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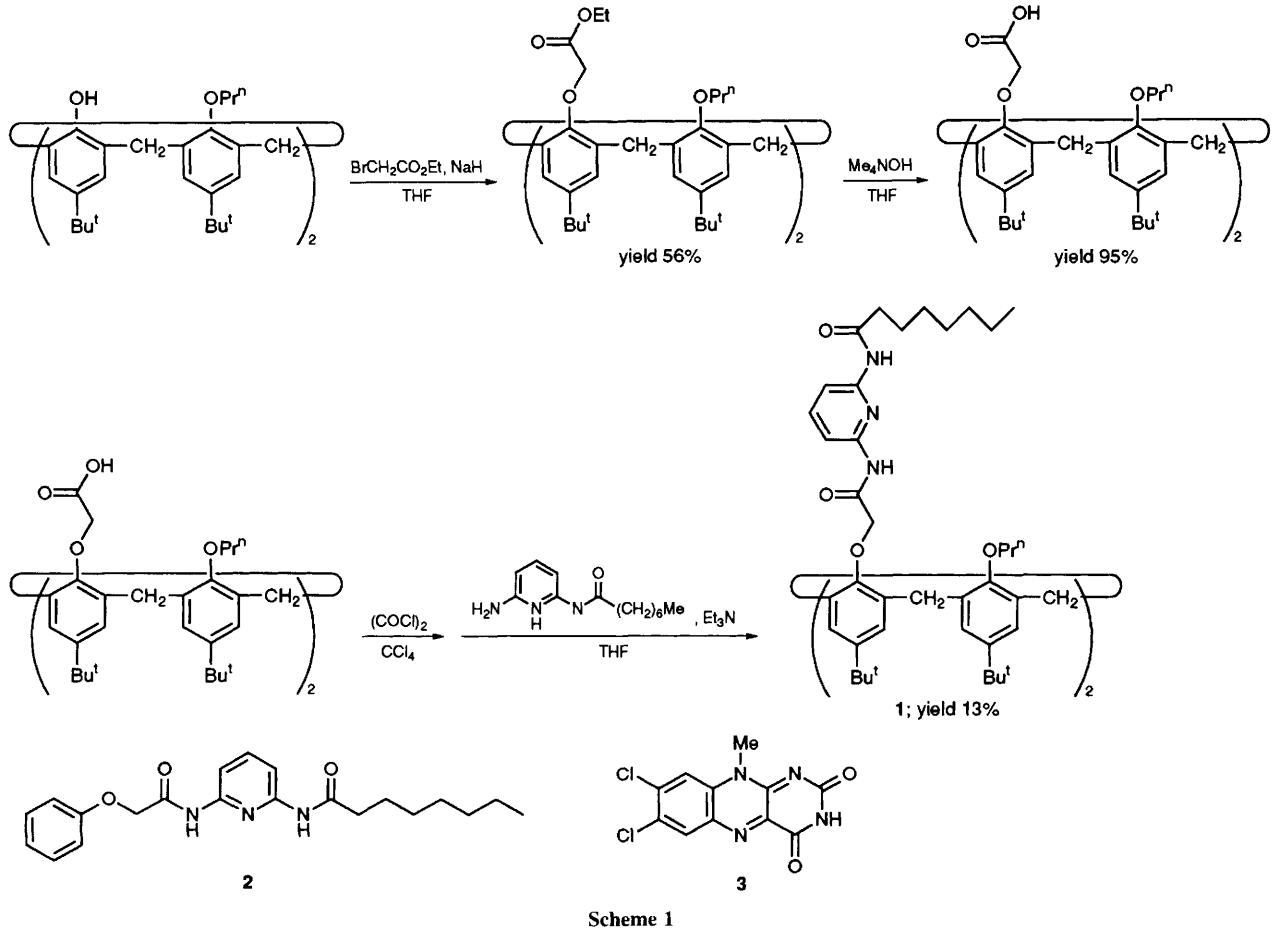
Metal-induced Conversion of a 'Closed' Receptor to an 'Open' Receptor on a *p-tert*-Butylcalix[4]arene Diamide Derivative; Fluorescence Detection of a Molecular Recognition Process

Hiroto Murakami and Seiji Shinkai*

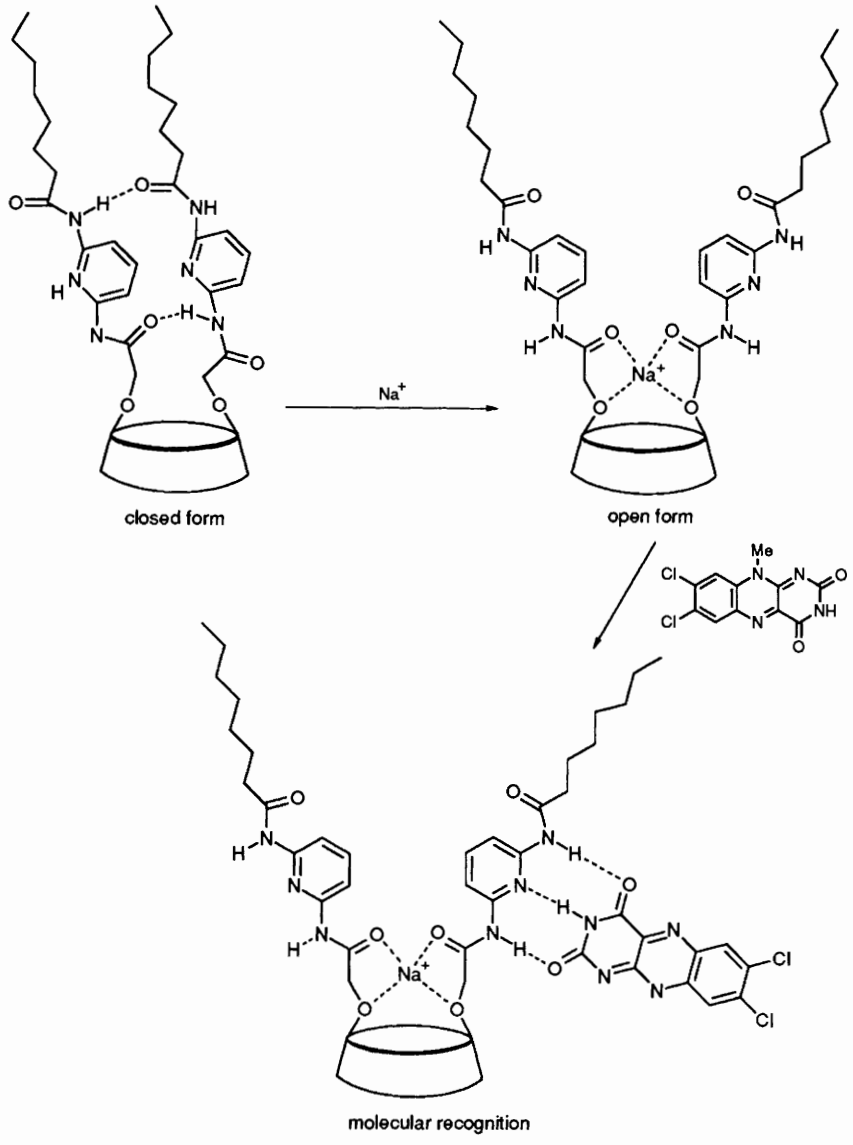
Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan

Molecular receptors, which change from a 'closed' form with intramolecular hydrogen bonds to an 'open' form with intermolecular hydrogen bonds with a pteridine guest upon Na^+-binding designed on a calix[4]arene platform are described; the conversion process is monitored easily by a fluorescence change in a flavin guest.

The molecular design of artificial receptors that can precisely recognise and specifically bind guest molecules has recently become a very active area of research. From the literature reported so far molecular recognition is achieved mainly through hydrogen-bonding interactions.[1–4] However, the artificial receptor bearing both hydrogen-bond donors and hydrogen-bond acceptors within a molecule inevitably tends to associate intramolecularly. To avoid such undesired association, a hard segment is inserted between the donor and the acceptor so that the two sites cannot form intramolecular hydrogen bonds. This limitation frequently hampers the design of artificial receptors with a structure complementary



Scheme 1



Scheme 2

to the guest molecule. More recently, Adrian and Wilcox[5] have designed a flexible receptor which features a conformational change from a 'closed' form to an 'open' form upon the guest binding. This stimulated us to design a new artificial receptor in which an 'open' form is generated from a 'closed' form only when it perceives a 'stimulus'. We already know that in calix[4]aryl esters and amides the four carbonyl groups are turned outwards to reduce electrostatic repulsion among carbonyl oxygens whereas bound Na^+ changes the *exo*-annulus carbonyls to the *endo*-annulus carbonyls to trap a Na^+ ion.[6] We thus considered that the metal-induced structural change can be useful to generate an 'open' form from a 'closed' form.

Compound **1** was synthesized according to Scheme 1 and identified by ^1H NMR and IR spectroscopy and elemental analysis.† The ^1H NMR spectra indicated that **1** is immobilized to a cone conformation (*i.e.* oxygen-through-the-annulus rotation is inhibited). As a functional group for molecular recognition we utilized a 2,6-diaminopyridine unit developed by Hamilton *et al.*[4] We arranged this molecular recognition site on a metal-binding site composed to two $ArOCH_2C(=O)$ groups.[7]

FTIR spectroscopy of a reference compound (**2**, chloroform, room temp., [**2**] = 30–300 mmol dm^{-3}) gave two ν_{NH} bands at 3400 and 3420 cm^{-1}. Under similar conditions **1** gave two ν_{NH} bands at 3275 (shoulder) and 3310 cm^{-1}; these bands were scarcely affected by the concentration change (2.0–50 mmol dm^{-3}). The distinct shift to the low frequency region and the fact that no concentration dependence was observed for **1** support the view that the 2,6-diaminopyridine groups form intramolecular hydrogen bonds. ^1H NMR spectra (−30 °C, $CDCl_3:CD_3CN$ = 9:1 v/v) support further this formation: **2** gave two singlet resonances at δ 8.05 and 8.79 and **1** at δ 9.22 and 10.24. The distinct shift to lower magnetic field observed for **1** is rationalized in terms of hydrogen-bonding interactions.[8]

Here, we have examined whether bound Na^+ is capable of disrupting the intramolecular hydrogen bonds. In ^1H NMR spectroscopy, addition of $NaClO_4$ gave new proton signals separately from those of uncomplexed **1** (Fig. 1). The NH

† *Selected data* for **1**: m.p. 193–194 °C; ν_{max} (Nujol)/cm^{-1} 3310 (NH) and 1690 (C=O); δ ($CDCl_3$, 25 °C, 250 MHz) 0.37 (6 H, t, $OCCCH_3$), 0.86 and 1.36 (18 H each, s each, Bu^t), 0.87 (6 H, t, COC_6CH_3), 1.3–1.4 [20 H, m, $COCC(CH_2)_4C$ and $OCCH_2C$], 1.71 (4 H, m, $COCCH_2$], 2.42 [4 H, t, $COCH_2$], 3.29 and 4.46 (4 H each, d each, $ArCH_2Ar$), 3.37 (4 H, t, OCH_2), 5.13 (4 H, s, OCH_2CO), 6.58 and 7.18 (4 H each, s each, ArH), 7.33, 7.60 and 8.06 (2 H each, d, q and d, PyH), 9.07 and 10.08 (2 H each, s each, NH). Satisfactory elemental analyses were obtained.

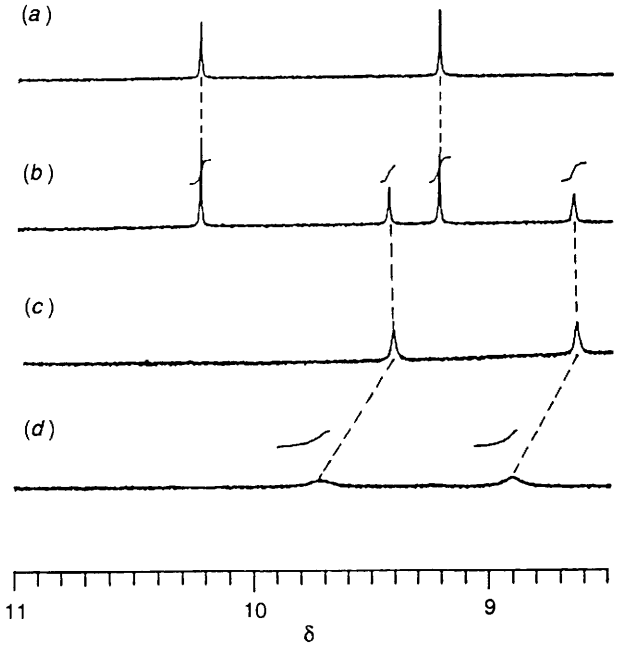


Fig. 1 Partial ^{1}H NMR spectra for NH protons (conc./mmol dm^{-3}): (*a*) **1** (2.50), (*b*) **1** (2.50) + $NaClO_4$ (1.25), (*c*) **1** (2.50) + $NaClO_4$ (2.50) and (*d*) **1** (2.50) + $NaClO_4$ (2.50) + **3** (0.18): −30 °C, $CDCl_3$:CD_3CN = 9:1 v/v, 400 MHz. The concentration of **3** could not be increased because of the poor solubility.

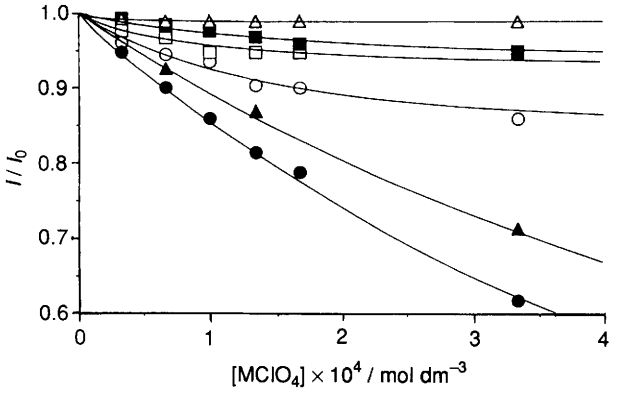


Fig. 2 Plots of I/I_0 *vs.* [$MClO_4$]; 30 °C, [**1**] = 1.00 mmol dm^{-3}, [**3**] = 1.00 × 10^{-5} mol dm^{-3}, $CHCl_3$:MeCN = 30:1 v/v, excitation wavelength 350 nm, emission wavelength 513 nm; ○ $LiClO_4$, ● $NaClO_4$, ▲ $NaClO_4$ and H_2O (180 mmol dm^{-3}), □ $KClO_4$, ■ $CsClO_4$ and △ $Bu^nMe_3NClO_4$

protons for the **1**·Na^+ complex appeared at δ 8.65 and 9.44, which shift to higher magnetic field by 0.57–0.80 ppm. We then added 7,8-dichloro-10-methylisoalloxazine **3** which has a pteridine moiety complementary to a diaminopyridine group.[8–10] The NH proton signals for the **1**·Na^+ complex shifted to a lower magnetic field (δ 8.90–9.75) whereas those for uncomplexed **1** were scarcely affected (Fig. 1). From these findings the following switching process can be illustrated: the Na^+-binding to the metal-recognition site induces the rotation of the carbonyl groups, which disrupts the intramolecular hydrogen bonds and eventually changes the 'closed' form to the 'open' form (Scheme 2).

It is known that flavins show strong fluorescence emission and when the pteridine moiety interacts with the 2,6-diaminopyridine unit through three hydrogen bonds, the singlet excited state is efficiently quenched.[9–11] This fluorescence

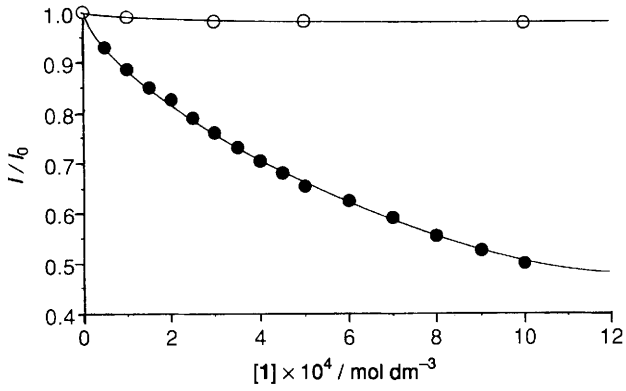


Fig. 3 Plots of I/I_0 vs. [**1**]: 30 °C, [**3**] = 1.00 × 10^{-5} mol dm^{-3}, [$NaClO_4$] = 0 mmol dm^{-3} (○) or 1.00 mmol dm^{-3} (●), $CHCl_3$:MeCN = 30:1 v/v. Other conditions as in caption to Fig. 2.

change is useful to detect the interaction between **1** and **3**. Fig. 2 shows the relative fluorescence intensity of **3** (I/I_0) against [$MClO_4$] (where M^+ = Li^+, Na^+, K^+, Cs^+ and $Bu^nMe_3N^+$); it can be seen that the Na^+ ion, which is specifically bound to calix[4]aryl esters and amides,[12] can effectively open the molecular recognition site. In Fig. 3, we plotted I/I_0 against [**1**] while the concentrations of **3** (1.00 × 10^{-5} mol dm^{-3}) and $NaClO_4$ (1.00 × 10^{-3} mol dm^{-3}) were maintained constant. It is expected that the **1**·Na^+ complex can accept two **3**s, but under the present conditions (*i.e.* [**1**] >> [**3**]) the major species should have the 1:1 stoichiometry. Thus, the plot was analysed according to the Benesi–Hildebrand equation for a 1:1 complex. We obtained a association constant K_a = 1200 dm^3 mol^{-1}, which is comparable with those in the similar systems (*e.g.* 2800 dm^3 mol^{-1} for 2,6-bis(acetylamino)pyridine and 10-*n*-hexylisoalloxazine).[9] On addition of water, the magnitude of the fluorescence decrease became smaller owing to interference in the interaction of **1** with **3** through the hydrogen bonds. Such a fluorescence decrease was negligible in the absence of $NaClO_4$.

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References

1 T. R. Kelly, C. Zhao and G. J. Bridger, *J. Am. Chem. Soc.*, 1989, **111**, 3744 and references cited therein.
2 M. C. Etter and D. A. Adsmond, *J. Chem. Soc., Chem. Commun.*, 1990, 589.
3 J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 245.
4 S.-K. Chang, D. V. Engen, E. Fan and A. D. Hamilton, *J. Am. Chem. Soc.*, 1991, **113**, 7640 and references cited therein: for a review see A. D. Hamilton, *Bioorg. Chem. Front.*, 1991, **2**, 115.
5 J. C. Adrian, Jr. and C. S. Wilcox, *J. Am. Chem. Soc.*, 1992, **114**, 1398.
6 I. Aoki, T. Sakaki and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1992, 730 and references cited therein; A. Arduini, E. Ghidini, A. Pochini and R. Ungaro, *J. Inclusion Phenom.*, 1988, **6**, 119.
7 Molecular receptors without a 'switch-function' have been constructed on the lower rim (T. Arimura and S. Shinkai, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1896) or on the upper rim (J.-D. van Loon, R. G. Janssen, W. Verboom and D. N. Reinhoudt, *Tetrahedron Lett.*, 1992, **33**, 5125).
8 K. Araki, K. Iwamoto, S. Shinkai and T. Matsuda, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 3480 and references cited therein.
9 S. Shinkai, G.-X. He, T. Matsuda, A. D. Hamilton and H. S. Rosenzweig, *Tetrahedron Lett.*, 1989, **30**, 5895.
10 Y. Yano, N. Tamura, K. Mitsui and T. Nabeshima, *Chem. Lett.*, 1989, 1655.
11 Y. Aoyama, K. Mizokami and H. Toi, *Chem. Lett.*, 1990, 651.
12 M.-J. Schwing and M. A. McKervey, *Top. Inclusion Sci.*, 1991, **3**, 149.