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NMR spectroscopy: a powerful tool for detecting the conformational features of symmetrical persubstituted mixed cyclomaltoheptaoses (β-cyclodextrins)

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Abstract—The conformation in solution of exhaustively derivatized mixed cyclomaltooligosaccharides (cyclodextrins) has been defined by NMR spectroscopy. Both tilting of glucopyranose units about the glycosidic linkages and ring deviations from the $^4C_1$ chair conformation are detected, the entities of which are strongly dependent on the nature of the derivatizing groups.

Keywords: Cyclomaltooligosaccharides; Cyclodextrins; NMR spectroscopy; Stereochemistry; Conformational distortions

1. Introduction

Cyclomaltooligosaccharides (cyclodextrins) are cyclic oligosaccharides having a truncated cone shape, the structural preorganization of which, together with the chirality of the single glucose units, is responsible for their complexing and enantiodiscriminating properties, which can be significantly affected by derivatization of their secondary and/or primary hydroxyl groups.[1]

During the last 10 years we have been paying attention to cyclodextrin derivatives to be used as Chiral Solvating Agents (CSAs)[2,3] that are able to induce NMR nonequivalence of the enantiotopic nuclei of enantiomeric mixtures, making them distinguishable in the NMR spectra. Alkylated or acetylated cyclodextrins, extensively employed in GC,[4] have shown great potentialities as CSAs for apolar substrates,[5–8] whereas benzoylated, benzylated and carbamoylated cyclodextrins have been successfully employed as $CDCl_3$-soluble CSAs for enantiodiscriminating polar chiral substrates.[9–11] These investigations also evidenced the distortions induced in the cyclomaltohexaose (α-cyclodextrin) structure due to the derivatization,[12] which consequently produced dramatic changes of their complexing properties. A recent detailed conformational analysis in solution[13] of the peracetylated cyclomaltoheptaose (β-cyclodextrin) revealed the presence of glucopyranose units having strong deviations from the $^4C_1$ conformation. In order to gain better insight on the conformational features of β-cyclodextrins, we have taken into consideration the exhaustively derivatized cyclodextrins having mixed carbamoyl/methyl or acetyl functions, heptakis[6-*O*-methyl-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (**1**), heptakis[6-*O*-acetyl-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (**2**), heptakis[2,3-di-*O*-methyl-6-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (**3**) and heptakis[2,3-di-*O*-acetyl-6-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (**4**) (Fig. 1), describing their synthesis and determining by NMR spectroscopy their stereochemistry.

2. Results and discussion

2.1. Synthesis of 1–4

The synthesis of **1** (Scheme 1) involves the protection of the primary hydroxyl groups as *tert*-butyldimethylsilyl

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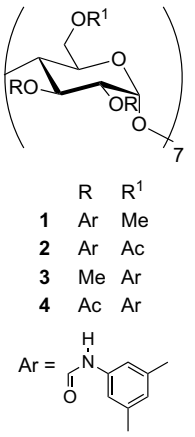
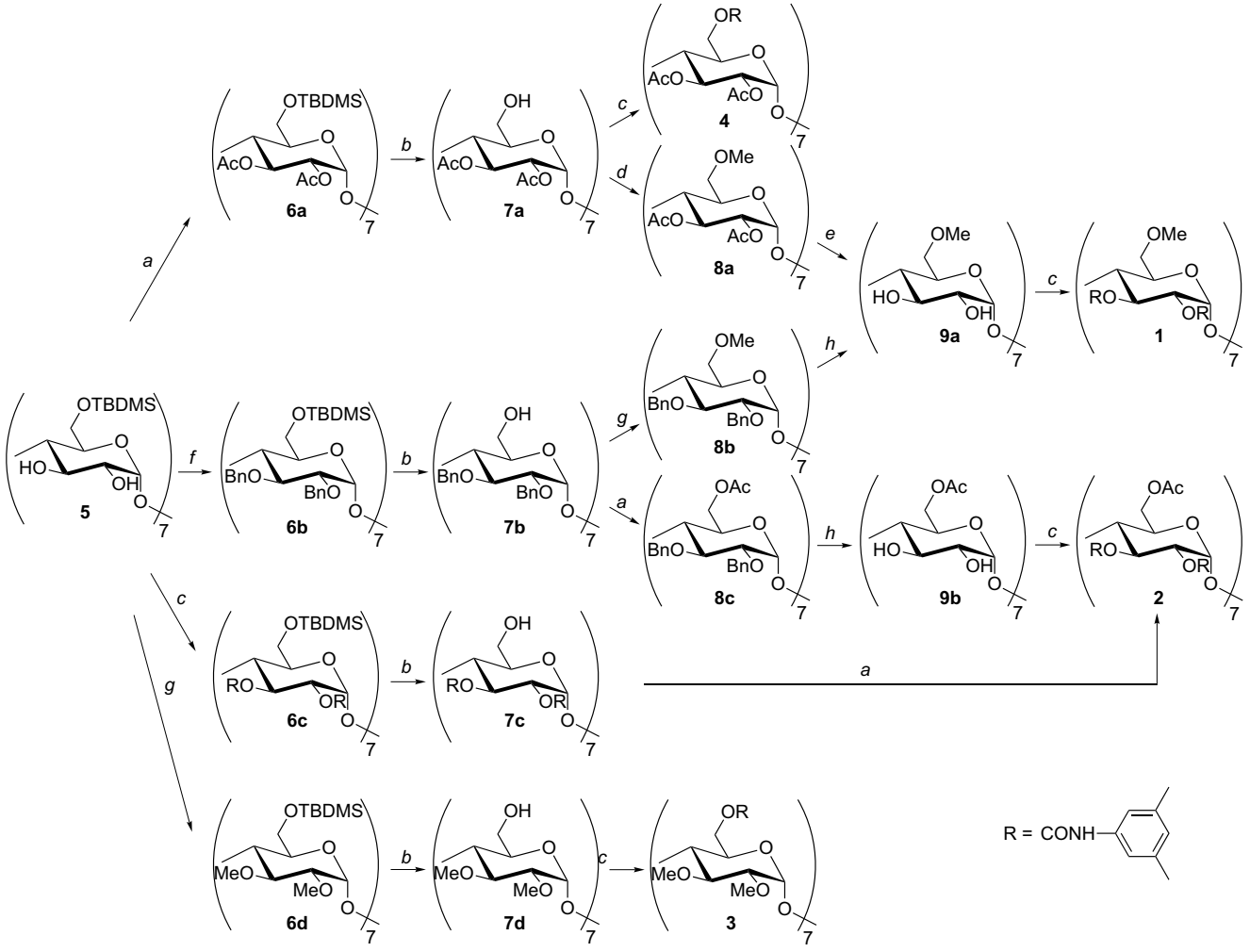


Figure 1. Persubstituted β-cyclodextrins **1**–**4**.

(TBDMS) ethers (**5**),[14] followed by protection of the secondary ones as acetyl esters (**6a**) or benzyl ethers (**6b**).

The removal of the TBDMS groups was carried out by using $BF_3{\cdot}OEt_2$ (**7a**–**b**, Scheme 1).[15] The methylation of the primary sites in the presence of acetyl groups on the secondary ones (**8a**) has been carried out by using methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine.[15] When the benzyl groups were present on the secondary sites, the primary ones could be methylated (**8b**) very simply by using the procedure involving the addition of an excess of MeI to the mixture in DMF containing the cyclodextrin and NaH. However, complete methylation (>99%) was achieved only by adding the preformed alcoholate to the DMF solution of MeI. The removal of the acetyl groups (**9a**) was performed by using MeONa–MeOH, whereas complete benzyl ether cleavage (Fig. 2a) involved the catalytic hydrogenation (10% Pd/C, 5 atm) of **8b** in MeOH containing a minimum amount of CH_2Cl_2 needed to dissolve the cyclodextrin. In fact, partial debenzylation or decomposition of cyclic maltoheptaose derivatives occurred by using only MeOH[16] or



Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine, 100 °C; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (c) 3,5-dimethylphenyl isocyanate, pyridine, 80 °C; (d) $CF_3SO_3CH_3$, CH_2Cl_2, 2,6-di-*tert*-butyl-4-methylpyridine; (e) MeONa–MeOH; (f) NaH, DMF, BnBr; (g) NaH, DMF, MeI; (h) H_2 (5 atm), Pd/C, MeOH–CH_2Cl_2.

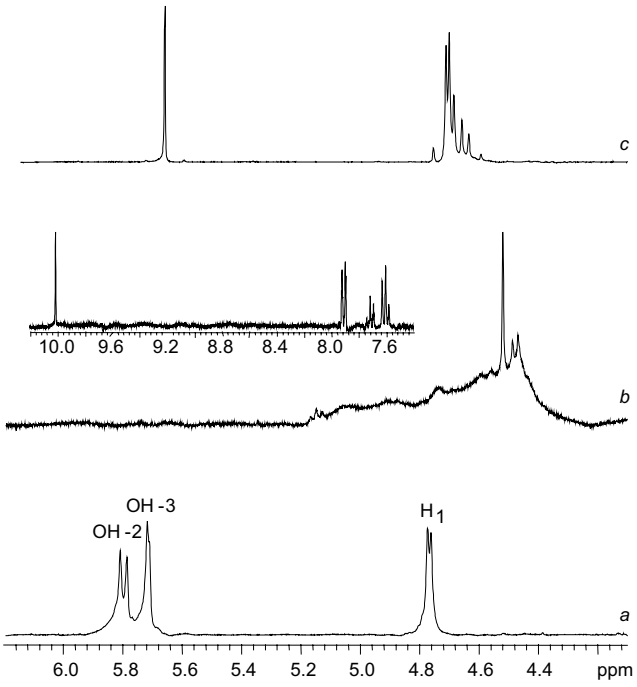


Figure 2. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) spectral regions corresponding to the secondary hydroxyls and the anomeric H-1 proton of the debenzylation products obtained by (a) H_2, Pd/C, MeOH–CH_2Cl_2, (b) $NaBrO_3$–$Na_2S_2O_4$ in AcOEt–H_2O and (c) EtSH–BF_3·OEt_2.

by applying the procedure[17] that involved the use of dioxane–EtOH and one drop of $HClO_4$. Compound **1** was finally obtained by reacting **9a** with 3,5-dimethylphenyl isocyanate in pyridine at 80 °C.

In regard to the removal of the benzyl protecting groups of **8b**, we also tried other methods reported in the literature[18–20] as alternative approaches to catalytic low-pressure hydrogenation. Of these, we took into consideration debenzylation employing $NaBrO_3$–$Na_2S_2O_4$ reagent under two-phase (ethyl acetate–water) conditions,[18] the deprotection in the presence of a hard acid, boron trifluoride etherate, and a soft nucleophile, EtSH,[19] and 'catalytic-transfer hydrogenation' involving the use of sodium hypophosphite associated with palladium–charcoal.[20]

An attempt to cleave benzyl ether C–O bonds in **8b** with sodium hypophosphite in the presence of 10% Pd/C in DMF–H_2O at 50 °C (4 h) gave only 15% of the *O*-debenzylated product as revealed by ^{1}H NMR analysis. The treatment of **8b** with $NaBrO_3$–$Na_2S_2O_4$ in ethyl acetate–H_2O at room temperature for 16 h resulted in the formation of a complex mixture whose ^{1}H NMR spectrum (Fig. 2b) indicated no removal of the benzyl groups (Fig. 2b compared to Fig. 2a) as the OH-2 and OH-3 signals of the fully debenzylated compound were not detected. Analogous results (Fig. 2c) were obtained in the case of the reaction of **8b** with ethanethiol in the presence of BF_3·OEt_2. The use of EtSH–BF_3·OEt_2 produced a distribution of the cyclodextrin NMR signals as shown for the H-1 proton in Figure 2c.

Also for the synthesis of system **2** we followed two different pathways (Scheme 1). The first involved carbamoylation of the secondary sites (**6c**) of the derivative **5**, which had its primary rim protected by silyl groups, the removal of its TBDMS groups (**7c**) and, finally, the acetylation of the primary hydroxyl groups (**2**) with acetic anhydride; the latter required the acetylation of the primary hydroxyl groups (**8c**) of the benzylated derivative **7b**, the cleavage of the benzyl ether bonds (**9b**) and the final carbamoylation of the secondary rim (**2**).

Cyclodextrins **3** and **4**, having inverted substitution on its primary and secondary sites with respect to **1** and **2**, respectively, were synthesized by carbamoylation of the 2,3-di-*O*-methyl- and 2,3-di-*O*-acetyl cyclodextrins **7d** and **7a** (Scheme 1).

Products **1**–**4** and their intermediates were characterized by ^{1}H NMR spectroscopy by comparison of the homonuclear DQF-COSY and ROESY maps. The ^{13}C NMR resonances were assigned on the basis of the heteronuclear scalar correlations detected in the HETCOR maps. The ^{1}H and ^{13}C NMR chemical shift data are reported in Section 4.

2.2. Conformational analysis of 1–4

The stereochemistry of the derivatives **1**–**4** has been investigated in $CDCl_3$ solution both by ROESY analyses and proton-selective relaxation measurements. Indeed, as recently reported for the per-*O*-acetyl-β-cyclodextrin,[13] selected traces of the ROESY maps are diagnostic in the detection of the macrocyclic distortion induced by the derivatization.

In particular, the H-1 traces contain information concerning the mutual rotation of adjacent glucose units around the glycosidic linkages (Fig. 3), being the interunit H-1–H-4′ NOE (the apex is referred to protons belonging to the adjacent unit) more intense than the intraunit H-1–H-2 NOE in the absence of such a rotation, as in the case of the parent β-cyclodextrin,[12] where the distance $r_{14'}$ is shorter than r_{12}.

The analysis of the H-3 and/or H-2 traces allows one to detect the glucopyranose ring conformational distortions. In fact, the distances of the proton pairs H-4–H-3 and H-3–H-2 assume the highest values (>3 Å) in the $^4C_1$ chair (Fig. 4a), but any ring distortion (Fig. 4) causes them to become shorter, as in the completely inverted $^1C_4$ chair (Fig. 4b).

Comparable H-1–H-4′ and H-1–H-2 NOEs were detected in the H-1 trace (Fig. 5) of derivative **4**, which was acetylated on the secondary rim, according to a degree of mutual rotation of the adjacent units, which is similar to that found for the peracetylated β-cyclodextrin.[13] By contrast, in the corresponding ROESY trace

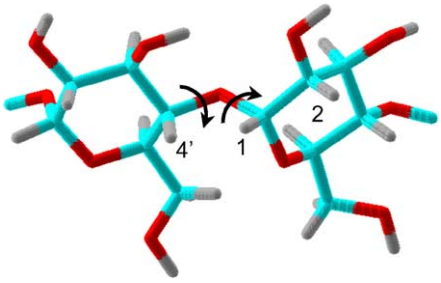


Figure 3. Two glucopyranose units of β-cyclodextrin.

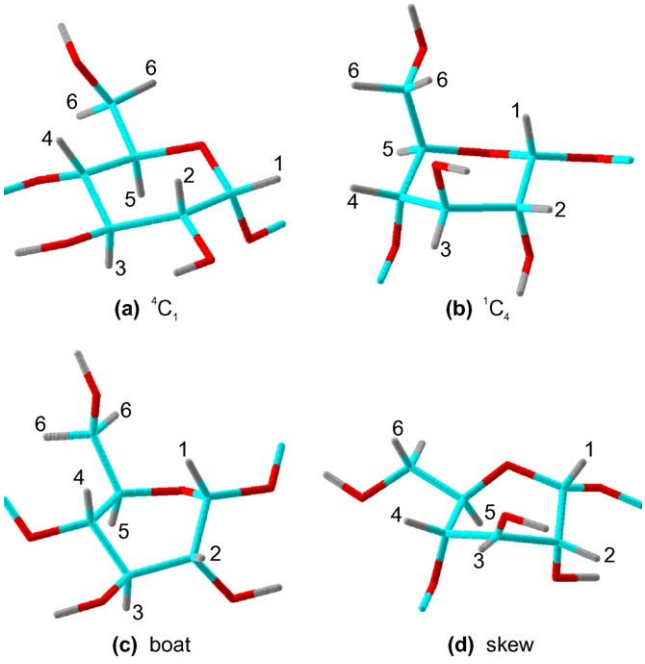


Figure 4. Representation of some glucopyranose ring conformation: (a) $^4C_1$ chair, (b) $^1C_4$ chair, (c) boat, (d) skew.

(Fig. 5) of the cyclodextrin **2**, having the acetyl moieties on the primary rim and the *O*-carbamate functions on the secondary one, a more intense H-1–H-4′ NOE than the H-1–H-2 one was observed as an evidence of a nearly retained coplanarity of the C-1–H-1 and C-4′–H-4′ bonds, which is expected for the truncated cone shape of the underivatized system.

An analogous trend of the relative intensities of the H-1–H-4′ and H-1–H-2 NOEs was observed in the traces of the anomeric protons of the corresponding *O*-methyl systems **1** and **3** (Fig. 5). Indeed, once again the derivative **1**, having the carbamoyl moieties on the cyclodextrin 2- and 3-positions, adopts an unperturbed stereochemical arrangement. On the contrary, the mutual rotation of adjacent rings around the glycosidic linkages was observed for the derivative **3**, which was carbamated on the primary rim.

The NOE data are in good agreement with the inter-proton distances ratios calculated from the cross-relaxation terms obtained by ^{1}H mono- and biselective

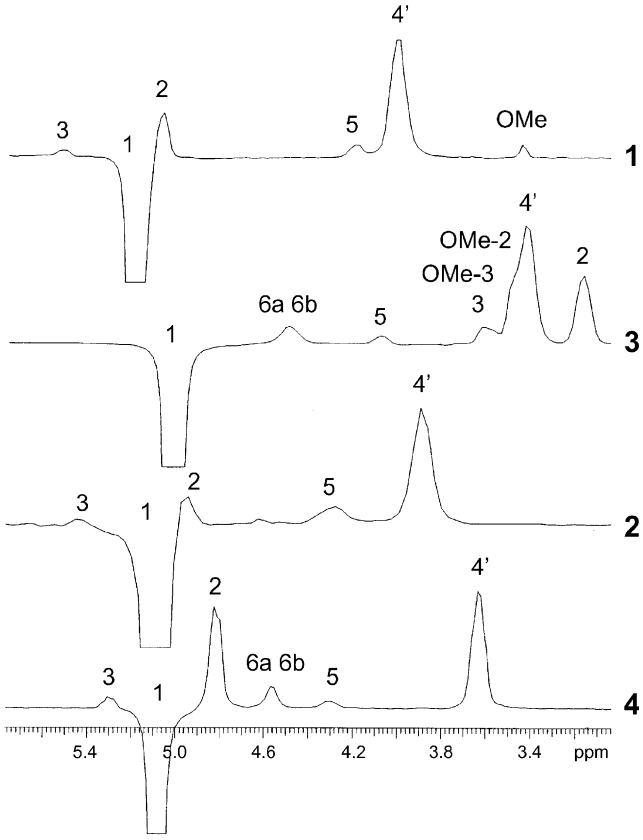


Figure 5. 2D ROESY (300 MHz, $CDCl_3$, 25 °C, τ_m = 0.3 s) analysis of derivatives **1**–**4**. Traces correspond to the H-1 proton.

relaxation measurements, at least in the cases of the derivatives **1**, **2** and **4**, which are characterized by well-separated proton resonances in their ^{1}H NMR spectra.

Indeed, in the initial rate approximation[21] the cross-relaxation term σ_{ij}, which describes the magnetization transfer between the proton pair *ij*, is a function of the reorientational correlation time σ_c of the vector connecting the two spins *i* and *j* and of their distance r_{ij}. In the fast and slow motion regimes, such parameters become a simple function of τ_c and r_{ij}, as reported in Eqs. 1 and 2:

$$\sigma_{ij} = 0.5\gamma^4\hbar^2 r_{ij}^{-6}\tau_c \text{ fast motion} \quad (1)$$

$$\sigma_{ij} = -0.1\gamma^4\hbar^2 r_{ij}^{-6}\tau_c \text{ slow motion} \quad (2)$$

where γ is the proton magnetogiric ratio and $\hbar$ is the reduced Planck constant.

In the hypothesis of isotropic motion, the same reorientational time can be attributed to all the molecule, and the ratio of the different σ_{ij} values are correlated to the ratios of the internuclear distances, as reported in Eq. 3:

$$\frac{\sigma_{ik}}{\sigma_{ij}} = \frac{r_{ij}^6}{r_{ik}^6} \quad (3)$$

The σ_{ij} parameters can be very simply calculated as differences between the biselective and monoselective relax-

ation rates for the proton pair *ij*. The monoselective relaxation rates R_i^{ms} are obtained by selective inversion of the spin *i* leaving unperturbed the other protons, whereas the biselective ones R_{ij}^{bs} are measured following the recovery of the proton *i* in the time under simultaneous inversion of the sole spin *j*.

In this way we calculated the σ_{12} and $\sigma_{14'}$ cross-relaxation terms by means of the biselective and monoselective relaxation rates R_{12}^{bs}, $R_{14'}^{bs}$ and R_1^{ms} indicated in Table 1, and, hence, by using Eq. 3, we determined the ratios between the interproton distances $r_{14'}$ and r_{12} (Table 1).

For cyclodextrins **1** and **2**, having carbamoylated secondary sites, these ratios are, respectively, 0.81 and 0.76, to indicate that the $r_{14'}$ distance is significantly shorter with respect to that of r_{12}. By contrast, the value 0.98 was calculated for **4**, having acetylated secondary functions, which is very close to the one obtained for the peracetylated cyclodextrin,[13] according to the presence of relative rotation of the glucosidic units around the glycosidic linkages.

We could not perform the same kind of analysis for the cyclodextrin **3** due to partial resonance superimpositions, which prevented us from selectively inverting the proton H-4′.

Regarding to the $^4C_1$ chair distortion, the ROESY traces of the H-2 protons (Fig. 6) for **1**–**4** and also of H-3 protons (Fig. 7) for the systems **1**, **2** and **4**, which gave rise to well-resolved proton resonances, were analyzed.

In the H-2 traces (Fig. 6), together with the usual H-2–H-1 and H-2–H-4 NOEs typical for the $^4C_1$ chair, H-2–H-3 dipolar interactions were detected for all the derivatives. These last NOEs are unexpected for 1,2-diaxial protons in the $^4C_1$ chairs and can be diagnostic of the presence of distorted units, having the two protons in pseudodiequatorial arrangements. However, the most interesting point is the comparison between the relative magnitudes of the H-2–H-4 and H-2–H-3 NOEs. In fact, for the cyclodextrins with the carbamoyl functions on the secondary rim and acetylated or methylated groups on the primary positions (**1**–**2**), the inter-NOE H-2–H-4 was largely prevailing on the H-2–H-3 effect, and, hence, only few distorted units are present.

Table 1. Measured mono- and biselective relaxation rates (R_i^{ms}, R_{ij}^{bs}, s^{-1}), calculated cross-relaxation parameters (σ_{ij}, s^{-1}) and interproton $r_{14'}/r_{12}$ ratios for **1**–**2** and **4**

CD	*ij*	R_i^{ms}	R_{ij}^{bs}	σ_{ij}	$r_{14'}/r_{12}$
1	12	2.49	2.32	−0.17	0.81
	14′	2.49	1.88	−0.61	
2	12	2.20	2.12	−0.08	0.76
	14′	2.20	1.80	−0.40	
4	12	2.26	2.11	−0.15	0.98
	14′	2.26	2.09	−0.17	

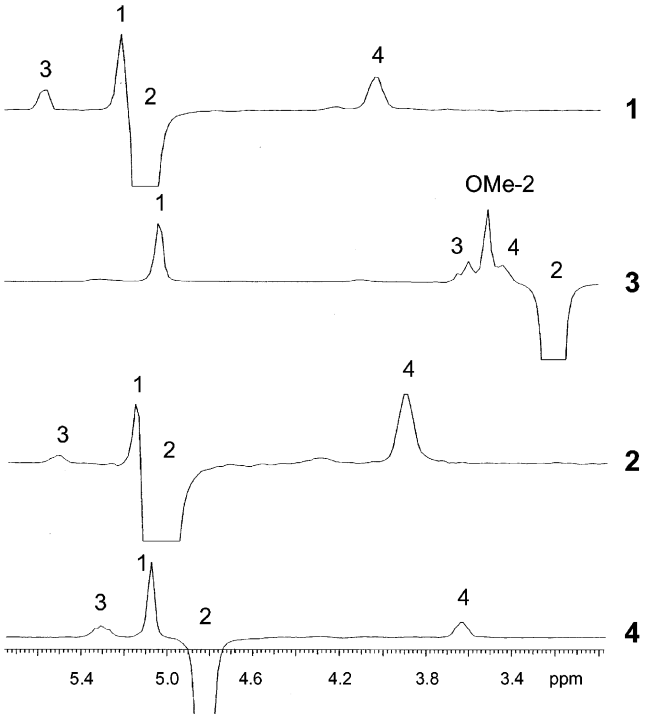


Figure 6. 2D ROESY (300 MHz, $CDCl_3$, 25 °C, τ_m = 0.3 s) analysis of derivatives **1**–**4**. Traces correspond to the H-2 proton.

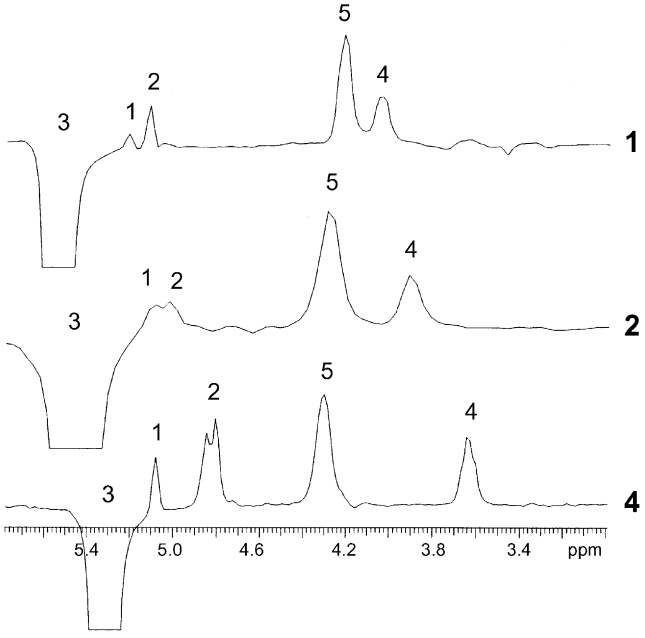


Figure 7. 2D ROESY (300 MHz, $CDCl_3$, 25 °C, τ_m = 0.3 s) analysis of derivatives **1**, **2** and **4**. Traces correspond to the H-3 proton.

By contrast, for the two cyclodextrins **3** and **4**, which are carbamoylated on the primary rim, these NOEs are comparable. This result indicates the presence of a significant population of distorted units and can be the consequence of two different phenomena: (1) the shortening of the H-2–H-3 distance and/or (2) the lengthening

of the H-2–H-4 distance, which could be concomitant in a distorted ring. This last conclusion is supported by the fact that in the two cyclodextrins **3** and **4**, the inter-NOEs H-2–H-4 become smaller with respect to the H-2–H-1 one, and, taking into account that any ring distortion cannot change the H-2–H-1 distance significantly, the H-2–H-4 distance must be larger in the distorted units relative to the $^4C_1$ chairs.

The traces of the H-3 proton showed the expected H-3–H-5 NOE corresponding to the undistorted $^4C_1$ conformation and significant H-3–H-4 and H-3–H-2 NOEs (Fig. 7), supporting the presence of some units in a stereochemical arrangement, which brings H-3 pseudoequatorial. The relative contribution of the distorted units with respect to the undistorted ones is well reflected in the relative intensities of the H-3–H-5 and H-3-H-4 or H-3–H-2 NOEs. As a matter of fact, the last ones are more significant for the cyclodextrin **4**, which is carbamoylated on the primary rim, than they are for **1** and **2**.

It is noteworthy that the traces of the protons H-1, H-2 and H-3 also allow us to exclude some kinds of ring distortions. In fact the completely inverted $^1C_4$ chair (Fig. 4b) should give rise to a strong contribution to the H-1–H-6 NOE, which is not detected. The boat conformation indicated in Figure 4c could keep the H-3 and H-4 protons diaxial as well. This is in disagreement with the relevant H-3–H-4 inter-NOE detected in all the H-3 traces. Therefore, our data support the presence of some units in a skew type conformation having pseudoequatorial the H-2, H-3 and H-4 protons, as shown in Figure 4d.

In the case of the peracetylated β-cyclodextrin, an analogous kind of ring distortion was evidenced, not only by NOE measurements, but also by determining the averaged interproton distances by means of proton-selective relaxation rates;[13] however, for cyclodextrins **1**–**4**, this approach was not possible as the resonances of the two diastereotopic protons H-6a and H-6b at fixed distance were partially superimposed on other signals. Hence, we could not determine their cross-relaxation term to be used to calculate other unknown proton distances by means of Eq. 3.

Finally, the relative positions of the substituents on the primary and secondary rims have been determined for the methylated–carbamoylated cyclodextrins **1** and **3**. For **3**, which is carbamoylated on the primary hydroxyl groups, inter-NOEs between the 3,5-dimethylphenyl and the methoxy groups in the 2- and 3-positions were observed (Fig. 8), which can be attributed to the tilting of adjacent units and to the relevant degree of glucopyranose distortions, which leads to the spatial proximity of the aromatic and methoxy moieties, as shown in Figure 9.

In the case of **1**, which is methylated on the primary rim, and for which a lesser degree of tilting and deviation from the $^4C_1$ chair were found, no dipolar interactions were observed between the OMe-6 and the

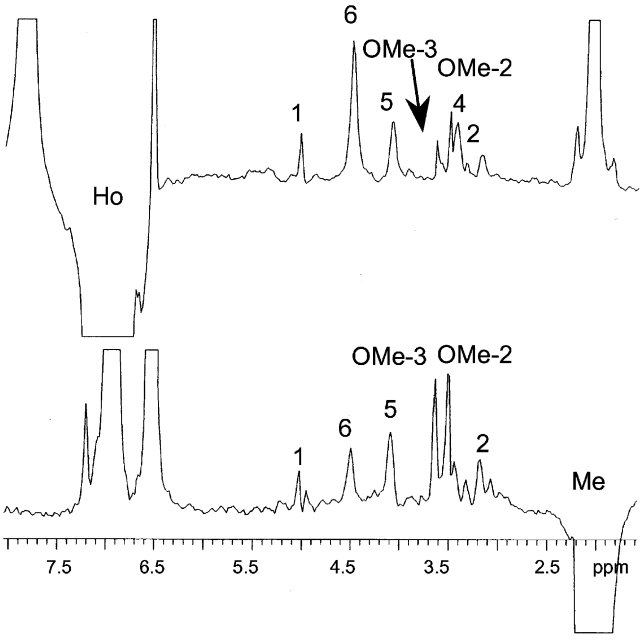


Figure 8. 2D ROESY (300 MHz, $CDCl_3$, 25 °C, τ_m = 0.3 s) analysis of **3**. Traces correspond to the *ortho* protons and the methyl groups of the 3,5-dimethylphenyl moiety.

carbamate functions (Fig. 10), which is in agreement with a nearly torus shape in which the carbamate moieties contribute to extend the cavity bringing them far away from the methoxy groups on the primary rim (Fig. 11).

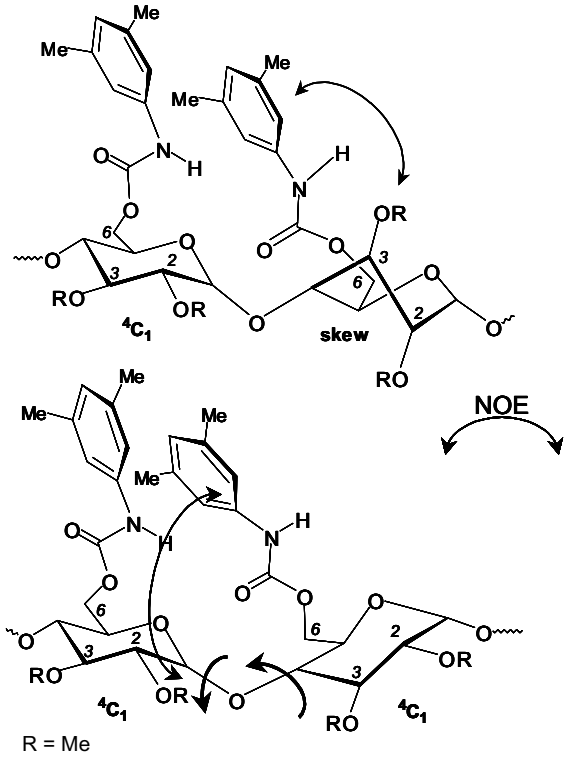


Figure 9. Stereochemical representation of **3**.

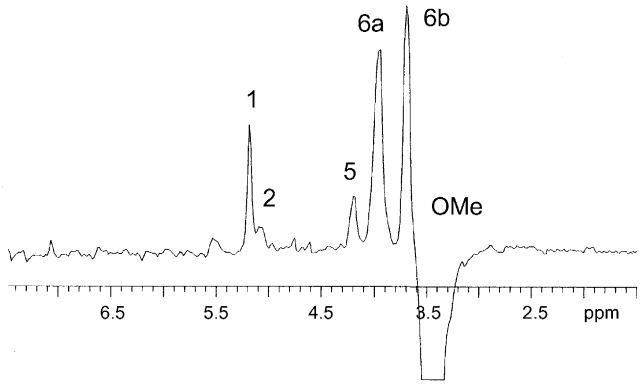


Figure 10. 2D ROESY (300 MHz, $CDCl_3$, 25 °C, $\tau_m = 0.3$ s) analysis of **1**. Trace correspond to the methoxy protons on the primary rim.

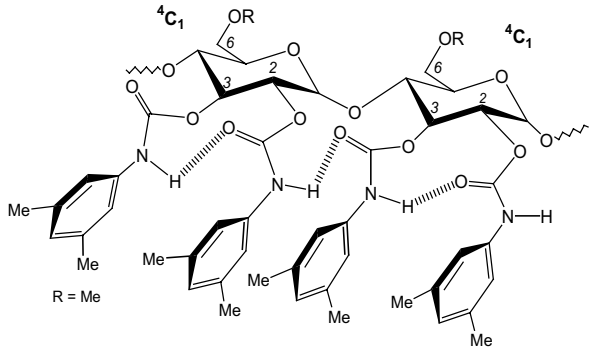


Figure 11. Stereochemical representation of **1**.

For the corresponding acetylated systems, **2** and **4**, the superimposition of the methyl resonances of the acetyl and 3,5-dimethylphenyl moieties precludes the analysis.

3. Conclusions

NMR spectroscopy is confirmed to constitute one of the most powerful tools of detection of conformational distortions originated by derivatization of the glucopyranose rings of cyclodextrins, in spite of their symmetry. In fact, intraunit and interunit dipolar interactions, due to interproton spatial proximity, can be efficiently detected by mono- and bidimensional techniques, allowing us to impose valid restraints in conformational analysis. In the case of symmetrical perderivatized β-systems, two kinds of distortions are detected: (1) the tilting of glucopyranose rings about the glycosidic linkages and (2) the deviation of units from the expected $^4C_1$ chair, leading to skew conformations. Both of the above effects give contributions to the molecular conformation, which strongly depend on the nature of the derivatizing groups and mainly on the nature of the groups introduced on the secondary sites. In particular, when hydrogen-bond acceptor/donor substituents that are able to stabilize interunit attractive interactions are present on the secondary rim, the cyclodextrin derivatives show a low degree of ring deformations and negligible tilting of adjacent units, which is a behaviour that is expected for an underivatized β-cyclodextrin. In these cases, the derivatizing groups can produce an extension of the truncated cone cavity, which, in principle, could retain its inclusive properties. By contrast, when the secondary sites are devoid of hydrogen-bond donor/acceptor groups, the truncated cone shape of cyclodextrins is strongly perturbed. This is due mainly to the glucopyranose ring deformations with a small, but significant, contribution from the tilting of the units. It is worth noting that analogous phenomena were determined by the derivatization of α-cyclodextrins.[9,12] In some cases, the tilting of the units led to a limit situation where reduction of the symmetry from C-6 to C-3 occurred,[9,22] and in the ^{1}H NMR spectra two different kinds of glucopyranose rings were observed, some of which deviated themselves from the $^4C_1$ structure. Therefore, in general, when these two effects, tilting and unit deformations, give strong contributions to the stereochemical arrangements of the cyclodextrins, then they can generate a flattening of the structure where the polarity differences between internal and external surfaces are made less pronounced, and, hence, the complexing properties could change dramatically. In these cases, inclusion processes could become less favoured relatively to superficial interactions, mainly driven by the nature of the derivatizing groups independently from the cyclic structure of the systems.

4. Experimental

4.1. General methods

NMR measurements were performed on a spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively, and the temperature was controlled to ±0.1 °C. All ^{1}H and ^{13}C NMR chemical shifts are referenced to Me_4Si as external standard. The 2D NMR spectra were obtained using standard sequences. The double-quantum-filtered (DQF) COSY experiments were recorded with the minimum spectral width required; 512 increments of eight scans and 2K data points were acquired. The relaxation delay was 5 s. The data were zero-filled to 2K × 1K and a Gaussian function was applied for processing in both dimensions. The HETCOR spectra were acquired with the minimum spectral width required in F_2 and in F_1 in 2K data points using 64 scans of the 512 increments. The relaxation delay was 1 s. The data were zero-filled to 2K × 1K, and a Gaussian function was applied for processing in both dimensions. The ROESY spectra were recorded in the phase-sensitive mode, by employing a mixing time ranging from 0.2 to

0.6 s. Within the above mixing time range any significant variation of NOE intensities were not observed. The spectral width used was the minimum required in both dimensions. The pulse delay was maintained at 5 or 10 s; 512 increments of eight scans and 2K data points each were collected. The data matrix was zero-filled to 2K × 1K, and a Gaussian function was applied for processing in both dimensions. The selective relaxation rates were measured in the initial rate approximation by employing a selective π pulse with the proton decoupler at the selected frequency for 25 ms. After the delay τ, a nonselective π/2 pulse was employed to detect the longitudinal magnetization. For the biselective measurements, the two protons were inverted consecutively. Thin-layer chromatography (TLC) was carried out on silica gel plates (E. Merck, Silica G-60 0.2 mm), and compounds were visualized with iodine vapour or by examination under UV light. Chromatography was carried out using Silica Gel 60 (70–230 mesh ASTM). Melting points were determined using a Koffler hot-stage apparatus.

4.2. Materials

Cyclomaltoheptaose (β-cyclodextrin) and *tert*-butylchlorodimethylsilane (TBDMSCl) were purchased from Fluka Chemical Co. Boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$), 3,5-dimethylphenyl isocyanate, Pd/C, methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine were obtained from Aldrich Chemical Co. β-Cyclodextrin was dried (8 h) at 110 °C/0.1 Torr, in the presence of P_2O_5. Heptakis(6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (**5**),[14] heptakis[6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (**6c**)[11] and heptakis[2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (**7c**)[11] were prepared as described elsewhere.

4.3. Heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (6a)[15]

Yield, 97%. ^{1}H NMR ($CDCl_3$, 25 °C): δ 0.017 (MeSi, s, 21H), 0.021 (MeSi, s, 21H), 0.86 (^{t}Bu, s, 63H), 2.02 (Me-3, s, 21H), 2.03 (Me-2, s, 21H), 3.70 (H-6′, d, $J_{6,6'}$ 11.9 Hz, 7H), 3.84 (H-5, br d, $J_{5,4}$ 6.6 Hz, 7H), 3.86 (H-4, dd, $J_{4,3}$ 9.8 Hz, $J_{4,5}$ 6.6 Hz, 7H), 4.02 (H-6, br d, $J_{6,6'}$ 11.9 Hz, 7H), 4.68 (H-2, dd, $J_{2,3}$ 10.1 Hz, $J_{2,1}$ 3.6 Hz, 7H), 5.14 (H-1, d, $J_{1,2}$ 3.6 Hz, 7H), 5.33 (H-3, dd, $J_{3,2}$ 10.1 Hz, $J_{3,4}$ 9.8 Hz, 7H). ^{13}C NMR ($CDCl_3$, 25 °C): δ −5.4 (MeSi), −5.1 (MeSi), 18.2 [$(CH_3)_3C$], 20.7 (Me-3), 20.8 (Me-2), 25.8 [$(CH_3)_3C$], 61.8 (C-6), 71.2 (C-2), 71.5 (C-3), 71.8 (C-5), 75.2 (C-4), 96.4 (C-1), 169.4 (CO, Ac-3), 170.8 (CO, Ac-2). Anal. Calcd for $C_{112}H_{196}O_{49}Si_7$: C, 53.3; H, 7.83. Found: C, 53.91; H, 7.04.

4.4. Heptakis(2,3-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (6b)

To a solution of **5** (7.50 g, 3.88 mmol) in dry DMF (120 mL) was added, at 0 °C, NaH (4.51 g, 188 mmol). The suspension was allowed to stir at 0 °C for 2 h, and then benzyl bromide (22.4 mL, 32.2 g, 188 mmol) was added. The reaction mixture was stirred for further 2 h at 0 °C and 12 h at room temperature and then quenched with MeOH. The organic layer was extracted with pentane, washed with H_2O, dried (Na_2SO_4) and finally concentrated to give **6b** (87%): ^{1}H NMR ($CDCl_3$, 25 °C): δ 0.01 (MeSi, s, 21H), 0.02 (MeSi, s, 21H), 0.88 (^{t}Bu, s, 63H), 3.39 (H-2, dd, $J_{2,3}$ 9.3 Hz, $J_{2,1}$ 3.2 Hz, 7H), 3.71 (H-6′, br d, $J_{6',6}$ 11.5 Hz, 7H), 3.74 (H-5, br d, $J_{5,4}$ 9.0 Hz, 7H), 4.0 (H-4, dd, $J_{4,5} = J_{4,3}$ = 9.0 Hz, 7H), 4.06 (H-3, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 9.0 Hz, 7H), 4.26 (H-6, br d, $J_{6,6'}$ 11.5 Hz, 7H), 4.49 and 4.53 (CH_2, Bn-2, d, J 12.0 Hz, 14H), 4.71 and 5.08 (CH_2, Bn-3, d, J 10.8 Hz, 14H), 5.32 (H-1, d, $J_{1,2}$ 3.2 Hz, 7H), 6.96–7.45 (Ar, Bn-2 and Bn-3, m, 70H). ^{13}C NMR ($CDCl_3$, 25 °C): δ −5.2 (MeSi), −4.8 (CH_3Si), 18.3 [$(CH_3)_3C$], 25.9 [$(CH_3)_3$ C], 62.4 (C-6), 72.5 (C-5), 72.6 (CH_2, Bn-2), 75.5 (CH_2, Bn-3), 77.7 (C-4), 79.3 (C-2), 80.9 (C-3), 97.9 (C-1), 126.8, 127.4, 127.5, 127.7, 127.9, 128.0 (CH, Bn-2 and Bn-3); 138.3, 139.3 (quaternary C, Bn-2 and Bn-3). Anal. Calcd for $C_{182}H_{252}O_{35}Si_7$: C, 68.39; H, 7.95. Found: C, 68.10; H, 7.81.

4.5. Heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)cyclomaltoheptaose (6d)

To a suspension of NaH (4.30 g, 0.18 mmol) in dry THF (30 mL) was added at 0 °C under stirring a solution of **5** (4.95 g, 2.56 mmol) in dry THF and iodomethane (16.2 mL, 36.9 g, 0.26 mol). The mixture was allowed to stir at 0 °C for 1 h and at room temperature for further 18 h. MeOH was added to quench the reaction. The organic solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was dried (Na_2SO_4), and the solvent was evaporated to give **6d**: mp 89–91 °C. ^{1}H NMR ($CDCl_3$, 25 °C): δ −0.03 (Me_2Si, s, 42H), 0.82 (^{t}Bu, s, 63H), 3.01 (H-2, dd, $J_{2,3}$ 9.7 Hz, $J_{2,1}$ 3.6 Hz, 7H), 3.46 (OMe-2, s, 21H), 3.50 (H-3, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 9.3 Hz, 7H), 3.55 (H-5, m, $J_{5,4}$ 9.3 Hz, $J_{5,6}$ 2.5 Hz, 7H), 3.60 and 4.07 (H-6–H-6′, dd, $J_{6,6'}$ 11.7 Hz, $J_{6,5}$ 2.5 Hz, 14H), 3.62 (OMe-3, s, 21H), 3.68 (H-4, t, $J_{4,3} = J_{4,5}$ = 9.3 Hz, 7H), 5.15 (H-1, d, $J_{1,2}$ 3.6 Hz, 7H). ^{13}C NMR ($CDCl_3$, 25 °C): δ −4.9 (MeSi), −5.2 (MeSi), 18.2 [$(CH_3)_3C$], 25.9 [$(CH_3)_3C$], 58.6 (OMe-2), 61.4 (OMe-3), 62.3 (C-6), 72.1 (C-5), 78.6 (C-4), 82.0 (C-3), 82.2 (C-2), 98.1 (C-1). Anal. Calcd for $C_{98}H_{196}O_{35}Si_7$: C, 55.23; H, 9.27. Found: C, 55.15; H, 9.11.

4.6. Heptakis(2,3-di-*O*-acetyl)cyclomaltoheptaose (7a)[15]

Yield, 98%. ^{1}H NMR (Me_2SO-d_6, 50 °C): δ 1.99 and 2.01 (Me-2 and Me-3, s, 42H), 3.63 (H-6′, dd, $J_{6',6}$ 11.8 Hz, $J_{6',OH}$ 4.6 Hz, 7H), 3.79 (H-6, dd, $J_{6,6'}$ 11.8 Hz, $J_{6,OH}$ 6.3 Hz, 7H), 3.80 (H-5, d, $J_{5,4}$ 8.7 Hz, 7H), 3.84 (H-4, dd, $J_{4,5}$ 8.7 Hz, $J_{4,3}$ 8.6 Hz, 7H), 4.62 (H-2, dd, $J_{2,3}$ 9.7 Hz, $J_{2,1}$ 3.4 Hz, 7H), 4.65 (OH, br dd, $J_{OH,6}$ 6.3 Hz, $J_{OH,6'}$ 4.6 Hz, 7H), 5.09 (H-1, d, $J_{2,1}$ 3.4 Hz, 7H), 5.26 (H-3, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 8.6 Hz, 7H). ^{13}C NMR (Me_2SO-d_6 50 °C): δ 20.2 and 20.3 (Me-2 and Me-3), 59.5, 70.4, 70.5, 71.8, 75.1, 95.8 (C-1–C-6), 169.1 and 169.9 (CO, Ac-2 and Ac-3). Anal. Calcd for $C_{70}H_{98}O_{49}$: C, 48.78; H, 5.73. Found: C, 49.11; H, 5.08.

4.7. Heptakis(2,3-di-*O*-benzyl)cyclomaltoheptaose (7b)

O-Desilylation of **6b** was carried out as described for the preparation of **7a** (94%):[15] ^{1}H NMR ($CDCl_3$, 25 °C): δ 3.46 (H-2, dd, $J_{2,3}$ 9.3 Hz, $J_{2,1}$ 3.7 Hz, 7H), 3.62 (H-4, dd, $J_{4,5}$ 8.8 Hz, $J_{4,3}$ 8.1 Hz, 7H), 3.77 (H-6′, $J_{6',6}$ 12.3 Hz, 7H), 3.91 (H-5, d, $J_{5,4}$ 8.8 Hz, 7H), 3.91 (H-6, d, $J_{6,6'}$ 12.3 Hz, 7H), 3.93 (H-3, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 8.1 Hz, 7H), 4.43 and 4.52 (CH_2, Bn-2, d, J 12.3 Hz, 14H), 4.67 and 4.87 (CH_2, Bn-3, d, J 12.3 Hz, 14H), 4.75 (OH, br s, 7H), 5.01 (H-1, d, $J_{1,2}$ 3.7 Hz), 7.01–7.43 (Ar, Bn-2 and Bn-3, m, 70H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 61.6 (C-6), 72.8 (CH_2, Bn-2), 73.0 (C-5), 74.9 (CH_2, Bn-3), 78.4 (C-2), 78.8 (C-4), 80.4 (C-3), 98.3 (C-1), 127.0, 127.3, 127.5, 127.8, 128.0, 128.2 (CH, Bn-2 and Bn-3), 138.3, 139.0 (quaternary C, Bn-2 and Bn-3). Anal. Calcd for $C_{140}H_{154}O_{35}$: C, 70.16; H, 6.48. Found: C, 70.61; H, 6.15.

4.8. Heptakis(2,3-di-*O*-methyl)cyclomaltoheptaose (7d)

O-Desilylation of **6d** was carried out as described for the preparation of **7a** (80%):[15] mp 158–160 °C. ^{1}H NMR ($CDCl_3$, 25 °C): δ 3.16 (H-2, dd, $J_{2,3}$ 8.9 Hz, $J_{2,1}$ 3.7 Hz, 7H), 3.44 (H-3, m, 7H), 3.47 (H-4, m, 7H), 3.47 (OMe-2, s, 21H), 3.59 (OMe-3, s, 21H), 3.74 (H-5, m, 7H), 3.79 and 3.80 (H-6, m, 14H), 4.78 (OH-6, s, 7H), 5.03 (H-1, d, $J_{1,2}$ 3.7 Hz). ^{13}C NMR ($CDCl_3$, 25 °C): δ 58.6 (OMe-2), 61.3 (OMe-3), 61.4 (C-6), 72.4 (C-5), 80.2 (C-4), 81.6 (C-2), 81.9 (C-3), 98.8 (C-1). Anal. Calcd for $C_{56}H_{98}O_{35}$: C, 50.52; H, 7.42. Found: C, 50.43; H, 7.49.

4.9. Heptakis(2,3-di-*O*-acetyl-6-*O*-methyl)cyclomaltoheptaose (8a) (92%)[15]

^{1}H NMR ($CDCl_3$, 25 °C): δ 2.02 and 2.05 (Me-2 and Me-3, s, 42H), 3.38 (OMe, s, 21H), 3.55 (H-6′, br d, $J_{6',6}$ 10.9 Hz, 7H), 3.82 (H-4, dd, $J_{4,5}$ 8.7 Hz, $J_{4,3}$ 8.4 Hz, 7H), 3.88 (H-6, dd, $J_{6,6'}$ 10.9 Hz, $J_{6,5}$ 5.1 Hz, 7H), 4.01 (H-5, br d, $J_{5,4}$ 8.7 Hz, 7H), 4.80 (H-2, dd, $J_{2,3}$ 10.1 Hz, $J_{2,1}$ 3.7 Hz, 7H), 5.12 (H-1, d, $J_{1,2}$ 3.7 Hz, 7H), 5.33 (H-3, dd, $J_{3,2}$ 10.1 Hz, $J_{3,4}$ 8.4 Hz, 7H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 20.7 and 20.8 (Me-3 and Me-2), 59.1 (OMe), 70.6 (C-5), 70.8 (C-2), 71.0 (C-6), 71.2 (C-3), 75.7 (C-4), 96.5 (C-1), 169.4 and 170.6 (CO, Ac-3 and Ac-2). Anal. Calcd for $C_{77}H_{112}O_{49}$: C, 50.77; H, 6.20. Found: C, 51.25; H, 6.34.

4.10. Heptakis(2,3-di-*O*-benzyl-6-*O*-methyl)cyclomaltoheptaose (8b)

To a solution of **7b** (4.31 g, 1.80 mmol) in dry DMF (50 mL) was added, at 0 °C, NaH (2.81 g, 117 mmol). The mixture was stirred at 0 °C for 1 h. The resulting suspension was added at 0 °C to a solution of iodomethane (0.9 mL, 2.05 g, 14.4 mmol) in dry DMF (14 mL). The reaction mixture was stirred at 0 °C for a further 1 h, then at room temperature for 3 h. The reaction was quenched at 0 °C by adding MeOH, and the mixture was concentrated. The residue was dissolved in CH_2Cl_2, washed with H_2O, $Na_2S_2O_3$ (10%), brine and dried (Na_2SO_4). Compound **8b** was obtained (92%) by removing the solvent under reduced pressure. ^{1}H NMR ($CDCl_3$, 25 °C): δ 3.26 (OMe, s, 21H), 3.45 (H-2, dd, $J_{2,3}$ 9.5 Hz, $J_{2,1}$ 3.6 Hz, 7H), 3.47 (H-6′, d, J 10.0 Hz, 7H), 3.85 (H-4, m, 7H), 3.87 (H-6, m, 7H), 3.87 (H-5, m, 7H), 3.99 (H-3, dd, $J_{3,2}$ 9.5 Hz, $J_{3,4}$ 8.5 Hz, 7H), 4.41 and 4.50 (CH_2, Bn-2, d, J 12.5 Hz, 14H), 4.76 and 5.06 (CH_2, Bn-3, d, J 10.9 Hz, 14H), 5.04 (H-1, d, $J_{1,2}$ 3.6 Hz, 7H), 7.10–7.30 (Ar, Bn-2 and Bn-3, m, 70H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 58.9 (MeO), 71.1 (C-5), 71.4 (C-6), 73.0 (CH_2, Bn-2), 75.4 (CH_2, Bn-3), 77.4 (C-4), 78.8 (C-2), 80.9 (C-3), 98.5 (C-1); 126.9, 127.2, 127.5, 128.0, 128.2 (CH, Bn-2 and Bn-3); 138.3, 139.3 (quaternary C, Bn-2 and Bn-3). Anal. Calcd for $C_{147}H_{168}O_{35}$: C, 70.82; H, 6.79. Found: C, 71.11; H, 6.97.

4.11. Heptakis(6-*O*-acetyl-2,3-di-*O*-benzyl)cyclomaltoheptaose (8c)[23]

To a solution of **7b** (7.53 g, 3.14 mmol) in dry pyridine (80 mL) was added Ac_2O (26.0 mL, 28.1 g, 276 mmol). The solution was stirred at 100 °C for 14 h and at room temperature for a further 83 h. The pyridine was removed under reduced pressure. The residue was dissolved in toluene, dried (Na_2SO_4) and concentrated to give **8c** (94%): ^{1}H NMR ($CDCl_3$, 25 °C): δ 2.17 (Me, s, 21H), 3.63 (H-2, dd, $J_{2,3}$ 9.1 Hz, $J_{2,1}$ 3.2 Hz, 7H), 3.85 (H-4, dd, $J_{4,3} = J_{4,5} = 8.7$ Hz, 7H), 4.18 (H-3, dd, $J_{3,2}$ 9.1 Hz, $J_{3,4}$ 8.7 Hz, 7H), 4.25 (H-5, d, $J_{5,4}$ 8.7 Hz, 7H), 4.56 (H-6, m, 14H), 4.55 and 4.71 (CH_2, Bn-2, d, J 12.3 Hz, 14H), 4.90 and 5.17 (CH_2, Bn-3, d, J 11.3 Hz, 14H), 5.11 (H-1, d, $J_{1,2}$ 3.2 Hz, 7H),

7.15–7.55 (Ar, m, 70H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 20.5 (Me), 63.3 (C-6), 69.7 (C-5), 72.9 (CH_2, Bn-2), 75.1 (CH_2, Bn-3), 78.5 (C-2), 79.6 (C-4), 80.2 (C-3), 98.6 (C-1), 126.9, 127.3, 127.5, 127.8, 128.0, 128.1 (C, Bn-2 and Bn-3), 138.1 and 138.9 (quaternary C); 170.2 (CO). Anal. Calcd for $C_{154}H_{168}O_{42}$: C, 68.74; H, 6.29. Found: C, 67.88; H, 6.03.

4.12. Heptakis(6-*O*-methyl)cyclomaltoheptaose (9a)

Method A.[15] To a solution of **8a** (1.66 g, 0.91 mmol) in anhyd MeOH (70 mL) was added MeONa in MeOH (0.07 mL, 1 M). The mixture was stirred at room temperature for 3 h, and then H_2O (70 mL) and Amberlite IR-120 [H^+] were added. The mixture was filtered, and the filtrate was dried (Na_2SO_4) and then concentrated to give **9a** (94%).

Method B. To a solution of **8b** (4.07 g, 1.63 mmol) in anhyd MeOH (180 mL) and CH_2Cl_2 (5 mL) was added Pd/C (10%) (3.0 g). The reaction was carried out under H_2 (5 atm) for 24 h at room temperature. The mixture was filtered and the organic layer was dried (Na_2SO_4) and then concentrated to give **9a** (60%): ^{1}H NMR (Me_2SO-d_6, 25 °C): δ 3.24 (OMe, s, 21H), 3.26 (H-4, dd, $J_{4,5}$ 9.9 Hz, $J_{4,3}$ 9.6 Hz, 7H), 3.31 (H-2, ddd, $J_{2,3}$ 8.8 Hz, $J_{2,1}$ 3.6 Hz, $J_{2,OH\text{-}2}$ 7.1 Hz, 7H), 3.56 (H-6 and H-6′, m, 14H), 3.59 (H-3, ddd, $J_{3,4}$ 9.6 Hz, $J_{3,2}$ 8.8 Hz, $J_{3,OH\text{-}3}$ 1.9 Hz, 7H), 3.71 (H-5, ddd, $J_{5,4}$ 9.9 Hz, $J_{5,6} = J_{5,6'} = 6.8$ Hz, 7H), 4.77 (H-1, d, $J_{1,2}$ 3.6 Hz, 7H), 5.72 (OH-3, d, J 1.9 Hz, 7H), 5.80 (OH-2, d, J 7.1 Hz, 7H). ^{13}C NMR (Me_2SO-d_6, 25 °C): δ 53.3 (OMe), 65.6 (C-5), 66.2 (C-6), 67.6 (C-2), 68.3 (C-3), 77.6 (C-4), 97.5 (C-1). Anal. Calcd for $C_{49}H_{84}O_{35}$: C, 47.72; H, 6.87. Found: C, 47.12; H, 6.09.

4.13. Heptakis(6-*O*-acetyl)cyclomaltoheptaose (9b)

To a solution of **8c** (3.36 g, 1.25 mmol) in anhyd MeOH (175 mL) and CH_2Cl_2 (5 mL) was added Pd/C (10%) (2.4 g). (Caution: extreme fire hazard!) The reaction was carried out under H_2 (5 atm) for 24 h at room temperature. The mixture was filtered, and the organic layer was dried (Na_2SO_4) and then concentrated to give **9b** (95%): ^{1}H NMR (Me_2SO-d_6, 25 °C): δ 1.97 (Me, s, 21H), 3.35 (H-2, ddd, $J_{2,3}$ 9.2 Hz, $J_{2,OH}$ 6.4 Hz, $J_{2,1}$ 3.4 Hz, 7H), 3.36 (H-4, dd, $J_{4,3}$ 9.2 Hz, $J_{4,5}$ 8.8 Hz, 7H), 3.62 (H-3, dd, $J_{3,2} = J_{3,4} = 9.2$ Hz, 7H), 3.83 (H-5, dd, $J_{5,4}$ 8.8 Hz, $J_{5,6'}$ 6.4 Hz, 7H), 4.11 (H-6′, dd, $J_{6',6}$ 11.0 Hz, $J_{6',5}$ 6.4 Hz, 7H), 4.34 (H-6, d, $J_{6,6'}$ 11.0 Hz, 7H), 4.87 (H-1, d, $J_{1,2}$ 3.4 Hz, 7H), 5.80 (OH-3, br s, 7H), 5.88 (OH-2, d, J 6.4 Hz, 7H). ^{13}C NMR (Me_2SO-d_6, 25 °C): δ 20.3 (Me), 63.1 (C-6), 69.1 (C-5), 72.1 (C-2), 72.9 (C-3), 82.2 (C-4), 102.1 (C-1), 170.1 (CO). Anal. Calcd for $C_{56}H_{84}O_{42}$: C, 47.06; H, 5.92. Found: C, 46.82; H, 6.04.

4.14. Heptakis[6-*O*-methyl-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (1)

A solution of **9a** (1.12 g, 0.91 mmol) and 3,5-dimethylphenyl isocyanate (2.7 mL, 2.82 g, 19.1 mmol) in dry pyridine (20 mL) was stirred at 80 °C for 20 h. The pyridine was removed under reduced pressure, and the residue, dissolved in $CHCl_3$, was filtered through Celite and PTFE filters (0.45 μm) to eliminate the insoluble fraction to give **1** (75%): ^{1}H NMR ($CDCl_3$, 25 °C): δ 1.88 (Me-2, s, 21H), 2.02 (Me-3, s, 21H), 3.45 (MeO, s, 21H), 3.70 (H-6′, br d, $J_{6',6}$ 10.8 Hz, 7H), 3.97 (H-6, br d, $J_{6,6'}$ 10.8 Hz, 7H), 4.02 (H-4, dd, $J_{4,5}$ 9.6 Hz, $J_{4,3}$ 9.4 Hz, 7H), 4.20 (H-5, br d, $J_{5,4}$ 9.6 Hz, 7H), 5.10 (H-2, dd, $J_{2,3}$ 10.4 Hz, $J_{2,1}$ 3.0 Hz, 7H), 5.18 (H-1, d, $J_{1,2}$ 3.0 Hz, 7H), 5.22 (H-3, dd, $J_{3,2}$ 10.4 Hz, $J_{3,4}$ 9.4 Hz, 7H), 6.39 (H_p-2, s, 7H), 6.42 (H_o-3, s, 14H), 6.46 (H_p-3, s, 7H), 6.64 (H_o-2, s, 14H), 6.64 (NH-3, s, 7H), 6.74 (NH-2, s, 7H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 20.8 (Me-3), 21.0 (Me-2), 59.1 (MeO), 71.0 (C-6), 71.2 (C-2 and C-5), 73.8 (C-3), 77.7 (C-4), 98.7 (C-1), 116.6 (C_o-3), 117.3 (C_o-2), 124.7 (C_p-3), 125.3 (C_p-2), 136.9 and 137.0 (CNH), 137.8 and 138.5 (quaternary C, *meta*), 152.5 and 153.0 (CO). Anal. Calcd for $C_{175}H_{210}N_{14}O_{49}$: C, 63.82; H, 6.43; N, 5.95. Found: C, 63.11; H, 6.89; N, 6.03.

4.15. Heptakis[6-*O*-acetyl-2,3-di-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (2)

Method A. A solution of **9b** (1.70 g, 1.19 mmol) and 3,5-dimethylphenyl isocyanate (3.5 mL, 3.66 g, 25 mmol) in dry pyridine (25 mL) was stirred at 80 °C for 20 h. The pyridine was evaporated under reduced pressure to give **2** (64%). Method B. To a solution of **7c** (1.95 g, 0.61 mmol) in dry pyridine (40 mL) was added Ac_2O (5 mL, 5.41 g, 53 mmol). The mixture was stirred at 100 °C for 7 h. The pyridine was removed, and the residual solvent was coevaporated with toluene. The residue was dissolved in CH_2Cl_2, and **2** was obtained (94%) by precipitation with hexane. ^{1}H NMR ($CDCl_3$, 25 °C): δ 1.89 and 2.02 (Me-2 and Me-3, s, 84H), 2.15 (Me-6, s, 21H), 3.93 (H-4, dd, $J_{4,3}$ 9.4 Hz, $J_{4,5}$ 9.3 Hz, 7H), 4.33 (H-5, dd, $J_{5,4}$ 9.3 Hz, $J_{5,6'}$ 5.0 Hz, 7H), 4.39 (H-6′, dd, $J_{6',6}$ 12.0 Hz, $J_{6',5}$ 5.0 Hz, 7H), 4.67 (H-6, d, $J_{6,6'}$ 12.0 Hz, 7H), 5.05 (H-2, dd, $J_{2,3}$ 10.5 Hz, $J_{2,1}$ 3.7 Hz, 7H), 5.15 (H-1, d, $J_{1,2}$ 3.7 Hz, 7H), 5.54 (H-3, dd, $J_{3,2}$ 10.5 Hz, $J_{3,4}$ 9.4 Hz, 7H), 6.42 (H_o-2 and H_p-3, s, 21H), 6.48 (H_p-2, s, 7H), 6.66 (H_o-3, s, 14H), 6.68 (NH-2, s, 7H), 6.74 (NH-3, s, 7H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 20.7 (Me-6), 20.8 (Me-3), 21.0 (Me-2), 62.5 (C-6), 70.0 (C-5), 71.3 (C-2), 73.3 (C-3), 78.1 (C-4), 98.6 (C-1), 116.5 (C_o-2), 117.2 (C_o-3), 124.9 (C_p-2), 125.5 (C_p-3), 136.8 and 137.0 (CNH), 137.8 and 138.6 (quaternary C, *meta*), 152.5 and 153.0 (CO, Carb), 170.3 (CO, Ac-6). Anal. Calcd for $C_{182}H_{210}N_{14}O_{56}$: C,

62.64; H, 6.07; N, 5.62. Found: C, 61.92; H, 6.15; N, 5.84.

4.16. Heptakis[2,3-di-*O*-methyl-6-*O*-(3,5-dimethylphenylcarbamoyl)]cyclomaltoheptaose (3)

To a solution of **7d** (2.81 g, 2.11 mmol) in dry pyridine (90 mL) was added 3,5-dimethylphenyl isocyanate (3.1 mL, 3.24 g, 22.2 mmol). The mixture was stirred at 80 °C for 20 h, the solvent was evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$ and filtered over Celite. The solid obtained was crystallized from $CHCl_3$–hexane to give **3** (93%): mp 155–157 °C. ^{1}H NMR ($CDCl_3$, 25 °C): δ 2.05 (Me–Ar, s, 42H), 3.19 (H-2, dd, $J_{2,3}$ 9.7 Hz, $J_{2,1}$ 3.5 Hz, 7H), 3.42 (H-4, dd, $J_{4,3} = J_{4,5} =$ 8.6 Hz, 7H), 3.51 (OMe-2, s, 21H), 3.62 (H-3, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 8.6 Hz, 7H), 3.65 (OMe-3, s, 21H), 4.09 (H-5, m, 7H), 4.49 (H-6, m, 14H), 5.03 (H-1, d, $J_{1,2}$ 3.5 Hz, 7H), 6.53 (H_p, br s, 7H), 6.93 (H_o, br s, 14H), 7.78 (NH, s, 7H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 21.1 (Me–Ar), 58.7 (OMe-2), 61.2 (OMe-3), 64.7 (C-6), 69.9 (C-5), 81.2 (C-3), 81.6 (C-4), 82.2 (C-2), 99.1 (C-1), 117.0 (C_o), 125.0 (C_p), 137.6, 138.2 (quaternary C), 154.0 (CO). Anal. Calcd for $C_{119}H_{161}O_{42}N_7$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.07; H, 6.62; N, 4.03.

4.17. Heptakis[2,3-di-*O*-acetyl-6-*O*-(3,5-dimethylphenylcarbamoyl)]-cyclomaltoheptaose (4)

A solution of **7a** (5.34 g, 3.1 mmol) and 3,5-dimethylphenyl isocyanate (4.5 mL, 4.70 g, 32 mmol) in dry pyridine (63 mL) was stirred at 80 °C for 20 h. The pyridine was removed under reduced pressure, and the residue was dissolved in $CHCl_3$, filtered through Celite and then concentrated. The crude residue was dissolved again in THF and centrifuged to eliminate the insoluble fraction. Finally, the residue was again filtered on PTFE filters (0.45 μm) to give, after evaporation of the solvent, pure **4** (87%): ^{1}H NMR ($CDCl_3$, 25 °C): δ 2.05 (Me-2, s, 21H), 2.08 (MeAr, s, 42H), 2.11 (Me-3, s, 21H), 3.64 (H-4, dd, $J_{4,3}$ 8.6 Hz, $J_{4,5}$ 4.3 Hz, 7H), 4.30 (H-5, br d, $J_{5,4}$ 4.3 Hz, 7H), 4.57 (H-6 and H-6′, br s, 14H), 4.83 (H-2, dd, $J_{2,3}$ 9.0 Hz, $J_{2,1}$ 3.7 Hz, 7H), 5.09 (H-1, d, $J_{1,2}$ 3.7 Hz, 7H), 5.30 (H-3, dd, $J_{3,2}$ 9.0 Hz, $J_{3,4}$ 8.6 Hz, 7H), 6.54 (H_p, s, 7H), 6.90 (H_o, s, 14H), 7.55 (NH, s, 7H). ^{13}C NMR ($CDCl_3$, 25 °C): δ 20.7 and 21.1 (Me-2 and Me-3), 63.5 (C-6), 69.7 (C-5), 70.2 (C-2), 70.8 (C-3), 77.7 (C-4), 97.0 (C-1), 117.3 (C_o), 125.2 (C_p), 137.3 (CNH), 138.2 (C_m), 153.6 (CO, carb), 169.4 and 170.6 (CO, Ac-2 and Ac-3). Anal. Calcd for $C_{133}H_{161}N_7O_{56}$: C, 58.01; H, 5.89; N, 3.56. Found: C, 57.61; H, 5.15; N, 3.87.

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