Capped Azaparacyclophane

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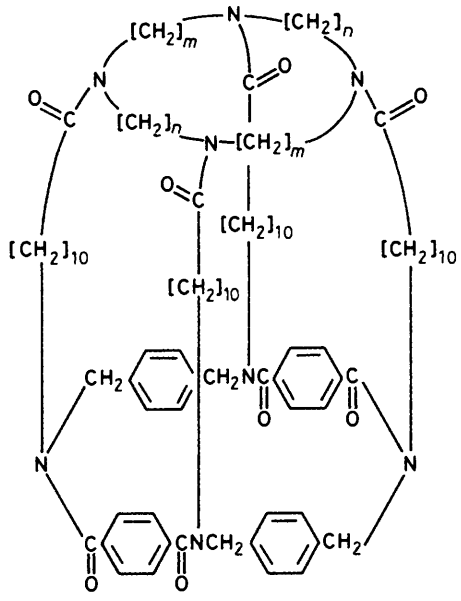
A novel capped azaparacyclophane was obtained by the reaction of *N,N′,N″,N‴*-tetrakis[10-(chloroformyl)decyl]-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane-3,10,21,28-tetraone with 1,4,8,11-tetra-azacyclotetradecane; its substrate-binding behaviour was examined in aqueous media and compared with that of uncapped azaparacyclophanes.

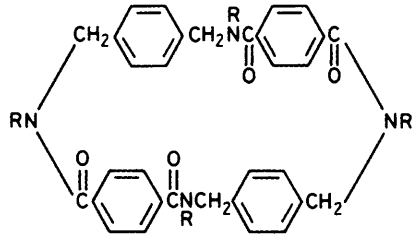
Recently, we have been dealing with cyclophanes which can provide hydrophobic cavities of various three-dimensional shapes and incorporate substrates of different bulk and hydrophobicity in aqueous media.[1] We report here on the preparation of a capped azaparacyclophane (**1**) as a novel host molecule and its binding ability toward various organic guest molecules in aqueous media. The present host molecule is constructed of two rigid macrocyclic skeletons, a tetra-aza[3.3.3.3]paracyclophane as the large ring and a tetra-azacyclotetradecane as the smaller one, with four flexible hydrocarbon chains connecting the macrocycles.

The host (**1**) was synthesized by condensation of the



(1)

($m=3, n=2; m=2, n=3$)



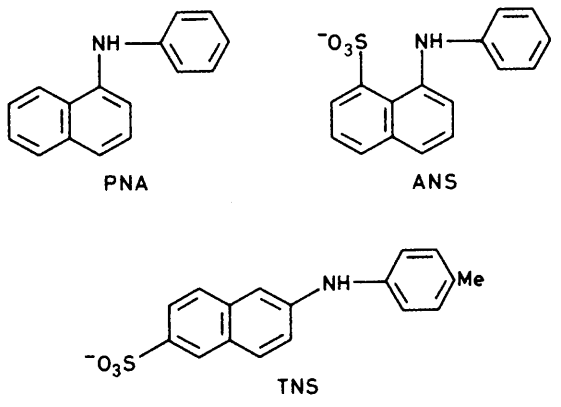
(2) $R=[CH_2]_{10}CO_2H$

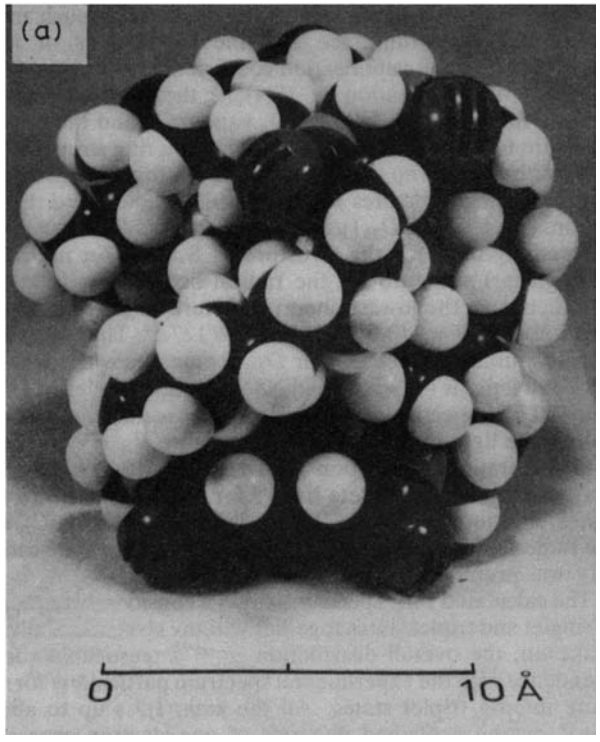
(3) $R=[CH_2]_{10}N^+Me_3 \cdot I^-$

corresponding tetra-acid chloride of *N,N′,N″,N‴*-tetrakis(10-carboxydecyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane-3,10,21,28-tetraone[2] (**2**) with 1,4,8,11-tetra-azacyclotetradecane under highly dilute conditions in dry benzene at room temperature. The product was purified by gel-filtration chromatography on a column of Toyopearl HW-40 Fine with methanol–chloroform (1 : 1 v/v) as an eluant to give a white solid (yield 13%, m.p. 138—140 °C). The structure was confirmed by spectroscopic [*m/z* 1396(M^+)] and elemental analyses.

The host–guest interaction of (**1**) with hydrophobic organic molecules in aqueous media was investigated by fluorescence spectroscopy. In a mixture of aqueous 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulphonate buffer [0.01 mol dm^{-3}, pH 8.0, μ 0.10 (KCl)] and ethanol [10% (v/v)] at 30.0 °C, the binding constant for inclusion of a non-ionic guest, *N*-phenyl-1-naphthylamine (PNA), with (**1**) was evaluated on the basis of the Benesi–Hildebrand-type treatment;[3]† 5.1 × 10^4 mol^{-1} dm^3. This value is one order of magnitude larger than those for the complexes of (**2**) and *N,N′,N″,N‴*-tetrakis[(10-trimethylammonio)decyl]-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane-3,10,21,28-tetraone tetra-iodide[4] (**3**) with the same guest molecule (1.6 × 10^3 and 4.6 × 10^3 mol^{-1} dm^3,

† The measurements were carried out for the concentration range of (**1**) from 1.0 × 10^{-5} to 1.0 × 10^{-4} mol dm^{-3} at a fixed concentration of the guests (1.0 × 10^{-6} mol dm^{-3}). For details, see ref. 5.





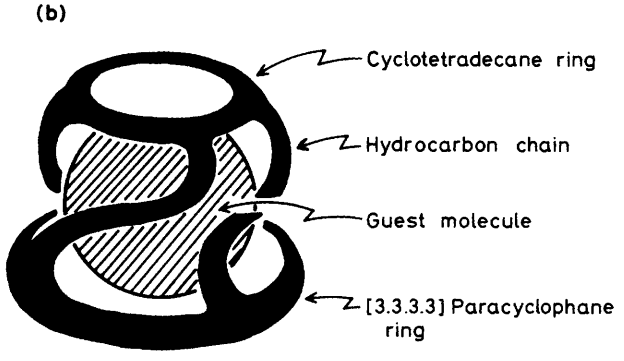


Figure 1. CPK molecular model of the inclusion complex formed with (**1**) and PNA (a) and its schematic representation (b).

respectively).[5,6] Ionic guests are also incorporated into (**1**) in a 1 : 1 stoicheiometry with smaller binding constants as compared with that for PNA: 1.7×10^4 and 9.1×10^3 mol^{-1} dm^3 for 8-anilinonaphthalene-1-sulphonate (ANS) and 6-(*p*-toluidinyl)naphthalene-2-sulphonate (TNS), respectively.

Microscopic polarities of the substrate-binding site were evaluated from fluorescence maxima originating from the guests. The fluorescence maximum observed for PNA in water ($\lambda_{max.}$ 464 nm) was shifted to a lower wavelength region upon complex formation with (**1**) ($\lambda_{max.}$ 408 nm). Similar blue shifts were observed for ANS and TNS when incorporated into (**1**) ($\lambda_{max.}$ 515 and 500 nm in water; 460 and 430 nm upon complex formation, respectively). Thus, for guests such as PNA and ANS, whose molecular shapes are similar to each other, (**1**) provides a microenvironment [$E_T(30)$[7] 37 kcal mol^{-}]‡ nearly equivalent to those provided by tetrahydrofuran [$E_T(30)$ 37.4 kcal mol^{-1}] and an octopus azaparacyclophane bearing eight hydrocarbon chains [$E_T(30)$ 38 kcal mol^{-1}].[6] This indicates that capping of the azaparacyclophane skeleton induces a drastic decrease in microscopic polarity within the hydrophobic cavity: both (**2**) and (**3**) provide microenvironments equivalent to that provided by methanol–water.[6] On the other hand, (**1**) provides a microenvironment with higher polarity for a guest molecule having a somewhat elongated structure; *i,e,* TNS, $E_T(30)$ 53 kcal mol^{-1}. The results imply that the hydrophobic cavity of (**1**) is closely packed with PNA or ANS relative to the case with TNS as confirmed by examination of the corresponding Corey–Pauling–Koltun (CPK) molecular models. Figure 1 shows a plausible status for complex formation between (**1**) and PNA; the hydrophobic entrapping of the non-ionic guest with the hydrophobic host would be most enhanced as the binding constant indicates. Such tight molecular association represses the molecular motion of the entrapped guest as reflected in the fluorescence polarization parameter; *P* being 0.33 for PNA.§

In conclusion, it became apparent that the capped azaparacyclophane (**1**) behaves as an excellent host for hydrophobic molecules in aqueous media. Since the four hydrocarbon chains linking the two macrocycles are expected to undergo flexible intramolecular motion, they seem to exercise the induced-fit function in the course of substrate-incorporation.

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‡ 1 kcal = 4.18 kJ.

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§ The fluorescence lifetime for PNA incorporated into (**1**) is nearly identical with that in butan-1-ol in the light of its fluorescence intensities in both media. The large fluorescence polarization parameter (*P*), relative to that obtained in butan-1-ol ($P = 0.01$), is primarily attributed to an increased relaxation time for rotational motion of PNA. On the other hand, the *P* value for PNA incorporated into (**3**) is 0.06. For the significance of *P* in detail, see ref. 6.