MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2003; **41**: 1015–1020
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mrc.1301

Note

Combined ^{1}H, ^{13}C and ^{11}B NMR and mass spectral assignments of boronate complexes of D-(+)-glucose, D-(+)-mannose, methyl-α-D-glucopyranoside, methyl-β-D-galactopyranoside and methyl-α-D-mannopyranoside

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Received 18 June 2003; Revised 15 August 2003; Accepted 25 August 2003

Complex formation between *N*-butylboronic acid and D-(+)-glucose, D-(+)-mannose, methyl-α-D-glucopyranoside, methyl-β-D-galactopyranoside and methyl α-D-mannopyranoside under neutral conditions was investigated by ^{1}H, ^{13}C and ^{11}B NMR spectroscopy and gas chromatography–mass spectrometry (GC–MS) D-(+)-Glucose and D-(+)-mannose formed complexes where the boronates are attached to the 1,2 : 4,6- and 2,3 : 5,6-positions of the furanose forms, respectively. On the other hand, the boronic acid binds to the 4,6-positions of the two methyl derivatives of glucose and galactose. Methyl α-D-mannopyranoside binds two boronates at the 2,3 : 4,6-positions. ^{11}B NMR was used to show the ring size of the complexed sugars and the boronate. GC–MS confirmed the assignments. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: boronate–saccharide complexes; NMR; ^{1}H NMR; ^{13}C NMR; ^{11}B NMR; COSY; HSQC; mass spectra; ring size

INTRODUCTION

Boronic acids have been shown to form reversibly strong covalent bonds with the diol functionalities of carbohydrates in form of cyclic esters[1–3] with association constants that range from 10 to 10^{4} M^{-1}, thus, making them more lipophilic and increasing their transport through bulk, liquid organic membranes.[4] Most monosaccharides form 1 : 2 saccharide–boronic acid complexes.[5,6] Although these sp^{2}-hybridized species are neutral and favourable to solvent extraction, they are relatively unstable and easily hydrolyzed in H_2O.[5] Several boronic acid derivatives which can selectively bind saccharides have been prepared. The PMR and mass spectral data of the benzene- and butaneboronates of arabinose, xylose, L-fucose, D-glucose, D-fructose and DL-glyceraldehyde have been reported.[7,8] In addition, the benzeneboronates of methyl-β-D-galactopyranoside, methyl-α-D-glucopyranoside and methyl-α-D-mannopyranoside have been studied by means of mass spectrometry.[9] In addition, the interaction of benzeneboronic acid, 4-methoxybenzeneboronic acid and 3-nitrobenzeneboronic acid with D-glucose, D-mannose and D-fructose at various pH values has been investigated by means of optical rotation methods.[10] The interaction of the different boronates with the saccharides is specific depending on the kind of boronic acid and the structure of the saccharide. For example, monosaccharides bearing five OH groups tend to form 1 : 2 monosaccharide–phenylboronic acid complexes.[11–15] The phenylboronic acid forms a five-membered ring with a *cis*-1,2-diol group, and it can form a six-membered ring with a *trans*-CH(OH)CH(CH_2OH)-diol group although the stability is inferior to that of the five-membered ring. However, the stability order of these complexes is always the same, depending on the structure of the monosaccharide.[3,16,17] As part of our program to develop drug carrier platforms based on saccharide–boron complexes, we are interested in determining the structure and stability of simple derivatives at first (for some recent NMR studies of boron complexes, see Ref. 18). In this work, the synthesis and the structure of the butylboronic acid complexes with D-(+)-glucose, D-(+)-mannose, methyl-α-D-glucopyranoside, methyl-β-D-galactopyranoside and methyl α-D-mannopyranoside under neutral conditions

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Contract/grant sponsor: Israel Science Foundation; Contract/grant number: 663/99-2.

was investigated by ^{1}H, ^{13}C and ^{11}B NMR spectroscopy and gas chromatography–mass spectrometry (GC–MS).

EXPERIMENTAL

Representative general synthetic procedure

For the preparation of the 1:1 butaneboronate, a solution (2%) of the sugar (1 mol) in dry pyridine was treated with butaneboronic acid (1.25 mol). The solution was refluxed for 1–4 h and cooled to room temperature and the pyridine was evaporated. A solution (2%) of the crude, liquid product in chloroform was extracted three times with 10% aqueous copper sulfate to remove both the residual pyridine and the excess boronic acid. Then the chloroform layer was extracted three times with distilled water, dried over Na_2SO_4 and concentrated. Vacuum distillation yielded mobile liquids of acceptable purity. For the preparation of the 1:2 product, a solution of the glucose (1 mol) in dry pyridine was treated with butaneboronic acid (3 mol).[7]

For the preparation of the butaneboronates of the methylated sugars, the same procedure was used and the extraction step was omitted.

Acetylation of the products for GC–MS analysis was carried out by adding acetic anhydride in pyridine, stirring for 24 h at 20 °C. The solution was evaporated and vacuum dried. An oily product was obtained.[17]

The compounds shown in Scheme 1 were thus prepared.

Preparation of 1

Prepared as described for the general procedure using D-glucose. ^{1}H NMR (DMSO-d_6), δ_H 0.7921 (CH_3), 0.5663 (CH_2B). 1.2126 (CH_2 near CH_3), 1.2864 (CH_2 near CH_2B).

Preparation of 2

Prepared as described for the general procedure using methyl-α-D-glucopyranoside. ^{1}H NMR (DMSO-d_6), δ_H 0.8141 (CH_3), 0.6017 (CH_2B), 1.2228 (CH_2 near CH_3), 1.2834 (CH_2 near CH_2B). ^{13}C NMR (DMSO-d_6), δ_C 14.54 (CH_3), 15.00 (CH_2B), 25.66 (CH_2 near CH_3), 26.94 (CH_2 near CH_2B).

Preparation of 3

Prepared as described above using methyl-β-galactopyranoside. ^{1}H NMR (DMSO-d_6), δ_H 0.8320 (CH_3), 0.5682 (CH_2B), 1.2508 (CH_2 near CH_3), 1.2963 (CH_2 near CH_2B). ^{13}C NMR (DMSO-d_6), δ_C 14.58 (CH_3), 15.00 (CH_2B), 25.59 (CH_2 near CH_3), 26.87 (CH_2 near CH_2B).

Preparation of 4

Prepared as described above using D-mannose. ^{1}H NMR (DMSO-d_6), δ_H 0.8406 (CH_3), 0.7303 (CH_2B), 1.2716 (CH_2 near CH_3), 1.3110 (CH_2 near CH_2B). ^{13}C NMR (DMSO-d_6), δ_C 14.50 (CH_3), 15.80 (CH_2B), 25.46 (CH_2 near CH_3), 26.54 (CH_2 near CH_2B).

Preparation of 5

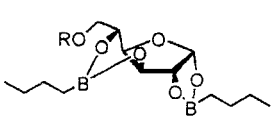
Prepared as described above using methyl-α-D-mannopyranoside. ^{1}H NMR (DMSO-d_6), δ_H 0.8375 (CH_3), 0.5730 (CH_2B), 1.2416 (CH_2 near CH_3), 1.304 (CH_2 near CH_2B). ^{13}C NMR (DMSO-d_6), δ_C 13.81 (CH_3), 14.98 (CH_2B), 24.83 (CH_2 near CH_3), 26.19 (CH_2 near CH_2B).

Butylboronic acid

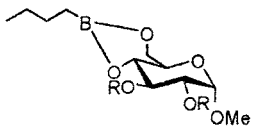
For comparison, the NMR data for butylboronic acid are as follows. ^{1}H NMR (DMSO-d_6), δ_H 0.8010 (CH_3), 0.5320 (CH_2B), 1.1860 (CH_2 near CH_3), 1.2587 (CH_2 near CH_2B). ^{13}C NMR (DMSO-d_6), δ_C 14.48 (CH_3), 15.79 (CH_2B), 25.73 (CH_2 near CH_3), 27.11 (CH_2 near CH_2B).

Spectra

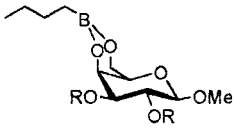
^{1}H and 2D NMR spectra were recorded on either a Varian 300 MHz or a Bruker 400 MHz instrument. ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer at a frequency of 75.9 (^{13}C). ^{11}B NMR spectra were recorded on both a Varian 300 MHz and a Bruker 400 MHz instrument at frequencies of 96.29 and a 128.38 MHz, respectively. All chemical shifts were reported with respect to $(CD_3)_2SO$ (δ_H 2.5, δ_C 39.5 ppm). All coupling constants are given as numerical values. The temperature for all the NMR experiments was held between 24 and 30 °C.



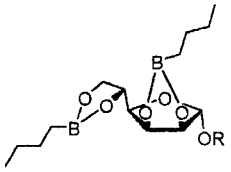
α–D-Glucofuranose cyclic 1,2:3,5-bis(butylboronate)
1: R=H
6: R=Ac



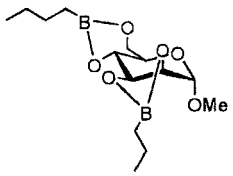
Methyl-α–D-glucopyranoside cyclic 4,6-butylboronate
2: R=H
7: R=Ac



Methyl-β–D-galactopyranoside cyclic 4,6-butylboronate
3: R=H
8: R=Ac



α-D-Mannofuranose cyclic 2,3:5,6-bis (butylboronate)
4: R=H
9: R=Ac



Methyl-α-D-mannopyranoside cyclic 2,3:4,6-bis (butylboronate)
5

Scheme 1

^{1}H NMR spectra were obtained with a spectral width of 8250.8 Hz, a 90° flip angle (5.59 μs) and 8 s relaxation delay in 32 scans. ^{13}C NMR spectra were obtained with a spectral width of 22 727.27 Hz with 1 s between transients and the 90° pulse was 7.19 μs. A 5 mm multinuclear probe was used for the standard 1D (^{1}H, ^{13}C) and 2D (COSY, HSQC) experiments. The two-dimensional homonuclear H,H-correlation experiments were acquired using phase-sensitive double quantum filtered COSY. The data were processed by sinusoidal multiplication in each dimension. Other parameters were as follows: number of increments in t_1, 1024; number of scans, 1; and relaxation delay, 2 s. The HSQC spectra were recorded using standard Bruker software (hsqcsi). These spectra were collected with 512 × 512 data points, a data acquisition of two scans × F_2 and 512 increments in t_1. Data were processed using sine functions for weighting in both dimensions. The spectral width of 2D spectra were optimized from 1D spectra.

GC–MS experiments

The acetylated derivatives of the boronated sugars were analyzed on a Hewlett-Packard (HP) G1800B GCD instrument having a 28 × 0.25 mm i.d. cross-linked 5% HP ME siloxane column with a 0.25 μm film thickness, programmed from 70 to 280 °C at 25 °C min^{-1}, interfaced with an HP Model 5971 mass-selective electron ionization detector.

RESULTS AND DISCUSSION

For all the monosaccharides, the two products, i.e. the 1 : 1 and the 1 : 2 sugar–butylboronic acid complexes, have almost identical NMR parameters. The data will be presented for the 1 : 2 products only (Tables 1–4).

The ^{1}H NMR spectrum for **1** shows that there is a triplet OH signal at 5.04 ppm coupled to H-6a and H-6b (Table 1). Therefore, **1** possesses a free hydroxymethylene group. ^{11}B NMR spectrum of **1** (Table 2) shows two peaks at 30.0 and 36.0 ppm, indicating the formation of six and five membered rings, respectively. The data shown in Table 3 for the J(H,H) coupling constants indicate that **1** is in the α-furanose and not in the α-pyranose form. The small size of J(2,3) and J(3,4) in the complex 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 the pyranose form of glucose. This disagrees with the results of Shinkai and co-workers[11,12,19,20] and agrees well with the findings of Norrild and Eggert.[14] Also, the J values are similar to those reported by Coxon[21] for the 1,2 : 3,5-di-*O*-benzylidine-α-D-glucofuranose ring [J(1,2) 3.6, $J(2, 3) < 0.4$ and J(3,4) 2.3 Hz]. The only exception in **1** is the slightly larger value for J(1,2) (4.1 Hz), which indicates a slightly greater flattening of the furanose ring by the boronate, and this may be due to the trigonal planar nature of the boron that might cause a flatter ring.[22] Furthermore, the ^1J(C1,H1) coupling constant is unexpectedly high (186 Hz, Table 4). Normally, ^1J(C1,H1) is in a range 160–175 Hz.[23] This high ^1J(C1,H1) gives further evidence of an α-furanose ring complexed in the 1,2-position for glucose as shown also for the 1,2-*O*-isopropylidine derivatives of α-furanoses that give an extremely high ^1J(C1,H1) value of 186 Hz.[14] Therefore, the similarities in the coupling constants suggest an identical conformation for **1** and that it is an envelope ^{3}E.[24] In addition, the acetylated product **6** was investigated by NMR and GC–MS methods. The NMR spectrum showed that the OH group on the boronated sugar disappeared, indicating that an acetyl group replaced the free OH group at C-6. This implies that the binding sites in **1** are the 1,2- and 3,5-positions on the glucose and the structure of **1** is α-D-glucofuranose cyclic 1,2 : 3,5-bis(butylboronate) as shown in Scheme 1. This is in agreement with the findings of Wood and Siddiqui[8] and Norrild and Eggert[14] and disagrees with those of Shinkai *et al*.[19]

For the boronic acid complex of the methyl-α-D-glucopyranoside **2**, the NMR data show that only one boronic acid is bound to the sugar. It is bound in the 4,6-position,

Table 2. ^{11}B chemical shifts (ppm) for the boronic complexes and butylboronic acid in $(CD_3)_2CO$

Compound	Butylboronic acid	Six-membered ring	Five-membered ring
Butylboronic acid	33.34		
1		30.00	36.00
2		29.86	
3		31.30	
4			35.12
5		31.43	35.63

Table 1. H chemical shifts (ppm) for the sugar part of the boronic complexes in DMSO-d_6

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	OH-1	OH-2	OH-3	OH-4	OH-6
α-D-Glucopyranose	4.88	3.09	3.37	3.01	3.52	3.58	3.43					4.33
1	5.97	4.61	4.31	4.12	4.05	3.49	3.49					5.04
Methyl-α-D-Glucopyranoside	4.50	3.18	3.34	3.01	3.27	3.41	5.85		4.68	4.74	4.84	4.46
2	4.63	3.34	3.48	3.41	3.59	3.69	3.93		5.02	5.20		
Methyl-β-D-Galactopyranoside	3.95	3.23	3.59	3.23	3.29	3.49	3.49		3.66	4.32	4.87	4.56
3	4.12	3.22	3.39	4.07	3.85	4.01	3.81		5.05	4.89		
D-Mannose	4.88	3.47	3.35	3.39	3.73	3.66	3.45	6.06	4.47	4.42	4.42	4.23
4	5.18	4.94	4.61	4.20	4.65	4.12	3.93					
α-Methylmannoside	4.46	3.56	3.44	3.37	3.22	3.41	3.65		4.69	4.68	4.53	4.45
5	4.57	3.67	3.41	3.43	3.50	3.93	3.73					

Table 3. *J*(H,H) coupling constants (Hz) for the sugar part of the boronic complexes

Compound	*J*(1,2)	*J*(2,3)	*J*(3,4)	*J*(4,5)	*J*(5,6a)	*J*(5,6b)	*J*(6a, 6b)
1[a]	4.3	0.0	2.6	0.0	2.14	2.14	M[c]
α-D-glucopyranose[b]	3.6	9.5	9.5	9.5	2.8	5.7	12.8
2[a]	3.66	8.15	9.15	9.8	4.99	4.99	9.57
Methyl-α-D-glucopyranoside[b]	4.0	10	10	10	2.8	5.8	12.8
3[a]	7.74	8.27	3.24	315	1.96	1.96	11.46
Methyl-β-D-galactopyranoside[b]	8.0	10	3.8	0.8	7.6	4.4	11.2
4[a]	4.01	6.22	4.21	4.41	4.43	4.43	8.67
D-Mannose[b]	1.8	3.8	10	9.8	2.8	6.8	12.2
5[a]	1.6	3.2	9.3	9.9	3.7	5.2	9.8
α-Methylmannoside[b]	1.6	3.5	10	10	1.9	5.8	12.0

[a] In DMSO-d_6.

[b] In D_2O (K. Bock, unpublished results).

[c] Multiplet.

Table 4. ^{13}C chemical shifts (ppm) and ^{1}J(C,H) coupling constants (Hz) for the sugar part of the boronic complexes in DMSO-d_6

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)
α-D-Glucopyranose	92.6	72.8	73.5	71.0	72.4	61.6	164	140	143	139	138	140
1	103.0	85.1	73.0	74.3	72.4	61.6	186	168	161	149	149	141
Methyl-α-D-Glucopyranoside	99.7	72.0	73.4	70.3	72.6	61.0	167	142	146	143	139	145
2	101.2	72.8	72.1	75.6	65.0	64.3	172	142	148	148	148	130
Methyl-β-D-Galactopyranoside	105.1	71.1	68.8	74.0	75.8	61.1	155	141	139	139	139	140
3	104.7	70.2	72.8	71.0	68.3	64.5	158	144	142	106	66	86
D-Mannose	94.6	72.0	68.0	71.2	73.7	62.1	166	143	142	147	136	140
4	101.5	80.5	86.0	80.9	74.5	66.7	174	164	155	158	153	152
α-Methylmannoside	101.6	70.8	71.6	67.6	74.4	61.8	168	145	142	145	144	135
5	101.7	70.5	66.9	68.0	65.4	63.5	170					

forming a six-membered ring product with the methyl-α-D-glucopyranoside remaining in the α-pyranose form. This is indicated by the appearance of two peaks in the ^{1}H NMR data for the free hydroxyl groups at positions 2 and 3 in the sugar (Table 1). Also, the ^{11}B NMR data show only one peak at 30.36 ppm, which is consistent with a six-membered ring (Table 2). Examination of *J*(H,H) for the product shows that there are no significant changes in the vicinal coupling constants, indicating no change in the conformation of the pyranose ring upon complexation with the boronic acid.

The methyl-β-galactopyranoside complex **3** is formed where one butylboronic acid is attached to the sugar at positions 4 and 6 as indicated by the ^{1}H, ^{13}C and ^{11}B NMR data. The presence of free hydroxyl groups in the ^{1}H NMR spectra gives correlations in the COSY to the protons at positions 2 and 3 in the sugar, and the peak at 31.30 ppm in ^{11}B NMR spectrum is indicative of the formation of a six-membered ring product at positions 4 and 6. Also, there are no changes in the *J*(H,H), coupling constants indicating no change in the pyranose ring upon complexation with the boronic acid. Therefore, the monodentate complexes, **2** and **3**, are assigned the structures methyl-α-D-glucopyranoside 4,6-butylboronate and methyl-β-D-galactopyranoside 4,6-butylboronate respectively (Scheme 1). This agrees with the results of Ferrier *et al*.[25,26] for the phenyl boronates of methyl-α-D-glucopyranoside and methyl-β-D-galactopyranoside.

For the D-(+)-mannose complex (**4**), ^{11}B NMR gave a single peak at 35.12 ppm, indicating the formation of a five-membered ring only, and the ^{1}H NMR spectrum of **4** in DMSO-d_6 shows a hydroxyl peak that connects to proton 1 in the COSY spectra. The data indicate the formation of a 2,3 : 5,6-ring system with two five-membered rings. The product shows small *J*(H,H) values for *J*(2,3) and *J*(4,5) (4.2–4.4 ppm) (Table 3), thus eliminating the possibility of the diaxial arrangement for these protons that should appear in the pyranose ring. Therefore, the product is in the furanose form and it is given the structure of D-mannofuranose cyclic 2,3 : 5,6-bis(butylboronate) (**4**) (Scheme 1). This agrees well with the data given for the *O*-ethyl boron derivatives and the isopropylidine derivatives of mannose.[27]

For the methylmannose **5**, the data show that it reacts readily to form the 2,3;4,6-diester. This is evidenced by the ^{11}B NMR spectrum, which shows two peaks at 31.43 and 35.63 ppm indicating the formation of a five- and a six-membered ring, respectively. This assignment is correlated by the connectivities in the COSY and the HSQC assignments. The spectra of the complex solution showed *J*(H,H) coupling constants almost unchanged to those of the free sugar and this shows that the protons remain in the diaxial arrangements and that the ring remains in the pyranose form. Therefore,

Table 5. GC–MS data

Compound	Major fragment ions: *m/z* (relative abundance, %)
1	43(100), 83(10), 127(10), 139(29), 168(29), 210(15), 237(3), 296, 296(8), 297(21)
2	43(100), 83(18), 115(27), 145(18), 157(23), 200(12), 243(6)
3	43(100), 74(10), 102(29), 144(15), 183(44), 227(7), 242(3), 270(3)
4	140(100), 18(6), 43(12), 61(25), 70(20), 111(12), 126(49), 169(3), 186(4), 210(3)
5	140(100), 18(6), 43(13), 61(25), 70(20), 111(12), 126(49), 169(2), 186(4), 210(2)

the structure of **5** is methyl-α-D-mannopyranoside 2,3 : 4,6-bis(butylboronate) (Scheme 1). The results agrees well with those of Ferrier.[25] Whereas **1**, **4** and **5** are the only products obtained with 1 equiv. of butylboronic acid (excess sugar is observed in the NMR spectra), **2** and **3** are the only products formed with 2 equiv. of butylboronic acid. This must be due to the locked-in *trans* relationship of the two free hydroxyl groups in **2** and **3**, preventing the formation of an additional ring. On the other hand, all the hydroxyl groups in **1**, **4** and **5** are *cis*, allowing facile formation of an additional five-membered ring.

The major mass spectral peaks are shown in Table 5. The data are consistent with the structures indicated by NMR (Scheme 1).

The prominent base peak at *m/z* 43 probably arises from the ion $[C_2H_3O]^{+\bullet}$ for the acetylated derivatives of D-(+)-glucose (**6**), methyl-α-D-glucopyranoside (**7**) and methyl-β-D-galactopyranoside (**8**).

The acetylated product of the glucose complex **6** gives a low-intensity (20%) peak at *m/z* 297 (M − 57), which is indicative of the loss of a butyl ($CH_3CH_2CH_2CH_2$) group. For the acetylated product of the methyl-α-D-glucopyranoside complex (**7**), a prominent peak at *m/z* 243 (M − 101) was observed that indicates a loss of two CH_3CO—and one CH_3 group.

For the acetylated product of the methyl-β-D-galactopyranoside complex (**8**), GC–MS indicates the presence of a mixture of two compounds, one completely acetylated and the other partially acetylated due to boronate coupling. The first compound either is due to the presence of free sugar or indicates the removal of the boronates by the acetate groups. The second product gives a peak with very low intensity (2.5%) at *m/z* 270 (M − 74), which is indicative of a loss of one methoxy (OCH_3) group and a propyl ($CH_3CH_2CH_2$) group or a CH_3CO group.

Similarly, the spectra of the acetylated mannose complex **9** gives a peak with a very low intensity (2.5%) at *m/z* 210 (M − 144) and this indicates the loss of an acetate group and two propyl groups. The ion at *m/z* 126 represents the radical ion $[C_6O_2BH_{11}]^{+\bullet}$, which is consistent with the 2,3-butaneboronate substituent (a five-membered boronate ring). Also, the ion peak at *m/z* 140 corresponds to $[C_7O_2BH_{13}]^{+\bullet}$ radical ion, which is consistent with the 5,6-five-membered ring system in the furanose ring.

For **5**, the GC–MS data for the non-acetylated product indicated that all the hydroxyl groups of the sugar are blocked. There is a low-intensity peak (2%) at *m/z* 210 (M − 117), which indicates the loss of one methoxy (OCH_3) group and a propyl ($CH_3CH_2CH_2$) group or a CH_3CO group. Also, there are peaks at *m/z* 126 and 140 indicating the presence of five- and six-membered rings, respectively.

Additional observable peaks for excess non-reacted sugars were observed only in the ^1H and ^{13}C NMR spectra of mannose and its methyl derivative. In addition, although the NMR parameters are identical for the 1 : 1 and 1 : 2 products with the methyl-β-galactopyranoside **3**, the reaction does not go to completion with a 1 : 1 ratio, i.e. only 50% of the sugar reacts. This is in accordance with the results of James *et al*.[5] indicating that the association constants of boronic acids to monosaccharides decrease in the order D-glucose ≫ D-galactose > D-mannose.

The methyl derivatives of the sugars were unstable under aqueous conditions, and this was markedly seen for the α-methylglucopyranoside product **2**. The non-bonded interactions between the axial methoxyl group and H-3 and H-5 are held to be responsible for destabilizing[27] the α-complex and also occur in the methyl-α-D-glucopyranoside 4,6-butylboronate **2**, and so it was expected that this ester would show greater susceptibility to hydrolysis than the methyl-β-D-galactopyranoside complex **3** and the methyl-α-D-mannopyranoside complex **5**.

It is well known that *trans*-six-membered rings are less stable than five-membered rings but the equilibrium is largely determined by the geometric arrangement of the diols.[28,29] With methyl-β-D-galactopyranose **3**, the 4,6-six-membered ring is a *cis* rather than a *trans* arrangement, and it is known from decalin that the *cis*-fused six-membered ring system is conformationally flexible whereas the *trans* system is fixed. In addition, the presence of a methyl group at the anomeric positions and the hydroxyls at positions 2 and 3 being *trans* leaves the 4,6-positions for the attachment with boronic acid. Also, with methyl-α-D-mannopyranose **5**, a *trans*-six-membered ring is formed because of the presence of a methyl group at the anomeric position that causes the first butaneboronate to attach itself to the *cis*-2,3 position and the second to form the *trans*-4,6-six-membered ring.

Acknowledgements

The authors thank the Israel Science Foundation, grant 663/99-2, for support of this work and a fellowship for R.S.

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