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A Novel Color-changeable Host for Molecules. Guest-induced Colorless-to-color Change of Phenolphthalein-modified β -Cyclodextrin

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Communication

A Novel Color-changeable Host for Molecules. Guest-induced Colorless-to-color Change of Phenolphthalein-modified β -Cyclodextrin

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For the purpose of constructing a novel color change indicator for organic compounds, phenolphthalein-modified β -cyclodextrin (**1**) was prepared. Upon addition of guest species into the solution of **1** at pH 9.70, **1** tends to undergo a colorless-to-color change to different degrees depending on the guest species. The color change of **1** is remarkable for ursodeoxycholic acid and chenodeoxycholic acid, among bile acids. 1-Adamantanecarboxylic acid and 1-adamantanol were also detected with similar high sensitivities.

Much attention has been paid to synthetic receptors that display marked changes in optical properties upon binding a substrate. They work as a transducer of substrate binding into spectral signals. Many types of artificial receptors based on crown ethers, cryptands, and calixarenes have been synthesized and their binding properties for metal ion or ammonium cation have been investigated.¹ On the other hand, cyclodextrins (CDs), which are composed of D-(+)-glucopyranose, are known as typical re-

ceptors for organic compounds. Modification of CDs with an appropriate chromophore makes them spectroscopically active hosts, and may alter the guest-binding properties of CDs. Recently we have prepared modified β -CD derivatives, each having methyl red,² *p*-methyl red,³ or *p*-nitrophenol unit,⁴ and observed guest-induced color changes in acidic or neutral media.

In the extension of our research for detecting organic molecules by color changes, we designed a new type of CD derivative which works in alkaline solutions. In this paper, we wish to report the synthesis and guest-binding properties of β -CD bearing a phenolphthalein moiety, **1**.

Phenolphthalein is known to change color from colorless to purple when the neutral solution becomes alkaline. This color change involves the structural change of phenolphthalein

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(Figure 1).⁵ Under alkaline conditions, the colorless lactonoid form existing under neutral conditions dissociates two protons to form a purple dianion, in which two phenol rings are incorporated into a planar resonance form. However, phenolphthalein was reported to be colorless in the presence of β -CD even at pH 10.5.⁵ This phenomenon suggests that phenolphthalein takes a constrained conformation in the β -CD cavity, existing as a lactonoid-like form even under alkaline conditions. Based on these features of phenolphthalein, we expected **1** to exhibit color change upon guest binding.

Compound **1** was prepared by the reaction of 6-deoxy-6-amino- β -CD with carboxyphenolphthalein in dimethylacetamide, using dicyclohexylcarbodiimide as a condensation reagent. The product was purified by ion-exchange chromatography on QAE-Sephadex column and HPLC with an ODS column, and characterized by ¹H-NMR spectra, and elemental analysis.⁶

Figure 2 shows the absorption spectra of **1** (1.0×10^{-6} M) at various pH values. A strong peak around 560 nm at pH 11.32, which is the origin of purple color, indicates that the chromophore of **1** exists as the dianion form. This peak decreased with lowering in pH of the solution and disappeared at pH 8.02. This spectral variation of **1** is similar to that of phenolphthalein, demonstrating that the acid dissociation equilibrium of the phenolphthalein moiety of **1** is basically the same as that of phenolphthalein itself. However, we observed the interesting phenomenon that the apparent pKa of the phenolphthalein unit of **1** is affected by the presence of guest spe-

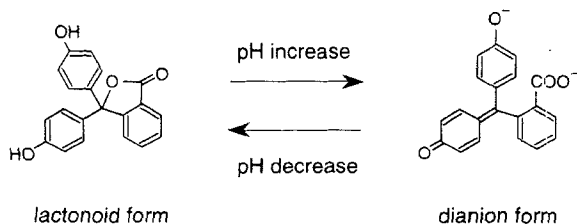


FIGURE 1 pH-Dependent structural change of phenolphthalein.

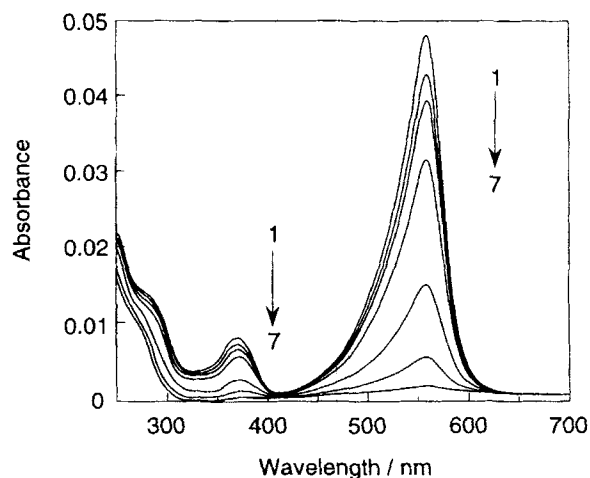


FIGURE 2 Effect of pH on absorption spectrum of **1**. pH: (1) 11.32, (2) 10.14, (3) 9.93, (4) 9.67, (5) 9.28, (6) 9.03, (7) 8.02.

cies as shown by the pKa shift from 9.50 for **1** alone to 9.28 for **1** in the presence of 1-adamantanol (3.0×10^{-5} M). Such a shift in the apparent pKa reflects that the environment around the chromophore unit of **1** is different from that of bulk water solution. This fact suggests that the phenolphthalein moiety of **1** is included, or at least partly included, in the hydrophobic CD

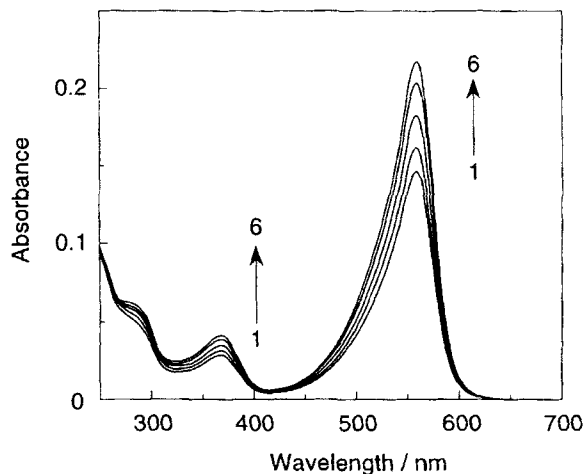


FIGURE 3 Guest-induced absorption variations of **1**. [**1**] = 5 μ M. Guest concentration: (1) 0 M, (2) 6 μ M, (3) 12 μ M, (4) 48 μ M, (5) 96 μ M.

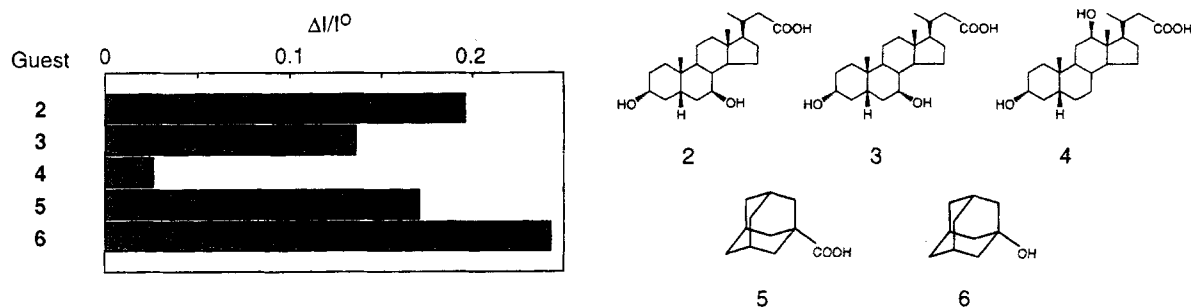


FIGURE 4 The sensitivity factor of $\Delta I/I^0$ of **1** for various guests. $[1] = 5 \mu\text{M}$, $[\text{Guest}] = 7.5 \mu\text{M}$.

cavity for **1** alone, but the moiety is excluded to outside of the cavity upon guest accommodation.⁷

At pH 9.70, we observed the guest-induced hyperchromic effect of **1** as shown in Figure 3. The absorption intensity around 560 nm increased upon addition of 1-adamantanol. This can be interpreted by the exclusion of the phenolphthalein unit of **1** from inside to outside of the cavity, thus resulting in the achievement of the resonance between two phenol units.

We have examined the sensor ability of **1**, using several compounds. The increase in the absorbance at 540 nm relative to its original value ($\Delta I/I^0$) was used as a sensitivity parameter. The results are shown in Figure 4. Among the steroidal compounds, ursodeoxycholic acid (**2**) and chenodeoxycholic acid (**3**) were detected with higher sensitivity than deoxycholic acid (**4**), which is different from **2** and **3** only in the position of hydroxyl group. The binding constants are 358000, 137000 and 16000 M^{-1} for **2**, **3** and **4**, respectively. The order of the sensitivities of three steroids is correlated with the binding constants between the host and guests. The similar trend in guest binding was obtained for adamantane compounds. The binding constants are 49800 and 96100 M^{-1} for 1-adamantanecarboxylic acid (**5**) and 1-adamantanol (**6**), respectively.

All the above results show that **1** is the first example of a host capable of detecting organic

compounds by color change in alkaline solution. Further work with many other guests is needed to clarify the molecular recognition ability of this host.

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- [6] Key data for **1**: $^1\text{H-NMR}$ (D_2O ; 500 MHz); d 1.64 (1H, d), 2.30 (1H, d), 2.59 (1H, d), 2.71 (1H, d), 2.80–4.20 (majority, m) (protons of CD unit), 4.78–5.05 (7H, m, anomeric protons); 5.33 (2H, d), 6.65 (2H, d), 6.69 (2H, d), 6.85 (2H, d), 8.14 (2H, s), 9.31 (1H, 2) (aromatic protons of phenolphthalein unit); Anal. Found: C, 49.75; H, 6.11; N, 0.92%. Calcd for $\text{C}_{63}\text{H}_{83}\text{N}_1\text{O}_{39} \cdot 3\text{H}_2\text{O}$: C, 49.38; H, 5.85; N 0.91%.
- [7] The concentration dependency of **1** in apparent pKa was observed, suggesting that the phenolphthalein unit of **1** may interact with another CD cavity in its concentrated solutions. Under the present conditions, **1** exists as a monomer.