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CHARGE-TRANSFER EFFECT ON SUBSTRATE-BINDING BEHAVIOR OF OCTOPUS-LIKE AZACYCLOPHANES

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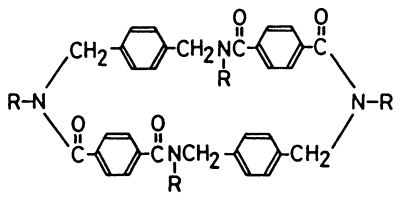
The guest-binding efficiency of octopus-like azacyclophanes was examined with five different charge-transfer donors by means of fluorescence spectroscopy. Relative contributions of the hydrophobic, electrostatic, and charge-transfer interactions in the overall guest-binding process were characterized.

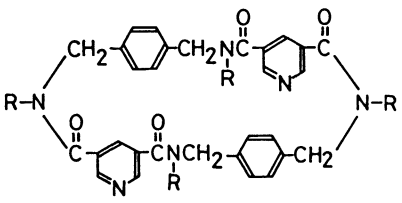
Macrocyclic compounds with a sizable hydrophobic cavity have been extensively examined from the viewpoint of host-guest chemistry. We have previously reported that azaparacyclophanes bearing multiple hydrophobic chains, octopus-like azacyclophanes, tend to capture various hydrophobic guest molecules in aqueous media by the induced-fit binding mode.[1] In this work, we prepared octopus-like azacyclophanes having either pyridyl or pyridinium moieties in their macrocyclic skeletons, $APyC(C_{10}CO_2H)_4$ and $APy^+C(C_{10}CO_2H)_4$, and their substrate-binding behavior was examined in comparison with that of other octopus-like azaparacyclophanes, $APC(C_n CO_2H)_4$ (n = 2, 10).

N,N'-Bis(10-methoxycarbonyldecyl)-p-xylylenediamine[1] was subjected to condensation with pyridine-3,5-dicarbonyl dichloride under high dilution conditions, and the product was hydrolyzed to afford $APyC(C_{10}CO_2H)_4$. The pyridyl nitrogens of $APyC(C_{10}CO_2H)_4$ were quaternized with methyl iodide to give $APy^+C(C_{10}CO_2H)_4$. $APC(C_2CO_2H)_4$ was prepared by the method adopted for the synthesis of $APC(C_{10}CO_2H)_4$.[1] All the novel products were purified by gel-filtration chromatography and identified by ^{1}H-NMR and IR spectroscopy as well as their elemental analyses.[2]

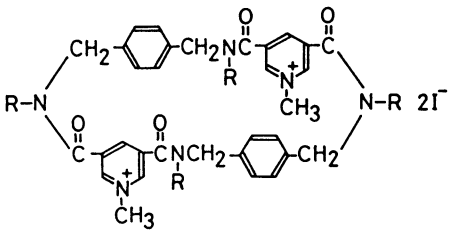
The substrate-binding behavior of the octopus-like azacyclophanes was examined by fluorescence spectroscopy in an aqueous 3-(cyclohexylamino)propanesulfonate (CAPS) buffer [0.01 mol dm^{-3}, pH 10.0, μ 0.10 (KCl)] containing 5%(v/v) di-



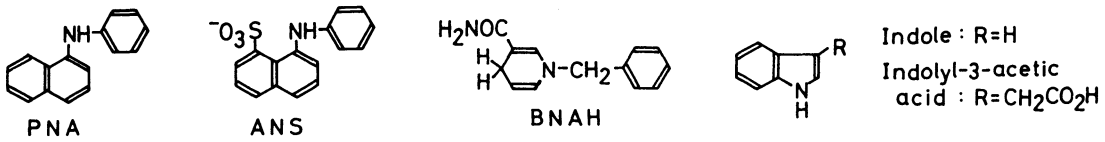
$APC(C_nCO_2H)_4$ (n=2,10)
$R=(CH_2)_nCO_2H$



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



$APy^+C(C_{10}CO_2H)_4$
$R=(CH_2)_{10}CO_2H$



methylsulfoxide at 30.0 °C. Five different guests were employed in order to characterize the relative extent of their charge-transfer (CT) interactions with the host molecules in the overall binding behavior: a nonionic, large, and poor donor, N-phenyl-1-naphthylamine (PNA); an anionic, large, and poor donor, 8-anilinonaphthalene-1-sulfonate (ANS); a nonionic, medium-sized, and good donor, 1-benzyl-1,4-dihydronicotinamide (BNAH); a nonionic, small, and good donor, indole; an anionic, small, and good donor, indolyl-3-acetic acid. Fluorescence spectra of the guest molecules (1.0×10^{-5} mol dm^{-3}) were measured at various concentrations of the host molecules (5×10^{-5}– 5×10^{-4} mol dm^{-3}). The binding constants for the inclusion complexes with PNA and BNAH were evaluated on the basis of the Benesi-Hildebrand relationship for the 1:1 host-guest interaction.[3)]

The fluorescence intensity of PNA increases upon complex formation with the azacyclophanes. The binding constant decreases in the following order: APC($C_{10}CO_2H$)$_4$ > APyC($C_{10}CO_2H$)$_4$ > APy$^+$C($C_{10}CO_2H$)$_4$ $\simeq$ APC(C_2CO_2H)$_4$ (Table 1). The results provide useful information in two aspects: (i) the deep hydrophobic cavity constructed with four hydrophobic chains and one macrocyclic skeleton of the octopus-like azacyclophanes is required for the strong binding interaction with bulky guest molecules such as PNA; (ii) as hydrophobicity of the macrocyclic skeleton decreases, the host-guest interaction is weakened. In addition, the polarity parameters for the microenvironments where the PNA molecule is incorporated were evaluated from the maximum wavelengths of its fluorescence spectra and found to be nearly equivalent to that in water: polarity parameters [$E_T(30)$], 61.0 and 62.6 for the inclusion complexes with APC($C_{10}CO_2H$)$_4$ and APyC($C_{10}CO_2H$)$_4$, respectively. Complex forma-

Table 1. Binding constants for the inclusion complexes of azacyclophanes[a)]

Guest	$10^{-3}K$[b)]/mol^{-1} dm^3			
	APC(C_2CO_2H)$_4$	APC($C_{10}CO_2H$)$_4$	APyC($C_{10}CO_2H$)$_4$	APy$^+$C($C_{10}CO_2H$)$_4$
PNA	——[c)]	1.6	0.73	——[c)]
BNAH	——[c)]	2.0	1.4	5.8
Indole	1.5	1.5	4.3	4.6
Indolyl-3-acetic acid	0.2	0.1	0.4	3.2

a) In an aqueous CAPS buffer [0.01 mol dm^{-3}, pH 10.0, μ 0.10 (KCl)] containing 5%-(v/v) dimethylsulfoxide at 30.0 °C. Concentrations in mol dm^{-3}: guests, 1.0×10^{-5}; hosts, 5.0×10^{-5}– 5.0×10^{-4}. b) Excitation and emission wavelengths in nm: PNA, 340 and 460; ANS, 375 and 515 (no complex formation); BNAH, 361 and 465; indole, 277 and 347; indolyl-3-acetic acid, 280 and 363, respectively. c) Complex formation was not detected by fluorescence spectroscopy.

tion was not observed when the anionic ANS was used as the guest for these anionic hosts. Similar behavior has also been observed for the interaction between APC-$(C_{10}CO_2H)_4$ and various anionic dyes.[1)]

When BNAH was used as a guest, its fluorescence intensity was found to increase upon complex formation with $APC(C_{10}CO_2H)_4$ and $APyC(C_{10}CO_2H)_4$. However, the host-guest interaction of $APy^+C(C_{10}CO_2H)_4$ with BNAH resulted in progressive fluorescence decay as the host concentration increases (Fig. 1). 1,4-Dihydronicotinamides are known to form CT complexes with their oxidized forms and the related electron deficient pyridinium derivatives, and the formation constants for such CT complexes are relatively small in aqueous media as confirmed by electronic absorption spectroscopy.[4)] The fluorescence originated from BNAH is quenched by its CT interaction with the corresponding oxidized species, 1-benzylnicotinamide chloride, in the aqueous buffer; the formation constant obtained here (4 mol^{-1} dm^3) is in good agreement with that evaluated by electronic absorption spectroscopy (3.76 mol^{-1} dm^3).[4)] Thus, it is clear that the decrease in fluorescence intensity observed for the $APy^+C(C_{10}CO_2H)_4$– BNAH system is caused by the CT interaction between the pyridinium moieties of the host and the dihydropyridine ring of BNAH.[5)] Such a CT interaction greatly favors the formation of inclusion complexes (Table 1).

The indolyl moiety is also a good donor for the CT interaction.[6)] Its fluorescence is quenched upon formation of the CT complex with the nicotinamide group.[7)] In fact, the fluorescence decay of indole and indolyl-3-acetic acid was observed when any of the present azacyclophanes was added. The binding constant increases in the following order with respect to the host molecules:[8)] $APC(C_2CO_2H)_4 \simeq APC-(C_{10}CO_2H)_4 < APyC(C_{10}CO_2H)_4 < APy^+C-(C_{10}CO_2H)_4$. This sequence seems to reflect the extent of CT interactions between the electron-deficient acceptor groups in the macrocyclic skeletons and the guest molecules. The small donor molecules such as indole and indolyl-3-acetic acid are considered to be completely incorporated into the cavities of the macrocyclic skeletons, and the face-to-face arrangement of the donor and acceptor moieties is attained effectively. As a consequence, the hydrophobic interactions between the long chain segments of the host and the guest molecule, which have been observed for the host-guest interac-

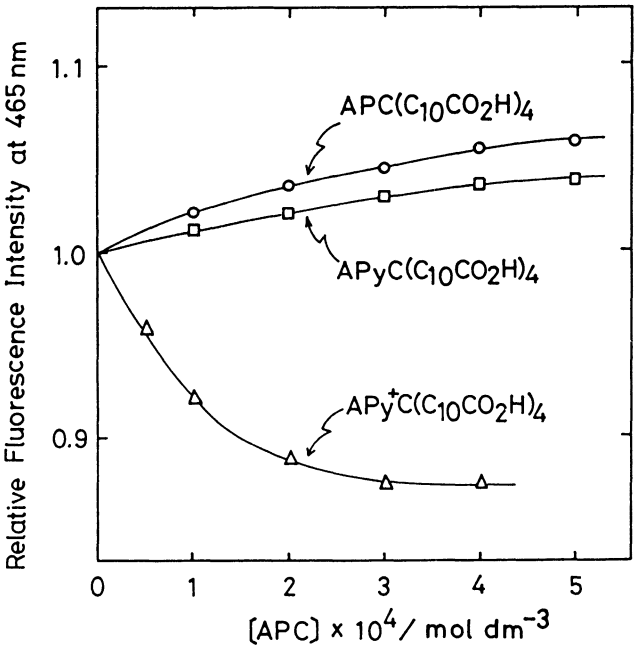


Fig. 1. Correlations between azacyclophane concentration ([APC]) and fluorescence intensity of BNAH (1.0×10^{-5} mol dm^{-3}) in an aqueous CAPS buffer [0.01 mol dm^{-3}, pH 10.0, μ 0.10 (KCl)] containing 5%(v/v) dimethylsulfoxide; excitation at 361 nm.

tion with larger guest molecules (vide supra), do not seem to make any significant contribution, although a desolvation effect on the guest may not be excluded in the binding process.

In conclusion, the binding modes of octopus-like azacyclophanes toward various guest molecules are divided into two categories. For small molecules which can be completely incorporated into the macrocyclic cavity, the CT interaction is of major importance for the host-guest association, and the hydrophobic interaction with the long chain segments makes much less contribution to the overall guest-binding process. On the other hand, for guest molecules larger than the macrocyclic cavity size, the induced-fit function exercised by the four hydrophobic chain segments is the predominant factor controlling the guest incorporation and the CT interaction is only an additional one, if any, for guest recognition.

References

1) 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.

2) APC(C_2CO_2H)$_4$ Found: C, 61.83; H, 5.66; N, 6.46%. Calcd for $C_{44}H_{44}N_4O_{12}\cdot 2H_2O$: C, 61.67; H, 5.65; N, 6.54%. APyC($C_{10}CO_2H$)$_4$ Found: C, 68.22; H, 8.40; N, 6.53 %. Calcd for $C_{74}H_{106}N_6O_{12}\cdot(3/2)H_2O$: C, 68.44; H, 8.46; N, 6.47%. $APy^+C(C_{10}CO_2H)_4$ Found: C, 57.90; H, 7.43; N, 5.36%. Calcd for $C_{76}H_{112}I_2N_6O_{12}\cdot H_2O$: C, 58.01; H, 7.30; N, 5.34%.

3) H. A. Benesi and J. H. Hildebrand, J. Am. Chem. Soc., 71, 2703 (1949). The binding constant (K) was calculated on the basis of the following equation: $1/\Delta I = 1/(\Delta I_c[G]_0) + 1/(\Delta I_c K[G]_0[H]_0)$, where ΔI is the extent of fluorescence intensity change upon addition of the host, ΔI_c stands for the difference in fluorescence intensity between the bound and free guest molecules, and $[G]_0$ and $[H]_0$ are the total concentrations of the guest and host molecules, respectively.

4) G. Cilento and S. Schreier, Arch. Biochem. Biophys., 107, 102 (1964).

5) Any detectable effect of potassium iodide on the fluorescence phenomenon was not observed under the conditions employed: $[I^-] \leq 1 \times 10^{-3}$ mol dm^{-3}.

6) G. Cilento and P. Tedeschi, J. Biol. Chem., 236, 907 (1961); S. Shinkai, K. Tamaki, and T. Kunitake, Bull. Chem. Soc. Jpn., 48, 1918 (1975).

7) S. F. Velick, J. Biol. Chem., 233, 1455 (1958); S. Shifrin, Biochim. Biophys. Acta, 81, 205 (1964); Y. Murakami, Y. Aoyama, J. Kikuchi, K. Nishida, and A. Nakano, J. Am. Chem. Soc., 104, 2937 (1982).

8) The binding constant (K) was calculated on the basis of the following equations: $K = [C]/([H][G])$ and $I/I_0 = ([G]/[G]_0)\exp[1.151(\varepsilon_G + \varepsilon_H - \varepsilon_C)([G]_0 - [G]) - 1.151\varepsilon_H[H]_0]$. Here, I and I_0 are the fluorescence intensities in the presence and absence of the host, respectively, $[G]_0$ and $[H]_0$ stand for the total concentrations of the guest and host molecules, respectively, and ε is the molar extinction coefficient at the excitation wavelength; the symbols G, H, and C refer to the guest, host, and complex species, respectively. For derivation of the latter equation, see: Th. Förster, "Fluorescenz Organischer Verbindungen," Vandenhoeck & Ruprecht, Göttingen (1951).

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