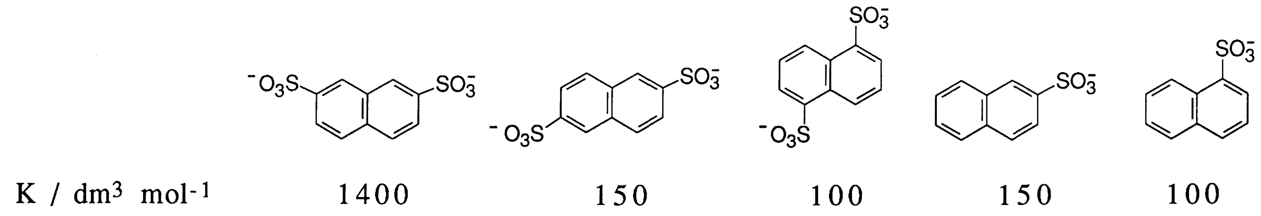


Chart 2.

tetracationic host in order to verify its selective molecular recognition toward isomeric guests through the electrostatic host-guest interaction. The K value for the fluorescent 8-anilinonaphthalene-1-sulfonate (ANS) at pH 4.0 was found to be 1.6×10^5 dm^3 mol^{-1}, twice as large as that for the nonionic analog, α-PNA. Thus, the cubic cyclophane is capable of discriminating guests through both hydrophobic and electrostatic interactions. For non-fluorescent naphthalenesulfonates, we evaluated the K values on the basis of their binding behavior in competition with α-PNA after the method reported by Diederich and Dick.8) As shown in Chart 2, an ANS analog lacking the hydrophobic anilino moiety, naphthalene-1-sulfonate, and its isomer, naphthalene-2-sulfonate, are incorporated into **1** with binding constants less than that for ANS. Although two isomeric naphthalenedisulfonates, naphtha-

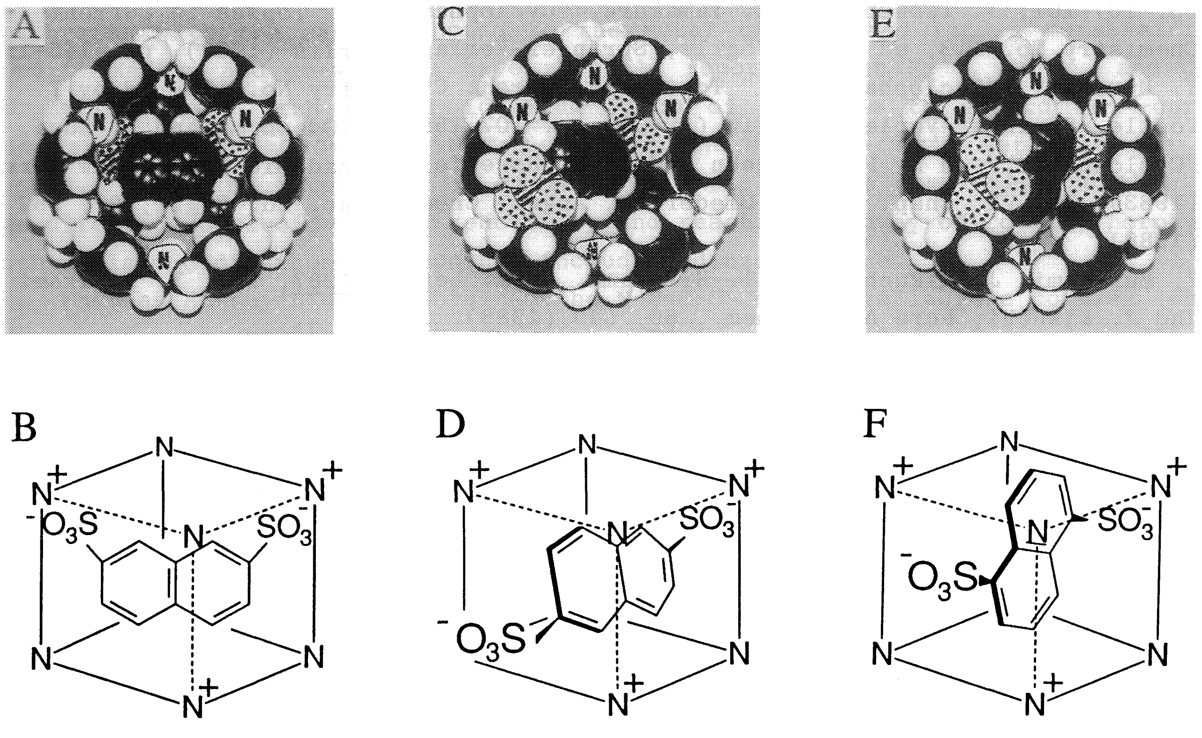


Fig. 1. CPK molecular models for host-guest complexes of the tetracationic host with 2,7-, 2,6-, and 1,5-isomers of naphthalenedisulfonate (A, C, and E) and their schematic representations (B, D, and F for A, C, and E, respectively). Three edges of the cubic molecular framework, schematically shown by dotted lines, are removed for construction of the molecular models, A, C, and E.

lene-1,5-disulfonate and naphthalene-2,6-disulfonate, are recognized by the host to extents comparable to those for the monosulfonates, the K value for naphthalene-2,7-disulfonate is increased by one order of magnitude relative to its isomers. Such marked selectivity in the host-guest complexation of the tetracationic host with the dianionic guests must originate from the specific geometrical arrangement of four positive charges of the host; plausibly tetrahedrally arranged to minimize the electrostatic potential energy. Under such geometrical conditions, the 2,7-isomer fits most favorably in the hydrophobic internal cavity provided by the host molecule so that the mutual electrostatic interaction is most enhanced, as shown in Figs. 1A and 1B. On the other hand, such an efficient electrostatic interaction is not allowed for the 1,5- and 2,6-isomers due to steric reasons in the light of investigation of their CPK molecular models (refer to C—F in Fig. 1).

In conclusion, it became apparent that the cationic cubic azaparacyclophane exercises marked molecular discrimination in aqueous media. The size-sensitive and regioselective host-guest interactions originate from rigid geometry of the hydrophobic cavity of host **1**.

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4) We also investigated the host-guest interaction of **1** with various hydrophobic guests by means of ^{1}H NMR spectroscopy. It is of interest to note that proton signals for a guest molecule, which is capable of forming a host-guest complex with **1**, completely disappeared in the presence of the cubic host. Therefore, the host-guest interaction was not evaluated quantitatively by ^{1}H NMR spectroscopy.
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