Synthesis and Characterization of the First Pair of an Unlocked and a Locked Self-inclusion Complex from a Permethylated α-Cyclodextrin Derivative

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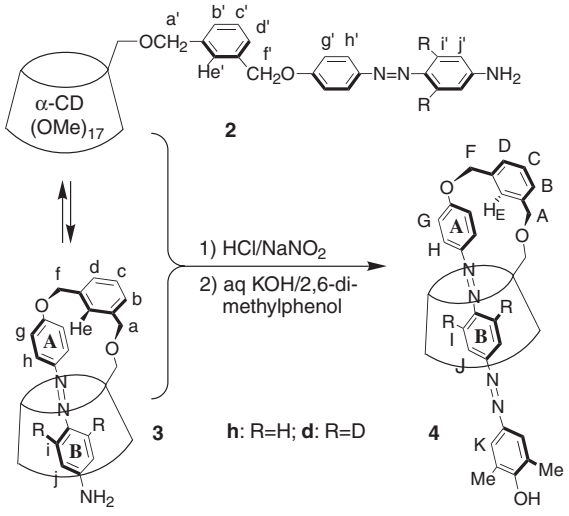
To examine self-inclusion phenomena, we intentionally synthesized the first pair of an unlocked and a locked self-inclusion complex, **3h** and **4h**, from a permethylated α-cyclodextrin-azobenzene dyad through an *m*-xylylene spacer. A d_2-labeled complex **4d** was also prepared for decisive ^{1}H NMR spectral assignments. In both complexes, the guests were bound in the CD cavities in a similar manner, whereas the mutual orientation of the spacer and the nearest benzene ring was unexpectedly different.

Improved performance of chemical events such as artificial emzymatic catalysis[1] and chemical sensing actions based on Ueno's approach[2] has been achieved by relevant chemical modifications of cyclodextrins (CDs), cyclic oligomers of α-D-glucopyranose. One who deals with such modified CDs bearing a substituent as a side chain must always consider the effect of intramolecular complexation. Indeed, there have been a number of papers published concerning self-inclusion phenomena.[3] However, most of the self-inclusion complexes have not been characterized well because of their labile structures in solution. In 1996, Bradshaw et al. isolated the first stable complex formed accidentally via a "built-in"[4b] inclusion process on the bis-*O*-*p*-(allyloxy)phenoxylation of $6^A,6^B$-bis-*O*-(2,4-dimethoxybenzene-1,5-disulfonyl)heptakis(2,3-di-*O*-methyl)-β-CD.[4] In this paper, we describe the first intentional formation of a pair of an unlocked and a locked complex via a "self-satisfaction"[5] and a "stoppering" process, respectively, to obtain insights into rather common self-inclusion phenomena in the chemistry of cyclodextrin.

Reaction of 6-monohydroxy permethylated α-CD[6] with an excess of 1,3-bis(bromomethyl)benzene gave 6-*O*-[(3-bromomethylphenyl)methyl]-permethylated α-CD (**1**)[7] in 91% yield. The desired hermaphrodite CD **2h**[7] was synthesized with a 77% yield by etherification of the benzyl bromide with 4-amino-4′-hydroxyazobenzene. Similarly, a d_2-labeled compound **2d**[8] was also prepared from 4-nitroaniline-2,6-d_2[8,9] for the decisive assignments of the ^{1}H NMR spectra.

The self-inclusion phenomenon on **2h** has been examined by temperature-, solvent- and concentration-dependent ^{1}H NMR methods. A spectrum observed from a CD_3OD solution of the hermaphrodite at ambient temperature is understood in terms of an equilibrium mixture of two species, **2h** and its complex (Figure 1). The new species formed was identified with the expected self-inclusion complex **3h**[7] since the ratios of **2h**:**3h** at equilibrium showed no concentration-dependency in the same solvent and at the same temperature. At 55 °C, the decomplexation proceeded. When a more hydrophilic medium, 3:1 CD_3OD-D_2O had been used, **3h** formed quantitatively. Thus, the bent *m*-xylylene spacer between the host and guest parts led to the self-inclusion. This is in marked contrast to the previous face-to-face dimerization[10] from the *p*-counterpart with a straight spacer.



Scheme 1.

To lock the unlocked complex **3h** by stoppering the guest-end with a bulky group, the equilibrium mixture described above was treated with 2,6-dimethylphenol[11] under usual azo coupling conditions. After flush-column chromatographic purification, we obtained the desired locked self-inclusion complex **4h**[7] (22%) as a red solid, which is thermally stable up to 130 °C in DMSO-d_6. The corresponding d_2-labeled complex **4d**[8] was also prepared from **2d** by the same treatment.

The azo dye groups of the molecules in this study played important roles not only as guests, but ^{1}H NMR probes as exemplified below. The aromatic protons of **3h** were assigned by selective decoupling and differential NOE methods (Figure 1c). The self-inclusion resulted in the following changes in chemical shift, $\Delta\delta$ (CD_3OD): −0.59 (H_e), −0.09 (H_g), −0.25 (H_h), +0.48 (H_i), and +0.11 ppm (H_j). The up-field shift by 0.59 ppm of H_e is consistent only with the structure **3h** where the diamagnetic ring-current due to a benzene ring "A" can affect the proton. In the case of **4h**, where protons H_I and H_J are exposed to almost the same magnetic environments, the unequivocal assignment of the aromatic protons was established by using **4d** (Figure 1d). The fact that the signal due to the residual H_I of **4d** appeared at 8.54 ppm as a tiny doublet provides conclusive evidence for the assignment.

It was interesting to compare the geometries of the unlocked **3h** and the locked **4h** as a pair. In both complexes, the remarkable down-field shifts by 0.48 ppm of H_i and by ca. 0.5 ppm of H_I suggested the proximity of the protons to the

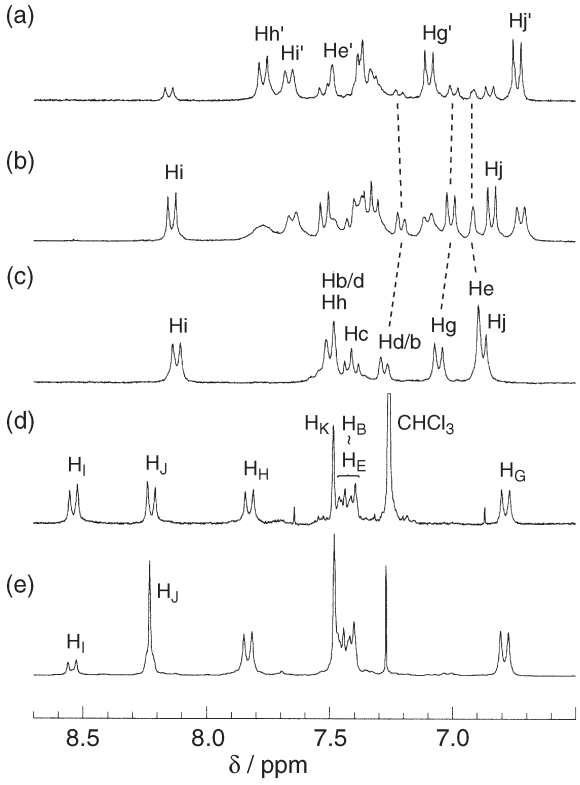


Figure 1. The aromatic region of 270 MHz ^{1}H NMR spectra of **2**-**4**:(a) a CD_3OD solution of **2h** at 55 °C; (b) at 23 °C; (c) **3h** in 4:1 CD_3OD-D_2O at 23 °C; (d) **4h** in $CDCl_3$ at 23 °C and (e) **4d**.

α-1,4-glucosidic oxygen atoms, according to our empirical rule.[12] Further, the eight protons on the "A" and "B" rings in each of **3h** and **4h** appeared as two pairs of doublets, indicating that the free-rotations of the rings were fast on the NMR time-scale despite the rigid *trans*-N=N double bond between the rings. On the other hand, in contrast with the remarkable up-field shift of H_e described above, H_E of **4h** showed almost no chemical shift change, although its precise chemical shift is unknown. This finding suggests that the H_E proton locates in the boundary between the shielding and deshielding regions due to the benzene ring "A." Therefore, there is an unexpected difference in the mutual orientation of the spacer and the nearest benzene ring. To understand this somewhat strange contrast, further studies are required.

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

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7 **1**: white foam, mp 212–215 °C. Anal. Found: C, 52.46; H, 7.44; Br, 5.87%. Calcd for $C_{61}H_{101}O_{30}Br$: C, 52.54; H, 7.30; Br, 5.73%. TOFMS (*m*/*z*) 1417 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.31-7.22 (m, 4H, *Ar*), 5.08 (m, 6H, CD-H_1), 4.60 (AB like, 2H, OCH_2Ar), 4.48 (s, 2H, CH_2Br), 3.94–3.16 (m, 73H). **2h**: orange solid, mp 115–118 °C. Anal. Found: C, 55.67; H, 7.18; N, 2.57%. Calcd for $C_{73}H_{111}O_{31}N_5{\cdot}3H_2O$: C, 55.47; H, 7.46; N, 2.66%. TOFMS (*m*/*z*) 1550 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.83 (d, $J = 8.9$ Hz, 2H, $H_{h'}$), 7.75 (d, $J = 8.9$ Hz, 2H, $H_{i'}$), 7.42 (s, 1H, $H_{e'}$), 7.35 (s, 3H, $H_{b'}$, $H_{c'}$, $H_{d'}$), 7.04 (d, $J = 9.2$ Hz, 2H, $H_{g'}$), 6.73 (d, $J = 8.9$ Hz, 2H, $H_{f'}$), 5.10 (s, 2H, $H_{f'}$), 5.10–5.07 (m, 6H, CD-H_1), 4.65 (AB like, 2H, $H_{a'}$), 4.03–3.14 (m, 100H). **3h**: ^{1}H NMR (270 MHz, 3:1 CD_3OD-D_2O): δ 8.12 (d, $J = 8.6$ Hz, 2H, H_i), 7.52-7.48 (m, 3H, H_h, H_b or H_d), 7.41 (t, $J = 7.4$ Hz, 1H, H_c), 7.28 (d, $J = 7.6$ Hz, 1H, H_d or H_b), 7.06 (d, $J = 8.6$ Hz, 2H, H_g), 6.90–6.86 (m, 3H, H_e, H_j), 5.20–4.64 (m, 10H, H_a, H_f, CD-H_1), 4.16-3.00 (m, 130H). **4h**: mp 159–162 °C. Anal. Found: C, 57.15; H, 6.73; N, 2.92%. Calcd for $C_{81}H_{118}O_{32}N_4{\cdot}2H_2O$: C, 57.37; H, 7.25; N, 3.30%. ESIMS (*m*/*z*) 1661 $[M+H]^+$. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.54 (d, $J = 8.6$ Hz, 2H, H_I), 8.22 (d, $J = 8.6$ Hz, 2H, H_J), 7.83 (d, $J = 8.9$ Hz, 2H, H_H), 7.49 (s, 2H, H_K), 7.46–7.40 (m, 4H, H_B, H_C, H_D, H_E), 6.79 (d, $J = 8.9$ Hz, 2H, H_G), 5.04 (AB like, 2H, H_F), 4.97–4.93 (m, 6H, CD-H_1), 4.82–4.49 (AB like, 2H, H_A), 4.14–3.04 (m, 110H), 2.35 (s, 6H, *Me*).
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