Cooperative Control of Ion and Molecular Recognition by Molecular Assembling

Tatsuya Nabeshima,*,† Takayoshi Takahashi,‡ Takeshi Hanami,† Akihiro Kikuchi,‡ Tohru Kawabe,‡ and Yumihiko Yano‡

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan, and Department of Chemistry, Gunma University, Kiryu, Gunma 376-8515, Japan

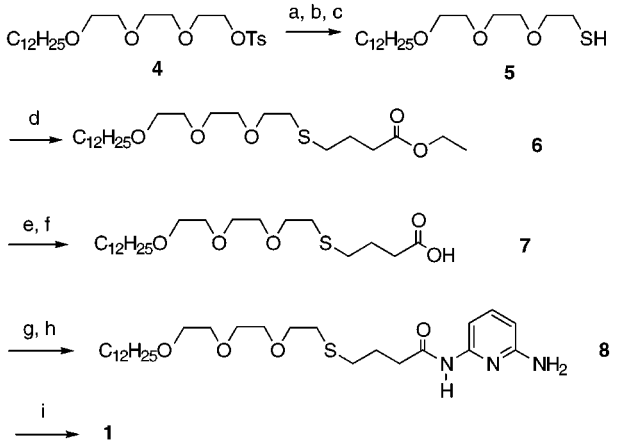
Received March 4, 1998

Cooperative control of molecular and ion recognition is one of the most important regulatory processes in metabolism.[1] Thus, many studies of artificial binding systems have been carried out to clarify the cooperative mechanisms and their application.[2−4] We now report the synthesis of a novel host **1** which exhibits cooperative behavior in molecular and ion recognition. We also present a concept of changing generations of artificial hosts to create a new molecular function different from the previous generation.[5]

Upon complexation of **1** with **2** via multiple hydrogen bonding,[6] the generated new host, **1·2** complex, was expected to show a binding ability toward alkali metal ions, if the three polyether chains are assembled and oriented in the same direction to make a new binding site for the metal ion (Figure 1). CPK model examination for **1·2** complex suggests that the three polyether chains of **1** and **2** are assembled to wrap a metal ion well. The number of oxygen atoms in the polyether chain was determined to be three because a single nonassembled polyether chain containing more than four oxygen atoms shows binding ability toward alkali metal ions.[7] In this case the binding strength of **1** with respect to **2** should be increased in the presence of Na^+ due to the interaction between the ion and the polyether chains, as compared to the absence of any such interaction. In the new system, the first generation host **1** captures guest **2**, and the **1·2** complex thus formed is considered to be a second generation host, because the latter is an ionophore.

The host **1** was prepared according to Scheme 1. The interaction between **1** and **2** was examined by ^{1}H NMR. The amide protons (H_a, H_b) of **1** were shifted downfield with the addition of the guest **2** in $CDCl_3$ (Figure 2). These changes are ascribed to formation of six hydrogen bonds between the host and guest, as shown in Figure 1. The association constants (K_a) with guests (**2**, **3**) were determined from the shifts of H_a (or H_b) using a nonlinear-least-squares method. The K_a values for **2** and **3** are 1400 and 1600 M^{-1}, respectively (Table 1). The difference between the substituents of the guests does not influence the values significantly. In the presence of 1 equiv of $Na^+[B(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_4]^-$ (**9**), **1·2** complexation due to the hydrogen bonding on the addition of **2** was more enhanced. The ^{1}H NMR spectra of 1:1 mixtures of **1** and **2** in the presence and absence of **9** show that the ratios of the host−guest complexes to free **1** are 5.8 and 0.97, respectively. The large enhancement of the ratio in the presence of Na^+ suggests that there is an effective cation−dipole interaction which makes the **1·2** complexation favorable. In **3**, however, an opposite effect of Na^+ on the ratio was observed. Hence, **9** decreased the hydrogen bonding strength between **1** and **3**, probably because the polarity of the solution increased due to the addition of **9**. This change also indicates that a cation−dipole interaction of the **1·3** system is quite small. The results presented here suggest that (1) the oriented and assembled three polyether chains of the host and guest are in the same direction to form a much more effective recognition site for metal ions, and that (2) the two chains are not sufficient to provide such a binding site in this system, although the two chains can approach each other more closely upon complexation compared to free **1**.

Scheme 1[a]



[a] Reagents and conditions: (a) thiourea, EtOH/H_2O, reflux, 20 h; (b) KOH, H_2O, reflux, 24 h; (c) H_2SO_4 (74% from **4**); (d) ethyl 4-bromobutylate, NaH, THF, rt, 5 h (84%); (e) NaOH, EtOH/H_2O; (f) HCl (89% from **6**); (g) $(COCl)_2$, CH_2Cl_2/DMF, 50 °C, 4 h; (h) 2,6-diaminopyridine, Et_3N, THF, rt, 3 h (83% from **7**); (i) glutaryl chloride, Et_3N, THF, rt, 19 h (76%).

Table 1. Binding Strength of 1 Determined by ^{1}H NMR (500 MHz) Titration in $CDCl_3$

	K_a (M^{-1}) (α = [**1**·guest complex]/[free **1**])	
guest	without Na^+	with Na^+
2	1400 ± 100[a]	nd[d]
	α = 0.97[b]	α = 5.8[c]
3	1600 ± 100[a]	nd[d]
	α = 1.0[b]	α = 0.69[c]

[a] [**1**] = 1.25×10^{-3} M. [b] [**1**] = [**2**] = 1.25×10^{-3} M. [c] [**1**] = [**2**] (or [**3**]) = [**9**] = 1.25×10^{-3} M. [d] Not determined because accurate binding constants of a ternary complexes including Na^+ could not be obtained.

† University of Tsukuba.
‡ Gunma University.

(1) (a) Cantor, C. R.; Schimmel, P. R. *Biophysical Chemistry*; Freeman: New York, 1980; Vol. I. (b) Perutz, M. F. *Mechanism of Cooperativity and Allosteric Regulation in Proteins*; Cambridge University Press: Cambridge, 1990.

(2) (a) Rebek, J., Jr. *Acc. Chem. Res.* **1984**, *17*, 258−264. (b) Tabushi, I. *Pure. Appl. Chem.* **1988**, *60*, 581−586. (c) Nabeshima, T. *Coord. Chem. Rev.* **1996**, *148*, 151−169.

(3) (a) Nabeshima, T.; Inaba, T.; Furukawa, N. *Tetrahedron Lett.* **1987**, *28*, 6211−6214. (b) Nabeshima, T.; Inaba, T.; Furukawa, N.; Hosoya, T.; Yano, Y. *Inorg. Chem.* **1993**, *32*, 1407−1416.

(4) (a) Ebmeyer, F.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1148−1150. (b) Schneider, H.-J.; Ruf, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1159−1160. (c) Schneider, H.-J.; Werner, F. *J. Chem. Soc., Chem. Commun.* **1992**, 490−491. (d) Sijbesma, R. P.; Nolte, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 6695−6696. (e) Toupance, T.; Ahsen, V.; Simon, J. *J. Am. Chem. Soc.* **1994**, *116*, 5352−5361.

(5) Nabeshima, T.; Tamura, N.; Kawazu, T.; Sugawara, K.; Yano, Y. *Heterocycles* **1995**, *41*, 877−881.

(6) (a) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035−5036. (b) Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318−1319. (c) Tecilla, P.; Dixon, R. P.; Slobodkin, G.; Alavi, D. S.; Waldeck, D. H.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9408−9410. (d) Tecilla, P.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1990**, 1232−1234. (e) Yano, Y.; Tamura, N.; Mitsui, K.; Nabeshima, T. *Chem. Lett.* **1989**, 1655−1658. (f) Tamura, N.; Mitsui, K.; Nabeshima, T.; Yano, Y. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2229−2237.

(7) (a) Irie, M.; Kato, M. *J. Am. Chem. Soc.* **1985**, *107*, 1024−1028. (b) Schepartz, A.; McDevitt, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 5976−5977.

S0022-3263(98)00406-X CCC: $15.00
Published on Web 05/20/1998

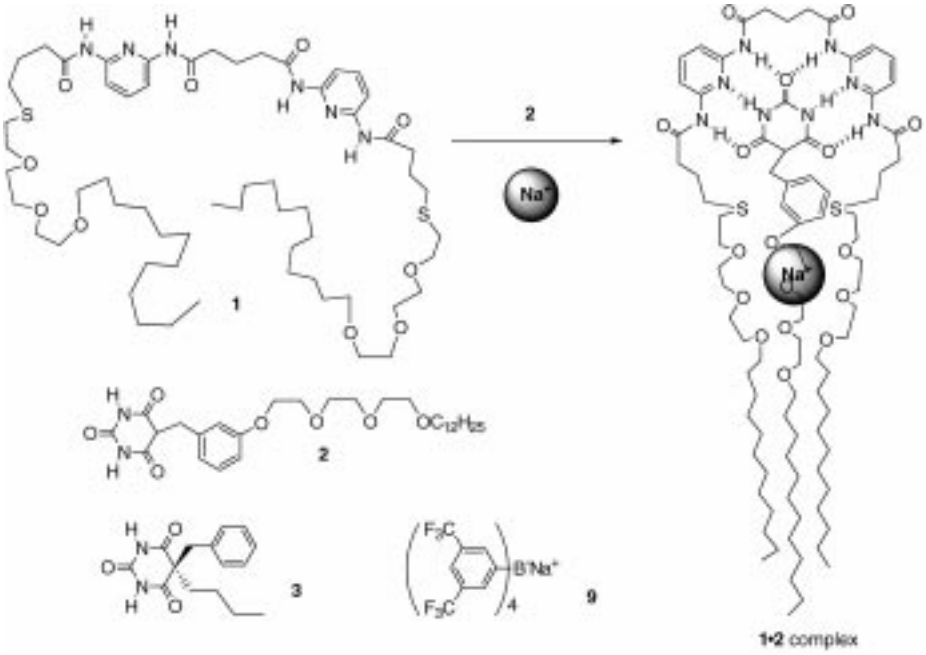


Figure 1. Formation of a second host (**1·2** complex) from a first host (**1**) due to hydrogen bonding.

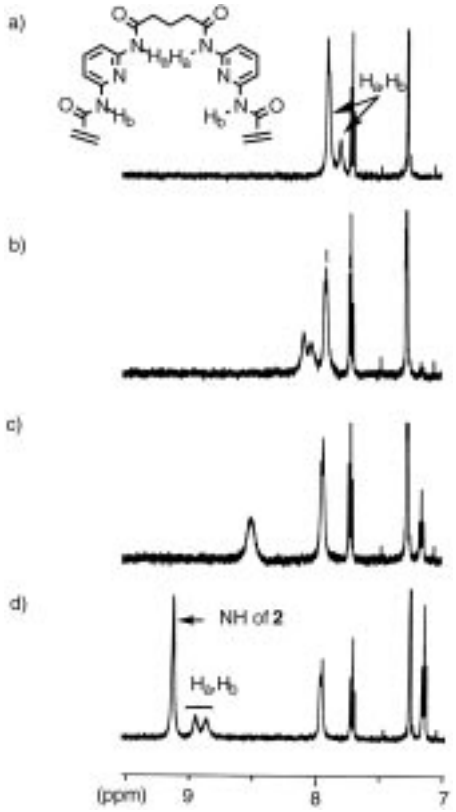


Figure 2. ^{1}H NMR spectral changes of **1** by the addition of **2**. [**1**] = 1.25×10^{-3} M in $CDCl_3$ (500 MHz). (a) Without **2**. (b) **1**:**2** = 1:0.25. (c) 1:1. (d) 1:3.

Ion transport experiments through a liquid membrane[3] also supported the formation of the binding site for alkali metal ions in the presence of **1** and the guest **2**. The amounts of sodium picrate transported in the receiving phase were determined by electronic absorption spectroscopy. Faster transport was observed by the use of a 1,2-dichloroethane solution containing **1** and **2** (1:1), compared to **1** or **2** alone. The overall enhancement of Na^+ ion transport (after 100 h) by **1·2** mixture is ca. 2.5 and 4-fold

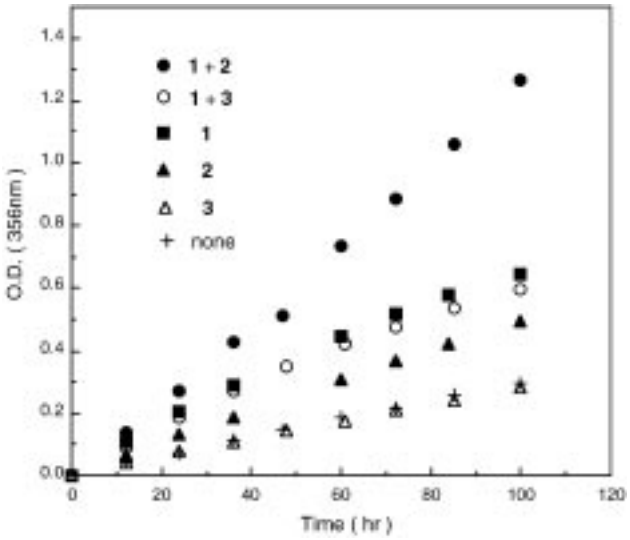


Figure 3. Transport of Na^+ by **1** and guests (**2**, **3**). A double cylindrical cell was used for the transport (ref 3). Source phase: $Na_2HPO_4-NaH_2PO_4$ buffer, 4 mL, [picric acid] = 0.01 M, pH 6.9. Receiving phase: distilled H_2O, 40 mL. Organic phase: CH_2ClCH_2Cl, 50 mL, [carrier] = 2×10^{-4} M, 25 °C, stirring rate: 200 rpm.

compared to **1** and **2**, respectively, when the amount of the control experiment is taken into account (Figure 3). The amounts of Na^+ transported by the mixture of **1** and **2** are larger than the sum of those carried by **1** or **2** alone. These results also strongly suggest that a new binding site for alkali metal ions is formed in the **1·2** mixture. An ESI-MS spectrum of a mixture of **1·2·**Na^+ shows the isotope pattern of M^+ for the complex ($[C_{88}H_{148}N_8O_{17}S_2Na]^+$) which is in good accordance with the theoretical one.

Acknowledgment. We thank Associate Professor Dr. Ernst Horn of the University of Tsukuba for reviewing the English text.

Supporting Information Available: Details of the synthetic procedures, ^{1}H and ^{13}C NMR data for **1**, **2**, and **5**−**8**, and ESIMS data of **1·2·**Na^+ (11 pages).

JO980406I