Synthesis and unique NMR behaviour of a novel capped α-cyclodextrin

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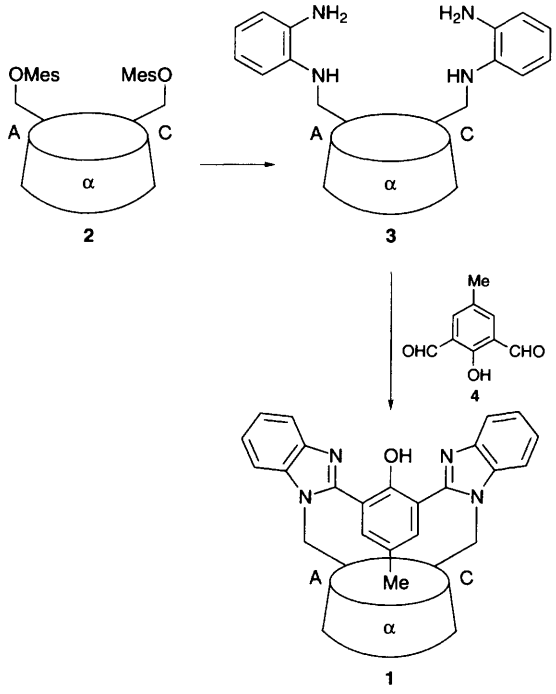
1,3-Bis(benzimidazol-2-yl)benzene-capped α-cyclodextrin 1 is synthesized by reaction of 6^A,6^C-bis-*O*-mesitylenesulfonyl substituted α-cyclodextrin with *o*-phenylenediamine and subsequent cyclocondensation with isophthaldehyde 4, and its highly resolved NMR spectra are described.

The study of cyclodextrin–guest interactions, which play an important role in many research fields, requires the complete analysis of the structural factors associated with the cyclodextrin component itself.[1,2] In this endeavour, 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.[3] For example, the influence of an aromatic entity on chemical shifts, although present in many systems, is small, and does not lead to comprehensive resolution of the resonances in most of the cyclodextrin derivatives reported to date.[4] Recently, we have found that introduction of a 1,3-bis(benzimidazol-2-yl)benzene group as a cap can resolve the NMR resonances of cyclodextrin, and therefore makes the capped cyclodextrin as good host candidate for elucidating host–guest interactions. Here we describe the synthesis and highly resolved NMR spectra of the novel capped α-cyclodextrin **1**.

The synthetic sequence for **1** is outlined in Scheme 1. 6^A,6^C-Bis-*O*-mesitylenesulfonyl substituted α-cyclodextrin **2** (labelling of glucoside rings and atoms is depicted in Fig. 1) was obtained by regioselective sulfonylation of α-cyclodextrin,[5] and converted to its amino derivative **3** by substitution with *o*-phenylenediamine. Cyclocondensation of **3** with isophthalaldehyde **4** led to capped α-cyclodextrin **1**. Thus, a solution of the sulfonylated cyclodextrin **2** and 10 equiv. of *o*-phenylenediamine in DMF was heated for 3 days at 80 °C and then added to a *ca.* 20-fold amount of acetone under stirring. The resultant precipitate was subjected to column chromatography on cation exchange resin, affording **3** in 93% yield. A dilute solution of **3** (200 mg) and dialdehyde **4** (26 mg) in methanol (150 cm^3) was stirred for 2 days at room temperature. The solvent was evaporated and the residue was subjected to chromatography on a reverse-phase column (Lobar Column LiChroprep Rp-18, size B, Merck) with a linear gradient elution from 20% aqueous methanol (1 dm^3) to 60% aqueous methanol solution (1 dm^3). Fractions 79–85 (each 18 cm^3) furnished a fluorescent product in 37% yield. This compound gives peaks of *m/z* 1277 and 1299 in the FAB MS spectrum, equivalent to the $[M + H]^+$ and $[M + Na]^+$ ions of capped α-cyclodextrin **1**. This compound gives complex NMR spectra, which are shown in Fig. 2.



Scheme 1

The proton spectrum was assigned in three stages. (i) intra-glucoside specification: the proton resonances are so highly resolved that the 2D COSY spectrum gives one isolated island for each correlation of adjacent protons except the methyl ones, and thus enables the extraction of H1–H6 within the individual units. (ii) Inter-glucoside sequence determination: the NOE signals between H1 and H4 protons in adjacent units reveal the connecting sequence of the glucosides. (iii) Assignment of the cap: obviously the cap should cause strong downfield shifts of the methylene protons in the modified glucosides (*i.e.* A and C), and this assignment was confirmed by the NOE enhancements of H6A″ and H6C″ on irradiating protons a and g.

The assignment of the ^{13}C NMR spectrum were derived from a ^{13}C–^1H COSY spectrum. The ^{13}C NMR spectrum [Fig. 2*b*)], in addition to presenting reasonably significant shifts for the carbons in modified glucosides, also shows differing shifts for other carbons. Introduction of the nitrogen-containing functionality causes large upfield shifts for C6A and C6C, much smaller upfield shifts for C5A and C5C and downfield shifts for C4A and C4C. The difference in the chemical shifts of C5A and C5C is noteworthy and indicative of the distinct difference between glucosides A and C. Indeed, all the six individual glucosides are spectrally different from each other, as shown by their highly resolved resonances. For example, three sets of six separated

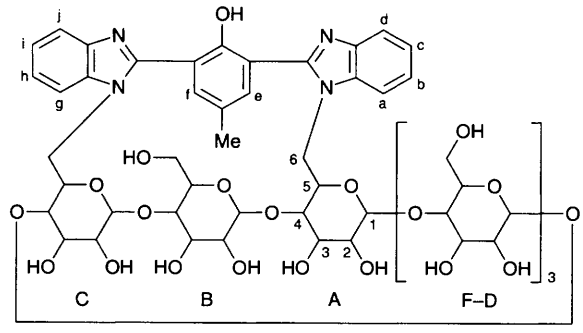


Fig. 1 Ring and atomic labelling

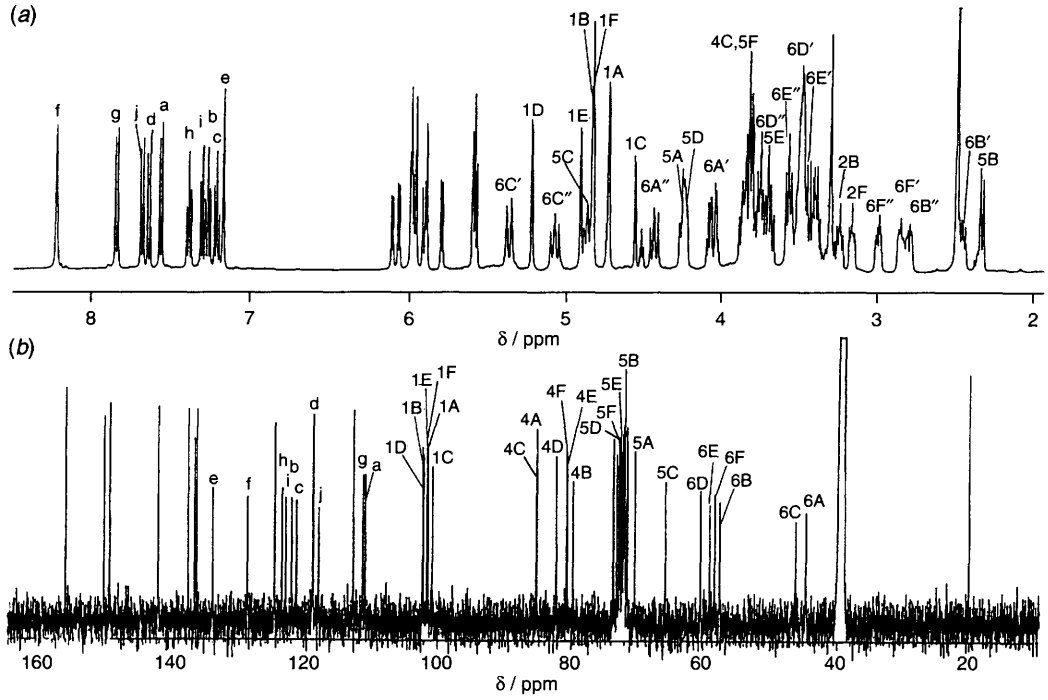


Fig. 2 (*a*) 500 MHz ^{1}H NMR and (*b*) 125 MHz ^{13}C NMR spectra of capped cyclodextrin **1** in $(CD_3)_2SO$. The primed numbers in (*a*) denote the methylene protons pointed towards the cyclodextrin cavity while the double primed ones indicate those pointed away from the cavity.

peaks can be unambiguously derived for C1 (δ 103–100), C4 (δ 86–80) and C6 (δ 61–44). The twenty separated resonances spreading between δ 160–110 are attributable to the aromatic cap, and imply that the cap is actually unsymmetrical.

Proton resonances are more sensitive to the chemical differences among the individual glucosides. In particular, the NMR signals associated with H6 and H5 are extremely dispersed. The resonances of H6C and H5C are shifted to the low field side of the region for anomeric protons, while those of H6A and H5A resonate between δ 4.5–4.0. A downfield shift comparable to that of H5A is observed for H5D. In contrast, H5B, H6B and H6F turn out to be strongly shielded. As a result, the resonances are spread between δ 2.46–5.37 for the H6 protons and δ 2.34–4.88 for the H5 protons. More significantly, each pair of methylene protons has resonances which are widely separated. This observation indicates that the magnetic non-equivalency of the two protons in each methylene group is magnified by the aromatic cap. Besides H6C and H5C, H4C still experiences a moderate deshielding effect whereas the aromatic proton H1C is subjected to a shielding effect. Other glucosidic protons H1–H4, although to a smaller extent, also present resolved resonances, which can be seen from the isolated islands associated with C1–H1 or C4–H4 correlations in the COSY spectrum. Furthermore, the aromatic protons are also differentiated, and a chemical shift difference as low as 1 ppm has been observed, for the two phenyl protons e and f.

All the above facts indicate compound **1** has a very strongly asymmetric nature which can be rationalised with the aid of TNNOESY experiments and CPK molecular model inspection. Irradiation of the e, f and methyl protons leads to large NOE enhancements for H5A and H5F, H5C, H5D and H6C′ and H5D, H5E and H5F, respectively, whereas irradiation of the benzimidazole protons furnishes considerable NOE signals for a–H6A″ and g-H6C″ only. We can therefore deduce that the methylphenyl residue inclines towards the cyclodextrin cavity while the benzimidazole residues lie outside. Molecular model analysis suggests a highly rigid structure in which the benzimidazole residues are only close to sugars F and B respectively. The residue next to sugar C is nearly coplanar with the middle phenyl ring while that next to sugar A is almost perpendicular to it. Such an arrangement of the cap should encase compound **1** in a strongly asymmetric electronic or inductive field, and provide a possibility of C–H–π interactions for H6F, H6B and H5B. This conformation is consistent with the observed NMR behaviour.

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Footnotes

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