

Fluorescent Chemo-Sensor for Metal Cations Based on Thiacalix[4]arenes Modified with Dansyl Moieties at the Lower Rim

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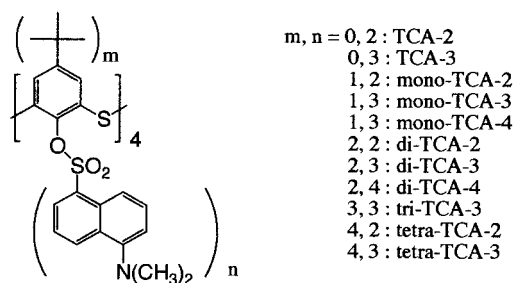
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Abstract—The selective de-*tert*-butylation of *p*-*tert*-butyl thiacalix[4]arene (*p*-*tert*-butyl TCA) with AlCl₃ at 80°C has been investigated. Mono-, di-, and tri-*p*-*tert*-butyl thiacalix[4]arene (mono-, di- and tri-TCA, respectively) were obtained in yields of 6.5, 20 and 21%, respectively, when *p*-*tert*-butyl TCA was treated with 7.1 equiv. of AlCl₃ for 30 min. De-*tert*-butyl TCA (TCA) was exclusively obtained when 10.5 equiv. of AlCl₃ was used. These derivatives are converted to fluorescent active derivatives by modification with dansyl moiety at the lower rim, which are used as metal sensors in aqueous solution. The extent of the fluorescent variations with the metal cations was used to display the sensing factors, $\Delta I/I_0$. These hosts show much higher sensitivity for transition metal cations such as Co²⁺, Ni²⁺, and Cd²⁺ than those of alkali metal cations such as Li⁺, Na⁺, and K⁺. The effect of *p*-*tert*-butyl groups on metal sensing ability of these hosts was studied. It was found that *p*-*tert*-butyl groups decrease the sensing ability of these hosts. It is the first example to show that water soluble TCA derivatives can detect metal cations directly in aqueous solution by variation of fluorescence intensity upon addition of a metal cation. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Fluorescent metal sensing by calixarene derivatives has been investigated by a couple of groups.¹ The molecular design was carried out by introduction of ligand and fluorescent active moiety on the upper or lower rim of calixarenes, because calixarene itself can hardly make a host–guest complexation with metal cations. On the other hand, thiacalix[4]arene (TCA) is composed of benzene rings, linked via sulfide bridges, which itself can make host–guest complexation with metal cations because the sulfide functional group has affinity for metal cations. Recently, a practical synthetic method of thiacalixarene has been reported by Kumagai et al.² Thus, a couple of TCA derivatives, such as thiacalix[4]arene-tetrasulfonate, tetra-*O*-alkylated at the lower rim of thiacalix[4]arene, sulfone-thiacalix[4]arene, and a chirally modified *p*-*tert*-butyl thiacalix[4]arene have been prepared to expand the func-

tions of TCA.³ In a previous paper, we first reported a metal sensor system based on water soluble di- and tri-dansyl modified *p*-*tert*-butyl TCA, (tetra-TCA-2 and tetra-TCA-3, respectively) (Scheme 1).⁴ These compounds show the highest sensitivity for Cd²⁺. As a further extension of the work, we synthesized nine new analogues of the TCA with dansyl moieties. We also investigate the effect of *tert*-butyl groups on the metal sensing ability of dansyl modified thiacalix[4]arene, because we succeeded in effecting selective removal of *p*-*tert*-butyl groups of *p*-*tert*-butyl TCA. Among



Scheme 1. The structure of dansyl modified TCA analogues.

Keywords: *p*-*tert*-butyl thiacalix[4]arenes; tri-TCA; dansyl moiety.

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Table 1. Crystal data for di-TCA

Compound	C ₃₂ H ₃₂ O ₄ S ₄
Molecular weight	608.84
Space group	P ₁ (No.2)
Cell constants	
<i>a</i> (Å)	10.394(1)
<i>b</i> (Å)	12.385(2)
<i>c</i> (Å)	12.961(2)
α (deg)	94.778(4)
β (deg)	104.478(2)
γ (deg)	112.129(1)
Cell volume (Å ³)	1466.9(3)
Dcalc (g/cm ³)	1.378
<i>Z</i>	2
<i>T</i> (K)	200
Radiation	Mo-K α
<i>U</i> (cm ⁻¹)	3.61
Sizes (mm)	0.4×0.2×0.15
Measured reflections	10418
Independent reflections	6090
GOF	2.11
<i>R</i>	0.044
<i>R</i> _w	0.052

these hosts, mono-*p*-*tert*-butyl TCA modified with tri-dansyl moieties (mono-TCA-3) show the highest sensitivity for most metal cations examined, whereas tetra-*p*-*tert*-butyl TCA modified with tri-dansyl moieties (tetra-TCA-3) can hardly detect metal cations.

Table 2. Positional parameters for di-TCA

Atom	<i>x</i>	<i>y</i>	<i>z</i>
S(1)	0.76831(8)	-0.15247(6)	1.19331(5)
S(2)	0.85427(8)	0.26168(6)	1.03801(5)
S(3)	0.43668(7)	-0.01555(6)	0.65455(5)
S(4)	0.41873(7)	-0.42904(6)	0.78564(5)
O(1)	0.5362(2)	-0.2209(2)	0.9803(2)
O(2)	0.6911(2)	0.0377(2)	1.1019(2)
O(3)	0.5871(2)	0.0426(2)	0.8888(2)
O(4)	0.3548(2)	-0.2186(2)	0.7759(2)
C(1)	0.6027(3)	-0.2959(2)	0.9889(2)
C(2)	0.7157(3)	-0.2743(2)	1.0845(2)
C(3)	0.7838(3)	-0.3516(2)	1.0991(2)
C(4)	0.7443(3)	-0.4493(3)	1.0186(3)
C(5)	0.6372(3)	-0.4694(2)	0.9222(2)
C(6)	0.5655(3)	-0.3933(2)	0.9066(2)
C(7)	0.8303(3)	0.0517(2)	1.1098(2)
C(8)	0.9186(3)	0.1511(2)	1.0778(2)
C(9)	1.0622(3)	0.1688(2)	1.0878(2)
C(10)	1.1155(3)	0.0882(3)	1.1265(2)
C(11)	1.0264(3)	-0.0107(2)	1.1566(2)
C(12)	0.8829(3)	-0.0307(2)	1.1480(2)
C(13)	0.6590(3)	0.1262(2)	0.8385(2)
C(14)	0.7862(3)	0.2275(2)	0.8928(2)
C(15)	0.8510(3)	0.3110(2)	0.8346(2)
C(16)	0.7947(3)	0.2959(2)	0.7226(2)
C(17)	0.6696(3)	0.1920(2)	0.6693(2)
C(18)	0.6017(3)	0.1096(2)	0.7259(2)
C(19)	0.4473(3)	-0.2189(2)	0.7182(2)
C(20)	0.5004(3)	-0.1302(2)	0.6607(2)
C(21)	0.6004(3)	-0.1332(2)	0.6076(2)
C(22)	0.6490(3)	-0.2238(2)	0.6071(2)
C(23)	0.5902(3)	-0.3138(2)	0.6621(2)
C(24)	0.4927(3)	-0.3121(2)	0.7176(2)
C(25)	0.8648(3)	0.3830(2)	0.6545(2)
C(26)	0.9857(3)	0.4991(3)	0.7252(3)
C(27)	0.7486(3)	0.4129(3)	0.5794(3)
C(28)	0.9290(4)	0.3239(3)	0.5851(3)
C(29)	0.7555(3)	-0.2289(3)	0.5463(2)
C(30)	0.8249(4)	-0.1130(3)	0.5084(3)
C(31)	0.8803(3)	-0.2504(3)	0.6202(2)
C(32)	0.6721(4)	-0.3313(3)	0.4465(3)

Results and Discussion

Selective removal of *p*-*tert*-butyl groups of TCA

For selective functionalization of the *p*-position of the calix[4]arene, selective removal of the *p*-*tert*-butyl groups of phenolic nuclei has been reported by David N. Reinhoudt and co-workers.⁵ In this study, the two *tert*-butyl groups were selectively removed from the phenolic nuclei, while the phenol ether rings did not react. Only a few examples of the selective Lewis acid catalyzed de-*tert*-butylation procedures have been reported in the literature.⁶ We tried to selectively remove *p*-*tert*-butyl groups from *p*-*tert*-butyl TCA. When we used 10.5 equiv. of AlCl₃ at 80°C, de-*tert*-butylation occurred perfectly. Using between 7.1 and 7.4 equiv. of AlCl₃, mono-, di- and tri-analogues were obtained in yields of 6.5, 20 and 21%, respectively. The starting material was not recognized in this condition. When less than 6 equiv. of AlCl₃ was used at 80°C, only starting material was recovered. The reaction hardly proceeded at room temperature — the reaction temperature needs to be over 60°C. When we used 6.3 equiv. of AlCl₃, tri-*tert*-butyl analogue was recognized on TLC with almost all starting material being recovered.

Modification of TCA derivatives with dansyl chloride

When we used 40 equiv. of dansyl chloride or less than 1 equiv. of dansyl chloride for the synthesis of dansyl

Table 3. Intramolecular bond angles for di-TCA involving the non-hydrogen atoms (angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses)

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(6)	S(1)	C(24)	101.8(1)	C(14)	C(15)	C(16)	122.1(2)
C(2)	S(2)	C(12)	102.1(1)	C(15)	C(16)	C(17)	117.2(2)
C(8)	S(3)	C(14)	106.5(1)	C(15)	C(16)	C(25)	124.0(2)
C(18)	S(4)	C(20)	100.0(1)	C(17)	C(16)	C(25)	118.8(2)
C(1)	C(1)	C(2)	118.1(2)	C(16)	C(17)	C(18)	121.6(2)
C(1)	C(1)	C(6)	123.2(2)	S(4)	C(18)	C(13)	120.0(2)
C(2)	C(1)	C(6)	118.7(2)	S(4)	C(18)	C(17)	119.4(2)
S(2)	C(2)	C(1)	121.2(2)	C(13)	C(18)	C(17)	120.6(2)
S(2)	C(2)	C(3)	118.4(2)	O(4)	C(19)	C(20)	123.1(2)
C(1)	C(2)	C(3)	120.3(3)	O(4)	C(19)	C(24)	118.2(2)
C(2)	C(3)	C(4)	120.8(3)	C(20)	C(19)	C(24)	118.7(2)
C(3)	C(4)	C(5)	119.7(3)	S(4)	C(20)	C(19)	119.3(2)
C(4)	C(5)	C(6)	120.4(3)	S(4)	C(20)	C(21)	120.7(2)
S(1)	C(6)	C(1)	121.0(2)	C(19)	C(20)	C(21)	120.0(2)
S(1)	C(6)	C(5)	118.8(2)	C(20)	C(21)	C(22)	122.4(2)
C(1)	C(6)	C(5)	120.1(2)	C(21)	C(22)	C(23)	116.4(2)
O(2)	C(7)	C(8)	117.7(2)	C(21)	C(22)	C(29)	122.4(2)
O(2)	C(7)	C(12)	121.4(2)	C(23)	C(22)	C(29)	121.1(2)
C(8)	C(7)	C(12)	120.9(2)	C(22)	C(23)	C(24)	122.5(2)
S(3)	C(8)	C(7)	120.5(2)	S(1)	C(24)	C(19)	118.8(2)
S(3)	C(8)	C(9)	120.5(2)	S(1)	C(24)	C(23)	121.3(2)
C(7)	C(8)	C(9)	118.7(2)	C(19)	C(24)	C(23)	119.9(2)
C(8)	C(9)	C(10)	120.7(2)	C(16)	C(25)	C(26)	112.2(2)
C(9)	C(10)	C(11)	120.0(2)	C(16)	C(25)	C(27)	109.7(2)
C(10)	C(11)	C(12)	120.7(3)	C(16)	C(25)	C(28)	108.8(2)
S(2)	C(12)	C(7)	119.0(2)	C(26)	C(25)	C(27)	108.1(2)
S(2)	C(12)	C(11)	121.9(2)	C(26)	C(25)	C(28)	109.0(3)
C(7)	C(12)	C(11)	118.9(2)	C(27)	C(25)	C(28)	109.1(3)
O(3)	C(13)	C(14)	123.7(2)	C(22)	C(29)	C(30)	112.3(2)
O(3)	C(13)	C(18)	117.6(2)	C(22)	C(29)	C(31)	110.5(2)
C(14)	C(13)	C(18)	118.7(2)	C(22)	C(29)	C(32)	108.5(2)
S(3)	C(14)	C(13)	120.8(2)	C(30)	C(29)	C(31)	107.0(2)
S(3)	C(14)	C(15)	118.9(2)	C(30)	C(29)	C(32)	109.0(3)
C(13)	C(14)	C(15)	119.8(2)	C(31)	C(29)	C(32)	109.6(2)

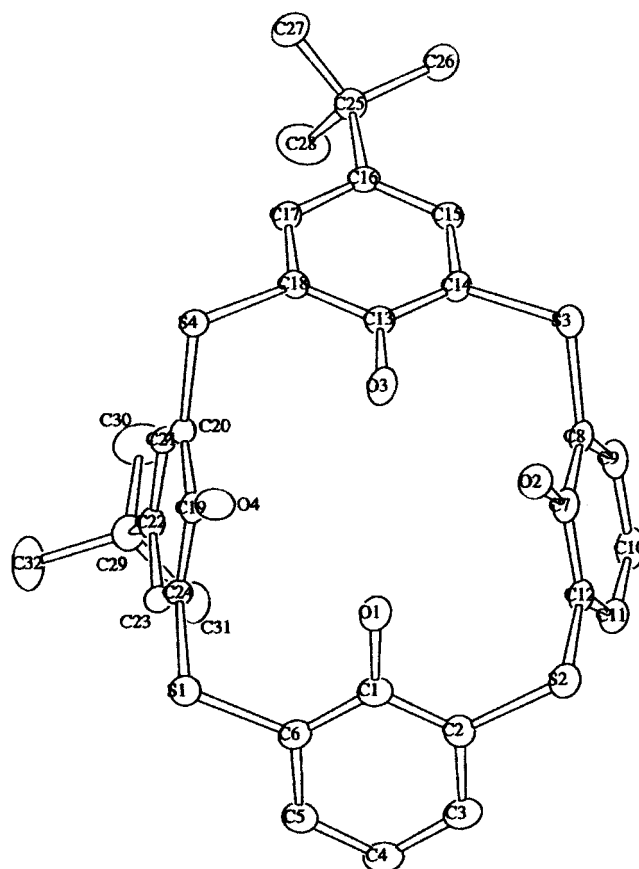


Figure 1. The X-ray structure of di-TCA.

modified TCA derivative, mono-dansyl modified TCA derivative was not obtained. Treatment of *p*-*tert*-butyl TCA, TCA, and mono-, di-*p*-*tert*-butyl TCA with dansyl chloride they gave di-, tri-, and di-, tri-, and tetra-substituted dansyl modified analogues, respectively. On the other hand, tri-*p*-*tert*-butyl analogue yielded only the tri-substituted derivative. These observations suggested that the number of *tert*-butyl group affects the reactivity of modification TCA analogues at the lower rim with dansyl moiety.

The X-ray structure of di-TCA

The positions of *p*-*tert*-butyl groups on the nuclei of di-TCA seem to be 1,2- or a distal position. Colorless, plate-shaped crystals of di-TCA were mounted in thin-walled glass capillaries. A summary of data collection parameters is given in Table 1. Hydrogen atoms were not located. The final values of the positional parameters are given in Table 2. Bond lengths, bond angles, and dihedral angles (Table 3)

were within the expected ranges. The structure of di-TCA shown in Fig. 1 was determined by X-ray analysis. It is supposed that the distal position for di-*p*-*tert*-butyl groups on the nuclei is reasonable because that is where there is the smallest steric hindrance. Surprisingly, selective *de*-*tert*-butylation occurred in the 1,2-position on the phenolic nuclei. Calix[4]arenes are found in one of four possible extreme conformations: the cone, partial cone, 1,2-alternate, and 1,3-alternate (Fig. 2). In the structure of di-TCA, the cone configuration is significantly flattened. The structures of mono- and tri-TCA were investigated by X-ray analysis, of which the configurations are determined as a flattened cone configuration.

Fluorescence spectra

Fig. 3 shows fluorescence spectra of TCA-3 in the presence and absence of potassium nitrate in a 10 vol.% DMF aqueous solution. In a previous paper, we reported the

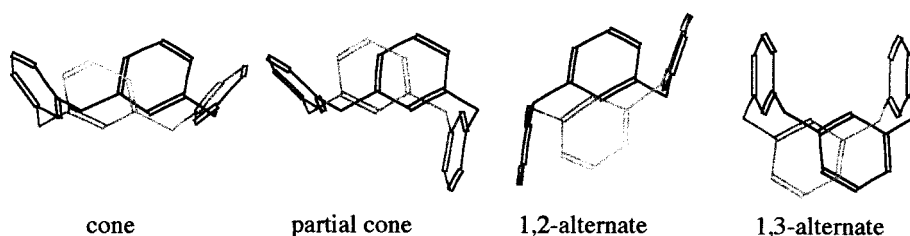


Figure 2. Extreme conformations of calix[4]arene.

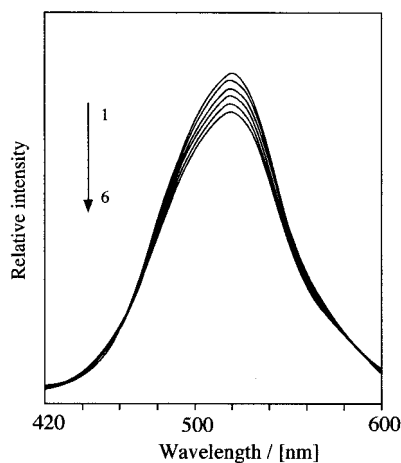


Figure 3. Fluorescence spectra of TCA-3 (1×10^{-6} M) in 10 vol.% DMF aqueous solution with various concentrations of K^+ : 1; 0 M, 2; 1.0×10^{-4} M, 3; 3.0×10^{-4} M, 4; 5.9×10^{-4} M, 5; 9.8×10^{-4} M, 6; 1.5×10^{-3} M.

fluorescent metal sensor ability of tetra-TCA-2 and tetra-TCA-3 in 10 vol.% DMF Sørensen buffer solution (pH 7.41). In this study, we used a 10 vol.% DMF aqueous solution, because a larger fluorescent intensity was obtained compared with that in 10 vol.% DMF Sørensen buffer solution. The pH change of the 10 vol.% DMF aqueous solution was not recognized when metal nitrate as a guest was added to the host solution. The fluorescence spectra of TCA-3 is composed of almost pure monomer emission with a peak around 520 nm, the fluorescence intensity decreases with increasing metal nitrate concentration. The result obtained from fluorescence change suggests that the dansyl moieties came out from the interior of the hydrophobic TCA cavity to outside bulk water environment while simultaneously a metal cation is included in the cavity.⁸ To display the sensing ability of dansyl modified TCA derivatives, the $\Delta I/I_0$ value was used as a sensitivity parameter. Here ΔI is I_0/I , where I_0 is the fluorescence intensity at 520 nm for the host alone, and I is the fluorescence intensity at 520 nm for a complex. Fig. 4 shows the parameter values of five new analogues, which are modified with tri-dansyl moieties on

the lower rim of the TCA with metal nitrate at 0.3 mM in a 10 vol.% DMF aqueous solution. It is evident that mono-*p*-*tert*-butyl derivatives show the highest sensing parameter among them, of which the highest parameter value is 0.1045 for Cd^{2+} . The sensing ability of the five hosts is almost in the order: mono-TCA-3 > TCA-3 > di-TCA-3 > tri-TCA-3 > tetra-TCA-3. Metals Li^+ and K^+ were detected with the highest sensitivity by TCA-3, and other metal cations were detected with mono-TCA-3. Tetra-TCA-3 can hardly detect these metal cations except Co^{2+} and Ni^{2+} . Fig. 5 shows the parameters of di-dansyl modified TCA analogues, which are almost the same detecting patterns with smaller parameter values ranging from 0 to 0.0669 as in the case of tri-dansyl modified analogues. The sensing parameter of TCA-2 for Cd^{2+} is very high, while Zn^{2+} is hardly recognized. It is obvious that Zn^{2+} interferes in the analysis of Cd^{2+} ,⁹ therefore, this result indicates that TCA-2 would be used as an ionophore in the selective analysis of Cd^{2+} in the presence of large amount of Zn^{2+} . All the parameter values obtained here are positive, which implies that the fluorescence intensity was decreased upon addition of metal cation. This is different from the results found using Sørensen buffer solution. When we used the buffer solution, the intensity for a couple of metal cations was increased. It is probably because an effect based on the buffer solution exists for the behavior of fluorescence alternation. Because there is a high sodium cation concentration in the buffer solution.

Pattern recognition of metal cations

It is interesting to examine the responses of the eleven hosts for each guest compound, because the shape representation is an indication of metal recognition of the hosts if each guest has its own sensing shape. Fig. 6 shows the sensing parameters ($\Delta I/I_0$) of eleven hosts for each metal cation at the guest concentration of 0.3 mM. As can be seen in Fig. 4, each host has its own definite shapes, which expand unsymmetrically. Zn^{2+} gives an extremely different shape in comparison with those patterns obtained from the other six metal cations, because TCA-2 shows no detecting ability

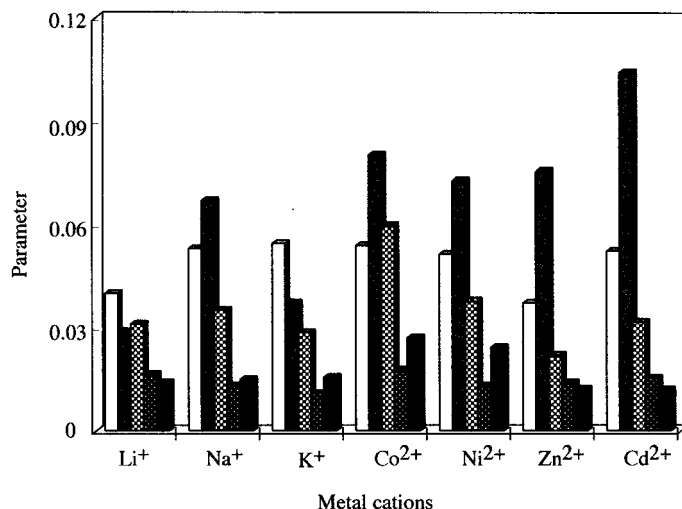


Figure 4. The parameters of tri-dansyl modified hosts (□): TCA-3, (■): mono-TCA-3, ▨: di-TCA-3, ▩: tri-TCA-3 and (■): tetra-TCA-3 in a 10 vol.% DMF aqueous solution.

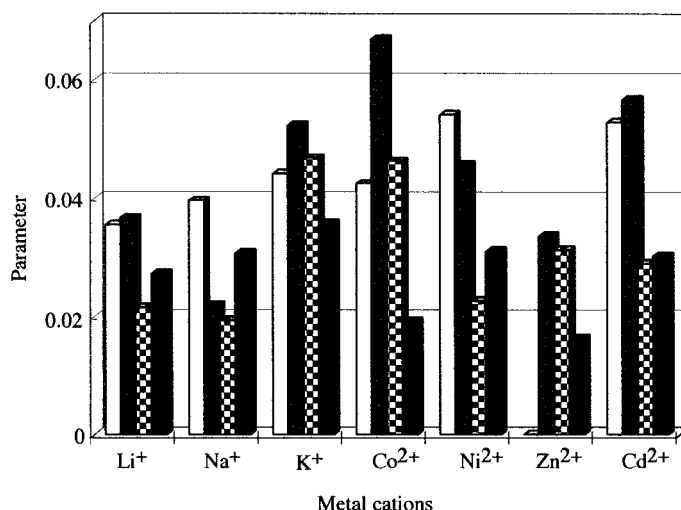


Figure 5. The parameters of di-dansyl modified hosts (□): TCA-2, (■): mono-TCA-2, (▨): di-TCA-2, (■): tetra-TCA-2) in a 10 vol.% DMF aqueous solution.

for Zn^{2+} , whereas other metal cations were recognized with the scale sensitivity ranging from 0.0356 to 0.0529.

The binding constants

The guest-induced fluorescence variation at 520 nm was employed to deduce the binding constants of these hosts

by using Eq. (1)¹⁰ as reported previously. Here, I is the fluorescence intensity at 520 nm (I_f for complex, I_{f0} 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 of eleven hosts for K^+ , Co^{2+} , and Cd^{2+} were obtained to examine the correlation between the fluorescence variations and the binding abilities of the hosts. The results are shown in Table 4. The order of the binding constants of each host for three metal cations is not parallel with the order of the sensitivity factor. This means that the sensitivity value gives a relative, but not an absolute, measure of the sensing ability.

$$\frac{1}{I_{f0} - I_f} = \frac{1}{a[\text{Host}]} + \frac{1}{a[\text{Host}]\text{K}[\text{G}]} \quad (1)$$

The effect of DMF content on a metal sensing parameter

The effect of DMF content on metal sensing was checked by using mono-TCA-3 as a host and Cd^{2+} as a guest. Fig. 7 shows the parameter values of mono-TCA-3 for Cd^{2+} at 520 nm in various aqueous DMF solutions. The parameter values of mono-TCA-3 decrease dramatically when DMF content increases from 10 to 30%, and then the values decrease with small magnitude, to a final value of 0.021. As the solvent is changed, the dansyl moiety might come out from the hydrophobic environment of TCA to outside of the cavity. When content of DMF is up to 30%, it seems that

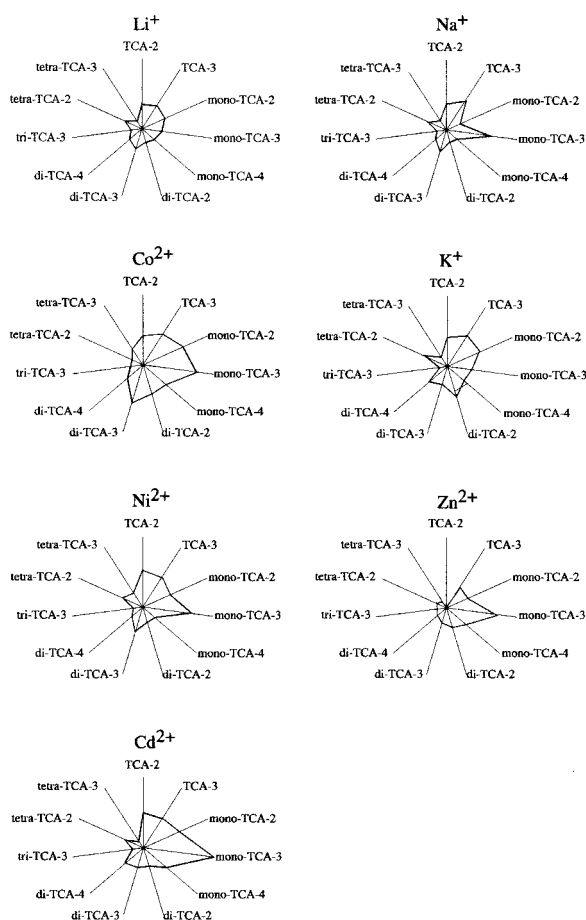


Figure 6. Variations of sensitivity factors of the eleven hosts (1×10^{-6} M) induced by various metal cations (0.3 mM).

Table 4. Binding constants of all hosts for K^+ , Co^{2+} and Cd^{2+}

	K^+	Co^{2+}	Cd^{2+}
TCA-2	2880 ± 120	2040 ± 170	3420 ± 140
TCA-3	1250 ± 70	910 ± 80	890 ± 100
mono-TCA-2	2050 ± 150	2260 ± 230	2550 ± 410
mono-TCA-3	620 ± 50	2380 ± 10	1510 ± 80
mono-TCA-4	230 ± 10	730 ± 160	380 ± 50
di-TCA-2	3980 ± 230	1720 ± 130	1950 ± 260
di-TCA-3	430 ± 70	1390 ± 270	1980 ± 300
di-TCA-4	3100 ± 290	140 ± 110	2700 ± 190
tri-TCA-3	540 ± 80	980 ± 220	1300 ± 290
tetra-TCA-2	110 ± 60	520 ± 70	690 ± 90
tetra-TCA-3	890 ± 140	130 ± 70	250 ± 40

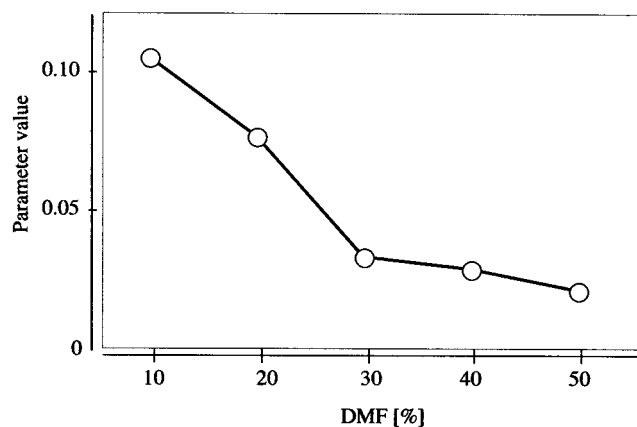


Figure 7. The effect of DMF content on a metal sensing parameter.

there is little interaction such as hydrophobic interaction between the TCA cavity and the appended moiety, because the parameter value is negligible. It is supposed that the appended moiety is perfectly coming out from the TCA cavity.

Conclusion

Nine new analogues of dansyl-modified-TCA together with two analogues reported previously, which are soluble in 10 vol.% DMF-aqueous solution, have been investigated their metal sensing ability by the change of fluorescent intensity on accommodation with metal cations. It seems that a *p*-*tert*-butyl group on the upper rim of TCA affects sensing of the metal cations, because there is an optimum number of *p*-*tert*-butyl groups on the TCA nuclei, which shows the highest sensitivity for metal cations. The set of eleven sensors of the series forms different shaped diagrams for different metal cations from fluorescence responses. Metal recognition as indicated by such shape representation for the responses of plural sensors might become an important approach to sensing metal cations.

Experimental

Measurements

Fluorescence spectra were measured at 25°C, with a Perkin Elmer LS 40B fluorescence spectrometer. For the fluorescence measurements, the excitation wavelength of the fluorescence spectra was 350 nm and emission slits were 10 nm. A 10 vol.% DMF aqueous solution was used as a solvent for hosts for the fluorescence spectra measurements because their solubility in pure water is poor. 15 microliters of metal (0.05 M) in aqueous solution were injected into a 10 vol.% DMF aqueous solution of host (2.5 mL) to make a sample solution with a host concentration of 1×10^{-6} M and guest concentration of 3×10^{-4} M.

Preparation of de-*p*-*tert*-butyl thiacalix[4]arene (TCA)

A suspension of *p*-*tert*-butyl TCA 5.0 g (6.93 mmol), phenol 3.15 g (3.67 mmol), and AlCl_3 (9.73 g, 73.0 mmol) in anhy-

drous toluene (200 ml) was stirred at 80°C for 2 h. After cooling, the reaction mixture was washed twice with water, then the solvent was evaporated in vacuo. The yellowish product was suspended in MeOH (100 ml) and refluxed for 30 min. After cooling, the resulting precipitates were filtered to afford pure TCA as a white powder: yield 2.64 g (76.6%). $^1\text{H NMR}$ (CDCl_3) $\delta=9.45$ (4H, s, -OH), 7.61 (8H, d, $J=7.8$, aromatic-H), 6.75 (4H, t, aromatic-H).

Selective de-*tert*-butylation of *p*-*tert*-butyl TCA

A suspension of *p*-*tert*-butyl TCA 5.0 g (6.93 mmol), phenol 3.15 g (3.67 mmol), and AlCl_3 (6.57 g, 49.3 mmol) in anhydrous toluene (200 ml) was stirred at 80°C for 30 min. After cooling, the reaction mixture was washed twice with water, then the solvent was evaporated in vacuo. The yellowish product was suspended in MeOH (100 ml) and refluxed for 30 min. After cooling, the resulting precipitates were filtered and dried. The crude product was purified by column chromatography (Lobar column, Lichroprep^R, Si 60, 40–63 μm). 2% Acetone/*n*-hexane eluted fractions were collected and evaporated to yield tri-*tert*-butyl thiacalix[4]arene (tri-TCA) (298 mg, 6.46% isolated yield); 3% eluted fractions gave di-*p*-*tert*-butyl thiacalix[4]arene (di-TCA) (834 mg, 19.8%); 5% filtered fractions yielded mono-*p*-*tert*-butyl thiacalix[4]arene (mono-TCA) (810 mg, 21.2%), and acetone eluted fractions gave TCA (600 mg, 17.4%).

tri-TCA: $^1\text{H NMR}$ (CDCl_3) $\delta=9.50$ (4H, br, -OH), 7.61–7.65 (8H, m, aromatic-H), 6.75 (1H, t, aromatic-H), 1.10 (27H, s, - CH_3), calcd for $\text{C}_{36}\text{H}_{40}\text{O}_4\text{S}_4 \cdot \text{CH}_3\text{OH}$, C 63.76%; H 6.36%, Found: C 64.02%; H 6.39%, MS (FAB): $m/z=664$ ($[\text{M}+\text{H}]^+$).

di-TCA: $^1\text{H NMR}$ (CDCl_3) $\delta=9.51$ and 9.63 (4H, br, -OH), 7.45 (8H, d-d, $J=7.8$, aromatic-H), 6.75 (2H, t, aromatic-H), 1.22 (18H, s, - CH_3), calcd for $\text{C}_{32}\text{H}_{32}\text{O}_4\text{S}_4$, C 63.13%, H 5.30%, Found: C 62.87%, H 5.44%, MS (FAB): $m/z=608$ ($[\text{M}+\text{H}]^+$).

Mono-TCA: $^1\text{H NMR}$ (CDCl_3) $\delta=7.49$ (2H, s, aromatic-H), 7.45 (6H, d, $J=7.5$ Hz, aromatic-H), 6.59 (3H, t, aromatic-H), 1.10 (9H, s, - CH_3), calcd for $\text{C}_{28}\text{H}_{24}\text{O}_4\text{S}_4$, C 60.84%; H 4.38%, Found: C 60.68%; H 4.46%, MS (FAB): $m/z=552$ ($[\text{M}+\text{H}]^+$).

Preparation of dansyl modified TCA derivatives (TCA-2 and TCA-3)

To a suspension of TCA (0.3 g, 0.6 mmol) and NaH (58 mg, 2.42 mmol) in 50 ml of THF, dansylsulfonylchloride (652 mg, 2.42 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, and the mixture was evaporated to yield the residue, which was resolved in chloroform. The organic layer was washed with water and dried with Na_2SO_4 . The filtrate was evaporated to residue, which was refluxed in MeOH to give precipitates. The crude precipitates were purified by column chromatography on silica gel (Kiesel gel 60, 230–400 mesh, Merck) with hexane/acetone mixtures as eluents. 25% acetone in *n*-hexane eluted fractions were collected and evaporated to yield mono-dansyl TCA (TCA-2) (105 mg, 18%); 33% acetone in

n-hexane eluted fractions gave tri-dansyl-modified TCA (TCA-3) (130 mg, 18%) as a yellow powder.

TCA-2: $^1\text{H NMR}$ (CDCl_3) δ =8.67 (4H, d, aromatic-H), 8.18 (2H, d-d, J =7.2, aromatic-H), 7.52–7.62 (4H, m, aromatic-H), 7.48 (4H, d, 6.78 aromatic-H), 6.78 (2H, t, aromatic-H), 6.54–6.60 (6H, m, aromatic-H), 5.77 (2H, s, aromatic-H), 2.90 (12H, s, N- CH_3), calcd for $\text{C}_{48}\text{H}_{38}\text{N}_2\text{O}_8\text{S}_6\cdot\text{CO}_2\cdot\text{H}_2\text{O}$, C 57.40%; H 3.93%; N 2.73%, Found: C 57.58%; H 4.28%; N 2.85%, MS (FAB): m/z =963 ($[\text{M}+\text{H}]^+$).

TCA-3: $^1\text{H NMR}$ (CDCl_3) δ =8.61 (2H, d, J =8.7, aromatic-H), 8.52 (2H, d, J =8.4, aromatic-H), 8.47 (1H, d, J =7.5, aromatic-H), 8.90 (2H, d-d, J =7.5, aromatic-H), 7.36–7.54 (10H, m, aromatic-H), 6.97–7.15 (5H, m, aromatic-H), 6.72 (1H, t, aromatic-H), 6.50 (2H, t, aromatic-H), 6.30 (2H, d-d, J =7.8, aromatic-H), 6.23–6.26 (3H, m, aromatic-H), 2.88 (6H, s, N- CH_3), 2.86 (12H, s, N- CH_3), calcd for $\text{C}_{60}\text{H}_{49}\text{N}_3\text{O}_{10}\text{S}_7\cdot\text{CO}_2\cdot\text{H}_2\text{O}$, C 58.21%; H 4.08%; N 3.34%, Found: C 57.99%; H 4.19%; N 3.43%, MS (FAB): m/z =1196 ($[\text{M}+\text{H}]^+$).

Preparation of di-, tri-, and tetra-dansyl modified mono-TCA derivatives (mono-TCA-2, mono-TCA-3, and mono-TCA-4, respectively)

The compounds mono-TCA-2, mono-TCA-3, and mono-TCA-4 were prepared by the same procedure as for TCA-2 and TCA-3. The crude products of mono-TCA-derivatives were purified with column chromatography on silica gel (Kiesel gel 60, 230–400 mesh, Merck) with hexane/acetone mixtures as eluents. 20% acetone in *n*-hexane eluted fractions were collected and evaporated to yield mono-TCA-2 (60 mg, 10.8%); 25% acetone in *n*-hexane eluted fractions gave mono-TCA-3 (130 mg, 18%); and 33% acetone in hexane eluted fractions afforded mono-TCA-4 (120 mg, 15%) as a yellow powder.

mono-TCA-2: $^1\text{H NMR}$ (CDCl_3) δ =8.68 (4H, d-d, aromatic-H), 8.18 (2H, d, J =7.2 Hz, aromatic-H), 7.45–7.59 (8H, m, aromatic-H), 7.21 (2H, d, J =7.8 Hz, aromatic-H), 6.56–6.79 (3H, m, aromatic-H), 6.54–6.58 (4H, m, aromatic-H), 2.90 (12H, s, N- CH_3), 1.29 and 0.83 (9H, s, $-\text{C}(\text{CH}_3)_3$), calcd for $\text{C}_{52}\text{H}_{46}\text{N}_2\text{O}_8\text{S}_6\cdot 2\text{CH}_3\text{OH}$, C 59.86%; H 5.02%; N 2.59%, Found: C 59.56%; H 4.74%; N 2.65%, MS (FAB): m/z =1018 ($[\text{M}+\text{H}-1]^+$).

mono-TCA-3: $^1\text{H NMR}$ (CDCl_3) δ =8.63 (2H, d, J =8.4 Hz, aromatic-H), 8.57 (2H, d, J =8.7 Hz, aromatic-H), 8.48 (2H, d, J =7.2 Hz, aromatic-H), 8.10 (2H, d, J =7.2 Hz, aromatic-H), 7.45–7.56 (6H, m, aromatic-H), 7.31–7.39 (4H, m, aromatic-H), 7.16 (2H, d, J =7.8 Hz, aromatic-H), 6.97 (2H, d, J =8.7 Hz, aromatic-H), 6.71 (1H, t, aromatic-H), 6.52 (2H, t, aromatic-H), 6.28 (4H, t, aromatic-H), 2.86 (18H, s, N- CH_3), 1.28 (9H, s, $-\text{C}(\text{CH}_3)_3$), calcd for $\text{C}_{64}\text{H}_{57}\text{N}_3\text{O}_{10}\text{S}_7\cdot\text{CO}_2\cdot 2\text{H}_2\text{O}$, C 58.58%; H 4.61%; N 3.15%, Found: C 58.94%; H 4.85%; N 3.12%, MS (FAB): m/z =1251 ($[\text{M}+\text{H}]^+$).

mono-TCA-4: $^1\text{H NMR}$ (CDCl_3) δ =8.93 (1H, d, J =7.2 Hz, aromatic-H), 8.90 (1H, d, J =8.7 Hz, aromatic-H), 8.77 (2H, d, J =9.0 Hz, aromatic-H), 8.74 (2H, d, J =8.4 Hz, aromatic-H), 8.22–8.27 (4H, m, aromatic-H), 7.72 (2H, t,

aromatic-H), 7.60 (2H, t, aromatic-H), 7.49–7.52 (4H, m, aromatic-H), 7.14–7.39 (5H, m, aromatic-H), 6.93–7.03 (4H, m, aromatic-H), 6.66–6.72 (2H, m, aromatic-H), 6.40 (2H, t, aromatic-H), 6.01 (4H, t, aromatic-H), 2.92 (12H, s, N- CH_3), 2.88 (12H, s, N- CH_3), 1.35 (9H, s, $-\text{C}(\text{CH}_3)_3$), calcd for $\text{C}_{76}\text{H}_{68}\text{N}_4\text{O}_{12}\text{S}_8\cdot\text{CO}_2\cdot 2\text{H}_2\text{O}$, C 59.06%; H 4.63%; N 3.58%, Found: C 58.83%; H 4.70%; N 3.61%, MS (FAB): m/z =1485 ($[\text{M}+\text{H}]^+$).

Preparation of di-, tri-, and tetra dansyl modified di-TCA derivatives (di-TCA-2, di-TCA-3, and di-TCA-4, respectively)

The compounds di-TCA-2, di-TCA-3, and di-TCA-4 were prepared by the same procedure as for TCA-2 and TCA-3. The crude products of di-TCA-derivatives were purified by column chromatography on silica gel (Kiesel gel 60, 230–400 mesh, Merck) with hexane/acetone mixtures as eluents. 14% acetone in *n*-hexane eluted fractions were collected and evaporated to yield di-TCA-2 (70 mg, 13.2%); 20% acetone in *n*-hexane eluted fractions gave di-TCA-3 (43 mg, 6.7%); and 33% acetone in hexane eluted fractions afforded di-TCA-4 (140 mg, 20%) as a yellow powder.

di-TCA-2: $^1\text{H NMR}$ (CDCl_3) δ =8.67 (4H, d, J =8.4 Hz, aromatic-H), 8.17 (2H, t, aromatic-H), 7.48–7.53 (8H, m, aromatic-H), 7.11 (2H, d, J =7.8 Hz, aromatic-H), 6.69–6.78 (4H, m, aromatic-H), 6.52–6.57 (2H, m, aromatic-H), 2.91 (12H, s, N- CH_3), 1.28 and 1.29 (12H, s, $-\text{C}(\text{CH}_3)_3$), 0.81 (6H, s, $-\text{C}(\text{CH}_3)_3$), calcd for $\text{C}_{56}\text{H}_{54}\text{N}_2\text{O}_8\text{S}_6\cdot\text{CH}_3\text{OH}$, C 61.82%; H 5.28%; N 2.53%, Found: C 61.95%; H 5.25%; N 2.61%, MS (FAB): m/z =1074 ($[\text{M}+\text{H}-1]^+$).

di-TCA-3: $^1\text{H NMR}$ (CDCl_3) δ =8.43–8.66 (5H, m, aromatic-H), 8.23–8.33 (1H, m, aromatic-H), 8.07–8.17 (2H, m, aromatic-H), 7.26–7.71 (11H, m, aromatic-H), 7.13–7.19 (1H, m, aromatic-H), 6.95–7.08 (2H, m, aromatic-H), 6.71 (1H, t, aromatic-H), 6.51–6.57 (2H, m, aromatic-H), 6.23–6.40 (3H, m, aromatic-H), 2.82–2.90 (18H, m, N- CH_3), 1.26–1.32 (12H, m, $-\text{C}(\text{CH}_3)_3$), 0.85 (6H, s, $-\text{C}(\text{CH}_3)_3$), calcd for $\text{C}_{68}\text{H}_{65}\text{N}_3\text{O}_{10}\text{S}_7\cdot\text{CO}_2\cdot 2\text{H}_2\text{O}$, C 60.46%; H 4.93%; N 3.07%, Found: C 60.36%; H 5.30%; N 3.14%, MS (FAB): m/z =1307 ($[\text{M}+\text{H}-1]^+$).

di-TCA-4: $^1\text{H NMR}$ (CDCl_3) δ =8.64 (4H, d, J =6.9 Hz, aromatic-H), 8.55 (4H, t, aromatic-H), 7.99 (2H, d, J =8.4 Hz, aromatic-H), 7.83 (2H, d, J =8.7 Hz, aromatic-H), 7.41 (4H, m, aromatic-H), 7.32 (2H, t, aromatic-H), 7.19 (2H, t, aromatic-H), 7.03–7.10 (4H, m, aromatic-H), 6.91 (4H, br, aromatic-H), 6.63–6.74 (6H, m, aromatic-H), 2.89 and 2.90 (24H, s, N- CH_3), 1.06 (18H, s, $-\text{C}(\text{CH}_3)_3$), calcd for $\text{C}_{80}\text{H}_{76}\text{N}_4\text{O}_{12}\text{S}_8\cdot 2\text{CO}_2\cdot\text{H}_2\text{O}$, C 59.76%; H 4.77%; N 3.40%, Found: C 59.62%; H 5.00%; N 3.42%, MS (FAB): m/z =1540 ($[\text{M}+\text{H}]^+$).

Preparation of tri-dansyl modified tri-TCA derivative (tri-TCA-3)

Compound tri-TCA-3 was prepared by the same procedure as for TCA-derivatives.

The crude product of tri-TCA-derivative was purified by column chromatography on silica gel (Kiesel gel 60, 230–

400 mesh, Merck) with hexane/acetone mixtures as eluents. 20% acetone in *n*-hexane eluted fractions were collected and evaporated to yield tri-TCA-3 (216 mg, 35%) as a yellow powder.

tri-TCA-3: ^1H NMR (CDCl_3) δ =8.48–8.53 (4H, m, aromatic-H), 8.31 (1H, d, J =8.7 Hz, aromatic-H), 8.27 (1H, d, J =8.7 Hz, aromatic-H), 8.14 (1H, d, J =7.5 Hz, aromatic-H), 8.08 (1H, d, J =6.9 Hz, aromatic-H), 7.72 (1H, d, J =8.7 Hz, aromatic-H), 8.14 (1H, d, J =7.5 Hz, aromatic-H), 8.08 (1H, d, J =6.9 Hz, aromatic-H), 7.72 (1H, d, J =8.7 Hz, aromatic-H), 7.29–7.62 (9H, m, aromatic-H), 7.18 (1H, t, aromatic-H), 7.01–7.07 (3H, m, aromatic-H), 6.52 (2H, br, aromatic-H), 6.29–6.40 (3H, m, aromatic-H), 2.90 (6H, s, N- CH_3), 2.83 and 2.84 (12H, s, N- CH_3), 1.26 and 1.32 (18H, s, - $\text{C}(\text{CH}_3)_3$), 0.83 (9H, s, - $\text{C}(\text{CH}_3)_3$), calcd for $\text{C}_{72}\text{H}_{73}\text{N}_3\text{O}_{10}\text{S}_7\cdot 4\text{CH}_3\text{OH}$, C 61.14%; H 6.01%; N 2.81%, Found: C 61.05%; H 5.79%; N 2.88%, MS (FAB): m/z =1363 ($[\text{M}+\text{H}-1]^+$).

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