New Water-Soluble Host Calixarenes Bearing Chiral Substituents

Takashi Arimura,[1] Hirosuke Kawabata,[1] Tsutomu Matsuda,[1] Tsuyoshi Muramatsu,[2] Hiroshi Satoh,[3] Kazunari Fujio,[3] Osamu Manabe,[3] and Seiji Shinkai*,[1]

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan, Faculty of Fishery, Nagasaki University, Nagasaki 852, Japan, and Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852, Japan

Received December 7, 1989

Chiral *p*-sulfonatocalix[n]arenes (n = 4, 6, and 8) bearing (*S*)-2-methylbutoxy groups (1(n)) have been synthesized. 1(n = 4) gave a simple, positive CD band, whereas 1(n = 6) and 1(n = 8) gave split CD bands characteristic of an exciton coupling at ^1L_a region. The sign (positive first Cotton effect and negative second Cotton effect) indicates that the chirality of excitons in these calixarenes is arranged in a clockwise direction. The difference between 1(n = 4) and the larger calixarenes 1(n = 6) and 1(n = 8) is accounted for by the difference in the ring rigidity: that is, 1(n = 6) and 1(n = 8) are flexible enough to allow interactions of excitons in the excited state, whereas 1(n = 4) is too rigid to allow the interactions. On the addition of guest molecules (aliphatic alcohols) the CD band of 1(n = 4) was scarcely changed, whereas those of 1(n = 6) and 1(n = 8) were weakened. This result, together with the ^1H NMR data, suggests that the conformational fluctuation in 1(n = 6) and 1(n = 8) is considerably suppressed upon inclusion of these guest molecules. In the presence of 1(n = 6) or 1(n = 8) ICD bands were also observed for certain dye molecules (e.g., 4-cyano-4′-(diethylamino)azobenzene and 4-nitro-4′-(diethylamino)azobenzene). Careful comparison of the ICD spectra with the absorption spectra established that the calixarene complexes having 2:1 guest/calixarene stoichiometry are ICD-active whereas those having 1:1 guest/calixarene stoichiometry are ICD-silent. Interestingly, the sign of the Cotton effect showed that 4-cyano-4′-(diethylamino)azobenzene included in 1(n = 6) gives a counterclockwise exciton coupling, whereas that included in 1(n = 8) gives a clockwise exciton coupling. Thus, the present study demonstrates that the CD spectral technique is very useful to obtain insights into calixarene conformations and calixarene complexation properties.

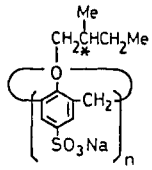
The chemistry of cyclodextrins has been a focus of interest in host–guest chemistry for the last two decades, and many functionalized host molecules which can partly mimic the in vivo action of enzymes have been exploited.[4-7] Why have cyclodextrins attracted the attention of so many chemists for so many years? We believe that it is related to the supramolecular nature of cyclodextrins: that is, cyclodextrins can provide (1) systematic change in the cavity size that plays an important role in molecular recognition, (2) water solubility that is indispensable to enzyme-mimicking host molecules, (3) transparency at UV–visible wavelength region that is convenient for spectrophotometric studies, and (4) chirality. "Calixarenes" are cyclic oligomers made up of benzene units as cyclodextrins are made up of glucose units. The work of Gutsche and co-workers have allowed the facile synthesis of a variety of calixarenes in good yields,[8] and they are now expected to be useful as a new recognition site in the design of enzyme mimics in totally synthetic systems.[8-15] In order to elaborate calixarenes as supramolecules comparable with cyclodextrins, one should introduce these four requirements into calixarenes. Since one can selectively synthesize calixarenes from tetramer to octamer, requirement 1 (systematic change in the cavity size) has already been satisfied. In order to satisfy requirement 2, we have synthesized several water-soluble calixarenes which can form host–guest-type complexes in an aqueous system.[11,12,16,17]

As the third step to supramolecular calixarenes, we are interested in the synthesis of chiral calixarenes which would eventually satisfy requirement 4.[13] Chiral recognition is one of the most sophisticated functions of enzymes which remains difficult to realize with artificial enzyme models. It is worthwhile to mention, however, that chiral recognition has already been achieved (although partly in some cases) in cyclodextrin-based artificial enzymes.[4-7] This is solely due to the chirality of the cyclodextrin cavity made up of D-glucose units. It thus occurred to us that introduction of chiral substituents into calixarenes would be of great value for development of a new class of artificial enzymes with the chiral recognition ability.[18,19] The CD technique is one of the most useful tools to evaluate asymmetric interactions between host and guest molecules in solution. When chiral host–guest interactions are evaluated by the CD spectroscopic method, there exist four

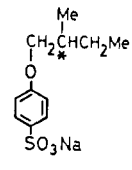
(1) Kyushu University.
(2) Faculty of Fishery, Nagasaki University.
(3) Faculty of Engineering, Nagasaki University.
(4) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.
(5) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.
(6) Bender, M. L.; Komiyama, M. *In Cyclodextrin Chemistry*; Springer-Verlag: New York, 1977.
(7) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146.
(8) For comprehensive reviews of calixarene chemistry, see: (a) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. (b) Gutsche, C. D. In *Synthesis of Macrocycles: The Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; John Wiley & Sons Inc.: New York, 1987; p 93.
(9) Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153.
(10) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.
(11) Shinkai, S. *Pure Appl. Chem.* **1986**, *58*, 1523.
(12) Shinkai, S.; Manabe, O. *Nippon Kagaku Kaishi* **1988**, *12*, 1917.
(13) (a) Shinkai, S.; Arimura, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1987**, 1495. (b) Arimura, T.; Edamitsu, S.; Shinkai, S.; Manabe, O.; Muramatsu, T.; Tashiro, M. *Chem. Lett.* **1987**, 2269.
(14) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.
(15) Casabianca, H.; Royer, J.; Satrallah, A.; Taty, C.-A.; Vicens, J. *Tetrahedron Lett.* **1987**, *28*, 6595.
(16) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409.
(17) A water soluble calixarene (*p*-*tert*-butylcalix[4]arenetetracarboxylic acid) was also reported by the Italian group, but the water solubility is not enough, especially, in the presence of salts: Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981. More water-soluble calixarenes were recently reported by Gutsche et al., (see ref 10): Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177. Arimura, T.; Nagasaki, T.; Shinkai, S.; Matsuda, T. *J. Org. Chem.* **1989**, *54*, 3766.
(18) Vicens et al. (*Tetrahedron Lett.* **1987**, *28*, 6595) and Böhmer et al. (*J. Org. Chem.* **1987**, *52*, 3200) have synthesized asymmetrically substituted calix[4]arenes, but these chiral calixarenes were not obtained in optically pure form.
(19) Gutsche et al. (*J. Org. Chem.* **1979**, *44*, 3962) have synthesized camphorsulfonyl derivatives of calix[8]arene. This is the first example of calixarenes bearing asymmetric substituents.

0022-3263/91/1956-0301$02.50/0

different combinations: they are interactions of (a) chiral, chromophoric host with guest, (b) host with chiral chromophoric guest, (c) chromophoric host with chiral guest, and (d) chiral host with chromophoric guest. Categories a and b are detected as a change in the CD spectra whereas categories c and d are detected as a change in the ICD spectra. The chiral recognition detected for cyclodextrin complexes[20-22] is classified as category d. We here report the first example of synthesis and host-guest properties of chiral, water-soluble calix[n]arenes (n = 4, 6, and 8: **1**(n)) with (*S*)-2-methylbutoxy groups. The present study is thus classified as categories a and d. We have found that the CD and ICD spectra of **1**(n) give useful information about calixarene conformations and guest inclusion properties.



1(n)



2

Experimental Section

Materials. Preparations of sulfonated calix[n]arenes (n = 4, 6, and 8) were described previously.[23]

5,11,17,23,29,35-Hexasulfonato-37,38,39,40,41,42-hexakis-[(*S*)-2-methylbutoxy]calix[6]arene (1(n = 6)). The hexasodium salt of 5,11,17,23,29,35-hexasulfonatocalix[6]arene (1.6 g, 1.2 mmol) in 8 mL of water containing NaOH (0.80 g, 20 mmol) and (*S*)-1-bromo-2-methylbutane (3.0 g, 20 mmol: purchased from Aldrich, optical purity 99%) in 32 mL of dimethyl sulfoxide were mixed in a Teflon flask, and the mixture was heated at 82–84 °C for 30 h. After cooling, the precipitated crystals were recovered by filtration and washed with cold methanol and then with methanol–water (4:1 v/v): mp >300 °C; yield 0.97 g (43%); IR (KBr) ν_{CH} 2950, 2910, 2860 cm^{-1}; ν_{SO} 1180, 1050 cm^{-1}; ^{1}H NMR (D_2O) δ 0.66 ($CH_3(CH_2)$, t (J = 6 Hz), 3 H), 0.70 ($CH_3(CH)$, d (J = 5 Hz), 3 H), 0.95 and 1.29 ($CH_2(CH_3)$, m, 1 H each), 1.62 (CH, m, 1 H), 3.34 and 3.48 (CH_2O, br s, 1 H each), 4.08 ($ArCH_2Ar$, s, 2 H), 7.54 (ArH, s, 2 H). Anal. Calcd for $(C_{12}H_{15}O_4SNa\cdot 2H_2O)_6$: C, 45.85; H, 6.09; S, 10.2. Found: C, 46.01; H, 5.79; S, 9.3. The S % was determined by a fluorescent X-ray method (Philips PV-9500). As the crystals were strongly hygroscopic, it was quite difficult to remove concomitant water molecules.

5,11,17,23,29,35,41,47-Octasulfonato-49,50,51,52,53,54,55,56-octakis[(*S*)-2-methylbutoxy]calix[8]arene (1(n = 8)). This compound was synthesized from 5,11,17,23,29,35,41,47-octasulfonatocalix[8]arene (1.0 g, 0.52 mmol) and (*S*)-1-bromo-2-methylbutane in a manner similar to that described for **1**(n=6): mp >300 °C; yield 0.33 g (25%); IR (KBr) ν_{CH} 2965, 2880 cm^{-1}; ν_{SO} 1185 cm^{-1}; ^{1}H NMR (D_2O) δ 0.66 ($CH_3(CH_2)$, t (J = 6.5 Hz), 3 H), 0.83 ($CH_3(CH)$, d (J = 5 Hz), 3 H), 1.17–1.89 (CH and $CH_2(CH_3)$, m, 3 H), 3.03–4.60 (CH_2O and $ArCH_2Ar$, m, 4 H), 7.54 (ArH, s, 2 H). Anal. Calcd for $(C_{12}H_{15}O_4SNa\cdot 2.8H_2O)_8$: C, 43.84; H, 6.32; S, 9.7. Found: C, 43.87; H, 6.38; S, 9.2.

5,11,17,23-Tetrasulfonato-25,26,27,28-tetrakis[(*S*)-2-methylbutoxy]calix[6]arene (1(n = 4)). This compound was synthesized from 5,11,17,23-tetrasulfonatocalix[4]arene (1.0 g, 1.6 mmol) and (*S*)-1-bromo-2-methylbutane, but the yield was relatively low because of the steric crowding of four (*S*)-2-methylbutoxy groups incorporated onto the small ring. We isolated the disubstituted calix[4]arene derivative as a byproduct. **1**(n = 4): mp >300 °C; yield 0.12 g (9%); IR (KBr) ν_{CH} 2980, 2890 cm^{-1}; ν_{SO} 1180 cm^{-1}; ^{1}H NMR (D_2O) δ 0.94 ($CH_3(CH_2)$, t (J = 6.5 Hz), 3 H), 1.03 ($CH_3(CH)$, d (J = 5 Hz), 3 H), 1.19 and 1.66 ($CH_2(CH_3)$, m, 1 H each), 2.08 (CH, m, 1 H), 3.85 and 4.04 (CH_2O, d (J = 6 Hz), 1 H each), 3.49 and 4.59 ($ArCH_2Ar$, d (J = 13 Hz), 1 H each), 7.25 (ArH, s, 2 H). Anal. Calcd for $(C_{12}H_{15}O_4SNa\cdot 1.6H_2O)_4$: C, 46.93; H, 5.97; S, 10.4. Found: C, 47.24; H, 5.71; S, 11.1.

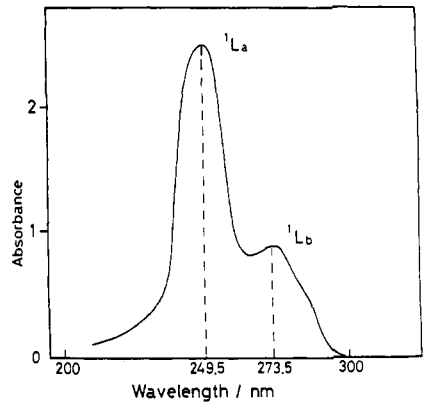


Figure 1. Absorption spectrum of **1**(n = 4): 20 °C, pH 6.9, with 0.067 M phosphate buffer, [**1**(n = 4)] = 5.00 × 10^{-4} M, water–Me_2NCHO (98:6:1.4 v/v).

Table I. Absorption Spectral Data of 1(n) and 2[a]

calixarene	λ_{max} (ϵ), nm	
	^1L_a	^1L_b
1(n = 4)	249.5 (5050)	273.5 (1790)
1(n = 6)	245.0 (6760)	270.0 (3250)
1(n = 8)	246.0 (9220)	270.0 (4540)
2	249.5 (3080)	277.0 (708)

[a] 20 °C, pH 6.9, with 0.067 M phosphate buffer.

Sodium (*S*)-4-(2-Methylbutoxy)benzenesulfonate (2). An aqueous solution (10 mL) containing sodium *p*-hydroxybenzenesulfonate (1.90 g, 8.3 mmol) and NaOH (0.68 g, 16 mmol) was mixed with 38 mL of isopropoyl alcohol containing (*S*)-1-bromo-2-methylbutane (2.5 g, 17 mmol), and the solution was refluxed for 50 h. After cooling, the solution was concentrated to about 15 mL in vacuo. The precipitated crystals were recovered by filtration, washed with isopropyl alcohol, and then recrystallized from methanol–water (10:1 v/v): mp >300 °C; yield 1.6 g (73%); IR (KBr) ν_{CH} 3090, 3040, 2960, 2910, 2860 cm^{-1}; ν_{SO} 1180, 1050 cm^{-1}; ^{1}H NMR (D_2O) δ 0.91 ($CH_3(CH_2)$, t (J = 7.5 Hz), 3 H), 0.99 ($CH_3(CH)$, d (J = 6.6 Hz), 3 H), 1.22 and 1.52 ($CH_2(CH_3)$, m, 1 H each), 1.86 (CH, m, 1 H), 3.91 and 4.00 (CH_2O, d (J = 6.8 Hz), 1 H each), 7.08 and 7.73 (ArH, d and d (J = 8.9 Hz), 2 H each). Anal. Calcd for $C_{11}H_{15}O_4SNa$: C, 49.62; H, 5.68. Found: C, 49.95; H, 5.62.

Spectroscopic Measurements. The CD spectra were measured at 20 °C in a 1.0-mm cell with a JASCO J-500 CD spectrophotometer. The spectral measurements were repeated at least five times on each sample solution, and the integrated spectra were finally taken out of a computer. The ^{1}H NMR spectra were measured at 20 °C with a 400-MHz NMR apparatus (JEOL GX-400).

Results and Discussion

Absorption and CD Spectra of 1(n). The purpose of the present study is related to the molecular recognition. Hence, the measurements must be carried out below the CMC's (critical micelle concentrations) of **1**(n) because not only the host–guest-type interaction but the binding to the aggregate must be taken into consideration above the CMC's. We thus determined the CMC's by electric conductance at 30 °C:[24] they were 2.0 × 10^{-3} M for **1**(n = 4), 1.1 × 10^{-3} M for **1**(n = 6), and 5.0 × 10^{-4} M for **1**(n = 8). The following measurements were all carried out under these CMC values.

(20) Takamura, K.; Inoue, S.; Kusu, F. *Chem. Lett.* **1983**, 233.
(21) Shimizu, H.; Kaito, A.; Hatano, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 513.
(22) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 465 and references cited therein.
(23) Shinkai, S.; Araki, K.; Tsubaki, T.; Arimura, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2297.
(24) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587.

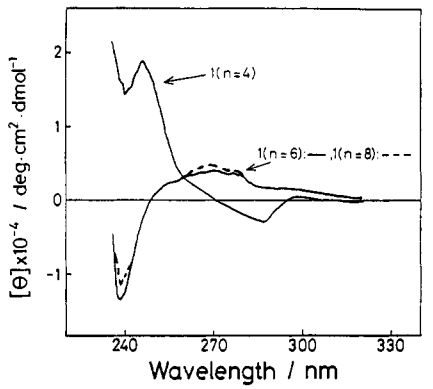


Figure 2. CD spectra of 1(n): 20 °C, pH 6.9, with 0.067 M phosphate buffer, [1(n = 4)] = 5.00 × 10^{-4} M, [1(n = 6)] = 3.30 × 10^{-4} M, [1(n = 8)] = 2.50 × 10^{-4} M, water–Me_2NCHO (98.6:1.4 v/v).

Table II. CD Spectral Data of 1(n)[a]

calixarene	λ_{max} (θ), nm
1(n = 4)	248.5 (+18900)
1(n = 6)	236.0 (−14100), 269.0 (+3300)
1(n = 8)	236.0 (−12200), 269.0 (+4030)

[a] 20 °C, pH 6.9, with 0.067 M phosphate buffer.

As a prelude to CD spectral studies, we measured the absorption spectra of 1(n) in water at 20 °C. 1(n) and **2** (noncyclic analogue) gave similar absorption spectra. A typical spectrum for 1(n = 4) is illustrated in Figure 1, and the absorption maxima (^1L_a and ^1L_b) are summarized in Table I. It is seen from these measurements that 1(n) and the reference compound **2** have two absorption bands at around 250 and 270 nm. The strong absorption band at around 250 nm is attributed to an electric transition moment along the long molecular axis (^1L_a) and the relatively weak absorption band at around 270 nm to that along the short molecular axis (^1L_b).

In the CD spectral measurements, **2** did not give any perceptible CD band even at the high concentration (50 mM). In contrast, 1(n) gave a strong positive Cotton effect in the ^1L_a region and a weak negative Cotton effect in the ^1L_b region, indicating that circular dichroism is observed more sensitively for the cyclic structure. Although the reason is not understood well at present, it should be related to a structure of 1(n = 4). In chiral compounds having two (or more than two) electric transition moments, a strong CD band is observed when the moments are oriented toward the same or nearly same direction.[25] In 1(n = 4) with a cone conformation, four electric transition moments orientate into the same direction. Conceivably, this unique structure is the origin of the perceptible CD band.

As shown in Figure 2, the CD spectra of 1(n = 6) and 1(n = 8) are similar but that of 1(n = 4) is quite different. The CD maxima (and minima) are summarized in Table II. Careful examination of Figures 1 and 2 and Tables I and II reveals several important insights into calixarene conformations in water. It is known that to give an exciton coupling two electric transition moments must experience an angle (ϕ) smaller than 90°. In this case the absorption maximum appears at shorter wavelength than that of the monomeric analogue with a single transition moment.[25] The λ_{max} (^1L_b) value for 1(n = 4) is equal to that for **2**. This implies that the exciton coupling is not expected for 1(n = 4). In contrast, the λ_{max} (^1L_b) values for 1(n = 6) and 1(n = 8) shift to shorter wavelengths by 3.5–4.5 nm: that is, the exciton coupling is expected for these calixarenes. 1(n = 6) and 1(n = 8) give the first, positive Cotton effect at 269 nm and the second, negative Cotton effect at 236 nm. The λ_{max} values for the first, positive Cotton effect move to longer wavelength by 23–24 nm from those for the ^1L_a band in the absorption spectra, and the λ_{max} for the second, negative Cotton effect move to shorter wavelength by 9–10 nm. The split CD spectral pattern suggests that the Cotton effects arise from an exciton coupling of each chromophoric benzene unit in 1(n = 6) and 1(n = 8).[26] The positive sign for the first Cotton effect indicates that the dipoles along the long molecular axis are oriented in a chiral, clockwise direction when they interact in the excited state.[25] These findings support the view that the calixarene rings of 1(n = 6) and 1(n = 8) are flexible enough to allow the molecular motion required for an exciton coupling. The conclusion is compatible with the ^1H NMR data: they give a singlet resonance peak at around 4.0 ppm for the $ArCH_2Ar$ protons, which is an indication of flexible calixarenes (Figure 3).[8,9]

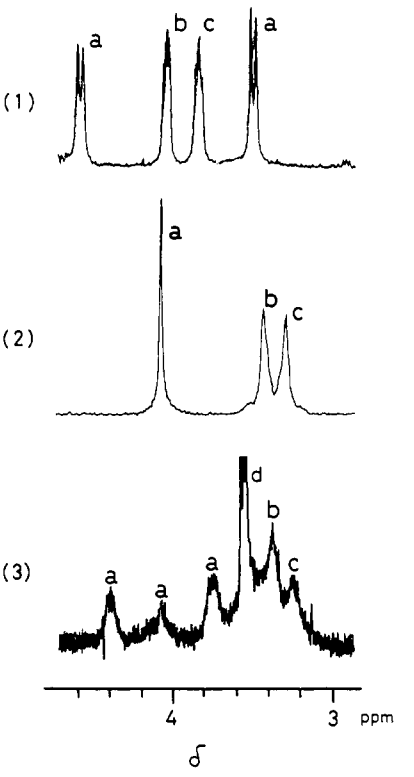


Figure 3. Partial ^1H NMR for the $ArCH_2Ar$ protons: (1) 1(n = 4), (a) $ArCH_2Ar$, (b) and (c) OCH_2; (2) 1(n = 6), (a) $ArCH_2Ar$, (b) and (c) OCH_2; (3) 1(n = 6) + 1-dodecanol (1.0 × 10^{-3} M), (a) $ArCH_2Ar$, (b) and (c) OCH_2 in 1(n = 6), (d) OCH_2 in 1-dodecanol, 25 °C, D_2O, [1(n)] = 3.30 × 10^{-4} M, internal standard DSS. The resolution in spectrum 3 was inferior to others probably because of suppression of the molecular motion. 1(n = 8) gave the ^1H NMR spectrum similar to 2.

In contrast, the ^1H NMR data: they give a singlet resonance peak at around 4.0 ppm for the $ArCH_2Ar$ protons, which is an indication of flexible calixarenes (Figure 3).[8,9]

In 1(n = 4), on the other hand, the λ_{max} in the CD spectrum (248.5 nm) is almost equal to that for ^1L_a in the absorption spectrum (249.5 nm). The agreement suggests the absence of an exciton coupling in 1(n = 4): that is, the electric transition moments in 1(n = 4) cannot adopt ϕ smaller than 90°, and each moment is electronically independent. Why is the CD spectrum for 1(n = 4) so

(25) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Harada, N.; Nakanishi, K. In *Circular Dichroic Spectroscopy*; Tokyo Kagaku Dojin: Tokyo, 1982.

(26) The CD spectra for 1(n = 6) and 1(n = 8) are not so symmetric as those expected for a typical exciton coupling. The positive CD bands may be partially due to the overlapping of two bands arising from ^1L_a and ^1L_b.

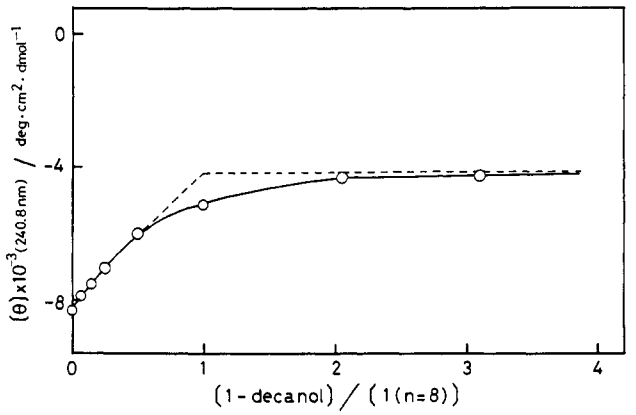


Figure 4. Plot of θ vs [1-decanol] for 1(n = 8) (2.50×10^{-4} M): the measurement conditions are recorded in a caption to Figure 2.

different from those for 1(n = 6) and 1(n = 8)? CPK models and X-ray crystallographic studies reveal that calix[6]arene and calix[8]arene constitute a cavity-shaped stoma composed of benzene units and the rings are relatively flexible, whereas calix[4]arene has a bowl-shaped structure (one side is open whereas another side is close) and the ring is very rigid.[27,28] The rigidity in calix[4]arene is caused by steric crowding with the OH groups on the narrow, lower rim. Introduction of alkyl substituents into the OH groups would make the ring more rigid. In fact, it is known that the *O*-alkylation reactions are frequently hampered by steric hindrance and often give partial alkylation products.[29-31] This steric rigidity would suppress the fluctuation of the 1(n = 4) ring and inhibit the exciton coupling.[32] As shown in Figure 3, the $ArCH_2Ar$ protons of 1(n = 6) and 1(n = 8) appear as a sharp singlet, whereas the $ArCH_2Ar$ protons of 1(n = 4) appear as a pair of doublets. This supports the view that 1(n = 4) is fixed as a cone and the molecular motion is fairly frozen by the bulky (*S*)-2-methylbutoxy groups. These ^1H NMR data are in line with the CD spectral data discussed above.

Host–Guest Complexation. It is of great significance to study how the calixarene conformation changes upon inclusion of guest molecules. We tried to study this through the CD spectral measurements. We chose aliphatic alcohols as guest molecules because they do not have any absorption band at ^1L_a region and are mostly commercially available.

The CD spectrum of 1(n = 4) was not affected at all by the addition of these guest molecules. We found, however, that ^1H NMR chemical shifts of aliphatic alcohols move to the higher magnetic field in the presence of 1(n = 4). This means that 1(n = 4) possibly forms host–guest-type complexes with these guest molecules. In fact, we have found that similar calix[4]arene derivatives can form host–guest-type complexes in water.[33,34] One can thus conclude that a conformational change in 1(n = 4) is not induced by the complex formation. The finding is also accounted for by the rigidity of the 1(n = 4) ring. In contrast, the CD spectral bands of 1(n = 6) and 1(n = 8) were affected by the addition of these guest molecules. The CD bands were weakened with increasing guest molecule concentrations (see Figure 1 in ref 13a). The spectral change occurred with several isosbestic points, indicating that in 1(n = 6) and 1(n = 8) the ring conformation is changed by guest inclusion. The stoichiometry for the complexes was investigated by the molar ratio method: for example, Figure 4 shows a plot of θ for 1(n = 8) against the 1-decanol concentration. The plot establishes that 1(n = 8) forms a 1:1 complex with 1-decanol. The same 1:1 stoichiometry was observed for other complexes. Hence, the association process is simply expressed by the equation, 1(n) + guest $\rightleftharpoons$ 1(n)·guest. The association constants (K) were determined from plots of θ vs [guest] using eq 1,[35] where θ_x, θ_H, and θ_{HG} are molar el-

$$K = \frac{\theta_x - \theta_H}{(\theta_{HG} - \theta_x)[C_G - C_H(\theta_x - \theta_H)/(\theta_{HG} - \theta_H)]} \quad (1)$$

lipticities (in deg cm^2 dmol^{-1}) for sample, calixarene alone, and highest guest excess and C_G and C_H are the total guest concentration and the total calixarene concentration, respectively. The results are summarized in Table III.

Table III. Association Constants (K)[a]

guest	$10^{-3}K$, M^{-1} 1(n = 6)	1(n = 8)
ethanol	nd	nd
1-butanol	nd	nd
1-hexanol	0.14	nd
1-heptanol	1.2	nd
1-octanol	7.8	0.07
1-decanol	5.1	1.1
1-dodecanol	14	10
2,2-dimethyl-3-hexanol	0.25	0.08
cyclohexanol	0.08	nd
β-ionone	9.4	8.8

[a] 20 °C, pH 6.9, with 0.067 M phosphate buffer, 3% vol *N*,*N*-dimethylformamide, [1(n)] = (2.5–3.3) $\times 10^{-4}$ M, [guest] = (0.2–7.5) $\times 10^{-4}$ M. Nd denotes that the CD spectral change was not detected.

The data in Table III lead to the following conclusions: (i) the CD spectral change is observed for alcohols higher than 1-butanol for 1(n = 6) and higher than 1-heptanol for 1(n = 8), (ii) the K values increase with increasing chain length in guest alcohols, and (iii) the K values for 1(n = 6) are generally greater than those for 1(n = 8). On the basis of X-ray crystallographic studies and CPK molecular models the upper-rim diameter of calix[6]arene is estimated to be 5.0 Å. Therefore, the molecular recognition pattern of calix[6]arene is expected to be similar to that of β-cyclodextrin (diameter 5.5–5.9 Å). The K for β-cyclodextrin and cyclohexanol is estimated to be 400 M^{-1}.[36] As the K for 1(n = 6) is estimated to be 80 M^{-1}, the cavity of 1(n = 6) may be less hydrophobic than that of β-cyclodextrin.

We now discuss why the CD spectra changed upon inclusion of guest molecules. As described above, the ^1H NMR measurements suggest that 1(n = 6) and 1(n = 8)

(27) (a) Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 1709. (b) *Ibid.* **1988**, *110*, 610.
(28) (a) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiano, P. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 197. (b) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B. L. *J. Org. Chem.* **1986**, *51*, 3581.
(29) Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I. *Pure Appl. Chem.* **1988**, *60*, 483.
(30) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 1747.
(31) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407.
(32) It is known that tetra-*O*-alkylcalix[4]arenes give conformational isomers because of steric inhibition of the oxygen-through-the-annulus rotation: The ^1H NMR spectrum of 1(n = 4), isolated in 9% yield, shows a pair of doublets for the $ArCH_2Ar$ protons, indicating that 1(n = 4) has a "cone" conformation. Probably, we isolated the cone 1(n = 4) through the purification process.
(33) Shinkai, S.; Araki, K.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1988**, 187.
(34) Shinkai, S.; Araki, K.; Manabe, O. *J. Am. Chem. Soc.* **1988**, *110*, 7214.
(35) Mack, M. P.; Hendrixson, R. P.; Palmer, R. A.; Ghirardelli, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 7830.
(36) Ueno, A.; Yoshimura, H.; Saka, R.; Osa, T. *J. Am. Chem. Soc.* **1979**, *101*, 2779.

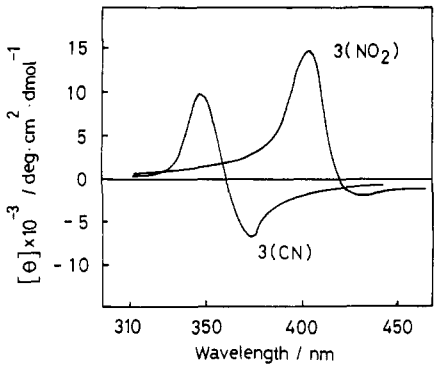


Figure 5. ICD spectra of 3(CN) and 3(NO_2) in the presence of 1(n = 6): 23 °C, pH 6.9, with 0.067 M phosphate buffer, [1(n = 6)] = 1.00 × 10^{-3} M, [3(CN)] = [3(NO_2)] = 1.2 × 10^{-4} M, water–Me_2NCHO (98.6:1.4 v/v).

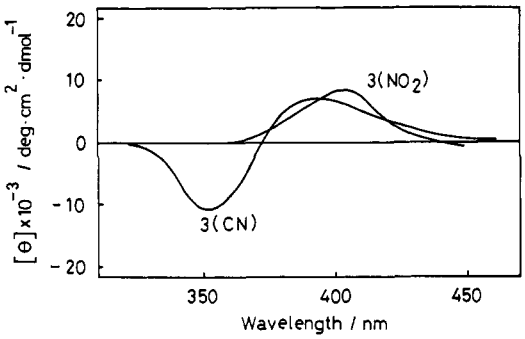


Figure 6. ICD spectra of 3(CN) and 3(NO_2) in the presence of 1(n = 8): the measurement conditions are recorded in a caption to Figure 5.

adopt an "alternate" conformation.[37] We found that the addition of guest molecules changes the ^{1}H NMR spectra (Figure 3): upon inclusion of guest molecules a singlet peak for the $ArCH_2Ar$ protons is divided into split peaks. It is clear, therefore, that the change in the CD spectra is related to the conformational change from alternate to more restricted conformations (e.g., cone or winged[8,9]). Although alternate calixarenes have a higher order of rotational freedom, they must change the cavity shape to cone (or winged) when they include guest molecules. These considerations lead to the view that guest inclusion by calixarenes occurs in an induced-fit manner. As described above, the CD bands are weakened in the presence of guest molecules. This means that inclusion of guest molecules suppresses the exciton coupling between benzene chromophores. Thus, the fluctuation of the calixarene ring is significantly inhibited when a guest molecule is included in the cavity. In conclusion, it is now clear that guest inclusion rigidifies the calixarene ring through the conformational change from alternate to cone (or winged) which is detected by both the ^{1}H NMR spectra and the CD spectra.

ICD Spectra of Dye Molecules. The CD spectral studies described above are classified as category a (complexation of chiral chromophoric host with guest). When chromophoric guests having the absorption bands at longer wavelengths are used, the chiral complexation process can be detected by the ICD spectra (category d, complexation of chiral host with chromophoric guest). We tested six 4-substituted 4′-(diethylamino)azobenzenes 3(R) (R = NMe_2, OMe, Me, SO_2Me, CN, and NO_2) and 3-nitro-4′-(diethylamino)azobenzene as chromophoric guests. Among them only two dye stuffs, 3(NO_2) and 3(CN), gave ICD spectra in the presence of 1(n = 6) or 1(n = 8) (Figures 5 and 6).

Table IV. Absorption Maxima (nm) of 3(R) at 30 °C[a]

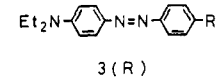
R	solvent					
					water	
	n-hexane	THF	methanol	water	SDS[b]	1(n = 6)[c]
NMe_2	421	–	466	450	–	–
OMe	404	–	414	474	–	–
Me	403	–	416	–	–	–
SO_2Me	431	–	462	488	–	–
CN	430	454	463	416	504	487
NO_2	453	482	489	416	417	418

[a] [3(R)] = 1.2 × 10^{-4} M, pH 6.9, with 0.067 M phosphate for aqueous systems. [b] [SDS] = 1.00 × 10^{-2} M. [c] [1(n = 6)] = 1.00 × 10^{-3} M.

Table V. ICD spectra of 3(CN) and 3(NO_2)[a]

guest	host	λ_{max} (θ), nm
3(CN)	1(n = 4)	nd
3(CN)	1(n = 6)	347 (+9000), 372 (−6100)
3(CN)	1(n = 8)	353 (−10100), 388 (+6800)
3(NO_2)	1(n = 4)	nd
3(NO_2)	1(n = 6)	402 (+14000), 430 (−1900)
3(NO_2)	1(n = 8)	403 (+8300)

[a] 20 °C, pH 6.9, with 0.067 M phosphate buffer; nd denotes that the ICD spectral change was not detected.



3(R)

As summarized in Table IV, the absorption maxima of these dyes shift to longer wavelength with increasing solvent polarity. This trend is quite reasonable because the charge-separated excited state is more stabilized in polar solvents. In contrast, the λ_{max} values for 3(CN) and 3(NO_2) in water are very unusual: they appeared at 416 nm, a blue shift of 47–73 nm from those in methanol. This is rationalized in terms of aggregate formation, which occurs because of dipole–dipole interactions among polar dye molecules.[38-41] Addition of SDS (sodium dodecylsulfate) or 1(n = 6) to aqueous 3(CN) caused a red shift to 487–504 nm. This shift is induced by deaggregation of 3(CN) in the presence of these "surfactant" molecules: that is, 3(CN) is solubilized discretely in the SDS micelle or in 1(n = 6). On the other hand, the λ_{max} for 3(NO_2) was scarcely affected by these additives: that is, the 3(NO_2) aggregates are formed even in the presence of surfactants. Probably, the dipole–dipole interaction in 3(NO_2) is stronger than that in 3(CN).

As summarized in Table V, the ICD spectra observed for 3(CN) and 3(NO_2) are fairly complex. We noticed, however, that the ICD spectral behavior can be explained through careful comparison with the absorption spectra. First, the ICD bands (347–430 nm) appear at shorter wavelength than the absorption maxima for monomeric 3(R) (i.e. 487–504 nm for 3(CN)). This indicates that the ICD-active species are not monomeric but aggregated 3(R). This view is in line with the fact that 3(NMe_2), 3(OMe), 3(Me), 3(SO_2Me), which exist discretely in water, are ICD-silent whereas 3(CN) and 3(NO_2), which form aggregates in water, are ICD-active. Second, we examined the spectral properties of 3(CN) in detail because the

(37) We consider that the "alternate" conformation is not single and fixed but involves several conformations, the exchange among which occurs faster than the NMR timescale, see: Araki, K., Shinkai, S., Matsuda, T. *Chem. Lett.* **1989**, 581.

(38) Sato, H.; Kawasaki, M.; Kasatani, K.; Nakashima, N.; Yoshihara, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3588.
(39) Kunitake, T. *Nippon Kagaku Kaishi* **1987**, 534.
(40) Kuhn, H. *Pure Appl. Chem.* **1971**, *27*, 421.
(41) Heesemann, J. *J. Am. Chem. Soc.* **1980**, *102*, 2167.

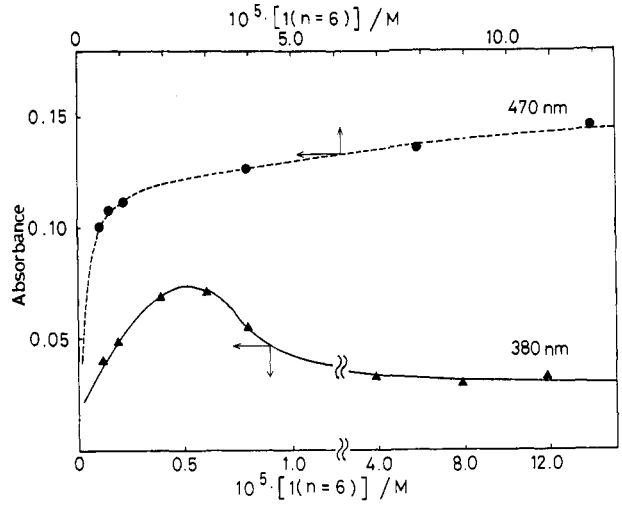


Figure 7. Plots of OD_{380} (solid line) and OD_{470} (dotted line) for 3(CN) (1.00×10^{-5} M) against [1(n = 6)]: the other measurement conditions are recorded in a caption to Figure 5.

monomer–aggregate equilibrium changes in water.[42] In Figure 7, the absorption bands for monomeric 3(CN) (at 470 nm) and aggregated 3(CN) (at 380 nm) are plotted against the 1(n = 6) concentration. It is seen from Figure 7 that a plot of OD_{380} vs [1(n = 6)] gives a maximum at [3(CN)]/[1(n = 6)] = 2.0 whereas that of OD_{470} vs [1(n = 6)] increases with increasing 1(n = 6) concentration. A plot of θ_{372} vs [1(n = 6)] gives a minimum at [3(CN)]/[1(n = 6)] = 2.0. The results support the idea that the complex with 2:1 [3(CN)]/[1(n = 6)] stoichiometry is ICD-active. The finding clearly explains the discrepancy between the absorption spectra and the ICD spectra: in the absorption spectra (measured at 3(CN) < 1(n = 6)) the major species with 1:1 stoichiometry gives an absorption maximum at 487 nm whereas in the ICD spectra the minor species with 2:1 stoichiometry gives ICD bands at 347 and 372 nm. Thus, the spectral behavior is totally expressed by Scheme I.

Scheme I

$$\text{3(CN) aggregate} \overset{1(n=6)}{\rightleftharpoons} \underset{\substack{\text{ICD-active}\\ \text{(2:1 stoichiometry)}}}{(\text{3(CN)})_2 \cdot 1(n=6)} \overset{1(n=6)}{\rightleftharpoons} \underset{\substack{\text{ICD-silent}\\ \text{(1:1 stoichiometry)}}}{\text{3(CN)} \cdot 1(n=6)}$$

(42) We attempted similar spectral studies about $3(NO_2)$, but we could not obtain satisfactory quantitative results because of the poor water solubility at $[1(n)]/[3(NO)_2)] < 1$.

It is not yet clear why the 1:1 complexes are ICD-silent and the 2:1 complexes are ICD-active. A possible rationale is that inclusion of two guest molecules would fill up the cavity space and significantly suppress the molecular motion. As a result, the dipoles in the dye molecules would be efficiently affected by the chirality in the calixarene rings.[43]

Interestingly, comparison of the ICD spectra for 3(CN) in Figures 5 and 6 reveals that the chirality sign of the Cotton effect is opposite between 1(n = 6) and 1(n = 8): that is, the exciton coupling in 1(n = 6) occurs in a counterclockwise direction, whereas that in 1(n = 8) occurs in a clockwise direction. This implies that the chiral recognition pattern is reversed between calix[6]arene and calix[8]arene. This result tells us that the cavity size should also play an important role in the chiral molecular recognition.

Concluding Remarks. The present study demonstrates that the CD spectral technique is very useful to obtain insight into calixarene conformations and calixarene complexation properties. We learned through this study, however, that in calixarene chemistry conformational changes may play a decisive role in guest inclusion. In this context we believe that the CD spectral technique will serve as one of the useful methods in the evaluation of the complexation properties. The novel findings obtained here are (i) the ring of calix[4]arenes is fairly rigid whereas those of calix[6]arenes and calix[8]arenes are still flexible, (ii) the ring conformation for calix[6]arenes and calix[8]arenes is fixed to cone (or winged) upon inclusion of guest molecules, and (iii) the ICD bands appear when calix[6]arenes and calix[8]arenes form 2:1 guest/calixarene complexes. Thus, chiral calixarenes 1(n) provide a new approach for studies of host–guest properties in calixarene chemistry. Applications to chiral recognition, separation of racemic compounds, asymmetric synthesis, etc. are being investigated in these laboratories.

Acknowledgment. We thank Professor Abraham Shanzer and Professor Volker Böhmer for helpful dicussions. This work was supported by the Grant-in-Aid from the Ministry of Education and Culture of Japan.

(43) Calixarenes 1(n = 6) and 1(n = 8) are supposed to have two binding sites, a calixarene cavity and a cavity composed of (*S*)-2-methylbutyl groups. It is feasible that dye molecules bound to the calixarene cavity are ICD-silent, whereas those bound to the (*S*)-2-methylbutyl cavity are ICD-active. To clarify this we measured the ^1H NMR spectrum of 1(n = 6) in the presence of 3(CN). However, the spectrum was too complex to obtain useful information about the association mode. At present, it is difficult to specify a relation between the binding site and the ICD-activity.