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Synthesis and Alkali Metal Ion Binding of Poly(3,6-anhydro)-α-cyclodextrins

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Abstract: Pentakis(3,6-anhydro)-α-cyclodextrin and three regioisomers of tetrakis(3,6-anhydro)-α-cyclodextrin were synthesized from the corresponding 6-*O*-sulfonates to investigate the relationship among the molecular geometry, hydrophobicity-hydrophilicity balance, and inclusion behavior of CD. Each of the CD derivatives exhibited characteristic cation binding ability reflecting the unique molecular structure.

Cyclodextrins (CDs) can form inclusion complexes with many kinds of hydrophobic guest compounds, because of their hydrophobic cavities. In order to advance the host-guest chemistry using CD, not only chemical "cutting" at the hydroxyl groups but also modification of CD cavity itself should be essential.

We developed a unique modification of CD which converted glucose units to 3,6-anhydroglucose units *via* 6-*O*-sulfonates.[1] Per(3,6-anhydro)CDs[2] were synthesized, which exhibited strong cation binding abilities.[2c] Unlike the normal glucose unit with a $^4C_1$ conformation, the 3,6-anhydroglucose unit is restricted to the $^1C_4$ conformation by its intramolecular ether bridge, and the remaining OH group at C-2 points toward the inside of the cavity. Therefore, the inner surfaces of per(3,6-anhydro)CDs are covered with hydrophilic layers composed of the axial 2-OHs and two kinds of acetal oxygen atoms, which reasonably accounts for their strong cation-binding ability.

Since this modification causes a marked change in the nature of the cavity wall of CD from hydrophobic to hydrophilic, it can be expected to construct host molecules whose cavities possess the desired geometry and hydrophobicity-hydrophilicity balance by changing the number and position of 3,6-anhydroglucose units. As a first step to this, we synthesized pentakis(3,6-anhydro)-α-CD (**1**) and three possible regioisomers of tetrakis(3,6-anhydro)-α-CD, namely ABCD- (**2**), ABCE- (**3**), and ABDE-isomers (**4**).

Compound **1** was synthesized from pentakis(6-*O*-tosyl)-α-CD (**5**) in 91% yield by treatment with 1N KOH/75% aq. MeOH at 50°C for 45 h, followed by reversed-phase column chromatography.[3] The pentatosylate **5** was prepared by the reaction of α-CD with tosyl chloride in pyridine followed by purification using an aminopropyl-modified silicagel column (yield 10.4%).[4] The starting materials for **2**–**4**, namely tetrakis(6-*O*-mesitylenesulfonyl)-α-CDs, were synthesized according to the previously reported method[5] except the products were purified by preparative HPLC using phenyl-modified silicagel. The ABCD-tetrasulfonate was treated with 1N KOH/75% aq. MeOH at 50°C for 25 h, followed by reversed-phase column chromatography, giving ABCD-tetrakis(3,6-anhydro)-α-CD (**2**) in 83% yield.[6] The ABCE- and ABDE-isomers, **3** and **4**, were synthesized similarly from the corresponding tetrasulfonates.[6]

We at first examined binding of **1**–**4** with alkali metal ions using SIMS, as described previously.[2c] In Fig 1 are summarized the observed intensities of the [poly(3,6-anhydro)CD + metal]$^+$ ion peaks which are assumed to be proportional to the affinities of the 3,6-anhydro-CDs for the metal cation. Interestingly, pentakis(3,6-anhydro)-α-CD (**1**) showed excellent specificity for Rb^+, in contrast to hexakis(3,6-anhydro)-α-CD (**6**), which exhibited affinity for the smaller K^+ ion.[2c] Inspection of molecular models suggests that **1**

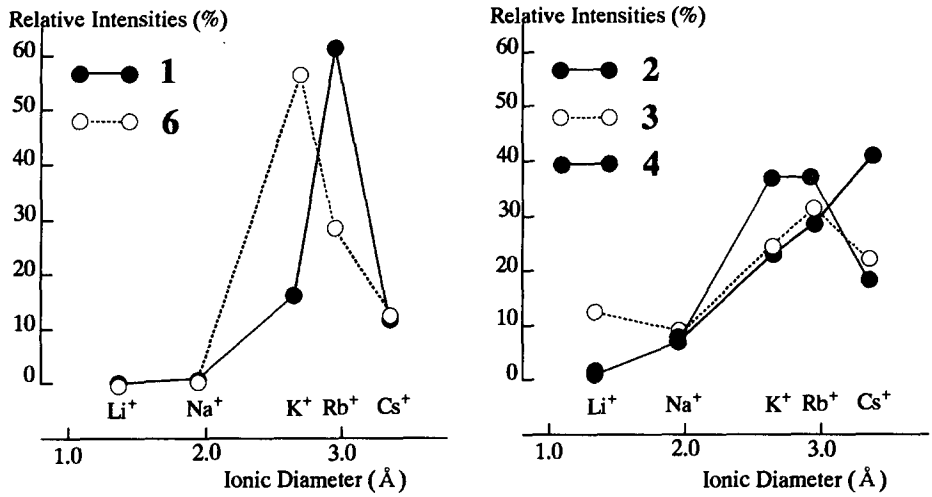

Figure 1. Relative Intensities of the [3,6-anhydro-α-CD + metal]$^+$ ions in the SIMS spectra.

possesses a distorted hydrophilic cavity wider than that of **6**. Each of compounds **2–4** exhibited characteristic specificities for metal ions. In **2–4** four 3,6-anhydroglucose units construct unique cavities, whose geometries, including the relative arrangement of hydrophobic and hydrophilic moieties, are different from each other. Therefore, guest molecules which are not globular, possessing both cationic and hydrophobic moieties, such as dialkylamines and amino acids, would be bonded to either isomer of tetrakis(3,6-anhydro)-α-CDs more specifically.

We are now studying the relationship between inclusion phenomena and the geometry and hydrophobicity-hydrophilicity balance of CD cavity using poly(3,6-anhydro)CDs and a variety of guest compounds. Application to chiral discrimination are also being undertaken.

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3. SIMS m/z 883.4 (M+H$^+$), 905.2 (M+Na$^+$), 921.0 (M+K$^+$), ^{1}H NMR (200 MHz, D_2O) δ 5.51, 5.30, and 5.21-5.28 (H1 of 3,6-anhydroglucose), 5.04 (H1' of glucose).
4. SIMS m/z 1765.6 (M+Na$^+$), 1781.4 (M+K$^+$), ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.35–7.50, 7.63–7.81 (aromatic protons).
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6. **2:** SIMS m/z 901.2 (M+H$^+$), 923.5 (M+Na$^+$), 939.3 (M+K$^+$), ^{1}H NMR (200 MHz, D_2O) δ 5.30 and 5.23 (H1 of 3,6-anhydroglucose), 5.06 and 5.05 (H1' of glucose); **3:** SIMS m/z 901.1 (M+H$^+$), 923.5 (M+Na$^+$), 939.4 (M+K$^+$), ^{1}H NMR δ 5.22–5.34 and 5.13 (H1), 5.21 and 5.03 (H1'); **4:** SIMS m/z 883.4 (M+H$^+$), 905.2 (M+Na$^+$), 921.0 (M+K$^+$), ^{1}H NMR δ 5.51, 5.30, and 5.21–5.28 (H1), 5.04 (H1').

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