

Supramolecular Formation of Mono- and Bis-Modified Pyrene Cavitands and Their Fluorogenic Metal Sensory System in an Aqueous Solution

Yoshihiko KONDO, Yoshiaki YAMAZAKI, Norio NASHIROZAWA,

Miyuki NARITA and Fumio HAMADA*

*Department of Materials-process Engineering and Applied Chemistry for Environments,
Faculty of Engineering Resource Science, Akita University, Tegata Akita 010-8502, Japan
E-mail : hamada@ipc.akita-u.ac.jp

In order to study the supramolecular formations of guest-responsive cavitand derivatives in aqueous solution, synthesis of water-soluble fluorogenic cavitands, which are modified with mono- and bis-pyrene units (1 and 2, respectively), and their metal sensing abilities have been investigated. Compound 2 showed monomer and excimer emissions in both an organic and aqueous, which was contained a 10 vol.% DMF, solution, whereas compound 1 indicated these two emissions in only aqueous solution. The fluorescence spectral patterns of compounds 1 and 2 were changed depending on DMF concentrations in an aqueous solution. The extent of the excimer emission of 2 was the highest in a 50 vol.% DMF, whereas drastic decrease of this excimer emission was observed in over 60 vol.% DMF. On the other hand, compound 1 showed the highest excimer emission intensity between 10-30 vol.% DMF and middle emission was recognized in 30 vol.% DMF. Finally, in over 50 vol.% DMF, no excimer emission of 1 was observed. The movements of the appended units of these compounds in various DMF concentrations were studied by the fluorescence and UV spectra and MM2-minimized structures. A ratio of excimer and monomer emission intensities of 1 and 2 were varied in 10-40 vol.% and 10-50 vol.% DMF contents in water, respectively. The UV spectra patterns of 1 or 2 were different between in 10-40 vol.%, 50 vol.% and over 60 vol.% or 10-50 vol.%, 60 vol.% and over 70 vol.% DMF aqueous solutions, respectively. The variations of fluorescence and UV spectra suggested that compounds 1 and 2 formed association dimer in 10-40 vol.% and 10-50 vol.% DMF aqueous solutions, respectively, and the canceling of these dimer formations was observed with increasing DMF content or metal concentration. Furthermore, fluorescent spectral changes and MM2-minimized structures suggested that the association dimer of 2, which formed one pair pyrene excimer in 10 vol.% DMF aqueous solution, was transformed into different configuration of association dimer making plural pyrene excimer pairs in 20-50 vol.% DMF aqueous solutions. In order to evaluate the metal sensing abilities of 1 and 2 in a 10 vol.% DMF aqueous solution, the ratio of decrement of an intensity of excimer emission with an addition of metal cation was used as a detecting parameter. Compounds 1 and 2 exhibited the highest sensing abilities for Na^{2+} and Co^{2+} , respectively.

Key Words : Cavitand, Pyrene, Metal sensing, Supramolecular formation

1. INTRODUCTION

Macrocyclic host molecules such as cyclodextrins, calixarenes and cavitands have attracted interest as an enzyme model or supramolecular compounds, because these hosts can accommodate a variety of guests such as organic molecules or metals in their cavity.^{1,2} The modifications of these macrocyclic molecules with spectroscopically active unit result in a new function which is hardly to show for native hosts.³ Our primary focus is in the design of luminescent active host-guest complexes as sensor and molecular probe. During a last decade, we have studied organic molecular sensing system based on fluorescent active cyclodextrins such as

bis-dansyl modified cyclodextrin analogs in an aqueous solution.^{4,5} The mechanism of the host-guest complexation is going on an induced-fit type of complex behavior, in which the appended fluorogenic moieties are moved out from the inside of the cyclodextrin cavity toward the outside with a decrement of the fluorescence intensity, because it is well known that the dansyl moiety is very sensitive to the polarity of an environment. In our previous studies on a metal cation detecting by macrocyclic hosts consisted of benzene rings such as calix[4]arene analogs, we have reported metal sensing by dansyl modified thiacalix[4]arene analogs in an aqueous solution,^{6,7} in which the dansyl unit also

moves out from the calixarene cavity to the outside, which is very polar environment. This calixarene system also exhibits very high sensing for metal, going on an induced-fit type of complex behavior as shown in the case of cyclodextrin derivatives. For further extension of our work, we attempted to synthesize new fluorogenic host molecules composed of benzene units based on cavita nd . The synthesis of cavita nd has been reported by Cram and co-workers⁸, and then many analogs of cavita nd have been prepared to study their host-guest complexation properties in an organic solvent or at a solid state.⁹⁻²⁶ A couple years ago, we have reported selective chloromethylation of cavita nd and the metal binding property of aza-crown-modified cavita nds in an organic solvent based on bis-chloromethyl cavita nd .²⁷ In order to continue our study on cavita nd chemistry, mono- and bis-pyrene-modified cavita nds (1 and 2, respectively) have been synthesized as water-soluble fluorogenic hosts from mono- and bis-chloromethylated cavita nds .²⁸ In this contribution, we would like to describe the association dimer formation and the host-guest binding behavior of the host compounds. Hosts 1 and 2 are existing as an association dimer in a 10 vol.% DMF aqueous solution, in which these hosts showed the metal detecting ability by the fluorescence spectral changes upon a metal addition.

2. Experimental

2.1 Preparations of compounds 1 and 2

A mixture of bis-chloromethylcavita nd 27 (100 mg, 0.145 mmol) and sodium pyrenebutylate (119 mg, 0.348 mmol) in 15 mL of DMF was stirred at room temperature for 20 h. The reaction mixture was concentrated in vacuo, and the product was extracted with chloroform. The organic phase was washed with water, dried over anhydrous Na_2SO_4 , and evaporated. The crude was dissolved on 5 mL of carbon tetrachloride, and the carbon tetrachloride soluble fraction was applied to a column chromatography (Lobar column Lichroprep Si60). Stepwise elution using 300 mL of 9 vol.%, 10 vol.%, 11 vol.%, 13 vol.%, 14 vol.%, 17 vol.%, and 20 vol.% ethylacetate/n-hexane solution, and 300 mL of 25 vol.% ethylacetate/n-hexane solution was applied to obtain bis-pyrenebutylate cavita nd 2 (yeild: 48%). Compound 1 was prepared by the same procedure as compound 2 using mono-chloromethylcavita nd 27 (yeild: 42%).

Compound 1: R_f 0.63 (*n*-hexane-AcOEt 2:1 by volume, TLC: silica gel 60F₂₅₄). ¹H-NMR spectra (CDCl_3 , 300 MHz): δ = 1.73 (12H, d, J =7.5 Hz, $-\text{CHCH}_3$ in cavita nd), 2.17-2.26 (4H, br, $-\text{COCH}_2\text{CH}_2\text{CH}_2-\text{Ar}$ in pyrenebutylate), 3.40 (2H, t, J =7.5 Hz, $-\text{COCH}_2\text{CH}_2\text{CH}_2-\text{Ar}$ in pyrenebutylate), 4.20 (2H, d, J =7.2 Hz, inner of CH_2 in cavita nd), 4.33 (2H, d, J =7.2 Hz, inner of CH_2 in cavita nd), 4.93 (4H, quintet, J =7.4 Hz, $-\text{CHCH}_3$ in cavita nd), 5.07 (2H, s, $-\text{OCH}_2-\text{Ar}$ at upper rim in cavita nd), 5.66 (2H, d, J =7.5 Hz, outer of CH_2 in cavita nd), 5.70 (2H, d, J =7.2 Hz, outer of CH_2 in cavita nd), 6.21 (2H, s, Ar-H at upper rim in cavita nd), 6.47 (1H, s, Ar-H at upper rim in cavita nd), 7.18 (3H, s, Ar-H at lower rim in cavita nd), 7.79-8.28 (9H, m, Ar-H in pyrenebutylate). Calcd. for $\text{C}_{78}\text{H}_{64}\text{O}_{12} \cdot 2\text{H}_2\text{O}$: C, 73.69; H 5.64 %. Found: C, 73.82; H 5.54 %. MS(FAB)[m/z]: 892 ($[\text{M}]^+$).

Compound 2: R_f 0.59 (*n*-hexane-AcOEt 2:1 by volume, TLC: silica gel 60F₂₅₄). ¹H-NMR spectra (CDCl_3 , 300 MHz): δ = 1.73 (12H, d, J =7.5 Hz, $-\text{CHCH}_3$ in cavita nd), 2.16 (8H, s, $-\text{COCH}_2\text{CH}_2\text{CH}_2-\text{Ar}$ in pyrenebutylate), 3.33 (4H, t, J =6.6 Hz, $-\text{COCH}_2\text{CH}_2\text{CH}_2-\text{Ar}$ in pyrenebutylate), 4.09 (4H, d, J =6.9 Hz, inner of CH_2 in cavita nd), 4.90 (4H, quintet, J =7.2 Hz, $-\text{CHCH}_3$ in

cavita nd), 5.06 (4H, s, $-\text{OCH}_2-\text{Ar}$ at upper rim in cavita nd), 5.61 (4H, d, J =7.2 Hz, outer of CH_2 in cavita nd), 5.94 (2H, s, Ar-H at upper rim in cavita nd), 7.11 (2H, s, Ar-H at lower rim in cavita nd), 7.19 (2H, s, Ar-H at lower rim in cavita nd), 7.69-8.21 (18H, m, Ar-H in pyrenebutylate). Calcd. for $\text{C}_{78}\text{H}_{64}\text{O}_{12} \cdot \text{H}_2\text{O}$: C, 77.34; H, 5.49 %. Found: C, 77.20; H, 5.72%. MS(FAB)[m/z]: 1192 ($[\text{M}]^+$).

2.2 Measurements

Fluorescence and ultraviolet spectra were measured at 25 °C with a Perkin-Elmer LS 40B Fluorescence spectrometer and a Perkin-Elmer Lambda 40 UV-VIS spectrophotometer, respectively. For the fluorescence measurements, the excitation wavelength of the fluorescence spectra was 355 nm and excitation and emission slits were 5 nm. A DMF aqueous solution (10 vol.%) was used as solvent for hosts for the spectroscopic measurements because the solubility of the hosts (1 and 2) in pure water was poor. Ten microliters of metal cations in pure water were injected into a 10 vol. % DMF aqueous solution of the hosts (2.5 mL) to make a sample solution with a host concentration of 5.0×10^{-7} M and metal nitrate concentration of 1.0 mM.

2.3 Energy-minimized structures

Energy-minimized structures of 1 and 2 were calculated by molecular mechanics using MM2 in CS Chem 3D. The parameters of MM2 are improved ones obtained from studies by Allinger²⁹ based on the TINKER system researched by Ponder.³⁰

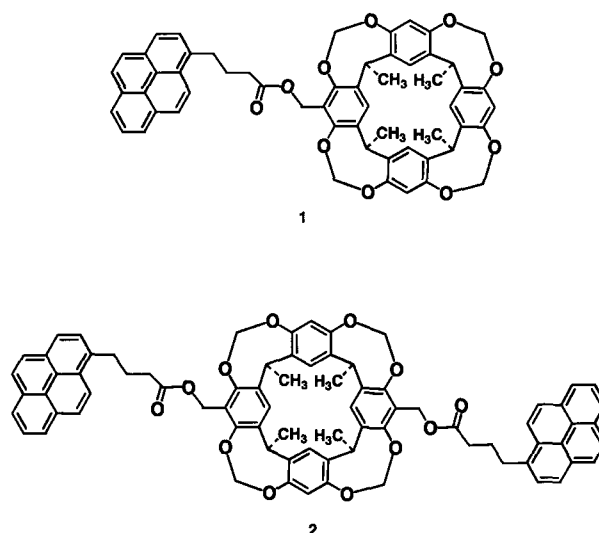
2.4 Determination of binding constants

The binding constants of 1 and 2 for several guests were obtained from the guest-induced fluorescence variations around 465 nm by employing a Benesi-Hildbrand-type equation, as reported previously.⁷

3. Results and discussion

3.1 Fluorescence and UV spectra of 1 and 2 in various aqueous-DMF solutions.

Figure 1 shows the fluorescence spectra of 1 and 2 in a CHCl_3 . The fluorescence spectra of 2 exhibit monomer and excimer emission, whereas 1 shows only monomer emission. This means



Scheme 1 Structures of 1 and 2.

that the pyrene excimer of 2 in organic solvent such as CHCl_3 derives from intramolecular interaction not intermolecular interaction.

The fluorescence spectra of 1 and 2 in various DMF aqueous solutions show different patterns as depicted in Figures 2 and 3a, respectively. Ranging from 10-30 vol.% DMF, the spectra patterns of 1 are almost same. The fluorescence intensity in excimer emission of 1 in 40 vol.% DMF decreases, moreover, in over 50 vol.% DMF, its excimer emissions do not appear and its monomer emissions are given larger intensities than those of 1 in 10-40 vol.% DMF. In this case, the pyrene excimer in a 10-40 vol.% DMF aqueous solutions should be produced by intermolecular interaction, namely, compound 1 forms the association dimer in 10-40 vol.% DMF aqueous solution. Although, compound 1 may exist as monomer in over 50 vol.% DMF aqueous solution. On the other hand, the spectra patterns of 2 are different from those of 1.

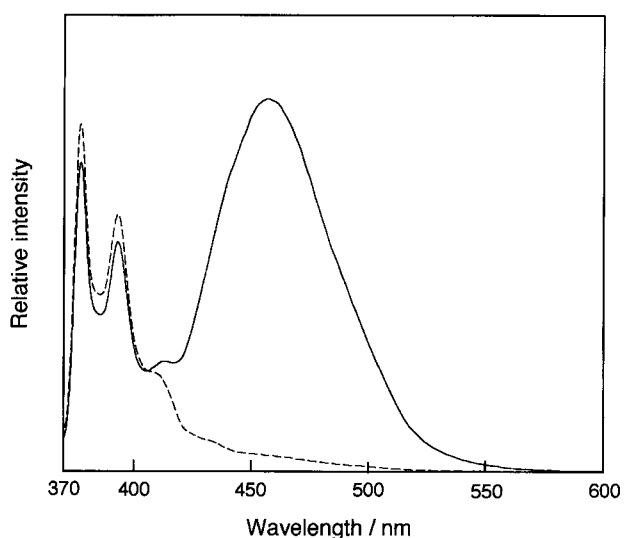


Figure 1 Fluorescence spectra of 1 (---) and 2 (—) (1.0×10^{-6} M, 25°C) in CHCl_3 solution.

In the spectra patterns of 2, the increment of DMF content leads enhancement of its excimer emission in 10-50 vol.% DMF. In contrast, the large extent in a decrement of excimer emission of 2 in 60-90 vol.% DMF was observed, however, its excimer emission does not disappear. These facts suggest that the pyrene excimer of 2 is produced in two different ways depending on the ratio of DMF contents, probably, one is produced by the intermolecular interaction and another one is produced by intramolecular interaction. In order to decide whether the pyrene excimer of 2 drives from intermolecular or intramolecular interactions, a ratio of monomer versus excimer emissions of 2 in various of DMF contents in an aqueous solution is figured out, as shown in Figure 3b. The values I_{ex}/I_{m1} and I_{ex}/I_{m2} were used as parameters, where I_{m1} and I_{m2} , and I_{ex}

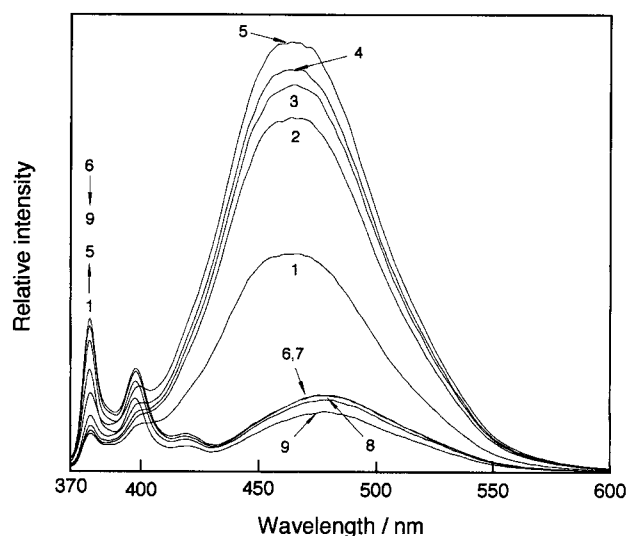


Figure 3a Fluorescence spectra of 1 (5.0×10^{-7} M, 25°C) in various ratio of DMF aqueous solution (1: 10, 2: 20, 3: 30, 4: 40, 5: 50, 6: 60, 7: 70, 8: 80, 9: 90 vol.%).

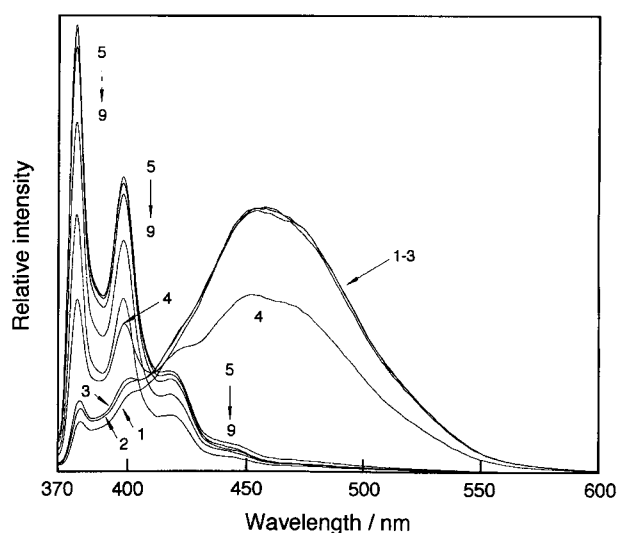


Figure 2 Fluorescence spectra of 1 (5.0×10^{-7} M, 25°C) in various ratio of DMF aqueous solution (1: 10, 2: 20, 3: 30, 4: 40, 5: 50, 6: 60, 7: 70, 8: 80, 9: 90 vol.%).

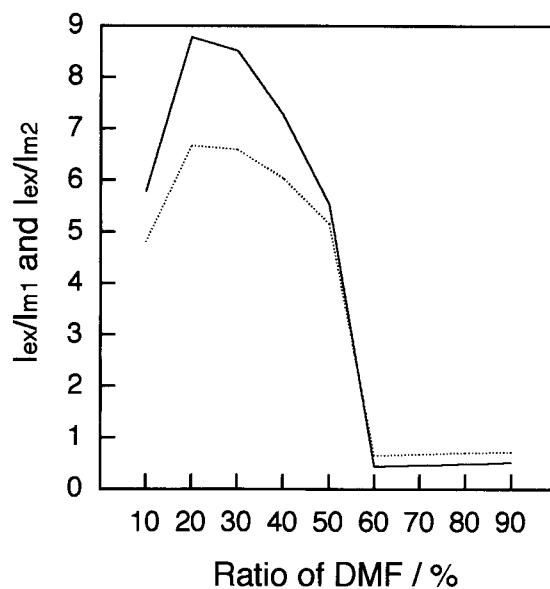


Figure 3b Parameters of I_{ex} versus I_m of 2 in various ratio of DMF aqueous solution (I_{ex}/I_{m1} : —, I_{ex}/I_{m2} : ·····).

are intensities of monomer emissions at 380 and 398 nm and excimer emission at 465 nm, respectively. The values I_{ex}/I_{m1} and I_{ex}/I_{m2} of 2 were changed in 10-50 vol.% DMF, and these values were regular in over 60 vol.% DMF. These results mean that the pyrene excimer in 10-50 vol.% DMF is caused by intermolecular interaction. In over 60 vol.% DMF aqueous solution, it is indicated that the emission of pyrene excimer is presumably due to intermolecular interaction. Therefore, compound 2 is seemed to form the association dimer in 10-50 vol.% DMF aqueous solution.

Figures 4 and 5 show the UV spectra of 1 and 2 in various aqueous-DMF solutions. In the spectra of 1, the patterns in 10-40 vol.% DMF are similar, although, those in over 50 vol.% DMF are different. In the spectra of 2, the patterns in 10-50 vol.%, 60 vol.% and over 70 vol.% DMF are dissimilar. It is suggested that the

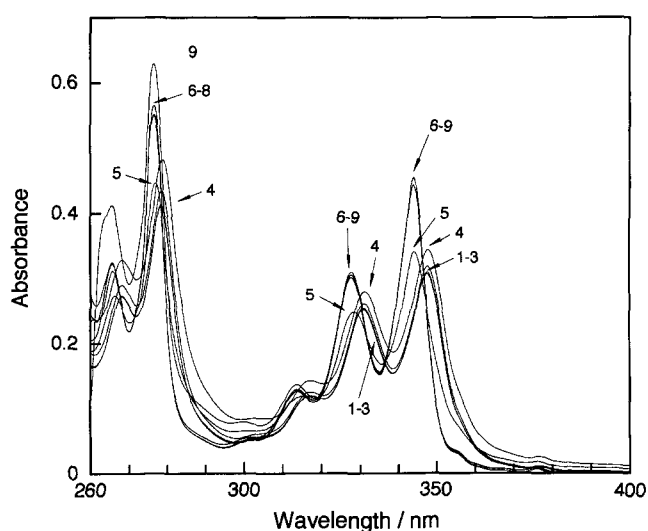


Figure 4 Absorption spectra of 1 (1.0×10^{-5} M, 25°C) in various ratio of DMF aqueous solution (1: 10, 2: 20, 3: 30, 4: 40, 5: 50, 6: 60, 7: 70, 8: 80, 9: 90 vol.%).

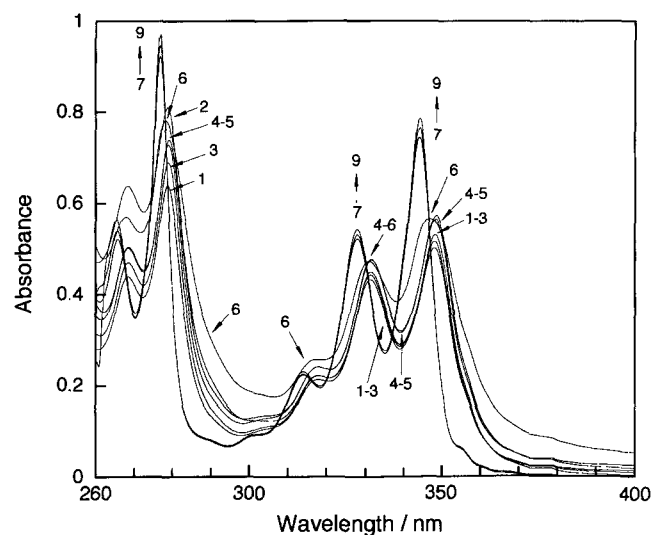
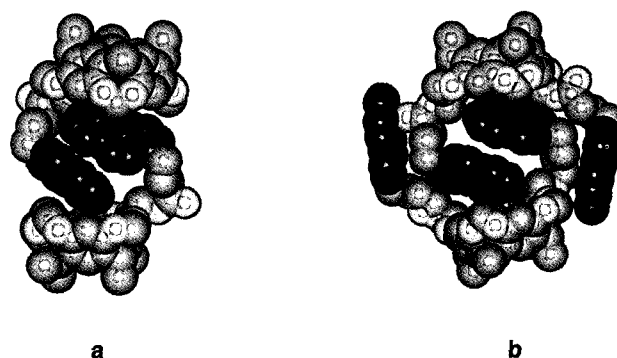


Figure 5 Absorption spectra of 2 (1.0×10^{-5} M, 25°C) in various ratio of DMF aqueous solution (1: 10, 2: 20, 3: 30, 4: 40, 5: 50, 6: 60, 7: 70, 8: 80, 9: 90 vol.%).

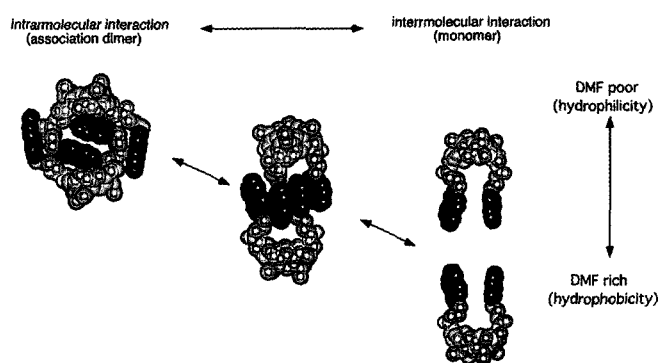
formation of the appended moieties of 1 or 2 is different in each concentration of DMF. The variations of these UV spectra are identical to the fluorescent spectral changes as mentioned above. Therefore, the UV spectral changes support the transformation of the pyrene excimer of 1 and 2, in which the association dimer of 1 and 2 is occurring between 10-40 vol.% and 10-50 % DMF, respectively.

In order to examine the formations of association dimer of 1 and 2, MM2-minimized structures of these hosts were calculated, as shown in Scheme 2. In this system, it is seemed that the pyrene moiety of 1 and 2 in 10 vol.% DMF aqueous solution is included into another cavitant cavity due to the hydrophobic interaction between the pyrene moiety and cavitant cavity similar to the case of cyclodextrin derivative.³¹ With the increasing of DMF content in an aqueous solution as a solvent, the pyrene excimer of 1 completely is cancelled by the weakening of the hydrophobic interaction. On the other hand, the association dimer formation of 2 is altered in various ways with the increment of DMF content in an aqueous solution, in which the pyrene moieties form strong excimer formation in 10 vol.% DMF and, in 20-50 vol.% DMF. Scheme 3 illustrates the movement of the pyrene units with increase of DMF content in water. Furthermore, in over 60 vol.% DMF, the formation of the pyrene excimer of 2 transforms intramolecule with canceling the association dimer.

Figures 6 and 7 show the fluorescent spectra changes of 1 and 2 in the presence and absence of Na^+ in a 10 vol.% DMF aqueous solution, respectively. The fluorescence spectra of 1 and 2 are



Scheme 2 Speculated structures of 1 (a) and 2 (b) obtained from MM2-minimized space-filling in a 10 vol.% DMF aqueous solution.



Scheme 3 Estimated transformation from association dimer to monomer of 2 in various DMF content of aqueous solutions.

composed of almost pure excimer emission with a peak around 465 nm, and the excimer fluorescence intensity decreases with increasing metal cation concentration. The excimer fluorescent intensity decrement suggests that the pyrene excimer formation is canceled. When a metal cation was added to the solutions of 1 and 2, the metal cation was probably introduced into the cavitand cavity, because we have already reported that native cavitand can make host-guest complexation with metal cation.²⁷ Accordingly, the metal binding mechanisms by these compounds seems to be illustrated as in Scheme 4. To examine a quenching effect of metal cations for fluorescence spectra of 1 and 2, the sensing parameter values were obtained in the presence of Co^{2+} . The ΔI was used as a sensing parameter value. Here ΔI is $I^0 - I$, where I^0 is the fluores-

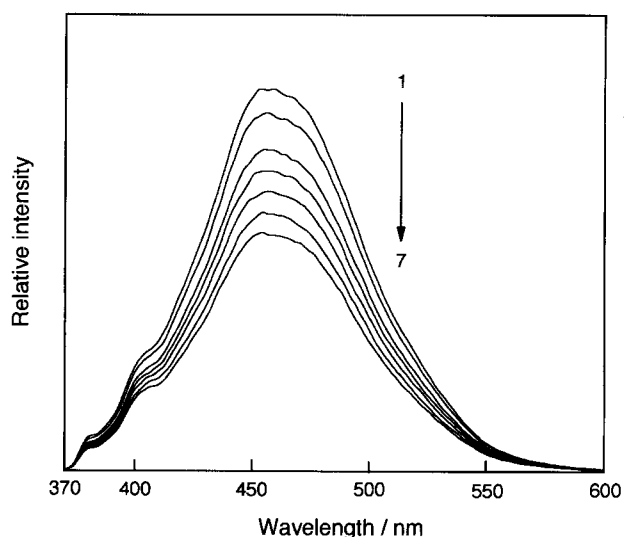


Figure 6 Fluorescence spectra of 1 (5.0×10^{-7} M, 25°C) in a 10 vol.% DMF aqueous solution with various concentrations of Na^+ (1: 0, 2: 1.0×10^{-4} , 3: 3.0×10^{-4} , 4: 6.0×10^{-4} , 5: 1.0×10^{-3} , 6: 1.5×10^{-3} , 7: 2.1×10^{-3} M).

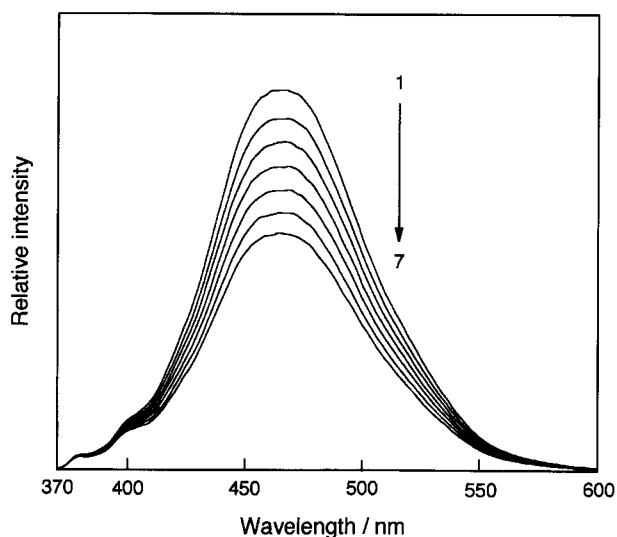
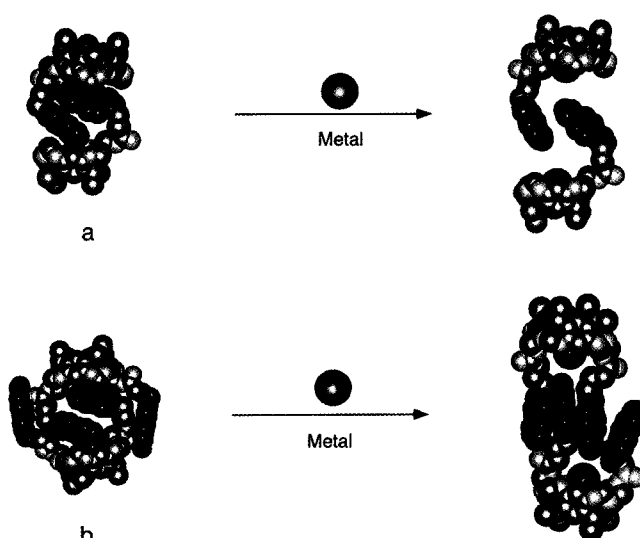


Figure 7 Fluorescence spectra of 2 (5.0×10^{-7} M, 25°C) in a 10 vol.% DMF aqueous solution with various concentrations of Na^+ (1: 0, 2: 1.0×10^{-4} , 3: 3.0×10^{-4} , 4: 6.0×10^{-4} , 5: 1.0×10^{-3} , 6: 1.5×10^{-3} , 7: 2.1×10^{-3} M).

cence intensity at 465 nm for the host alone, and I is the fluorescence intensity at 465 nm for a complex with Co^{2+} . Figure 8 shows the parameter values when the concentrations of Co^{2+} were ranging from 10^{-4} M to 4.42×10^{-3} M. The parameter values are going up to 0.340, of which the value is constant when the concentration is up to 2.77×10^{-3} M, and then the values are increased again. These results suggest that no quenching by metal cations for the fluorescent intensity is existing.

3.2 Metal sensing abilities of 1 and 2

The extent of variation of the fluorescence intensity of 1 and 2 depends on the nature of a metal cation, even at low concentration; therefore, these compounds can be used to be sensing molecule. To display the sensing abilities of 1 and 2, the ΔI was used as a sensitivity parameter. Figure 9 shows the sensing parameters of 1



Scheme 4 Speculated mechanisms on the host-guest complexation of 1 (a) and 2 (b) in a 10 vol.% DMF aqueous solution.

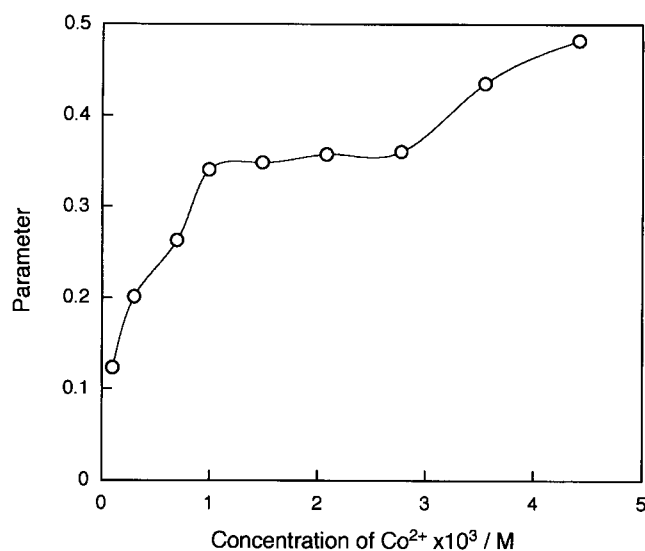


Figure 8 Sensing parameters of 2 (5.0×10^{-7} M) in a 10 vol.% DMF aqueous solution with various concentration of Co^{2+} .

Table 1 Binding constants ($K/\text{mol}^{-1} \text{dm}^3$) of 1 and 2 ($5.0 \times 10^{-7} \text{M}$, 25°C) in a 10% DMF aqueous solution.^{a)}

Metal	1	2
Na ⁺	1566 ± 90 ^{b)}	935 ± 56
Li ⁺	351 ± 16	1986 ± 83
K ⁺	1293 ± 130	754 ± 54
Cr ²⁺	541 ± 49	1176 ± 76
Co ²⁺	1266 ± 102	1443 ± 56
Ni ²⁺	1384 ± 43	2560 ± 99
Zn ²⁺	862 ± 46	2945 ± 107
Cd ²⁺	5179 ± 300	2999 ± 122
Al ³⁺	2286 ± 162	611 ± 34

a) The K values were obtained from guest-induced fluorescence variations.

b) The statistical errors were values of standard deviation assessed by guest-induced fluorescence variations.

and 2 for a couple of metal cations lined as their metal size order. Compound 1 detects Na⁺ with the highest parameter and the sequence of the sensing parameter is Na⁺ > K⁺ > Ni²⁺ > Cd²⁺ > Cr²⁺ > Al³⁺ > Co²⁺ = Zn²⁺ > Li⁺. It is suggested that sensing ability of 1 is not depended on metal cation size. In contrast, compounds 2 detects Co²⁺ with the highest parameter and the sequence of the sensing parameter of 2 is Co²⁺ > Ni²⁺ > Na⁺ > Zn²⁺ > Li⁺ > Cr²⁺ = Cd²⁺ > Al³⁺ > K⁺. Decreasing the order of metal cation size of Cd²⁺ > Li⁺ > Zn²⁺ > Ni²⁺ > Co²⁺, sensing parameters of 2 increase, however, smaller metal sized cations such as Cr²⁺ and Al³⁺ are detected with lower sensing parameter than those metal cations such as Cd²⁺ to Co²⁺. It is recognized that sensing abilities of 2 are depended on metal cation size such as Cd²⁺ to Co²⁺ lined up, as

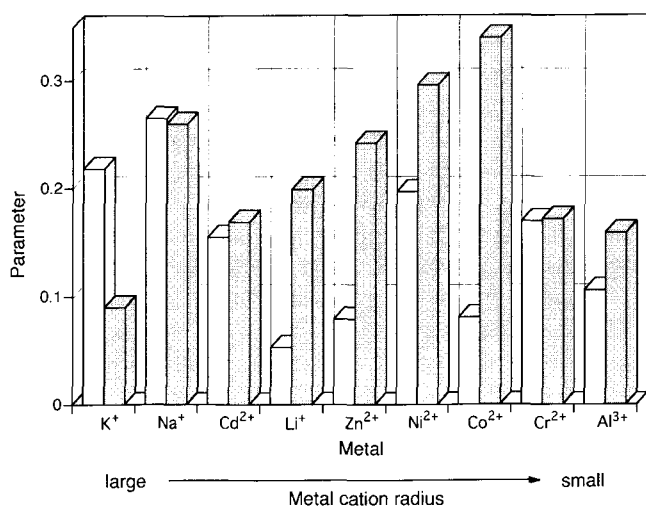


Figure 9 Sensitivity factors of 1 (□) and 2 (■) ($5.0 \times 10^{-7} \text{M}$, 25°C) in a 10 vol.% DMF aqueous solution for all metal cations examined ($1.0 \times 10^{-3} \text{M}$).

shown in Figure 9. We obtained binding constant by using Equation (1) as reported previously.^{7,32,33}

$$\frac{1}{I_{ex} - I_{ex}^0} = \frac{1}{a[\text{Host}]} + \frac{1}{a[\text{Host}]K} \times \frac{1}{[\text{Metal}]} \quad (1)$$

Here, I is the fluorescence intensity at 465 nm (I_{ex} for complex, I_{ex}^0 for the host alone), $[\text{Host}]$ is the total host concentration, $[\text{G}]$ is the total guest concentration, a is a constant. The binding constants were obtained to examine the correlation between the fluorescence variations and the binding abilities of the hosts. The results are shown in Table 1. The order of the binding constants of the host for metal cations is not parallel with the order of the sensitivity factor. This means that the sensitivity value gives primary value to show how much familiar for the guest molecule examined at some concentration.

4. Conclusion

This study performed elucidation of metal sensory system based on fluorogenic mono- and bis-pyrene appended cavitanths in aqueous solution, in which water-soluble cavitanths could be synthesized for the first time. These compounds show association dimer in water rich solvent, whereas the association dimer formation was canceled or transformed in polar solvent. In an aqueous solution containing 10 vol.% DMF, these cavitanth derivatives recognized metal cations such as Co²⁺, Ni²⁺, Na⁺, and Zn²⁺ with high sensitivity. The decrement of pyrene excimer was used as a detecting parameter. This work has clarified that these pyrene-appended cavitanths compose supramolecule formation such as association dimer. We are now wrestling with self-folding system using compounds 1 and 2 as a molecular device for a nanoscale in the next generation of cavitanth chemistry.

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