Different Aggregating Properties of Two Conformationally Frozen Isomers of a Water-Soluble Bridged Calix[6]arene

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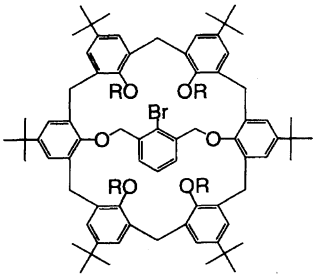
Two conformationally frozen isomers (cone and 1,2,3-alternate) of a water-soluble calix[6]arene were synthesized and found to show the critical micelle concentrations quite different from each other, which was explained in terms of their monomer structures with different arrangements of the charged groups.

A variety of water-soluble derivatives of calixarenes have been synthesized so far and their aggregating properties have been studied.[1] Recently, much attention has been paid to regulating the three-dimensional architecture of aggregates by designing the corresponding monomer molecule elaborately. Shinkai and co-workers synthesized water-soluble, conformationally frozen calix[4]arenes with cone and 1,3-alternate conformations and demonstrated that they have considerably different aggregating properties.[2] As for calix[6]arene derivatives with much greater flexibility, however, the structure of a monomer molecule in the aggregates is quite obscure owing to the conformational equilibrium, and it has been very difficult to control their aggregation modes by the monomer structure.[3] We previously reported on the first isolation of two conformationally frozen isomers of calix[6]arene **2**,[4a] where the lower rim of the *m*-xylene-bridged calix[6]arene **1**[4b] is benzylated. Very recently, we reported on the crystal structures of the conformational isomers of **3** bearing 4-pyridylmethyl groups.[4c] Their water-soluble derivatives are expected to solve the problem of the conformational flexibility of calix[6]arenes in aggregate formation. In this paper, we describe the synthesis of conformationally frozen isomers (cone and 1,2,3-alternate) of water-soluble calix[6]arene **4** and the relation between their structures and aggregating properties (Chart 1).



1 R = H

2 R = CH_2–C$_6$H$_5$

3 R = CH_2–C$_5$H$_4$N

4 R = CH_2–C$_6$H$_4$–$NMe_3^+Cl^-$

Chart 1.

Results and Discussion

In compound **4**, the trimethylammonio groups are appended to the lower-rim aromatic rings. The preparations of its conformational isomers, **4a** (cone) and **4b** (1,2,3-alternate), were effected according to Scheme 1. The reaction of the bridged calix[6]arene **1** with *N*-[4-(bromomethyl)-phenyl]-*N*-methylformamide under basic conditions resulted in the formation of two tetrabenzylated conformational isomers, **5a** and **5b**, with cone and 1,2,3-alternate conformations, respectively, which were separated by silica-gel chromatography. The amide groups of **5a** and **5b** were then reduced to give the corresponding dimethylamino derivatives **6a** and **6b**, and subsequent quaternization with methyl iodide followed by subjection to an ion-exchange column afforded **4a** and **4b**, respectively. Compounds **4a** and **4b** were soluble in water, methanol, and ethanol.

In the ^{1}H NMR spectra in methanol-d_4, both isomers **4a** and **4b** showed the spectral features essentially the same as those of the corresponding isomers of **2**;[4a] the well-resolved sharp signals were observed both at room temperature and at 60 °C. On the other hand, in D_2O, **4a** and **4b** showed spectral behaviors quite different from each other. In the spectrum of the cone isomer **4a**, the signals are significantly broadened at 30 °C, although they are sharp at 90 °C (Fig. 1A). The line broadening observed at 30 °C is considered to result from micelle formation, as has been reported for other monocyclic water-soluble calix[6]arenes and calix[8]arenes.[5] In contrast, the 1,2,3-alternate isomer **4b** showed well-resolved spectra

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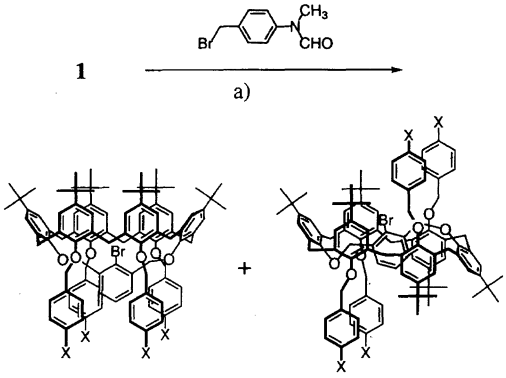
at both 30 and 90 °C (Fig. 1B).

Such spectral behavior indicates that the two isomers, **4a** and **4b**, have quite different ability for micelle formation. The critical micelle concentrations (cmcs) of the isomers **4a** and **4b** were determined by light-scattering, electric-conductivity, and NMR methods (Table 1). The cmc of the cone isomer **4a** (about 1×10^{-5} M) (1 M = 1 mol dm^{-3}) was considerably lower than that of the 1,2,3-alternate isomer **4b** (about 6×10^{-4} M). The large difference between the cmcs of **4a** and **4b** can be reasonably explained in terms of the surface shape of these isomers. In the cone isomer **4a**, all four charged groups are directed to one side of the cavity to form both hydrophobic and hydrophilic faces in the same molecule. On the other hand, the 1,2,3-alternate isomer **4b** has two ammonio groups on one face and the other two on the opposite face to form a smaller hydrophobic surface. Apparently, the rather high cmc value of **4b** results from the absence of conformational equilibrium including the cone isomer **4a**, which is more prone to form aggregates. Similar results have been reported for conformationally frozen water-soluble calix[4]arenes; the cone isomer forms micellar aggregates at around 10^{-5} M, whereas the 1,3-alternate isomer with a cylindrical shape does not form such aggregates for concentrations up to 10^{-2} M.[2]



b) **5a** X = $N(CH_3)CHO$ **5b** X = $N(CH_3)CHO$
b) **6a** X = $N(CH_3)_2$ **6b** X = $N(CH_3)_2$
c) **4a** X = $N(CH_3)_3{}^+Cl^-$ c) **4b** X = $N(CH_3)_3{}^+Cl^-$

Scheme 1. Reagents and conditions: (a) NaH, THF–DMF (10 : 1), reflux, **5a**: 83%, **5b**: 9%; (b) BH_3, THF, r.t., (c) CH_3I, r.t., then Dowex® 1X8 (Cl^-), **4a**: 94% for 2 steps, **4b**: 68% for 2 steps.

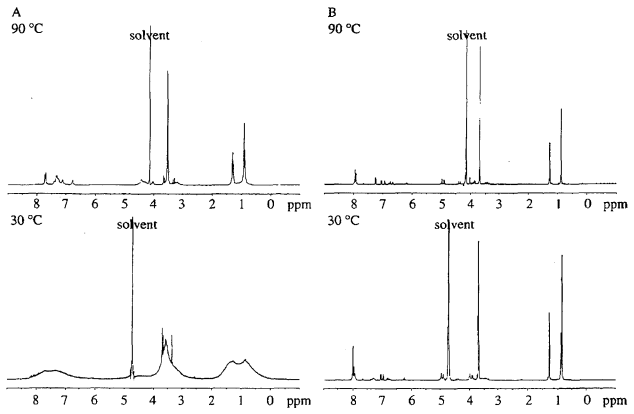


Fig. 1. ^{1}H NMR spectra of the cone isomer **4a** (A) and 1,2,3-alternate isomer **4b** (B) of water-soluble bridged calixarenes. (270 MHz, D_2O, 5×10^{-4} M).

Table 1. Critical Micelle Concentrations (cmcs) of the Water-Soluble Calix[6]arenes in Aqueous Solution

	cone (**4a**)	1,2,3-alternate (**4b**)
Light-scattering method	7.6×10^{-6} M	6.2×10^{-4} M
Conductivity	1.3×10^{-5} M	$>3\times10^{-4}$ M
NMR method	—[a]	5×10^{-4} M

a) Not determined because of severe broadening of the signals.

In summary, control of the aggregation modes of a calix[6]arene by the structure of the monomer molecules has been achieved by using two conformationally frozen isomers of the water-soluble bridged calix[6]arene **4**.

Experimental

Melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. Preparative TLC was carried out with Merck Kieselgel 60 PF254 Art. 7747. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500, a JEOL JNM-A500, or a JOEL EX-AL270 spectrometer. Elemental analyses were performed by the Microanalytical Laboratory of the Department of Chemistry, Faculty of Science, the University of Tokyo. *N*-Methyl-*N*-(4-methylphenyl)formamide[6] and bridged calix[6]arene **1**[4b] were prepared according to the literature. The intensity of light scattering was measured on a Hitachi Fluorescence Spectrophotometer 650-50.

***N*-[4-(Bromomethyl)phenyl]-*N*-methylformamide.** A mixture of *N*-methyl-*N*-(4-methylphenyl)formamide (1.49 g, 10 mmol), *N*-bromosuccinimide (2.49 g, 14 mmol), and benzoyl peroxide (50 mg) in carbon tetrachloride (20 mL) was refluxed for 4 h. After filtration and removal of the solvent, the residue was chromatographed on silica gel (chloroform) to give a yellow oil, which was crystallized from chloroform/hexane to give colorless crystals (890 mg, 39%); mp 51—55 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.32 (s, 3H), 4.50 (s, 2H), 7.15 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 8.51 (s, 1H).

Tetraamide 5a and 5b. To a suspension of NaH (60% in oil, 160 mg, 4.0 mmol) in THF (1 mL) was added a solution of **1** (230 mg, 0.20 mmol) in THF (9 mL) and DMF (1 mL). After the mixture was stirred at room temperature for 1 h, *N*-[4-(bromomethyl)phenyl]-*N*-methylformamide (274 mg, 1.2 mmol) was added and the reaction mixture was refluxed for 2 d. After the addition of water, the mixture was poured into aqueous NH_4Cl and extracted with chloroform. The extract was dried over $MgSO_4$ and the chloroform was evaporated. Separation of the residue by preparative TLC (silica gel, $CHCl_3$–EtOAc, 1 : 1) afforded the cone isomer **5a** (290 mg, 83%) and the 1,2,3-alternate isomer **5b** (32 mg, 9%).

5a: Colorless crystals; mp 240—242 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ = 1.04 (s, 36H), 1.45 (s, 18H), 3.20 (d, J = 15.0 Hz, 2H), 3.25 (s, 12H), 3.33 (d, J = 15.0 Hz, 4H), 3.88 (s, 4H), 4.33 (d, J = 15.0 Hz, 2H), 4.47 (s, 8H), 4.49 (d, J = 15.0 Hz, 4H), 6.77 (t, J = 7.5 Hz, 1H), 6.84 (s, 4H), 6.92 (d, J = 8.2 Hz, 8H), 7.11 (d, J = 8.2 Hz, 8H), 7.15 (d, J = 7.5 Hz, 2H), 7.21 (s, 4H), 7.32 (s,

4H), 8.36 (s, 4H). Found: C, 74.89; H, 7.11; N, 3.67; Br, 4.72%. Calcd for $C_{110}H_{125}BrN_4O_{10}\cdot H_2O$: C, 75.02; H, 7.27; N, 3.18; Br, 4.54%.

5b: Colorless crystals; mp > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.92 (s, 18H), 0.94 (s, 18H), 1.28 (s, 9H), 1.31 (s, 9H), 3.32 (d, J = 16.0 Hz, 2H), 3.38 (s×2, 12H), 3.41 (d, J = 15.9 Hz, 2H), 3.57 (dd, J = 7.6, 1.6 Hz, 1H), 3.76 (d, J = 12.6 Hz, 2H), 3.81 (d, J = 12.6 Hz, 2H), 3.95 (s, 2H), 4.06 (d, J = 16.0 Hz, 2H), 4.08 (s, 2H), 4.40 (d, J = 15.9 Hz, 2H), 4.79 (d, J = 11.0 Hz, 2H), 4.79 (d, J = 10.7 Hz, 2H), 4.87 (d, J = 11.0 Hz, 2H), 4.93 (d, J = 10.7 Hz, 2H), 6.10 (t, J = 7.6 Hz, 1H), 6.58 (brs, 2H), 6.70 (brs, 2H), 6.82 (dd, J = 7.6, 1.6 Hz, 1H), 6.93 (d, J = 2.2 Hz, 2H), 7.04 (d, J = 2.2 Hz, 2H), 7.12 (s×2, 4H), 7.25 (d, J = 8.2 Hz, 4H), 7.26 (d, J = 8.2 Hz, 4H), 7.62 (d, J = 8.2 Hz, 4H), 7.69 (d, J = 8.2 Hz, 4H), 8.53 (s×2, 4H). Found: C, 74.31; H, 7.16; N, 3.18; Br, 4.35%. Calcd for $C_{110}H_{125}BrN_4O_{10}\cdot 2H_2O$: C, 74.26; H, 7.31; N, 3.15; Br, 4.49%.

Water-Soluble Calix[6]arene 4a. To a solution of tetraamide **5a** (70 mg, 0.040 mmol) was added a solution of borane in THF (1.0 M, 1.6 mL) and the mixture was stirred at room temperature for 3 h. After the addition of water, the organic layer was extracted with chloroform. The extract was dried over $MgSO_4$ and the chloroform was evaporated to give the crude product of tetraamine **6a**, which was dissolved in methyl iodide (3 mL); the mixture was stirred for 12 h. Removal of the excess methyl iodide afforded the iodide analog of **4a**. A methanol solution of the iodide was subjected to an ion-exchange column (Dowex® 1X8-400, Cl^-) to give the crude product of chloride **4a**, which was recrystallized from methanol/ether to give colorless crystals of **4a** (71 mg, 94%); ^{1}H NMR (500 MHz, CD_3OD, 30 °C) δ = 1.04 (s, 36H), 1.45 (s, 18H), 3.16 (d, J = 15.1 Hz, 2H), 3.31 (d, J = 14.7 Hz, 4H), 3.71 (s, 36H), 3.93 (s, 4H), 4.27 (d, J = 15.1 Hz, 2H), 4.41 (d, J = 14.7 Hz, 4H), 4.55 (d, J = 13.0 Hz, 4H), 4.61 (d, J = 13.0 Hz, 4H), 6.88 (d, J = 2.0 Hz, 4H), 7.26 (d, J = 2.0 Hz, 4H), 7.37 (s, 4H), 7.39—7.47 (m, 3H), 7.43 (d, J = 9.0 Hz, 8H), 7.93 (d, J = 9.0 Hz, 8H); ^{13}C NMR (125 MHz, CD_3OD, 30 °C) δ = 27.89 (t), 31.62 (t), 32.20 (q), 32.24 (q), 35.12 (s), 35.23 (s), 58.03 (q), 73.83 (t), 74.74 (t), 121.15 (d), 123.99 (s), 126.17 (d), 127.14 (d), 127.27 (d), 127.60 (d), 129.85 (d), 130.38 (d), 132.93 (s), 133.21 (s), 135.23 (s), 138.59 (s), 142.09 (s), 146.13 (s), 146.91 (s), 147.77 (s), 153.40 (s), 153.93 (s). Found: C, 67.72; H, 8.11; N, 3.29%. Calcd for $C_{114}H_{145}BrCl_4N_4O_6\cdot 7H_2O$: C, 67.94; H, 7.95; N, 2.78%.

Water-Soluble Calix[6]arene 4b. Compound **4b** was prepared from **5b** (35 mg, 0.020 mmol) in a manner similar to that of **4a** in 68% yield. **4b**: Colorless crystals; ^{1}H NMR (500 MHz, CD_3OD, 60 °C) δ = 1.00 (s, 18H), 1.02 (s, 18H), 1.28 (s, 9H), 1.31 (s, 9H), 3.27 (d, J = 16.0 Hz, 2H), 3.39 (d, J = 15.7 Hz, 2H), 3.738 (s, 18H), 3.742 (s, 18H), 3.77 (dd, J = 7.5 and 1.7 Hz, 1H), 3.83 (d, J = 12.8 Hz, 2H), 3.89 (d, J = 12.8 Hz, 2H), 4.01 (s, 2H), 4.02 (d, J = 16.0 Hz, 2H), 4.18 (s, 2H), 4.45 (d, J = 15.7 Hz, 2H), 4.89 (d, J = 11.8 Hz, 2H), 4.94 (d, J = 11.6 Hz, 2H), 5.04 (d, J = 11.8 Hz, 2H), 5.10 (d, J = 11.6 Hz, 2H), 6.02 (t, J = 7.5 Hz, 1H), 6.67 (br, 2H), 6.77 (d, J = 2.4 Hz, 2H), 6.82 (dd, J = 7.5 and 1.7 Hz, 1H), 7.03 (d, J = 2.1 Hz, 2H), 7.12 (d, J = 2.4 Hz, 2H), 7.145 (s, 2H), 7.154 (s, 2H), 7.89 (d, J = 8.9 Hz, 4H), 7.97 (d, J = 9.0 Hz, 4H), 8.04 (d, J = 8.9 Hz, 4H), 8.05 (d, J = 9.0 Hz, 4H); ^{13}C NMR (125 MHz, CD_3OD, 60 °C) δ = 30.09 (t), 30.53 (t), 32.01 (q), 32.05 (q), 32.18 (q), 32.20 (q), 34.96 (s), 35.04 (s), 35.14 (s), 35.19 (s), 35.93 (t), 58.21 (q), 58.24 (q), 72.62 (t), 73.81 (t), 74.44 (t), 74.72 (t), 121.39 (d), 121.47 (d), 125.50 (d), 126.51 (d), 126.61 (d), 128.15 (s), 128.34 (d), 128.82 (d), 129.49 (d), 129.26 (d), 130.88 (d), 131.49 (d), 131.92 (d), 132.95 (d), 133.21 (s), 133.44 (s), 133.77 (s), 133.84 (s), 133.95 (s), 134.74 (s), 137.91 (s), 142.40 (s), 142.67 (s), 146.11 (s), 146.43 (s), 146.48 (s), 146.87 (s), 148.18 (s), 148.32 (s), 151.03 (s), 154.28 (s), 155.16 (s), 155.65 (s). Found: C, 65.64; H, 7.75; N, 2.81%. Calcd for $C_{114}H_{145}BrCl_4N_4O_6\cdot 11H_2O$: C, 65.60; H, 8.06; N, 2.68%.

Determination of Critical Micelle Concentrations (cmcs). The critical micelle concentrations were determined using the following three methods: (a) Light-scattering method: The intensity of light scattering at 90° at a wavelength of 375 nm at 300 K was plotted against the concentration of the aqueous solution of each isomer, and the break point where the slope increased was determined. (b) Conductivity method: The electric conductivity of the degassed aqueous solution of each isomer at 300 K was plotted against the concentration, and the break point where the slope decreased was determined. (c) NMR method: The concentration dependence of the chemical shifts of the ^{1}H NMR spectra of each isomer in D_2O at 300 K was monitored, and the break point where the chemical shifts became dependent on the concentration was determined.

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