A New Water-Soluble Host Molecule Derived from Thiacalixarene

Nobuhiko Iki,* Toyohisa Fujimoto, and Sotaro Miyano*
Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba, Aoba-ku, Sendai 980-8579

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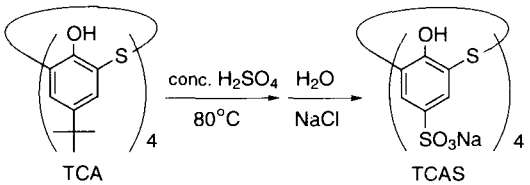
A new water soluble host molecule, thiacalix[4]arene-tetrasulfonate (TCAS), was obtained by direct sulfonation of *p-tert*-butylthiacalix[4]arene. TCAS showed size- and shape-selectivity to bind small chlorinated organic molecules in its hydrophobic cavity by a 1:1 or 1:2 manner in aqueous solution.

Calixarenes, cyclic oligomers of *p*-alkylphenols bridged by methylene groups, are one of the key compounds in the host-guest chemistry.[1] Unlike cyclodextrins, calixarenes are inherently insoluble in water, which had forced their use in organic solvent. In 1984, Shinkai *et al.* first reported water-soluble calixarenes by the sulfonation,[2] which enables to exploit the chemistry of complexation of organic molecules and metal ions with the calixarenes in aqueous phase. Recently, we reported facile synthesis of *p-tert*-butylthiacalix[4]arene (TCA),[3] in which four *p-tert*-butylphenols are linked by four sulfide groups instead of methylene groups. As an example of the advantageous effect of replacing the methylene by the sulfide linkage, we demonstrated that TCA has high complexation ability to transition metal ions, which had been totally unexpected from *p-tert*-butylcalix[4]arene because it has very poor complexing ability.[4] In order to extend the function of TCA, herein we synthesize a new water-soluble thiacalixarene and demonstrate its complexation behavior for small organic molecules in aqueous solution.

The Shinkai's method for direct sulfonation of calixarenes[5] was followed here to obtain the water-soluble TCA. Briefly, a mixture of 1.5 g of TCA and 80 cm^3 of conc. H_2SO_4 was heated at 80°C for 4 h. After cooling, the reaction mixture was carefully poured into 500 cm^3 of ice-water, then the solid residue was filtered off. To the clear solution of the tetrasulfonic acid was added NaCl (100 g) to salt out the sodium salt with the exclusion of HCl. Precipitation from aqueous ethanol was repeated for several times to yield colorless powder of tetrasodium thiacalix[4]arenetetrasulfonate, TCAS (1.2 g, 63%y).[6]



The complexation behavior of TCAS as host (H) with guest molecules (G) in aqueous solution was examined by precipitation and NMR titration methods. The guest molecules used are listed in Table 1.

In the precipitation method, to a D_2O solution of TCAS (1.0 cm^3, the total concentration H_T = 50 mM) was added an amount of a guest as bulk liquid (*ca.* 0.1 cm^3). Then, the mixture was stirred well to allow the guest to attain equilibrium partition between the bulk guest layer and the aqueous phase which contained the host to complex, if possible, with the guest. Finally, NaCl (0.25 g) was added to the aqueous phase to salt out the TCAS complex. The precipitate was recovered by filtration[7] and dissolved again into D_2O to determine the composition of the complex by integrating the relevant proton signals of the ^1H NMR spectrum. Thus, Table 1 lists the average numbers of the guests ($\bar{n}$) which accompanied the precipitated TCAS complexes. It can be seen that the CH_2Cl_2-TCAS precipitate holds nearly two guest molecules, while other chlorinated guests but 1,1,1-trichloroethane are retained in a 1:1 manner (see below). Benzene and toluene are hardly retained in the TCAS precipitates. Molecular models indicate that 1,1,1-trichloroethane does not differ so much from the 1,1,2-isomer in molecular volume, while it scarcely formed the TCAS complex indicating that TCAS has substantial ability to discriminate the shape as well as the size of the guests.

On the basis of these results, the complex formation process was further investigated by NMR titration method as follows, assuming that (1) TCAS forms inclusion complexes with pertinent guests and (2) incidental co-precipitation of free guest with TCAS (either H or TCAS complex) may be negligible. The procedure is as follows; a D_2O solution of TCAS (H_T = 0 ~ 120 mM) containing 20 mM of 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard was saturated with a guest. After equilibration, aliquot of D_2O phase was subjected to ^1H NMR to determine the chemical shift (δ) and the total concentration of the guest (G_T) by calibrating with the methyl resonance of DSS at 0.015 ppm.

Figure 1a shows the dependence of G_T on H_T. As H_T rose up, G_T increased linearly, that implies that the host could solubilize guest molecules into aqueous phase *via* inclusion (eq. 1),

$$H + iG \rightleftarrows H{\cdot}G_i \qquad (i = 1 \text{ to } n) \qquad (1)$$

where $H{\cdot}G_i$ is the 1:*i* host-guest complex and *n* is the maximum number of guest molecules bound to a host. Hence the ^1H NMR signal intensity for host and guest corresponds to *all host* and *guest bound to host* in eq. 1, $\bar{n}$ is written by eq. 2.

Table 1. Estimated average number of binding ($\bar{n}$) and solubility ([G]) of various guest molecules

Guest	$\bar{n}$ [a]	$\bar{n}$ [b]	[G]/mM[b]
CH_2Cl_2	1.92	1.79	171.9
$CHCl_3$	1.03	1.00	47.1
1,2-dichloroethane	1.05	0.95	72.3
1,1,1-trichloroethane	0.18	~0.29	103.0
1,1,2-trichloroethane	0.99	0.90	27.1
1,1,2,2-tetrachloroethane	0.88	0.93	12.0
Trichloroethylene	0.06	0.13	7.3
Benzene	0.18	0.35	15.9
Toluene	0.08	0.09	5.2

[a] Determined by precipitation method. [b] By NMR titration.

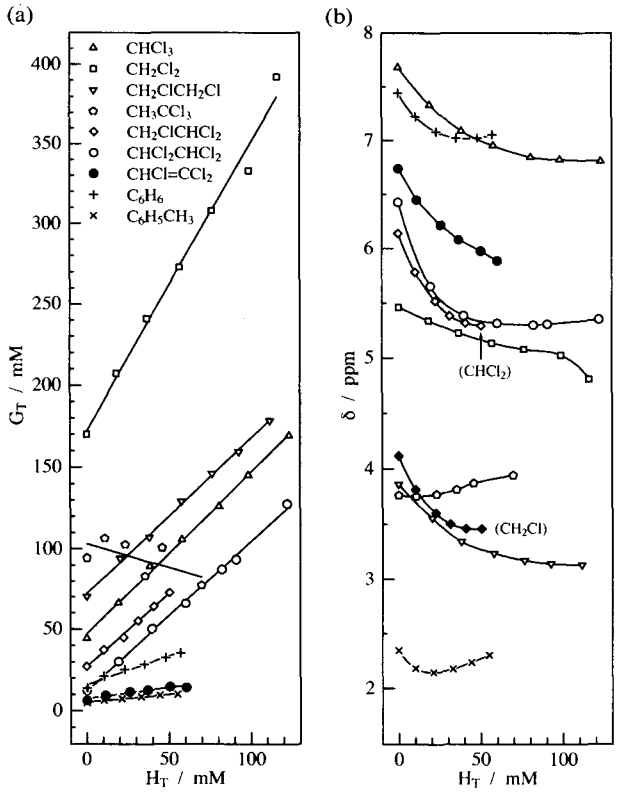


Figure 1. The effect of total concentration of TCAS (H_T) on (a) the total concentration (G_T) and (b) the chemical shift (δ) of guest molecules in D_2O phase at 300K.

$$\bar{n} \equiv \frac{\text{G bound to H}}{\text{All H}} = \frac{G_T - [G]}{H_T} \qquad (2)$$

Since the bulk phase of guest existed after equilibration, the [G] is the saturated concentration, namely the solubility in D_2O. Here we rewrote eq. 2 into eq. 3, which was fitted to the data in Figure 1a to elucidate $\bar{n}$ as well as [G] (Table 1).

$$G_T = \bar{n} \cdot H_T + [G] \qquad (3)$$

The $\bar{n}$ values by the NMR titration shown in Table 1 agreed quite well with those by the precipitation method, which justified the assumptions (1 and 2). Small guest molecules had $\bar{n} \approx 1$ or 2 while larger guests such as benzene and toluene had $\bar{n} \approx 0$. The latter may be caused by two reasons, poor solubility and instability of the complex, since $\bar{n}$ is the function of both [G] and β_i, the overall formation constant of $H \cdot G_i$ given by eq. 4.[8]

$$\beta_i = \frac{[H \cdot G_i]}{[H][G]^i} \qquad (i = 1 \text{ to } n) \qquad (4)$$

The difference in the β_i by the size of guest is one of the evidences that TCAS included the guest into the hydrophobic cavity (as shown in graphical abstract) to recognize the difference in the size. In Figure 1a and Table 1, 1,1,1-trichloroethane again showed no formation of complex with TCAS even it has relatively high [G]. This supports the ability of TCAS to discriminate the shape of guest molecules.

NMR chemical shift data also provide useful information on the nature of the TCAS complexes (Figure 1b). Only single resonance was observed for all guest due to fast exchange between free G and $H \cdot G_i$ in eq. 1 on the NMR time scale. As H_T increased, the δ value decreased (except 1,1,1-trichloroethane), that is caused by shielding effect of aromatic rings in TCAS. Benzene and toluene further showed increase after the decrease, which might be caused by the self-association of $H \cdot G_i$ and free host molecules. Also association of DSS to TCAS might contribute to the chemical shift change of those as well as 1,1,1-trichloroethane. The complex with 1,1,2-trichloroethane showed the presence of two sets of protons due to the vicinal $CHCl_2$ and CH_2Cl protons (J = 4.3 Hz). Furthermore, the $CHCl_2$ protons were more shielded ($\Delta\delta$ = -0.85 ppm) than the CH_2Cl proton ($\Delta\delta$ = -0.66 ppm) on complexation (H_T = 50.4 mM), which strongly suggests that the former moiety of the guest penetrates more deeply into the hydrophobic cavity of the host than the latter part.

By use of data in Figure 1b, we attempted to clarify the β_1 for guests of $\bar{n}$ = 1 without success because β_1 was quite large (more than 10^4 M^{-1} for $CHCl_3$) and the amount of free [H] was too small to estimate β_1 at sufficient accuracy. At least we could judge that TCAS quantitatively formed 1:1 complexes (H·G) with small organic molecules.

In this paper, we demonstrated direct sulfonation of TCA to TCAS, which behaved as a host molecule bearing hydrophobic cavity. Since TCAS could include chlorinated organic molecules strongly, we are now studying TCAS as a reagent to sense or remove such environmentally hazardous chemicals in water.

References and Notes

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6 Tetrasodium 25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiacalix[4]arene-5,11,17,23-tetrasulfonate. m.p.: decomp. at 390°C, ^1H NMR (δ from DSS, D_2O) 8.04 ppm (s, 8H, ArH); ^{13}C NMR (δ from CH_3CN, D_2O) 118.32, 132.14, 132.82, 158.03 ppm (Ar).
7 The recovery of TCAS by salting-out was quantitative (99.1%) as confirmed by measuring UV absorption of the solution after filtration.
8 The mass balance for guest and host in D_2O are given by eqs. 5 and 6.
$$G_T = [G] + [H \cdot G] + \cdots + i[H \cdot G_i] + \cdots + n[H \cdot G_n] \qquad (5)$$
$$H_T = [H] + [H \cdot G] + \cdots + [H \cdot G_i] + \cdots + [H \cdot G_n] \qquad (6)$$
By introducing eqs 5, 6 and 4 into eq 2 gave eq 7.
$$\bar{n} = \left(\sum_{i=1}^{n} i\beta_i[G]^i\right) \Big/ \left(1 + \sum_{i=1}^{n} \beta_i[G]^i\right) \qquad (7)$$