Evidence for Mono- and Bisdentate Boronate Complexes of Glucose in the Furanose Form. Application of $^1J_{C-C}$ Coupling Constants as a Structural Probe

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Abstract: Complex formation between aromatic boronic acids and D-glucose was investigated by ^1H and ^{13}C NMR spectroscopy both under neutral nonaqueous and alkaline aqueous conditions. The structure of the bisdentate complex between 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid and glucose was reinvestigated and reassigned. The reactions studied are shown in Scheme 1. The complexes contain in all cases the furanose form of glucose bound to two boronic acid groups where the one is bound in the (1,2) position. The binding site for the second boronic acid group is (3,5) under neutral nonaqueous conditions. In aqueous alkaline solution the second binding site varies from the mono- to the diboronic acid. The second monoboronic acid binds to the (3,5,6) position in a tris coordinating manner, and the diboronic acid binds its second boronic acid group only to the (5,6) position. Two closely related complexes (ratio 4:1) are observed in the spectra with the monoboronic acid. This is ascribed to diastereomerism from the 1,2-complexed stereocenter. $^1J_{C-C}$ are used in the structure assignment. Exceptionally low values of 34–35 Hz for $^1J_{C-C}$ are measured for vicinal diols when the O–C–C–O fragment becomes incorporated in a five membered ring as is the case in cyclic boronic esters with a vicinal ester bonding.

Introduction

Aromatic boronic acids have recently gained attention as sensor molecules that can specifically recognize carbohydrates.[2–5] Molecular design of boronic acids to meet the criterion of binding certain carbohydrates and/or to have a high binding constant requires a precise knowledge of the structure of the complexes formed. Even though studies on these complexes have been performed for half a century, no unequivocal conclusions about their structure have been reached.

Böeseken[6] was among the first to predict an interaction between D-glucose and boric acid, and he deduced the formation of a complex in water between boric acid and the α-furanose form of glucose. In 1954 Foster[7] concluded that glucose could interact with two boric acid units when in the furanose form, and he suggested an α-D-glucofuranose-1,2:3,5,6-bis(borate) complex.

Complex formation between an aromatic boronic acid and different polyols was first mentioned in 1957 by Kuivila and co-workers[8] and several papers on the subject followed.[9–11] During the 1960s various boronic esters of carbohydrates were synthesized and isolated under nonaqueous conditions. Thus, Ferrier and co-workers[12,13] reported on a methyl α-D-glucopyranoside-4,6-phenylboronate and later, in 1965, Bourne *et al.*[14,15] isolated a bisphenyl boronate of glucose and suggested the structure to be α-D-glucofuranose-1,2:3,5-bis(phenylboronate). In 1974 Yurkewich and co-workers[16] as well as Wood and Siddiqui[17] reported ^1H- and ^{13}C-spectra on this derivative and supported the structure suggested by Bourne.

Only a few studies have dealt with the structure of complexes between glucose and aromatic boronic acids in aqueous solution,[2,18–23] and there are still different opinions about the structure. For both boric and boronic acids, however, there is a general acceptance of an interaction with the furanose form of glucose under alkaline aqueous conditions.[18,24–27] In a series

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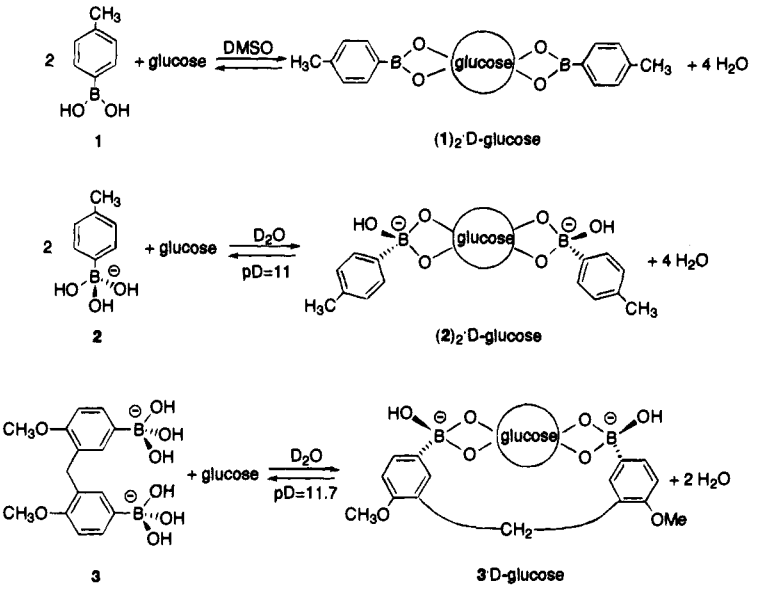
Scheme 1



of publications Shinkai and co-workers[2,19-23] nevertheless conclude that a pyranose complex is formed both in nonaqueous and in alkaline aqueous solution. Dawber *et al.*[28] also conclude the pyranose form of glucose to interact with a solution of sodium borate. The studies performed by Shinkai are especially interesting. Shinkai is the first to report on a bisdentate complex between a diboronic acid **3** (Scheme 1) and D-glucose. He deduces a 1,2:4,6-α-D-glucopyranose complex with 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid at pH = 11.7 on the basis of a contemporary NMR study.

We have investigated here the complexes formed between aromatic boronic acids and glucose under both nonaqueous neutral and aqueous alkaline conditions and have repeated the investigation with the diboronic acid. The reactions studied are shown in Scheme 1. It is found that the reported complexes in all cases contain the furanose form of glucose, with one boronic acid bound in the 1,2-position. The binding sites for the second boronic acid depend upon the experimental conditions and the type of boronic acid.

Results

In order to investigate the structure of the complexes formed between D-glucose and aromatic boronic acids we chose *p*-tolylboronic acid (**1**, Scheme 1) as the ligand. The *p*-tolylboronic acid was easy to obtain in a pure form and in large amounts. The *p*-tolylboronic acid complexes studied in this paper contain two boronic acids as seen by two sets of signals from the tolyl part relative to one set from the glucose part in the ^1H and ^{13}C NMR spectra. In experiments with excess of *p*-tolylboronic acid new signals from the free species are observed.

For solubility reasons we have used DMSO-d_6 as solvent for experiments under neutral nonaqueous conditions. By mixing the ligand and D-glucose in a 2:1 stoichiometric ratio in DMSO-d_6 the ^1H and ^{13}C NMR spectra of the equilibrated solution showed signals from uncomplexed sugar (~20%) in addition to those attributed to the complex, (**1**)$_2$·D-glucose (Scheme 1). The pure complex was obtained by azeotropic removal of the water formed (see Experimental Section). It displayed NMR signals identical to those found in the equilibrium mixture. Figure 1 displays the glucose part of the ^1H NMR spectrum of this complex in DMSO-d_6.

By dissolving *p*-tolylboronic acid in D_2O at pD −11−12 we obtained **2** (Scheme 1). By subsequent addition of D-glucose to a stoichiometric ratio of 2:1, signals corresponding to two complexes, named (**2a**)$_2$·D-glucose and (**2b**)$_2$·D-glucose, in the ratio 4:1, respectively, appeared in the ^1H and ^{13}C NMR spectra. Signals corresponding to free glucose did not appear. The lines of the complexes were broadened with $\Delta\nu_{1/2} \sim 3-4$ Hz at room temperature, both in ^1H and ^{13}C NMR. By cooling to −1 °C, the lines sharpened. Figure 1 shows the ^1H NMR spectrum of the glucose part of this equilibrium mixture at −1 °C. When pH of the solution was lowered to between 9 and 10 the lines broadened further, and signals from free glucose appeared. If pH was lowered further the ligand precipitated. pK_a of the *p*-tolylboronic acid is 9.3.[29]

The bisdentate complex, **3**·D-glucose (Scheme 1), between 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid **3** and D-glucose in aqueous alkaline solution was prepared as described by Shinkai *et al.*[19] Shinkai *et al.* showed a very high circular dichroism of the complex solution, originating from the aromatic absorption, which confirms that the complex indeed has a 1:1 bisdentate structure.[19] The ^1H and ^{13}C NMR spectra of this complex solution showed signals corresponding to the presence of one complex with only slightly broadened lines at room temperature. The ^1H NMR spectrum measured by us is in agreement with that published by Shinkai *et al.*[27]

The assigned ^{13}C chemical shifts and $^1J_{CH}$ coupling constants for the glucose part of the complexes studied are contained in Table 1. Table 2 contains the analogous ^1H chemical shifts. For comparison, data for α-D-glucose measured under equivalent experimental conditions are included in both tables. ^{13}C chemical shifts for the boronic acid part of the complexes are given in the Experimental Section. The chemical shift assignments are in agreement with information obtained from $^1H-^1H$ COSY and $^{13}C-^1H$ heterocorrelated spectra obtained for all complexes studied. The assignments are confirmed by experiments with ^{13}C-1 and ^{13}C-6 labeled D-glucose for experiments with *p*-tolylboronic acid and with ^{13}C-6 labeled D-glucose for the bisdentate complex. Besides an unambiguous assignment of the labeled site, $^1J_{CC}$ coupling gives the chemical shift of the

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Table 1. ^{13}C Chemical Shifts (ppm) and $^{1}J_{CH}$ Coupling Constants (Hz) for the Glucose Part of Boronic Complexes and a Reference Compound

compound	C-1	C-2	C-3	C-4	C-5	C-6	J_{C1-H1}	J_{C2-H2}	J_{C3-H3}	J_{C4-H4}	J_{C5-H5}	J_{C6-H6}[c]
(**1**)$_2$·D-glucose[a]	104.0	85.8	73.6	74.7	70.8	62.0	186	164	161	150	150	142
(**2a**)$_2$·D-glucose[b]	107.6	85.7	79.5	81.1	73.9	67.0	177	153	150	150	154	146
(**2b**)$_2$·D-glucose[b]	107.5	86.5	79.3	80.8	74.1	67.0						
3·D-glucose[b]	105.7	86.1	79.2	83.3	72.2	67.3	177	154	155	143	144	145
3·(3-O-methyl-D-glucose)[b]	105.6	82.2	88.6	82.6	72.1	67.1	176	153	152	142	146	144
α-D-glucopyranose[b]	94.9	74.3	75.4	72.3	74.0	63.3	169	140	139	147	143	144
α-D-glucopyranose[a]	92.4	72.5	73.2	70.7	72.1	61.4	164	140	143	139	138	140

[a] In DMSO d_6. [b] In D_2O at pD = 11−12. [c] Coupling to H-6a and H-6b. The signal observed is a triplet.

Table 2. ^{1}H Chemical Shifts (ppm) for the Glucose Part of Boronic Complexes

compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	OH
(**1**)$_2$·D-glucose[a]	6.24	5.01	4.67	4.35	4.30	3.64	3.64	5.14[d]
(**2a**)$_2$·D-glucose[b,c]	6.01	4.40	4.22	3.94	4.44	3.76	3.68	
(**2b**)$_2$·D-glucose[b,c]	5.92	4.25	4.29	4.33	4.53	3.90	3.7	
3·D-glucose[b]	5.77	4.43	4.09	3.71	4.02	3.82	3.42	
3·3-O-methyl-D-glucose[b]	5.72	4.56	3.68	3.72	4.02	3.80	3.43	

[a] In DMSO-d_6. [b] In D_2O at pD = 11−12. [c] At −1 °C. [d] Triplet J = 5.1 Hz.

Table 3. $^{1}J_{CC}$ Coupling Constants (Hz)

compound	$J_{1,2}$	$J_{5,6}$
(**1**)$_2$·D-glucose	34	42
(**2a**)$_2$·D-glucose	36	34
3·D-glucose		35
5[a]	34	35
α-D-glucopyranose	46[b]	44[c]

[a] Referencee 34. [b] Reference 50. [c] Reference 51.

Table 4. J_{H-H} Coupling Constants (Hz) for the Glucose Part of Boronic Complexes and Selected Model Compounds

compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
(**1**)$_2$·D-glucose[a]	4.1	~0	2.4	~0	2.4	2.4	m
(**2a**)$_2$·D-glucose[b]	3.6	~0	2.8	2.6	~0	5.1	8.8
(**2b**)$_2$·D-glucose[b]	3.8	~0	2.5	2.8	~0	5−6[d]	9.0
3·D-glucose[b]	4.0	~0	2.4	9.5	6.0	3.5	9.0
3·3-O-methyl-D-glucose[b]	4.2	~0	2.8	9.8	6.1	3.2	9.0
4[b]	3.7	~0	2.6	8.6	3.1	6.0	12.0
5[b]	3.6	~0	2.8	6.8	6.4	5.5	8.8
6[a]	3.6	~0	3.0	1.3	~0	5.2	7.9
α-D-glucopyranose[c]	3.6	9.5	9.5	9.5	2.8	5.7	12.8

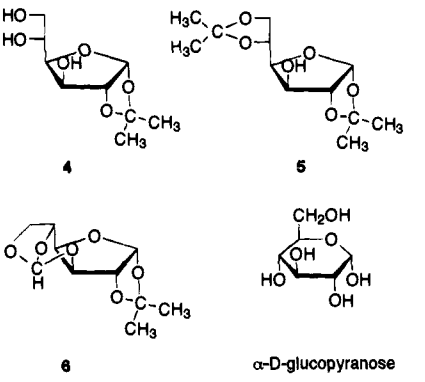
[a] In DMSO-d_6. [b] In D_2O at pD = 11−12. [c] In D_2O. Data taken from ref 52. [d] Could not be precisely determined.

neighboring carbon atoms (C-2 and C-5). The measured $^{1}J_{CC}$ coupling constants are listed together with literature values for two reference compounds in Table 3. For the minor isomer (**2b**)$_2$·D-glucose the $^{1}J_{CC}$ and $^{1}J_{CH}$ coupling constants were not measured due to extensive peak overlap with the major isomer. Table 4 contains the proton−proton coupling constants for the glucose part of the complexes together with values measured by us for the model compounds used.

To support the structure assignment we prepared complexes of 3-*O*-methyl-D-glucose with **2** and **3** under alkaline aqueous conditions. The ligand:carbohydrate stoichiometric ratios were 3:1 and 1:1, respectively, and pH in the final solutions was held between 11 and 12. The ^{1}H and ^{13}C NMR spectra of these solutions showed signals corresponding to the presence of four complexes (ratio 46:28:20:6) with **2** and one complex with **3.** The ^{1}H and ^{13}C NMR data for the **3**·3-*O*-methyl-D-glucose complex are included in Tables 1, 2, and 4. Due to the formation of four similar complexes with **2**, the ^{1}H NMR spectrum of this mixture was not fully analyzed.

We have also studied the complexation between **3** and D-glucose under neutral and nonaqueous conditions. The ^{1}H and ^{13}C NMR spectra of **3** and D-glucose (1:1) in DMSO-d_6 showed chemical shifts for the sugar part of the complex identical with those of the *p*-tolylboronic acid complex (**1**)$_2$·D-glucose together with 20% free glucose. However, the lines are considerably broadened ($\Delta\nu_{1/2}$ ~ 8 Hz), and signals from the aromatic part are extensively split.

Scheme 2



Discussion

$^{1}J_{CC}$. Substituent effects on $^{1}J_{CC}$ are generally small, and the effects become negligible if the substituents are not directly attached to the coupling fragment. A general and well defined trend is the increase of $^{1}J_{CC}$ with an increasing number of electronegative substituents attached to the coupled carbon atoms.[30,31] $^{1}J_{CC}$ has been widely used in the study of carbohydrates and $^{1}J_{CC}$ coupling constants for ~45 aldopyranoses, and ~15 aldofuranoses have been summarized in a recent review.[30] Subsequently, $^{1}J_{C1-C2}$ values for series of 5-*O*-methylpentofuranoses, 5-deoxypentofuranoses, and 5-deoxypentofuranosiduronic acids have been reported by Serianni *et al.*[32,33] The pattern of $^{1}J_{CC}$ coupling constants observed for these carbohydrates is remarkably constant. $^{1}J_{C1-C2}$ is found to be 46 Hz in both α- and β-glucopyranose. Variation with stereochemistry and derivation as methylation and acetylation gives a range for $^{1}J_{C1-C2}$ of 46−49 Hz for the glucopyranoses, and this range expands to 41−49 Hz if results for aldofuranoses are included. $^{1}J_{C5-C6}$ is found between 42 and 46 Hz both in cases of pyranoses and furanoses. However, in one derivative, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **5** (Scheme 2), unexpectedly low values of 34 and 35 Hz have been reported for both the C1−C2 and C5−C6 carbon couplings in the five membered cyclic acetal rings.[34] These values correspond in size to those expected for the unsubstituted cyclopentane

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hydrocarbon. Similar low values (see Table 3) for both $^1J_{C1-C2}$ and $^1J_{C5-C6}$ were found in the (**2a**)$_2$·D-glucose complex, while the neutral (**1**)$_2$·D-glucose complex shows a low value only for C1−C2 coupling. The bisdentate complex, **3**·D-glucose was only labeled in the C-6 position and gives a low $^1J_{C5-C6}$ value of 35 Hz.

These results lead us to the following conclusions: The structure of the neutral and anionic complexes, (**1**)$_2$·D-glucose and (**2a**)$_2$·D-glucose, must differ by more than the hybridization of the boron substituent. Low values of $^1J_{C1-C2}$ coupling constants point to a cyclic boronic ester with a cis 1,2-bonding. Likewise, values of 34−35 Hz for $^1J_{C5-C6}$ in (**2a**)$_2$·D-glucose and **3**·D-glucose point to the conclusion that C-6 and C-5 in these complexes are part of a five-membered cyclic boronic ester. The value of 42 Hz found for $^1J_{C5-C6}$ in (**1**)$_2$·D-glucose suggests that this fragment is not part of such a ring.

The above given results are interesting in light of Serianni *et al.*'s recent calculations on torsional effects on $^1J_{CC}$ coupling constants in ethylene glycol.[35] As predicted from data on carbohydrate systems, $^1J_{CC}$ was found to depend on the C−C dihedral angle in the HO−C−C−OH fragment. A maximum was calculated for a trans arrangement and a minimum for the eclipsed situation of the OH substituents. However, an even larger variation was calculated for C−*O* torsions, reaching a maximum when the hydroxyl proton is anti to a carbon and a minimum in gauche configurations. Thus, according to the calculations, a minimum value for $^1J_{CC}$ should be expected for a structure with nearly eclipsed geometry for all three torsional angles in the fragment. The findings in this study of the extremely low $^1J_{CC}$ values, ascribed to cyclic five membered boronic esters, are in agreement with this prediction.

***J*$_{HH}$.** The data shown in Table 4 present evidence that all the boronic acid complexes studied involve glucose in the α-furanose form and not in the α-pyranose form, as given recently by Shinkai *et al.*[19−23] The values measured for $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ of the various complexes are in close agreement with those of **4**, **5**, and **6** (Scheme 2), all being α-furanose derivatives. The small size of $J_{2,3}$ and $J_{3,4}$ in the complexes excludes the vicinal diaxial arrangements of the H-2, H-3 and the H-3, H-4 hydrogen atoms, as should be the case for a pyranose form of glucose.

The *p*-tolylboronic acid complex in neutral DMSO-d_6 solution, (**1**)$_2$·D-glucose, shows a triplet OH signal at 5.14 ppm coupled to H-6a and H-6b (Table 2 and Figure 1) and therefore possesses a free hydroxy methylene group.

In Table 4 it can be seen how all J_{HH} of (**2a**)$_2$·D-glucose and (**2b**)$_2$·D-glucose fits to those of the 1,2-*O*-isopropylidene-3,5,6-tri-*O*-formyl-α-D-glucofuranose **6** and how especially $J_{4,5}$ and $J_{5,6a}$ differ from the other two model compounds **4** and **5**. Likewise it can be seen that the vicinal J_{HH} coupling constants of the bisdentate complex **3**·D-glucose correspond closely to those of model compound **5**, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.

Both the mono and bisdentate anionic complexes show the unexpected low $^1J_{C5-C6}$ value of 34−35 Hz (Table 3) indicating that the C-5 and C-6 hydroxyl group is complexed to boronic acid. Furthermore, the ^{13}C chemical shifts and $^1J_{CH}$ coupling constants are very similar for these complexes (Table 1). However, as seen from J_{HH} (Table 4), the structure of the complexes between **3** and glucose is not equivalent with the (**2a**)$_2$·D-glucose and (**2b**)$_2$·D-glucose complexes under the same conditions. Both $J_{4,5}$ and $J_{5,6a}$ differ by 6−7 Hz corresponding to entirely different dihedral angles in this part of the complexes.

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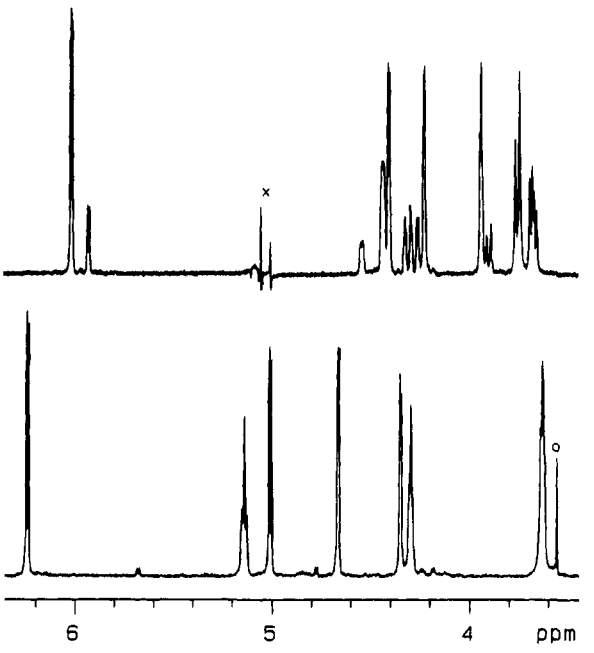

Figure 1. Carbohydrate regions of 400 MHz ^{1}H NMR spectra of glucose complexes with *p*-tolylboronic acid. Bottom: (**1**)$_2$·D-glucose complex in DMSO-d_6 solution (O = dioxane). Top: (**2a**)$_2$·D-glucose and (**2b**)$_2$·D-glucose in D_2O at pH ~ 11−12 (−1 °C) (× = residual decoupled solvent top).

In conclusion the J_{HH} data is in accordance with complexation of glucose in the furanose form[36] and the data further points to the binding sites 1,2:3,5 for (**1**)$_2$·D-glucose, 1,2:3,5,6 for (**2a**)$_2$·D-glucose and (**2b**)$_2$·D-glucose, and 1,2:5,6 for **3**·D-glucose.

***J*$_{CH}$.** The $^1J_{C1-H1}$ coupling constant of the neutral complex (**1**)$_2$·D-glucose is unexpectedly high (186 Hz, Table 1). Normally $^1J_{C1-H1}$ is in a range from 160−175 Hz for comparative compounds.[37] C-1 shows long range couplings, which are seen as triplets with splittings of 5 Hz. This splitting is due to a $^2J_{C1-H2}$ and a $^3J_{C1-H3}$ coupling having about the same size. By inspection of the data of A. S. Perlin and J. A. Schwarcz[38] together with a measurement of J_{CH} data for **6**, the 5 Hz triplet structure is found to be characteristic for 1,2-*O*-isopropylidene derivatives of α-glucofuranoses. Those derivatives force the furanose ring into a conformation with C-1,H-3 dihedral angle around 140° and eclipsed 1,2-cis arrangement, giving rise to large vicinal and geminal C-1,H coupling constants.[39] Furthermore, the 1,2-*O*-isopropylidene derivatives of α-furanoses (including **6**) also show an extremely high $^1J_{C1-H1}$ value of 186 Hz.

The proton coupled ^{13}C spectra of the anionic complexes (**2a**)$_2$·D-glucose and **3**·D-glucose have the same triplet fine structure (J = 5 Hz) for C-1 as the neutral complex (**1**)$_2$·D-glucose. For both complexes $^1J_{C1-H1}$ are 9 Hz less than found in the neutral complex, but they are still quite high values compared to those of reported pyranose- and furanose derivatives.[32,37] Thus the J_{C1-H} coupling pattern observed in all the complexes studied points to an α-furanose ring complexed in the 1,2-position.

(36) A recent paper by Aoyama *et al.* (Aoyama *et al. Bull. Chem. Soc. Jpn.* **1993**, *66*, 2965) describes the interaction between 5-indolylboronic acid and a number of oligosaccarides having a glucose residue as the reducing terminus. The authors observe a notable selectivity of the binding strength between different linkage isomers. The finding that 1,6-linked isomers bind more strongly than 1,4-isomers suggests that rearrangement into a furanose is a prerequisite for strong boronate complexation.

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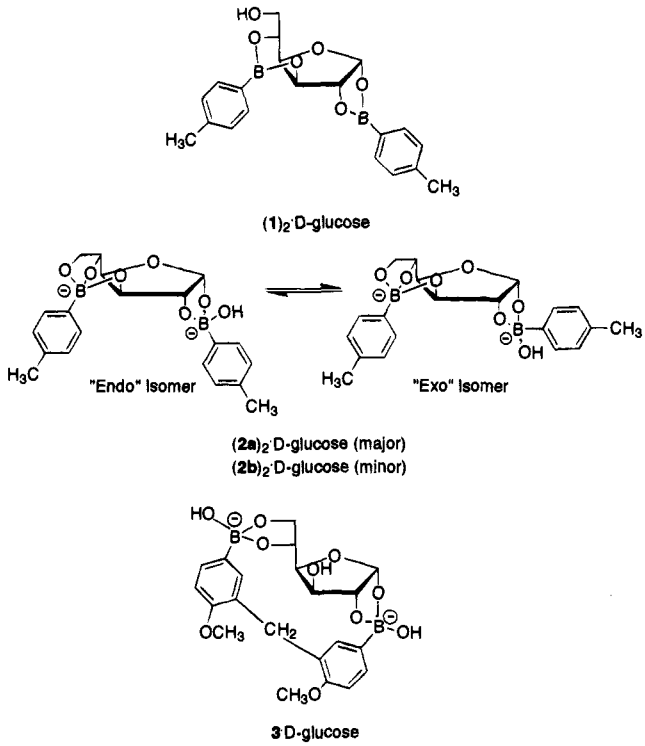

Figure 2. Structures of the glucose complexes formed with **1**, **2**, and **3**. The minor and major complexes with **2** are not assigned to specific endo or exo configuration.

Conclusion

From the above discussed NMR parameters we conclude the structure of the complex of *p*-tolylboronic acid and D-glucose under neutral nonaqueous conditions, $(\mathbf{1})_2$·D-glucose, to be 1,2:3,5-di-(*p*-tolylboronate)-α-D-glucofuranose shown in Figure 2. This is in agreement with the findings of Yurkewich *et al.*[16] and Wood *et al.*[17] and disagrees with the recent published findings of Shinkai *et al.*[20] The structure of the *p*-tolylboronic acid complex formed under aqueous alkaline conditions corresponds to the 1,2:3,5,6-di-*p*-tolylboronate-α-D-glucofuranose in accordance with the suggestion of G. de Wit.[18] However, two complexes are formed under these conditions: $(\mathbf{2a})_2$·D-glucose and $(\mathbf{2b})_2$·D-glucose. The two complexes have almost identical NMR parameters. Tetra coordinating boronate species provide additional stereocenters, and we suggest the two complexes to be two diastereomers of the structure given, where one has an "endo" and the other an "exo" tolyl function around the 1,2-bonded boron atom as shown in Figure 2. The two diastereomers will be in equilibrium under the experimental conditions applied. The structure given only has the isomer possibility for the boronate complexed at the 1,2-position.

Very recently the complexation between 4-fluorobenzeneboronic acid and D-glucose in aqueous solution at pH = 11.3 was studied by ^{19}F NMR.[40] Three ^{19}F resonances, of which one exhibited a shoulder, were resolved. The authors listed several possible explanations for the number of peaks observed, including the formation of a chiral center at the boron nucleus. However, a direct comparison of the ^{19}F results with those of the present study is not possible due to their use of a much higher glucose:ligand ratio, which probably causes additional complexes to form.[18]

The bisdentate complex **3**·D-glucose is assigned the structure 1,2:5,6-(2′,2″-dimethoxydiphenylmethane-5′,5″-diboronate)-α-D-glucofuranose (Figure 2). This does not agree with the structure previously published by Shinkai *et al.* who assigned a 1,2:4,6-α-D-glucopyranose type of structure to the complex.[19,21,23] A priori four diastereomers, originating in the two boronate stereocenters, are possible for the above assigned structure. Using "endo" and "exo" as defined in relation to the furanose ring for the monodentate complex, the isomer with endo(1,2)−exo(5,6) configuration is geometrically impossible. The two exo(1,2) diastereomers are geometrically possible but strained, while the endo(1,2)−endo(5,6) is without significant steric distortions according to Dreiding molecular models. This diastereomer also has a large (~180°) H-4, H-5 dihedral angle in accordance with the measured $^3J_{H4-H5}$ coupling constant of 9.5 Hz (Table 4). In the two isomers with the exo(1,2) configuration, these dihedral angles are both significantly smaller, and intermediate sizes of the corresponding $^3J_{H4-H5}$ coupling constants are expected. We therefore suggest the endo-(1,2)−endo(5,6) diastereomer shown in Figure 3 as the preferred isomer formed in the reaction of D-glucose with the bisdentate **3** under alkaline aqueous conditions.

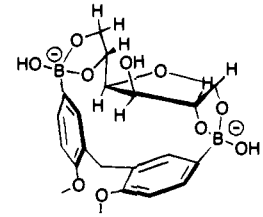

Figure 3. Assigned structure of **3**·D-glucose, α-D-glucofuranose-1,2,5,6-(2′,2″-dimethoxydiphenylmethane-5′,5″-diboronate).

As a final test for the assigned structures of the mono- and bisdentate anionic complexes we recorded the ^{1}H and ^{13}C NMR spectra of the complexes with 3-*O*-methyl-D-glucose. The spectra of the complex solution with **3** showed J_{HH} coupling constants almost unchanged as compared to the **3**·D-glucose complex (Table 4), and ^{1}H and ^{13}C chemical shift changes are as expected for simple 3-*O*-methyl derivation (Tables 1 and 2). Such a simple picture does not appear from the complex solution with **2**, and signals from four complexes are observed. These results are in accordance with the complexation sites assigned for mono- and bisdentate anionic complexes.

Under neutral nonaqueous conditions with trigonal planar boron atoms the 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid glucose complex gives almost identical ^{13}C chemical shifts for the sugar part of the complex as compared to $(\mathbf{1})_2$·D-glucose. However, a 1:1 complex with 1,2:3,5 substitution on the sugar is structurally impossible. The ^{13}C and ^{1}H lines for both the sugar and the aromatic part are broadened, and the signals from the aromatic part are extensively split. This is not seen for the *p*-tolyl complex where the spectrum shows sharp and well defined lines (Figure 1). This might be interpreted as if a polymeric and not a bisdentate complex was present, which is indeed possible for such a diboronic acid. If this is the case the large CD observed in alkaline solution may not show up under neutral nonaqueous conditions.

Experimental Section

NMR Experiments. ^{1}H NMR and 2D NMR spectra were recorded either at 400 MHz (Varian Unity 400) or at 500 MHz (Bruker AM 500) NMR instruments. ^{13}C NMR spectra were recorded at 100 MHz (Varian Unity 400). J_{CH} values have been obtained from a first order analysis. The spectra are referenced internally to TMS for nonaqueous and DSS for aqueous solutions, and chemical shifts are in ppm. All coupling constants are given as numerical values. Unless otherwise stated the solutions were made 1−2% in carbohydrate, and the temperature for the NMR experiments was held between 24−30 °C.

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Compounds. D-[1-^{13}C]-Glucose and D-[6-^{13}C]-glucose were purchased from Sigma Chemical Co. 3-*O*-Methyl-D-glucose was prepared as in ref 41.

4-Methylphenylboronic Acid (*p*-Tolylboronic Acid) (1).[42,43] *p*-Bromotoluene (150.0 g, 0.88 mol) was turned into the Grignard reagent with Mg (22.6 g, 0.93 mol) in 500 mL of dry THF under argon. During 2 h the resulting Grignard solution was added in parallel with a solution of $B(OMe)_3$ (130 mL, 1.14 mol) in 500 mL of dry THF to 200 mL of dry THF under argon. This was done in a way so that there was always an excess of $B(OMe)_3$. Mechanical stirring was applied, and the temperature in the reaction flask was held at −30 °C or lower by cooling in a liquid N_2/EtOAc bath. After addition, the reaction mixture was allowed to warm up to room temperature and left overnight with stirring. The resulting reaction mixture (thick white paste) was hydrolyzed at 0 °C first with 300 mL of ice water and then ca. 320 mL of 4 M HCl to pH ≈ 3−4. The THF was evaporated. The resulting solid product was extracted with ether, washed twice with water and with saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent one obtained crude *p*-tolylboronic acid (104 g). The crude material was recrystallized from ca. 2.7 L of water. Yellow insoluble material was filtered off (ditolylborinic acid), and the solution was allowed to cool. After slowly cooling colorless needles were filtered off and washed with ice water: after air drying 84.1 g (70%); mp ~255 °C (of the boroxin);[44] ^{13}C NMR (DMSO-d_6) δ_C 139.4 (**C**-quart), 133.6 (**C**-B(OH)$_2$, br), 134.2 (**C**H), 128.0 (**C**H), 21.1 (CH_3). Anal. Calcd for $C_7H_9BO_2$: C, 61.84; H, 6.67. Found: C, 61.74; H, 6.63.

2,2′-Dimethoxy-5,5′-dibromodiphenylmethane.[27,45] *p*-Bromoanisol (38.08 g, 0.20 mol) was dissolved in 100 mL of CH_2Cl_2, and the stirred solution was cooled to 0 °C. $AlCl_3$ (16.0 g, 0.12 mol) was added. Methoxyacetylchloride (10.9 g, 0.10 mol) in 50 mL of CH_2Cl_2 was added dropwise with stirring during ca. 1 h. CO was slowly evolved. Stirring was continued at 0 °C for 1 h. The color was changing to dark red. The solution was heated to room temperature for 1 h and then poured on ice. The white suspension was diluted with CH_2Cl_2 and washed several times with 2.5 M NaOH to remove aluminum salts. The CH_2Cl_2 phase was then washed twice with water and once with saturated NaCl and dried over $MgSO_4$. Evaporation in vacuum gave 35 g of a thick yellow oil, which partly crystallized overnight in colorless needles. Recrystallization from 150 mL of absolute EtOH yielded 15.9 g (41%) of white crystals contaminated with a little yellow oil. A further recrystallization yielded 11.57 g (30%) of 2,2′-dimethoxy-5,5′-dibromodiphenylmethane (slightly yellowish): mp 102−106 °C (lit. 107−109 °C).[21] A further recrystallized sample for analysis gave mp 107−109 °C: ^{1}H-NMR ($CDCl_3$) 60 MHz δ_H 3.74 (6H, s, **CH**$_3$), 3.82 (2H, s, **CH**$_2$), 6.64 (d, 2H, J = 8.4 Hz, Ar**H**), 7.12 (m, 3H, J = 2.5 Hz, Ar**H**), 7.28 (d, 1H, J = 2.5 Hz, Ar**H**). Anal. Calcd for $C_{15}H_{14}Br_2O_2$: C, 46.66; H, 3.65; Br, 41.39. Found: C, 47.04; H, 3.75; Br, 41.35.

2,2′-Dimethoxydiphenylmethane-5,5′-diboronic Acid (3).[27,46] 2,2′-Dimethoxy-5,5′-dibromodiphenylmethane (8.00 g, 20.7 mmol) was turned into the Grignard reagent by reaction with Mg (1.16 g, 47.7 mmol) in 45 mL of dry THF. Reflux for 12 h. The Grignard reagent was added slowly under argon during 2 h to a solution of $B(OMe)_3$ (9.5 mL, 2 equiv) in 70 mL of dry THF at −70 °C to yield a clear solution. The mixture was allowed to heat up to room temperature and left overnight with stirring. The resulting thick white suspension was hydrolyzed at 0 °C with 2 M H_2SO_4 to pH ≈ 3−4 and was then diluted with water and THF was evaporated. The resulting white solid was isolated on a sintered glass funnel and washed three times with ice water. This raw product was boiled in 160 mL of 70% EtOH. The insoluble white material was collected on a sintered glass funnel, and the filtrate "A" was stored. The solid was recrystallized from 40 mL of absolute EtOH. After standing at 5 °C overnight a white crystalline product had precipitated. Filtration and air drying yielded 1.55 g of (23%) of a white solid which was recognized as the 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid by NMR: mp 223−226 °C (lit. 177−180 °C);[21] ^{13}C NMR (DMSO-d_6) δ_C 158.9 (**C**-OMe), 136.2 (**C**-H), 133.8 (**C**-H), 109.6 (**C**-H), 127.2 (C-quart), 55.2 (OCH_3), 29.2 (CH_2). Anal. Calcd for $C_{15}H_{18}B_2O_6 \cdot {}^1/_2H_2O$: C, 55.45; H, 5.89. Found: C, 55.09; H, 5.83.

The first filtrate "A" was heated again and 50 mL of water was added. After standing at 5 °C overnight another 1.68 g (25%) could be isolated (Anal. Found: C, 52.00; H, 5.57). This fraction was turning slightly yellow by standing. This fraction was not further characterized.

α-D-Glucofuranose-1,2:3,5-bis(4-methylphenylboronate), (1)$_2$·D-glucose. α-D-Glucose·H_2O (4.0 g, 20 mmol) and tris(4-methylphenyl)-boroxin[44] (4.76 g, 13.5 mmol) were mixed in 50 mL of dioxane. The azeotrope was slowly distilled for 1 h, and the remaining solvent was evaporated in vacuum. The product was recrystallized from benzene/hexane yielding 6.79 g: mp 157−160 °C; ^{13}C NMR (DMSO-d_6) sugar part see Table 1, boronate part δ_C 142.0 (**C**-quart), 140.4 (**C**-quart), 134.8 (**C**H), 133.8 (**C**H), 128.8 (**C**H), 128.2 (**C**H), 21.4 (CH_3). Anal. Calcd for $C_{20}H_{22}O_6B_2$: C, 63.21; H, 5.84. Found: C, 63.42; H, 5.96.

α-D-Glucofuranose-1,2:3,5,6-bis(4-methylphenylboronate), (2)$_2$·D-glucose. *p*-Tolylboronic acid (16.2 mg, 0.12 mmol) was dissolved in D_2O (1 mL) by addition of 0.2 M NaOD. D-Glucose (11.8 mg, 0.06 mmol) was added. After equilibration (overnight) NaOD was added to a pH between 11 and 12: ^{13}C NMR (D_2O) sugar part Table 1, boronate part δ_C 139.4 (**C**-quart), 138.9 (**C**-quart), 134.9 (**C**H, two signals, Δppm < 0.1), 131.0 (**C**H, two signals, Δppm < 0.1), 23.4 (CH_3), 23.5 (CH_3).

α-D-Glucofuranose-1,2:5,6-(2′,2″-dimethoxydiphenylmethane-5′,5″-diboronate), 3·D-glucose. Prepared as described in ref 19: ^{13}C NMR (D_2O) sugar part Table 1, boronate part δ_C 157.9 (**C**-quart), 157.8 (**C**-quart), 137.4 (**C**H), 136.9 (**C**H), 134.1 (**C**H), 133.3 (**C**H), 130.2 (**C**-quart), 130.0 (**C**-quart), 114.3 (**C**H), 113.9 (**C**H), 59.0 (OCH_3), 58.7 (OCH_3), 30.0 (CH_2).

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose. Prepared by the method of O. T. Schmidt:[47] ^{13}C NMR (DMSO-d_6) δ_C 104.7 (**C**1), 85.1 (**C**2), 73.3 (**C**3), 81.0 (**C**4), 72.4 (**C**5), 66.2 (**C**6), 110.7 (**C**-quart), 107.9 (**C**-quart), 26.8 (CH_3), 26.6 (CH_3), 26.1 (CH_3), 25.3 (CH_3). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.14; H, 7.71.

1,2-*O*-Isopropylidene-α-D-glucofuranose. Prepared by the method of O. T. Schmidt:[48] ^{13}C NMR (DMSO-d_6) δ_C 104.4 (**C**1), 84.6 (**C**2), 73.3 (**C**3), 80.0 (**C**4), 68.4 (**C**5), 63.6 (**C**6), 110.4 (**C**-quart), 26.6 (CH_3), 26.0 (CH_3). Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.56; H, 7.22.

1,2-*O*-Isopropylidene-3,5,6-tri-*O*-orthoformyl-α-D-glucofuranose. Prepared by the method of H. Beermann *et al.*[49] ^{13}C NMR (DMSO-d_6) δ_C 105.6 (**C**1), 83.1 (**C**2), 72.7 (**C**3), 75.0 (**C**4), 71.5 (**C**5), 65.7 (**C**6), 111.1 (**C**-quart), 109.7 (**C**H), 26.7 (CH_3), 26.1 (CH_3). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.10; H, 6.21.

3·(3-*O*-Methyl-D-glucose). Prepared in analogy to (**2**)$_2$·D-glucose. ^{13}C NMR (D_2O) sugar part Table 1, boronate part within measuring uncertainty identical to those of **3**·D-glucose.

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