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A NOVEL WATER-SOLUBLE CYCLOPHANE AS A HOST FOR CATIONIC, ANIONIC, AND NEUTRAL AROMATIC GUESTS

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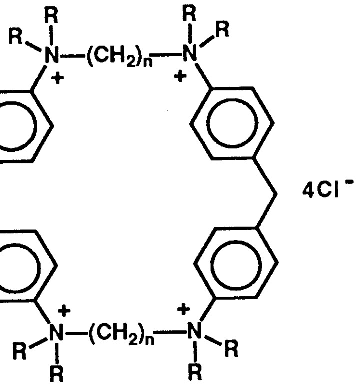
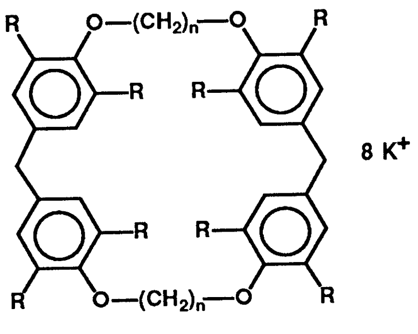
A water-soluble cyclophane (**9**) having eight carboxyl groups that are attached to the aromatic rings via a spacer (-CH_2SCH_2-) was designed and synthesized. By ^1H NMR spectral analysis, it is shown that **9** forms inclusion complexes in particular geometries with cationic, anionic, and neutral aromatic guests in D_2O at pD 7.9.

KEYWORDS macrocyclic compound; water-soluble cyclophane; aromatic guest; host-guest complex; inclusion compound; shielding effect

Water-soluble cyclophanes constitute a promising class of artificial hosts having a hydrophobic cavity of definite shape and size that form inclusion complexes with various organic guests in aqueous solution.1) We have previously reported two types of water-soluble cyclophanes that are composed of two diphenylmethane units and two bridging chains that are connected via four hetero atoms, and have charges to get water-solubility. The one type is the cationic cyclophanes (**1**),1e,2) which have four ammonium nitrogens at the periphery of the cavity, and form inclusion complexes with anionic and neutral, but not with cationic, aromatic compounds. The other type is the anionic cyclophanes (**2**),3) which have eight carboxylate groups that are directly attached to the aromatic rings, and form inclusion complexes with cationic, but not with anionic and neutral, aromatic compounds. Since charge interactions in addition to hydrophobic interactions between the host and the guest are considered to be operating at complex formation,1e) we assumed that cyclophanes having charges remote from the cavity would work as hosts for any of the cationic, anionic, and neutral aromatic guests.4) We therefore designed an anionic water-soluble cyclophane (**3**) which has two diphenylmethane units and two tetramethylene bridges that are connected via four oxygens, and has eight carboxylate groups that are attached to the aromatic rings via a spacer (-CH_2SCH_2-).



1 R = H, Me
n ≥ 4



2 R = CO_2^-, n = 4, 6
3 R = $CH_2SCH_2CO_2^-$, n = 4

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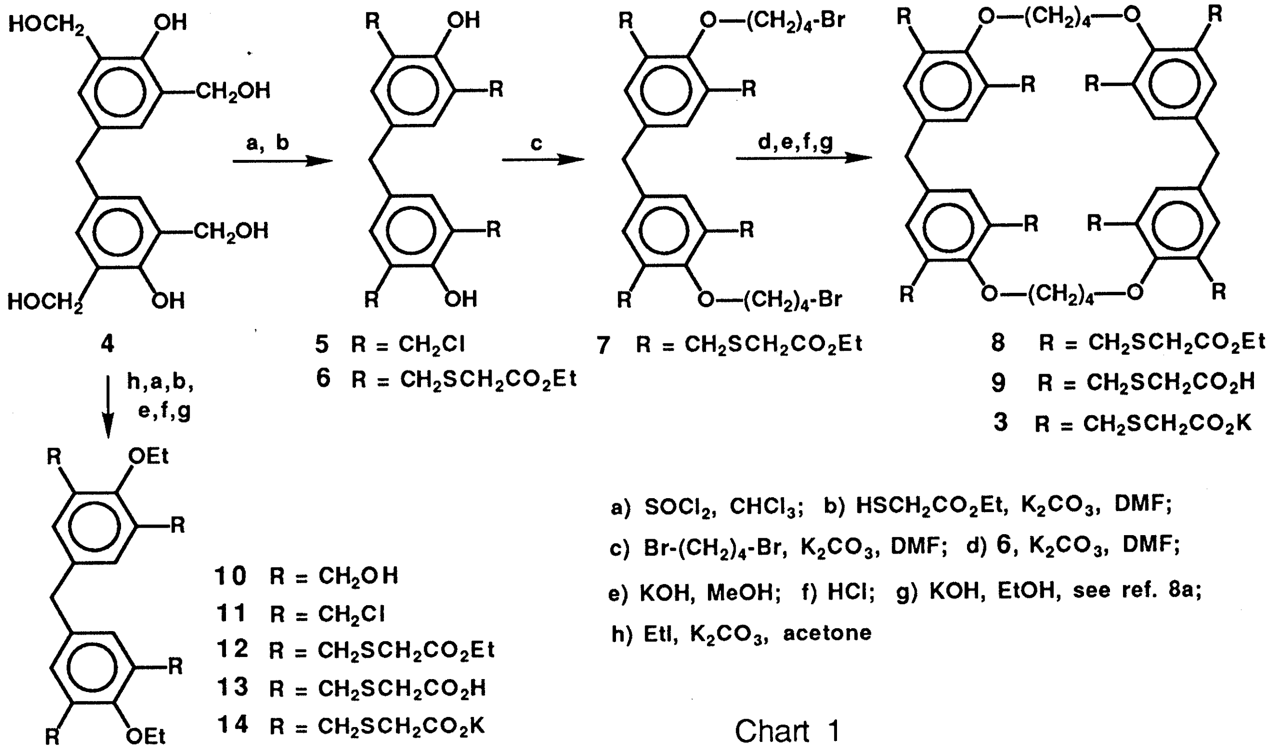


4

5 R = CH_2Cl

6 R = $CH_2SCH_2CO_2Et$

7 R = $CH_2SCH_2CO_2Et$

8 R = $CH_2SCH_2CO_2Et$

9 R = $CH_2SCH_2CO_2H$

3 R = $CH_2SCH_2CO_2K$

10 R = CH_2OH

11 R = CH_2Cl

12 R = $CH_2SCH_2CO_2Et$

13 R = $CH_2SCH_2CO_2H$

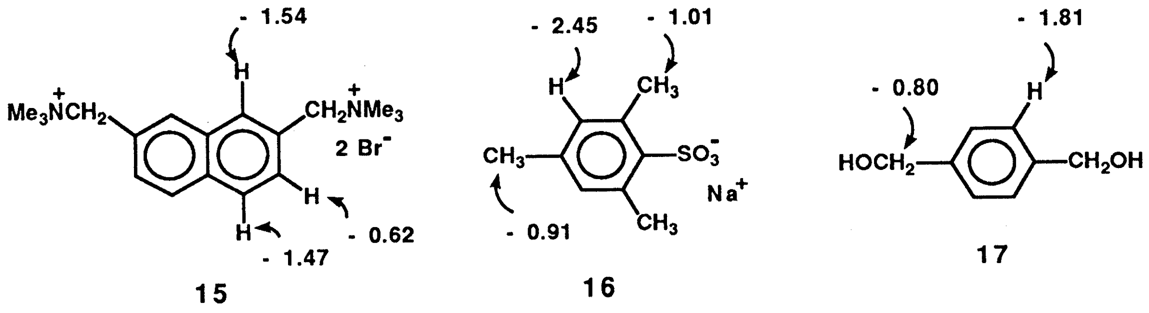
14 R = $CH_2SCH_2CO_2K$

a) $SOCl_2$, $CHCl_3$; b) $HSCH_2CO_2Et$, K_2CO_3, DMF; c) Br-$(CH_2)_4$-Br, K_2CO_3, DMF; d) **6**, K_2CO_3, DMF; e) KOH, MeOH; f) HCl; g) KOH, EtOH, see ref. 8a; h) EtI, K_2CO_3, acetone

Chart 1

The parent cyclophane (**9**) was synthesized from the known **4**[5] as shown in Chart 1.[6] Macrocyclization of **7** with **6** was carried out under high dilution condition to give **8** in 17% yield. An acyclic compound **13** was prepared from **4** and was used as a reference.

For studying cyclophane inclusion complexation in solution, proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy is the method of choice, because the inclusion of an aromatic guest into a cyclophane cavity can be convincingly demonstrated by a strong intermolecular shielding effect due to the aromatic ring(s) of the other component of the complex.[7] Therefore, NMR spectral examinations on the complex formation of **9** and **13** with cationic (**15**), anionic (**16**), and neutral (**17**) aromatic guests were made in D_2O at pD 7.9.[8] By using **9**, marked changes in chemical shifts were observed for the proton signals of the guests. The $\Delta\delta$[10] values of **15**, **16**, and **17** under the same condition[11] are shown in Chart 2. The magnitudes of $\Delta\delta$ values are dependent on the ratio of the host to the guest. Marked upfield shifts indicate the formation of the inclusion complex.[7] Stability constants (Ks) of the complexes were calculated[12] to be 2.8 x10^{3} M^{-1}, 1.7 x10^{3} M^{-1}, and 1.5 x10^{3} M^{-1} for **15**, **16**, and **17**, respectively.



15 **16** **17**

Chart 2

In contrast to the marked upfield shifts of the proton signals of these aromatic guests induced by **9**, only small changes (less than 0.2 ppm) were induced by the acyclic reference compound (**13**) under the same condition. It is thus concluded that the novel cyclophane (**9**) can work as a host to form inclusion complexes with any of the cationic, anionic, and neutral aromatic guests in weakly alkaline water.

It should be noted that each proton signals of the guests (**15**, **16**, and **17**) shifted in a different degree, indicating that the complex is formed in a particular geometry and not in a random fashion. In the case of **9·15** complex, H-1 and H-4 signals of **15** shifted upfield to a similar extent (1.54 and 1.47 ppm, respectively), while H-3 signal shifted upfield to a much smaller extent (0.62 ppm) as shown in Chart 2. This pattern is quite similar to those found for the complex between **1** (R=H, n=4) and 2,7-dihydroxynaphthalene7), and for the complex between **2** (n=4) and **15**3) reported previously. This means that the structures of the cavities of **1**, **2**, and **3** are quite similar at the complexed states and form complexes with naphthalene derivatives by "pseudoaxial inclusion." 1e,3,4)

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7) K. Odashima, A. Itai, Y Iitaka, Y. Arata, and K. Koga, *Tetrahedron Lett.*, **21**, 4347 (1980).

8) a) Since it was difficult to get **3** and **14** in analytically pure states due to their hygroscopic nature, their solutions were prepared by dissolving the corresponding **9** and **13** in KD_2PO_4(0.50 M)-KOD(0.40 M) in D_2O buffer (pD 7.9). It is not yet clear how many of the carboxyl groups of **9** and **13** are converted to the carboxylate groups in this solution. b) The critical micelle concentration (CMC) of **9** was found to be not less than 6.0×10^{-2} M by ^{1}H-NMR spectral analysis. Therefore, all experiments were carried out below 6.0×10^{-2} M about **9**. d) ^{1}H-NMR spectra were taken using tetramethylsilane as an external reference.

9) Since the system is in the NMR chemical shift fast-exchange limit, the proton signals appear at the weighed averages of the chemical shifts of the free and complexed forms.

10) $\Delta\delta = \delta$(host + guest) - δ(guest only). Negative values of indicate upfield shifts.

11) [Host] = 3.0×10^{-2} M, [Guest] = 1.0×10^{-2} M.

12) Ks values were calculated from the host-induced upfield shifts of the guest proton signals.7)

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