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Synthesis and Properties of Phenylenebisbenzimidazole Capped β-Cyclodextrins

De-Qi Yuan,[1] Kazutaka Koga, and Kahee Fujita*

Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852, Japan

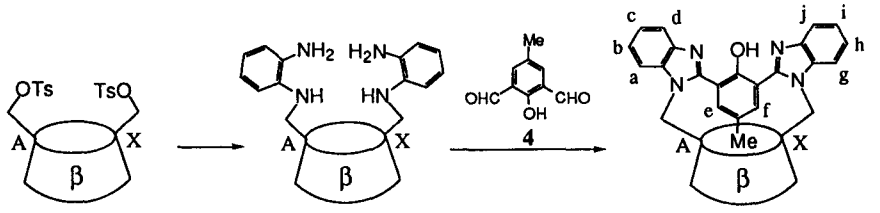
Masatoshi Yamaguchi

Faculty of Pharmaceutical Sciences, Fukuoka University, Jonan-ku, Fukuoka 814-01, Japan

Abstract: Novel capped β-cyclodextrins were synthesized by reaction of $6^A,6^C$ (or $6^A,6^D$)-bis-*O*-tosyl substituted β-cyclodextrins with *o*-phenylenediamine and subsequent cyclocondensation with *iso*-phthalaldehyde **4**. Their highly resolved NMR spectra and binding property are also described. © 1997 Elsevier Science Ltd.

The study of cyclodextrin-guest interactions requires the complete analysis of the structural factors associated with the cyclodextrin component itself.[2,3] In this endeavor, NMR is probably the most important tool, since the chemical shift patterns and NOE signals offer a direct probe of the host-guest interactions. However, this kind of NMR analysis is often hindered by extensive overlap of the resonances, which can be only partially remedied by chemical modification of the cyclodextrin.[4] Recently, we reported that introduction of 2,2′-(1,3-phenylene)bisbenzimidazole as a $6^A,6^C$-cap can resolve the NMR resonances of α-cyclodextrin.[5] Here we describe the synthesis, NMR behavior and binding property of the capped β-cyclodextrins **1**.

The synthetic sequence for **1** involves regioselective bistosylation of β-cyclodextrin, subsequent substitution of **2**[6] with *o*-phenylenediamine and final condensation of **3** with *iso*-phthalaldehyde **4**. Thus,



2 **3** **1**

a X = C; b X = D

The sugar units of β-CD are labeled clockwise A~G on being faced from the primary hydroxy side.

2 and 10 equiv. of *o*-phenylenediamine in DMF was heated for 3 days at 80 ℃. Precipitation with acetone and subsequent chromatography on cation exchange resin gave **3** in 85 ~ 95% yield. A dilute methanol solution of **3b** (200 mg, 0.15 mmol) and dialdehyde **4** (25 mg, 0.15 mmol) was stirred for 40 hours at room temperature. After the evaporation of the solvent, the residue was dissolved in 1 L of 30% *aq.* methanol and applied to HPLC analysis (Fig. 1). Chromatography of the *aq.* solution on a reverse-phase column furnished the fluorescent product **1b** in 55% yield. By a similar procedure, the $6^A,6^C$-isomer **1a** was obtained in 60% yield. Both products give highly resolved NMR spectra (Fig. 2) and correct (pseudo)molecular ion peaks with *m/z* at 1439 ($M + H^+$) and 1461 ($M + Na^+$) in the FAB-MS spectra.

The capping reaction proceeds almost exclusively. TLC shows that the amino cyclodextrin is completely converted to one final product. Both the elution patterns of HPLC (Fig. 1) and column chromatography of the final reaction mixture exhibit only one peak which corresponds the capped β-cyclodextrin.

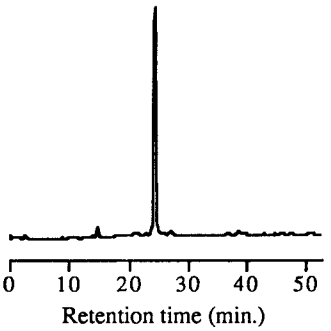


Fig. 1 HPLC analysis of the reaction mixture of **1b** and **4**.
Column: ODS-120T
Elution: 10~60% *aq.* MeCN, 30 mL x 2
Flow rate: 1 mL /min.
Detected at 210 nm.

Compound **1a** shows very complicated NMR spectra (Fig 2a and b).[7] The highly resolved ^{1}H-NMR resonances in the aromatic region and the twenty separated ^{13}C-NMR signals in the region of δ 160-110 indicate that the phenylenebisbenzimidazole cap is actually unsymmetrical. Proton e is exposed to a strong shielding effect while proton f is subject to strong deshielding effect. These facts incorporating NOE experiments and CPK molecular model inspection suggest that the cap has a rigid structure in which the methylphenyl residue inclines towards the cyclodextrin cavity, nearly coplanar with the benzimidazole residue next to sugar C but almost perpendicular to the benzimidazole next to sugar A. Such an arrangement of the cap seems to encase compound **1a** in a strongly asymmetric electronic or inductive field. In agreement with this, all the seven individual glucosides are spectrally quite different from each other, as shown by the three sets of seven separated peaks for C1 (δ 103 ~ 100), C4 (δ 86 ~ 80) and C6 (δ 61 ~ 44) and also by the highly resolved ^{1}H-NMR resonances. The resonances of H6C are shifted to the very low fields (δ 5.49 and 4.95), while those of H6A resonate at much higher fields (δ 4.48 and 4.25). In contrast, H6B and H6G experience strong shielding effect and resonate in the region of very high fields. The resonances of all the other protons are also shifted in a differing extent. Moreover, even the *gem*-protons of each methylene protons are

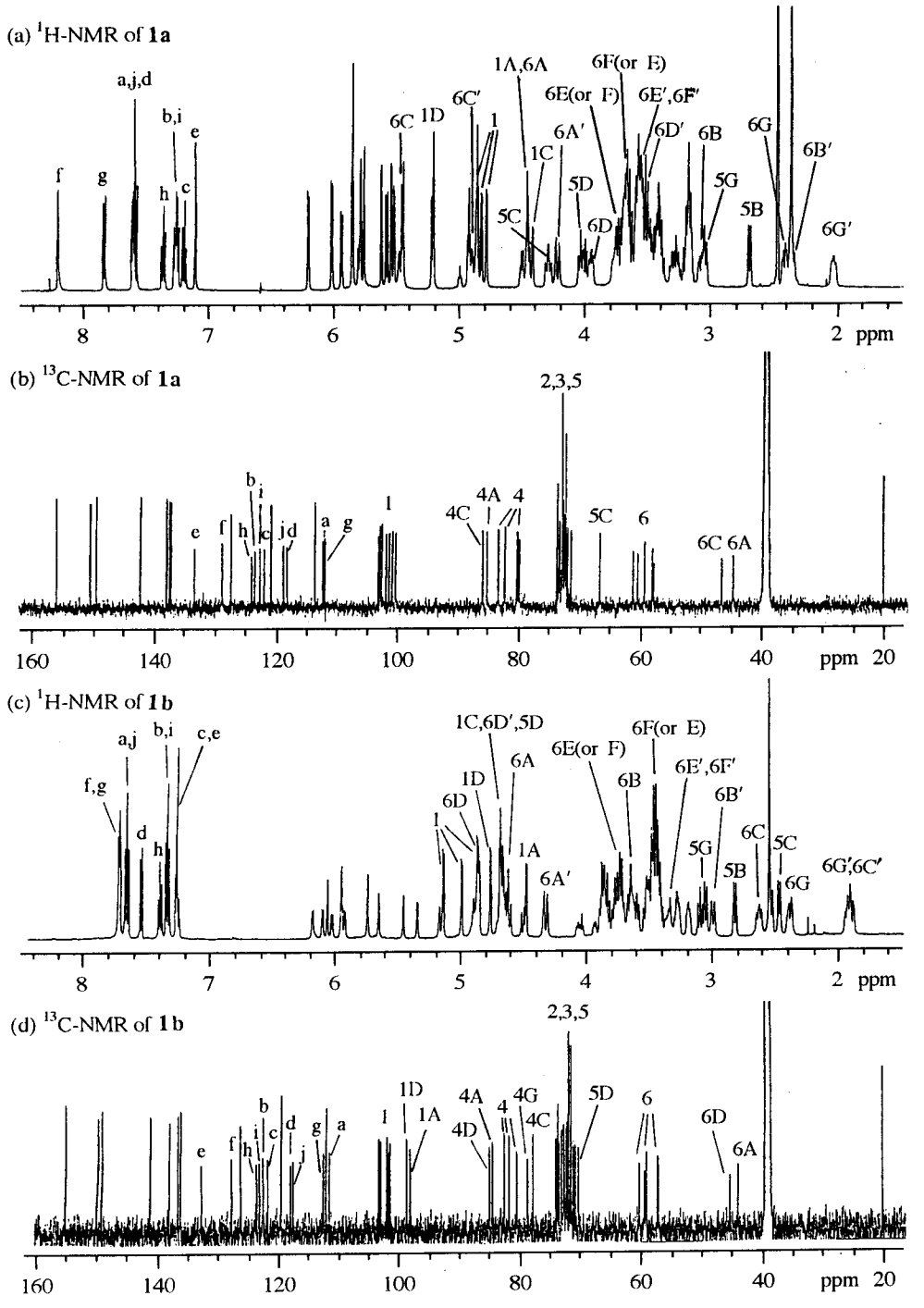


Fig. 2 500 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectra of capped cyclodextrins **1** in Me_2SO-[$^{2}H_6$].

differentiated from each other by a chemical shift difference of 0.1 ~ 0.6 ppm.

The basic effects of the phenylenebisbenzimidazole cap on the subunits of a cyclodextrin and similar chemical shift patterns are also demonstrated in the NMR spectra of Compound **1b** (Fig 2c and d). This indicates that compound **1b** has a conformation similar to that of **1a**. However, comparison of their ^{1}H-NMR spectra reveals that the magnetic environment of proton f of **1b** is obviously different from that of **1a**. The much smaller chemical shift of proton f in **1b** reflects that it experiences a much weaker deshielding effect than in **1a** and thus suggests that the methylphenyl ring is no longer coplanar with the benzimidazole next to the glucoside D. This twisting results in a deeper penetration of the methylphenyl moiety in the cyclodextrin cavity. In agreement with this, compound **1a** shows much stronger guest-binding than **1b** as shown below.

Adamantane-1-carboxylate is employed as a guest to probe the cavities of the capped β-cyclodextrins **1a** and **1b**. These capped cyclodextrins have fluorescent emission around 490 nm in *aq.* solution. On the addition of the guest, the emission intensity of **1a** in pH 6.86 standard buffer solution decreases. This change was followed at 492.0 and 494.8 nm by fixing the concentration of **1a** at 2.06×10^{-5} M and varying the concentration of guest in the region of $1.83 \times 10^{-5} \sim 2.20 \times 10^{-4}$ M. Treatment of the titration data by Scatchard method gives an association constant of 5.0×10^4 M^{-1}. In the case of compound **1b**, neither the UV absorption nor the fluorescence emission spectrum shows obvious changes on the addition of the guest, indicating no notable binding occurs between the cyclodextrin host and the adamantane guest. It is quite interesting to note that the capping position influences dramatically the binding ability of the capped cyclodextrin.

Since these novel capped cyclodextrin host are easily prepared and have unique spectral behavior, enhanced asymmetric feature and binding properties, they seem attractive host candidates for the study of host-guest interactions and chiral recognition.

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References and Notes

1. Present address: Department of Chemistry, Sichuan University, Chengdu 610064, China.
2. Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry* , Springer-Verlag, Berlin, **1978**.
3. Wenz, G. *Angew. Chem., Int. Ed. Engl.* , **1994**, 33, 803-822.
4. (a) Jiang, T.; Sukumaran, D. K.; Soni, S.; Lawrence, D. S. *J. Org. Chem.*, **1994**, 59, 5149-5155; (b) Hanessian, S.; Benali, A.; Laferriere, C. *J. Org. Chem.*, **1995**, 60, 4786; (c) Nakamura, A.; Okutsu, S.; Oda, Y.; Ueno, A.; Toda, F. *Tetrahedron Lett.*, **1994**, 35, 7241-7244.
5. Yuan, D.-Q.; Koga, K.; Yamaguchi, M.; Fujita, K. *Chem. Commun.*, **1996**, 1943-1944.
6. Fujita, K.; Matsunaga, A.; Imoto, T. *Tetrahedron Lett.*, **1984**, 25, 5533-5536.
7. The proton and carbon spectra were assigned according to the NMR technique described in Ref. 5.

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