

The First Lipophilic Face-to-Face Dimers of Permethylated α -Cyclodextrin-Azobenzene Dyads through a *p*-Xylylene Spacer

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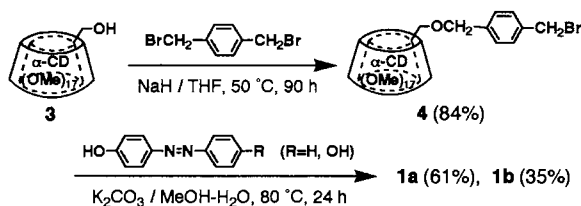
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The synthesis of two new permethylated α -cyclodextrin derivatives **1** and their self-association to stable lipophilic face-to-face dimers **2** are described.

The research on cyclic cyclodextrin (CD) oligomers where several CD monomers self-associate to form a cyclic array only by noncovalent bond would offer not only an approach to elucidate the chemical events where supermolecules¹ are concerned, but also the basic information which is useful, when molecular devices and machines² are designed. Recently, we have observed the self-association of an α -CD bearing an azobenzene moiety to the first well-characterized hydrophilic face-to-face dimer which is very stable in water at room temperature.³ In order to judge whether the self-association to face-to-face or cyclic dimers is a general or special phenomenon, we have designed and synthesized new lipophilic monomers **1** composed of a permethylated α -CD as host, an azobenzene moiety as internal guest⁴ and a *p*-xylylene spacer inserted between the two. This paper deals with the first synthesis of lipophilic face-to-face dimers **2** from **1**.

Reaction of permethylated α -CD monoalcohol **3**⁵ with an excess of 1,4-bis(bromomethyl)benzene gave the corresponding monobromide **4**⁶ in 84% yield. The desired compounds **1a**⁶ and **1b**⁶ were obtained in 61 and 35% yields, respectively, by etherification of the reactive precursor **4** with azophenols under basic conditions.



The self-association of the monomers **1** has been examined by the solvent-, temperature-, and concentration-dependent ¹H NMR methods. In CD₃OD, an additional species already exists at room temperature (Figure 1b). The minor species which can be seen as at least four separated doublets disappeared com-

pletely at 55 °C and the spectrum similar to that recorded in CDCl₃ was obtained (Figure 1a). Thus, the major species is allowed to assign to uncomplexed **1**. At higher concentration, however, the minor species as a complex increases in its contents (Figure 1c), suggesting the occurrence of intermolecular association. Finally, it should be emphasized that the complex exists as a single species in 1:1 CD₃OD-D₂O (Figure 1d). The appearance of the six clear doublets demonstrates that the complex must be a symmetrical cyclic n-mer where the three aromatic rings in each side arm free-rotate faster than the NMR time scale; in contrast to this, the exchange rate is slower. Unfortunately, the vapor pressure osmometry to estimate the molecular weight is unable to apply to mixed solvent systems. However, the fact that the complexed and uncomplexed species exhibit their own signals enables us to determine the association number *n*=2 as described below.

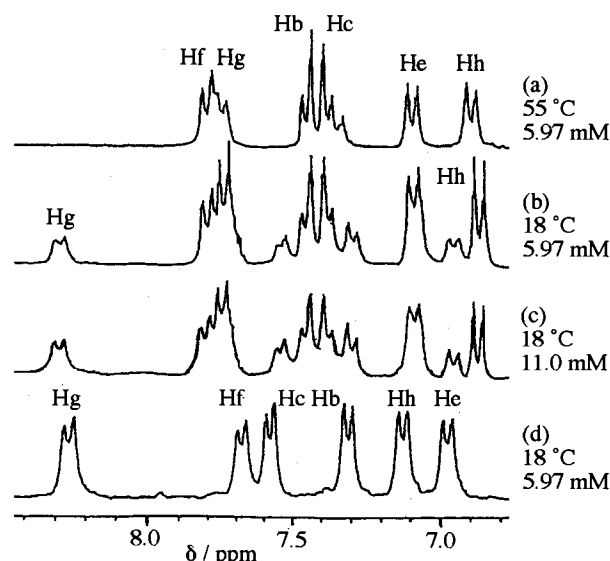
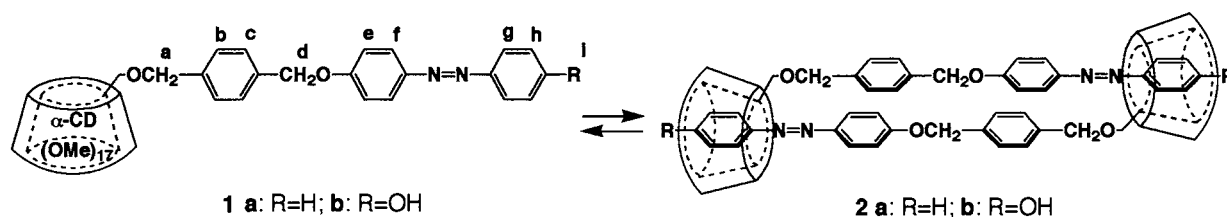
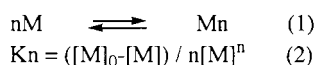


Figure 1. 270 MHz ¹H NMR spectra of **1b**: (a)-(c) in CD₃OD; (d) in 1:1 CD₃OD-D₂O.



Assuming a monomer M associates to form only a single n -mer M_n (Eq (1)), the K_n is represented:



$$K_n = ([M]_0 - [M]) / n[M]^n \quad (2)$$

where $[M]$ is the monomer concentration at an equilibrium state and $[M]_0$ the initial concentration of the monomer. Here the value of $[M]$ is calculated with both the known value $[M]_0$ and the ratio $[M]:[M_n]^8$ which is given simply by taking the ratio of integrated intensities for the corresponding signals, ex. Hg and Hh in Figure 1b. Thus for each n , a value of K_n can be obtained from Eq (2). The results are summarized in Table 1. We have selected $n=2$ with $K_n=29.0$ (av.) because the association constant should be independent on the initial monomer concentration.

Table 1. The association constants K_n for **2b** calculated from Eq. (2)

$[M]_0$ mM	$K_n / (10^{n-1} \cdot M^{n-1})$				
	$n=$	1	2	3	4
11.0	0.43	2.79	24.2	236	2660
5.50	0.28	3.27	50.8	888	32100
3.67	0.17	2.65	56.4	1330	900000

The aromatic protons of **2b** could be assigned by HH-COSY and NOESY experiments in 1:1 CD_3OD-D_2O and CD_3OD , respectively. The appearance of three diagonal cross peaks due to Hb-Hc, He-Hf, and Hg-Hh correlations and of four sets of exchange peaks between **1b** and **2b** (He-h) is compatible with the assignment shown in Figure 1d. The chemical shift differences on the dimerization are listed in Table 2. The table also contains the data on the compound **1a** to which all the treatments of the foregoing were applied successfully. It is worthwhile to point out that the dimerization of **1** brings about the chemical shift changes of almost the same magnitude. The remarkable downfield shifts of Hg suggest the proximity of the protons to the α -1,4-glucosidic oxygen atoms, whereas the appreciable upfield shifts of He may be attributed to the shielding effects due to the p -xylylene nucleus in the counterpart as expected from the unique layered structures **2**. Similar up- and downfield shifts were also observed with a hydrophilic face-to-face dimer.³

Table 2. Chemical shift differences, $\Delta\delta=\delta(2)-\delta(1)$ in ppm

Compound	Hb	Hc	He	Hf	Hg	Hh
a	+0.10	-0.05	-0.15	-0.10	+0.55	+0.15
b	+0.08	-0.08	-0.14	-0.06	+0.54	+0.22

Finally, which would one expect to be the more stable, cyclic dimer **2a** or **2b**? To solve the question, the association constants for **2** were determined in 6:1 CD_3OD-D_2O at 18 °C: K_a , 130 for **2a** and $540 M^{-1}$ for **2b**. Thus, the latter stabilizes 4.5 times further than the former. Additional studies would be necessary to understand the roles of the terminal hydroxyl substituent for the stabilization.

In conclusion, we have demonstrated that the 6^A-monosubstituted permethylated α -CD derivatives self-associate to the stable lipophilic face-to-face dimers. Such dimerization must be a general phenomenon in appropriate 1:1 CD-internal guest systems.

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References and Notes

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- 4 For azobenzene-containing supramolecular complexes: M. Asakawa, P. R. Ashton, V. Balzani, C. L. Brown, A. Credi, O. A. Matthews, S. P. Newton, F. R. Raymo, A. N. Shipway, N. Spencer, A. Quick, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Chem. Eur. J.*, **5**, 860 (1999) and references cited therein.
- 5 J. H. Jung, C. Takehisa, Y. Sakata, and T. Kaneda, *Chem. Lett.*, **1996**, 147.
- 6 **1a**: orange solid, mp 121–123 °C. Anal. Found: C, 58.30; H, 7.09; N, 1.98%. Calcd for $C_{73}H_{110}N_2O_{31}$: C, 58.00; H, 7.33; N, 1.85%. FAB-MS (m/z): 1536 $[M+Na]^+$. ¹H NMR (270 MHz, $CDCl_3$, 23 °C): δ 7.92 (d, $J = 8.9$ Hz, 2H, Hf), 7.87 (d, $J = 7.7$ Hz, 2H, Hg), 7.53–7.35 (m, $J = 8.3$ Hz, 7H, Hh,c,b,i), 7.08 (d, $J = 9.0$ Hz, 2H, He), 5.14 (s, 2H, Hd), 5.08–5.04 (m, 6H, CD-H1), 4.65 (dd, 2H, Ha), 3.96–3.16 (m). **1b**: yellow powder, mp 146–150 °C. Anal. Found: C, 56.15; H, 6.83; N, 2.02%. Calcd for $C_{73}H_{110}N_2O_{32}+2H_2O$: C, 56.06; H, 7.35; N, 1.79%. MALDI-TOF-MS (m/z): 1553 $[M+Na]^+$. ¹H NMR (270 MHz, $CDCl_3$, 23 °C): δ 7.85 (d, $J = 9.0$ Hz, 2H, Hf), 7.82 (d, $J = 8.8$ Hz, 2H, Hg), 7.39 (AB, $J = 8.3$ Hz, 4H, Hb,c), 7.05 (d, 2H, $J = 9.0$ Hz, He), 6.92 (d, $J = 8.8$ Hz, 2H, Hh), 5.12 (s, 2H, Hd), 5.08–5.04 (m, 6H, CD-H1), 4.64 (AB, $J = 12$ Hz, 2H, Ha), 3.96–3.16 (m). **4**: white foam, mp 220–225 °C. Anal. Found: C, 52.79; H, 7.10; Br, 5.47%. Calcd for $C_{61}H_{101}O_{30}Br$: C, 52.56; H, 7.30; Br, 5.73%. TOF-MS (m/z): 1417 $[M+Na]^+$. ¹H NMR (270 MHz, $CDCl_3$, 23 °C): δ 7.33 (AB, $J = 7.6$ Hz, 4H, ArH), 5.05 (m, 6H, CD-H1), 4.62 (AB, $J = 12$ Hz, 2H, ArCH₂O), 4.49 (s, 2H, ArCH₂Br), 3.94–3.16 (m).
- 7 This assumption is supported by the fact that no chemical shift changes were observed within the error in a range of concentration, 6.0–0.32 mM, indicating no additional fast exchange process causing a weighted average of the relevant resonance frequencies. An excellent review for the studies on fast self-association equilibria such as hydrogen bonding is available: K.A. Connors, in "Binding Constants," John Wiley & Sons, New York (1987), Chapt. 5, p. 189.
- 8 $[M_n]$: the n -mer concentration at an equilibrium state.