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DESIGN, SYNTHESIS, AND PROPERTIES OF NOVEL WATER-SOLUBLE CYCLOPHANES HAVING NAPHTHYLPHENYLMETHANE UNITS AS HOSTS FOR ALIPHATIC AND AROMATIC GUESTS

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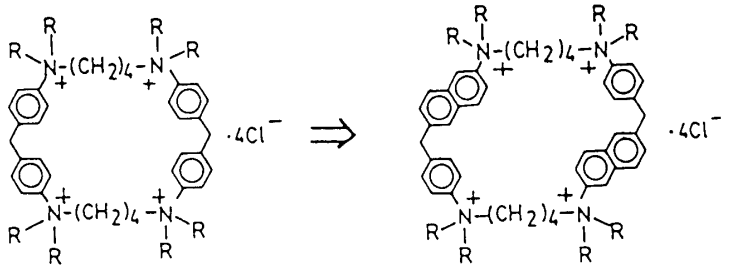
Novel water-soluble cyclophanes (**2a**, **2b**) which act as hosts having hydrophobic cavities were made by connecting two naphthylphenylmethane units and two tetramethylene bridges via four nitrogens. ^{1}H NMR spectral studies have shown that in water these cyclophanes form inclusion complexes with aliphatic as well as aromatic guests.

KEYWORDS —— cyclophane; host-guest complex; hydrophobic cavity; inclusion complex; stability constant; naphthylphenylmethane

Water-soluble cyclophanes[2] constitute a group of artificial hosts that in water can form inclusion complexes with hydrophobic guests. For complexation to occur in particular geometries and with remarkable selectivities, the importance of the fit in steric structure and charge between the cavities of the hosts and hydrophobic moieties of the guests has been recognized.[2a] Therefore, these cyclophanes are highly attractive because their cavities can be modified chemically in many ways.

We have previously reported[3] that paracyclophanes such as **1**, made by connecting two diphenylmethane units and two oligomethylene bridges via four nitrogens, work as hosts in water for aromatic guests, but not for aliphatic guests.[4] The structures of the complexes in solution were analyzed by ^{1}H NMR.[3b] The cavity of **1a** in its crystalline complexes is already known by X-ray analysis to have rectangularly shaped open ends (∿3.5x7.9 Å) with a depth of 6.5 Å.[3a] By CPK



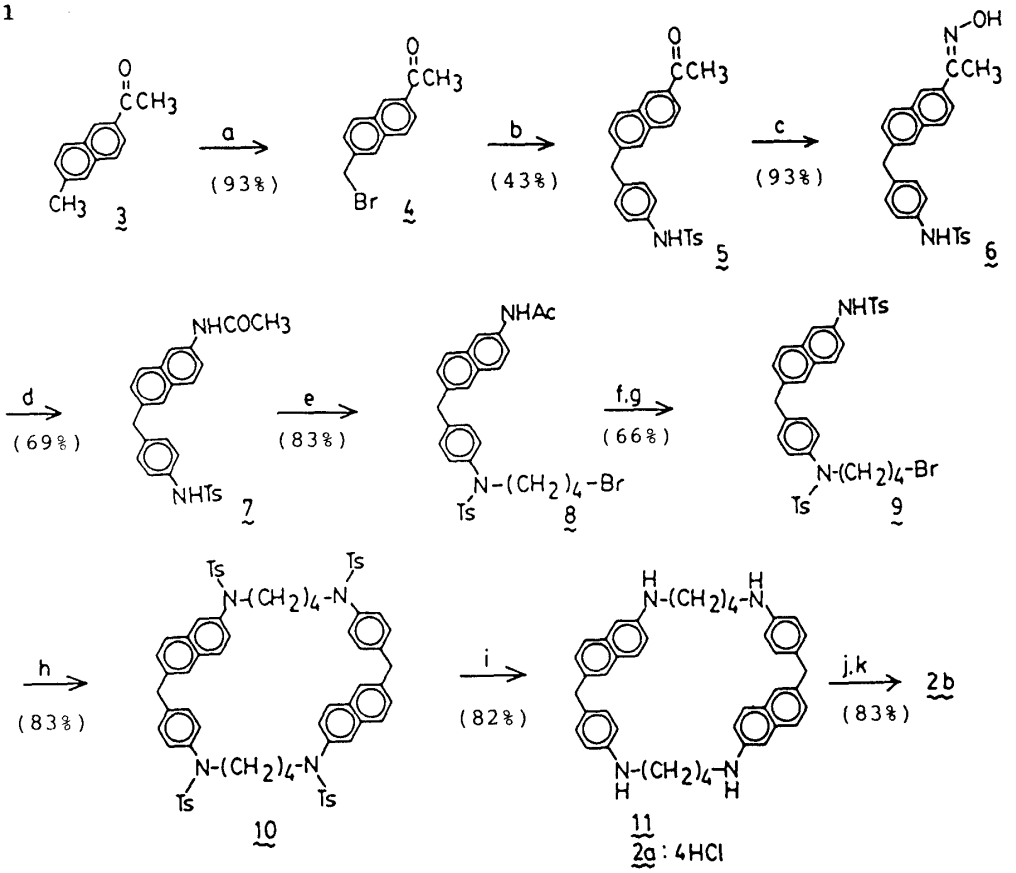
1a : R=H
1b : R=Me

2a : R=H
2b : R=Me

molecular model studies, selective complexation of **1** with aromatic guests seems to be reasonable because the shorter side of this rectangle fits well with the thickness of the aromatic ring (3.4 Å). But it is too narrow to accomodate aliphatic guests such as camphorsulfonate (**12**). To get complexes with aliphatic guests,[4] novel hosts (**2**) having cavities wider than **1** were designed[5] by substituting two of the four benzene rings of **1** with two naphthalene rings. The synthetic route is shown in Chart 1.

Complex formation between these hosts (**1**, **2**[6]) and several types of aliphatic (**12**, **13**, **14**) and aromatic (**15**, **16**, **17**) guests was investigated by ^{1}H NMR (100 MHz)[2,3b] under host concentrations below CMC.[7] The spectra of camphorsulfonate (**12**) in the absence or presence of **1a** or **2a** in acidic aqueous methanol and of deoxycholate (**14**) in the absence or presence of **1b** or **2b** in D_2O are shown in Fig. 1. Marked upfield shifts of the protons of these aliphatic guests are observed only in the presence of **2a** or **2b**. These marked upfield shifts can be ascribed to a shielding effect of the aromatic rings of the hosts, and indicate the formation of inclusion complexes.[2,3b]

Chart 1



(a) NBS, CCl_4. (b) C_6H_5-NHTs, $AlCl_3$, $CHCl_3$. (c) $NH_2OH \cdot HCl$, AcONa, MeOH. (d) H_3PO_4. (e) $Br(CH_2)_4Br$, K_2CO_3, DMF. (f) HCl, aq. MeOH. (g) TsCl, pyridine. (h) K_2CO_3, DMF. (i) 47% aq. HBr, phenol. (j) MeI, n-Bu_3N, DMF. (k) Dowex-1(chloride form), H_2O.

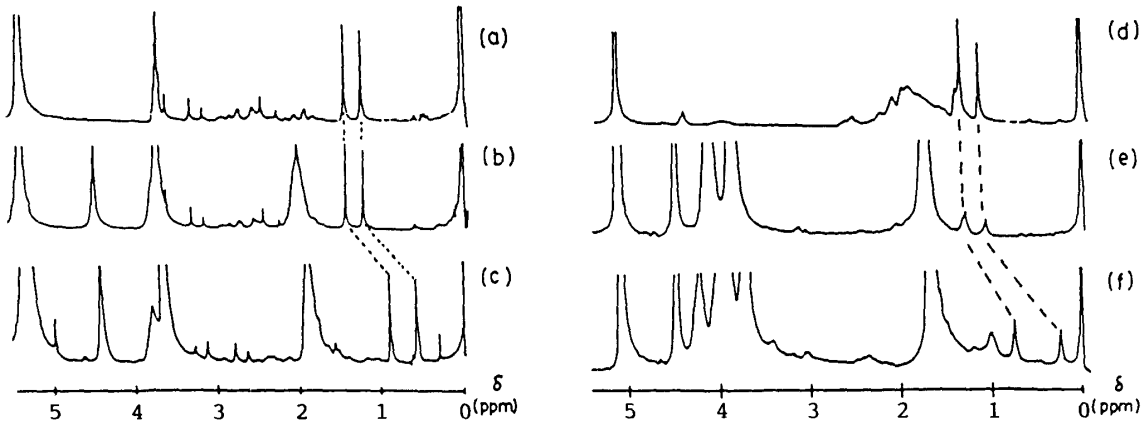
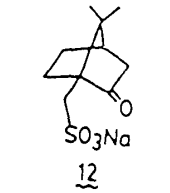


Fig. 1. ^{1}H NMR Spectra (100 MHz) of (a) **12**, (b) **12** + **1a**, (c) **12** + **2a** in CD_3OD: 0.33M DCl-D_2O (1:4) and (d) **14**, (e) **14** + **1b**, (f) **14** + **2b** in D_2O [Host]=1.0 x 10^{-2}M. [Guest]=0.5x10^{-2}M. TMS(neat) was used as an external reference.

Table I. Stability Constants (10^{-2}Ks [M^{-1}]) of the Complexes

Guest \ Host	**1a**[a]	**1b**[b]	**2a**[a]	**2b**[b]
12	-[c]	-[c]	0.2	0.8
13	-[c]	-[c]	-[d]	6
14	-[d]	-[c]	-[d]	40
15	3	33	0.3	5
16	2	9	0.8	3
17	8	15	2	3

a) In CD_3OD:0.33M DCl-D_2O (1:4). b) In D_2O. c) No evidence for complex formation. d) Not measured due to the insolubility of the guest.



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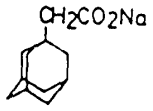

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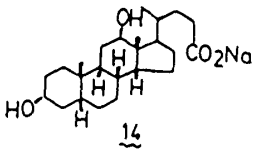

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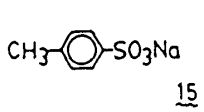

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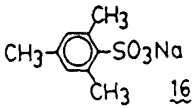

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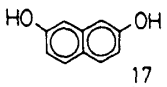

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The Benesi-Hildebrand method[9] for determining stability constants (Ks) from ^{1}H NMR chemical shift changes was applied to the complexes between these hosts (**1**, **2**) and several aliphatic and aromatic guests in aqueous solvents. The values obtained are shown in Table I.

The data show the following: (1) In contrast to hosts (**1**), hosts (**2**) form complexes with relatively large aliphatic guests (**12**, **13**, **14**). This means that, as expected, the cavities of the hosts (**2**) in their complexed states are wider than those of the hosts (**1**). (2) Aromatic guests (**15**, **16**, **17**) also form complexes with hosts (**2**), but their Ks values are smaller than those of the corresponding complexes with hosts (**1**). These differences in Ks values are considered to be due to

the differences in the fit between hosts and guests.

The novel cyclophanes (**2**) prepared here are demonstrated to work as hosts whose ability is different from that of **1**; i.e., hosts (**2**) fit aliphatic guests well, while hosts (**1**) fit aromatic guests. Thus, the cavities of cyclophanes are shown to be manipulatable by chemical modifications.

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4) Some examples of complex formation between cyclophanes and aliphatic compounds are known. See a) ref. 2d; b) ref. 2e; c) F. Vögtle and W. M. Müller, Angew. Chem Int. Ed. Engl., 21, 147(1982); d) J. Franke and F. Vögtle: ibid., 24, 219(1985).

5) In their expanded face conformations, these novel cyclophanes (**2**) can form cavities whose shortest widths are longer than 6 Å according to CPK molecular model studies.

6) Elemental analyses (as a free base (**11**) for **2a**, and as the corresponding tetraperchlorate for **2b**) and spectral data are consistent with the assigned structures.

7) Critical micelle concentrations (CMC) of **1a** (>80 mM in 0.25M HCl-H_2O), **1b** (>200 mM in H_2O), **2a** (>15 mM in MeOH:0.33M HCl-H_2O (1:4)) and **2b** (140 mM in H_2O) were determined by surface tension measurements.[8)]

8) Cf. Y. Murakami, A. Nakano, R. Miyata, and Y. Matsuda, J. Chem. Soc. Perkin Trans. 1, 1979, 1669.

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