The First Competitive Formation of [4] and [2]Supercyclodextrins by Self-Association of an α-Cyclodextrin Bearing a Bisazophenol Group

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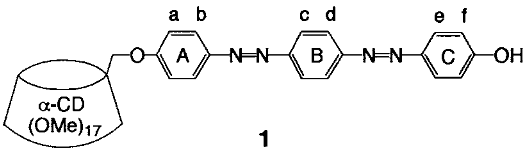
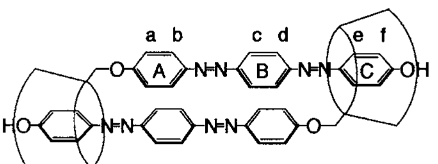
A new lipophilic α-cyclodextrin **1** bearing a bisazophenol group as an internal guest self-associates to form a cyclic dimer **2** and the first [4]supercyclodextrin **3p** competitively, and the two successive association equilibria have been first analyzed.

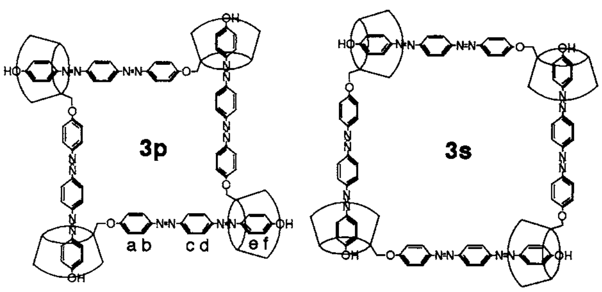
A wide variety of supermolecules have been prepared from cyclodextrin (CD) building blocks[1] with the unique shape like a bottomless flowerpot.[2] Very little attention, however, has been paid to synthetic works on cyclic CD oligomers[3] in which we have been interested since we considered possible loop structures for the self-aggregates of a 2:1 α-CD–azophenol system.[4] Interesting physicochemical properties, especially new functions and high stability would be expected for the new supramolecular cyclic array. Recently, we have synthesized and characterized the first α-CD face-to-face or cyclic dimers,[5] namely the smallest members of such cyclic n-mers which are called here "[n]supercyclodextrins". This paper describes the competitive self-association of 6^A-*O*-[4-(4-(4-hydroxyphenylazo)phenylazo)phenyl]-substituted permethylated α-CD (**1**) to [2] and [4]supercyclodextrins **2** and **3p**, respectively.



1



2



The desired compound **1**[6] was obtained in 46% yield by the reaction of 6^A-*O*-tosyl permethylated α-CD[3] with an excess of 1,4-bis(4-hydroxyphenylazo)benzene[7] in *N*,*N*-dimethylformamide at 80 °C for 24 h.

^{1}H NMR spectra of **1** are susceptible to the conditions such as solvent, temperature, and concentration (Figure 1). Such variable spectra can be explained by means of two successive association equilibria involving two different complexes **2** and **3p** in addition to uncomplexed **1** as mentioned below. The first equilibrium to the first complex **2** is already established at ambient temperature in CD_3OD which allows to occur decomplexation at 55 °C. In 4:1 $CD_3OD–D_2O$ (Figure 1e), the equilibrium shifts to the complexation to give a spectrum of almost pure **2** with six clear doublets. These signal appearances indicate that the six aromatic rings in **2** free-rotate fast on the NMR time scale; contrary, the exchange rate is slow.

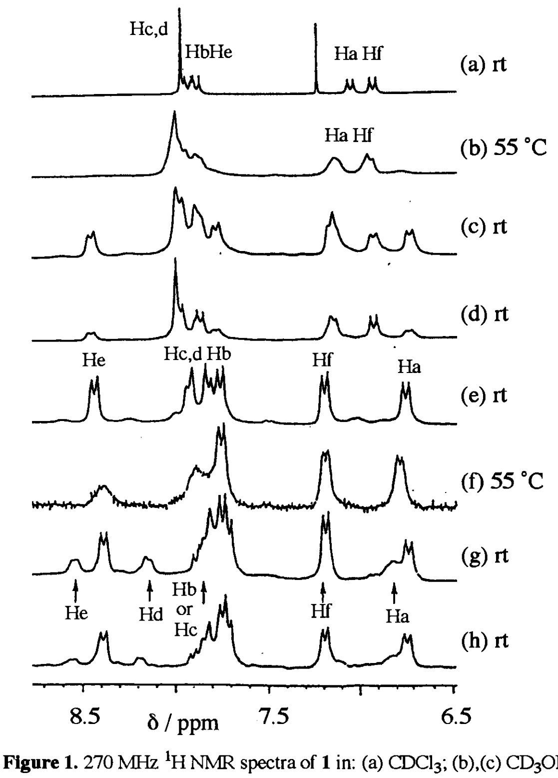


Figure 1. 270 MHz ^{1}H NMR spectra of **1** in: (a) $CDCl_3$; (b),(c) CD_3OD, 4.08 mM; (d) CD_3OD, 1.36 mM; (e) 4:1 CD_3OD-D_2O, 4.08 mM; (f),(g) 1:1 CD_3OD-D_2O, 4.08 mM; (h) 1:1 CD_3OD, 2.04 mM.

The second equilibrium between **2** and the second complex **3p** was found to be established at ambient temperature in 1:1 $CD_3OD–D_2O$ where the latter is less stable than the former at higher temperature and at lower total concentration of the monomer (Figure 1f–h). Attempts to increase the contents of **3p** by raising the D_2O contents and the total concentration were unsuccessful because of the solubility problem. It is quite reasonable, however, that there are no complexes other than **2** and **3p**, because one can recognize five of the six signals expected for **3p** at near 8.55, 8.15, 7.85 (overlapped), 7.20 (overlapped), and 6.80 ppm as shown in Figure 1g.

As described above, the first and second equilibria correspond to the cases of x = 1 and 2 of Eq 1 in Scheme 1, respectively. To evaluate the association numbers of the complexes by concentration-dependent NMR experiments, we have refined the previous method[5] and led Eq 6[8] from which we obtained the values of 1.92 ± 0.03 and 4.09 ± 0.15 as association numbers of **2** and **3p**, respectively.[10] Thus, the first and second complexes have been identified with [2] and [4]supercyclodextrins. To our knowledge, this evaluation is the first successful analysis of the two successive self-association equilibria.

$$ySx \xrightleftharpoons{K} xSy \quad (1) \qquad C_0 = x[Sx] + y[Sy] \quad (2)$$

$$K = \frac{[Sy]^x}{[Sx]^y} \quad (3) \qquad I_0 = \frac{Iy}{Ix} = \frac{y\,[Sy]}{x\,[Sx]} \quad (4) \qquad [Sx] = \frac{C_0}{x(1+I_0)} \quad (5)$$

$$y \cdot \ln \frac{[Sx]_j}{[Sx]_i} = x \cdot \ln \frac{C_{0j} - x[Sx]_j}{C_{0i} - x[Sx]_i} \quad (6)$$

Scheme 1. A general two-component self-association equilibrium: [Sx], concentration of x-mer Sx; [Sy], concentration of y-mer Sy; C_0, total concentration of monomer S_1. The suffixes "i" and "j" mean the entry number in the concentration-dependent experiments.

The aromatic protons of **2** were assigned by HH-COSY and NOESY experiments in 4:1 CD_3OD–D_2O and CD_3OD, respectively. The appearances of three diagonal cross peaks due to Ha–Hb, Hc–Hd, and He–Hf correlations and of three exchange peaks between **1** and **2** (Ha,e,f) are compatible with the assignment shown in Figure 1e. The large upfield shift of Ha (−0.41 ppm) after the dimerization resembles those observed with the other [2]supercyclodextrins[5] with the unique layered structure. The downfield shifts of He (+0.59) and Hf (+0.23 ppm) provide the strong evidence for the binding aromatic ring "C", not "B", with the CD cavity in **2**. This selective inclusion of the ring is probably due to the solvent effects by which the lipophilic molecular surface exposed to the hydrophilic surroundings is forced to diminish.

For the [4]supercyclodextrin, there are two possible isomers **3p** and **3s** where all the guest parts are inserted from the primary faces (p-mode) and the secondary ones (s-mode), respectively. In order to judge which isomer is acceptable, further experiments of HH-COSY, selective decoupling, NOESY, and differential NOE have been performed. Unfortunately, we do not succeed in getting any useful sign with respect to the five ^{1}H signals described above. However, the p-mode has great advantage over the s-mode when one takes into account the most rational possible mechanism for the formation of **3** from **2**, that is, **3p** can be formed from two molecules of **2** without complete dissociation to the monomers, in other words, **2** comes loose to result the corresponding linear dimer which can dimerize to **3p**, however **3s** can not. Thus, we suggest the structure **3p** for the [4]supercyclodextrin. The tentative assignment shown in Figure 1g is consistent with **3p** whose aromatic rings "C" are also bound with the CD cavities. The cyclic tetramer is the first example for higher homologues of [n]supercyclodextrins and creates a new large cavity where a porphyrin molecule can enter.

References and Notes

1 G. Wenz, *Angew. Chem., Int. Ed. Engl.*, **33**, 803 (1994).
2 a) A. Harada, J. Li, and M. Kamachi, *Nature*, **370**, 126 (1994) and references cited therein. b) Z. Chen, J. S. Bradshow, Y. Habata, and M. L. Lee, *J. Heterocycl. Chem.*, **34**, 983 (1997) and references cited therein. c) S. A. Nepogodiev and J. F. Stoddart, *Chem. Rev.*, **98**, 1959 (1998) and references cited therein. d) A. Ueno, A. Ikeda, H. Ikeda, T. Ikeda, and F. Toda, *J. Org. Chem.*, **64**, 382 (1999) and references cited therein. e) F. M. Raymo and J. F. Stoddart, *Chem. Rev.*, **99**, 1643 (1999) and references cited therein.
3 The following paper discussed the self-association of mono-6-(alkylamino)-β-CDs to cyclic oligomers: R.C. Petter, J. S. Salek, C. T. Sikorski, G. Kumaravel, and F.-T. Lin, *J. Am. Chem. Soc.*, **112**, 3860 (1990).
4 J. H. Jung, C. Takehisa, Y. Sakata, and T. Kaneda, *Chem. Lett.*, **1996**, 147.
5 T. Fujimoto, Y. Uejima, H. Imaki, N. Kawarabayashi, J. H. Jung, Y. Sakata, and T. Kaneda, *Chem. Lett.*, **2000**, 564.
6 **1**: orange solid, mp 154–157 °C. Anal. Found: C, 54.34; H, 7.09; N, 3.21%. Calcd for $C_{71}H_{106}N_4O_{31}$+$3H_2O$: C, 54.46; H, 7.21; N, 3.58%. TOF-MS (*m/z*) 1534 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$, 23 ˚C): δ 7.96 (s, 4H), 7.92 (d, *J*=8.9 Hz, 2H), 7.88 (d, *J*=8.9 Hz, 2H), 7.06 (d, *J*=8.9 Hz, 2H), 6.93 (d, *J*=8.9 Hz, 2H), 5.10–4.97 (m, 6H, CD-H_1), 4.50–3.05 (m, 6H, CD-H).
7 H. A. J. Schoutissen, *J. Am. Chem. Soc.*, **55**, 4541 (1933).
8 Usually, fast self-association equilibria such as hydrogen bonding have been studied by NMR methods.[9] Here, we consider a relatively slow equilibrium between x-mer S_x and y-mer S_y of monomer S_1 as shown in Scheme 1. The apparent equilibrium constant *K* and the stoichiometric equation are given by Eqs 2 and 3. When the components exhibit their own ^{1}H NMR signals independently just like the present case, the ratio I_0 of the integrated intensities for the corresponding signals is represented by Eq 4. Combining Eqs 2 and 3, and 3 and 4 give Eqs 5 and 6, respectively. Thus, we can obtain "y" using the function of "x" and "y", if "x" could be available.
9 K. A. Connors, in "Binding Constants," John Wiley & Sons, New York (1987), Chap. 5, p. 189.
10 The following sets for C_0 and [Sx] in Eq 6 were used for the calculation: (4.08, 2.20), (2.72, 1.64), and (1.36, 0.97) for **2**, and (4.08, 1.38), (2.04, 0.80), and (0.91 mM, 0.40 mM) for **3p**.