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# Anionic Cyclophanes as Hosts for Cationic Aromatic Guests

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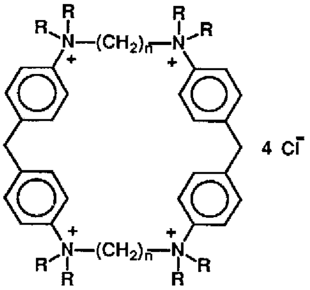
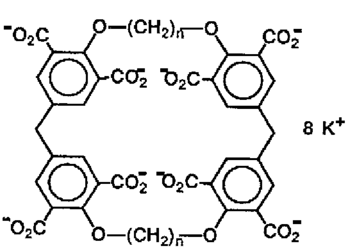
*Key Words:* cyclophanes; inclusion complexes; nmr spectra; upfield shift; stability constant of the complex

***Abstract:*** *Negatively-charged cyclophanes (2a,2b) having eight carboxylate groups on the aromatic rings were designed and synthesized. It is shown that they work as hosts that form inclusion complexes selectively with positively-charged aromatic compounds as guests in alkaline water.*

Water-soluble cyclophanes having a hydrophobic cavity constitute a promising class of artificial hosts to form inclusion complexes with various organic compounds as guests in aqueous solution.[1] We have previously reported that water-soluble cationic cyclophanes (**1**), having two diphenylmethane units and two bridging chains that are connected via four positively-charged nitrogens, form inclusion complexes in aqueous solution with anionic and neutral aromatiac compounds, but not with cationic aromatic ompounds.[1e] Cyclophanes capable of forming complexes selectively with cationic aromatic compounds were not known. Since charge interactions in addition to hydrophobic interactions between the host and the guest are considered to be important for complex formation, cyclophanes having negative charges around the cavity are expected to work as hosts for cationic aromatic guests. Based on the facts that cationic cyclophanes (**1**) provide a cavity by face conformation in which all aromatic rings are perpendicular to the macrocyclic ring, introduction of negatively-charged substituents on the aromatic rings will not interfere the expected cavity in face conformation, and seems to be a reasonable approach

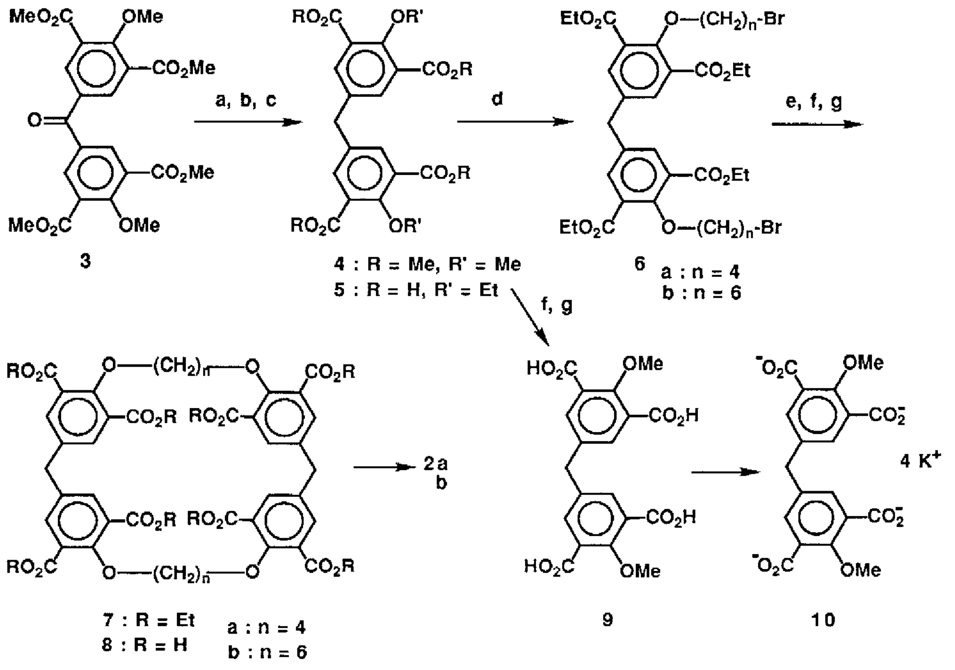


**1** R = H or Me



**2** a : n = 4
b : n = 6

Scheme 1



a) $Et_3SiH$, THF; b) $BBr_3$, $CH_2Cl_2$; c) TsOH, EtOH; d) Br-$(CH_2)_n$-Br, $K_2CO_3$, DMF; e) **5**, $K_2CO_3$, DMF; f) KOH, MeOH; g) HCl

for this purpose. Anionic cyclophanes (**2a**,**2b**) designed in the present study are $D_2$-symmetric. They have two diphenylmethane units and two bridging chains that are connected via four oxygens, and have eight carboxylate groups on the aromatic rings as shown.

The hosts (**2a**,**2b**) were synthesized from the known **3**[2] as shown in Scheme 1.[3] Macrocyclization reactions of **6a** and **6b** with **5** were carried out under high dilution condition to give **7a** and **7b** in 23% and 28% yields, respectively. An acyclic compound (**10**) having four carboxylate groups was prepared from **4** and was used as a reference compound for **2a** and **2b**.

Examinations on the complex formation of **2a**, **2b**, and **10** with several aromatic compounds (**11**-**18**) were made by $^1H$ NMR in $D_2O$[4] at pD 12.5. As an example, $^1H$ NMR spectra of (a) **11**, (b) **2a**, and (c) their mixture are shown in Figure 1.[5] In Figure 1c, marked changes in chemical shifts were observed for all the aromatic proton signals of **11**, and for the tetramethylene proton signals of **2a**. The data are shown in Figure 2. The magnitudes of $\Delta\delta$[6] values are dependent on the ratio of the host (**2a**) and the guest (**11**) in solution as shown in Figure 3 for the aromatic proton signals of **11**. Marked upfield shifts can be ascribable to a strong intermolecular shielding effect due to the aromatic ring(s) of the other component, and strongly suggest the formation of the complex between **2a** and **11**. Stability constant (*Ks*) of **2a** **11** complex was calculated[7] to be $5.8 \times 10^4$ $M^{-1}$. Similarly, marked upfield shifts of the protons signals of cationic aromatic compounds (**12**-**16**) were observed in the presence of **2a** or **2b** under the same condition.

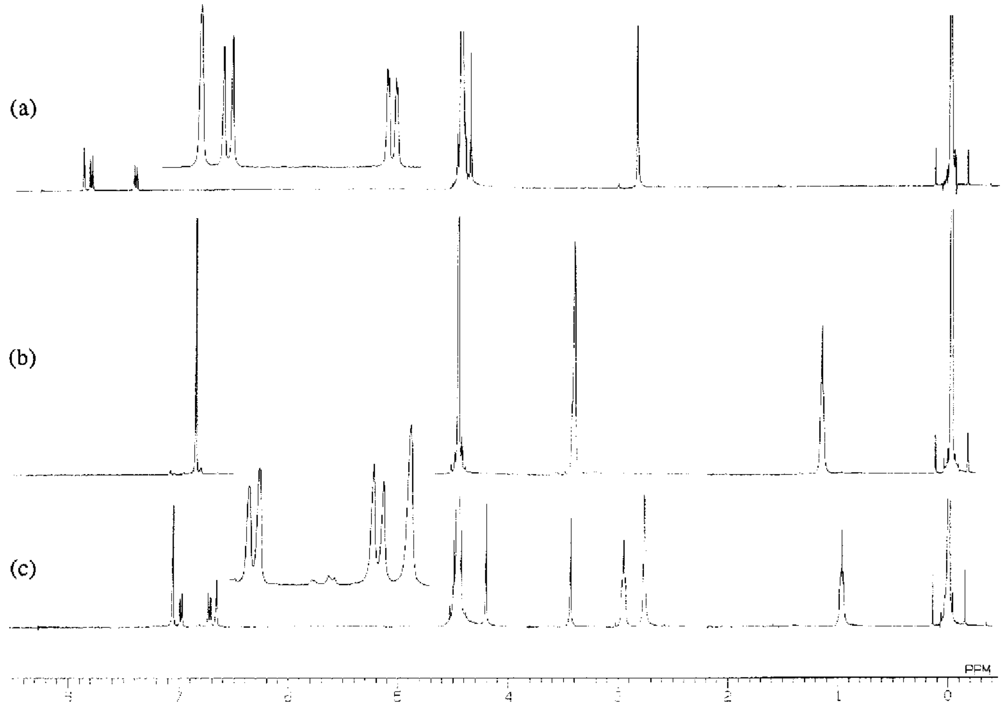


**Figure 1.** $^1H$ NMR spectra of (a) $1.0\times10^{-1}M$ **11**, (b) $1.0\times10^{-1}M$ **2a**, and (c) $1.0\times10^{-1}$ M each of **11** and **2a** in $D_2O$ solution of pD 12.5 at ambient temperature.

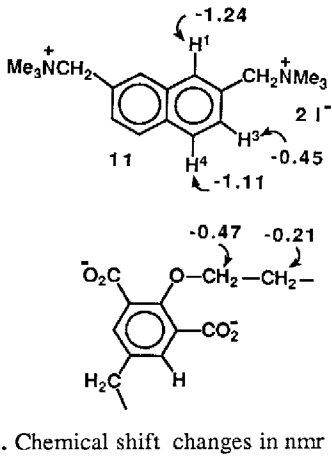


**Figure 2.** Chemical shift changes in nmr spectra.

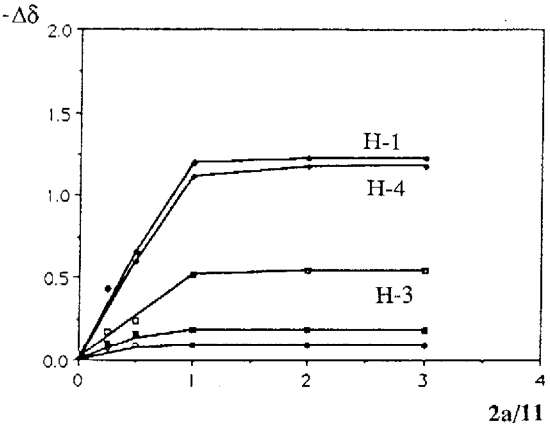
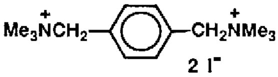
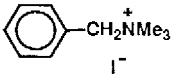


**Figure 3.** Relationship between Δδ and **2a**/**11** ratio.

In contrast to the marked chemical shift changes of the proton signals of cationic aromatic compounds induced by **2a** and **2b**, only small changes (less than 0.1 ppm) were induced by an acyclic reference compound (**10**) under the same condition. It is also shown that neutral (such as **17**) and anionic (such as **18**) aromatic



**12**



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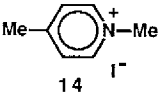

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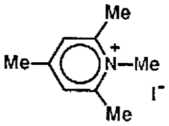

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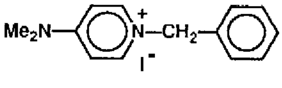

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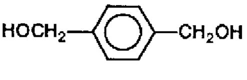
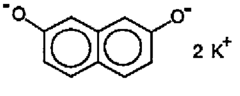


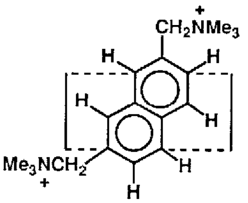
**17**



**18**

compounds do not give any evidence for complex formation with **2a** and **2b**. It is thus concluded that **2a** and **2b** work as hosts that from complexes selectively with cationic aromatic compounds as guests in alkaline water.

It should be noted that each proton signals of the host and the guest shifted to a different degree. This phenomenon indicates that the complex is formed in a particular geometry and not in a random manner. In the case of **2a 11** complex shown above, H-1 and H-4 signals of **11** shifted upfield to a similar extent (1.24 and 1.11 ppm, respectively), while H-3 signal shifted upfield to a much smaller, but still remarkable extent (0.45 ppm), and the two kinds of tetramethylene proton signals of **2a** shifted upfield to a different degree (0.47 and 0.21 ppm). This pattern is quite similar to that found for the complex between **1** (n=4, R=H) and 2,7-dihydroxynaphthalene reported previously,[8] and suggests that **2a 11** complex is formed by "pseudoaxial" inclusion as shown in **19**.



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References and Notes

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2. Seebach, F. *Ber.*, **1939**, *72*, 1635.
3. All synthetic intermediates gave satisfactory spectral and elemental analysis data.
4. a) Since it was difficult to get **2a**, **2b**, and **10** in analytically pure states due to their hygroscopic nature, their solutions were prepared by dissolving **8a**, **8b**, and **9** in alkaline $D_2O$. b) The critical micelle concentration (CMC) of **2a** in $D_2O$ was found to be not less than $10^{-1}$ M by $^1H$ NMR spectral analysis. Therefore, all experiments were carried out below $10^{-1}$ M about the hosts. c) $^1H$ NMR spectra were taken using tetramethylsilane as an external reference.
5. 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 the complexed forms.
6. $\Delta\delta = \delta$ (host + guest) - $\delta$ (host or guest only). Negative values of $\Delta\delta$ indicates upfield shifts.
7. The stability constants were calculated from the data of host-induced upfield shifts of the guest proton signals by the Benesi-Hildebrand plots.
8. Odashima, K.; Itai, A.; Iitaka, Y.; Arata, Y.; Koga, K. *Tetrahedron Lett.*, **1980**, *21*, 4347.

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