A Cyclodextrin Derivative with Cation Carrying Ability: Heptakis(3,6-anhydro)-*β*-cyclodextrin 2-*O*-*p*-Phenylazobenzoate

Hatsuo Yamamura,* Hirotake Kawai, Tadahiro Yotsuya, Tamotsu Higuchi, Yasuo Butsugan, Shuki Araki, Masao Kawai, and Kahee Fujita†

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466
†Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852

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A cation-complexing host, heptakis(3,6-anhydro)-β-cyclodextrin, was converted to a mono-*p*-phenylazobenzoyl derivative, which exhibited alkali metal-carrying ability in CH_2Cl_2-H_2O system.

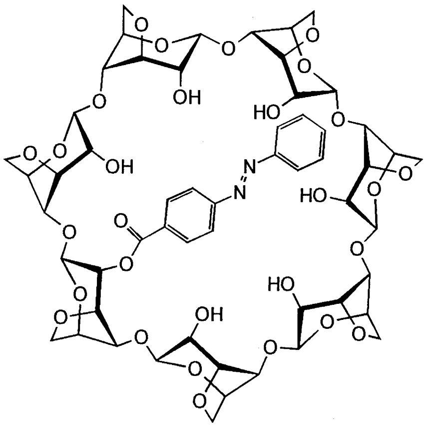
Cyclodextrins (CyDs) are unique cyclic oligosaccharides which can include hydrophobic guest molecules.[1] As an extension of CyD chemistry leading to profound application of CyDs, a novel kind of derivatives, namely 3,6-anhydro-CyDs, were synthesized by us and also by other research groups.[2] Each of them demonstrated a specific cation binding, reflecting its unique hydrophilic cavity.[2e,f] Further modification of the 3,6-anhydro-CyDs can be expected to afford novel sophisticated host compounds. Recently, 2-*O*-methylated derivative was synthesized by the method consisting of methoxylation of native CyD followed by 3,6-anhydration.[3] This developed an excellent "pre"-modification procedure.

Heptakis(3,6-anhydro)-β-CyD **1**, which is soluble in H_2O and also aqueous alcohol, was found to complex Rb^+ most strongly.[2e] We studied a "post"-functionalization at the secondary OH group of **1**, leading to a host molecule with more hydrophobicity which can behave as a cation carrier under hydrophobic circumstance such as a lipid bilayer.

Reaction of **1** with acyl chlorides such as benzoyl chloride and tosyl chloride in pyridine or aq.NaOH did not give the desired mono 2-*O*-substituted derivative as a main product.[4] This unexpected reactivity of **1** is very unique and quite different from that of parent CyD.[5] As a result of the survey, *p*-phenylazobenzoyl chloride was found to give preferentially a monosubstituted derivative which is suitable for our purpose.

Compound **1** (200 mg, 1.98 x 10^{-4} mol) was dissolved in dry pyridine (15 cm^3) was treated with *p*-phenylazobenzoyl chloride (48.2 mg, 1.98 x 10^{-4} mol) at 10 ℃ for 15 min. The reaction mixture showed an orange spot[6] on TLC as a major product which also showed distinct coloration with sugar staining.[7] After evaporation of the solvent, the residue was dissolved in $CHCl_3$ and washed with H_2O.[8] After Na_2SO_4 treatment followed by concentration, it was applied to silica gel chromatography to remove by-products with higher Rf. values. The elution with $CHCl_3$ and then H_2O/1-propanol/ethyl acetate (5/7/7(v/v/v)) gave pure heptakis(3,6-anhydro)-β-CyD 2-*O*-phenylazobenzoate **2** (47.8 mg, 3.93 x 10^{-5} mol, 19.8%).[9]

The cation extraction experiment[11] performed according to the previously reported method.[12] The decrease of absorbance in aqueous layer after treatment with the host solution in CH_2Cl_2 reflect the quantity of cation extracted by host from aqueous layer to CH_2Cl_2 layer. Figure 1 shows that compound **2** can extract cations more efficiently than dibenzo-18-crown-6 as the standard compound. Its selectivity was as follows; $Cs^+>Rb^+>K^+>>Na^+$, although the parent **1** bound Rb^+ most strongly.[2e] This alternation in cation selectivity may be due to the change of cavity by 2-*O*-modification. We previously observed a drastic change of cation specificity in 3,6-anhydro-CyDs probably caused by the difference of their molecular shape.[2f] In addition, the modification might make **2** flexible to fit the cation which is larger than that of the optimal size for **2**, showing a "plateau" selectivity.[13]



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The azo group in **2** is present almost exclusively as the stable (*E*)-form, and photoisomerization of the azo group was also preliminary examined. The UV light irradiation caused an isomerization from (*E*) to (*Z*)-isomer, 64% in toluene and 42% in $CHCl_3$, respectively. This isomerization was reversible by

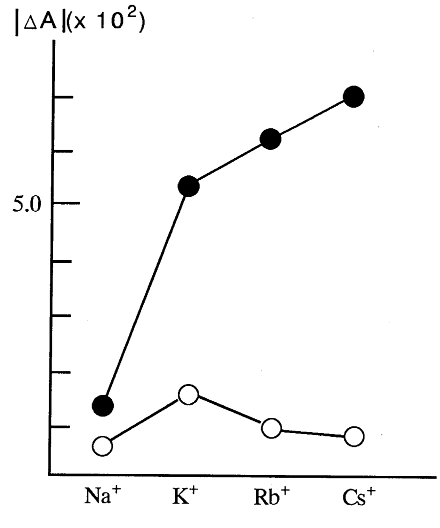

Figure 1. Absorbance change of aqueous layers by treatment of **2** (●—●) and dibenzo-18-crown-6 (○—○) in CH_2Cl_2 layers.

visible light irradiation or under dark. Isomerization of the azo group causes both conformational change and polarity change of the whole molecule. Thus an unprecedented property of **2** in solubility and cation specificity and affinity could be expected, leading to a regulation of cation carrying ability of **2** as the reported case of crown ethers.[12]

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4 For example, the reaction of **1** with benzoyl chloride (over 20 eq.) in pyridine gave a trace of a benzoyl derivative with the recovery of most of **1**. In the case with the use of tosyl chloride, no reaction occurred. The reaction with large excess of benzenesulfonyl chloride (over 150 eq.) gave only a small amount of a product both in pyridine and in aq. NaOH. The reaction of **1** with 4-dimethylaminoazobenzene-4'-sulfonyl chloride gave no product in aq. NaOH and a mixture of polysubsituted derivatives in pyridine.

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6 The orange coloration of **2** based on phenylazobenzoyl group was very convenient to detect **2** during its preparation.

7 Spot detection was carried out with 0.1% 1,3-dihydoxynaphthalene in EtOH/H_2O/H_2SO_4 (200/157/43(v/v/v)).

8 Almost 50% of the used **1** was recovered from H_2O fraction.

9 FABMS (m/z) 1239 ($M+Na^+$), 1255 ($M+K^+$), ^1H NMR (200 MHz, DMSO-*d6*) δ 5.00–5.50 (7H, H1 of CyD), 7.59-7.67 (3H, H3', 4', and 5' of azobenzene), 7.90-8.03(4H), 8.34 (2H, *J*=8.7 Hz). In the region of δ 6.80-7.45, a trace of *Z* isomer proton signals were observed.[10]

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11 Equal volumes of CH_2Cl_2 containing 2.00×10^{-4} mol dm^{-3} **2** and an aqueous solutions containing 2.00×10^{-3} mol dm^{-3} MCl (M, Na^+, K^+, Rb^+, or Cs^+) and 2.00×10^{-5} mol dm^{-3} methyl orange were agitated thoroughly on a mixer for 5 min. The solution was equilibrated, the CH_2Cl_2 and aqueous layers were separated, and the spectra were recorded, respectively. The extractability was determined by reading the difference of absorbance (464 nm) between the above layers and the control solution.

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