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STRONG HYDROPHOBIC BINDING BY WATER SOLUBLE MACROCYCLIC HETEROCYCLOPHANE

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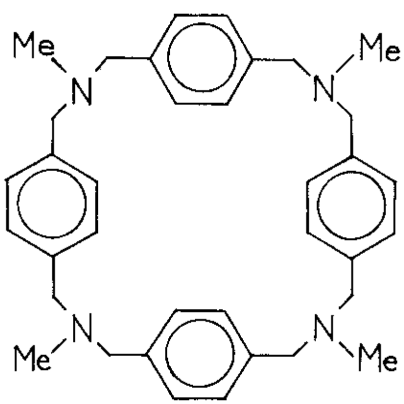
In the past decade, cyclodextrins have attracted increasing attention as the sole class of inclusion hosts which form one to one molecular complexes with a variety of hydrophobic guest molecules[1]. Recently, another class of inclusion hosts, a crown family, were newly added to hydrophobic inclusion hosts, some of which exhibit even chiral recognition[2], promising versatile field in the organic chemistry.

We have been currently investigating polyparacyclophanes in order to afford a new class of inclusion host molecules[3]. In this communication, we wish to report the excellent binding capacity of N,N',N",N"'-tetramethyl-2,11,20,29-tetraaza[3.3.3.3] paracyclophane (I). The CPK molecular model of I shows that it has a square hydro-



I

phobic cavity surrounded by walls of benzene rings[4]. Its cavity size (distance between parallel sides) is about 5.5 Å and expected to be capable of including phenyl

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or naphtyl moiety.

Hetrocyclophane I was prepared by the reported procedure[5] with slight modification and it was recrystalized from methylene chloride. Very soluble is I in water below pH 6, though only poorly soluble in less acidic aqueous condition. This high solubility is signficant for the hydrophobic inclusion since the hydrophobic inclusion can only take place by introducing a hydrophobic cavity in water(or aqueous polar solvent). The successful incorporation of a hydrophobic organic molecule into the hydrophobic cavity of I was ascertained by means of the fluorescence measurement of sodium 1-anilino-8-naphthalenesulfonate (1,8-ANS) as a fluorescent guest molecule. Fluorescence of 1,8-ANS is known to be strengthened, when bound in hydrophobic surrounding such as that in enzyme[6] or in cyclodextrin[1b]. As shown in Fig.1, the

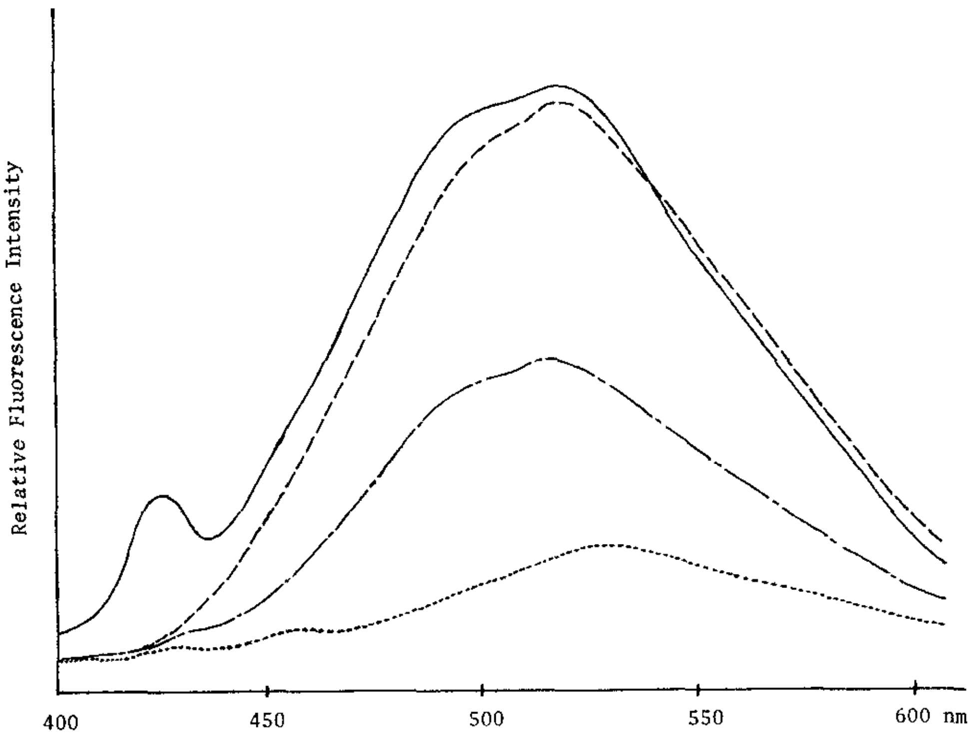

Fig. 1 Fluorescence spectrum of 0.5 x 10^{-4}M 1,8-ANS(--------) on addition of 1 x 10^{-3}M β-cyclodextrin(—·—), of 1 x 10^{-2}M β-cyclodextrin(-----) and of 1 x 10^{-3}M I(———) at pH 4.2. The exitation wave length was 375 nm.

fluorescence spectrum of 1,8-ANS in water (pH 4.2) was shifted to shorter wave length by 10 nm and strengthened by ca. 5 fold on addition of β-cyclodextrin in $1x10^{-2}M$. To be noteworthy is that the remarkable enhancement of the fluorescence intensity is observed on addition of **I**, much more remarkable than β-cyclodextrin, strongly suggesting the guest molecule is strongly incorporated into the hydrophobic cavity of **I**. Hildebrand and Benesi type analysis[7)] of the fluorescence intensity gave the association constant of **I** and 1,8-ANS, $K_{ass}=380M^{-1}$, which is by sixteen fold greater than that of β-cyclodextrin[8)].

The alkaline titration of tetrahydrochloride of **I** shows the first and second pK_a to be 3.0 and ca. 6, respectively, and at pH 6 the precipitation began, suggesting that the water soluble species of **I** are tri- and tetraprotonated **I**. At pH 4.2, 1,8-ANS is incorporated mainly by $I\cdot(H^+)_3$ ($K_{ass}\approx380$), but by $I\cdot(H^+)_4$ ($K_{ass}\approx550$) at pH 2.

Further applications of **I** to inclusion catalysts are now under way.

REFERENCES

1) a) F.Cramer and W.Dietsche, Chem.Ber., 92 378, 1739 (1959)

b) F.Cramer, W.Saenger and H.-Ch.Spatz, J.Amer.Chem.Soc., 89 14 (1967)

c) R.L. van Etten, G.A.Clowes, J.F.Sebastian and M.L.Bender, ibid., 89 3253 (1967)

d) F.Cramer and G.Mackensen, Chem.Ber., 103 2138 (1970)

e) R.Breslow and L.E.Overman, J.Amer.Chem.Soc., 92 1076 (1970)

f) K.Flohr, R.M.Paton and E.T.Kaiser, ibid., 97 671 (1975)

2) a) E.B.Kyba, K.Koga, L.R.Sousa, M.G.Siegeland and D.J.Cram, J.Amer.Chem.Soc., 95 2692 (1973)

b) R.C.Helgeson, K.Koga, J.M.Timko and D.J.Cram, ibid., 95 3021, 3023 (1973)

c) D.J.Cram, and J.M.Cram., Science 183 803 (1974)

d) M.Newcomb and D.J.Cram, J.Amer.Chem.Soc., 97 1259 (1975)

3) a) I.Tabushi, H.Yamada, Y.Yoshida and R.Oda., Tetrahedron 27 4845 (1971)

b) I.Tabushi, H.Yamada, K.Matsushita, Z.Yoshida, Y.Kuroda and R.Oda, ibid., 28 3381 (1972)

c) F.Imashiro, Z.Yoshida and I.Tabushi, ibid., 29 3521 (1973)

d) I.Tabushi, Z.Yoshida and F.Imashiro, ibid., 31 1833 (1975)

e) I.Tabushi, H.Yamada and Y.Kuroda, J.Org.Chem., 40 1946 (1975)

4) The NMR study showed that the benzene rings of [2^n]-paracyclophanes favored a "face" conformation (benzenes are perpendicular to the hypothetical molecular plane) in a statistical sense. See ref. 3e).

5) Y.Urushigawa, T.Inazu and T.Yoshino, Bull.Chem.Soc.Japan., 44 2546 (1971)

6) D.C.Turner and L.Brand., Biochemistry, 7 3381 (1968)

7) H.A.Benesi and J.H.Hildebrand, J.Amer.Chem.Soc., 71 2703 (1949); T.Kinoshita, F. Iinuma and A.Tsuji, Chem.Pharm.Bull., 22 2413 (1974)

8) Acyclic analog, N,N,N',N'-tetramethylxylylenediamine(II), shows the negligible enhancement of the fluorescence of 1,8-ANS in the same concentration range. Hildebrand and Benesi type plotting for more concentrated solution of II (0.1~0.01 M) gives K_{ass} value to be ca. 4.