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Recognition of Alkaline Metals and Amines by a Chromogenic Homooxacalix[3]arene Receptor

Kazunori Tsubaki,* Tatsuya Morimoto, Tadamune Otsubo, and Kaoru Fuji*

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

tsubaki@fos.kuicr.kyoto-u.ac.jp

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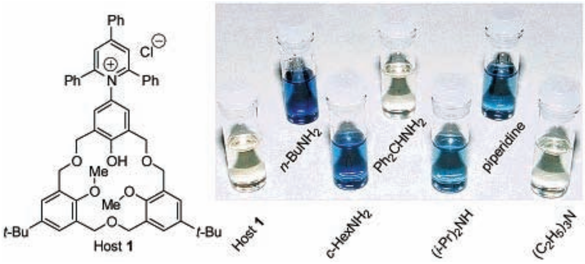
ABSTRACT



The artificial host molecule 1, consisting of homooxacalix[3]arene and pyridinium *N*-phenolate dye (Reichardt dye E_T1) has been prepared. Host 1 contains a proton-ionizable phenol group that acts as a chemical switch to generate color change against alkaline metals and various kind of amines.

In the field of supramolecular chemistry, calixarene skeletons have been extensively investigated as host compounds that may be functionalized to induce specific recognition for target guest molecules.[1] Simultaneously, a number of calixarene analogues have also been synthesized.[2] Among such analogues, homooxacalix[3]arene has attracted a significant amount of attention with its unique structural features, such as a cavity composed of an 18-membered ring and C_3-symmetry.[3] Since our initial work on the stepwise construction of homooxacalix[3]arenes,[4] we have become interested in multitalented host molecules with the ability to change color when complexed to appropriate guest molecules. We have designed the host molecule **1**, shown in Figure 1, consisting of homooxacalix[3]arene and pyridinium *N*-phenolate dye (Reichardt dye E_T1) to realize this concept. Pyridinium *N*-phenolate betaine dyes have been investigated by Reichardt and co-workers as solvatochromic reagents.[5] Thus, large negative solvatochromic shifts, based on a charge-transfer (CT) absorption band in the visible region, were used as empirical parameters of solvent polarities (E_T values). Some host molecules in which betaine dyes were added onto crown ethers have been reported by Reichardt.[6] Furthermore, a calix[4]arene-type dye and cryptand-type dye were studied by Bitter and Sutherland, respectively.[7,8] Most of these hosts have been used in the betaine form except Bitter's host. In this paper, we report the highly function-

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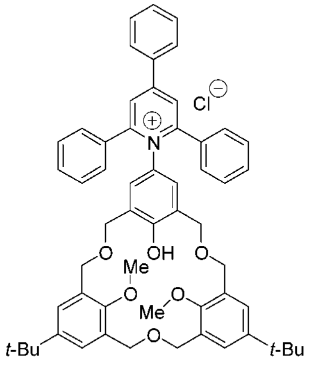
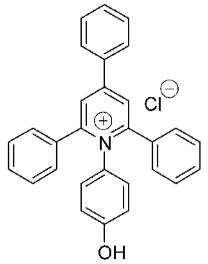


Host **1**



$E_T(1)\cdot HCl$ (**2**)

Figure 1. Structure of host **1** and $E_T(1)\cdot HCl$ (**2**).

alized homooxacalix[3]arene host **1**, with a proton-ionizable phenol group that acts as chemical switch to generate color change against alkaline metals and amines.[9]

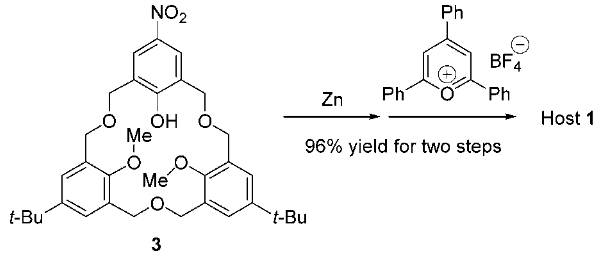


Figure 2. Synthetic route for host **1**.

A synthetic route to host **1** is shown in Figure 2. Nitrohomooxacalix[3]arene **3**,[10] with two phenolic hydroxy groups that are protected as methoxy groups, was reduced by zinc powder prior to treatment with 2,4,6-triphenylpyrylium tetrafluoroborate. The tetrafluoroborate salt was substituted with hydrochloric acid salt by treatment of aqueous hydrochloric acid to afford the desired host **1** in 96% overall yield from **3**. $E_T1\cdot HCl$ (**2**) was synthesized in a manner similar to the reference compound.

Figure 3. Solvatochromism between host **1** and various solvents. The concentration of host **1** was 1.0×10^{-3} M in the presence of *n*-hexylamine (1.0×10^{-1} M) at 25 °C.

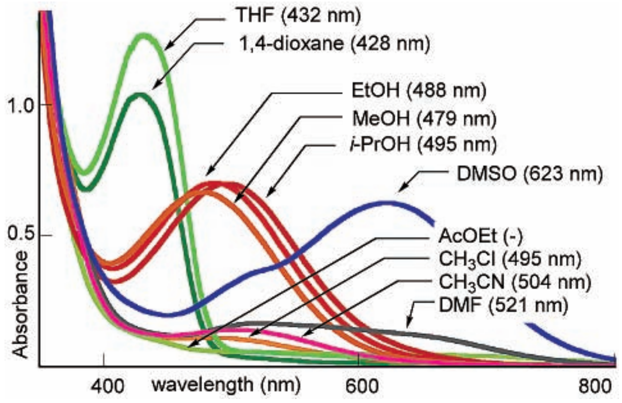


Figure 4. UV−vis spectra of host **1** (1.0×10^{-3} M) in various solvents in the presence of large excess of *n*-hexylamine (1.0×10^{-1} M) at 25.0 ± 0.1 °C.

First, the solvatochromic ability of host **1** was investigated. Since host **1** does not exist in the betaine form, addition of a large excess of amine (in this case: *n*-hexylamine, 100 equiv) is necessary to generate the colored betaine form. The dramatic color developments in various solvents are shown in Figure 3, while the UV−vis absorption spectrum is shown in Figure 4. Unexpected positive solvatochromism, where λ_{max} was shifted to longer wavelengths with increasing solvent polarity, was roughly observed. Reichardt reported that with increasing solvent polarity the highly charge separated ground state of betaine dye was relatively more stabilized by polar solvents, and shorter wavelength shifts were observed. The experimental difference between Reichardt's system and the current one is in the betaine form of the host. Reichardt's compounds existed in the betaine form; alternatively, the betaine form of host **1** is generated in situ by treatment with a large excess of amine. Therefore, in the current system, the halochromic character between the phenoxide of the betaine form of host **1** and the ammonium of the guest amine as well as the solvatochromic character must be considered. In polar solvents, a solvent-separated ion pair is presumably generated that induces a long wavelength shift of the CT band. Consequently, shifting of the CT band may be controlled by the opposite two (solvatochromic and halochromic) characters.

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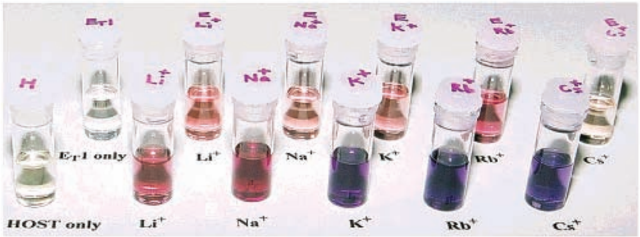

Figure 5. Color development by the hosts **1** and **2** and metal acetates. The concentration of hosts **1** and **2** were 1.0 × 10^{-3} M, and those of guests were 5.0 × 10^{-2} M in DMSO/water = 21/1 at 25 °C.

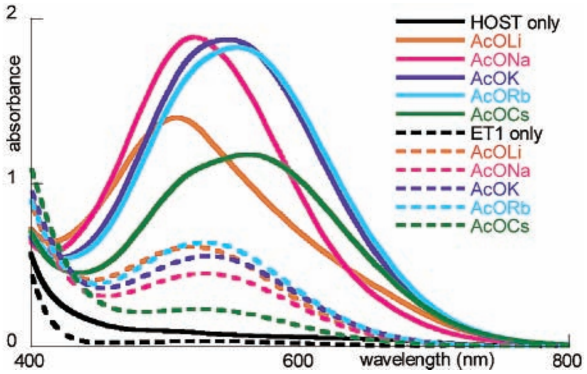

Figure 6. UV−vis spectra of host **1** (solid lines) or $E_T(1)$·HCl (**2**) (dotted lines) with metal acetates. The concentration of hosts **1** and **2** were 1.0 × 10^{-3} M, and those of guests were 5.0 × 10^{-2} M in DMSO/water = 21/1 at 25.0 ± 0.1 °C.

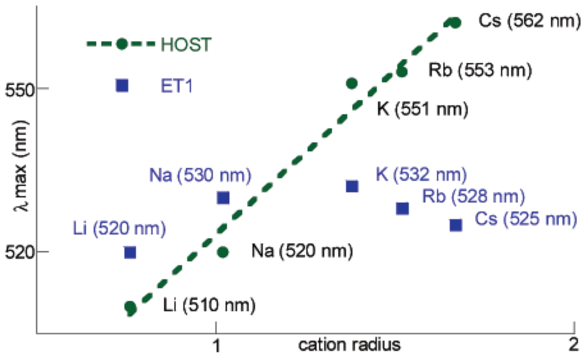

Figure 7. Relationship between λ_{max} and alkaline metal radius.

Figure 8. Color development by the hosts **1** and **2** with various amines. The concentration of hosts **1** and **2** were 1.0 × 10^{-3} M and those of amines **4**−**10** were 1.0 × 10^{-1} M in DMSO at 25 °C: **4**, *n*-hexylamine; **5**, cyclohexylamine; **6**, benzhydrylamine; **7**, diisopropylamine; **8**, piperidine; **9**, triethylamine; **10**, *n*-ethylpiperidine.

When alkaline metal acetates were added to host **1** in a DMSO/water (21/1) solution, clear color development was observed as depicted in Figures 5 and 6. λ_{max} of the CT bands were shifted to longer wavelengths with increasing ionic radius. Furthermore, a linear relationship exists between λ_{max} and the ionic radii (Figure 7). In contrast, both the strength of color development and the degree of the λ_{max} shift were diminutive in the case of E_T1·HCl (**2**). These results obviously indicate that the capabilities of the dye were enhanced by combination with the homooxacalix[3]arene frame.

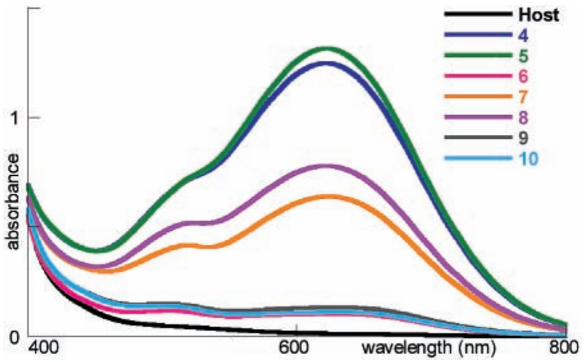

Figure 9. UV−vis spectra of host **1** with various amines. The concentration of host **1** was 1.0 × 10^{-3} M and those of amines **4**−**10** were 1.0 × 10^{-1} M in DMSO at 25 °C.

Next, the complexation between host **1** and various amines was investigated. Addition of primary amines, such as **4** and **5**, to a DMSO solution of host **1** strongly produced a blue color based on increasing of the absorption around 610 nm (Figures 8 and 9). Combination of secondary amines (**7** and **8**) and host **1** revealed a pale blue color. In the case of tertiary amines (**9** and **10**), no color development was observed by the naked eye. Additionally, no meaningful color development between E_T1·HCl (**2**) and amines was obtained. Association constants (K_a) between host molecule **1** and amines in DMSO at 25 °C were determined by UV−vis titration and analyzed by the Rose−Drago method (Table 1).[11,12] Although both association constants (K_a) and molar absorption coefficients (ϵ) were small, differences among primary, secondary, and tertiary amines were observed.[13] Furthermore, the neighboring two phenyl groups were too bulky to generate the complex between host **1** and benzhy-

Table 1. Association Constants (K_a) and Molar Absorption Coefficients (ϵ) of Complexes of the Host **1** with Amines **4**−**10** at 25.0 °C in DMSO

amine	K_a (M^{-1})	ϵ
4	135.7 ± 6.1	683 ± 21
5	55.1 ± 1.7	1019 ± 16
6	13.6 ± 1.2	81 ± 3
7	43.8 ± 2.3	580 ± 17
8	53.4 ± 3.5	725 ± 14
9	7.6 ± 0.8	260 ± 31
10	7.3 ± 0.8	174 ± 15

drylamine (**6**). These findings indicate that bulkiness around the amino group plays a crucial role in color development. During screening of amines, we found unusual behavior for 2-amino-1-phenylethanol (**14**). In Figures 10 and 11, no color development was detected by the naked eye when using **14** as the guest amine. The more bulky amine **13** or ones with the same β-amino alcohol skeleton (**15**−**17**) were able to generate color. We assume that (1) acidity of the hydroxyl group of **14** is slightly greater than those of β-amino alcohols (**15**−**17**) by the neighboring electron-withdrawing phenyl group, (2) intramolecular five-membered hydrogen bonding between the hydroxy and amino groups may be formed, and (3) the trigger acid−base reaction between the phenolic hydroxy group of host **1** and the amino group of guest **14** will be blocked by that hydrogen bonding network, and consequently, no color development was observed by the naked eye.

Figure 10. Color development by the hosts **1** and **2** with various amines. The concentration of hosts **1** and **2** were 1.0 × 10^{-3} M and those of amines **11**−**14** were 1.0 × 10^{-1} M in DMSO at 25 °C: **11**, phenethylamine; **12**, 1-amino-2-phenylpropane; **13**, 2,2-diphenylethylamine; **14**, 2-amino-1-phenylethanol.

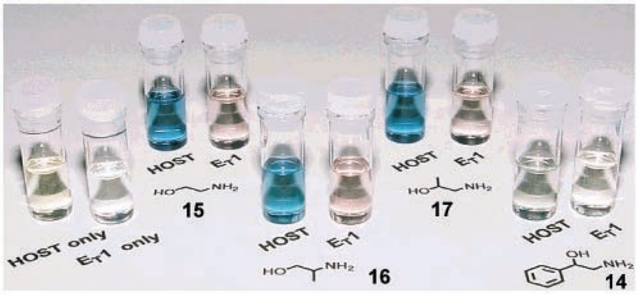

Figure 11. Color development by the hosts **1** and **2** with various amines. The concentration of hosts **1** and **2** were 1.0 × 10^{-3} M and those of amines **14**−**17** were 1.0 × 10^{-1} M in DMSO at 25 °C: **15**, ethanolamine; **16**, 2-amino-1-propanol; **17**, 1-amino-2-propanol.

In conclusion, we have developed the highly functionalized homooxacalix[3]arene **1** that can make clear color development against alkali metals and various kind of amines. We are currently synthesizing optically active analogues of host **1** to discriminate chirality of guest molecules based on a color change.

Supporting Information Available: The procedures and characterization data of host **1** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] The association constants between host **1** and alkaline metals follow: $K_a = 206 \pm 21$ (Li), $K_a = 225 \pm 38$ (Na), $K_a = 199 \pm 33$ (K), $K_a = 377 \pm 87$ (Rb), $K_a = 204 \pm 10$ (Cs) in DMSO/H_2O = 21/1 at 25 °C.

[13] We tried to determine the complex structure between host **1** and *n*-hexylamine by variable-temperature 2D-NMR in DMSO-d_6, MeOH-d_4, and $CDCl_3$. However, no meaningful information of shape of complex could be obtained by NOESY spectrum.