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MODIFICATIONS OF HYDROPHOBIC CAVITY AND THEIR EFFECTS ON THE COMPLEX FORMATION WITH A HYDROPHOBIC SUBSTRATE

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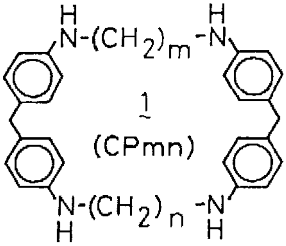
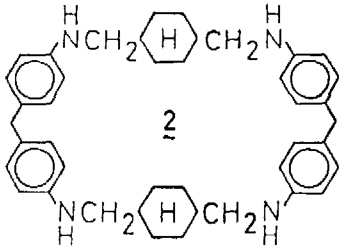
Abstract: The derivatives of CP44 (**1a**) were designed and synthesized to modify the natures of its hydrophobic cavity, and the effects on the complex formation with a hydrophobic substrate in aqueous solution were examined.

In the previous papers we have reported the crystallographic[1] and NMR spectral[2] studies showing that a novel water-soluble paracyclophane, CP44,[3] forms an inclusion host-guest complex with hydrophobic substrates in a particular geometry. For inclusion to occur in a particular geometry, the formation of a *hydrophobic* cavity having *definite* shape and size that *fits well* with the hydrophobic moiety of the substrate is considered to be very important. From this viewpoint it is interesting to modify CP44 (**1a**) by changing the natures (size, hydrophobic area, hydrophobicity, stability) of its cavity. We wish to report here the design and syntheses of the derivatives of CP44 (**1b**-g, **2**-**5**) and their complexation properties toward a hydrophobic substrate. In these modified hosts the length of the bridging moieties (**1b**-g), the unit of the bridging moieties (**2**, **3**), and the unit of the skeleton moieties (**4**, **5**) are changed, respectively, which are easy to carry out synthetically in this simple artificial system.



1 (CPmn)

1a	(CP44)	m = 4, n = 4
1b	(CP33)	m = 3, n = 3
1c	(CP55)	m = 5, n = 5
1d	(CP35)	m = 3, n = 5
1e	(CP45)	m = 4, n = 5
1f	(CP56)	m = 5, n = 6
1g	(CP58)	m = 5, n = 8



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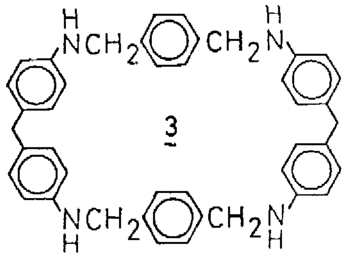

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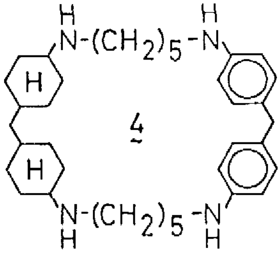

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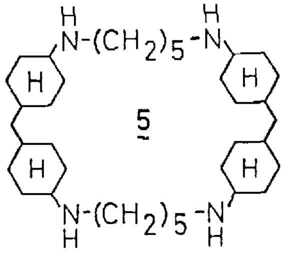

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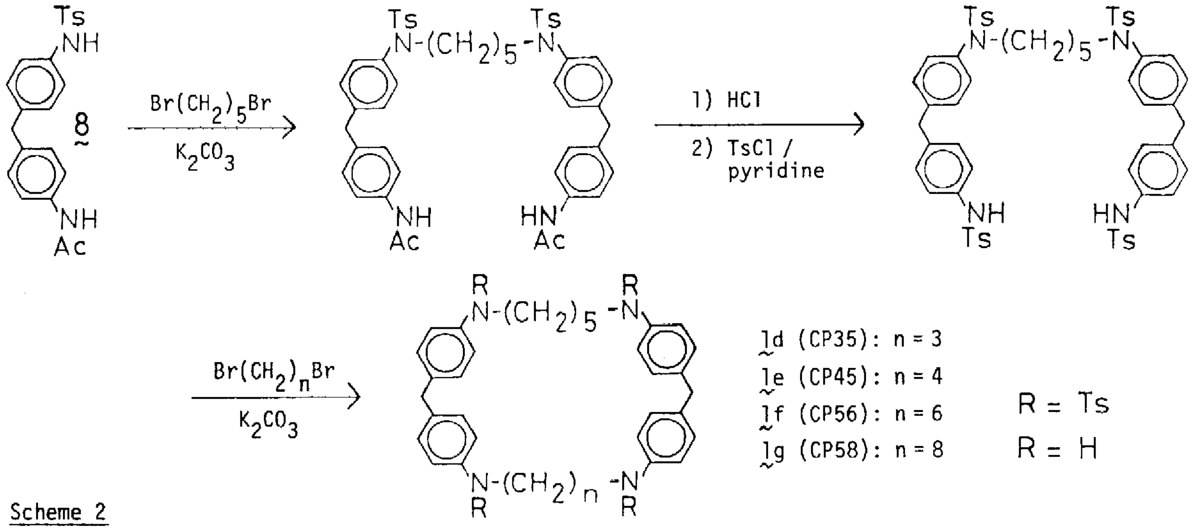
* All the 1,4-cyclohexylene units are *trans*.

Hosts 1b, 1c, 2, 3 and 5 were synthesized by a similar procedure as described for CP44 (1a),[1] starting from N,N'-ditosyl-4,4'-diaminodiphenylmethane (6)[4] or N,N'-ditosyl-trans,trans-bis-(4-aminocyclohexyl)methane (7).[5] Hosts 1d-g, having two bridging methylene chains of different lengths, were synthesized as shown in Scheme 1, starting from N-acetyl-N'-tosyl-4,4'-diaminodiphenylmethane (8).[4] Host 4, having two skeleton moieties of different units, was synthesized as shown in Scheme 2. The cyclic structures of all the host compounds were confirmed on the basis of their mass spectra.[6]

As described in ref. 1, remarkable fluorescence enhancement and blue shift were observed in the fluorescence spectrum of 1-anilinonaphthalene-8-sulfonate (ANS) upon an addition of CP44 (1a), suggesting that the substrate was included within the hydrophobic cavity of CP44.[7] The dissociation constant (K_d) of the 1:1 complex was 1.6×10^{-4} M, showing a strong complex formation. Using the same hydrophobic substrate, fluorescence spectrum and dissociation constant were measured for each modified host under the same conditions,[8] and the effect of modification was examined. With the hosts 1c, 1e-g and 2, the above fluorescent changes were observed remarkably

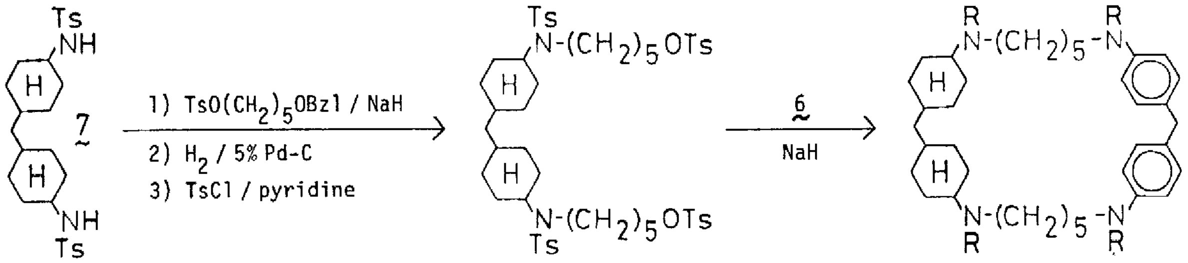
Scheme 1



1d (CP35): n = 3
1e (CP45): n = 4
1f (CP56): n = 6
1g (CP58): n = 8

R = Ts
R = H

Scheme 2



in the increasing order of **1a** ≈ **1e** < **1c** < **1g** < **1f** << **2**, which was parallel with the decreasing order of the dissociation constant (i.e., the increasing order of the stability of the complex) as listed in Table 1. On the contrary, only small fluorescent changes were observed with the hosts **1b**, **1d**, **3**, **4** and **5**, suggesting a weak complex formation with ANS.

From these observations the effects of the modification can be considered as follows:

(1) The complex formation is affected by the modification of cavity size. (**1**a-g) The strongest complex formation observed with **1f** (CP56) may be explained by the best fitness of its cavity with the naphthalene ring of ANS,[9] as suggested by molecular models.[10]

(2) Retaining the size and increasing the hydrophobic area of the cavity greatly improves the complex formation.[11] Thus the modification of the pentamethylene unit (**1c**) to the cyclohexane-trans-1,4-dimethylene unit (**2**) have resulted in 50-fold stronger complex formation. On the contrary, decreasing the hydrophobicity of the cavity (**3**) is greatly unfavorable for the complex formation.[11]

(3) The diphenylmethane skeleton seems to contribute to the formation of an inclusion cavity while the corresponding aliphatic skeleton does not. (**1c**, **4**, **5**) The major reason may be the preference of the "face" conformation in the diphenylmethane skeleton, which might be a critical condition to form a stable inclusion cavity.[12,13]

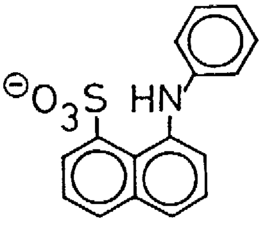
Thus, retaining the two diphenylmethane skeletons, the simple modifications that optimize the cavity size and increase the hydrophobic area have improved the complex formation with ANS by 80-fold. (From $K_d = 1.6 \times 10^{-4}$ M by **1a** (CP44) to $K_d = 2.0 \times 10^{-6}$ M by **2**.)

This is the first systematic modification of the cavity nature of a water-soluble host compound, and as it can be carried out easily in this simple artificial system, a simple modification have resulted in by far the strongest complex formation with ANS ($K_d = 2.0 \times 10^{-6}$ M) by an artificial host compound.[14]

Table 1 Dissociation constants of the 1:1 complexes between ANS and the modified hosts.

Host	K_d [M]	
1a (CP44)	1.6×10^{-4}	(1.0)
1e (CP45)	1.6×10^{-4}	(1.0)
1c (CP55)	9.9×10^{-5}	(1.6)
1f (CP56)	2.2×10^{-5}	(7.3)
1g (CP58)	2.6×10^{-5}	(6.2)
2	2.0×10^{-6}	(80)

* The values in the parentheses are the relative stabilities ($1/K_d$) of the 1:1 complexes.



ANS

References and Notes

1) K. Odashima, A. Itai, Y. Iitaka and K. Koga, J. Am. Chem. Soc., 102, 2504 (1980).

2) K. Odashima, A. Itai, Y. Iitaka, Y. Arata and K. Koga, the preceding paper.

3) In a protonated form.

4) F. E. Ray and L. Soffer, J. Org. Chem., 15, 1037 (1950).

5) Plates, mp 221-222°C. Satisfactory ^{1}H NMR spectrum and elemental analyses (C, H, N) were obtained. For the corresponding diamine, see: R. Richter and G. H. Themme, J. Org. Chem., 43, 1825 (1978).

6) **1b**: mp 224-226°C (dec.);^{a,b} **1c**: mp 173-175°C (dec.);^{a,b} **1d**: mp 128.5-129.5°C (dec.);^{a,b} **1e**: mp 189-190.5°C (dec.);^{a,b} **1f**: mp 164.5-166°C;^{a,b} **1g**: mp 104.5-105.5°C;^{a,b} **2**: mp 258°C (dec.);^{a,b} **3**: mp 256-257°C (dec.);^{a,b} **4**: mp 125-127°C;^{a,b} **5**: wax.^{a} (a) Satisfactory ^{1}H NMR spectra were obtained. Molecular ions were observed in their mass spectra. (b) Satisfactory elemental analyses (C, H, N) were obtained.

7) For the similar fluorescent changes by cycloamyloses, see for example: F. Cramer, W. Saenger and H.-Ch. Spatz, J. Am. Chem. Soc., 89, 14 (1967).

8) KCl-HCl buffer (pH 1.95); 25.0 ± 0.1°C; excited at 375 nm; measured at 505 nm; [ANS] = $2 - 10 \times 10^{-6}$ M. All the modified hosts were soluble in this acidic buffer.

9) There are two hydrophobic moieties in ANS, the benzene ring and the naphthalene ring, that may be included within the hydrophobic cavity of host. The complex in which the naphthalene ring is included is expected to be stronger than that in which the benzene ring is included, since the positive charges of the host ($Ar\text{-}NH_2^+\text{-}CH_2$) and the negative charge of the substrate (SO_3^-) come closer in the former complex than in the latter.

10) Molecular models also suggest that the cavities of **1c** (CP33) and **1d** (CP35) are too small to include the benzene ring, thus the weak complex formation with ANS can be predicted.

11) Hydrophobic area of the cavity is expected to increase in the order of **1c** < **2** ≈ **3**. Hydrophobicity of the cavity is expected to increase in the order of **3** < **1c** << **2**.

12) Though the aliphatic skeleton is expected to be more hydrophobic than the corresponding aromatic skeleton, it does not seem to be a suitable unit to form an inclusion cavity. One possible reason is that it is not the "face" conformation but the "lateral" conformation[13b] that is preferred in the aliphatic skeleton. As a result the aliphatic skeleton might fill up its own cavity so as to make it unfavorable to include the substrate within the cavity.

13) For the spectral studies of the conformation of paracyclophane in solution, see: (a) D. J. Cram and M. F. Antar, J. Am. Chem. Soc., 80, 3103 (1958); (b) I. Tabushi, H. Yamada and Y. Kuroda, J. Org. Chem., 40, 1946 (1975).

14) Dissociation constants of 1.8×10^{-3} M,[14a] 6.3×10^{-4} M,[14b] 9.1×10^{-5} M[14c] (water-soluble paracyclophanes), and 7.7×10^{-4} M[14d] (modified cycloheptaamylose) have been reported for 1:1 complex formation between ANS and an artificial host compound in aqueous solution. (a) I. Tabushi, Y. Kuroda and Y. Kimura, Tetrahedron Lett., 3327 (1976); (b) I. Tabushi, H. Sasaki and Y. Kuroda, J. Am. Chem. Soc., 98, 5727 (1976); (c) Y. Murakami, Y. Aoyama, M. Kida and A. Nakano, Bull. Chem. Soc. Jpn., 50, 3365 (1977); (d) I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata and K. Fujita, J. Am. Chem. Soc., 98, 7855 (1976).

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