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Seven-membered ring boronates at *trans*-diol moieties of carbohydrates

Marcel Meiland, Thomas Heinze, Wolfgang Guenther, Tim Liebert *

Center of Excellence for Polysaccharide Research, Friedrich Schiller University of Jena, Humboldtstrasse 10, 07743 Jena, Germany

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ABSTRACT

MS and ^{1}H, ^{13}C and ^{11}B NMR results are presented revealing the formation of cyclic seven-membered boronate structures at *trans*-1,2-diol moieties of carbohydrates providing new opportunities for the activation, protection and analysis of glucopyranose-based oligomers and polymers such as cellulose or starch. 'Coordination-induced shifts' in ^{13}C NMR spectra were identified for the esterification by boronic acids of carbohydrates, which can be applied for further studies.

The interaction of widespread glucopyranose-based compounds with boric acid or its derivatives, for example, salts or boronic acids, is, in principle, very useful for the analysis, activation, protection and cross-linking of carbohydrates;[1] however, in most cases the structures formed are poorly understood. In general, strong bonds with diol moieties of carbohydrates are formed, resulting in cyclic esters or complexes.[1,2] In the most abundant glucopyranose-based oligomers and polymers, mainly the *trans*-1,2-diol system in positions 2 and 3 is available for a ring formation. Five- and six-membered rings are not reasonable because of high ring tension. Nevertheless, beneficial effects of boric acid or its salts as activating agents in commercial modification procedures of polyglucans such as cellulose are known but scarcely applied because of unpredictable reactions.[3–7] Controlled processes may result in new opportunities for the chemical modification and analysis of glucopyranose-based compounds. In case of oligo- and polyglucans, the so-called derivatizing solvents[8] could be accessible where dissolution occurs via intermediate formation of covalent bonds or complexes leading to soluble, instable derivatives suitable for subsequent functionalization under defined homogeneous conditions.[9–11] Therefore, a basic understanding of the borate and boronate formation of glucopyranose-based compounds is indispensable.

Although own NMR studies on mixtures of soluble cellodextrins converted with boric acid in DMSO yielded badly resolved spectra, the data indicated derivatization of the carbohydrates at the *trans*-diol moiety and fast transesterification reactions. In order to limit the structural diversity, the reaction of the relevant *trans*-diol moiety with a model system consisting of methyl-α-D-glucopyranoside (Me-α-D-glcp) and phenylboronic acid (PBA) was studied in detail. Different papers showed that Me-α/β-glcp binds the borate through their flexible hydroxyls in positions 4 and 6.[12,13] Consequently, only the diol structure at positions 2 and 3 of the monosaccharide is accessible for further modification, making this system a reasonable model for the conversion of a oligo- or polyglucan. For non-aqueous media, Ferrier first mentioned esterification of the secondary hydroxyls of Me-α-D-glcp with PBA after azeotropic distillation in the presence of benzene, but the products were only characterized by elemental analysis.[14,15] A seven-membered ring including two boron atoms with the *trans*-1,2-diol moiety in positions 2 and 3 is suggested. Up to now, NMR spectroscopy was not able to confirm such a large ring system.[16]

In a set of experiments, the transformation of Me-α-D-glcp with PBA was studied by means of mass spectrometry (MS). The phenylboronates (Fig. 1) were prepared by dissolving different ratios of dry carbohydrates and triphenylboroxole in a mixture of *N*,*N*-dimethylformamide and 2,2-dimethoxypropane, which may result in different molecular ions and fission products (Fig. 1). A solution of derivatized methyl-glycopyranoside was evaporated in the MS probe crucible, and was introduced into the mass spectrometer. The spectra were measured using electron impact (EI) ionization.[17]

An equimolar conversion of Me-α-D-glcp with PBA yields a methyl-4,6-*O*-phenylboronate-α-D-glucopyranoside (**1**) that was confirmed by a peak for the molecular ion at *m*/*z* 280 and one fragment ion **I** at *m*/*z* 160 for a 1,3,2-dioxaborinane structure. If an excess of PBA is applied, the methyl-2,3-*O*-(diphenylpyroboronate)-4,6-*O*-phenylboronate-α-D-glucopyranoside (**2**) should be formed. The MS spectrum of the compound obtained shows significant fragment ions at *m*/*z* 160 (**I**) and at *m*/*z* 250 (**II**) in addition to

* Corresponding author. Tel.: +49 (0) 3641 948270; fax: +49 (0) 3641 948272.
E-mail address: tim.liebert@uni-jena.de (T. Liebert).

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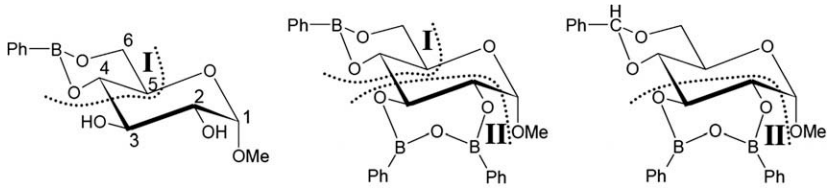


Figure 1. Boronate structures and expected fission processes.

a peak for the molecular ion at *m*/*z* 470, revealing the existence of a seven- and a six-membered boronate ring. The formation of such a complex seven-membered ring structure during the reaction of the carbohydrate with PBA was verified by additional experiments with methyl-4,6-*O*-benzylidene-2,3-*O*-(diphenylpyroboronate)-α-D-glucopyranoside (**3**). Again, a fragment ion at *m*/*z* 250 (**II**) is found, and the molecular ion at *m*/*z* 472 is detectable. Moreover, the modification of the carbohydrate with 2,6-dimethylphenylboronic acid yields a product giving signals of a molecular ion at *m*/*z* 554 and fragment ions at *m*/*z* 188 and *m*/*z* 306. For a comparable experiment with *n*-butylboronic acid relevant peaks for fragment ions appeared at *m*/*z* 140 and *m*/*z* 210. Further evidence is gained from the comparison of patterns and intensities of mass peaks with calculated isotope patterns. On the basis of the isotope distribution of carbon and boron (^{10}B:^{11}B = 1:4.2), the patterns for the main signals were simulated giving two additional peaks at lower *m*/*z* and two small signals at higher *m*/*z* values. A perfect fit of the predicted pattern with the fragment peaks for ion **II** of the 1,3,5,2,4-trioxadiborepane structure, and the signal for the molecular ion of **2** were found (Fig. 2). These MS studies confirm the transformation of *trans*-1,2-diol moiety in positions 2 and 3 with aryl and alkyl boronic acids as first proposed by Robinson or Ferrier.[14,17]

In contrast to mass spectrometric analyses of the boronate structures, which are combined with a separate modification during the analytic step (ionization and fission processes), NMR spectroscopy may yield direct evidence for the existence of different cyclic systems at carbohydrates. Nevertheless, NMR studies[16] have not succeeded in directly proving the existence of seven-membered boronate substituents at *trans*-1,2-diol groups up to now. Thus, the stepwise esterification of Me-α-D-glcp with PBA in aprotic solvents applying azeotropic removal of water was studied by NMR spectroscopy. First, the small amount of water produced during the esterification was removed with a soxhlet apparatus filled with molecular sieve. Here, PBA binds to OH-4/6 and forms Me-^{4,6}(PhB)-α-D-glcp (**1**) in quantitative yield (Scheme 1). A completely esterified product **2** should be obtained by a subsequent transformation of **1** with an excess of triphenylboroxole.

^{1}H NMR spectra of the products obtained by the steps depicted in Scheme 1 were acquired in DMSO-d_6. Spectra of the starting Me-α-D-glcp show relevant signals for the protons of the OH moieties and the proton at the anomeric carbon between 4.4 and 4.8 ppm (Fig. 3a). Separate signals for OH-2 at 4.62 ppm (d), OH-3 at 4.67 ppm (d), OH-4 at 4.79 ppm (d), OH-6 at 4.40 ppm (t) and H-1 at 4.51 ppm (d) can be determined. This assignment was confirmed with NMR correlation methods. After the first step of the esterification, formation of the Me-^{4,6}(PhB)-α-D-glcp (**1**) was concluded from the disappearance of the OH-6 and the OH-4 signal and the occurrence of two doublets in the ^{1}H NMR spectra (Fig. 3b). The two downfield-shifted signals could be identified as protons of OH-2/3 (OH-2 at 4.99 ppm, d, OH-3 at 5.24 ppm, d). The ^{1}H NMR spectrum of the compound obtained in a second step shows only one signal in the spectral region discussed (Fig. 3c). The doublets for the hydroxyl protons are missing. The remaining signal corresponds to the proton at the anomeric carbon at 4.95 ppm, which is shifted downfield (0.44 ppm) in comparison to the H-1 of unmodified Me-α-D-glcp. This can be explained with complete functionalization in position 2. Consequently, these ^{1}H NMR studies reveal the conversion of all accessible OH functions. This is the first NMR spectroscopic evidence for the formation of Me-^{2,3}(PhB)$_2$-^{4,6}(PhB)-α-D-glcp (**2**). These findings are supported by esterification reactions with methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (Me-^{4,6}(Bz)-α-D-glcp). The pyroboronate Me-^{4,6}(Bz)-^{2,3}(PhB)$_2$-α-D-glcp (**3**) was synthesized in a similar way, and the ^{1}H NMR spectrum shows a comparable shift of the proton in position 1 and the disappearance of the signals for the hydroxyl groups in positions 2 and 3. Nevertheless, ^{1}H NMR spectra did not yield a final proof for the existence of a large cyclic system, such as a seven-membered ring.

Therefore, ^{11}B NMR spectroscopy was applied for the determination of the boronate ring size. Because of the fact that ^{11}B NMR spectroscopy is a rather insensitive method, it was necessary to

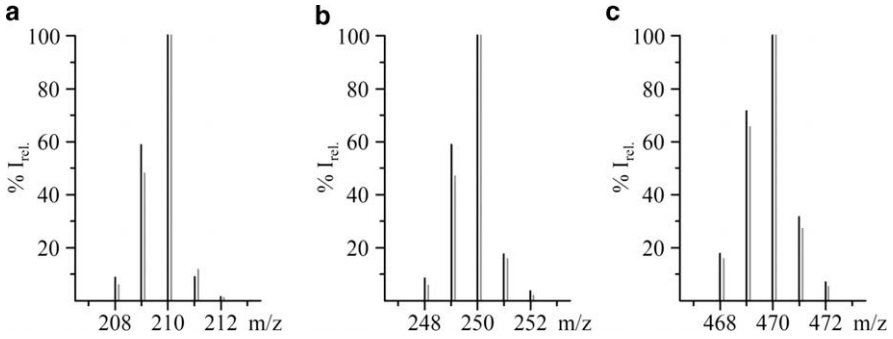
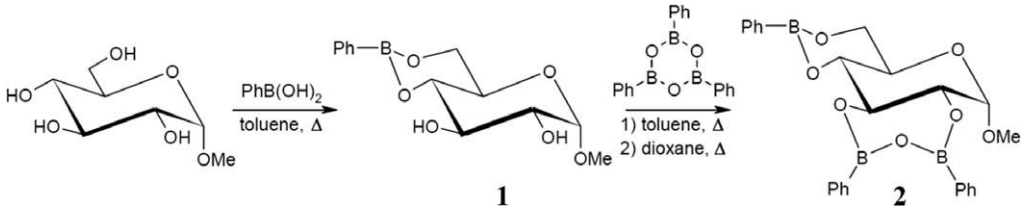


Figure 2. Comparison of calculated isotope pattern (grey) with fragment peaks for ion **II** of (a) methyl-2,3-*O*-(dibutylpyroboronate)-4,6-*O*-butylboronate-α-D-glucopyranoside (**2a**); (b) Me-^{2,3}(PhB)$_2$-^{4,6}(PhB)-α-D-glcp (**2**) and molecular ion of (c) Me-^{2,3}(PhB)$_2$-^{4,6}(PhB)-α-D-glcp (**2**).



Scheme 1. Synthesis of phenylboronates (**1** and **2**) of methyl-α-D-glucopyranoside.

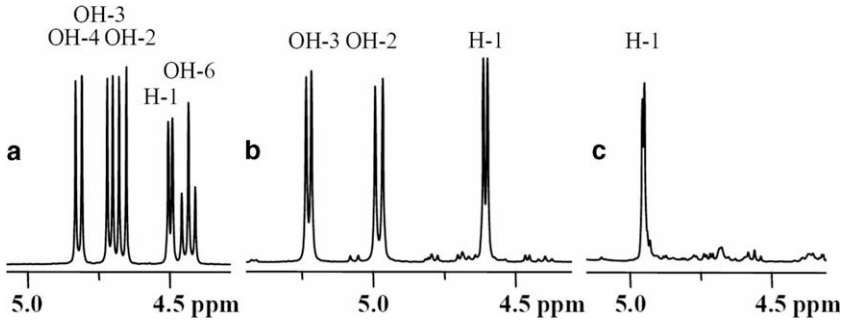


Figure 3. ^{1}H NMR spectra (in the region of hydroxyl and anomeric protons) of (a) Me-α-D-glcp; (b) Me-^{4,6}(PhB)-α-D-glcp (**1**); (c) Me-^{2,3}(PhB)$_2$-^{4,6}(PhB)-α-D-glcp (**2**) in DMSO-d_6.

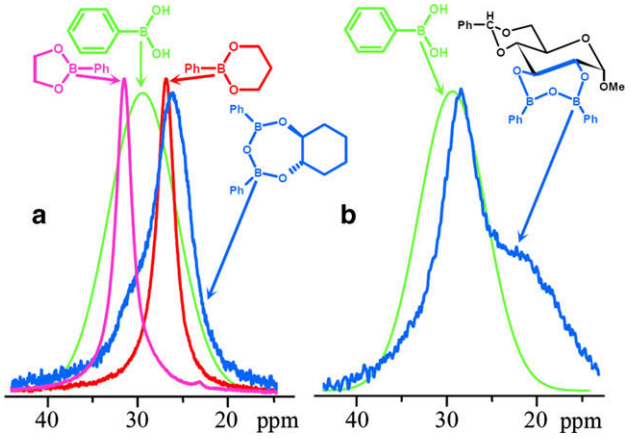


Figure 4. ^{11}B NMR spectra of (a) model compounds **4** (pink), **5** (red) and **6** (blue); (b) phenylboronate **3** (blue) in comparison with PBA (green) in DMSO-d_6.

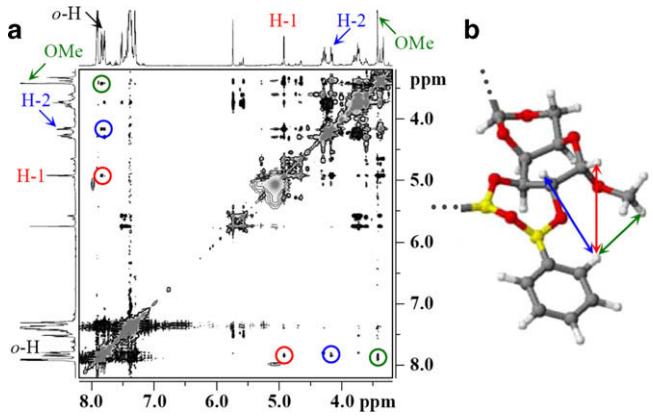


Figure 5. (a) 2D [^{1}H, ^{1}H] NOESY NMR spectrum of **3** in DMSO-d_6; (b) ball-and-stick model[20] of Me-^{4,6}(Bz)-^{2,3}(PhB)$_2$-α-D-glcp (**3**).

prepare model compounds of diol molecules with five-, six- and seven-membered boronate structures for 'comparison'. In Figure 4a, spectra of phenylboronate esters of 1,2-ethanediol **4**, 1,3-propanediol **5** and *trans*-cyclohexane-1,2-diol **6** are displayed.[18] The conversion of PBA to a five-membered ring boronate (**4**) leads to a downfield-shift of the ^{11}B NMR signal in comparison to the PBA. In contrast, the resonance signal of 2-phenyl-1,3,2-dioxaborinane (**5**) is shifted upfield but less than the signal of **6,** the seven-membered ring boronate, in relation to PBA (Fig. 4a). These data were used to evaluate the boronic acid transformation experiments (Scheme 1). The spectrum of Me-^{4,6}(PhB)-α-D-glcp (**1**) shows only a signal at 28 ppm consistent with the six-membered boronate model compound **5**. The second step usually yields a broad signal corresponding to a mixture PBA, six- and seven-membered ring system, but in case of the modification of Me-^{4,6}(Bz)-α-D-glcp with PBA a well-defined shoulder at the signal for PBA (blue) is observed in the ^{11}B NMR spectrum (Fig. 4b). This is a further evidence for a seven-membered diphenylpyroboronate ring at the *trans*-1,2-diol moiety at C-2/3 of the carbohydrate.

An additional indication for the formation of such a complex moiety was two dimensional NMR spectroscopy of Me-^{4,6}(Bz)-^{2,3}-(PhB)$_2$-α-D-glcp (**3**). The nuclear Overhauser effect NMR spectroscopy[19] (Fig. 5a) shows several cross-peaks for non-covalent coupling of protons, which can only be explained with diboronate structures in positions 2 and 3 of the carbohydrate. In particular, the proton in *ortho*-position of the phenylboronate moiety (δ(*o*-H) = 7.8 ppm) couples with protons of the carbohydrate backbone (arrows in Fig. 5b). On the one hand, there are cross-peaks indicating a coupling to H-1/2 and on the other hand, coupling to the methyl protons of anomeric methoxyl group is observed.

Based on this information concerning the formation of a seven-membered boronate ring at carbohydrates, the trend of signal movement in ^{13}C NMR spectra as a result of esterification with PBA was investigated.[21] Comparison of the signal distribution of Me-α-D-glcp with phenylboronates **1**–**3** shows (Fig. 6) that binding-site carbons (e.g., C-2/3 in compound **3**) are shifted downfield in the range of 2–5 ppm, whereas for carbon atoms between or in neighbourhood (e.g., C-5 or C-3 in compound **1**) to functionalized

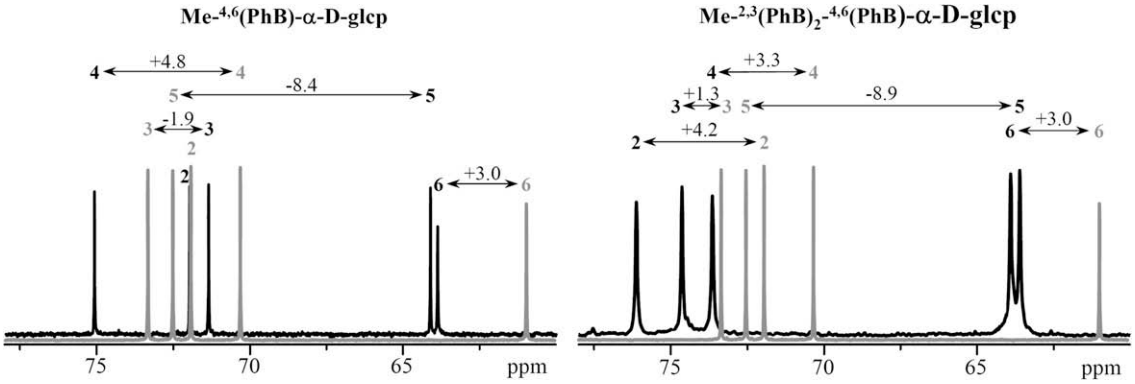


Figure 6. ^{13}C NMR spectra with depicted 'coordination-induced shifts' (arrows) of Me-^{4,6}(PhB)-α-D-glcp (**1**) and Me-^{2,3}(PhB)$_2$-^{4,6}(PhB)-α-D-glcp (**2**) in DMSO-d_6 (grey: Me-α-D-glcp, black: phenylboronate).

carbons an upfield-shift of 1–9 ppm is observed. Due to these identified 'coordination-induced shifts', a transformation of all hydroxyl groups of phenylboronate **2** is certified. All carbon peaks are shifted downfield except the signals for C-5 and C-1. On the basis of these results, standard ^{13}C NMR spectroscopy can be established as a fast and sensitive tool for the investigation of the interaction of cellooligomers and finally cellulose with boric acid derivatives.

In summary, detailed NMR studies on the transformation of the *trans*-1,2-diol system in Me-α-D-glcp with PBA support the structures suggested on the basis of MS analyses. NMR analyses confirmed the existence of a seven-membered diboronate ring at *trans*-1,2-diol moieties of C-2/3 in glucopyranose-based carbohydrates for the first time. Analyses of 'coordination-induced shifts' in ^{13}C NMR spectra can be applied for further studies on the transformation of glucans with boric acid derivatives. The information can be used to investigate the structures formed at cellooligomers towards a basic understanding of the interaction boric acid derivative with polyglucan.

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Supplementary data

Supplementary data (experimental procedures, characterization data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.043.

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18. For syntheses of 2-phenyl-1,3,2-dioxaborolane (**4**), 2-phenyl-1,3,2-dioxaborinane (**5**), 1,3,5,2,4-trioxadiborepane model compound (**6**), see: (a) Bowie, R. A.; Musgrave, O. C. *J. Chem. Soc.* **1963**, 3945–3949; (b) Sugihara, J. M.; Bowman, C. M. *J. Am. Chem. Soc.* **1958**, *80*, 2443–2446.
19. 2D [^{1}H, ^{1}H] NOESY NMR spectrum of **3** was measured using a mixing time of 0.4 s. Due to the fact that the rotating correlation time τ_c for this molecule is short (molar mass below 500 and NMR sample solution with low viscosity), we observe NOESY correlation signals with inverse phase to the diagonal signals.
20. Ball-and-stick model was converted by means of ACD/3D-Viewer version 4.5 for Microsoft Windows without consideration of NOESY correlation signals.
21. All ^{13}C NMR spectra are fully assigned by means of 2D NMR techniques. See Supplementary data.