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Borate esters of the methyl D-glucopyranosides

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Abstract—Methyl α- and β-D-glucopyranoside act as moderate chelators of a boron centre through their O-4/6 binding site whereas the trans/trans arrangement of the O-2/3/4 hydroxy functions is not suited to form a chelate with the small boron central atom. In this work we report the crystal structure of the bisdiolatoborate $Na_2[B(Me\ \alpha\text{-D-Glc}p4,6H_{-2})(Me\ \alpha\text{-D-Glc}p3,4,6H_{-3})]\cdot NaOH\cdot 8H_2O$ (**1**) along with a combined ^{11}B and ^{13}C NMR spectroscopic studies of borate–pyranoside solutions at different concentrations and pH. It is shown that crystallisation of a bisdiolatoborate needs both a high pH and a high total concentration.

Keywords: Carbohydrates; Glucosides; Borates

1. Introduction

Borate–ester formation of a carbohydrate's diol functions has been used for a long time for the synthesis, analysis and separation of carbohydrates. Despite this long-term use, investigations that use crystal structure analysis as a method, which provides unambigous structural data are rare. The obvious reason for the limited use of X-ray data is the low tendency of diolatoborates to form crystals instead of syrupy precipitates from the respective crystallisation batches. Focussing on boric acid esters of glycosides and the parent monosaccharides, there is, to the best of our knowledge, only the structure determination on a bisdiolatoborate with methyl β-D-ribofuranoside as the diol.[1] Though nucleation was delayed for months even in this case, the ribofuranosides are particularly well-suited ligands for the small boron central atoms: they are able to transform the entire boron content of a slightly alkaline solution into the bisdiolatoborate in terms of ^{11}B and ^{13}C NMR spectra. As a general rule it may be stated that furanoidic ligands conform to small central atoms best due to the high flexibility of the five-membered rings, which allow diol torsion angles close to 0° and thus flat chelate rings. Including simple diols, one more crystal structure analysis of a bisdiolatoborate has been reported, namely the one of the sodium bisethanediolatoborate $Na[B(C_2H_4O_2)_2]$.[2]

Herein we report the crystallisation of a bisdiolatoborate species derived from methyl α-D-glucopyranoside (Chart 1) and the results of an accompanying NMR solution study. A characteristic that has to be taken into account in the coordination chemistry of the glucopyranosides is the large 'bite' of the trans-configured O-2/3 and O-3/4 diol functions, which makes them unsuited for chelate formation with a small central atom such as boron, leaving the O-4/6 site as the only suited one. In a recent work on glucopyranoside borates by Miyazaki et al., a 20-fold molar excess of the glucoside over borate is used (pH ca. 8, total borate concentration below 0.02 mol L^{-1} to suppress polyborate formation).[3]

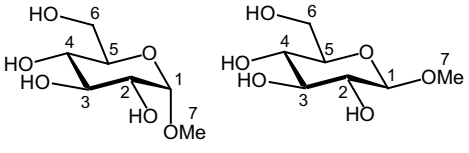

Chart 1. Atom numbering in the methyl D-glucopyranosides: α (left), β (right).

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Even at this high diol-borate ratio, the main solution species is boric acid/borate with mono- and bisdiolatoborates as minor species. In agreement with earlier publications, the most abundant species among the rather unstable diolatoborates is reported to be the O-4,6-bonded bisdiolatoborate. However, the large glucoside excess is detrimental in light of two goals: crystallisation batches result in the formation of a badly defined glucoside-rich solid, and the ^{13}C NMR spectra are dominated by the free glucoside. Both draw-backs are overcome by using pH values of 12 and higher. Under these alkaline conditions (1) the crystallisation of a bisdiolatoborate succeeded from solutions whose composition matched the stoichiometry of the desired product, and (2) both ^{11}B and ^{13}C NMR spectra could be assigned. For the assignment of borate species in the ^{11}B NMR spectra we refer to the publications by the van Bekkum group.[4,5] The ^{13}C NMR spectra were fully assigned by means of 2D NMR techniques (COSY, HMBC, HMQC).

2. Results and discussion

2.1. Synthesis and structure of a crystalline bis(glucopyranosid-4,6-ato)-borate

Orthorhombic crystals of the bisdiolatoborate Na_2[B-(Me α-D-Glc*p*4,6H$_{-2}$)(Me α-D-Glc*p*3,4,6H$_{-3}$)]·NaOH·8H_2O (**1**) have been obtained after a prolonged period of time from strongly alkaline, concentrated syrupy borate solutions, which contained the double molar amount of the glucoside over borate. The result of the structure determination is shown in Figure 1. The asymmetric unit contains 1 formula unit (space group $P2_12_12_1$). Both pyranoside rings are in the usual $^4C_1$ conformation. The boron centre is coordinated tetrahedrally by the O-4/6 diol function of two methyl α-D-glucopyranoside anions thus avoiding the unsuitable trans-diol functions. One of the glucoside ligands is deprotonated at the binding site only, while the other one is deprotonated at three oxygen atoms (O-3, O-4, O-6). The additional site of deprotonation (O-3) is indicated by one of four remarkably short intermolecular O···O distances, the other three being related to hydrated hydroxide ion (see below): the O-31···O-32^{i} distance is only 2.517(2) Å ($^{i}1-x,\ 1/2+y,\ 1/2-z$) long. Difference Fourier syntheses and subsequent refinement result in a short hydrogen bond of the O–H···O$^-$ type [O-31–H 0.88(2), H···O32 1.64(2) Å, O–H···O 176(2)°].

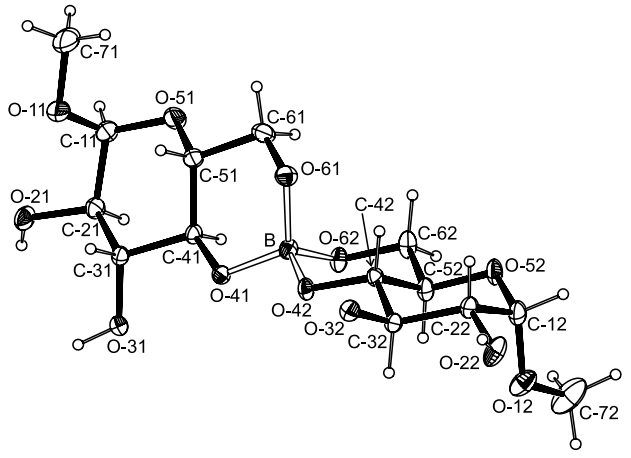

Figure 1. The structure of the almost C_2-symmetrical bisdiolatoborate ion in crystals of **1** (60% ellipsoids). Distances/Å ($\sigma = 0.002$): from B to: O-61 1.472, O-42 1.474, O-62 1.476, O-41 1.480; C-11–O-51 1.409, C-11–O-11 1.410, C-11–C-21 1.535, C-21–O-21 1.415, C-21–C-31 1.544, C-31–O-31 1.416, C-31–C-41 1.530, C-41–O-41 1.431, C-41–C-51 1.526, C-51–O-51 1.431, C-51–C-61 1.520, C-61–O-61 1.421, C-71–O-11 1.436, C-12–O-12 1.407, C-12–O-52 1.423, C-12–C-22 1.532, C-22–O-22 1.411, C-22–C-32 1.544, C-32–O-32 1.404, C-32–C-42 1.531, C-42–O-42 1.434, C-42–C-52 1.530, C-52–O-52 1.440, C-52–C-62 1.517, C-62–O-62 1.424, C-72–O-12 1.436.

2.2. Solution equilibria

Though protolysis is diminished to such an extent that both ^{11}B and ^{13}C NMR spectra show the various diolatoborate complexes in strongly alkaline solution, the low stability of the borate esters results in substantial amounts of both free borate and carbohydrate. Hence the main boron-containing solution species in equimolar solutions of borate and methyl α-D-glucopyranoside is free tetrahydroxidoborate (Fig. 2, top). The typical shift of a monoborate signal indicates the formation of a six-membered chelate ring, that is, the O-4/6 binding site is observed. No signals of diolatoborate species with five-membered chelate rings occur as well as the bisdiolato complex is not formed at this molar ratio. In the ^{13}C NMR spectra free carbohydrate was observed (Fig. 3). The carbon resonances of the complex species were identified and show significantly different shifts than the free carbohydrate (Table 1). Typical for six-membered chelate rings, downfield 'coordination-induced shifts' (CIS) of 4.5 (C-4) and 1.7 ppm (C-6) are observed for the binding-site itself, whereas an upfield shift (−6.5 ppm) is observed for the signal of C-5.

The related methyl β-D-glucopyranoside reacts in a similar way. An O-4/6-bonded monodiolatoborate is formed as well and also the NMR-spectroscopical characteristics match the α anomer. Notably, the monodiolatoborate appears to be slightly more stable and thus occurs as the main solution species in an equimolar solution (Table 2). Bisdiolatoborate species become observable to a small extent when the carbohydrate:borate molar ratio is increased. However, even at an eightfold glucoside excess over borate (pH of 12.42), the extent of bisdiolatoborate formation is limited (Fig. 2). Extrapolation of the observed trends shows that successful crystallisation of the bisdiolatoborate complex can be ascribed to the high total concentrations in the syrupy

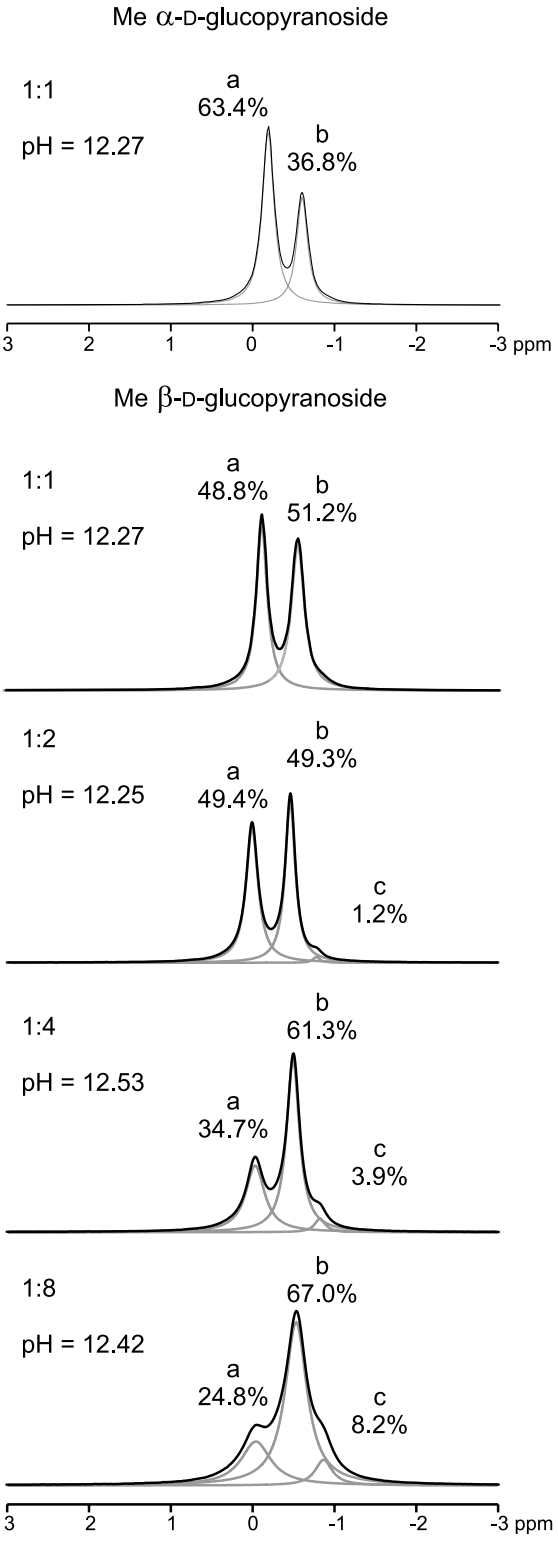

Figure 2. ^{11}B NMR spectra of aqueous solutions of boric acid and the methyl D-glucopyranosides at different stoichiometries, total boron concentration: 0.5 mol L^{-1}. Fitted Lorentz functions are shown as grey lines. Percentages of the solution species are given for various molar ratios of boron:glucoside. Species: (a) tetrahydroxidoborate, (b) 4,6-monodiolatoborate, (c) 4,6-bisdiolatoborate.

crystallisation batches that were reached in the course of the slow evaporation process of the solvent.

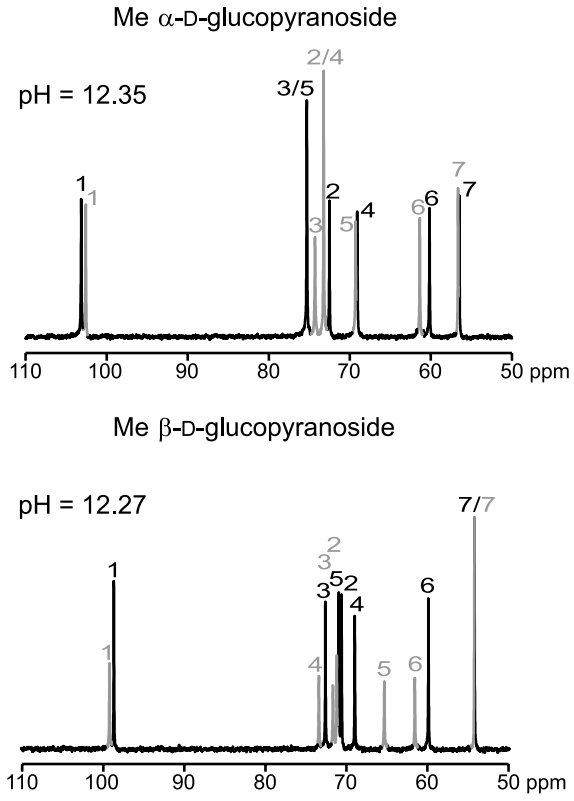

Figure 3. ^{13}C NMR spectra of equimolar aqueous solutions of boric acid and methyl α- and β-D-glucopyranoside at total concentrations of 0.5 mol L^{-1}. Black: free glucoside, grey: monodiolatoborate.

The typical coordination behaviour of the glucosides is contrasted by experiments with methyl α-D-mannopyranoside. The formation of three different species was observed (Fig. 4). Now, the O-2/3 site is cis-configured and thus suited to bind the small boron centre. Accordingly, mono- and bisdiolatoborates with five-membered chelate rings are observed with the monodiolatoborate being the main species. The C-2 and C-3 signals experience a typical CIS of 4.1 ppm and 3.3 ppm. A O-4/6-bonded monodiolatoborate is observed as well, but only as a minor species. In agreement with the glucoside, the C-4 and C-6 signals are shifted downfield whereas the C-5 signal experiences an upfield shift.

The differences of the strongly alkaline pH regime on the one hand and an about neutral medium on the other are underlined by a spectroscopical study of equimolar solutions. At a pH value of 7.92, no signals of borate esters is observed with the glucopyranosides at a total borate concentration of 0.5 mol L^{-1}. Accordingly, equimolar solutions of borate and the methyl mannopyranosides as the better ligands show higher borate consumption in the alkaline regime. Figure 4(top) shows a total of about 78% of non-coordinating borate species at the low pH but only about 25% in an alkaline solution of borate and methyl α-D-mannopyranoside. Note that the O-4/6 bonding mode, which is the only one

Table 1. ^{13}C NMR spectra of equimolar mixtures of methyl α-D-glucopyranoside and boric acid; c(B) = 0.5 mol L^{-1}, 100.5 MHz, 25 °C, pH 12.27

		C-1	C-2	C-3	C-4	C-5	C-6	C-7
[B(Me α-D-Glc*p*4,6H$_{-2}$)(OH)$_2$]$^-$	δ/ppm	99.3	71.4	71.9	73.7	65.7	61.9	54.6
	Δδ/ppm	0.5	0.6	−0.9	**4.5**	−6.5	**1.7**	0.0
Me α-D-Glc*p*	δ/ppm	98.8	70.8	72.8	69.2	71.2	60.2	54.6

Atom numbering refers to Chart 1. Δδ values that indicate a CIS are in boldface.

Table 2. ^{13}C NMR spectra of equimolar mixtures of methyl β-D-glucopyranoside and boric acid; c(B) = 0.5 mol L^{-1}, 100.5 MHz, 25 °C, pH 12.35

		C-1	C-2	C-3	C-4	C-5	C-6	C-7
[B(Me β-D-Glc*p*4,6H$_{-2}$)(OH)$_2$]$^-$	δ/ppm	103.0	73.1	74.2	73.1	69.2	61.3	56.5
	Δδ/ppm	0.6	−0.3	−1.0	**4.1**	−6.0	**1.2**	0.1
Me β-D-Glc*p*	δ/ppm	102.4	73.4	75.2	69.0	75.2	60.1	56.4

Atom numbering refers to Chart 1. Δδ values that indicate a CIS due to coordination are in boldface.

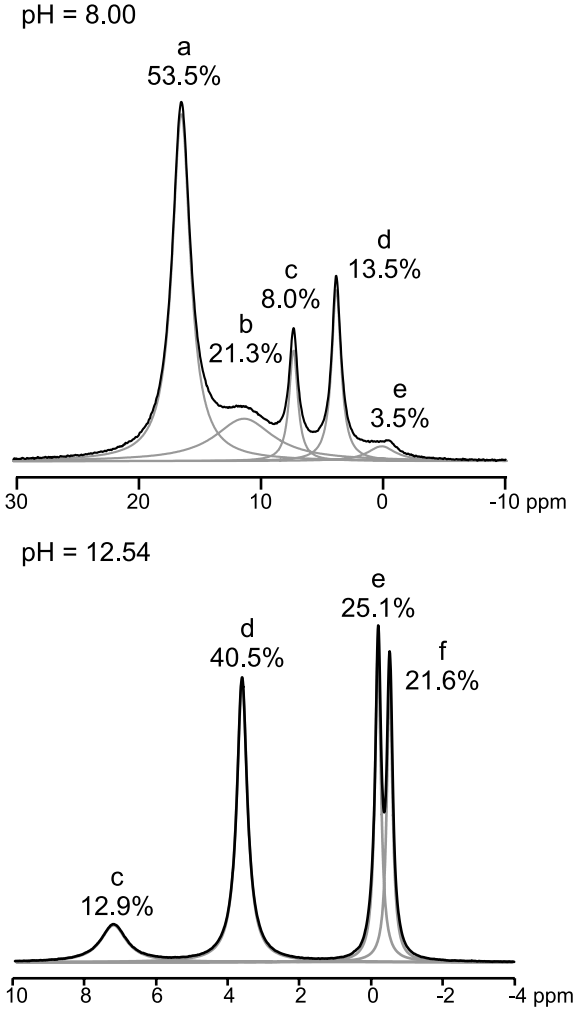

Figure 4. ^{11}B NMR spectra of equimolar aqueous solutions of boric acid and methyl α-D-mannopyranoside at pH 8.00 and pH 12.54 at a total concentration of 0.5 mol L^{-1}. Fitted Lorentz functions are shown as grey lines. Percentages of the following solution species are given: (a) boric acid, (b) polyborate, (c) O-2/3-bonded bisdiolatoborate, (d) O-2/3-bonded monodiolatoborate, (e) tetrahydroxidoborate, (f) O-4/6-bonded monodiolatoborate.

adoptable for a glucopyranoside, is observed at a high pH only.

2.3. Hydrated hydroxide

Crystals of **1** formed in strongly alkaline solution, which contained excess sodium hydroxide (5 mol hydroxide was added per mole boron; of these, 1 mol is spent if only bis(diolato)borate formation is taken into account, 3 mol is needed to transform boric acid into **1**). The hydroxide ion in **1** is monohydrated and hydrogen-bonded to the carbohydrate, meaning there is an $H_3O_2^-$ ion in the crystal structure embedded in a carbohydrate-based donor pair (Chart 2).

The observed O–O distance of only 2.44 Å is at the lower limit for a non-ligating hydroxide-hydrate anion,[6] which may exhibit still smaller distances when acting as a ligand in a metal complex.[7] Difference Fourier syntheses do not indicate a symmetrical hydrogen bond even for the small O–O distance in **1** but indicate an asymmetrical hydrogen bond with a disordered proton. One should note, however, the low reliability of hydrogen positions determined by X-ray data. Although not convincingly proved by experiment, the proton disorder makes sense chemically: as a rule, in water-containing crystals of polyolato complexes there are ordered hydrogen positions along the often cooperative hydrogen-

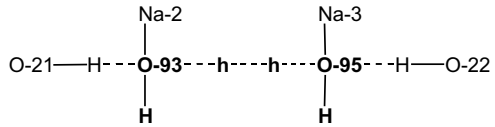

Chart 2. The non-crystallographically C_2-symmetrical surroundings of the $H_3O_2^-$ ion (bold) in crystals of **1** (no symmetry codes given). h ≡ 1/2 H; the hydrogen atoms at O-93 and O-95 in fully occupied position do not act as donors in further hydrogen bonds. Distances/Å: O-21–O-93 2.529(2), O-93–O-95 2.444(2), O-95–O-22 2.540(2); O-93–Na-2 2.353(2), O-95–Na-3 2.312(2).

bond paths; usually these paths start with a hydrogen-bond donor and end with an acceptor. The surroundings of the $H_3O_2^-$ ions in crystals of **1** exhibit non-crystallographic C_2-symmetry (Chart 1), hence a driving force for ordering the proton sequence is missing.

3. Conclusions

There is a close resemblance of the isosteric carbon and B^- centres in terms of bonding distances and angles, the radius of the boron centre being slightly larger. Borate ester formation hence appears to follow the well-known rules of the closely related reactions that are used to prepare carbon analogues. Examples include the formation of isopropylidene acetals, orthoesters or benzylidene acetals in carbohydrate-protection-group chemistry. In all these reactions, either 1,3-dioxane or 1,2-dioxolane rings are formed, the former with the 4,6-diol function of a pyranose, the latter with furanose and pyranose cis-diol functions. trans-1,2-Diol functions are unreactive in all these transformations.[8] The only boron-binding site of the methyl glucopyranosides thus is the O-4/6 site. Accordingly, the methyl xylopyranosides are revealed to be unreactive in an attempted borate ester synthesis. The formation of the various diolatoborates strongly depends on the pH value. While the 4,6-diol function is only addressed as a binding site in strongly alkaline solutions, cis-diol functions, such as in methyl α-D-mannopyranoside, may act as binding sites even at about neutral pH. Coordination through cis-diol functions thus is the most favoured reaction of a pyranoside, with the monodiolatoborates being the main solution species at every pH and concentration.

The lower stability of O-4/6-bonded chelates, in particular the bischelate, becomes obvious in terms of NMR spectra from the low amount of the bisdiolatoborate in stoichiometrically matching solutions even at a high pH and a high total concentration. Attempts to crystallise such species thus need, on the one hand, the syrupy solutions of highest achievable concentration. On the other hand, crystals preferentially are grown at lower concentrations in solvents in which the substance is moderately soluble. Since these optimum conditions are not given in our case, the prolonged nucleation periods observed correspond to the well-established rules of thumb for crystallisation.

4. Experimental

4.1. General methods

^{11}B NMR spectra were recorded on a Jeol EX400 at a resonance frequency of 128.266 MHz and on a Jeol GSX270 at a resonance frequency of 86.860 MHz for ^{11}B. Signals are referred to the BF_3 etherate complex as an external standard. Overlapping signals were resolved into individual peaks by a Lorentzian-curve fitting method (Origin 6.0). The one- and two-dimensional ^{13}C and ^{1}H NMR experiments (HMQC, HMBC, TOCSY, COSY) were performed on a Jeol Eclipse 400 with resonance frequencies of 400 MHz for ^{1}H and 100.525 MHz for ^{13}C. Quartz tubes of 5 mm were used for all measurements.

4.1.1. [B(Me α-D-Glc*p*4,6H$_{-2}$)(OH)$_2$]$^-$. ^{11}B NMR (D_2O) δ −0.59. ^{13}C NMR (D_2O) δ 99.33 (C-1), 73.68 (C-4), 71.89 (C-3), 71.44 (C-2), 65.66 (C-5), 61.92 (C-6), 54.56 (C-7). ^{1}H NMR (D_2O) δ 4.78 (d, 1H, H-1, $^3J_{1,2}$ 3.8 Hz), 3.86 (m, 1H, H-6b), 3.64 (m, 1H, H-6a), 3.64 (dd, 1H, H-3, $^3J_{2,3}$ 9.3 Hz, $^3J_{3,4}$ 9.3 Hz), 3.58 (dd, 1H, H-2, $^3J_{1,2}$ 3.8 Hz, $^3J_{2,3}$ 9.3 Hz), 3.56 (m, 1H, H-5, $^3J_{4,5}$ 9.3 Hz), 3.45 (dd, 1H, H-4, $^3J_{3,4}$ 9.3 Hz, $^3J_{4,5}$ 9.3 Hz), 3.40 (s, 3H, OCH_3).

4.1.2. [B(Me β-D-Glc*p*4,6H$_{-2}$)(OH)$_2$]$^-$. ^{11}B NMR (D_2O) δ −0.56. ^{13}C NMR (D_2O) δ 103.01 (C-1), 74.17 (C-3), 73.11 (C-2/C-4), 69.16 (C-5), 61.24 (C-6), 56.53 (C-7). ^{1}H NMR (D_2O) δ 4.42 (d, 1H, H-1, $^3J_{1,2}$ 7.9 Hz), 3.81 (m, 1H, H-6b, $^3J_{5,6b}$ 4.6 Hz, $^2J_{6a,6b}$ −10.1 Hz), 3.62 (dd,

Table 3. Crystallographic data

	1
Net formula	$C_{14}H_{40}BNa_3O_{21}$
M_r/g mol^{-1}	624.235
Crystal size/mm	0.41 × 0.33 × 0.19
ρ/g cm^{-3}	1.5157(2)
T/K	200(3)
Radiation	Mo Kα
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	9.2735(6)
b/Å	14.4680(11)
c/Å	20.3790(19)
V/Å^3	2735.6(4)
Z	4
μ/mm^{-1}	0.179
Reflections measured	20907
R_{int}	0.0305
Mean $\sigma I/I$	0.0344
θ Range/°	2.44–27.94
Observed reflections	5335
x, y (Weighting scheme)	0.0384, 0
Hydrogen refinement	Mixed
Flack parameter	0.2(2)
Reflections in refinement	6483
Parameters	516
Restraints	0
$R(F_{obs})$	0.0297
$R_w(F^2)$	0.0645
S	0.948
Shift/error$_{max}$	0.001
Maximum electron density/e Å^{-3}	0.340
Minimum electron density/e Å^{-3}	−0.217

1H, H-6a, $^{3}J_{5,6a}$ 9.4 Hz, $^{2}J_{6a,6b}$ −10.1 Hz), 3.56 (s, 3H, OCH_3), 3.49 (dd, 1H, H-3, $^{3}J_{2,3}$ 9.3 Hz, $^{3}J_{3,4}$ 9.3 Hz), 3.45 (dd, 1H, H-4, $^{3}J_{3,4}$ 9.3 Hz, $^{3}J_{4,5}$ 9.3 Hz), 3.31 (m, 1H, H-5, $^{3}J_{4,5}$ 9.3 Hz, $^{3}J_{5,6a}$ 9.4 Hz, $^{3}J_{5,6b}$ 4.6 Hz), 3.26 (dd, 1H, H-2, $^{3}J_{1,2}$ 7.9 Hz, $^{3}J_{2,3}$ 9.3 Hz).

4.1.3. Sodium bis(methyl α-D-glucopyranosid-4,6-ato)-borate sodium hydroxide water (1:1:8) (1). Methyl α-D-glucopyranoside (0.78 g, i.e., 4.0 mmol), boric acid (0.13 g, i.e., 2.0 mmol) and sodium hydroxide (0.40 g, i.e., 10 mmol) were dissolved in 3.0 mL water. On slow evaporation colourless crystals of Na_2[B(Me α-D-Glc*p*4,6H$_{-2}$)(Me α-D-Glc*p*3,4,6H$_{-3}$)]·NaOH·8H_2O (**1**) formed in the course of half a year.

4.2. NMR sample preparation

Total concentrations of boric acid/borate were adjusted to 0.02 mol L^{-1} or 0.5 mol L^{-1} in H_2O. The pH value of the solutions was adjusted with NaOH. pH values were measured using a Mettler Toledo MP 220 with a glass electrode at 25 °C. Samples for two-dimensional NMR experiments were prepared as follows: $Na_2B_4O_7$ was dissolved in D_2O. Pyranosides were dried in vacuo prior to use and then added at a molar ratio of 1:1. The pH value was adjusted with a solution of NaOD in D_2O. The total concentration was adjusted to 0.5 mol L^{-1}.

4.3. Crystal structure determination and refinement

Crystals suitable for X-ray crystallography were selected with the aid of a polarisation microscope, mounted on the tip of a glass fibre and investigated on a Stoe IPDS diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å, cf. Table 3). The structure was solved by Direct Methods (SHELXS) and refined by full-matrix least-squares calculation on F^2 (SHELXL-97). Anisotropic displacement parameters were refined for all non-hydrogen atoms. CCDC 646622 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgement

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