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Calixarenes as new functionalized host molecules

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Abstract - Water-soluble calixarenes with various substituents have been synthesized for the first time. It was demonstrated that these water-soluble calixarenes serve as a new class of catalysts, surfactants, ligands, and host molecules.

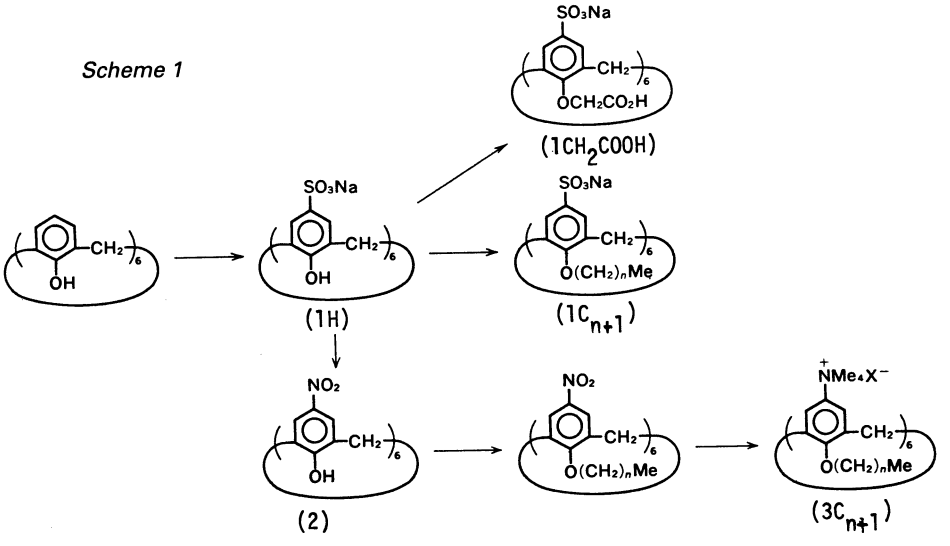
INTRODUCTION

"Calixarenes" are cyclic oligomers made up of benzene units in a similar way to that in which cyclodextrins are made up of glucose units and thus have been expected to be useful as a new class of host molecules. Although calixarenes can include sereral small molecules in the solid state (ref. 1), there exist only a few examples for the inclusion properties of calixarenes in solution (ref. 2-5). This is is sharp contrast to cyclodextrins which can form a variety of host-guest-type solution complexes. The difference stems, we believe, from the poor solubility of calixarenes: that is, they are sparingly soluble in several organic solvents but insoluble in water. We considered, therefore, that the experimental efforts should be directed primarily toward solubilization of calixarenes, which would lead to the exploitation of new host molecules and eventually to that of calixarene-based enzyme mimics. With these objects in mind, we synthesized water-soluble anionic and cationic calixarene derivatives (mainly calix[6]arene derivatives).

SYNTHESIS OF WATER-SOLUBLE CALIXARENES

Introduction of functional groups into each benzene ring in calixarenes is similar in a sense to polymeric reactions: that is, it is very difficult to isolate the fully-substituted product from the lower substituted products. Therefore, one must choose the reaction which gives the almost quantitative yield. The synthetic route to water-soluble calixarenes is illustrated in scheme 1. Sulfonation is one of the useful reactions which satisfy the above prerequisite: that is, sulfonation of calix[6]arene in conc. H_2SO_4 at 100 °C gave (1H) in 75% yield (ref. 3,5). (1H) serves as a starting material to synthesize ($1C_{n+1}$) and ($1CH_2COOH$).

Scheme 1



Nitration of calixarenes was repeatedly attempted in the past, but it failed. In fact, Gutsche (ref. 1) describes that attempts to obtain a nitration product have not been successful. We noticed that the reaction conditions for direct nitration should be too drastic. As shown in scheme 1, we exploited a new route to p-nitrocalix[6]arene (2) via (1H) (ref. 6). The first advantage of this method is that the calix[6]arene skeleton is protected from oxidation by introducing the electron-withdrawing sulfonate groups. In direct nitration, it was very difficult to isolate a hexanitrated product from lower nitrated products. In the present method, the water-solubility of (2) is largely different from sulfonate-containing, incompletely substituted products. This is the second advantage leading to the successful isolation of pure (2). (2) serves as a starting material to synthesize ($3C_{n+1}$).

pK_a DETERMINATION OF THE OH GROUPS

It is known that the OH groups in calixarenes form very strong hydrogen bonding (ref. 1). This implies that the pK_a's should be quite different from those of the corresponding noncyclic analogs. Determination of the pK_a's has been attempted repeatedly, but to the best of our knowledge there exist no reliable reported data. Conceivably, this is due to the difficulty to synthesize calixarene derivatives usable for titration: for example, water-soluble calixarenes for potentiometric titration or chromophoric calixarenes for phototitration. In this respect, (1H) and (2) are ideal molecules to estimate the pK_a's of the OH groups.

The titration data are summarized in Table 1. Examination of Table 1 reveals that (i) the first dissociation occurs in very acidic pH region, pK_{a1} being lower than 1, and (ii) the dissociation of the last proton occurs in very acidic pH region, the pK_{a4} being higher than 11. Therefore, these molecules have a super-acidic proton as well as a super-basic oxy-anion within a molecule. The remarkable pK_a separation is attributed to intramolecular hydrogen bonding in calix[6]arene.

TABLE 1. pK_a values for (1H), (2), and the noncyclic analogues[a]

Compound	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}
(1H)	<1	3.0±0.4	4.0±0.4	>11
p-Hydroxy-benzene-sulfonate	8.9±0.1			
(2)[b]	<0	10.3±0.3	13±1	>14
p-nitro-phenol[b]	7.1±0.1			

[a] 30 °C.

[b] Water:tetrahydrofuran = 70:30 (v/v). The pK_a values are not corrected.

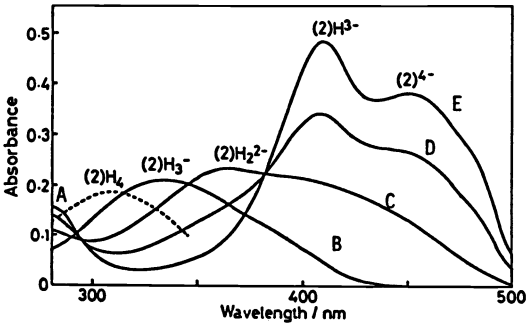


Fig. 1. pH-Dependent spectral change in (2) (8.90×10^{-6} M) in water:THF = 70:30 (v/v) at 30 °C. The spectra were recorded at 12% $HClO_4$ (A), pH 3.5-8.5 (B), pH 11.5 (C), pH 13.5 (D), and pH 14 (E).

Interestingly, (2) gave pH-dependent five different absorption maxima at 315,332, 365, 410, and 450 nm which could be attributed to five species of (2), that is $(2)H_4$, $(2)H_3^-$, $(2)H_2^{2-}$, $(2)H^{3-}$, and $(2)^{4-}$ (Fig 1). Under the identical conditions the absorption maxima of p-nitrophenol and p-nitrophenolate appeared at 318 and 406 nm, respectively. It is worth mentioning that the absorption maximum of $(2)^{4-}$ shifts to longer wavelength by 44 nm as compared with that of p-nitrophenolate. We now consider that the unusual red shift is related to the "alternate" conformation of $(2)^{4-}$.

Here, we assessed the possible relation between the calixarene conformation and the dissociation of the OH groups. The "cone" conformers can be conveniently discriminated from others by ^{1}H-NMR (ref. 1): observing the resonances arising from the $ArCH_2Ar$ methylene protons of calixarenes, the pattern of "cone" calixarenes gives a pair of doublets below room temperature. When the ^{1}H-NMR spectrum of (1H) was taken in D_2O-Me_2SO-d_6 (2:1 v/v), the $ArCH_2Ar$ methylene protons gave a pair of doublets at pH 9.0 and a singlet at 0.04 M H_2SO_4 (Fig. 2). The difference suggests that the "cone" conformation is favorably adopted by dissociated (1H) rather than by undissociated (1H). That is, in an aqueous system the oxy-anions can form stronger intramolecular hydrogen bonding leading to fixation of the calixarene conformation to "cone".

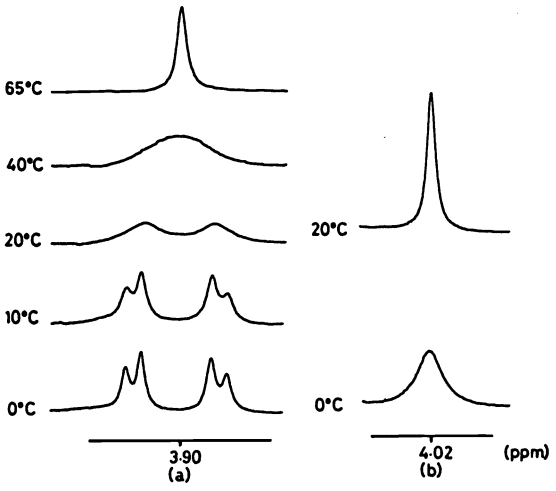


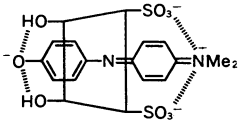
Fig. 2. ^{1}H-NMR spectra of the $ArCH_2Ar$ methylene protons of (1H) in D_2O:Me_2SO-d_6 (2:1 v/v). (a) pH 9.0 with borate buffer, (b) 0.04 M H_2SO_4.

HOST-GUEST COMPLEXATION

Since calixarenes possess a cylindrical architecture similar to cyclodextrins, they are expected to form inclusion complexes. However, the data reported so far have been limited to only the solid state (ref. 1,7,8). In contrast, one can expect the water-soluble calixarenes to form solution complexes which would be more important to design calixarene-based enzyme mimics.

We have found that in an aqueous system (1H), ($1CH_2COOH$), and ($1C_{n+1}$) form solution complexes with pyrene, Phenol Blue, Orange OT, and 1-benzyl-1,4-dihydronicotinamide. The association constants for lipophilic dyestuffs were about 10^5 M^{-1} while those for more hydrophilic 1-benzyl-1,4-dihydronicotinamide were 287-2160 M^{-1} (ref. 4,5).

Phenol Blue acts as a solvent property indicator: the absorption maximum (658 nm in water) shifts to shorter wavelengths in nonpolar solvents (e.g., 552 nm in cyclohexane). Measurements of the absorption maximum in the presence of (1H) and ($1C_{n+1}$) established that (i) the absorption maximum in the presence of (1H) shifts to longer wavelengths (685 nm) and (ii) the plot for ($1C_{12}$) is biphasic, a large blue shift (by 66 nm) followed by a relatively small blue shift (by 28 nm). The red shift (by 27 nm) observed for (1H) implies that apparently, (1H) can provide a reaction field more polar than water. On the other hand, ($1C_1$) cannot induce such a large red shift and sodium p-toluenesulfonate, a noncyclic analogue of (1H), has almost no effect. These findings support that Phenol Blue is bound into the cavity of (1H) and the OH groups stabilize the charge-separated excited state through hydrogen bonding.

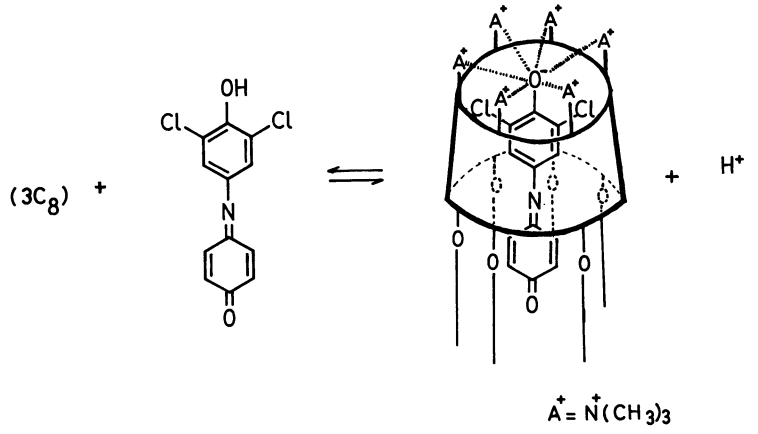


excited state of Phenol Blue

The solubilization of lipophilic dyestuffs is frequently used to evaluate the solubilization power of surfactants. We employed Orange OT (1-(2'-methylphenylazo)-2-naphthol) to test the solubilization power of ($1C_{n+1}$) (ref. 5). In aqueous SDS, the solubilization of Orange OT was obsesrved only above the cmc, and the concentration increased linearly with increase in the SDS concentration. The slope which corresponds to a molar ratio of the Orange OT-SDS complex was 0.0096: that is, 104 molecules of SDS bind one Orange OT. Similarly, ($1C_6$) showed the micelle-like dependence, the slope being 0.053: that is, 19 molecules of ($1C_6$) can bind one Orange OT. In contrast, aqueous ($1C_{12}$) gave a linear plot crossing the abscissa at [($1C_{12}$)] = 0 M. The slope (0.61) indicates that 1.6 molecules of ($1C_{12}$) can bind one Orange OT. The result strongly suggests that ($1C_{12}$) acts as a "unimolecular micelle". In other words, ($1C_{12}$) and Orange OT associate according to a host-guest-type 1:1 manner.

Fluorescence intensities and emission maxima of anilinonaphthalene derivatives show a strong solvent dependence. We employed 2-anilinonaphthalene as a fluorescence probe. The emission maximum (447 nm in water and 420 nm in methanol) correlates linearly with the methanol concentration in water-methanol mixed solvent. In aqueous ($1C_6$) and ($1C_{12}$), the emission maximum shifted to shorter wavelengths and was saturated at 427 and 420 nm, respectively (ref. 5). These wavelengths correspond to the mixed solvents containing 70 and 100 vol% of methanol, respectively. Under the identical conditions the SDS micelle was estimated to be 65 vol% aqueous methanol. Therefore, ($1C_{12}$) can form the hydrophobic domain much stronger than the SDS micelle.

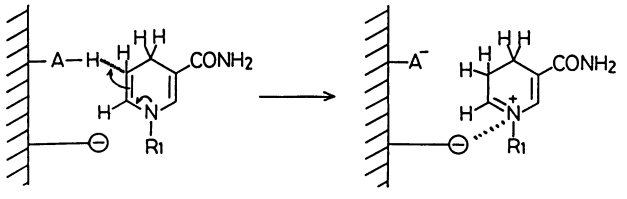
2,6-Dichlorophenolindophenol (DCPI) is an excellent probe to detect the hydrophobic domain constructed in aqueous solutions: for example, the cmc of cationic micelles in dilute HCl solution can be determined on the basis of the color change from lgiht red (undissociated phenol, 517 nm) to blue (phenolate anion, 640 nm). This dissociation is induced by complexation between DCPI and cationic surfactants. Hexadecyltrimethylammonium chloride (CTAC) gave a clear OD_{640} jump at 1.1×10^{-3} M, which corresponds to the cmc of this surfactant. In contrast, the plot of OD_{640} vs. [($3C_8$)] gave a simple saturation curve and the blue color appeared at the very low ($3C_8$) concentration (around 1×10^{-4} M). The continuous variation method established that the blue species consists of a 1:1 complex between DCPI and ($3C_8$). These findings support that as illustrated below, ($3C_8$) forms a host-guest-type solution complex with DCPI and the six cationic charges on the edge strongly facilitate the deprotonation of DCPI.



Dansyl derivatives serve as probes useful to estimate the microviscosity of probe-binding sites since the fluorescence polarization (p) increases in viscous media. We used N-dansylaniline to estimate the microviscosity of ($3C_8$) in an aqueous system. The p-value (0.02 in water) increased up to 0.05 in the presence of the CTAB micelle, indicating that the micellar phase is somewhat more viscous than bulk water. Surprisingly, N-dansylaniline bound to ($3C_8$) gave p = 0.18, which is much greater than the micellar system and comparable with those of the liposomal membranes below their T_c (p = 0.1-0.2) where the molecular motion is almost frozen. These data indicate that the cavity of ($3C_8$) is considerably viscous enough to suppress the molecular motion of guest molecules.

APPLICATIONS AS HOST-GUEST-TYPE ACID CATALYSTS

NADH and 1,4-dihydronicotinamides undergo an acid-catalyzed hydration reaction in aqueous solution. It is known that glyceraldehyde-3-phosphate dehydrogenase can rapidly catalyze this reaction to afford hydrated NADH. 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.



(1)

We noticed that (1H) and ($1CH_2COOH$) fully satisfy the requirements of the above equation: they have acidic protons and anionic groups at the two edges of the cylindrical cavity. The hydration reaction of 1-benzyl-1,4-dihydronicotinamide (BNAH) was carried out at 30 C in buffered aqueous solution (pH 6.30 with 0.10 M phosphate). The first-order rate constant (k_1) in the presence of SDS sharply increased above its cmc

(ca. 6×10^{-3} M: ref. 4,5). Examination of plots of k_1 vs. calixarene concentrations reveals that (i) ($1C_1$) acts as a weak catalyst whereas ($1C_{12}$) catalyzes the hydration reaction more efficiently than SDS, (ii) (1H) and ($1CH_2COOH$) serve as very efficient catalysts, the rate constants being greater by 426-1220 fold than those for noncyclic analogues, 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.

The kinetic parameters determined on the basis of scheme 2 are summarized in Table 2.

TABLE 2 Kinetic Parameters for Scheme 2[a]

additive	$10^4 \cdot k_1$[b] s^{-1}	$10^4 \cdot k_c$ s^{-1}	K M^{-1}
(1H)	46.2	131	564
($1CH_2COOH$)	26.6	47.5	1340
($1C_1$)	0.36	3.08	287
($1C_{12}$)	3.31	6.23	2160[d]
SDS (< cmc)	~0	—	—
SDS (6.00 mM)	1.13	—	—
HO-p-$C_6H_4SO_3^-$	0.038	—	—
($1CH_2COOH$)[c]	328	668	1020
$HOOCCH_2O$-p-$C_6H_4SO_3^-$[c]	0.77	—	—

[a] 30 °C, pH 6.30 (0.01 M phosphate), [BNAH] = 1.01×10^{-4} M.

[b] $k_1 = k_{obs} - k_{buffer}$ 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).

Scheme 2

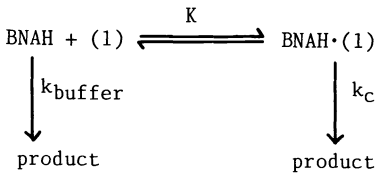
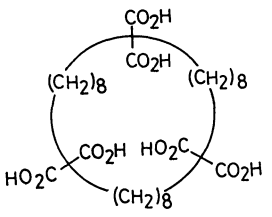


TABLE 3. UO_2^{2+} selectivity

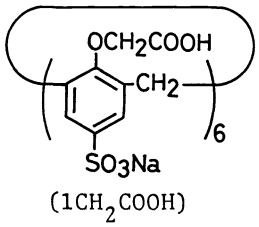
Metal	($1CH_2COOH$)		(4)	
	log K	UO_2^{2+} selectivity	log K	UO_2^{2+} selectivity
UO_2^{2+}	18.7	—	16.4	—
Mg^{2+}	—	$>10^6$	—	31000
Ni^{2+}	5.7	10^{13}	—	210
Zn^{2+}	6.2	10^{12}	—	80
Cu^{2+}	6.7	10^{12}	—	—

MOLECULAR DESIGN OF 'SUPER-URANOPHILES'

It has been established that uranyl ion (UO_2^{2+}) adopts a pseudo planar six-coordinate structure which is quite different from the coordination structures of other metal ions. This suggests that a macrocyclic host having a nearly coplanar arrangement of six ligand groups would serve as a specific ligand for UO_2^{2+}. Tabushi et al. (ref. 9) have currently been interessted in this approach and reported the macrocyclic host molecule (4) having six carboxylate groups in the ring.



(4)



($1CH_2COOH$)

Calix[6]arene is an ideal molecule for the design of uranophiles, because introduction of ligand groups into each benzene unit exactly provides the required pseudoplanar six-coordinate structure. We thus used ($1CH_2COOH$) bearing six carboxylate groups on the edge of calix[6]arene (ref. 10).

We first corroborated on the basis of a continuous variation method that ($1CH_2COOH$) and UO_2^{2+} form a 1:1 complex in aqueous solution. The association constant (K) was estimated by a displacement method using $UO_2(CO_3)_3^{4-}$ at pH 10.4: log K = 18.7. This value is greater by 2.3 log units than log K for (4). Further interesting is the finding that ($1CH_2COOH$) has the remarkably high selectivity for UO_2^{2+}. As shown in Table 3, the UO_2^{2+} selectivity of (4) is 80-210 for Ni^{2+} and Zn^{2+}, whereas that of ($1CH_2COOH$) is 10^{12}-10^{13}! The markedly large difference between the K values for UO_2^{2+}

and the other metal cations could stem from the rigidity of ($1CH_2COOH$) which would firmly maintain the coplanar six-coordination geometry. The remarkably high selectivity would allow ($1CH_2COOH$) to be called a "super-uranophile".

CONCLUSIONS

The foregoing results indicate that water-soluble calixarenes serve as a new class of catalysts, surfactants, ligands, and host molecules. We believe that in near future, calixarenes will become a new rival for cyclodextrins.

REFERENCES

1. For a comprehensive review see C. D. Gutsche, Acc. Chem. Res. 16, 161-170 (1983).
2. C. D. Gutsche and L. J. Bauer, J. Am. Chem. Soc. 107, 6052-6075 (1985).
3. S. Shinkai, S. Mori, T. Tsubaki, T. Sone and O. Manabe, Tetrahedron Lett. 25, 5315-5318 (1984).
4. S. Shinkai, H. Koreishi, S. Mori, T. Sone and O. Manabe, Chem. Lett. 1033-1036 (1985).
5. S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki and O. Manabe, J. Am. Chem. Soc. 108, 2409-2416 (1986).
6. S. Shinkai, T. Tsubaki, T. Sone and O. Manabe, Tetrahedron Lett. 26, 3343-3344 (1985).
7. G. D. Andreetti, R. Ungaro and A. Pochini, J. Chem. Soc. Chem. Commun. 1005-1007 (1979).
8. M. Coruzzi, G. D. Andreetti, V. Bocchi, A. Pochini and R. Ungaro, J. Chem. Soc., Perkin Trans. 2, 1133-1138 (1982).
9. I. Tabushi, Y. Kobuke, K. Ando, M. Kishimoto and E. Ohara, J. Am. Chem. Soc. 102, 5947-5948 (1980).
10. S. Shinkai, H. Koreishi, K. Ueda and O. Manabe, J. Chem. Soc., Chem. Commun. 233-234 (1986).