Preparation of Octakis(3,6-anhydro)-γ-cyclodextrin and Characterization of its Cation Binding Ability

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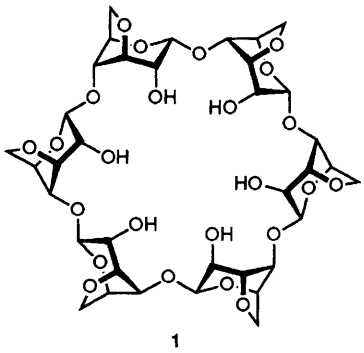
Octakis(3,6-anhydro)-γ-cyclodextrin **3** has been prepared by the reaction of octakis(6-*O*-tosyl)-γ-cyclodextrin with KOH; **3** shows a specific binding ability to alkali metal ions with larger ionic diameters, owing to its hydrophilic cavity which is similar to the layered crown ethers.

Cyclodextrins (CDs) are cyclic oligoglucosides which possess a hydrophobic cavity. Although ordinary cyclodextrins include hydrophobic guests,[1] there have been few derivatives which possess ion binding ability. In order to develop the science of artificial enzymes (or receptors) using CDs, derivatives which can bind and transport ionic species should be essential. We have previously prepared hexakis(3,6-anhydro)-α-CD **1** and heptakis(3,6-anhydro)-β-CD **2**, which consisted of six and seven 3,6-anhydroglucoses, respectively,[2] other research groups have also prepared **1** and **2**.[3] Because these 3,6-anhydro-CD derivatives possess hydrophilic cavities, we and other research groups have expected for them to exhibit strong cation binding abilities. In this report, we describe the preparation of this type of γ-CD derivative, octakis(3,6-anhydro)-γ-CD **3** which is composed of eight 3,6-anhydroglucoses and also the characterization of the cation binding abilities of **1**–**3**.

As the synthetic intermediate, octakis(6-*O*-tosyl)-γ-CD (tosyl = *p*-$MeC_6H_4SO_2$) was synthesized by the reaction of γ-CD with tosyl chloride in pyridine and purified by the use of aminopropyl-modified silica gel chromatography.[4] The octatosylate was treated with 1 mol dm^{-3} KOH–75% (aq) MeOH at 60 °C for 48 h, followed by reversed-phase chromatography giving **3** in 95.2% yield. ^1H and ^{13}C NMR spectra established the structure of **3** as octakis(3,6-anhydro)-γ-cyclodextrin.†

Complex formation between crown ether and metal cations has often been examined by use of fast atom bombardment mass spectrometry (FABMS) to determine the cation binding ability of the crown ether.[5] As secondary ion mass spectrometry (SIMS) is similar to FABMS, we estimated the cation binding abilities of 3,6-anhydro-CDs **1**–**3** using SIMS. Three identical solutions were prepared each containing equimolar amounts of Li^+, Na^+, K^+, Rb^+ and Cs^+ to which was added either **1**, **2** or **3**, and each solution was subjected to SIMS analysis. The observed intensity of the [3,6-anhydro-CD + metal]$^+$ peak in the SIMS spectrum was assumed to be proportional to the affinity of 3,6-anhydro-CD for the metal cation. As summarized in Table 1, all these 3,6-anhydro-CDs showed a binding ability to K^+, Rb^+ and Cs^+, while their affinity for the smaller ions, Li^+ and Na^+, was found to be negligible. Compound **3** binds the larger alkali metal cations more strongly, *i.e.* in the order; $Cs^+ > Rb^+ > K^+$. On the other hand, the order is reversed in the case of hexakis(3,6-anhydro)-α-CD **1** which possesses a smaller cavity than **3**. Heptakis(3,6-anhydro)-β-CD **2** has a cavity size intermediate between **1** and **3**, and binds Rb^+ the most strongly. In contrast to **1**–**3**, none of the ordinary CDs showed specific ion selectivities.

Since the conformation of the 3,6-anhydroglucose residue is restricted to $^1C_4$ by its intramolecular ether bridge, the cavities of **1**–**3** are cylindro-conically shaped with the primary hydroxy sides more open than the opposite sides, which possess axial secondary hydroxy groups pointing towards the inside of the cavities. The two types of hemiacetal oxygen atoms in the 3,6-anhydroglucose units are located at the inner surface of the 3,6-anhydro-CD constituting two layers of crown ether.



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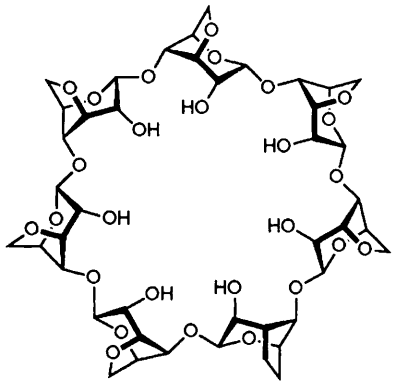

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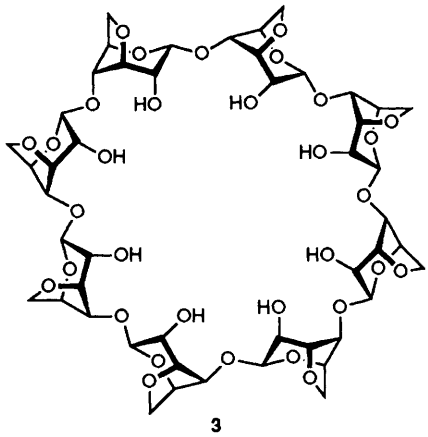
† ^1H NMR (200 MHz, D_2O) δ 3.94 (8H, br t, $J_{2,1}$ 3.0, $J_{2,3}$ 3.5 Hz, 2-H), 4.04 (8H, dd, $J_{6,5}$ 3.0, $J_{6,6'}$ 11.0 Hz, 6-H), 4.29 (8H, d, $J_{6',6}$ 11.0 Hz, 6'-H), 4.38 (8H, dd, $J_{4,3}$ 5.0, $J_{4,5}$ 2.5 Hz, 4-H), 4.48 (8H, br t, $J_{3,2}$ 3.5, $J_{3,4}$ 5.0 Hz, 3-H), 4.64 (8H, br s, 5-H), 5.32 (8H, d, $J_{1,2}$ 3.0 Hz, 1-H); ^{13}C NMR (50 MHz, D_2O) δ 70.4 (C-2), 71.3 (C-6), 73.9 (C-3), 76.7 (C-5), 79.3 (C-4), 100.5 (C-1). The result of secondary ionization mass spectrometry (SIMS) also supported the structure of **3**: *m/z* 1153 (M + H^+), 1175 (M + Na^+), 1191 (M + K^+).

Table 1 Relative abundances of alkali metal-incorporating 3,6-anhydro-CD ions[a] in SIMS spectra[b]

Alkali metal ion (ionic diameter[c]/Å)	Li^+ (1.36)	Na^+ (1.94)	K^+ (2.66)	Rb^+ (2.94)	Cs^+ (3.34)
3,6-Anhydro-CDs					
α-**1**	—[d]	—	47.5	34.7	17.8
β-**2**	—	—	24.8	38.5	36.7
γ-**3**	—	—	7.4	40.4	52.2

[a] Abundances are shown as the relative intensity of the corresponding peak to the sum of the intensities of [3,6-anhydro-CD + metal]$^+$ peaks in the spectrum. No ions corresponding to [3,6-anhydro-CD + H]$^+$ were observed in any of the spectra. The intensities for K^+ and Rb^+ were calculated as (the intensity of [3,6-anhydro-CD + $^{39}K]^+$) × 1.07 and (the intensity of [3,6-anhydro-CD + $^{85}Rb]^+$) × 1.39, respectively. [b] Aqueous solutions containing each of the 3,6-anhydro-CDs (**1** 1.16 × 10^{-2} mol l^{-1}, **2** 9.91 × 10^{-3} mol l^{-1} or **3** 8.67 × 10^{-3} mol l^{-1}) and all of alkali metal chloride (2.30 × 10^{-2} mol l^{-1}, respectively) were used as the analytical samples. [c] Ref. 6. [d] Not observed.



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The size and shape of this hydrophilic cavity may account for the observed ion selectivity of **1**–**3**.

These 3,6-anhydro-CDs possess specific cation binding abilities according to their hydrophilic cavities. They are considered as important materials to construct artificial enzymes (or receptors) which will maintain the cation binding ability. Further studies on the cation binding and cation transport ability of these 3,6-anhydro-CDs are now underway.

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