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pH-Dependent Molecular Recognition Performed by a Polycationic Cubic Azaparacyclophane

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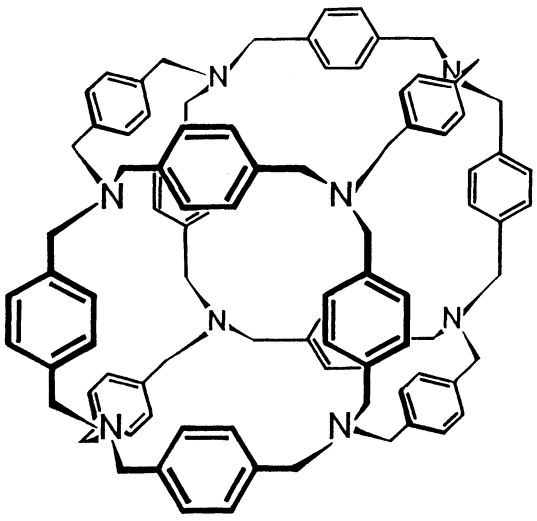
A cubic cyclophane surrounded by six faces, each being constructed with the [3.3.3.3]azaparacyclophane ring, behaved as a polycationic host in acidic aqueous media and exhibited pH-dependent binding behavior toward an anionic guest, ANS, since microenvironmental properties of the host cavity are varied by the extent of protonation at the nitrogen atoms.

Development of artificial hosts capable of providing a three-dimensionally extended and highly functionalized hydrophobic space in aqueous media is of great importance in the field of host-guest chemistry.[1] Recently, we have prepared so-called 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] This host molecule incorporates various hydrophobic guests in acidic aqueous media and exhibits size-sensitive and regioselective molecular recognition that originates from an ingenious lock-and-key mechanism.[3] In this communication, we describe pH-dependent microenvironmental properties of the guest recognition site provided by the cubic cyclophane, as experienced by an anionic guest, and their effects on the guest-binding behavior.



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Cyclophane **1** is soluble in acidic aqueous media below pH 4 and behaves as a polycationic host. While all the amino nitrogens of **1** are protonated in a pH region below 2.5, **1** mainly exists as a tetracationic species at pH 4.0 with four tertiary amino moieties protonated in a tetrahedral arrangement, as confirmed by ^{1}H NMR spectroscopy.[3] Now, we examined pH-dependent microenvironmental properties of the

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internal cavity of **1** as experienced by an anionic and hydrophobic fluorescent probe, 8-anilinonaphthalene-1-sulfonate (ANS). Figure 1 shows fluorescence spectra of ANS incorporated into **1** under various pH conditions. Fluorescence originating from ANS in a bulk aqueous phase is extremely weak and neglected under the present conditions. The fluorescence intensity increased along with concomitant blue shift of the fluorescence maximum as medium pH was raised. This spectral behavior indicates that hydrophobicity of the internal cavity of **1** is enhanced as an extent of deprotonation at the nitrogen atoms increases. Four stepwise proton dissociation equilibria for the host-guest complex composed of **1** and ANS were detected in a pH range of 2.5—4.0 by fluorescence spectroscopic titration (Fig. 2): pK_1, 2.85; pK_2, 3.15; pK_3, 3.5; pK_4, 3.8. The binding constants (K) were evaluated on the basis of the Benesi-Hildebrand relationship[4] 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[5] were obtained at respective pH's. The pH-dependent variation of the K value is shown in Fig. 3 together with that of the polarity parameter, $E_T(30)$,[6] which was evaluated from the maximum emission wavelength for ANS bound to the host in a manner similar to that reported previously.[5] The K value changes drastically in a narrow pH region of 2.5—4.0, showing a maximum value at pH 3.7, whereas the microscopic polarity experienced by the ANS molecule incorporated into the host cavity decreases monotonously as an extent of deprotonation of the host increases.

The fluorescence polarization parameter (P) for ANS incorporated into **1** is relatively large in comparison with those in homogeneous solutions[5] and depends on medium pH; 0.15, 0.15, 0.19, 0.25, and 0.24 at pH 2.6, 3.0, 3.3, 3.7, and 4.0, respectively, under conditions identical with those given in Fig. 2. The P value is subjected to change by the fluorescence lifetime (τ) and the rotational correlation time (θ) of a probe, according to the following relationship.[7]

$$(1/P - 1/3) = (1/P_0 - 1/3)(1 + \tau/\theta) \qquad (1)$$

In this equation, P_0 refers to the maximal value of P for a probe without any rotational motion and 0.43 is assigned to ANS.[8] In order to evaluate the microscopic viscosity, which is reflected in the θ value, we measured the τ values at various pH's and then obtained the θ values on the basis of Eq. 1, as shown in Fig. 4. Although the τ value increases as an extent of deprotonation of the host increases, the θ value shows a maximum at pH 3.7, identical with that giving the maximum binding constant.

Thus, the cubic cyclophane recognizes ANS through both hydrophobic and electrostatic interactions. The CPK molecular model for **1** clearly demonstrates that all the lone-pair orbitals of the amino nitrogens are directed toward the interior cavity rather than stick out from the molecular skeleton. This state of orbital orientation provides reasonable explanation for weakened hydrophobicity at lower pH's and marked enhancement of the hydrophobicity at higher pH's. It may be suggested that the pentacationic host, in which five tertiary amino moieties of **1** are protonated, exhibits the highest binding ability toward ANS among the polycationic host species formed under various pH conditions. The molecular motion of the in-

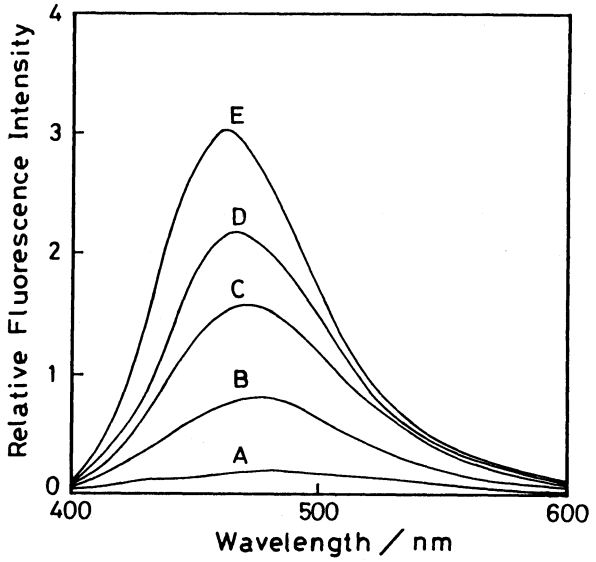

Fig. 1. Fluorescence spectra of ANS (1.0×10^{-6} mol dm^{-3}) upon addition of **1** (1.0×10^{-5} mol dm^{-3}) in aqueous acetate buffer (0.01 mol dm^{-3}, μ 0.10 with KCl) at 30.0 °C under various pH conditions: A, 2.6; B, 2.9; C, 3.2; D, 3.4; E, 4.0. Excitation wavelength, 375 nm.

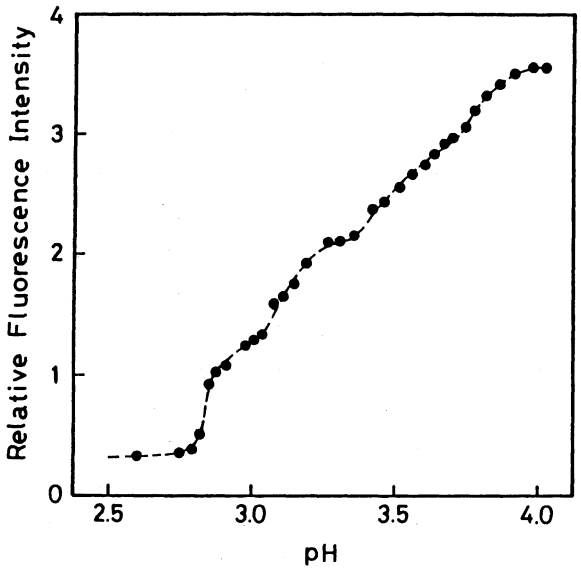

Fig. 2. Correlation of fluorescence intensity of ANS (1.0×10^{-6} mol dm^{-3}) with pH upon addition of **1** (1.0×10^{-5} mol dm^{-3}) in aqueous acetate buffer (0.01 mol dm^{-3}, μ 0.10 with KCl) at 30.0 °C. Excitation and emission wavelengths are 375 and 462 nm, respectively.

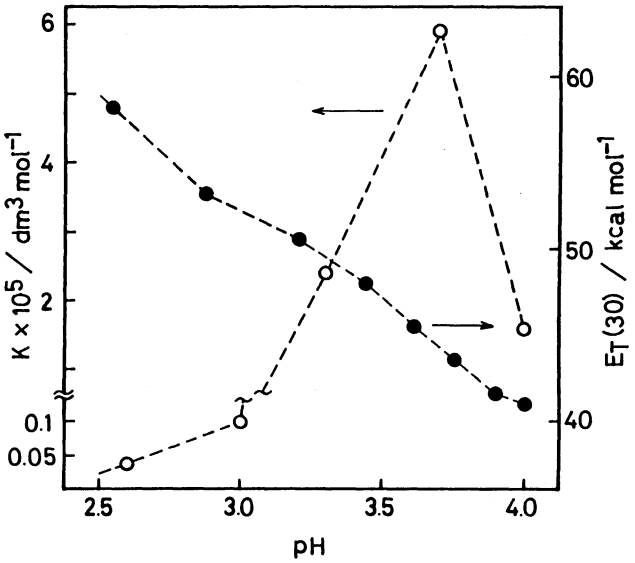

Fig. 3. pH-Dependent variations of binding constant (K) for the complex of **1** with ANS and microenvironmental polarity experienced by ANS [$E_T(30)$] in the internal cavity of **1**, in aqueous acetate buffer (0.01 mol dm^{-3}, μ 0.01 with KCl) at 30.0 °C.

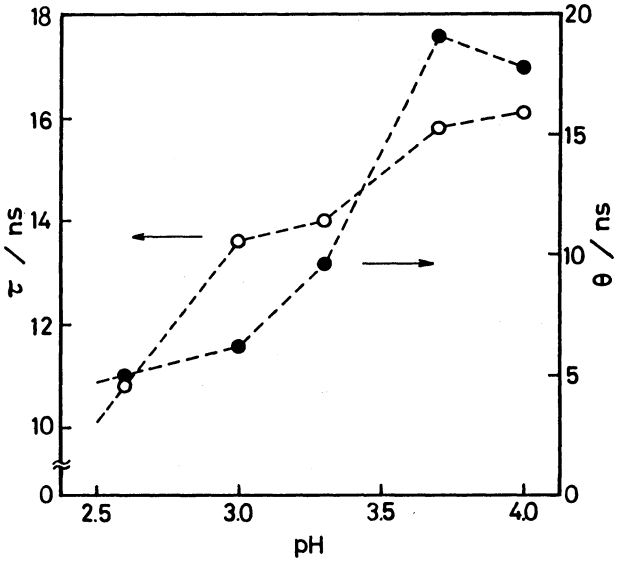

Fig. 4. pH-Dependent variations of fluorescence lifetime (τ) and rotational correlation time (θ) for ANS (1.0×10^{-6} mol dm^{-3}) upon addition of **1** (1.0×10^{-5} mol dm^{-3}) in aqueous acetate buffer (0.01 mol dm^{-3}, μ 0.10 with KCl) at 30.0 °C.

corporated guest seems to be most efficiently restricted by using the pentacationic host. A desolvation effect exercised by the host cavity must enhance the cooperative hydrophobic and electrostatic interactions between the host and the guest.

It needs to be noted that the fluorescence lifetime of the guest incorporated into **1** is much increased. For example, the τ value for ANS bound to **1** is 16.1 ns at pH 4.0 under aerobic conditions. Since a microenvironmental polarity experienced by ANS in the host cavity under such conditions is equivalent to that of tetrahydrofuran, the τ values for the guest were also measured in the same organic solvent; 9.2 and 16.0 ns under aerobic and anaerobic conditions, respectively. This implies that the molecular cage of the cubic cyclophane perfectly protects the incorporated guest from oxygen attack.

In conclusion, it became apparent that the cationic cubic azaparacyclophane exercises pH-dependent molecular recognition in aqueous media. The marked change in guest-binding ability comes from the specific microenvironment, provided by the three-dimensional hydrophobic cavity, that is subjected to change as pH is varied in view of its hydrophobic and electrostatic properties.

References

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