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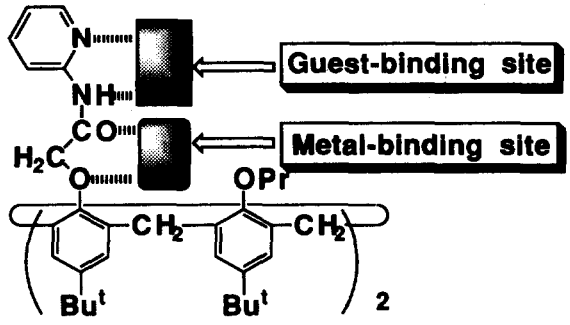
"Metal-Switched" Molecular Receptor Site Designed on a Calix[4]arene Platform

Hiroto Murakami and Seiji Shinkai*

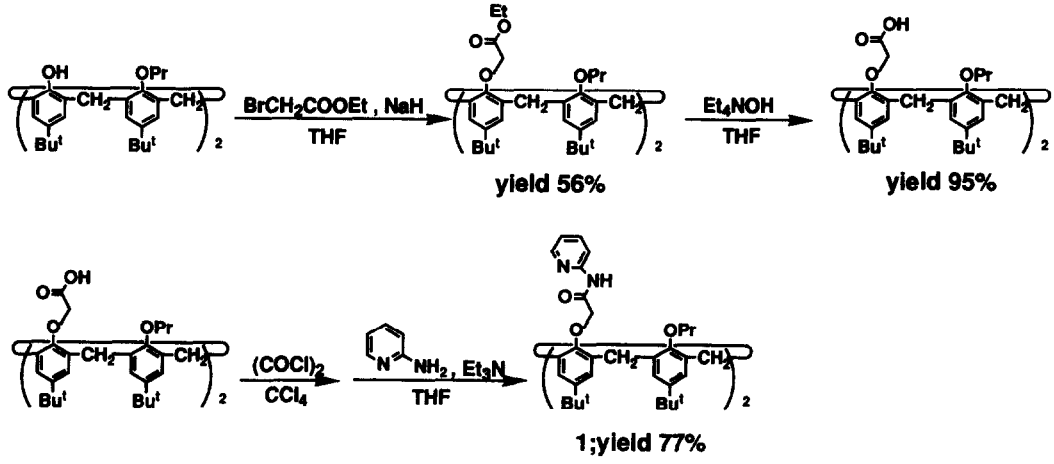
Department of Organic Synthesis, Faculty of Engineering,
Kyushu University, Fukuoka 812, Japan

Summary: New calix[4]arene having a hydrogen-bonding receptor site near an ionophoric site was synthesized. The receptor site was activated from a "closed" form to an "open" form by the Na^+-binding to the ionophoric site: that is, Na^+ acts as a trigger for the "opening" of the molecular receptor site.

The molecular design of receptor molecules that can precisely recognize and specifically bind guest molecules has been the focus of much recent attention.[1-4] In the papers reported so far it seems that molecular recognition through hydrogen-bonding interactions plays a central role.[1-4] However, the host molecule bearing both hydrogen-bond-acceptors and hydrogen-bond-donors within a molecule inevitably tends to associate intramolecularly as well as intermolecularly with the guest and result in a deactivated, "closed" receptor site. To avoid such intramolecular association, for example, one has to use a hard segment so that the receptor site cannot form intramolecular hydrogen-bonds. This limitation frequently hampers us to design the molecular receptor which has the complementary structure for the guest molecule. Recently, Adrian and Wilcox[5] designed a flexible receptor molecule which features a conformational change from a "closed" form to an "open" form upon the guest-binding. This stimulated us to design a new receptor in which an "open" form is generated from a "closed" form only when it perceives a stimulus. With this object in view we synthesized **1** which has a metal-binding site near a hydrogen-bonding receptor site on the lower rim of calix[4]arene.[6] We have found that the guest-binding to the receptor site occurs only when the "closed" receptor site is switched to the "open" one by the metal-binding.



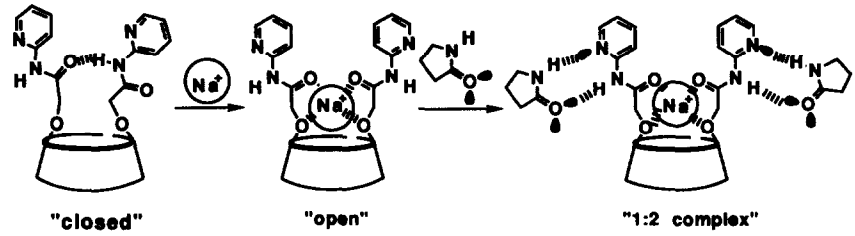
Compound **1** (mp 238 °C) with a cone conformation was synthesized from 5,11,17,23-tetra-*tert*-butyl-25,27-dipropoxycalix[4]arene-26,28-diol and identified by IR, ^{1}H NMR, and elemental analysis.[7]



FT-IR spectroscopy of **1** (chloroform, room temperture) gave two ν_{NH} bands at 3390 and 3303 cm^{-1} in a 1.0:1.5 intensity ratio. The intensity ratio was scarcely affected by the concentration (2.5-60 mM). The monomeric analogue, N-(2-pyridyl)-phenoxyacetamide gave a ν_{NH} band at 3395 cm^{-1}, which was also unaffected by the concentration (10-100 mM). Since the hydrogen-bonded ν_{NH} band appears at 3330-3060 cm^{-1}, the results support the views that the two ν_{NH} bands are assigned to the "free" and the "intramolecularly-hydrogen-bonded" NH, respectively and that both **1** and the monomeric analogue exist discretely at this concentration range.

The above-mentioned proposals were further supported by ^{1}H NMR measurements. The δ_{NH} ($CDCl_3$:CD_3CN = 9:1 v/v, -50 °C) for **1** appeared at 10.21 ppm, much lower magnetic field than the δ_{NH} for the monomeric analogue (9.79 ppm). Since the hydrogen-bonded OH and NH protons tend to shift to lower magnetic field,[8] the result implies that the NH protons in **1** are subject to the intramolecular hydrogen-bonding interaction. At -50 °C, the addition of $NaClO_4$ (1.25 mM) gave new signals for **1**·Na^+ complex separated from those for free **1** (Fig. 1): the δ_{NH} for free **1** and **1**·Na^+ complex appeared at 10.21 and 9.61 ppm, respectively. The up-field shift for **1**·Na^+ complex evidences that the intramolecular hydrogen-bonds are partly disrupted. When γ-butyrolactam (BL, specific guest for **1**: 40 mM) was added, only the NH signal for **1**·Na^+ complex moved to lower magnetic field (11.35 ppm). The results substantiate a view that a "closed" receptor site in **1** is switched by the metal-binding to an "open" receptor site (as in scheme 1). It is known that in calix[4]aryl tetraesters and tetraamides the four carbonyls are turned outward to reduce electrostatic repulsion among carbonyl oxygens whereas bound Na^+ changes the exo-annulus carbonyls to the endo-annulus carbonyls to bind Na^+ ion.[9] Similarly in this system, intramolecular hydrogen-bonds including carbonyl groups are

disrupted so that the carbonyl groups can coordinate to Na^+ ion. In other words, a "closed" NHPy receptor site can be activated to an "open" receptor site by a metal-switch.[10]



Scheme 1

We confirmed by ^1H NMR that **1** is totally converted to the Na^+ complex in the presence of 2 equiv. $NaClO_4$ (*i.e.*, [**1**] = 2.5 mM, [$NaClO_4$] = 5.0 mM). Under this condition we determined δ_{NH} as a function of BL concentration. As shown in Fig. 2, δ_{NH} shifted to lower magnetic field with increasing BL concentration and finally reached a plateau. From analysis of the plot by an equation $\mathbf{1} + nBL \rightleftharpoons \mathbf{1}\cdot BL_n$ ($K = [\mathbf{1}\cdot BL_n] / [\mathbf{1}]\,[BL]^n$), we obtained n = 2, supporting that "open" **1** is capable of binding two guest molecules. We could determine K_1 (= [**1**·BL] / [**1**] [BL]) and K_2 (= [**1**·BL_2] / [**1**·BL] [BL]: $K = K_1K_2$) separately by nonlinear least-squares method[11]: $K_1 = 1.32 \times 10^2\ M^{-1}$ and $K_2 = 1.05 \times 10^2\ M^{-1}$. Since two association constants are similar, the binding process is non-cooperative.

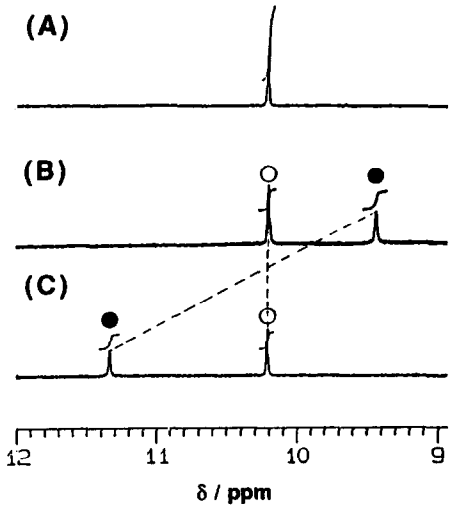


Fig. 1. ^1H NMR spectra of (A) **1** (2.5 mM),(B) **1** + $NaClO_4$ (1.25 mM), (C) **1** + $NaClO_4$ + BL (40 mM). ○ and ● denote signals assignable to free **1** and **1**·Na^+ complex, respectively. For measurement conditions see text.

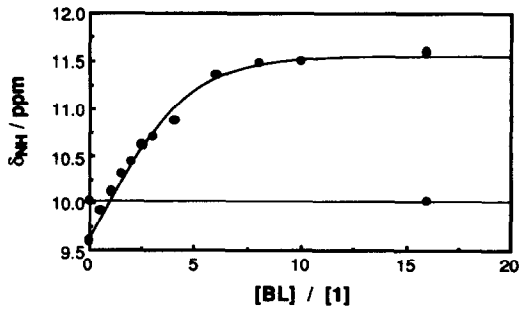


Fig. 2. Plots of δ_{NH} against BL concentration: ○ free **1** + BL, ● **1**·Na^+ complex + BL. For measurement conditions see text.

In conclusion, the present study demonstrated a "metal-switched" on-and-off system in molecular recognition. The behavior is similar to the allosteric effect frequently seen in a biological system. We are currently trying to design "switched-on" molecular receptors which feature more sensitive and more drastic changes in the guest-binding.

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7. IR (Nujol) ν_{NH} 3280 cm^{-1} and $\nu_{C=O}$ 1675 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, room temperture) δ 0.58 (CH_3, t, 6H), 0.98 and 1.23 (Bu^t, s each, 18H each), 1.62 (CCH_2C, m, 4H), 3.25 and 4.48 ($ArCH_2Ar$, d (J = 12.7 Hz) each, 4H each), 3.90 (OCH_2C, t, 4H), 4.73 (OCH_2CO, s, 4H), 7.00 and 7.26 (ArH. s each, 4H each), 7.26, 7.56, 7.94, and 8.31 (PyH, q, q, d, and d, 2H each). Found: C, 76.30; H, 8.04; N, 5.57%. Calcd for $(C_{32}H_{40}O_3N_2)_2$: C, 76.77; H, 8.05; N 5.60%.
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