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PREPARATION AND CHARACTERIZATION OF AN OCTOPUS AZAPARACYCLOPHANE AS A HOST FOR VARIOUS HYDROPHOBIC GUEST MOLECULES

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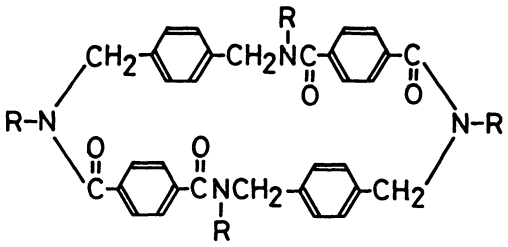
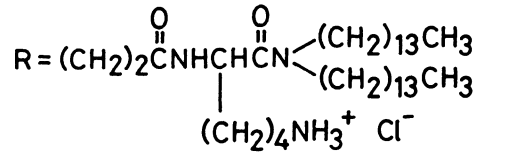
An octopus azaparacyclophane bearing eight hydrophobic chains, N,N',N'',N'''-tetrakis[2-[N-[1-(N,N-ditetradecylcarbamoyl)-5-ammonio-1-pentyl]carbamoyl]ethyl]-3,10,21,28-tetraoxo-2,11,20,29-tetraaza[3.3.3.3]paracyclophane tetrachloride [APC(C_2Lys2C_{14})$_4$], was prepared and its substrate-binding behavior was examined in comparison with that of related azaparacyclophanes.

The hydrophobic interaction is the most prevailing driving force for molecular recognitions in aqueous media, and cyclophanes are typical artificial hosts capable of providing hydrophobic binding sites.[1] However, those cyclophanes without modifications with hydrophobic substituents constitute relatively small and shallow cavities for host-guest interactions. Recently, we have shown that the octopus-like azaparacyclophanes provide deep hydrophobic cavities constructed with a rigid macrocyclic skeleton and four flexible hydrocarbon chains and incorporate various substrates into their cavities by the induced-fit binding mode.[2] In order to enhance further such hydrophobic binding efficiency, we prepared in this work a real octopus azaparacyclophane having eight hydrophobic chains, APC-(C_2Lys2C_{14})$_4$, and investigated its substrate-binding behavior.

The synthetic route for APC(C_2Lys2C_{14})$_4$ is shown in Scheme 1. N,N',N'',N'''-Tetrakis(2-carboxyethyl)-3,10,21,28-tetraoxo-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (1) was prepared according to a procedure similar to that adopted for the synthesis of N,N',N'',N'''-tetrakis(10-carboxydecyl)-3,10,21,28-tetraoxo-2,11,20,29-tetraaza[3.3.3.3]paracyclophane, APC($C_{10}CO_2H$)$_4$,[2] and converted into the corresponding acid chloride (2). N,N-Ditetradecyl-N$^{\varepsilon}$-(benzyloxycarbonyl)-L-lysinamide (4) was prepared by condensation of N$^{\alpha}$-(t-butoxycarbonyl)-N$^{\varepsilon}$-(benzyloxycarbonyl)-L-lysine (3)[3] with N,N-ditetradecylamine, followed by elimination of the t-butoxycar-

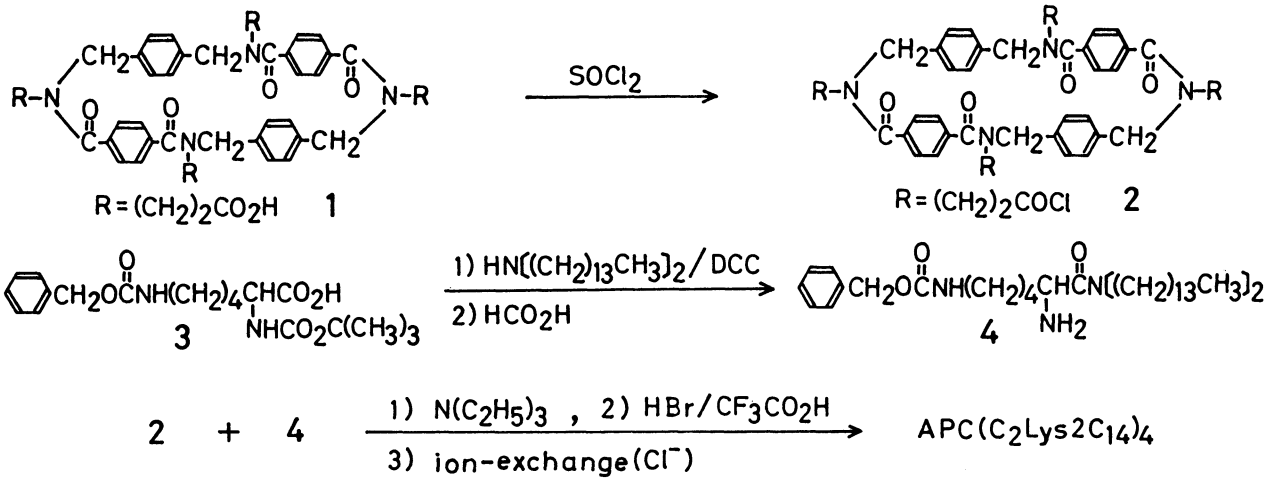




APC(C_2Lys2C_{14})$_4$

R = $(CH_2)_{10}N^+(CH_3)_3$ I^- : APC($C_{10}N^+$)$_4$

R = $(CH_2)_{10}CO_2H$: APC($C_{10}CO_2H$)$_4$



Scheme 1.

bonyl group. Condensation of 2 with 4, followed by removal of the benzyloxycarbonyl group and exchange of the counterions with the chloride ion, gave APC(C_2Lys-$2C_{14}$)$_4$ as the tetrahydrochloride salt.[4)]

The substrate-binding behavior of the octopus azacyclophane, APC(C_2Lys$2C_{14}$)$_4$, was examined by fluorescence spectroscopy in an aqueous 2-(N-morpholino)ethanesulfonic acid (MES) buffer [0.01 mol dm^{-3}, pH 6.0, μ 0.10 (KCl)] containing 5%-(v/v) ethanol at 30.0 °C. All the spectroscopic measurements were carried out for a range below the critical aggregate concentration (CAC) of APC(C_2Lys$2C_{14}$)$_4$; CAC being 1 x 10^{-4} mol dm^{-3} by the surface tension method based on the Wilhelmy principle. N,N',N'',N'''-Tetrakis(10-trimethylammoniodecyl)-3,10,21,28-tetraoxo-2,11,20,29-tetraaza[3.3.3.3]paracyclophane tetraiodide, APC($C_{10}N^+$)$_4$,[2)] was used as a reference host, and the following fluorescent probes were chosen as guest compounds: anionic, 8-anilinonaphthalene-1-sulfonate (ANS) and 6-p-toluidinylnaphtalene-2-sulfonate (TNS); nonionic, N-phenyl-1-naphthylamine (PNA); cationic, 1-dimethylaminonaphthalene-5-sulfonamidoethyltrimethylammonium (DASP). The fluorescence intensity for each guest molecule increased upon addition of any of the host compounds cited above, and the binding constants were evaluated according to the Benesi-Hildebrand equation in a manner as reported elsewhere[5)] (Table 1). The binding constants for the host-guest interactions of APC(C_2Lys$2C_{14}$)$_4$ with the anionic and nonionic guest molecules are much greater than the corresponding values for APC($C_{10}N^+$)$_4$, whereas both cationic hosts do not show any binding affinity toward the cationic guest. This means that these azacyclophanes, APC(C_2Lys$2C_{14}$)$_4$ and APC($C_{10}N^+$)$_4$, are the potent hydrophobic hosts showing substrate selectivity originated in the electrostatic effect.

The microscopic polarities of environments around the incorporated guest mole-

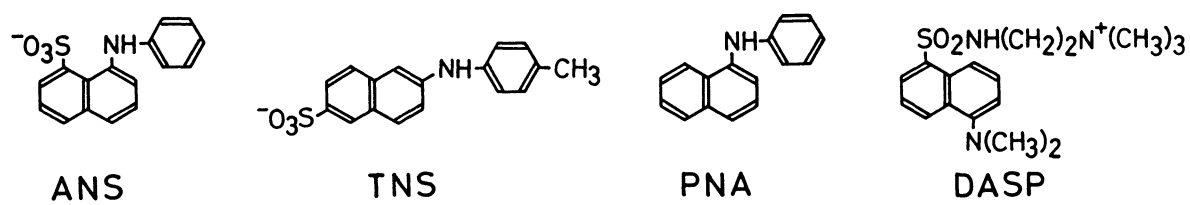


Table 1. Binding constants ($K/mol^{-1}dm^3$) and microenvironmental polarity parameters ($E_T(30)$/kcal mol^{-1}) for the interactions of azacyclophanes with various guests[a)]

Guest	Host			
	$APC(C_2Lys2C_{14})_4$		$APC(C_{10}N^+)_4$	
	K	$E_T(30)$[b)]	K	$E_T(30)$[b)]
ANS	2.8×10^5	40 (461)	1.1×10^4	55 (481)
TNS	3.0×10^5	52 (425)	7.5×10^3	55 (440)
PNA	1.3×10^6	38 (410)	4.6×10^3	62 (455)

a) In an aqueous MES buffer [0.01 mol dm^{-3}, pH 6.0, μ 0.10 (KCl)] containing 5%-(v/v) ethanol at 30.0 °C. Concentrations in mol dm^{-3}: guests, 1.0×10^{-6}; $APC-(C_2Lys2C_{14})_4$, 5.0×10^{-6}– 3.0×10^{-5}; $APC(C_{10}N^+)_4$, 5.0×10^{-5}– 3.0×10^{-4}. No complex formation was detected with DASP as a guest. b) C. Reichardt, "Solvent Effects in Organic Chemistry," Verlag Chemie, Weinheim (1979), pp.270-272; 1 kcal = 4.184 kJ. Fluorescence maxima (in nm) are given in parentheses.

cules were evaluated from their fluorescence maxima. In order to obtain the reference data, the fluorescence maxima of PNA were measured in various solvents as shown in Fig. 1; the fluorescence maximum being shifted to the lower wavelength region as the solvent polarity decreases. $APC(C_2Lys-2C_{14})_4$ provides a microenvironment equivalent to that provided by THF, which is less polar than those provided by the CTAB (hexadecyltrimethylammonium bromide) micelle and azacyclophanes bearing four hydrophobic chains such as $APC(C_{10}N^+)_4$ and $APC(C_{10}CO_2H)_4$ (Table 1 and Fig. 1).

Relatively large fluorescence polarization (P) values[6)] were obtained for the probes incorporated into $APC(C_2Lys2C_{14})_4$: 0.29, 0.31, and 0.21 for ANS, TNS, and PNA, respectively. Meanwhile, the P values in ordinary media are much smaller: 0.02, 0.01, 0.006, and 0.002 for PNA in water, 1-butanol, 2-propanol, and THF, re-

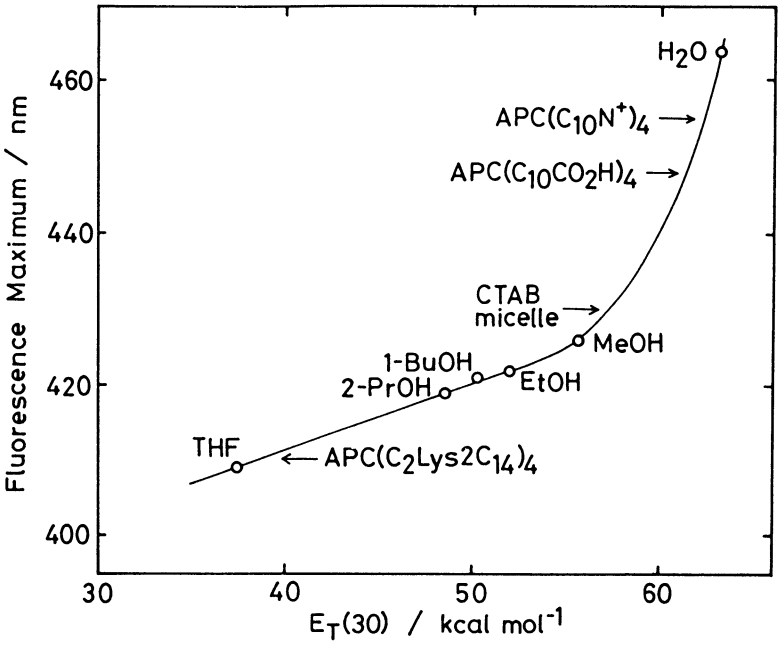


Fig. 1. Solvent effect on fluorescence of PNA: $APC(C_2Lys2C_{14})_4$ and $APC(C_{10}N^+)_4$, in an aqueous MES buffer [0.01 mol dm^{-3}, pH 6.0, μ 0.10 (KCl)] containing 5%(v/v) ethanol; $APC(C_{10}CO_2H)_4$, in an aqueous 3-cyclohexylaminopropanesulfonate buffer [0.01 mol dm^{-3}, pH 10.0, μ 0.10 (KCl)] containing 5%(v/v) dimethylsulfoxide.

spectively; 0.01 for ANS in 1-butanol; 0.03 for TNS in 1-butanol. The fluorescence lifetime (τ; refer to Eq. 2) undergoes variation commensurate with the fluorescence intensity and was found to increase with a decrease in medium polarity. While ANS and PNA incorporated into APC(C_2Lys2C_{14})$_4$ exhibit intensities nearly identical with those measured in 1-butanol, TNS bound to the host shows an intermediate value between those measured in 1-butanol and water. These results clearly indicate that the large P values observed in the presence of the host primarily reflect the high microscopic viscosity (i.e., the large relaxation time of rotation of probes; refer to Eq. 2) in the hydrophobic cavity of APC(C_2Lys2C_{14})$_4$.

In conclusion, the octopus azaparacyclophane, APC(C_2Lys2C_{14})$_4$, behaves as an effective cationic host for the anionic and nonionic guest molecules, providing a highly apolar and viscous binding site. In addition, the present host molecule incorporates relatively large coenzyme models such as a hydrophobic vitamin B_{12}, heptapropyl dicyanocobyrinate,[7] into its hydrophobic cavity constructed with the rigid macrocyclic skeleton and the eight flexible hydrocarbon chains so that it is promising to utilize the present host as an effective apoenzyme model.

References

1) J. H. Fendler, "Membrane Mimetic Chemistry," John Wiley & Sons, New York (1982), Chap. 7; Y. Murakami, in "Cyclophanes II," Topics in Current Chemistry No. 115, ed by F. Vögtle, Springer-Verlag, Berlin (1983), pp. 107-155.

2) Y. Murakami, A. Nakano, R. Miyata, and Y. Matsuda, J. Chem. Soc., Perkin Trans. 1, 1979, 1669; Y. Murakami, A. Nakano, K. Akiyoshi, and K. Fukuya, ibid., 1981, 2800.

3) E. Bayer, G. Jung, and H. Hagenmaier, Tetrahedron, 24, 4853 (1968).

4) Found: C, 71.19; H, 10.28; N, 7.15%. Calcd for $C_{180}H_{324}Cl_4N_{16}O_{12}$: C, 70.97; H, 10.72; N, 7.36%.

5) H. A. Benesi and J. H. Hildebrand, J. Am. Chem. Soc., 71, 2703 (1949). For the computational procedure in detail, see: Y. Murakami, J. Kikuchi, and H. Tenma, Chem. Lett., submitted for publication.

6) The fluorescence polarization (P) was calculated by Eq. 1, where I is the fluorescence intensity, and the subscripts v and h refer to the orientations, vertical and horizontal, respectively, for the excitation and analyzer polarizers in this sequence. C_f is the grating correction factor, given by I_{hv}/I_{hh}.

$$P = (I_{vv} - C_f I_{vh})/(I_{vv} + C_f I_{vh}) \quad (1)$$

The P value is also given by Eq. 2, where τ is the fluorescence lifetime of a probe, ρ is the relaxation time of rotation of a probe, and P_0 refers to the maximal value of P in the absence of any rotational motion of a probe.

$$1/P - 1/3 = (1/P_0 - 1/3)(1 + 3\tau/\rho) \quad (2)$$

For the significance of Eq. 2, see: G. Weber, Adv. Prot. Chem., 8, 415 (1953).

7) Y. Murakami, Y. Hisaeda, and T. Ohno, Bull. Chem. Soc. Jpn., 57, 2091 (1984). The microenvironmental polarity around the hydrophobic cobalt complex placed in the host is equivalent to that provided by propionitrile; $E_T(30)$ = 43.7.

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