ORGANIC LETTERS

2002
Vol. 4, No. 4
509−512

Inclusion Behavior of Thiacalix[4]arenetetrasulfonate toward Water-Miscible Organic Molecules Studied by Salting-Out and X-ray Crystallography

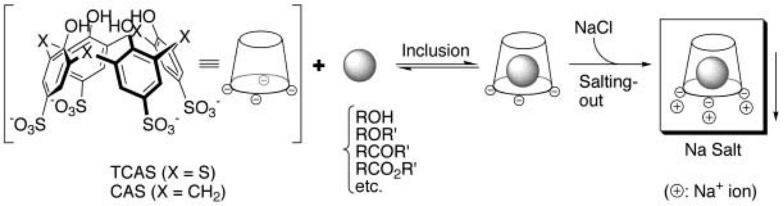
Nobuhiko Iki,[†],* Takehiro Suzuki,[†] Katsuyoshi Koyama,[†] Chizuko Kabuto,[‡] and Sotaro Miyano*,[†],[§]

Department of Biomolecular Engineering, Graduate School of Engineering,
Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan, and
Instrumental Analysis Center for Chemistry, Graduate School of Science,
Tohoku University, Aramaki-Aoba, Aoba-ku, Sendai 980-8578, Japan

iki@orgsynth.che.tohoku.ac.jp

Received November 15, 2001

ABSTRACT



Inclusion ability of thiacalix[4]arenetetrasulfonate (TCAS) toward water-miscible organic molecules such as alcohols, ketones, cyclic ethers, and so on was studied by salting-out of the inclusion complex. NMR spectra of the recovered precipitates showed size selectivity to include the guest molecules. X-ray crystallographic analyses of TCAS salts including acetone and 1,4-dioxane suggested that guests are retained with the aid of cation coordination and H-bonding.

Separation of water-miscible noncharged substances such as alcohol, ether, and ketone from aqueous solutions is a key technology in industrial and environmental processes. As exemplified by distillation,[1,2] adsorption,[3] and freezing-out,[4] however, conventional methods have an intrinsic drawback in that the separation selectivity is limited by differences in physicochemical properties of solutes. On the other hand, recent progress in host−guest chemistry has successfully yielded host molecules recognizing a particular guest molecule.[5] During the course of studying functions of the sulfur-bridged analogue of calixarene,[6] we found that thiacalix[4]arenetetrasulfonate (TCAS) can include organohalogens such as chloroform and dichloroethane in the cavity by a 1:1 manner in aqueous solution.[7] Furthermore, TCAS can retain a guest molecule in the cavity upon salting-out of the TCAS−guest complex by NaCl. The fact prompted us to build a removal method of organohalogens from water by trapping the TCAS−guest complex onto an anion-exchenge resin.[8] On the basis of these schemes, a combination of

---

[†] Department of Biomolecular Engineering.
[‡] Instrumental Analysis Center for Chemistry.
[§] E-mail address for S.M.: miyano@orgsynth.che.tohoku.ac.jp.

(1) Peters, T. L. *Anal. Chem.* **1980**, *52*, 211−213.

(2) Bruce, M. L.; Lee, R. P.; Stephens, M. W. *Environ. Sci. Technol.* **1992**, *26*, 160−163.

(3) Radovic, L. R. *Tanso* **1998**, *185*, 326−331.

(4) Shapiro, J. *Anal. Chem.* **1967**, *39*, 280.

(5) Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Basel, 1995.

(6) Iki, N.; Miyano, S. *J. Incl. Phenom. Macrocycl. Chem.*, in press.

(7) Iki, N.; Fujimoto, T.; Miyano, S. *Chem. Lett.* **1998**, 625−626.

10.1021/ol017053l CCC: $22.00

molecular recognition of water-miscible organic compounds and phase transition would make an intriguing strategy to selectively separate such molecules from water. Recently, Ungaro et al. reported an NMR study to show that calix[4]-arenetetrasulfonate (CAS) included small organic molecules such as alcohols, ketones, and nitriles.[9] This prompted us to report our results on the study of inclusion ability of the sulfur-bridged analogue, TCAS, toward a wide variety of water-miscible guest molecules by the salting-out protocol and by X-ray crystallography. We also reported the salting-out of complexes of CAS as compared with those of TCAS, because comparison of the structurally related hosts should provide suggestive information concerning the inclusion mechanism.

After the inclusion between the guests and hosts had been equilibrated in D_2O, a 100-fold excess of NaCl was added to precipitate quantitatively the complexed and, if any, remaining free host as the sodium salts (see the abstract graphic).[10] The molar ratio of the included guest against the host molecule in the precipitate, which means the average number of bound guests per molecules of the host, was calculated by use of eq 1,

$$\bar{n} = G_{\mathrm{ppt}}/H_{\mathrm{ppt}} \qquad (1)$$

where G_{ppt} and H_{ppt} are the amount of guest and host molecules in the precipitates, respectively.[10]

Figure 1 shows the $\bar{n}$ values for a wide variety of guest species including alcohols, aldehydes, carboxylic acids, ketones, cyclic ethers, esters, nitriles, nitro compounds, amines, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). In many cases, the guest was trapped in the precipitates of the host by $\bar{n} \approx 1$. Concerning the inclusion ability of the host, TCAS seemed to be able to accommodate more members of the guest molecules examined than CAS did in general, suggesting that TCAS has a larger cavity to accommodate a wider range of guest molecules. This is consistent with the fact that the thiacalix[4]arene ring has a larger cavity than calix[4]arene does as studied by X-ray crystallography.[11] By contrast, small guests such as CH_3OH, HCOOH, CH_3CN, and CH_3NO_2 were more efficiently included by CAS probably because of a better fitting into the smaller cavity. The efficiency of the host to give precipitates upon addition of NaCl should be another criterion to judge the performance. In most cases, quantitative formation (>99.9%) of the sodium salt of the hosts was confirmed by monitoring the UV absorption of residual hosts in the aqueous phase. However, when n-C_3H_7COOH, $CH_3COC_2H_5$, tetrahydrofuran (THF), n-C_3H_7CN, and *N*-methylated amines were used as the guest, CAS was not salted out, showing that these guests increased the solubility of the CAS-Na salt.

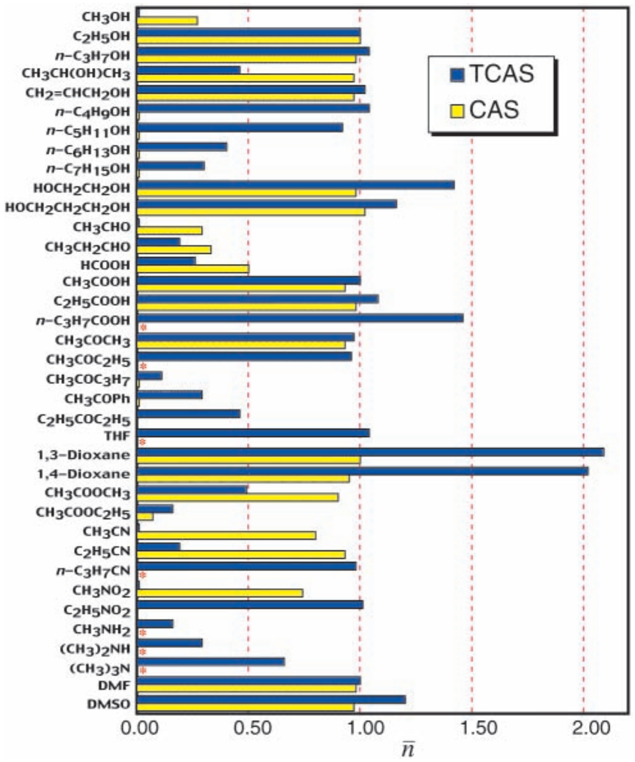


Figure 1. The average number of binding of various guest molecules toward host molecules. A red asterisk indicates that precipitation was not formed with these guest species upon addition of NaCl.

As TCAS could form precipitates with a wider range of guest molecules than CAS as was found above, we then concentrated our attention on the inclusion behavior of TCAS, which considerably varied depending upon the guest. Alcohols provided good examples to demonstrate the selectivity of TCAS toward guest molecules. For a series of n-alkyl alcohols, the inclusion ability of TCAS is in the order:

$$C_2H_5OH \approx n\text{-}C_3H_7OH \approx n\text{-}C_4H_9OH > n\text{-}C_5H_{11}OH > n\text{-}C_6H_{13}OH > n\text{-}C_7H_{15}OH \gg CH_3OH$$

indicating that TCAS shows a preference for rather small alcohols except CH_3OH. Notably, the TCAS salt retained C_2H_5OH in vacuo (1 mmHg) even at 80 °C for 1 h, indicating that the inclusion complex was very stable in the solid state. On the other hand, the smallest guest CH_3OH was barely included in the precipitate, which may be accounted for by

---

(8) Iki, N.; Fujimoto, T.; Shindo, T.; Koyama, K.; Miyano, S. *Chem. Lett*. **1999**, 777−778.

(9) Arena, G.; Contino, A.; Gulino, F. G.; Magrì, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett*. **2000**, *41*, 9327−9330.

(10) To a vial containing 1.0 cm^3 of a D_2O solution of a host ($[Host]_T$ = 55 mM, 5.5×10^{-5} mol) was added 1.1 mmol of a pure liquid of guest (1.1 M). Here, 20-fold excess of the guest molecule was used for the sake of experimental convenience. After the mixture was shaken well for 1 min, 0.31 g (5.3 mmol) of NaCl was added and shaken to salt out the precipitate, which was filtered, dried for 20 min under suction on the filter, and then dissolved in D_2O (0.6 cm^3) to measure the ^1H NMR spectrum by use of 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an external standard. The peak areas for host and guest were read to estimate H_{ppt} and G_{ppt}, respectively.

(11) (a) Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett*. **1997**, *38*, 3971−3972. (b) Iki, N.; Kabuto, C.; Fukushima, T.; Kumagai, H.; Takeya, H.; Miyanari, S.; Miyashi, T.; Miyano, S. *Tetrahedron* **2000**, *56*, 1437−1443.

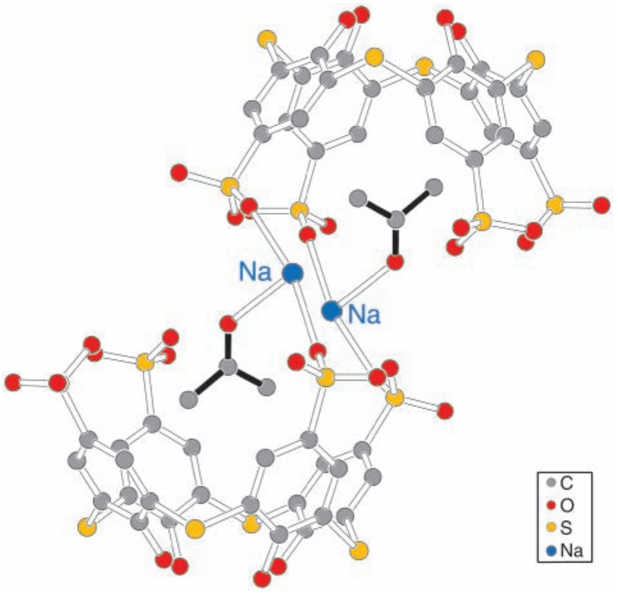


Figure 2. The X-ray crystallographic structure of a sodium salt of TCAS including acetone. Dimeric unit, connected by SO_3^-······Na^+······SO_3^- and O(acetone)······Na^+······O(SO_3^- of TCAS) bonds, is drawn. For clarity, water molecules are omitted. Crystallographic data: $C_{24}H_{12}O_{16}S_8Na_4 \cdot C_3H_6O \cdot 9H_2O$, $M = 1125.01$, colorless, sizes = 0.20 × 0.20 × 0.20 mm, triclinic, $a = 10.6994(9)$ Å, $b = 14.505(2)$ Å, $c = 14.225(1)$ Å, $\alpha = 99.615(3)°$, $\beta = 92.942(1)°$, $\gamma = 93.324(2)°$, $V = 2168.8(4)$ Å^3, space group $\bar{n}$ (No. 2), $Z = 2$, $D_{calc} = 1.723$ g/cm^3, $T = 200$ K, μ(Mo Kα) = 5.43 cm^{-1}, 23328 measured reflections ($2\theta < 59.2°$), 8968 independent reflections ($R_{int} = 0.118$), final $R = 0.056$, $R_w = 0.066$ for 6474 observed reflections ($I_0 > 5.0\sigma(I_0)$), GOF = 2.12. ρ_{max}, ρ_{min} = 0.49, −0.45 e/Å^3. All hydrogen atoms were located from D-map, which were refined in a few cycles of refinement and finally fixed. O(acetone)−Na = 2.314(4) Å.

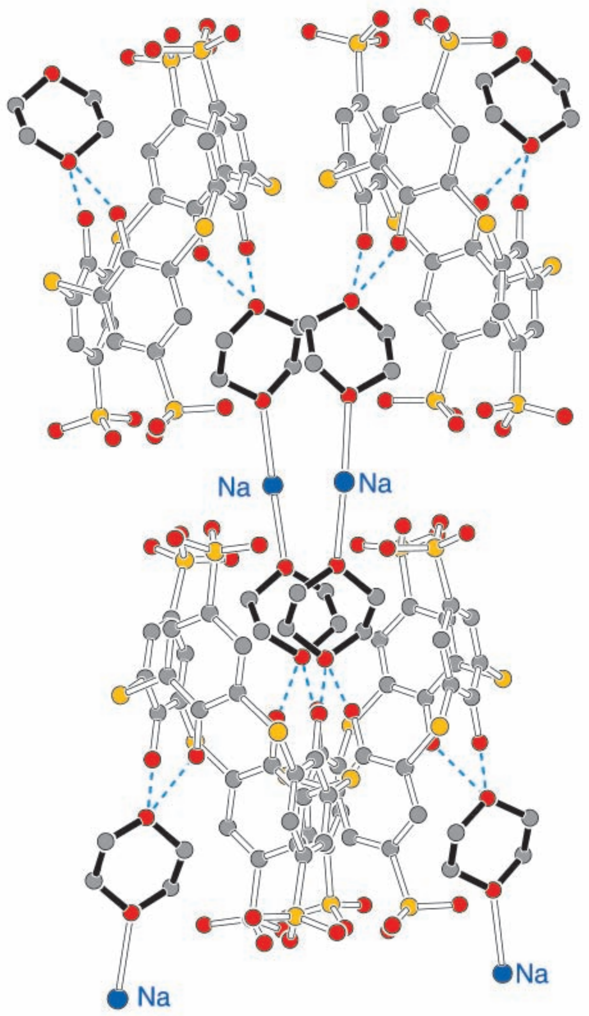


Figure 3. The X-ray crystallographic structure of the sodium salt of TCAS including two 1,4-dioxane molecules. For clarity, water molecules are omitted. A tetrameric unit is drawn, in which each pair of TCAS molecules is connected by OH(TCAS)······O(dioxane) (blue broken lines) and O(dioxane)······Na^+······O(dioxane). Other Na ions held by the SO_3^- group are omitted for clarity. Crystallographic data: $2[C_{24}H_{12}O_{16}S_8Na_4 \cdot 2C_4H_8O_2] \cdot 9H_2O$, $M = 2324.14$, colorless, sizes = 0.07 × 0.20 × 0.20 mm, monoclinic, $a = 15.9724(4)$ Å, $b = 11.6743(6)$ Å, $c = 24.625(2)$ Å, $\beta = 101.5874(4)°$, $V = 4498.2(4)$ Å^3, space group Pn (No. 7), $Z = 2$, $D_{calc} = 1.716$ g/cm^3, $T = 230$ K, μ(Mo Kα) = 5.25 cm^{-1}, 19256 measured reflections ($2\theta < 55.0°$), 9419 independent reflections ($R_{int} = 0.033$), final $R = 0.063$, $R_w = 0.067$ for 7841 observed reflections ($I_0 > 1.0\sigma(I_0)$), GOF = 1.66. ρ_{max}, ρ_{mix} = 0.61, −0.41 e/Å^3. Hydrogens of TCAS were located from D-map and those of dioxane were calculated, which were fixed in the refinement. Two independent TCAS complexes, having approximately 2-fold axis symmetry, are included in the unit cell. O(dioxane)−Na = 2.432−2.544 Å (av. 2.472(8) Å), O(dioxane)−O(TCAS) = 2.651−2.738 Å (av. 2.7034(7) Å).

two factors. First, CH_3OH is too hydrophilic to be included into the hydrophobic cavity of TCAS. Second, the larger cavity of TCAS might retain only loosely the small CH_3OH guest. Furthermore, electrostatic interaction between the -SO_3^- and -OH groups also seems to play a crucial role for complexation of alcohols by the hosts (vide infra). Therefore, the inclusion ability of TCAS gradually diminished for a guest larger than n-C_4H_9OH, suggesting that it becomes unfavorable for a longer methylene chain to be accommodated into the hydrophobic cavity while retaining the electrostatic interaction between the polar groups.

Recently, Ungaro et al. studied the inclusion behavior of CAS and the analogues toward C_2H_5OH in D_2O and proposed an inclusion manner: the CH_3- part penetrates into the cavity of CAS more deeply than the -CH_2-, while the OH group was anchored by the sulfo group via hydrogen bonding -SO_3^-·····HO-.[12] The ^{1}H NMR of the precipitated TCAS−C_2H_5OH complex showed that the chemical shift values of CH_3- and -CH_2- decreased 0.14 and 0.10 ppm, respectively, from the original ones measured in D_2O. This suggests that the CH_3- group was more shielded by the benzene ring than -CH_2- was, indicating an inclusion fashion of TCAS similar to that proposed by Ungaro et al. for CAS. Therefore, it is natural to assume that the anchoring effect may be also responsible for inclusion of ethanol into TCAS.

---

[12] Arena, G.; Casnati, A.; Contino, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett*. **1997**, *38*, 4685−4688.

The $\bar{n}$ values of the alcohols containing three carbon atoms are in the order:

$$n\text{-}CH_3CH_2CH_2OH \approx CH_2{=}CHCH_2OH > (CH_3)_2CHOH$$

suggesting that the TCAS cavity prefers a linear alcohol to a branched one.

Concerning other kinds of guests than alcohol, there are several compounds which gave an $\bar{n}$ value larger than unity. For instance, ethylene glycol and 1,3-propanediol gave $\bar{n} = 1.4$ and 1.2, respectively, suggesting that the inclusion manner of the host in a structure other than the cone conformation may be responsible (vide infra). Aldehydes were trapped better by CAS than TCAS as judged by the -CHO signal on ^{1}H NMR. As for carboxylic acids, the larger one was included more to the limit of practical water-solubility. In this case, hydrophobic resting of the alkyl chain in the cavity of the host, as well as the hydrogen bonding between -COOH and the anchoring -SO_3^-, may contribute to the stabilization of the inclusion complex as in the case of alcohol.

From the discussion above, ketone did not seem to be preferred because of its nonlinear shape with no hydrogen donor. Contrarily, TCAS included smaller ketones better in the order:

$$\text{acetone} \approx \text{methyl ethyl ketone} > \text{diethyl ketone} > \text{acetophenone} \gg \text{methyl butyl ketone}$$

This implies that an inclusion manner other than the one suggested for alcohols may be operating. In fact, the X-ray structure of the sodium salt including acetone revealed that the two methyl groups were accommodated by the cone-shaped cavity of TCAS, while the carbonyl oxygen coordinated to a Na^+, which is also coordinated by -SO_3^- groups (Figure 2).[13] This indicates that coordination of the guest to the counter Na^+ ion for TCAS anion is another important driving force to retain it in the precipitate.

Cyclic ethers were highly included in the precipitates. Notably, two molecules of 1,3- and 1,4-dioxanes were retained by one TCAS, which seems to be quite anomalous if they are included in a cone-shaped cavity of TCAS. Surprisingly, the X-ray structure of the sodium salt including 1,4-dioxane revealed that TCAS adopted 1,2-alternate conformation, sandwiched by two guests associating via hydrogen bonding to the OH groups and coordination to the Na^+ ions (Figure 3).[13] The inclusion complex was thus characterized to be a supramolecular complex rather than a simple host−guest one.

Although ethyl acetate was sufficiently soluble under the experimental conditions, the $\bar{n}$ value of the ester significantly decreased as compared to that of methyl acetate. Nitrile and nitro compounds showed that size and hydrophobic/hydrophilic balance may be responsible for the inclusion behavior. CAS was not salted out in the presence of methylamines as stated before, which may be caused by the dissociation of the OH group of CAS by basic amine to give increased solubility. By contrast, TCAS gave the precipitates containing the amines in the order:

$$(CH_3)_3N > (CH_3)_2NH > CH_3NH_2$$

Interestingly, dipolar aprotic solvents such as DMF and DMSO could be trapped as the precipitates by $\bar{n} = 1$.

In conclusion, it has been shown that TCAS exhibits size-dependent selectivity toward water-miscible guest molecules. The supramolecular complexes of acetone and 1,4-dioxane in the solid state suggest that salting-out may “freeze” the dynamic host−guest complex formed in the aqueous solution via coordination to the Na^+ ions. We believe that the combination of molecular recognition and phase transition such as salting-out could be a new rationale for separation of water-miscible organic molecules from the aqueous solutions.

Acknowledgment. This work was supported by the Proposal-Based New Industry Creative Type Technology R&D Promotion Program from the NEDO of Japan.

Supporting Information Available: Details of crystallographic data (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

OL017053L

---

(13) The crystals with X-ray quality were grown by vapor diffusion of the guest into an aqueous solution of TCAS.