Hexasulfonated Calix[6]arene Derivatives: A New Class of Catalysts, Surfactants, and Host Molecules[1]

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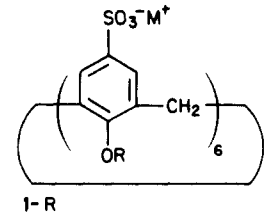
Abstract: Water-soluble hexasulfonated calix[6]arenes with various substituents (**1**-R) have been synthesized for the first time and applied as host molecules in an aqueous system. Dynamic ^1H NMR studies established that calix[6]arene-*p*-hexasulfonate (**1**-H) adopts a "winged" or "hinged" conformation in D_2O–Me_2SO-d_6 (2:1 v/v) owing to hydrogen bonding among the OH groups, while 5,11,17,23,29,35-hexasulfonato-37,38,39,40,41,42-hexakis(hexyloxy)calix[6]arene (**1**-C_6) adopts a similar conformation in D_2O owing to hydrophobic bonding among the hexyl groups. The aggregation behavior in water was examined about **1**-C_6 and **1**-C_{12}. Physical (light-scattering, surface tension, and conductance) and spectral (fluorescence and absorption spectroscopies) studies established that **1**-C_6 has a cmc at ca. 6×10^{-4} M, as does sodium dodecyl sulfate (SDS), while **1**-C_{12} has no detectable cmc and rather acts as a "unimolecular" micelle. In fact, **1**-C_6 associated with small molecules (pyrene, 2-anilinonaphthalene, and Orange OT) according to the micelle-like biphasic concentration dependence, while **1**-C_{12} formed host–guest-type 1:1 complexes with these molecules. It was found that these calix[6]arene derivatives efficiently accelerate acid-catalyzed hydration of 1-benzyl-1,4-dihydronicotinamide and the reaction proceeds according to the Michaelis–Menten kinetics. In particular, the rate constants for **1**-H and **1**-CH_2COOH, which both have acidic protons to catalyze the reaction and anionic sulfonates to stabilize the cationic intermediate at the two edges of the cavity, were greater by 426–1220-fold than those for noncyclic analogues. These findings indicate that hexasulfonated calix[6]arenes serve as a new class of catalysts, surfactants, and host molecules. This is the first example for the host–guest-type behavior of calixarenes observed in an aqueous system.

The chemistry of cyclodextrins and cyclophanes has occupied a central interest in host–guest chemistry for the last two decades, and many functionalized host molecules which can mimic the in vivo action of enzymes by means of simple in vitro chemical systems have been exploited.[2-6] Recently, Gutsche and coworkers[7,8] have reported on a series of new cyclic molecules called "calixarenes" which are cyclic oligomers made up of benzene units as cyclodextrins are made up of glucose units. Since calixarenes possess a cylindrical architecture similar to cyclodextrins, they are expected to be useful to design enzyme mimics in totally synthetic systems.[7,8] Several groups have reported on the ionophoric properties of calixarenes which were obtained by introducing ether and/or ester groups into the edge of the cylindrical architecture.[9-13] In contrast, almost nothing is known with certainty as to the inclusion properties of calixarenes in solution, which should be more important in the design of the enzyme mimics. The data reported so far have been limited to only the solid state,[7,8,14,15] and in fact, Gutsche stated in his recent review article that there are no published data in support of solution complexes of calixarenes.[8,16] This is in sharp contrast to cyclodextrins, which can form a variety of host–guest-type solution complexes. We noticed that the difference would stem mainly from the poor solubility of calixarenes; they are sparingly soluble in several organic solvents but insoluble in aqueous solutions. Therefore, the experimental efforts should be directed toward solubilization of calixarenes, which would eventually lead to the exploitation of calixarene-based host molecules and enzyme mimics. Here, we wish to report the synthesis and the solution properties of new water-soluble hexasulfonated calix[6]arenes (**1**-R). We have found that they serve not only as host molecules in an aqueous system but also as a new class of surfactants and acid catalysts.



1-R

1-H	R=H
1-CH_2COOH	R=CH_2COOH
1-C	R=CH_3
1-C_6	R=*n*-C_6H_{13}
1-C_{12}	R=*n*-$C_{12}H_{25}$

M^+=H^+, Na^+, or NH_4^+

Experimental Section

Materials. *p-tert*-Butylcalix[6]arene was synthesized according to Gutsche's method.[17] This was debutylated by treatment with $AlCl_3$ in toluene.[18] Calix[6]arene thus obtained was hexasulfonated and then treated with the corresponding alkyl halides to give **1**-R.

Calix[6]arene-*p*-hexasulfonate (1-H). Calix[6]arene (7.78 g, 12.2 mmol) was mixed with 60 mL of concentrated H_2SO_4, and the solution

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was heated at 80 °C for 3 h. An aliquot was withdrawn from the solution and poured into water to determine the progress of the reaction. The reaction was completed when no water-insoluble material was detected. After cooling, the precipitate was recovered by filtration. The precipitate was dissolved in water, and the solution was neutralized by $BaCO_3$. Precipitated $BaSO_4$ was removed by filtration, and then Na_2CO_3 was added to the filtrate in order to exchange the countercation. When the pH had reached 8–9, the addition of Na_2CO_3 was stopped. The solution was treated with active charcoal, the filtrate being concentrated in vacuo. The remaining white powder was dissolved in water, and an insoluble material (if any) was removed by filtration. The filtrate was treated with active charcoal once again. Then, the solution was concentrated, and ethanol was added to the remaining solution. We thus obtained the hexasodium salt of calix[6]arene-*p*-hexasulfonate as a white precipitate. A small amount of the product could be recovered by the similar treatment of the H_2SO_4 filtrate: mp >320 °C; total yiled 75%-; single spot on paper chromatography (PC) (water–2-propanol 1:1 v/v); IR (KBr) ν_{OH} 3440 cm^{-1}, ν_{SO_3} 1160, 1040 cm^{-1}; ^1H NMR (D_2O at 20 °C) δ 4.32 (CH_2, s, 12 H), 7.84 (Ar H, s, 12 H). Anal. $(C_7H_5O_4SNa)_6$ C, H, S.

5,11,17,23,29,35-Hexasulfonato-37,38,39,40,41,42-hexamethoxycalix[6]arene (1-C). The hexasodium salt of **1-H** (3.00 g, 1.92 mmol) was mixed with NaOH (2.35 g, 58.8 mmol) in 15 mL of water and methyl iodide (8.40 g, 59.2 mmol) in 60 mL of dimethyl sulfoxide, and the reaction mixture was heated at 50 °C for 24 h. After cooling, the solution was diluted with methanol to precipitate the product. The precipitate was recovered by filtration and dissolved in 10 mL of water. After an insoluble material was removed by filtration, the product was precipitated from the filtrate by diluting with ethanol. This operation was repeated 3 times in order to remove NaI, which was more soluble in ethanol than **1-C**: mp >320 °C; yield 62%; single spot on PC (water–2-propanol 1:2 v/v); IR (KBr) no ν_{OH}, $\nu_{C\text{-}O\text{-}C}$ 1210 cm^{-1}, ν_{SO_3} 1190, 1150 cm^{-1}; ^1H NMR (D_2O at 20 °C) δ 3.34 (OCH_3, s, 18 H), 4.08 (CH_2, s, 12 H), 7.50 (Ar H, s, 12 H). We converted the hexasodium salt to the hexaammonium salt and subjected it to elemental analysis. Anal. $[C_8H_{11}O_4S(NH_4)]_6$ C, H, N, S. The titration of the sulfonic acid groups after treatment with ion-exchange resin gave a neutralization equivalent commensurate with the hexasulfonate structure **1-C**. It is worth remarking that **1-C** is less soluble in ethanol than NaI.

5,11,17,23,29,35-Hexasulfonato-37,38,39,40,41,42-hexakis(hexyloxy)calix[6]arene (1-C_6). **1-C_6** was prepared from **1-H** and *n*-hexyl bromide according to the method similar to that of **1-C**: mp >320 °C; yield 58%; single spot on PC (water–2-propanol 1:2 v/v); IR (KBr) no ν_{OH}, $\nu_{C\text{-}O\text{-}C}$ 1210 cm^{-1}, ν_{SO_3} 1190, 1155 cm^{-1}; ^1H NMR (D_2O–Me_2SO-d_6 2:1 v/v at 20 °C) δ 0.84 (CH_3, t, 18 H), 1.20 ($Me(CH_2)_3$–, m, 36 H), 1.64 (O–C–CH_2, q, 12 H), 3.64 (ring CH_2, br, 12 H), 4.60 (OCH_2, t, 12 H), 7.50 (Ar H, s, 12 H). Anal. $(C_{13}H_{17}O_4SNa)_6$ C, H. The titration after treatment with ion-exchange resin gave a neutralization equivalent commensurate with the structure of hexasulfonated **1-C_6**.

5,11,17,23,29,35-Hexasulfonato-37,38,39,40,41,42-hexakis(dodecyloxy)calix[6]arene (1-C_{12}). Similarly, **1-C_{12}** was prepared from **1-H** and *n*-dodecyl bromide: mp >320 °C; yield 96%; single spot on PC (water–2-propanol 1:2 v/v); IR (KBr) no ν_{OH}, $\nu_{C\text{-}O\text{-}C}$ 1210 cm^{-1}, ν_{SO_3} 1180, 1055 cm^{-1}; ^1H NMR (D_2O–Me_2SO-d_6 2:1 v/v at 20 °C) δ 0.87 (CH_3, t, 18 H), 1.22 ($Me\text{–}(CH_2)_{10}$–, m, 120 H), 3.60 (ring CH_2, br, 12 H), 4.50 (O–CH_2, br, 12 H), 7.48 (Ar H, br, 12 H). Anal. $(C_{19}H_{29}O_4SNa)_6$ C, H.

5,11,17,23,29,35-Hexasulfonato-37,38,39,40,41,42-hexakis(carboxymethoxy)calix[6]arene (1-CH_2COOH). The hexasodium salt of **1-H** (1.0 g, 0.80 mmol), NaOH (1.0 g, 25 mmol), and monobromoacetic acid (1.67 g, 12.0 mmol) in 10 mL of water were heated at 80 °C for 24 h. The progress of the reaction was followed by PC. After cooling, the solution was concentrated to dryness in vacuo. The remaining solid was dissolved in 10 mL of 0.01 N NaOH aqueous solution and heated at 80 °C for 4 h. This experiment was done to decompose the polyester produced from monobromoacetic acid. Then, the solution was concentrated to dryness in vacuo once again. The resultant crystals were washed with hot methanol to remove NaBr, which was more soluble in hot methanol than **1-CH_2COOH**: mp >320 °C; hygroscopic, yield 77%; IR (KBr) $\nu_{C=O}$ 1610 cm^{-1}, ν_{SO_3} 1200, 1120 cm^{-1}. NMR peaks of the hexasodium salt of **1-CH_2COOH** were so broad that it was almost impossible to determine the chemical shifts. Therefore, we neutralized the sulfonate groups by treatment with ion-exchange resin and then measured the NMR spectrum; ^1H NMR (D_2O) of the hexasulfonic acid at 35 °C δ 4.05 ($ArCH_2$, br, 12 H), 4.32 (CH_2CO, s, 12 H), 7.61 (Ar H, br, 12 H). As the hexasodium salt was hygroscopic and complete elimination of inorganic salts was difficult, we converted it to the dodecaammonium salt and subjected it to elemental analysis. Anal. $(C_9H_{14}O_6N_2S_6)_6$ C, H, N.

Kinetic Measurements. The hydration of 1-benzyl-1,4-dihydronicotinamide (BNAH) was followed spectrophotometrically by monitoring the disappearance of the absorption band at 357 nm. Under all reaction conditions employed, the reaction obeyed the first-order kinetics. The final absorption spectrum was in accord with that of 1-benzyl-6-hydroxy-1,4,5,6-tetrahydronicotinamide (λ_{max} 290 nm).[19,20]

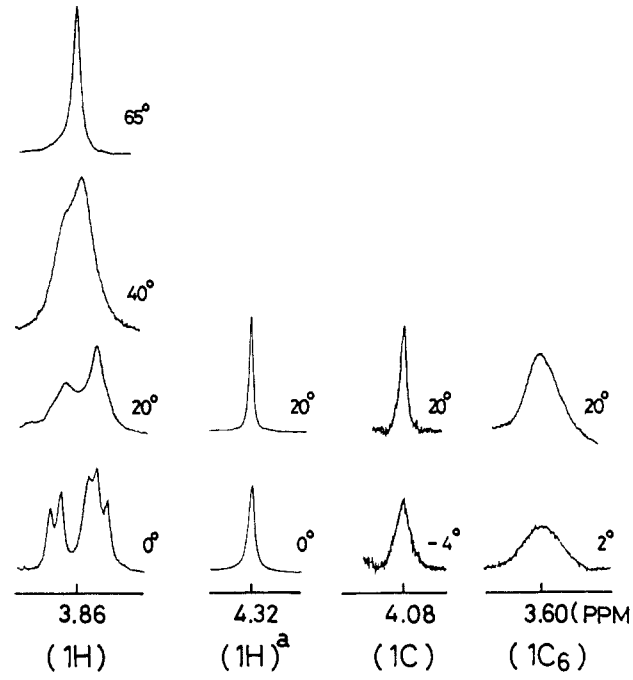

Figure 1. ^1H NMR spectra of the $ArCH_2Ar$ methylene protons in **1-R** at various temperatures in D_2O–Me_2SO-d_6 (2:1 v/v). **1-H**[a] was measured in D_2O.

Solubilization Test of 1-(2′-Methylphenylazo)-2-naphthol (Orange OT). The solubilization abilities of **1-C_6**, **1-C_{12}**, and SDS were estimated with a lipophilic dye, Orange OT. **1-R** was dissolved in 30 mL of water in a stoppered ampule, and the solution was equilibrated to the desired temperature in a thermostatted water bath. After excess Orange OT (60 mg) was added, the sealed ampule was agitated drastically for 5 min. The ampule was immersed in the water path for 30 min and then agitated again. This operation was repeated 3 times. After 1 day, the supernatant was filtered by suction and the filtrate was diluted with 2-propanol–water (1:1 v/v). The concentration of Orange OT solubilized in water was estimated spectrophotometrically by a calibration curve.

Miscellaneous. The surface tension of aqueous **1-R** was measured in pure water at 30 °C by the Wilhelmy method (Kyowa Kagaku Co., Model ESB-IV). Molecular weights of aqueous **1-R** were estimated in pure water at 30 °C by the light-scattering method (Toyo Soda Kogyo Co., Model LS-8; λ 6328 Å, He–Ne laser; [**1-R**] = 1.0×10^{-3} M). ^1H NMR spectra were taken with JOEL FT-NMR, Type FX90Q.

Results and Discussion

Conformational Properties of 1-R. The possibility of conformational isomerism of calixarenes was made explicit by Cornforth et al.[21] They pointed out that in calix[4]arene, for instance, four discrete forms can exist which Gutsche et al.[7,8] refer to an "cone", "partial cone", "1,2-alternate", and "1,3-alternate" conformations. These conformers can be conveniently discriminated by ^1H NMR.[7,8,16,17] From observation of the resonances arising from the $ArCH_2Ar$ methylene protons of calixarenes, the pattern of "cone" calixarenes is a sharp singlet above room temperature while it is a pair of doublets below room temperature.[8] According to the recent studies by Gutsche and Bauer,[16] however, the conformational aspect of calixarenes is not so simple. The ^1H NMR data are commensurate with a "cone" conformation for the cyclic tetramers and cyclic pentamers, a "winged" or "hinged" conformation for cyclic hexamers, and a "pleated-loop" conformation for the cyclic octamers.[16]

Here, we measured the ^1H NMR spectra of **1-H**, **1-C**, **1-C_6**, and **1-CH_2COOH**. The NMR peaks of **1-C_{12}** were so broad in

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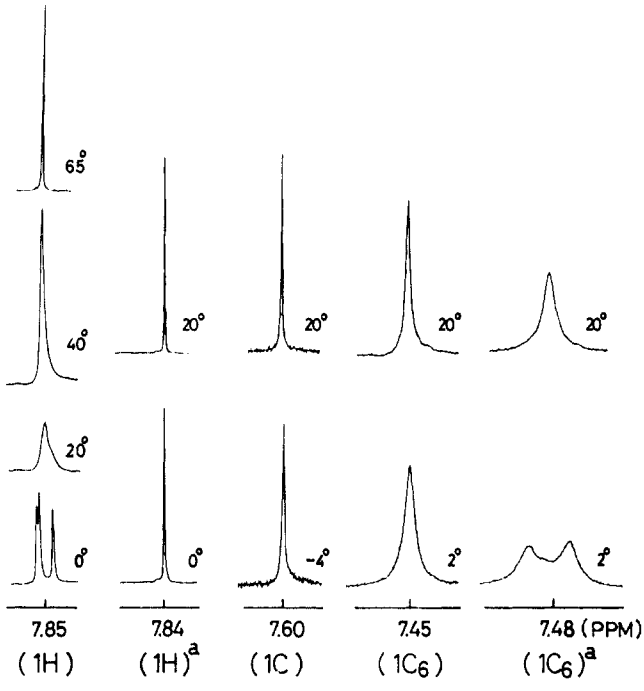

Figure 2. ^{1}H NMR spectra of the benzene protons in **1**-R at various temperatures in D_2O–Me_2SO-d_6 (2:1 v/v). **1**-H^a and **1**-C$_6^a$ were measured in D_2O.

D_2O that we could not discuss the conformation accurately. In this experiment it would be most intriguing to know if the "cone" conformation is destabilized by electrostatic repulsion among the sulfonate groups and if it is stabilized by hydrophobic force among the hexyl groups. As illustrated in Figure 1, the $ArCH_2Ar$ methylene protons of **1**-H in D_2O gave a sharp singlet at 20 °C and a somewhat broadened singlet at 0 °C. On the other hand, the ^{1}H NMR spectrum taken in D_2O–Me_2SO-d_6 (2:1 v/v) at 0 °C gave a pair of doublets at 3.86 ppm,[22] and from the coalescence temperature of ca. 40 °C the rate of interconversion was estimated to be ca. 130 s^{-1}. The finding suggests that the structure of **1**-H in D_2O–Me_2SO-d_6 is somewhat distorted from the "cone" conformation and rather close to the "winged" or "hinged" conformation.[22] The difference in the dynamic ^{1}H NMR spectra between the solvents suggests that this conformation would be stabilized by hydrogen bonding among the OH groups, because it should operate more strongly in D_2O–Me_2SO-d_6 than in D_2O. According to Kämmerer et al.,[23,24] who first carried out dynamic ^{1}H NMR studies of *p*-alkylcalix[4]arenes, the coalescence temperatures are about 45 °C and the rates of interconversion are ca. 100 s^{-1}. The more recent T_c determination in various solvents indicates that the T_c values vary from 15 to 21 °C for *p-tert*-butylcalix[4]arene and from −54 to 11 °C for *p-tert*-butylcalix[6]arene.[16] Thus, the T_c for **1**-H is rather comparable with those for *p-tert*-butylcalix[4]arene. This implies that the destabilization due to electrostatic repulsion among the sulfonate groups is rather unlikely (at least, in these solvents). Neither **1**-C nor **1**-CH_2COOH gave a pair of doublets in these solvents. Therefore, these calix[6]arenes, which have no OH group to stabilize the "cone" conformation, would adopt the mobile conformations other than "cone".

The conformational change in calixarenes can be detected not only by the $ArCH_2Ar$ protons but also by the benzene protons.

(22) In the ^{1}H NMR spectrum of **1**-H in D_2O–Me_2SO-d_6 (2:1 v/v) at 0 °C, a third singlet peak appeared at 3.82 ppm (Figure 1). The integral intensity indicates that this peak is also attributed to the $ArCH_2Ar$ methylene protons. Similarly, the aromatic protons in D_2O–Me_2SO-d_6 (2:1 v/v) gave three peaks at 0 °C (Figure 2). These ^{1}H NMR data are commensurate with the "winged" or "hinged" conformation.[16]

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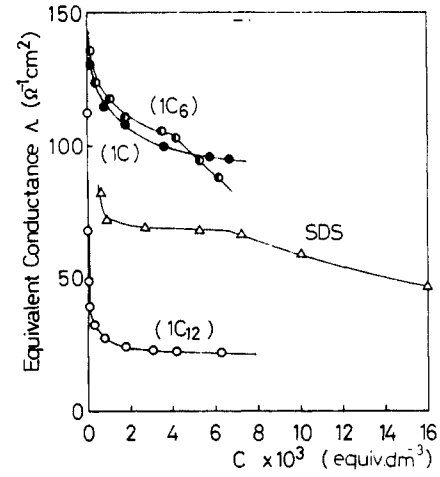


Figure 3. Equivalent conductance plotted against surfactant concentration (C, equiv dm^{-3}) at 30 °C.

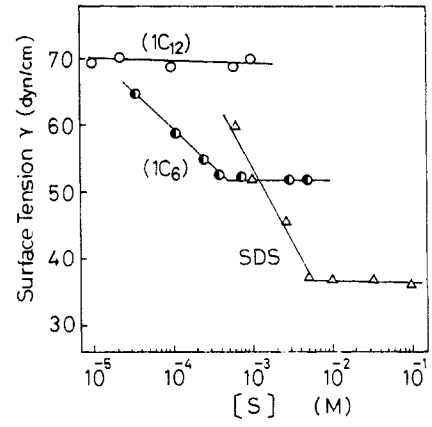


Figure 4. Surface tension plotted against surfactant concentration ([S], M) at 30 °C.

As shown in Figure 2, **1**-H in D_2O–Me_2SO-d_6 (2:1 v/v) gave the well-separated peaks at 0 °C. This is probably ascribed to a "winged" or "hinged" conformation.[16] Interestingly, we noticed that the similar peak separation is observable for **1**-C$_6$ in D_2O but not in D_2O–Me_2SO-d_6 (2:1 v/v) at 2 °C. This implies that the conformational inversion of **1**-C$_6$ occurs faster in aqueous Me_2SO-d_6 than in D_2O. The fact that the peak separation occurs only in D_2O indicates that this conformation would be stabilized by hydrophobic bonding among the hexyl groups.

Aggregation Number, Electric Conductance, and Surface Tension. The aggregation number of aqueous **1**-C$_6$ and **1**-C$_{12}$ (1.0×10^{-3} M) was estimated at 30 °C by a light-scattering method. The average molecular weights thus obtained were surprisingly small: 10000 ± 3000 for **1**-C$_6$ and 5000 ± 2000 for **1**-C$_{12}$. These values correspond to hexamer for **1**-C$_6$ and dimer or trimer for **1**-C$_{12}$. These results clearly indicate that **1**-C$_6$ favorably forms small micelles but **1**-C$_{12}$ does not form such micellar aggregates, unlike conventional surfactants.

Electrical conductance is often used to measure the critical micelle concentration (cmc) of surfactants because a plot of conductance vs. surfactant concentration provides a clear break point at the cmc. We synthesized *p*-(*n*-hexyloxy)benzenesulfonate, *p*-(*n*-octyloxy)benzenesulfonate, and *p*-(*n*-dodecyloxy)benzenesulfonate as noncyclic analogues of **1**-C$_6$ and **1**-C$_{12}$. *p*-(*n*-Hexyloxy)benzenesulfonate was well soluble in water but did not form the micelle. The water solubility of *p*-(*n*-octyloxy)-benzenesulfonate and *p*-(*n*-dodecyloxy)benzenesulfonate was so poor that they precipitated before forming the micelle. We therefore employed a well-known anionic surfactant, sodium dodecyl sulfate (SDS), as a reference. Figure 3 shows plots of equivalent conductance vs. calixarene (or SDS) concentration. The unit of abscissa is C (equiv dm^{-3}), that is, C = [SDS] or

Table I. Critical Micelle Concentrations (cmc, M) Determined by Various Methods (30 °C)

surfactant	method		
	surface tension	conductance	spectroscopy[a]
SDS	5.6×10^{-3}	6.6×10^{-3}	7.0×10^{-3}
1-C_6	5.0×10^{-4}	6.7×10^{-4}	ca. 5.0×10^{-4}
1-C_{12}	none	none	none

[a] Determined by the fluorescence intensity of pyrene (see text).

6[**1**-R]. The plot for SDS gave a break point at 6.6×10^{-3} equiv dm^{-3}, which is in good accord with the cmc in the literature (8.1×10^{-3} equiv dm^{-3}).[25] Similarly, **1**-C_6 gave a clear break point at 4.0×10^{-3} equiv dm^{-3}, indicating that **1**-C_6 is capable of forming aggregates large enough to be detected by conductometry. In contrast, **1**-C_{12} had no break point at the concentration range where it was soluble in water ($C \leq 6.4 \times 10^{-3}$ equiv dm^{-3}). This implies that a drastic change from monomer to aggregate is not the case for aqueous **1**-C_{12}.

Surface tension of aqueous **1**-C_6 and **1**-C_{12} was measured at 30 °C in "pure" water. As shown in Figure 4, the surface tension (γ, dyn cm^{-1}) for SDS decreased gradually with the increase in the SDS concentration and a break point appeared at [SDS] = 5.6×10^{-3} M. This concentration corresponds to the cmc of SDS. The γ value above the cmc was 38 dyn cm^{-1}. The aqueous solution containing **1**-C_6 bubbled when shaken and the surface tension decreased with the increase in the **1**-C_6 concentration. The plot gave a clear break point at 5.0×10^{-3} M, and the γ value above the cmc (52 dyn cm^{-1}) was greater than that of SDS. This indicates that **1**-C_6 is surface-active though the activity is somewhat inferior to that of SDS. In contrast, the aqueous solution containing **1**-C_{12} was not bubbly, and a significant change in the surface tension was not observed ($\gamma = 71 \pm 1$ dyn cm^{-1}; pure water 71.1 dyn cm^{-1}). The absence of the surface-active nature suggests that **1**-C_{12} favorably dissolves in water as a monomer or as an oligomer rather than forming a monolayer assembly at the air–water interface.

The foregoing data consistently support the idea that **1**-C_6 can form small aggregates; that is, the physical properties are more or less similar to those of conventional surfactants. On the other hand, **1**-C_{12} is not surface-active and exists as a monomer or as an oligomer in water. Conceivably, **1**-C_{12}, which has six dodecyl chains within a molecule, can form a stable, micelle-like closed shell by itself. **1**-C_6, which has six hexyl chains within a molecule, cannot form the "unimolecular" micelle by itself but rather forms the micelle-like aggregate in water and the monolayer at the air–water interface. Probably, six hexyl groups are not enough to satisfy the geometrical and/or hydrophobic requirements to form the stable closed shell.

The cmc values determined in the above experiments are summarized in Table I. The cmc values for SDS are invariably between 5.6 and 7.0 mM. The cmc values for **1**-C_6 are smaller by about 1 order of magnitude. In contrast, no physical behavior related to the aggregate formation was found for **1**-C_{12}.

Solubilization Test of Orange OT. The solubilization of lipophilic dyestuffs is frequently used to evaluate the solubilization power of surfactants.[26,27] We here employed Orange OT (1-(2′-methylphenylazo)-2-naphthol) to test the solubilization power of **1**-R. In Figure 5, the equilibrium concentration of Orange OT solubilized in water is plotted against the concentration of SDS, **1**-C_6, and **1**-C_{12}. In aqueous SDS, the solubilization of Orange OT was observed only above the cmc, and the concentration increased linearly with increase in the SDS concentration. The slope may be regarded as a molar ratio of the Orange OT–SDS complex. The least-squares computation gave the slope 0.0096, indicating that 104 molecules of SDS bind 1 Orange OT. A similar, micelle-like behavior was observed for **1**-C_6; the slope

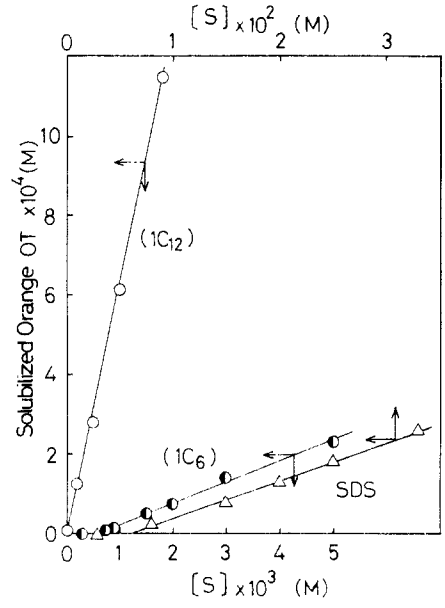


Figure 5. Solubilized Orange OT plotted against surfactant concentration ([S], M) at 30 °C.

Table II. Association Constants (K, M^{-1}) Determined by Various Methods (30 °C)

surfactant	substrate		
	Orange OT[a]	2-anilinonaphthalene[b]	Phenol Blue[c]
1-H			5.6×10^2
1-C_6[d]	2.3×10^7	8.3×10^5	
1-C_{12}[e]	5.2×10^5	3.4×10^5	2.0×10^5
SDS[d]	6.3×10^6		

[a] From the solubilization test. [b] From the fluorescence intensity. [c] From the absorption spectroscopy. [d] The K is defined by eq 2. [e] The K is defined by eq 1.

(0.053) indicates that 19 molecules of **1**-C_6 can bind 1 Orange OT. In contrast, aqueous **1**-C_{12} gave a linear plot crossing the abscissa at [**1**-C_{12}] = 0 M. The slope (0.61) indicates that 1.6 molecules of **1**-C_{12} can bind 1 Orange OT. This result strongly suggests that **1**-C_{12} acts apparently as a "unimolecular micelle"; in other words, **1**-C_{12} and Orange OT associate according to a host–guest-type 1:1 manner.

Here, we estimated the association constants (K) for Orange OT. We used eq 1 for **1**-C_{12} assuming the formation of the 1:1

$$K = \frac{[\text{solubilized Orange OT}]}{[\textbf{1}\text{-}C_{12}][\text{Orange OT}]} \quad (1)$$

complex, where the concentration of uncomplexed Orange OT is equal to the solubility of Orange OT in the absence of calixarenes (i.e., 3.1×10^{-6} M). In Figure 5, one K value could be calculated at each **1**-C_{12} concentration; the average value was 5.2 (± 0.3) $\times 10^5$ M^{-1}. This value is much greater than those determined for the association between cyclodextrins and dyestuffs (ca. 10^3 M^{-1}). The plots for SDS and **1**-C_6 were analyzed according to the equation established in the micellar system (eq 2),[25]

$$K = \frac{[\text{solubilized Orange OT}]}{[(S_t - S_{cmc})/N][\text{Orange OT}]} \quad (2)$$

where N denotes the aggregation number of surfactants (S) (i.e., 104 for SDS and 19 for **1**-C_6)[28] and S_t and S_{cmc} are the total concentration and the cmc of surfactants, respectively. The K values determined by eq 1 and 2 are recorded in Table II.

(25) Fender, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular Systems"; Academic Press: New York, 1975.
(26) (a) Negoro, K.; Saida, K.; Shigemi, T. *Yuki Gosei Kagaku Kaishi* **1972**, *30*, 559. (b) Negoro, K.; Goto, Y. *Ibid.* **1973**, *31*, 915.
(27) Negoro, K.; Nagao, M. *Nippon Kagaku Kaishi* **1972**, 110.

(28) We obtained $N = 19$ from the solubilization test and $N = 6$ from the light-scattering method. It is not clear yet why the N values are different between two measurement methods. Presumably, Orange OT, a liphophilic dyestuff added into aqueous **1**-C_6 would facilitate the aggregation of **1**-C_6, resulting in the greater N value.

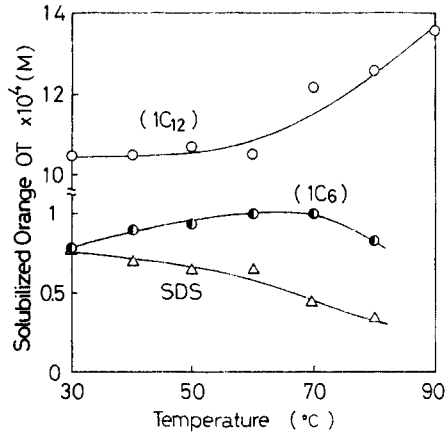


Figure 6. Temperature dependence of solubilized Orange OT: [SDS] = 1.39×10^{-2} M, [**1**-C_6] = 2.00×10^{-3} M, [**1**-C_{12}] = 1.70×10^{-3} M.

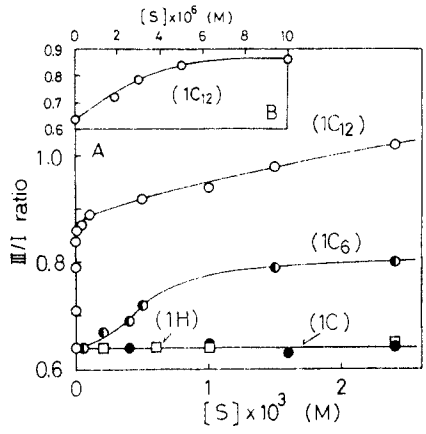


Figure 7. Plots of III:I ratio vs. [S] in pyrene fluorescence at 30 °C: [pyrene] = 2.00×10^{-6} M, excitation 310 nm.

Figure 6 shows a temperature dependence of solubilized Orange OT. The solubilization ability of SDS decreased with increasing temperature. This trend would be related to destabilization of the micelle structure at the high-temperature region. Interestingly, the solubilization ability of **1**-C_{12} increased with increasing temperature, and at 80–90 °C 1 mol of **1**-C_{12} could solubilize 0.9 mol of Orange OT. This clearly supports the association between **1**-C_{12} and Orange OT being based on the hydrophobic force, because it features a positive change in entropy.[29] **1**-C_6 showed a medium dependence on temperature, giving rise to a maximum at 70 °C. Probably, this resulted from two opposing effects: With increasing temperature, the association occurring with the aid of the hydrophobic force becomes stronger but the aggregate of **1**-C_6 becomes more destabilized.

Spectral Properties. Kalyanasundaram and Thomas[30] have demonstrated that vibronic band intensities in pyrene monomer fluorescence are a convenient probe to accurately determine cmc values; the ratio (band III:band I) = 0.63–0.66 in water below cmc and 0.90 above cmc in aqueous SDS. As shown in Figure 7A, **1**-H and **1**-C showed almost no effect on the III:I ratio. On the other hand, it clearly increased in the presence of **1**-C_6 and **1**-C_{12}, indicating that these calixarenes constitute a hydrophobic domain in water. Careful examination of a plot for **1**-C_6 reveals that the curvature is sigmoid although the jump at the cmc is not so clear as SDS.[30] Thus, the cmc was approximated to be 5×10^{-4} M. Interestingly, the III:I ratio for **1**-C_{12} sensitively increased at the very low **1**-C_{12} concentration and was almost saturated at 4×10^{-6} M (Figure 7B). As the concentration of pyrene used in the fluorescence measurements was 2.00×10^{-6} M, the formation of a 1:1 complex between **1**-C_{12} and pyrene is suggested again. One may conclude on the basis of these fluorescence data that (i) the inner cavity of **1**-H and **1**-C is not large enough to accept the pyrene molecule and (ii) therefore, in aqueous **1**-C_6 and **1**-C_{12} the pyrene molecule is bound to the hydrophobic domain constituted by the aliphatic chains.

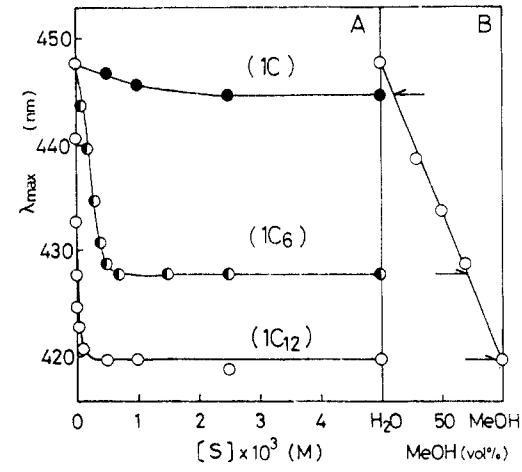


Figure 8. (A) Florescence maximum of 2-anilinonaphthalene (3.06×10^{-5} M) in aqueous **1**-R and (B) fluorescence maximum of 2-anilinonaphthalene (6.12×10^{-5} M) in a water–methanol mixed solvent: 30 °C, excitation 310 nm.

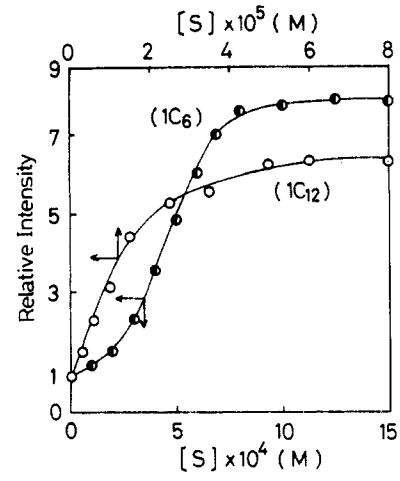


Figure 9. Fluorescence intensity of 2-anilinonaphthalene (3.06×10^{-5} M) at 420 nm (30 °C): excitation 310 nm.

It is known that fluorescence intensities and emission maxima of anilinonaphthalene derivatives show a strong solvent dependence.[31] Here, we employed 2-anilinonaphthalene (AN) as a fluorescence probe. As shown in Figure 8B, the emission maximum of AN (447 nm in water) correlates linearly with the methanol concentration (in vol %) in water–methanol mixed solvent. The fluorescence maximum of AN in water was scarcely affected by the addition of **1**-H (no shift) and **1**-C (3-nm blue shift). In aqueous **1**-C_6 and **1**-C_{12}, on the other hand, the emission maximum shifted significantly to shorter wavelengths and was saturated at 427 and 420 nm, respectively (Figure 8A). These wavelengths correspond to the mixed solvents containing 70 and 100 vol % of methanol, respectively. Since the SDS micelle was estimated to be 65 vol % aqueous methanol according to the similar fluorescence method, **1**-C_{12} can form the hydrophobic domain much stronger than the SDS micelle. Also significant in Figure 8 is that the spectral change in aqueous **1**-C_{12} is saturated at ca. 3×10^{-5} M. This value is exactly identical with the concentration of AN. The finding supports again that **1**-C_{12} and AN also form a 1:1 complex.

(29) Tanford, C. "The Hydrophobic Effect"; Wiley: New York, 1973.
(30) Kalyanasundaram, K.; Thomas, J. K. *J. Am. Chem. Soc.* **1977**, *99*, 2039.
(31) Murakami, Y.; Kikuchi, J.; Suzuki, M.; Takaki, T. *Chem. Lett.* **1984**, 2139 and references cited therein.

Table III. Absorption Maxima of Phenol Blue (30 °C)

additive	concn, M	λ_{max}, nm	$\Delta\lambda$,[a] nm
none		658	0
1-H	5.00×10^{-3}	685	-27
1-C	5.00×10^{-3}	662	-4
1-C_6	5.00×10^{-3}	643	15
1-C_{12}	1.00×10^{-5}	592	66
1-C_{12}	5.00×10^{-3}	630	28
sodium benzenesulfonate	2.00	672	-14
sodium *p*-hydroxybenzenesulfonate	3.00×10^{-2}	654	4
sodium poly(*p*-styrenesulfonate)	5.00×10^{-3} (monomeric unit)	612	46
SDS	1.00×10^{-2}	630	28
KCl	2.00	657	1

[a] $\Delta\lambda = \lambda_{water} - \lambda_{max}$.

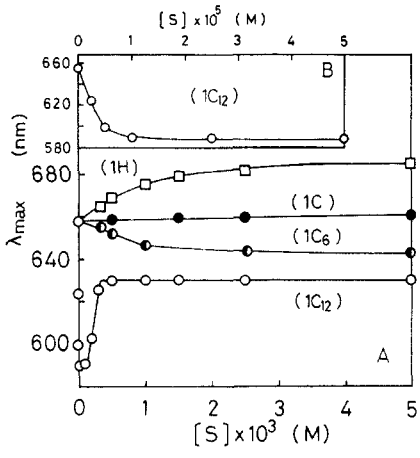


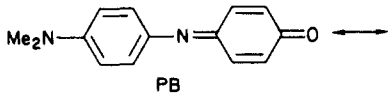
Figure 10. Absorption maximum of Phenol Blue (1.00×10^{-5} M) at 30 °C.

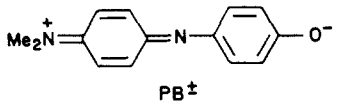
From a concentration dependence of the fluorescence intensity at 420 nm (Figure 9), we estimated the K for the association between 1-C_{12} and AN by using an equation similar to eq 1 at low 1-C_{12} concentrations and eq 3 at high 1-C_{12} concentrations

$$\frac{1}{I - I_0} = \frac{1}{\alpha[\mathrm{AN}]_0} + \left(\frac{1}{\alpha[\mathrm{AN}]_0 K}\right)\left(\frac{1}{[\mathbf{1}\text{-}\mathrm{C}_{12}]}\right) \qquad (3)$$

where $K = 3.4 \times 10^5$ M^{-1}, I_0 and I are the fluorescence intensities in the absence and the presence of 1-C_{12}, and $[AN]_0$ and [1-C_{12}] are the concentrations of AN and 1-C_{12}, respectively. The plot for 1-C_6 showed a sigmoid curve (Figure 9). We therefore analyzed the curvature above the cmc by the combination of eq 2 and 3; $K = 8.3 \times 10^5$ M^{-1}.

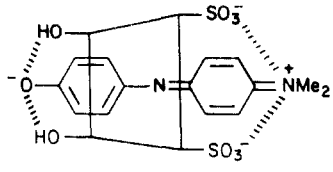
Brooker and Sprauge[32] suggested the use of Phenol Blue (PB) as a solvent property indicator; the absorption maximum (668 nm in water,[32] 658 nm according to our measurement at 30 °C) shifts to shorter wavelengths in nonpolar solvents (e.g., 552 nm in cyclohexane). The blue shift is attributed to destabilization of the polar excited state PB±. The absorption maxima in the presence





(4)

of 1-R are summarized in Figure 10 and Table III. Examination of Figure 10 reveals two noteworthy behaviors: (i) the λ_{max} in the presence of 1-H shifts to longer wavelengths (685 nm) and (ii) the plot for 1-C_{12} is biphasic, a large blue shift ($\Delta\lambda$ = 66 nm) followed by a relatively small blue shift ($\Delta\lambda$ = 28 nm). The red shift (by 27 nm) observed for 1-H implies that apparently, *1-H can provide a reaction field more polar than water.* We added several salts in order to "make water more polar" and measured the absorption spectrum of PB. However, these salts could not induce such a large red shift. Only when 2.00 M sodium benzenesulfonate was added, the λ_{max} shifted to a longer wavelength by 14 nm. In Table III, there are two important clues to rationalize the red shift in the presence of 1-H: (i) 1-C cannot induce such a large red shift, and (ii) sodium *p*-hydroxybenzenesulfonate, a noncyclic analogue of 1-H, has almost no effect on the λ_{max}. These findings support that PB is bound into the cavity of 1-H but not to the outside of the cavity, and more importantly, the OH groups in 1-H play a crucial role in the red shift. The possible elucidation for the red shift is, therefore, that the polar excited PB± in the cavity is stabilized both by the hydrogen bonding with the OH groups and by the electrostatic interaction with the sulfonate groups.

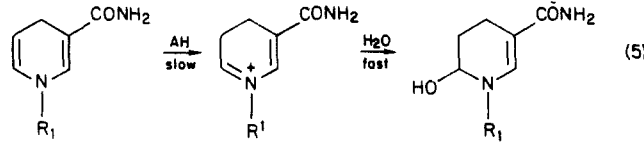


This bifunctional stabilization of the excited state would induce the marked red shift that could not be achieved by other additives.

It is more difficult to rationalize the biphasic plot for 1-C_{12}. The finding implies that 1-C_{12} provides two different binding sites for PB, a strongly hydrophobic site at the low-concentration region ($\sim 10^{-5}$ M) and a less hydrophobic site at the high-concentration region (7.5×10^{-4} M). The minimum value of the λ_{max} vs. [1-C_{12}] plot appears at ca. 1×10^{-5} M, which is in accord with the concentration of PB (1.00×10^{-5} M). This suggests that most probably, the formation of a 1:1 PB–1-C_{12} complex would be the origin of the large blue shift. At the high-concentration region, the λ_{max} becomes constant at 630 nm, which is exactly the same wavelength as that induced by the SDS micelle. On the basis of this information, one may tentatively envisage the following binding manner: Conceivably, PB is bound into or near the cavity of the calix[6]arene at the low-concentration region, while it is favorably bound to the hydrophobic domain constituted by the aliphatic chains at the high-concentration region. It is not yet explicable, however, why the binding site changes from the cavity to the aliphatic chains.

The association constants for 1-H and 1-C_{12} (for the low-concentration region) were estimated from the plots of OD_{700} vs. [1-H] or [1-C_{12}], assuming the formation of a 1:1 complex (Table II).

Applications as Host–Guest-Type Acid Catalysts. It has been established that NADH and its synthetic model compounds (1,4-dihydronicotinamides) undergo an acid-catalyzed hydration reaction in aqueous solution.[19] The hydration reaction causes shifts of a characteristic absorption band of 1,4-dihydronicotinamide in the 340–360-nm region downward to around 290 nm. The 290-nm absorbing compound was later verified to be 6-hydroxy-1,4,5,6-tetrahydronicotinamide.[20] The following reaction scheme was thus suggested, in which protonation of 1,4-dihydronicotinamide is involved in the rate-determining step.



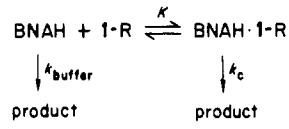
(5)

It is known that glyceraldehyde-3-phosphate dehydrogenase can rapidly catalyze this reaction to afford hydrated NADH.[33]

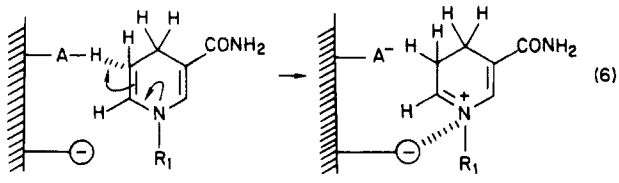
(32) Brooker, L. G. S.; Sprauge, R. H. *J. Am. Chem. Soc.* **1941**, *63*, 3214.

(33) Johnson, S. L.; Tuazon, P. T. *Biochemistry* **1977**, *16*, 1175 and references cited therein.

Scheme I



Although the mechanistic view is not clear yet, some charge-transfer stabilization of the cationic intermediate as well as the presence of some proton-donating group is suggested.[34,35] Thus, it would be of value to design such an enzyme model which has within a molecule both an anionic charge and a proton-donating group (eq 6).



(6)

We noticed that **1**-H and **1**-CH_2COOH fully satisfy the requirements of eq 6: They have acidic protons and anionic groups at the two edges of the cylindrical cavity, and the cavity can include certain molecules like PB. We decided to employ 1-benzyl-1,4-dihydronicotinamide (BNAH) as a substrate because it not only has the molecular shape similar to PB but also acts as a fluorescence probe.[36] In order to assess if BNAH is really included in the cavity of **1**-R, we measured the fluorescence spectra. It is known that the fluorescence intensity (I/I_0) of BNAH increases when it is bound to the hydrophobic domain formed in water.[36] A plot of I/I_0 vs. [SDS] gave a sharp sigmoid curve (see Figure 3 in ref 1b), indicating that the micelle formation occurs at around 6×10^{-3} M. Similarly, I/I_0 increased with increase in the **1**-C_{12} concentration, but the plot is a simple saturation curve. This plot suggests again the formation of a 1:1 complex between **1**-C_{12} and BNAH. On the other hand, it decreased with the increase in the concentration of **1**-H and **1**-CH_2COOH. Conceivably, these two calixarenes provide a microenvironment more polar than water. The finding is in line with the spectroscopic data obtained for PB. Noncyclic analogues such as sodium *p*-hydroxybenzenesulfonate and sodium *p*-(carboxymethoxy)-benzenesulfonate showed no effect on the fluorescence intensity. These fluorescence data support that BNAH is bound into the cavity of the calixarene derivatives. From eq 3, we estimated the association constant for **1**-C_{12} to be 2860 M^{-1}. The smaller K value relative to PB (2.0×10^5 M^{-1}; see Table II) may be accommodated by high water solubility of BNAH.

The hydration reaction of BNAH was carried out at 30 °C in buffered aqueous solution (pH 6.30 with 0.10 M phosphate) unless otherwise stated. The titration data indicate that at pH 6.30, **1**-H and **1**-CH_2COOH have five and two undissociated protons, respectively.[37] It is known that anionic micelles can catalyze eq 5, because the anionic charge on the micelle surface efficiently stabilizes the cationic intermediate.[38,39] The first-order rate constants (k_1) in the presence of SDS sharply increased above its cmc (ca. 6×10^{-3} M; see Figure 1 in ref 1b). Examination of plots of k_1 vs. calixarene concentrations (Figures 1 and 2 in ref 1b) reveals that (i) **1**-C acts as a weak catalyst whereas **1**-C_{12} catalyzes eq 5 more efficiently than SDS, (ii) **1**-H and **1**-CH_2COOH, which have acidic protons on the calixarene edge, serve as very efficient catalysts, the rate constants at 1.0 mM (Table IV) being greater by 426–1220-fold than those for noncyclic analogues such as *p*-hydroxybenzenesulfonate and *p*-(carboxymethoxy)benzenesulfonate, and (iii) most importantly, plots of k_1 vs. calixarene concentration provide simple saturation curves. The finding (iii) suggests that the reaction catalyzed by these calixarenes proceeds via BNAH–calixarene complexes (Scheme I),[40] where k_{buffer} and k_c denote the first-order rate constants for the buffer-catalyzed term in the absence of **1**-R and for the reaction occurring from the BNAH·**1**-R complex, respectively. On the other hand, noncyclic analogues such as *p*-hydroxybenzenesulfonate and *p*-(carboxymethoxy)benzenesulfonate gave linear k_1 vs. concentration plots. Hence, the reaction catalyzed by these benzenesulfonates proceeds according to the conventional second-order kinetics. The reaction occurring according to Scheme I can be analyzed by eq 7, which holds for the

Table IV. Kinetic Parameters for Scheme I[a]

additive	$10^4 k_1$,[b] s^{-1}	$10^4 k_c$, s^{-1}	K, M^{-1}
1-H	46.2	131	564
1-CH_2COOH	26.6	47.5	1340
1-C	0.36	3.08	287
1-C_{12}	3.31	6.23	2160[d]
SDS (<cmc)	~0		
SDS (6.00 mM)	1.13		
p-HO-$C_6H_4SO_3^-$	0.038		
1-CH_2COOH[c]	328	668	1020
p-$HOOCCH_2O$-$C_6H_4SO_3^-$[c]	0.77		

[a] 30 °C, pH 6.30 (0.01 M phosphate), [BNAH] = 1.01×10^{-4} M. [b] $k_1 = k_{obsd} - k_{buffer}$ at [additive] = 1.00×10^{-3} M. [c] pH 4.00 (0.01 M acetate). [d] 2860 M^{-1} from the fluorescence intensity (pH 10.11).

$$\frac{k_{buffer}}{k_1 - k_{buffer}} = \left(\frac{1}{qK}\right)\left(\frac{1}{[\text{1-R}]}\right) + \frac{1}{q} \qquad (7)$$

formation of a 1:1 complex,[41] where $q = (k_c/k_{buffer}) - 1$. The K and k_c values thus determined are recorded in Table IV. Examination of Table IV reveals again that **1**-H and **1**-CH_2COOH act as excellent acid catalysts for hydration of BNAH. In particular, the catalytic activity of **1**-CH_2COOH was further enhanced at the low-pH region because of the increase in the number of the undissociated carboxylic acid groups. The greater association constant for **1**-CH_2COOH relative to **1**-H and **1**-C may be rationalized in terms of the elongated cavity size which would favorably interact with the BNAH molecule. We feel, however, that in this system, not only the hydrophobic force but also the hydrogen-bonding force is operative, because the K for **1**-H is greater by about twofold than that for **1**-C, and the fluorescence study (Figure 3 in ref 1b) indicates that BNAH is bound to the rather nonhydrophobic site.

Conclusion

As described earlier, there are few published data in support of solution complexes of calixarenes for a long period.[8,16] The acceptor molecule which can serve as a host molecule in an aqueous system must have within a molecular both a hydrophobic site to bind a substrate and a hydrophilic site to solubilize the host molecule in water. The two requisites are apparently opposing. Fortunately, introduction of sulfonate groups into calixarenes can fully satisfy the above opposing requisites. As described in the Experimental Section, hexasulfonated calixarenes are very soluble in water and at the same time can provide a cavity to associate with small molecules in water. Also significant is the fact that they act as surfactants when proper aliphatic chains are introduced. Therefore, one may consider this new class of calixarenes to be "*surfactants with a host–guest-type recognition site*". As catalysts, we here demonstrated only one example, acid-catalyzed hydration

(34) Moras, D.; Olsen, K. W.; Sabesan, M. N.; Buehner, M.; Ford, G. C.; Rossman, M. G. *J. Biol. Chem.* **1975**, *250*, 9137.
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of BNAH. Further applications as acid catalysts, metal ligands, and ion carriers are currently continued in this laboratory.

Acknowledgment. We are grateful to Professor T. Kunitake and N. Higashi for the use of the light-scattering apparatus. We thank Professor Y. Nakamato (Kanazawa University) for helpful discussions. Also, appreciation is expressed to S. Yamamoto (Osaka Municipal Technical Research Institute) for elemental analysis of sulfur. This research was supported in part by a grant from the Ministry of Education of Japan.

Equilibrium Constants and Rate Constants for the Transformations in Aqueous Solution of a Spirocyclic Hydroxyphosphorane

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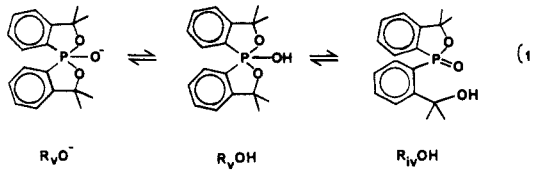
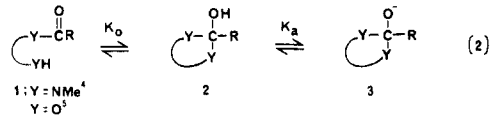
Abstract: A quantitative study is reported for the reactions in water of the hydroxyphosphorane R_vOH (Granoth and Martin, *J. Am. Chem. Soc.* **1978**, *100*, 5229; **1979**, *101*, 4618). This species equilibrates with the isomeric phosphinate $R_{iv}OH$ ($K_1 = [R_vOH]/[R_{iv}OH]$). Addition of base results in the phosphoranoxide R_vO^-, the conjugate base of R_vOH ($K_2 = [R_vO^-][H^+]/[R_vOH]$). This interconversion occurs with an apparent acidity constant $K_1K_2/(1 + K_1)$ of 1.6×10^{-11}. With estimates of K_1, pK_2 is calculated to lie in the range 9–10. Base solutions of this system are not stable; a slower transformation produces the phosphinate anion RO_2^-, the hydrolysis product of $R_{iv}OH$. RO_2^- is converted back to $R_{iv}OH/R_vOH$ in acid solutions. The overall equilibrium ($R_vOH + R_{iv}OH$) $\rightleftarrows$ RO_2^- has an apparent acidity constant of 1.8×10^{-8}. At equilibrium the ratio of the concentrations of the two anions $[RO_2^-]:[R_vO^-]$ is 1.3×10^3. Kinetics of the overall equilibrium have been studied as a function of pH. An analysis is presented in terms of hydronium ion and hydroxide ion catalyzed interconversion of $R_{iv}OH$ and RO_2H, the latter the conjugate acid of RO_2^-. The equilibration of $R_{iv}OH$ and R_vOH or R_vO^- is too rapid to be studied by stopped-flow spectroscopy at all pH. Comparison to analogous carbonyl group systems suggests that pentavalent intermediates of phosphoryl transfer reactions may be kinetically less stable than tetrahedral intermediates of acyl transfer reactions.

Granoth and Martin[1,2] have reported the isolation of the ion R_vO^- as its solid sodium salt. This anion, termed a phosphoranoxide ion,[1] is one of the few examples of its type and serves as a model for the pentavalent intermediate[3] of the basic hydrolysis (or alcoholysis) of phosphate esters. The conjugate acid of this ion, the hydroxyphosphorane R_vOH, was also prepared. This was found to exist in equilibrium with the isomeric phosphinate ester $R_{iv}OH$, with the position of equilibrium between the two being dependent upon temperature and solvent.[1]



We have recently reported[4] quantitative kinetic and equilibrium studies of two carbonyl group systems where an acyl derivative **1** and an isomeric cyclic tetrahedral intermediate **2** exist in equilibrium, and the addition of base shifts the equilibrium toward the tetrahedral form by converting it to its conjugate base **3**. The ionization which occurs at high pH has an apparent acidity constant equal to $K_0K_a/(1 + K_0)$. Only the tetrahedral anion **3** forms in base since the OH group in **2** is considerably more acidic than the YH group in **4**.



The phosphoryl system described in eq 1 is obviously closely related, since it involves an equilibrium between two neutral forms with a relatively acidic OH group in the adduct. We felt it of interest to determine if this system were amenable to quantitative analysis, and in this paper we report the results of our study.

Results

Our analysis involves equilibrium and kinetic studies using UV spectroscopy in aqueous solutions. The mixture of neutrals **2** and **3** was prepared as described previously.[2] Curve A of Figure 1 shows the UV spectrum which is obtained when this is dissolved in acidic solutions. The addition to 0.1 M NaOH produces a different spectrum shown as curve B1 in Figure 1. This spectrum changes with time, and the curve B1 is in fact that obtained by extrapolation to zero time. Curve B2 describes the stable final spectrum. The effect of pH on these spectra was studied in two ways. In one set of experiments a weakly acidic solution (0.002 M HCl) was mixed in a stopped-flow spectrophotometer with various base solutions. The wavelength monitored was 275 nm, where there is a significant difference in spectra A and B1. Absorbance readings were obtained 10–50 ms after mixing and, as will become apparent after discussing kinetics, represent any absorbance change associated with the process responsible for A → B1, while the further process forming B2 has not yet begun. This experiment results in a spectroscopic titration curve (Figure 2, curve I) corresponding to an acid with an acidity constant of 1.6×10^{-11}. This constant is defined as K_{fast}(app). (The symbol "app" represents apparent.) In a second set of experiments solutions were allowed to stand for 1 month, a time sufficient for complete transformation to B2 at all pH values. The final spectra in solutions with pH less than 6 were found to be identical to curve A of Figure 1, while the spectra above pH 9.5 were identical to

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