"Molecular Magic''. Formation of a Self-inclusion Complex from a Dumbbell-shaped Permethylated β-Cyclodextrin Derivative

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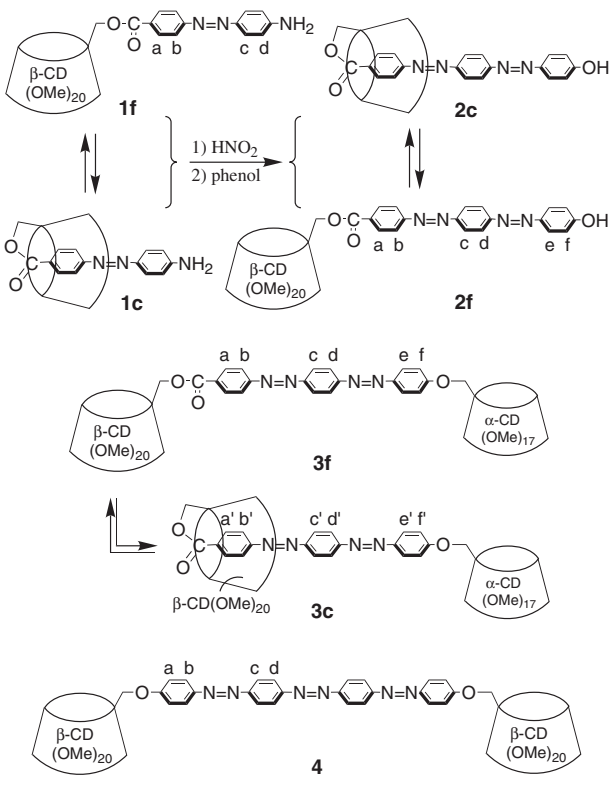
Hermaphroditic permethylated β-cyclodextrins **1f** and **2f** and the relevant dumbbell-shaped CD dimers **3f** and **4** were synthesized and their intramolecular complexation was examined by ^{1}H NMR methods. The dumbbell **3f** was found to isomerize to a self-inclusion complex **3c** at room temperature in CD_3OD, but not **4**. The isomerization was explained by means of a "somersault mechanism," which involves turning the glucose bearing the internal guest through 360°.

Cyclodextrins (CDs), cyclic oligomers of α-D-glucopyranose are versatile, highly potential starting materials for supramolecular architecture because of their inclusion ability.[1] This complexing ability is due to a unique shape like a bottomless flowerpot that is stabilized by the systematic intramolecular O-2···O-3′ hydrogen bonds, and all the glucose units exclusively take the normal, so-called $^4C_1$ chair conformation.[2] On the other hand, such stabilization is absolutely impossible in fully functionalized CDs. The question then arises: to what extent are permethylated CD frameworks flexible? Harata,[3] Carira,[4] and Saenger[5] and collaborators visualized the deformed CD geometries that included a glucose unit with a $^0S_2$ skew-boat conformation, with a $^1C_4$ chair one, or as being flipped in the crystalline state. In solution, a similar glucose flipping, leading to an intramolecular inclusion complex in this case, was suggested by Lehn et al.[6] Bradshaw et al. discussed a mechanism involving the rotation of a substituted glucose unit about its glucosidic oxygen atoms to explain equilibration between two conformational isomers of 6^A,6^B-bis-*O*-[*p*-(allyloxy)phenyl]heptakis(2,3-di-*O*-methyl)-β-CD *under basic conditions*.[7] We report here the first, conclusive evidence for a glucose rotation of 360°, as an answer to the above question, through which a dumbbell-shaped molecule **3f** underwent isomerization to an intramolecular complex **3c**.

A new hermaphroditic permethylated β-CD **1f**[8] was prepared in 90% yield by a similar method to that for the corresponding α-CD analogue.[9] The aniline derivative was azo-coupled with phenol to yield another hermaphrodite **2f**[8] (78%) with an elongated guest part. By a reaction with 6-monotosyl permethylated α-CD,[10] the phenol **2f** was converted to an (α,β)-CD heterodimer **3f**[8] (84%). Similarly, a (β,β)-CD homodimer **4**[8] (68%) was obtained from the corresponding tosylate[10] and 4-[4-[4-(4-hydroxyphenylazo)phenylazo]-phenylazo]phenol.[11]

Hermaphroditic permethylated β-CD monomers **1f** and **2f** never showed any positive evidence for self-associative complexation in lipophilic media as expected. In CD_3OD-D_2O solvent systems, however, we encountered a complicated phenomenon involving a competitive formation between an intramolecular[12] and presumably a dimeric[9] complex. Attempts to isolate the complex **2c** by azo-coupling **1c** with phenol were unsuccessful; **2f** was the only product identified (Scheme 1). Furthermore, the intramolecular complexation observed with **2f** seemed to be strange because its linear rigid guest part would be too long to enter the CD cavity from the primary face. Therefore, a special CD dimer **3f**, whose guest end is surely blocked with a duly bulky α-CD skeleton to result in a dumbbell-shaped molecule, was examined.



Scheme 1.

The aromatic protons of **3f** were easily assigned as shown in Figure 1a on the basis of the Ha-Hb and Hf-He correlations observed by selective decoupling in $CDCl_3$. The Hc and Hd were tentatively assigned under consideration of substitution effects due to the ester and ether groups on the conjugated π-system. When the dumbbell was dissolved in CD_3OD at room temperature, unexpectedly and rather surprisingly, it isomerized to a sterically "incredible" self-inclusion complex **3c**. The two species composed an equilibrium mixture and exhibited the individually separated peaks for their aromatic protons (Figure 1b). The ratio of **3c**:**3f** determined by peak integrations showed no concentration-dependency, supporting intramolecular com-

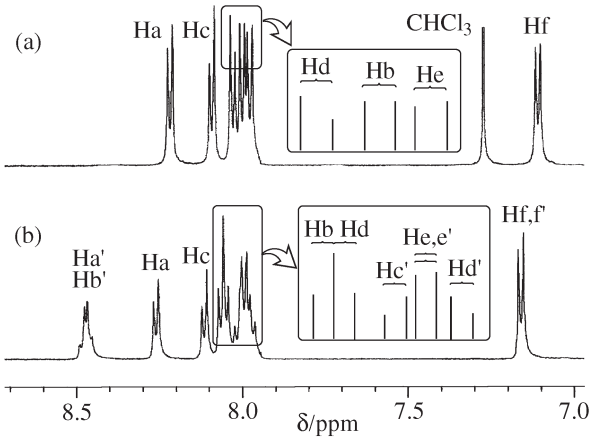


Figure 1. The aromatic region of 600 MHz ^{1}H NMR spectra of: (a) **3f** in $CDCl_3$ and (b) a CD_3OD solution of **3f**.

plexation, and it gave a formation constant for **3c**: K_a (CD_3OD, 21 °C) 0.55.

The ^{1}H NMR spectrum of the equilibrium mixture could be assigned as follows. The peaks were grouped to each species on the basis of the facts that the complexation became predominant in more hydrophilic media and the decomplexation proceeded at higher temperature. The correlations of Ha-Ha′ and of Ha-Hb, Hf-He, and Hf′-He′ were observed by NOESY and by selective decoupling, respectively. The self-inclusion of **3f** brought about the chemical shift changes, $\Delta\delta$ (CD_3OD): +0.21 (Ha′), +0.41 (Hb′), −0.10 (Hc′),[13] and −0.08 (Hd′);[13] almost no changes in the protons outside the cavity. The remarkable down-field shift by 0.41 ppm of Hb′ suggested the proximity of the protons to the α-1,4-glucosidic oxygen atoms, according to our empirical rule.[9] The four protons on the benzoate ring of **3c** appeared as a pair of doublets as well as **3f**, indicating that the free-rotation of the aromatic ring was fast on the NMR time-scale, even in the CD cavity. In contrast to **3f**, a symmetrical dumbbell molecule **4**, with the only ether junction between the host and guest, did not form any kind of complexes.

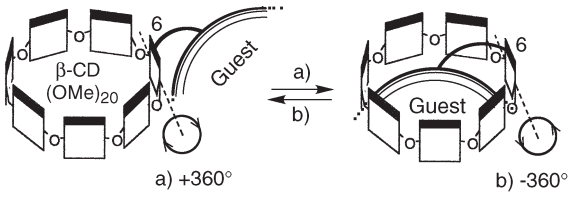


Figure 2. A schematic representation of a "somersault mechanism" to generate the self-inclusion complex **3c** from **3f**. Each panel represents a permethylated glucose unit.

At first the spontaneous conversion of **3f** to **3c** seemed to be magic due to its dumbbell structure until we notice the following "somersault mechanism" for such isomerization. As shown in Figure 2, the mechanism involves turning one formal somersault of the glucose panel bearing the internal guest, or rather a cooperative rotation among the peripheral glucoses. This mechanism provides the only way to produce **3c** from **3f** and probably **2c** from **2f**. It seems to be characteristic of permethylated β-CD frameworks with a 6-ester junction known to date, and demonstrates the unexpected flexibility of the frameworks.

This paper is dedicated to Emeritus Professor Soichi Misumi on the occasion of his 77th birthday.

References and Notes

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8 **1f**: orange foam, mp 140–143 °C (dec). Anal. Found: C, 54.65; H, 7.74; N, 2.58%. Calcd. for $C_{75}H_{119}N_3O_{36}$: C, 54.97; H, 7.32; N, 2.56%. MALDI-TOFMS: *m/z* 1661 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$, selected data): δ 8.16 (d, *J* = 8.6 Hz, 2H, *Ha*), 7.87 (d, *J* = 8.6 Hz, 2H, *Hb*), 7.83 (d, *J* = 8.6 Hz, 2H, *Hc*), and 6.74 (d, *J* = 8.6 Hz, 2H, *Hd*). **2f**: reddish orange solid, mp 142–144 °C (dec). Anal. Found: C, 55.41; H, 7.08; N, 2.93%. Calcd. for $C_{81}H_{122}N_4O_{37}$: C, 55.79; H, 7.05; N, 3.21%. MALDI-TOFMS: *m/z* 1766 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$, selected data): δ 8.19 (d, *J* = 8.6 Hz, 2H, *Ha*), 8.03 (d, *J* = 8.6 Hz, 2H, *Hc*), 7.97 (d, *J* = 8.6 Hz, 4H, *Hb*, *d*), 7.86 (d, *J* = 8.6 Hz, 2H, *He*), 6.96 (d, *J* = 8.6 Hz, 2H, *Hf*). **3f**: reddish orange solid, mp 145–148 °C (dec). Anal. Found: C, 54.24; H, 7.31; N, 1.60%. Calcd. for $C_{134}H_{214}N_4O_{66}\cdot 2H_2O$: C, 54.13; H, 7.39; N, 1.88%. MALDI-TOFMS: *m/z* 2960 $[M+Na]^+$. ^{1}H NMR (600 MHz, $CDCl_3$, selected data): δ 8.22 (d, *J* = 8.8 Hz, 2H, *Ha*), 8.09 (d, *J* = 8.8 Hz, 2H, *Hc*), 8.03 (d, *J* = 8.8 Hz, 2H, *Hb*), 8.00 (d, *J* = 8.8 Hz, 2H, *Hd*), 7.98 (d, *J* = 8.8 Hz, 2H, *He*), 7.10 (d, *J* = 8.8 Hz, 2H, *Hf*). **4**: red solid, mp 166–169 °C (dec). Anal. Found: C, 55.19; H, 7.59; N, 2.22%. Calcd. for $C_{148}H_{234}N_6O_{70}$: C, 55.25; H, 7.33; N, 2.61%. MALDI-TOFMS: *m/z* 3240 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$, selected data): δ 8.02 (d, *J* = 8.9 Hz, 4H, *Hd*), 7.98 (d, *J* = 8.6 Hz, 4H, *Hc*), 7.90 (d, *J* = 8.4 Hz, 4H, *Hb*), 7.02 (d, *J* = 8.9 Hz, 4H, *Ha*).
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12 The formation of **1c** and **2c**, which showed their independent signals, has been confirmed by the observation of no concentration dependency in the ^{1}H NMR spectra.
13 The protons were tentatively assigned, as were Hc and Hd of **3f** described above.

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