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^1H NMR studies on the hydrogen-bonding network in mono-*altro*-β-cyclodextrin and its complex with adamantane-1-carboxylic acid

Birgit Hakkarainen,[a] Kahee Fujita,[b] Stefan Immel,[c]
Lennart Kenne[a] and Corine Sandström[a,*]

[a]*Department of Chemistry, Swedish University of Agricultural Sciences, PO Box 7015, SE-750 07 Uppsala, Sweden*
[b]*Department of Medicinal Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852-8521, Japan*
[c]*Clemens-Schöpf-Institute of Organic Chemistry and Biochemistry, Technical University of Darmstadt, D-64287 Darmstadt, Germany*

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Abstract—The hydrogen-bond network in mono-*altro*-β-cyclodextrin and in its inclusion complex with adamantane-1-carboxylic acid were investigated by ^1H NMR spectroscopy using the chemical shifts, temperature coefficients and vicinal coupling constants of the exchangeable hydroxy protons. The chemical shifts of the 3-OH signals indicated that the hydrogen-bond network between the 2-OH and 3-OH groups was disturbed not only on each side of the altrose residue, but also along the whole dextrin chain. Upon addition of adamantane-1-carboxylic acid, altrose underwent a conformational change from the $^1C_4$ to the $^OS_2$ form, allowing a more continuous belt of hydrogen bonding, as evidenced by the downfield shift experienced by the 3-OH proton signals of the glucose residues.

Keywords: Conformation; Hydrogen bonding; Hydroxy protons; Inclusion complex

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1. Introduction

Due to the ability of cyclodextrins (CDs) to form inclusion complexes with specific guest molecules, their potential use as drug carriers or as model systems to study enzyme–substrate interactions has been widely investigated.[1] The CDs are rigid structures because the (1→4)-linked α-D-glucopyranosyl rings adopt exclusively the energetically favoured $^4C_1$ chair form and there is only limited rotation around the glycosidic bond.[2] Thus, since enzymes are able to change conformation to accommodate the substrate, CDs have only a limited use as lock-and-key[3] enzyme models. Molecular dynamics simulations and generation of molecular lipophilicity patterns anticipated that modified CDs containing residues with axial hydroxy groups would undergo more profound changes in shape, cavity size and guest-binding properties.[4,5] Modified CDs were synthesised and tested as hosts in inclusion complexes.[6–8] One of those, *cyclo*[(1→4)-α-D-altropyranosyl-hexakis-(1→4)-α-D-glucopyranosyl, Scheme 1], in which one glucose residue has been replaced by an altropyranose unit with axial hydroxy groups, was shown to produce an adaptable host that could be used as an induced-fit enzyme model.[9] From the measurements of the proton vicinal coupling constants ($^3J_{H,H}$) of altrose in mono-*altro*-β-cyclodextrin (**1**), it was found that in D_2O solution, the altrose residue exists in a 61:31:8 equilibrium between the $^1C_4$, $^OS_2$ and $^4C_1$ conformations. Upon inclusion of adamantane-1-carboxylic acid, the equilibrium shifted to 80% of $^OS_2$ conformation.[9]

In β-CD, the secondary hydroxy groups, 2-OH and 3-OH, form a circle of consecutive inter-residue hydrogen bonds. These hydrogen bonds were found in the crystal structure,[1b] in dimethyl sulfoxide (DMSO)

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[*] Corresponding author. Tel.: +46 18671568; fax: +46 18673476; e-mail: corine.sandstrom@kemi.slu.se

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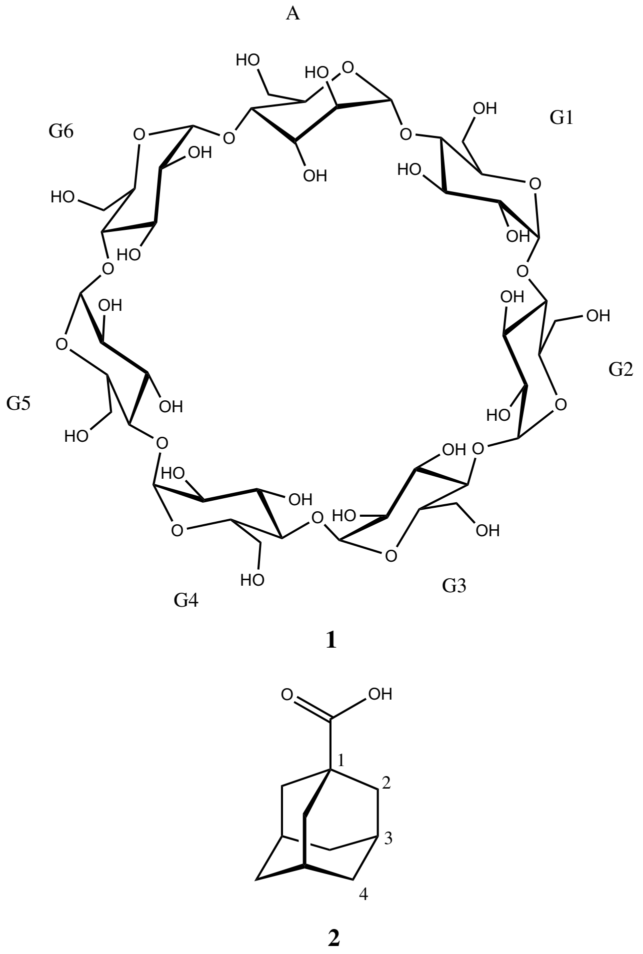

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Scheme 1. Structure of mono-*altro*-β-cyclodextrin (**1**) and adamantane-1-carboxylic acid (**2**). In the structure of mono-*altro*-β-cyclodextrin the α-D-Glc*p* units are numbered starting with the unit substituted at C-4 of α-D-Alt*p*. A represents the α-D-Altp unit.

solutions,[10–12] and in aqueous solutions.[13] In this work, we have investigated how the conformational changes brought by the altrose residue affect the hydrogen bond network in mono-*altro*-β-cyclodextrin and in its complex with adamantane-1-carboxylic acid. For this, the chemical shifts, temperature coefficients and vicinal coupling constants of the hydroxy protons in mono-*altro*-β-cyclodextrin alone and in the complex have been measured and compared to those of β-CD. The complete assignment of the ring protons is also reported. This work is part of a larger study on the use of hydroxy protons for structural and intermolecular interaction studies.

2. Result and discussion

2.1. Assignment of resonances

The chemical shifts for the NMR signals of exchangeable and non-exchangeable protons in mono-*altro*-β-cyclodextrin (**1**) are reported in Tables 1 and 2. DQF-COSY and TOCSY were used to assign the spin system in each individual sugar. Inter-residual NOEs and ^1H–^{13}C heteronuclear chemical shift correlation spectra were used to assign the position of each spin system in the cyclodextrin chain. The one-dimensional NMR spectrum (Fig. 1) showed that the 2-OH signals had a larger dispersion in chemical shifts and larger values of vicinal coupling constants than the 3-OH signals. The sequence of the G2–G5 residues (Scheme 1) was determined from the NOE between the anomeric protons of one glucose residue and the H-4 of the next glucose residue. The G6 residue was assigned from an NOE between its anomeric proton (at δ_H 5.06 ppm) and H-4 of altrose (at δ_H 4.009 ppm). The G1 residue was assigned by the chemical shift of its C-4 signal. In the HMBC spectrum, a cross peak was observed from H-1 of altrose and a C-4 at δ_C 80.2 ppm. This C-4 was slightly more shielded than the C-4 of the other glucose residues which had ^{13}C chemical shifts close to 81.2 ppm.

2.2. Hydrogen-bonding network in mono-*altro*-β-cyclodextrin

It has been shown that hydroxy proton chemical shifts could be used not only to monitor the formation of intermolecular hydrogen bonds but also hydration changes.[13,14] Thus, in strongly hydrated systems, interactions between bulk water and hydroxy groups were found to be the key factors contributing to the chemical shifts of the hydroxy proton signals. When the hydration of a hydroxy group in an oligosaccharide was reduced due to steric factors, the hydroxy proton signal was shifted upfield when compared to the signal of the same proton in the monosaccharide. When a hydroxy group was involved in hydrogen bonding as a donor with another hydroxy group, its proton signal was shifted downfield. In β-CD, the 2-OH and 6-OH signals had chemical shifts similar to those in methyl α-D-glucopyranoside (Table 2), whereas the 3-OH signal was shifted downfield by 0.3 ppm.[13] This downfield shift together with the small $^3J_{C(3)H,O(3)H}$ value of <3 Hz was interpreted as the involvement of 3-OH as a donor in hydrogen bond interaction with O-2 of the next residue.[13] In mono-*altro*-β-cyclodextrin, the signals of 3-OH of the glucose residues have chemical shifts between δ 6.61 and 6.66 ppm with the exception of that of 3-OH of G1, which resonates upfield at δ 6.49 ppm, a chemical shift similar to that of the 3-OH signal in methyl α-D-glucopyranoside. The ball and stick models of mono-*altro*-β-cyclodextrin were built for the three conformations taken by altrose, $^4C_1$, $^OS_2$ and $^1C_4$, using reported dihedral angles[7,9] (Fig. 2). In the $^4C_1$ conformation, the distance from O-2 of altrose to 3-OH of G1 was 5.41 Å (Fig. 2, left entry; 6.01 Å for O-2 A to

Table 1. ^{1}H NMR chemical shift (ppm) of mono-*altro*-β-cyclodextrin (**1**) at 35 °C and at −10 °C with CIS[a] (85% H_2O/15% $(CD_3)_2CO$)

		H-1	H-2	H-3	H-4	H-5	H-6
G1[b]	35 °C	5.055	3.629	3.881	~3.6[c]	3.752	[d]
	−10 °C	5.058 (0.014)	3.622 (0.026)	3.890 (0.008)	3.649 ([e])	3.757 (0.078)	3.852 (0.052) 3.980 (0.011)
G2	35 °C	5.057	3.637	3.952	3.588	3.812	[d]
	−10 °C	5.058 (0.002)	3.633 (−0.026)	3.944 (−0.112)	~3.6[c]([e])	3.833 (0.033)	3.912 (−0.002)
G3	35 °C	5.076	3.663	3.913	3.608	3.802	[d]
	−10 °C	5.077 (0.000)	3.649 (0.006)	3.921 (−0.003)	3.614 (0.000)	3.810 (0.011)	3.936 (−0.011)
G4	35 °C	5.117	3.686	3.889	3.592	3.763	[d]
	−10 °C	5.128 (−0.027)	3.676 (0.002)	3.899 (0.017)	3.608 (0.018)	3.767 (0.081)	3.898 (−0.012)
G5	35 °C	5.153	3.696	3.887	3.581	3.774	[d]
	−10 °C	5.169 (−0.112)	3.692 (−0.045)	3.901 (0.001)	3.592 ([e])	3.792 (0.003)	3.867 (0.027)
G6	35 °C	5.060	3.643	3.962	~3.6[c]	3.871	[d]
	−10 °C	5.070 (0.018)	3.630 (0.043)	3.998 (−0.103)	~3.6[c]([e])	3.890 (−0.046)	3.899 (−0.01)
A	35 °C	4.836	3.803	3.873	4.009	4.237	3.769, 3.875
	−10 °C	4.851 (−0.006)	3.808 (0.076)	3.878 (−0.081)	4.011 (0.049)	4.322 (−0.29)	3.773 (−0.05) 3.878 (−0.04)
β-CD[f] −10 °C		5.072 (0.000)	3.654 (0.000)	3.904 (0.007)	3.604 (0.000)	3.779 (0.012)	3.889 (0.000)
Me-α-D-Glc*p* −10 °C		4.811	3.571	3.680	3.408	3.658	3.776, 3.888

[a] Complexation-induced ^{1}H NMR shift (CIS) is the chemical shift of mono-*altro*-β-cyclodextrin aliphatic protons compared to the chemical shift in the complex with adamantane-1-carboxylic acid.

[b] Numbering according to Scheme 1.

[c] The signals could not be assigned due to spectral overlap with respective H-2.

[d] The H-6 were not assigned at this temperature.

[e] The signals were not assigned in the complex due to spectral overlap.

[f] Data taken from Ref. 13.

Table 2. ^{1}H NMR chemical shifts (δ), $\Delta\delta$, temperature coefficients ($d\delta/dT$) and vicinal coupling constants ($^3J_{OH,CH}$) for hydroxy protons of mono-*altro*-β-cyclodextrin (**1**) at −10 °C in 85% H_2O/15% $(CD_3)_2CO$

	2-OH				3-OH				6-OH		
	δ (ppm)	$\Delta\delta$[a] (ppm)	$d\delta/dT$ (ppb/°C)	$^3J_{OH,CH}$ (Hz)	δ (ppm)	$\Delta\delta$[a] (ppm)	$d\delta/dT$ (ppb/°C)	$^3J_{OH,CH}$ (Hz)	δ (ppm)	$\Delta\delta$[a] (ppm)	$d\delta$ /dT (ppb/°C)
G1[b]	6.27	−0.11	−7.0	6.1	6.49	0.08	−9.6		5.81	−0.20	−9.6
G2	6.22	−0.16	−6.6	7.7	6.66	0.25	−8.4	<3	6.08	0.07	−11.2
G3	6.36	−0.01	−7.1	6.2	6.64	0.23	−8.1	<3	6.07	0.06	−11.7
G4	6.52	0.14	−8.3	7.3	6.62	0.21	−7.6		6.04	0.03	−11.6
G5	6.59	0.21	−9.1	6.6	6.61	0.20	−6.5	<3	5.99	−0.01	−11.2
G6	6.45	0.08	−10.4	7.0	6.63	0.22	−7.3		5.89	−0.12	−11.6
A	6.49		−8.7		6.11		−11.7		6.19		−10.4
β-CD[c]	6.40	0.02	−7.1	6.7	6.71	0.30	−8.1	<3	6.06	0.05	−12.7
Me-α-D-Glc*p*[d]	6.38		−12.1	6.0	6.41		−11.2	5.1	6.01		−12.6

Values for methyl α-D-glucopyranoside and β-CD are reported for comparison.

[a] Values obtained by subtracting the chemical shift of methyl α-D-glucopyranoside.

[b] Numbering according to Scheme 1.

[c] Vicinal coupling constants taken from Ref. 13.

[d] Vicinal coupling constants taken from Ref. 24.

O-3 G1) and was therefore not favourable for hydrogen bonding.[15] Moreover, this conformation was not favoured in the equilibrium since it extends the axially oriented 3-OH group into the interior of the cavity, causing steric interactions. With altrose adopting the $^OS_2$ and $^1C_4$ conformations, the latter calculated to be the predominant conformation,[9] the inter-atomic distance between O-2 of altrose and 3-OH of G1 was small enough (2.36 and 2.03 Å, respectively) for hydrogen bonding. For these three conformations of altrose, the 3-OH of residues G2–G6 had the proper distance and orientation to O-2 of the next sugar residue (Fig. 2) to

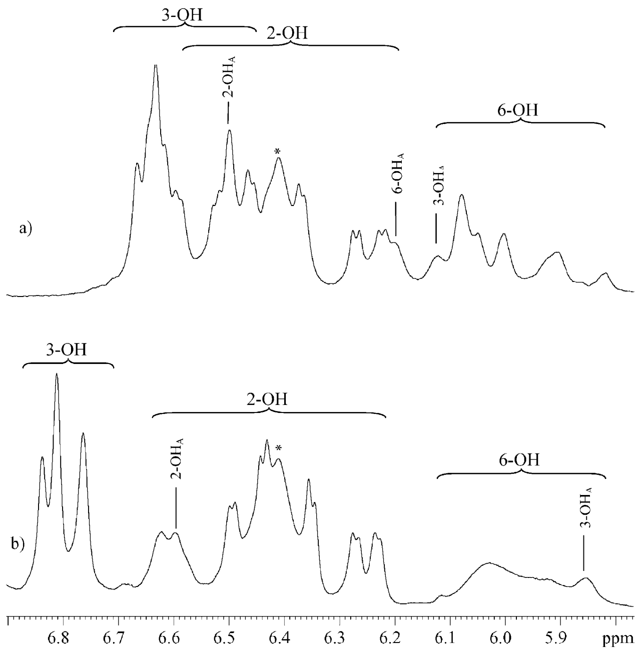

Figure 1. Hydroxy proton region of the 1D ^{1}H NMR spectra of (a) mono-*altro*-β-cyclodextrin and (b) mono-*altro*-β-cyclodextrin in complex with adamantane-1-carboxylic acid, at pH 6.3. *Impurity.

be involved in hydrogen bonds and should therefore be deshielded if compared to methyl α-D-glucopyranoside. Indeed, inspection of Table 2 showed that the 3-OH of G2–G6 was deshielded by more than 0.2 ppm, while the 3-OH signal of G1 had a chemical shift very similar to that in the monosaccharide methyl glycoside.

The five 3-OH of G2–G6 residues were however shielded relative to 3-OH in β-CD ($\Delta\delta = 0.30$ ppm)[13] where a complete belt of hydrogen bonds is formed. This indicated that in **1**, the hydrogen bond network is disrupted not only around the altrose residue but also along the whole dextrin chain. The 2-OH of G1–G6 had chemical shifts between δ 6.22 and 6.59 ppm, the 2-OH of G1 and G2 being shielded relative to those of methyl α-D-glucopyranoside and β-CD. According to the Karplus equation derived for hydroxy protons, vicinal coupling constants, $^3J_{\mathrm{CH,OH}}$, of the order of 5.5 ± 0.5 Hz indicate a free rotation of the hydroxy group around the C–O bond.[16] Deviation from average values indicates restricted rotation due to, for example, hydrogen bonding. Figure 1 and Table 2 clearly show that 3-OH of G1–G6 had small $^3J_{\mathrm{CH,OH}}$ values (<3 Hz), whereas 2-OH had large $^3J_{\mathrm{CH,OH}}$ values around 7 Hz. These values are similar to the values of $^3J_{\mathrm{C(2)H,O(2)H}}$ of 6.7 and $^3J_{\mathrm{C(3)H,O(3)H}}$ <3 Hz measured for β-CD and thus support the chemical shift data on the existence of hydrogen-bond interactions.

Hydroxy protons involved in strong hydrogen bonds should have temperature coefficients ($|\mathrm{d}\delta/\mathrm{d}T|$ values)

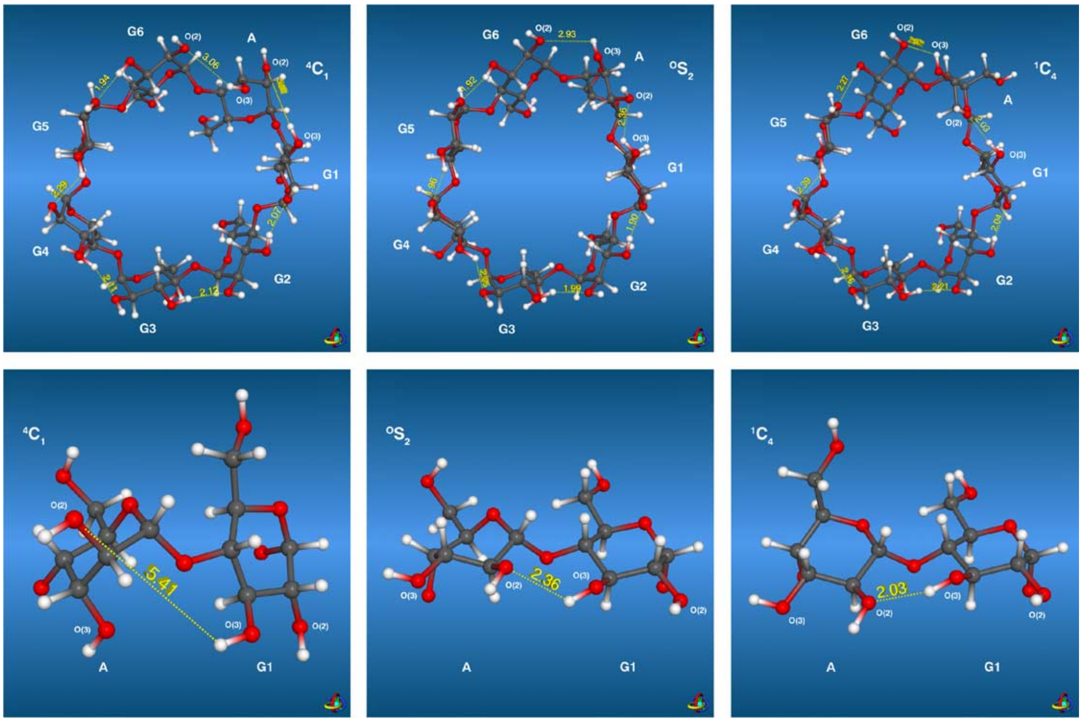

Figure 2. Ball-and-stick models of mono-*altro*-β-CD with three different conformations of altrose (left: $^4C_1$, centre: $^OS_2$, right: $^1C_4$). In the top row, the pyranose moieties of the macrocycles are labelled (cf. Scheme 1) A (altrose unit) and G1–G6 (glucose residues); the dotted yellow lines indicate the O-2···3-OH distances between neighbouring units (O···H distances given in Å). The bottom row graphics provide an enlarged view on the A-G1 segments of the corresponding macrocycles, and the geometrical restraints for the formation of hydrogen bonds between 3-OH of G1 and O-2 of altrose (A). These graphics were generated from the structure proposed in Ref. 9 using the program MolArch$^+$.

below 3.0 ppb/°C.[17,18] Table 2 shows that all hydroxy protons had larger |dδ/dT| values, revealing that no strong hydrogen-bond interaction exists in aqueous solution of mono-*altro*-β-cyclodextrin.

2.3. Complexation with adamantane-1-carboxylic acid

The altrose and G1 to G6 glucose residues were assigned by following the chemical shift changes of the 2-OH signal in mono-*altro*-β-cyclodextrin (**1**) at different molar ratios of adamantane-1-carboxylic acid (**2**, Scheme 1). The assignment of the protons in each monosaccharide was obtained, as for **1** alone, from DQF-COSY and TOCSY spectra recorded at −10 °C. The complexation-induced ^{1}H NMR shifts (CIS) of the aliphatic protons in **1** after addition of one equivalent of adamantane-1-carboxylic acid are given in Table 1, while the chemical shifts, temperature coefficients and vicinal coupling constants of the hydroxy protons are reported in Table 3. The chemical shifts of the 2-OH signals of G1–G6 were not significantly changed upon addition of the guest molecule. On the other hand, the 3-OH of G3–G6 were deshielded by more than 0.15 ppm upon formation of inclusion complex (Table 3, Fig. 1). The 3-OH of G1 was deshielded by as much as 0.27 ppm after addition of **2**, to reach a chemical shift similar to that of the other 3-OH. This downfield shift suggests that 3-OH of G1 is also involved in hydrogen bonding with O-2 of altrose. This hydrogen bond is possible, since upon inclusion of the guest molecule, the altrose changes conformation to 80% of the $^{O}S_2$ form.[9] The hydroxy protons of neighbouring residues have the proper distance and orientation to afford hydrogen bond interaction for all the 3-OH of the glucose residues (Fig. 2). On the other hand, the conformational change of altrose from $^1C_4$ to $^{O}S_2$ leads to a larger distance between O-2 of G6 and 3-OH of A (2.62 Å in $^1C_4$ and 2.93 Å in $^{O}S_2$, Fig. 2) giving a weaker hydrogen bonding and being reflected in the upfield shift of the 3-OH signal of altrose (Table 3). No significant changes in the values of the vicinal coupling constants or temperature coefficients were observed upon formation of an inclusion complex (Table 3).

The existence of an inclusion complex was also confirmed by the observation of cross-peaks between H-3 of **1** and the H-3 and H-4 of adamantane-1-carboxylic acid in the NOESY and ROESY spectra (Fig. 3). The absence of NOE with H-5 of **1** suggested partial inclusion.

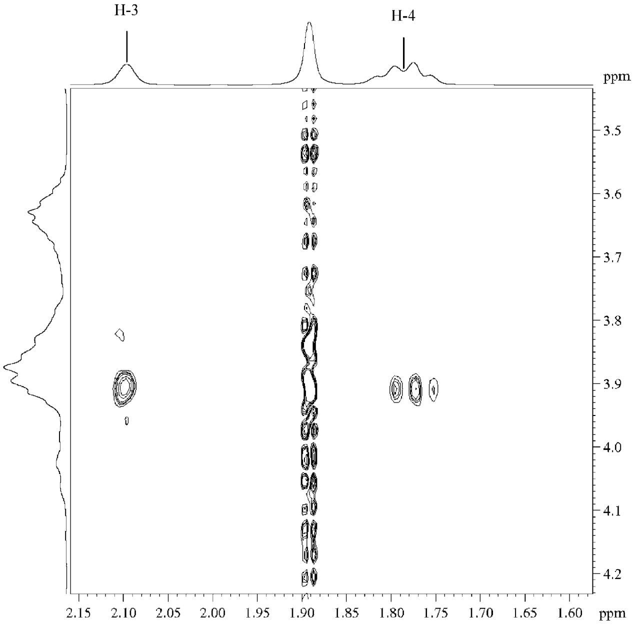

Figure 3. Aliphatic proton region of a ROESY spectrum recorded at −10 °C on the complex of mono-*altro*-β-cyclodextrin and adamantane-1-carboxylic acid. The H-3 and H-4 protons of adamantane-1-carboxylic acid have NOE to H-3 of mono-*altro*-β-cyclodextrin.

Table 3. ^{1}H NMR chemical shifts (δ), $\Delta\delta$ and temperature coefficients (dδ/dT) for hydroxy protons of mono-*altro*-β-cyclodextrin (**1**) in complex with adamantane-1-carboxylic acid (**2**) at −10 °C in 85% H_2O/15% $(CD_3)_2CO$

	2-OH				3-OH			6-OH		
	δ (ppm)	$\Delta\delta$[a] (ppm)	dδ/dT (ppb/°C)	$^3J_{OH,CH}$ (Hz)	δ (ppm)	$\Delta\delta$[a] (ppm)	dδ/dT (ppb/°C)	δ (ppm)	$\Delta\delta$[a] (ppm)	dδ/dT (ppb/°C)
G1[b]	6.27	−0.11	−6.5	6.6	6.76	0.35	−9.5	5.88	−0.13	−11.5
G2	6.23	−0.15	−6.8	5.7	6.69	0.28	−7.0	6.08	0.07	−12.0
G3	6.35	−0.03	−6.5	6.6	6.81	0.40	−10.5	6.07	0.06	−11.9
G4	6.49	0.12	−7.7	6.1	6.84	0.43	−8.7	6.05	0.04	−12.4
G5	6.62	0.25	−10.7	[c]	6.76	0.35	−6.7	6.01	0.00	−11.2
G6	6.44	0.06	−6.9	7.2	6.81	0.40	−10.7	5.98	−0.03	−12.4
A	6.59		−9.7	[c]	5.85		−10.2	[c]		[c]
β-CD	6.40	0.02	−7.1		6.71	0.30	−8.1	6.06	0.05	−12.7
Me-α-D-Glc*p*	6.38		−12.1		6.41		−11.2	6.01		−12.6

Values for methyl α-D-glucopyranoside and β-CD are reported for comparison. The data for O(6)H was collected for solutions at pH 7.4.

[a] Values obtained by subtracting the chemical shift of methyl α-D-glucopyranoside.

[b] Numbering according to Scheme 1.

[c] Not measured due to spectral overlap.

No conclusions were drawn from the CIS of H-3 and H-5 since the changes measured might be due to either formation of a complex or to the change in the conformation of altrose (Table 1). The upfield shift of the H-5 signal of altrose by 0.29 ppm was due to change in the ring conformation upon formation of the inclusion complex.[9]

In previous studies, we have shown that changes in hydration could be monitored from the chemical shifts of the hydroxy protons.[13,14] This work further shows that changes in chemical shifts of hydroxy protons can be used to monitor small changes in hydrogen bond network. The change in the altrose conformation from $^1C_4$ to $^OS_2$ leads to a change in the shape of the hydrophobic cavity, the more elliptical cavity for the $^OS_2$ form, allowing inclusion of the guest molecule. This conformational change also leads to a more regular hydrogen bond network in mono-*altro*-β-cyclodextrin, as evidenced by the chemical shifts of the 3-OH signals of the glucose residues. While changes in the altrose conformation can be followed from the $^3J_{CH,CH}$ values and the existence of an inclusion complex from NOE experiments, structural information on hydrogen bonding can only be obtained from the hydroxy protons.

3. Experimental

3.1. Sample preparation

The synthesis of mono-*altro*-β-cyclodextrin has been reported previously.[19] The samples were dissolved in 85% H_2O/15% $(CD_3)_2CO$ at a sample concentration of 5 mM. To minimise release of impurities from glassware, the NMR sample tubes were soaked in an aqueous 100 mM sodium phosphate buffer of pH 7 for at least 2 h and rinsed with Milli-Q® purified water.[20] The pH of the sample containing mono-*altro*-β-cyclodextrin and adamantane-1-carboxylic acid was adjusted with HCl or NaOH solutions to 6.3 for observation of 2-OH and 3-OH signals and to 7.4 for observation of 6-OH signals.

3.2. NMR Spectroscopy and molecular modelling

All spectra were recorded on a Bruker DRX 600 spectrometer using a 5 mm H/C/N/P inverse probe. The NMR spectra of the samples dissolved in 85% H_2O/15% $(CD_3)_2CO$ were obtained using the WATERGATE pulse sequence for water suppression.[21] The chemical shifts were obtained by setting the residual aceton-d_5 signal to δ_H 2.204 ppm. The 2D homonuclear NMR spectra were recorded in the phase-sensitive mode using the States-TPPI method.[22] TOCSY and COSY spectra were recorded at −13, −10, −5 and 0 °C to obtain the temperature coefficients of hydroxy protons. The ^1H–^1H homonuclear DQF-COSY, TOCSY, NOESY and ROESY spectra and ^1H–^{13}C heteronuclear HMBC, HSQC-DEPT and HSQC-TOCSY spectra were recorded with 4K data points in t_2 and 512 or 400 increments in t_1 using a minimum of 32 scans per increment and a relaxation delay of 1.5 s. The NOESY was run with a mixing time (τ_m) of 300 ms and the ROESY with a spin-lock pulse width of 200 ms. The assignment was done using the SPARKY software (Goddard, T. D.; Kneller, D. G.; 3.111 ed., University of California, San Francisco). Molecular modelling and generation of the graphics was accomplished by using the program MolArch$^+$.[23]

Acknowledgements

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