COMMUNICATION

ChemComm
www.rsc.org/chemcomm

A facile synthesis of novel types of cyclodextrin derivatives by insertion of an aromatic dicarbonyl spacer into a permethylated α-cyclodextrin skeleton†

Toshiyuki Kida,* Takao Michinobu, Wanbin Zhang, Yohji Nakatsuji and Isao Ikeda*
Department of Molecular Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: kida@chem.eng.osaka-u.ac.jp; Fax: +81-6-6879-7359; Tel: +81-6-6879-7357

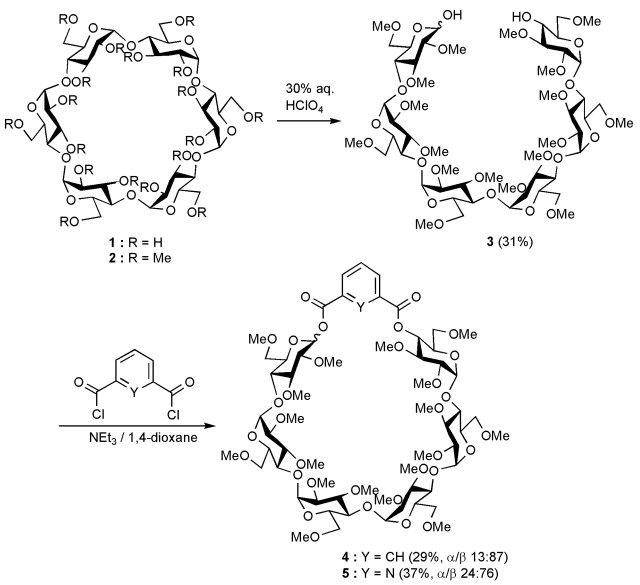
Received (in Cambridge, UK) 22nd May 2002, Accepted 11th June 2002
First published as an Advance Article on the web 25th June 2002

Novel types of cyclodextrin derivatives are easily synthesized by the insertion of an aromatic dicarbonyl spacer into the skeleton of permethylated α-cyclodextrin, and the isophthaloyl-inserted one shows almost the same complexing ability toward *p*-nitrophenol as permethylated β-cyclodextrin.

Cyclodextrins (CDs) are a class of cyclic oligosaccharides consisting of several α-(1,4)-linked D-glucopyranose units, and their ability to form inclusion complexes with a wide range of organic guest molecules has found applications in many areas.[1] A great deal of effort has been devoted to the modification of the hydroxy groups on the upper and/or lower rims of CDs, such as capping, introduction of ionic groups and dimerization, in order to improve and control their inclusion ability.[2] On the other hand, much less attention has been paid to the modification of the CD ring by the insertion of noncarbohydrate spacers into the CD skeleton,[3–5] because such modification process requires considerably more reaction steps than that of the CD hydroxy groups. Recently, Vasella *et al*. reported the synthesis of interesting CD derivatives in which a substituted buta-1,3-diyne or a 1,2,3-triazole unit is inserted into one glucosidic linkage of α- or γ-CD.[6] This synthetic approach, however, still consists of more than 10 reaction steps starting from natural CD and, to the best of our knowledge, the inclusion ability of the resulting host molecules has not yet been reported. If new methodology for the facile synthesis of this 'spacer-inserted' CD is developed, one can easily construct novel types of CD derivatives in which the secondary bonding interaction between the incorporated guest and the spacer in the host is possible, and the cavity size and shape are well adjusted to the structure of a given guest by the choice of the spacer to be inserted. In this communication, we report a facile synthesis of novel types of spacer-inserted CDs starting from α-CD and their inclusion ability toward *p*-nitrophenol.

We have chosen the spacer-inserted CDs **4** and **5** as the target compounds, in which isophthaloyl and 2,6-pyridinedicarbonyl spacers are inserted into a permethylated α-CD skeleton, respectively. Scheme 1 shows the synthetic route to **4** and **5**. α-CD was converted into permethylated derivative **2** according to the previously reported method.[7] Insertion of an aromatic dicarbonyl spacer into **2** was carried out in two reaction steps, that is, the ring-opening of **2** by cleavage of a single glucosidic bond and the subsequent cyclization of the resulting acyclic maltohexaose derivative **3** with an aromatic dicarbonyl dichloride. Kuzuhara *et al*.[8] and Vasella *et al*. [5] have reported that acetolysis of fully acetylated α-CD with Ac_2O–conc.H_2SO_4 (or Ac_2O–70% aq. $HClO_4$) is an efficient method for the selective cleavage of only one of the glucosidic bonds to give the acyclic maltohexaose peracetate. The application of this procedure to the permethylated α-CD **2**, however, gave a complex mixture of products including the oligosaccharide derivatives of lower molecular weights than the desired maltohexaose derivative. We found the selective cleavage of the one glucosidic bond of **2** was effected by treatment with 30% aq. $HClO_4$ at room temperature for 42 h to afford an acyclic maltohexaose derivative **3** bearing two free hydroxy groups in 31% isolated yield. In this case, 27% of unreacted **2** was recovered; thus, the yield based on the consumed **2** was 42%. The ^{1}H NMR spectrum in $CDCl_3$ shows that **3** is obtained as a nearly 1:1 mixture of the α- and β-anomers. Reaction of **3** with isophthaloyl dichloride in the presence of triethylamine in 1,4-dioxane gave the corresponding cyclic product **4** in 29% yield. The use of 2,6-pyridinedicarbonyl dichloride instead of isophthaloyl dichloride in the reaction somewhat increased the yield of the desired product. This cyclization proceeded with high β-isomer selectivity (α:β = 13:87 for **4**, α:β = 24:76 for **5**). The β-isomers **4β** and **5β** were separated from the corresponding α/β anomeric mixtures by silica gel column chromatography using chloroform-methanol (150:1) as an eluent. The structures of these novel macrocycles **4β** and **5β** are confirmed by NMR, mass and IR spectra.‡ Intense molecular ion signals at *m*/*z* 1396 (*M* + Na) and 1397 (*M* + Na) were observed in MALDI-TOF MASS spectra of **4β** and **5β**, respectively. The ^{1}H NMR spectra in $CDCl_3$ show six anomeric protons of each compound are not chemically equivalent and six doublets are observed in the range of 5.1 to 6.0 ppm.

We determined the stability constants of the complexes of these host molecules with *p*-nitrophenol (PNP) by the ^{1}H NMR titration method in CD_3OD–D_2O (1:4). The upfield shift of the signals of both the aromatic and carbohydrate parts of these hosts was observed upon addition of PNP. Fig. 1 illustrates the upfield shift of the aromatic proton signals of **4β** induced by the complexation with PNP. The Job plots clearly indicate both



Scheme 1

† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of **4β** and **5β**. See http://www.rsc.org/suppdata/cc/b2/b204960k/

DOI: 10.1039/b204960k

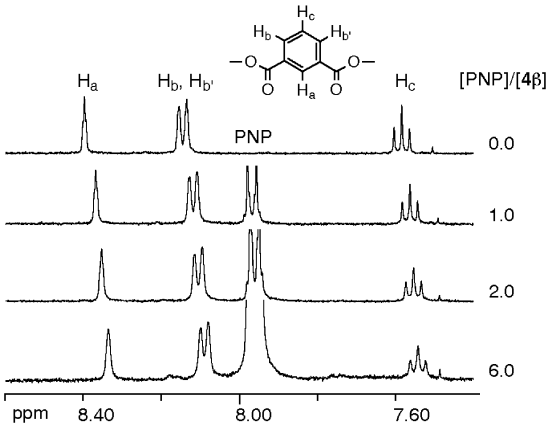


Fig. 1 ^{1}H NMR spectral changes observed for host **4β** (5×10^{-3} M) in CD_3OD–D_2O (1 : 4) upon addition of *p*-nitrophenol (PNP) at 25 °C.

hosts form a 1 : 1 complex with PNP. Host **4β** bearing an isophthaloyl spacer exhibits a much higher complexing ability toward PNP ($K = 190 \pm 18$ M^{-1}) than host **5β** with a 2,6-pyridinedicarbonyl spacer ($K = 15 \pm 4$ M^{-1}), indicating that the type of the spacer remarkably affects the inclusion ability of the host molecule. The stability constant of the complex of **4β** with PNP is almost the same as that ($K = 200 \pm 15$ M^{-1}) of the permethylated β-CD–PNP complex.

In conclusion, we have successfully developed a facile synthetic route to novel types of CD derivatives by the insertion of an aromatic dicarbonyl spacer into a permethylated α-CD skeleton. The stability constants obtained in this work clearly demonstrate that the inclusion ability of the host molecule is controllable by the type of the spacer to be inserted. Work on elucidation of the structures of the host molecules and their complexes with PNP by X-ray crystallography is now in progress in our laboratory.

Notes and references

‡ Spectroscopic data for **4β**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (t, 1H, J = 1.5 Hz), 8.32 (dt, 1H, J = 8.1, 1.5 Hz), 8.19 (dt, 1H, J = 8.1, 1.5 Hz), 7.59 (t, 1H, J = 8.1 Hz), 5.95 (d, 1H, J = 7.7 Hz), 5.51 (d, 1H, J = 3.3 Hz), 5.33 (d, 1H, J = 3.7 Hz), 5.26 (d, 1H, J = 3.7 Hz), 5.17–5.25 (m, 3H), 4.19 (m, 1H), 3.93 (m, 2H), 3.30–3.90 (m, 82H), 3.17–3.30 (m, 4H); MALDI-TOF *m*/*z*: 1396 [M + Na]$^+$; IR (KBr) 2931, 2827, 1736, 1155, 1108 (cm^{-1}).

For **5β**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, 1H, J = 7.7 Hz), 8.11 (d, 1H, J = 7.7 Hz), 7.98 (t, 1H, J = 7.7 Hz), 5.90 (d, 1H, J = 7.3 Hz), 5.47 (d, 1H, J = 3.3 Hz), 5.31 (d, 1H, J = 3.3 Hz), 5.13–5.26 (m, 4H), 4.17 (m, 1H), 3.97 (m, 1H), 3.25–3.90 (m, 83H), 3.13–3.25 (m, 4H); MALDI-TOF *m*/*z*: 1397 [M + Na]$^+$; IR (KBr) 2931, 2827, 1736, 1111, 1072 (cm^{-1}).

1 G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 803; J. Szejtli and T. Osa, *Comprehensive Supramolecular Chemistry, Vol. 3*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle and J.-M. Lehn, Pergamon, Oxford, 1996.
2 A. P. Croft and R. A. Bartsch, *Tetrahedron*, 1983, **39**, 1417; C. J. Easton and S. F. Lincoln, *Chem. Soc. Rev.*, 1996, **25**, 163; A. R. Khan, P. Forgo, K. J. Stine and V. T. D'Souza, *Chem. Rev.*, 1998, **98**, 1977; R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997.
3 R. Bürli and A. Vasella, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1852.
4 J. C. Morales, D. Zurita and S. Penadés, *J. Org. Chem.*, 1998, **63**, 9212.
5 B. Hoffmann, D. Zanini, I. Ripoche, R. Bürli and A. Vasella, *Helv. Chim. Acta*, 2001, **84**, 1862.
6 B. Hoffmann, B. Bernet and A. Vasella, *Helv. Chim. Acta*, 2002, **85**, 265.
7 J. Boger, R. J. Corcoran and J.-M. Lehn, *Helv. Chim. Acta*, 1978, **61**, 2190.
8 N. Sakairi, L.-X. Wang and H. Kuzuhara, *J. Chem. Soc., Chem. Commun.*, 1991, 289.