Synthesis and Inclusion Properties of "Neutral" Water-Soluble Calixarenes

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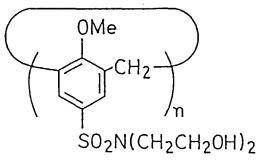
Synopsis. "Neutral" water-soluble calix[n]arenes, $\mathbf{1}_n$ (n=6 and 8) were synthesized for the first time. Below the critical micelle concentrations, they formed host-guest-type complexes with naphthalenesulfonate derivatives used as fluorescence probes. The binding sites showed the hydrophobicity comparable with those of cyclodextrins, and the cavities showed the shape selectivity for these guest molecules.

Calixarenes are cyclic oligomers made up of phenol units and have a cavity-shaped stoma in the center. They are expected, therefore, to be useful building blocks in the design of functionalized host molecules.[1-3] Nevertheless, little evidence supporting the formation of host-guest-type complexes was found in organic solvents.[4] In contrast, calixarenes bearing anionic or cationic charges are water-soluble and can include various organic guest molecules.[3,5,6] The difference between organic and aqueous media is related to the specific character of water as solvent: in water, organic compounds generally tend to associate owing to hydrophobic interactions.[7] In the course of our studies on host-guest complexation in water, we noticed that the guest selectivity of these calixarenes is primarily governed by the charge and secondly by the cavity size.[3,5,6,8,9] For example, anionic calixarenes strongly bind cationic guest molecules whereas cationic calixarenes strongly bind anionic guest molecules, and the guest selectivity on the basis of the cavity size appears as a seconddary factor. This leads us to synthesize new water-soluble calixarenes without "charges". In this note, we report a new synthesis of "neutral" water-soluble calixarenes ($\mathbf{1}_n$) and their host-guest properties in water.



$\mathbf{1}_n$

Experimental

Materials. The synthesis of 37,38,39,40,41,42-hexamethoxyhexa[*p*-sulfonato]calix[6]arene ($\mathbf{2}_6$) was reported previously.[5] 49,50,51,52,53,54,55,56-Octamethoxy-*p*-sulfonatocalix[8]arene ($\mathbf{2}_8$) was synthesized in a manner similar to that for $\mathbf{2}_6$: mp>300 °C, yield from *p*-sulfonatocalix[8]arene 85%: ^{1}H NMR (D_2O) δ=3.27 (3H, s, CH_3), 3.96 (2H, s, CH_2), 7.51 (2H, s, Ar-H). Found: C, 42.81; H, 3.07%. Calcd for $(C_8H_7O_4SNa)_8$: C, 43.25; H, 3.84%.

37,38,39,40,41,42-Hexamethoxyhexakis[*p*-chlorosulfonyl]calix[6]arene ($\mathbf{3}_6$). $\mathbf{2}_6$ (3.0 g; 2.3 mmol) was refluxed in thionyl chloride (30 ml) in the presence of a few drops of *N*,*N*-dimethylformamide (DMF). After 4 h, the reaction mixture was cooled and poured into an ice-water mixture. The precipitates were recovered by filtration and dried in vacuo: mp (dec) ca. 200 °C, yield 81%. Found: C, 43.11; H, 3.15; S, 14.72; Cl, 16.22%. Calcd for $(C_8H_7O_3SCl)_6$: C, 43.95; H, 3.23; S, 14.66; Cl, 16.21%.

49,50,51,52,53,54,55,56-Octamethoxyoctakis[*p*-chlorosulfonyl]calix[8]arene ($\mathbf{3}_8$). This compound was synthesized in a manner similar to that for $\mathbf{3}_6$: mp (decomp) ca. 200 °C, yield 99%. Found: C, 43.93; H, 3.33; S, 14.58; Cl, 15.65%. Calcd for $(C_8H_7O_3SCl)_8$: C, 43.95; H, 3.23; S, 14.66; Cl, 16.21%.

37,38,39,40,41,42-Hexamethoxyhexakis[*p*-bis(2-hydroxyethyl)aminosulfonyl]calix[6]arene ($\mathbf{1}_6$). $\mathbf{3}_6$ (3.0 g; 2.29 mmol) and bis(2-hydroxyethyl)amine (6.0 g; 57.1 mmol) were mixed in 70 ml of anhydrous tetrahydrofuran (THF) under a nitrogen stream. The solution was refluxed for 12 h. When cooled, the solution separated into two layers. The oily and colored layer was separated and diluted with methanol. The precipitates were recovered by filtration and recrystallized from 1-propanol: mp (decomp) ca. 240 °C, yield 30%; IR (KBr) ν_{so} 1140 and 1330 cm^{-1}, ν_{OH} 3380 cm^{-1}; ^{1}H NMR (Me_2SO-d_6, 100 °C) δ=3.08 (4H, t, NCH_2), 3.32 (3H, s, OCH_3), 3.51 (4H, t, OCH_2), 4.06 (2H, s, $ArCH_2Ar$), 7.41 (2H, s, Ar-H). The ^{1}H NMR spectrum was measured at 100 °C because it broadened at room temperature. Found: C, 50.11; H, 5.93; N, 4.75; S, 11.25%. Calcd for $(C_{12}H_{17}NO_5S)_6$: C, 50.16; H, 5.96; N, 4.87; S, 11.16%.

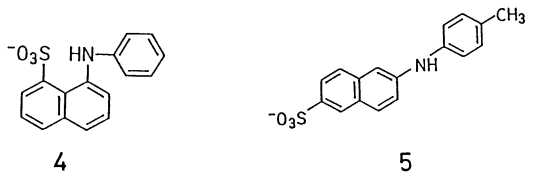
49,50,51,52,53,54,55,56-Octamethoxy-octakis[*p*-bis(2-hydroxyethyl)aminosulfonyl]calix[8]arene ($\mathbf{1}_8$). This compound was synthesized in a manner similar to that for $\mathbf{1}_6$: mp (decomp) ca. 230 °C, yield 40%; IR (KBr) ν_{so} 1140 and 1320 cm^{-1}, ν_{OH} 3360 cm^{-1}; ^{1}H NMR (Me_2SO-d_6, 100 °C) δ=3.09 (4H, t, NCH_2), 3.45 (3H, s, OCH_3), 3.50 (4H, t, OCH_2), 4.09 (2H, s, $ArCH_2Ar$), 7.42 (2H, s, Ar-H). Found: C, 50.12; H, 5.91; N, 4.86; S, 11.00%. Calcd for $(C_{12}H_{17}NO_5S)_8$: C, 50.16; H, 5.96; N, 4.87; S, 11.16%.

Miscellaneous. The surface tension of aqueous $\mathbf{1}_n$ was measured in pure water at 30 °C by the Wilhelmy method (Kyowa Kagaku Co., Model ESB-IV). The details of the experimental method were described previously.[5] The fluorescence spectra were measured at 30 °C with 8-anilino-1-naphthalenesulfonate (**4**) and 6-(*p*-toluidino)-2-naphthalenesulfonate (**5**) as fluorescence probes. The excitation wavelengths used were 365 nm for **4** and 366 nm for **5**.

Results and Discussion

The neutral calixarenes $\mathbf{1}_6$ and $\mathbf{1}_8$ were soluble in water owing to hydrophilic bis(2-hydroxyethyl)-aminosulfonyl groups. The purpose of the present study was concerned with the formation of host-guest-type complexes with neutral calixarenes ($\mathbf{1}_n$). Thus, the measurements performed must be below the cmc's (critical micelle concentrations) of $\mathbf{1}_n$. The cmc's determined at 30 °C by surface tension were 1.05×10^{-4} M** for $\mathbf{1}_6$ and 8.18×10^{-5} M for $\mathbf{1}_8$. These cmc values are considerably lower than those for anionic and

** 1 M=1 mol dm^{-3}.



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cationic water-soluble calixarenes (ca. 10^{-3} M).[5,6,8,9] The following measurements were carried out in a concentration range lower than these cmc's.

Host-guest properties of $\mathbf{1}_n$'s were estimated by fluorescence probes, 8-anilino-1-naphthalenesulfonate (**4**) and 6-(*p*-toluidino)-2-naphthalenesulfonate (**5**). Compounds **4** and **5** are useful to detect a hydrophobic domain formed in an aqueous solution because the emission maxima (λ_{EM}: 521 nm for **4** and 497 nm for **5** in water at 30 °C) correlate linearly with ethanol concentration (in vol%) in water-ethanol mixed solvent (Fig. 1). Also, the fluorescence intensity (I) increases with the increase in the strength of the hydrophobic domain.[10] Since the molecular shape of these two fluorescence probes is quite different, the molecular recognition ability of $\mathbf{1}_n$ may be evaluated (if any) from the association constants.

Figure 2 shows continuous variation plots of ΔF ($=I-I_0$) for $\mathbf{1}_n$+**4** which were followed by the fluorescence intensity. It is clearly seen from Fig. 2 that both $\mathbf{1}_6$ and $\mathbf{1}_8$ form a 1 ; 1 complex with **4**. Figure 3 shows plots of ΔF against calixarene concentrations. These are typical saturation curves which can be analyzed according to the Benesi-Hildebrand's equation.[11] We thus obtained association constants (K) for a 1 : 1 complex. Also, we could estimate the microenvironment of the binding sites from $\Delta\lambda_{EM}$

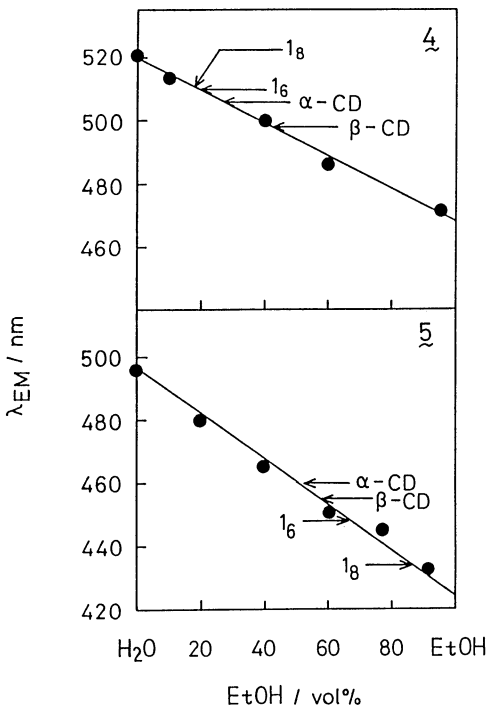

Fig. 1. Fluorescence maxima (λ_{EM}) of **4** and **5** in a water-ethanol mixed solvent at 30 °C. α-CD and β-CD denote α- and β-cyclodextrins, respectively.

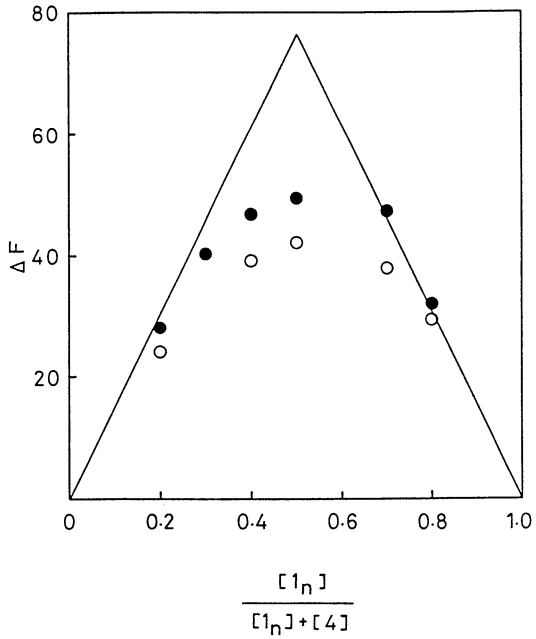

Fig. 2. Continuous variation plots of ΔF for the association of $\mathbf{1}_6$ (●), and $\mathbf{1}_8$ (○) with **4**: 30 °C, [$\mathbf{1}_6$ or $\mathbf{1}_8$]+[**4**]=1.0×10^{-5} M. ΔF is the difference of fluorescence intensities, $I-I_0$.

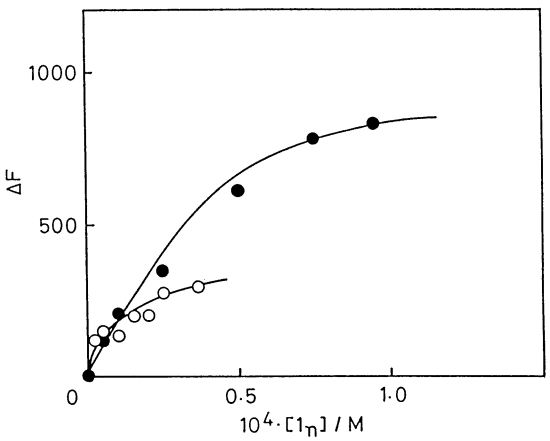

Fig. 3. Fluorescence intensity of **4** (5.0×10^{-6} M) plotted against calixarene concentrations: 30 °C, excitation 365 nm, $\mathbf{1}_6$ (●), $\mathbf{1}_8$ (○).

($=\lambda_{EM}$ at $[\mathbf{1}_n]\gg[\mathbf{4}]-\lambda_{EM}$ at $[\mathbf{1}_n]=0$). On the other hand, the fluorescence intensity of **5** sharply increased with increasing calixarene concentrations and the saturation curve was not observed for up to the cmc's. Thus, we could not estimate the K from plots of ΔF against calixarene concentrations. The result suggests that **5** is bound to $\mathbf{1}_6$ and $\mathbf{1}_8$ more strongly than **4**. Thus, we estimated only the micro environment of the binding sites from $\Delta\lambda_{EM}$ just below the cmc's. The results are summarized in Table 1.

Examination of Table 1 reveals that the λ_{EM} of **4** shifts to shorter wavelengths by 10—11 nm on the addition of $\mathbf{1}_n$, which correspond to the hydrophobicity of 15—17 vol% EtOH. Under the same measurement conditions, the hydrophobic environments of α- and β-cyclodextrins (α-CD and β-CD, respectively)

Table 1. Association Constants (K) and Shift of the Emission Maxima ($\Delta\lambda_{EM}$)

Calixarene	4			5	
	K /M^{-1}	$\Delta\lambda_{EM}$[a] /nm	Environment[c] /vol% EtOH	$\Delta\lambda_{EM}$[b] /nm	Environment[c] /vol% EtOH
$\mathbf{1}_6$	2.3×10^4	−11	17	−49	60
$\mathbf{1}_8$	9.7×10^4	−10	15	−63	85

a) $\Delta\lambda_{EM}=\lambda_{EM}$ at $[\mathbf{1}_n]\gg[\mathbf{4}]-\lambda_{EM}$ in the absence of $\mathbf{1}_n$. b) $\Delta\lambda_{EM}=\lambda_{EM}$ (just below the cmc) $-\lambda_{EM}$ (at $[\mathbf{1}_n]=0$). c) Estimated from Fig. 1.

were estimated to be 25 vol% EtOH and 41 vol% EtOH, respectively. These results indicate that in case the binding sites are evaluated with **4**, the hydrophobicity of $\mathbf{1}_n$ is apparently weaker than that of cyclodextrins. In contrast, when **5** was used as a probe, the binding sites of $\mathbf{1}_6$ and $\mathbf{1}_8$ were evaluated to be 60—85 vol% EtOH. Under the same measurement conditions, the hydrophobic environments of α-CD and β-CD were estimated to be 52 vol% EtOH and 59 vol% EtOH, respectively. Hence, calixarenes $\mathbf{1}_n$'s apparently provide the binding sites more hydrophobic than cyclodextrins. How can we explain the discrepancy between **4** and **5**? The possible rationale is that the difference is attributed to the molecular shape of fluorescence probes. Compound **5**, having a linear molecular shape, would be bound deeply into the calixarene cavity. In particular, $\mathbf{1}_8$, which is derived from the most flexible calix[8]arene,[1,2] can accept **5** deeply into the cavity in an induced-fit manner. Compound **4**, having a more or less round molecular shape, would be bound rather shallowly onto the calixarene cavity. Thus, the binding sites were estimated to be less hydrophobic. Calixarenes and cyclodextrins have a similar cavity-shaped architecture, but there exists a basic difference in the conformational freedom: that is, the conformational freedom (the rotation of each phenol unit) still remains in the calixarene cavity, whereas the cyclodextrin cavity is conformationally fixed. The present results suggest that the hydrophobicity of microenvironments, which is evaluated with probes, changes more sensitively in conformationally-free host molecules than that in conformationally-fixed host molecules.

Table 1 also shows that although the hydrophobicity of the binding sites (estimated with **4**) is similar, compound $\mathbf{1}_8$ has the K 4.2 times greater than $\mathbf{1}_6$. We previously studied the binding of organic ammonium cations to anionic water-soluble calixarenes.[12] It was shown that the K values for calix[6]arene derivatives are greater by about one order of magnitude than those for calix[8]arene derivatives. Examination of thermodynamic parameters established that the increase in K for calix[8]arene derivatives is attributed to the increase in the ΔS term. This indicates that calix[8]arene derivatives are advantageous in an induced-fit-type complexation and the driving force for complexation is the hydrophobic force.[7] This trend is quite understandable because flexible calix[8]arenes easily adopt a face-to-face orientation, required for hydrophobic interactions,[7] to guest molecules. Thus, the results indicate again that the association with water-soluble calixarenes occurs in an induced-fit manner.

In conclusion, the present paper demonstrated the first example for complexation properties of "neutral" water-soluble calixarenes. The higher guest selectivity would be achieved, in future, by controlling the conformational freedom remaining in the ring system.

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