Pergamon

Tetrahedron Letters, Vol. 38, No. 21, pp. 3743-3744, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00742-9

Synthesis of Secondary Face-to-face Cyclodextrin Dimers Linked at Each 2-position

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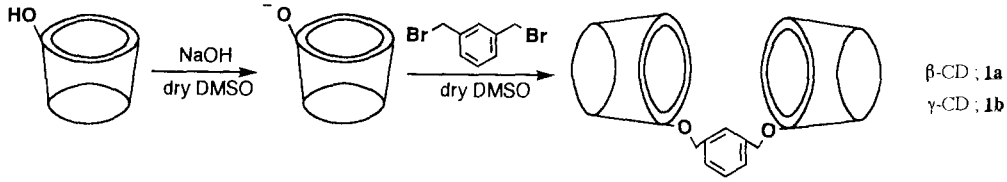
Abstract : A useful method for the synthesis of secondary face-to-face cyclodextrin dimers retaining the glucoside form was achieved. © 1997 Elsevier Science Ltd.

Recently, a number of reports[1] have been published on the synthesis and characterization of cyclodextrin dimers with various linkers. These dimers had ability for strong binding of biologically important chemical species in comparison with the corresponding cyclodextrin monomer. However, it has been difficult not only to synthesize the cyclodextrin dimers, all the sugar units of which are glucoside form, but also to monofunctionalize readily a secondary hydroxyl group. Therefore, we tried to synthesize open face-to-face cyclodextrin dimers linked with each secondary hydroxyl group *via* an oxyanion of the cyclodextrin. Our synthetic method for cyclodextrin dimers linked at each C2 position is shown in Scheme 1.



The procedure was as follows. A dry DMSO solution (10 ml) of a cyclodextrin (2 mmol) and finely grounded NaOH (20 mmol) was heated under argon atmosphere at 55 ° C for abou 0.5 h. Then, 2,2'-bis(bromomethyl)benzene (1 mmol), which was dissolved in dry DMSO (5 ml), was added dropwise over 5 min., and stirred for 2hr at 55°C. After removal of the solvent, the residue was added to vigorously stirred acetone, then these were filtered off. The filtrate was purified by Sephalex G-25, and then by dialysis membrane (Spectra/Pro 6 MWCO: 2,000). The purity was checked by HPLC (Shimadzu SBC-C8 H_2O/MeOH 1/1; Detected at 254 nm) and TLC (MERK Silica gel 60 F_{254} H_2O/*i*-PrOH 1/4 Rf=0.2). The yieldss of cyclodextrin dimers (**1a**, **b**) were 10 and 37%, respectively.

As explained in previous reports[3,4], the substituted position of the xylene bridge was unambigously determined by ^{13}C NMR of **1**. For example, ^{13}C NMR spectrum of **1a** in D_2O at 303 K is shown in Figure 1. The upfield-shifted signal at 100.4 ppm was assigned the C1' position, and the large downfield-shifted signal at 80.0 ppm was assigned the C2' position. However, the C3' position was not assigned. The C3' position overlaps the C5 position due to a small upfield shift. Generally, a downfield shift of the α-carbon, as well as an upfield shift of the β-carbon, are caused by alkylation of a hydroxyl group of the C2 position,

as reported previously .[3,4] The signal at 75 ppm was assigned to the linked benzyl carbons by the DEPT spectra. Four signals at the aromatic region indicate the xylene bridge with the expected symmetric pattern. The integrated intensities from the ^{1}H NMR spectra are consistent with the number and type of protons in each cyclodextrin dimer. The ^{13}C NMR of **1b** also showed an analogous pattern of **1a**. Microanalytical data of **1**[2] were consistent with the proposed structures.

From those results, it is clear that a hydroxyl group at the 2-position, the most acidic hydroxyl proton with a *pKa* of 12.1, is readily deprotonated by NaOH to yield an oxyanion of cyclodextrins. The oxyanion of cyclodextrins reacted with an 2,2'-bis(bromomethyl)benzene to afford mono-substituted cyclodextrin dimers. It was assumed that in this reaction condition finely grounded NaOH played an important role, that is, that considerable deprotonation ability due to the increasing surface area and the efficiency in removing water *in situ* was operative in comparison with priviously reported results.[4] We concluded that cyclodextrin dimers were obtained very easily by this reaction method.

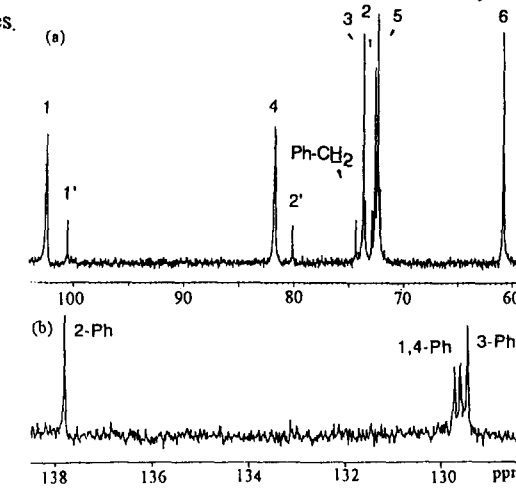


Figure 1. The carbohydrate region (a) and aromatic region (b) of ^{13}C NMR spectra of 1b in D_2O at 303 K

Acknowledgements: Y. I. thanks Dr. T. Williams of Jasco International Inc. for measurement of TOF mass spectrum and thank Mr. T. Koyama for measurement of FAB mass spectrum.

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2. β-CD dimer **1a** (selected data). ^{1}H NMR (δ, D_2O at 303K): 7.46 (1H), 7.35 (3H), 5.28 (1H), 4.7-4.6 (4H), 5.2-5.1 (14H), 3.4-4 (84H). ^{13}C NMR (δ, D_2O at 303K): 137.8, 129.7, 129.6, 129.4, 102, 100.4, 82, 80, 75, 74, 73, 72, 61. TOF-MS Calcd for $C_{92}H_{146}O_{70}$+Na ; M.W.=2393.8. γ-CD dimer **1b** (selected data). ^{1}H NMR (δ, D_2O at 303K): 7.63 (1H), 7.52 (3H), 5.44 (1H), 5.2-5.1 (16H), 4.8-4.9 (4H), 3.4-4.0 (96H). ^{13}C NMR (δ, D_2O at 303K): 137.8, 129.8, 129.7, 129.5, 102, 100, 80, 75, 74, 73, 72, 61. TOF-MS Calcd for $C_{104}H_{166}O_{80}$+Na ; M.W.=2717.9.
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(*Received in Japan* 25 *February* 1997; *revised* 17 *April* 1997; *accepted* 18 *April* 1997)