Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3311–3322

TETRAHEDRON: *ASYMMETRY*

Chirality sensing of saccharides using a boronic acid-appended chiral ferrocene derivative

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Received 7 June 2000; accepted 27 July 2000

Abstract

A diboronic acid-appended chiral ferrocene derivative **(*R*)-9** was designed and synthesized. This chiral ferrocene scaffold was obtained by resolution of the diastereomer with a monosaccharide derivative. One can therefore expect that **(*R*)-9** would show D/L selectivity for specific monosaccharides. The complex formation of **(*R*)-9** with various saccharides using the two boronic acid functions was conveniently monitored by a change in the circular dichroism (CD) spectra. The CD spectral change ($\Delta[\theta]$) induced by added monosaccharides was chiroselective: in particular, D/L-alloses and D/L-galactoses induced the 8.0- and 7.0-fold difference in the magnitude of the CD spectral change. The association constants for D- and L-saccharides (K_D and K_L, respectively) were determined: among them, **(*R*)-9** showed a significant discrimination ability for mannose ($K_L/K_D = 2.6$) and arabinose ($K_L/K_D = 1/2.4$). The origin of D/L selectivity was discussed on the basis of computational studies on **(*R*)-9**·saccharide complexes.

1. Introduction

Boronic acids, which have been known to form covalently-bonded complexes with diols, now attract a great deal of attention as a new interactive tool for saccharide recognition in aqueous systems. In most reported synthetic receptors developed so far, assuming their operation manner in aprotic media, hydrogen-bonding interactions play a central role.[1] It is shown, however, that hydrogen-bonding interactions are effective in aprotic solvents but less effective in aqueous media. Covalent-bond formation between arylboronic acids and saccharides has been applied to affinity chromatography by Wulff et al.[2] More recently, our group[3] reported the formation of

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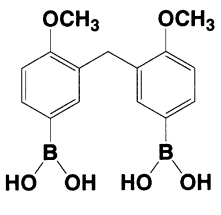
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00307-4

rigid, cyclic complexes of diboronic acids **1** and **2** with mono- and disaccharides, respectively. The chirality induced upon formation of rigid, chiral complexes was conveniently monitored by circular dichromism (CD) spectroscopy. Yoon and Czarnik[4] also reported fluorescence suppression of anthrylboronic acids in the presence of saccharides. The suppression is due to the intramolecular fluorescence quenching by the boronate anion developed after complexation with saccharides.[4] In these systems, saccharide sensing can be carried out only in the basic pH region. To detect saccharides in the more useful neutral pH region we designed a diboronic-acid compound **3**, which includes a fluorescent anthracene moiety and a photo-induced electron-transfer (PET) contrivance within a molecule.[5,6] This compound has enabled us for the first time to detect glucose with high selectivity and high sensitivity in neutral pH region.[5,6]



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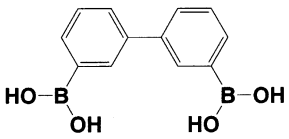

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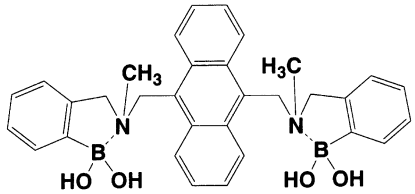

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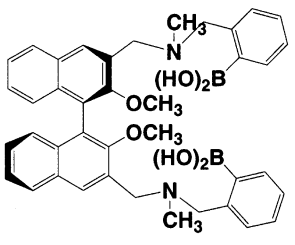
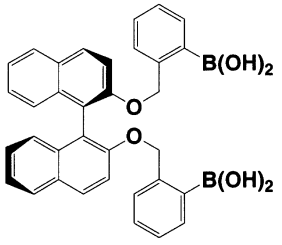
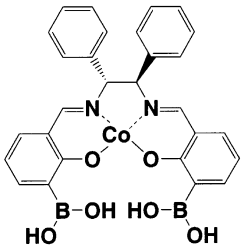
In spite of these efforts, another important sensing target has been left unsolved, which is a high D/L discrimination of saccharides. Successful examples for chiral discrimination in saccharide sensing are still very limited. To the best of our knowledge, there are only four precedents in which a significant level of chiral discrimination has been observed. Compound **(*R*)-4** was the first artificial receptor designed for chiral saccharide recognition and actually showed the chiral discrimination ability for fructose, the ratio of the association constants for **(*R*)-4** being D-fructose:L-fructose = 1.0:3.2.[7] Compound **(*R*)-5**, which has a more rigid diboronic acid skeleton, showed a chiral discrimination ability of 8.7-fold for D/L-xylose.[8] Diboronic acid appended-chiral cobalt(II) salen complexes **(*R*)-6** and **(*R*)-7** showed the preferential affinities for L-saccharides without any exceptions for all examined therein. In contrast, the investigation into the chiral discrimination ability with a monoboronic acid derivative was carried out on a chiral ferrocenylboronic acid **(*R*)-8** bearing an intramolecular chiral tertiary amine. Compound **(*R*)-8** can bind saccharides at pH 7 and showed a chiral discrimination ability of D/L = 1.4 for certain linear saccharides.[9] To the best of our knowledge, this is the sole example of monoboronic acid which can achieve chiral discrimination. This finding suggests that chiral ferrocene derivatives may be promising scaffolds[10] for the design of saccharide receptors with a high chiral recognition ability. In fact, we previously attempted the synthesis of a C_2-symmetrical diboronic acid version of **(*R*)-8**, which has both a boronic acid group and a *tert*-amino group in each cyclopentadienyl ring, but failed.[11]



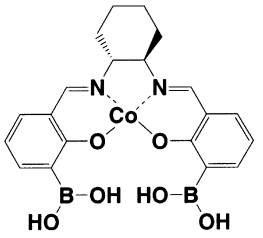
(*R*)-4



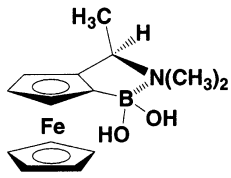
(*R*)-5



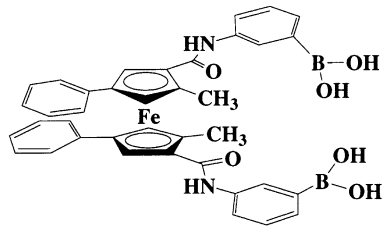
(*R*)-6



(*R*)-7

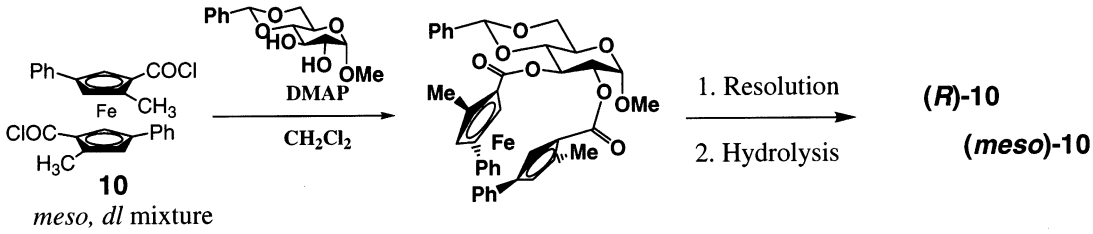


(*R*)-8



(*R*)-9

Recently, the Okayama group of this paper has established a new methodology by which inherently-chiral ferrocene derivatives can be resolved through complexation with saccharides.[12] From the resolution of diastereomeric saccharide complexes, chiral ferrocene derivatives were recovered (Scheme 1).[12]



Scheme 1. Optical rotation of **10**

Judging from these successful results, it is reasonable to consider that the chiral ferrocene skeleton resolved by the saccharide might be useful as a scaffold for chiral discrimination of the saccharide. Hence, the chiral ferrocene complexes should be applicable as new scaffolds for the design of a saccharide sensing system **(*R*)-9** related to chiral discrimination.

Each cyclopentadienyl ring of compound **(*R*)-9** has a large dipole in the skeleton. This character would generate CD-active saccharide complexes using the two boronic acid groups as a saccharide-binding site and enable us to measure the subtle differences in the saccharide-induced rotational angle of two cyclopentadienyl rings. In general, the structural difference induced by D/L-saccharides is relatively small and therefore very difficult. However, if the small differences in the physical quantities can be magnified to the big spectral change by the large dipole–dipole interaction, we will be able to establish a new sensing system for chiral discrimination of D/L-saccharides.

2. Experimental

2.1. Materials

2.1.1. 1,1′-Bis-(3-(1,3-dioxaborinanyl)phenylcarbamido)-2,2′-dimethyl-4,4′-diphenylferrocene (R)-9′

Compound **(*R*)-10** (30 mg, 66 μmol) was converted into bis(chlorocarbonyl)ferrocene by treatment with excess $SOCl_2$. To a THF solution containing 3-(1,3-dioxaborinan-2-yl)aniline (25

mg, 139 μmol) and triethylamine (0.06 ml, excess) was added dropwise a CH_2Cl_2 solution containing bis(chlorocarbonyl)ferrocene prepared above. The mixture was stirred for 24 h at room temperature. The precipitate was removed by filtration, the filtrate being concentrated in vacuo. The residue was purified by column chromatography (silica gel –$CHCl_3$/MeOH = 5/1 (v/v)) to give a brown powder (12 mg, 23%); ^{1}H NMR (250 MHz, $CDCl_3$, 27°C) δ/ppm 1.52 (CH_3-Cp, s, 6H), 2.07 (–CH_2C$H_2$$CH_2$–, q, 4H), 4.18 (–O–$CH_2$–, t, 8H), 4.61 (Cp-3H, s, 2H), 4.89 (Cp-5H, s, 2H), 7.21 (Ar-4H, t, 2H), 7.25–7.28 (Ar-3,5H, t, 4H), 7.34 (Ar-2,6H, d, 4H), 7.39 (Ar-5′H, t, 2H), 7.56 (Ar-6′H, d, 2H), 7.90 (Ar-2′H, br, 2H), 8.08 (Ar-4′H, br, 2H), 8.49 (amide-NH, br, 2H). Anal. calcd for $C_{44}H_{42}B_2N_2O_6Fe$: C; 68.31, H; 5.32, N; 3.71. Found: C; 68.41, H; 5.32, N; 3.63.

2.2. Computational methods

Theoretical calculations were carried out with Insight II/Discover 3 (Molecular Simulations Inc.), ESFF forcefield. Initially, stable structures were generated by MD at 500 K and then energy-minimized using MM forcefield.

2.3. Miscellaneous

Absorption spectra, ^{1}H NMR spectra, and CD spectra were measured with Shimadzu 2500-PC, Bruker AC-600P, and JASCO J-720 spectrophotometers, respectively. Throughout the present experiments, 'pH' values are indicated by those of aqueous solution used for the preparation of water–methanol 1:1 (v/v) buffer solutions.

3. Results and discussion

3.1. pH dependence of the absorption spectra

In general, it is very difficult to purify boronic acid derivatives because there is no good recrystallization solvent and such treatment gives rise to anhydrides (–B=O) or anhydrated trimeric cyclic compounds. Purification by TLC or column chromatography is also difficult because they are strongly adsorbed onto the silica immobile phase. Here, we purified **(*R*)-9** as its 1,3-dioxaborinane-protected derivative **(*R*)-9′**. In related dibronic acid derivatives, it has been confirmed by ^{1}H NMR spectroscopy that these protecting groups (1,3-propanediol) are readily eliminated in aqueous media.[13,14] In fact, addition of 1,3-propanediol ($\sim 10^{-4}$ mol dm^{-3}) scarcely affected the CD intensity versus [saccharide] plots in the present system. Hence, one can use **(*R*)-9′** without deprotection treatment as an equivalent of **(*R*)-9** in aqueous media.

The pH-dependent absorption spectra of **(*R*)-9** are shown in Fig. 1. With increase in the medium pH the decrease of A_{257} and the appearance of A_{322} were observed with a tight isosbestic point (304 nm). It is known that ferrocene derivatives have two characteristic absorption bands based on the n–π* transition and the d–d transition. In the case of diboronic acid-appended ferrocene derivative **(*R*)-9**, the absorption spectra should consist of the ferrocene band and the phenylboronic acid band. Judging from the fact that the spectral change at medium pH is scarcely induced in ferrocene derivatives, this spectral change is due to the structural change related to the phenylboronic acid groups. From analysis of a plot of A_{257} versus pH (Fig. 1,

right), the pK_a value of the phenylboronic acid groups is estimated to be 8.4 (Scheme 2). Since the titration curve is sufficiently simulated with one pK_a, one may consider that the two boronic acid groups are dissociated simultaneously.

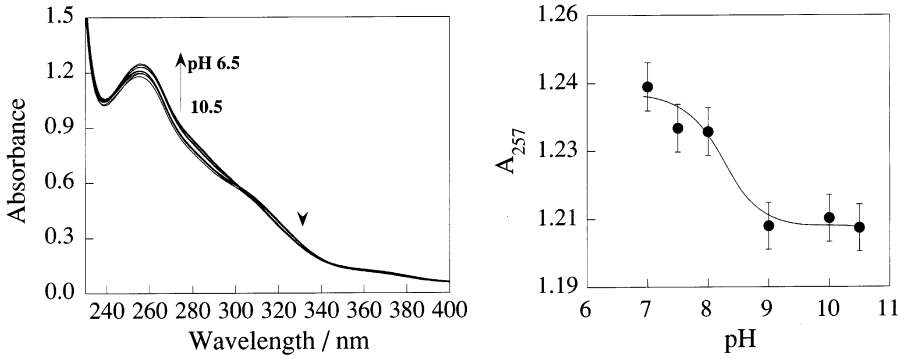
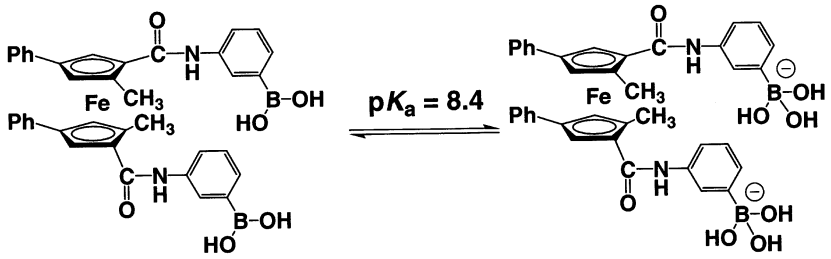


Figure 1. pH dependence (6.5–10.5) of the absorption spectra of **(*R*)-9** (4.5×10^{-5} mol dm^{-3}): 25°C, water (50 mmol dm^{-3} buffer)–methanol = 1:1 (v/v)



Scheme 2. Acid dissociation of **(*R*)-9**

3.2. CD Spectra of (R)-9

Various chiral ferrocene derivatives have been reported to date, which are classified into two different types.[15] One has a central chirality: that is, chiral functional groups are included in their skeletons. The other has a planer chirality. The CD spectra of these chiral ferrocene derivatives have not been studied in detail so far, because the utility of these chiral ferrocene derivatives is to apply them as chiral ligands for asymmetric catalytic reactions. The major purpose of the present study is to use the CD spectral change as a read-out tool for the saccharide binding and to evaluate whether this chiral ferrocene shows the chiral discrimination ability for D/L saccharides.

The CD spectral changes induced by addition of various saccharides are shown in Figs. 2 and 3. One can see several characteristic CD spectral changes induced by these saccharides. Firstly, the CD maximum at 324 nm changes to the opposite direction between D/L enantiomers of glucose and xylose, whereas they change within the same direction between those of galactose, mannose, allose, and arabinose (Table 1). One can easily imagine that these phenomena are caused by the mechanistic difference in the chiral discrimination process. Secondly, the larger CD spectral change is observed for D-saccharides rather than for L-saccharides (except the 324 nm band for mannose: Table 1). The difference suggests that D-saccharides enforce a larger

rotation of the cyclopentadienyl rings from the energy-minimum structure of free **(*R*)-9**. In particular, the large D/L difference in the CD spectral change at the 324 nm band (i.e., $\Delta[\theta]_{324}$) was observed for allose (8.0-fold) and galactose (7.0-fold) (Table 1: also refer to Fig. 5 shown later). Thirdly, there are a few exciton-coupling-type CD bands in Figs. 2 and 3. However, the saccharide binding cannot change the CD spectra so much that the CD signs in the Cotton effect be inverted.

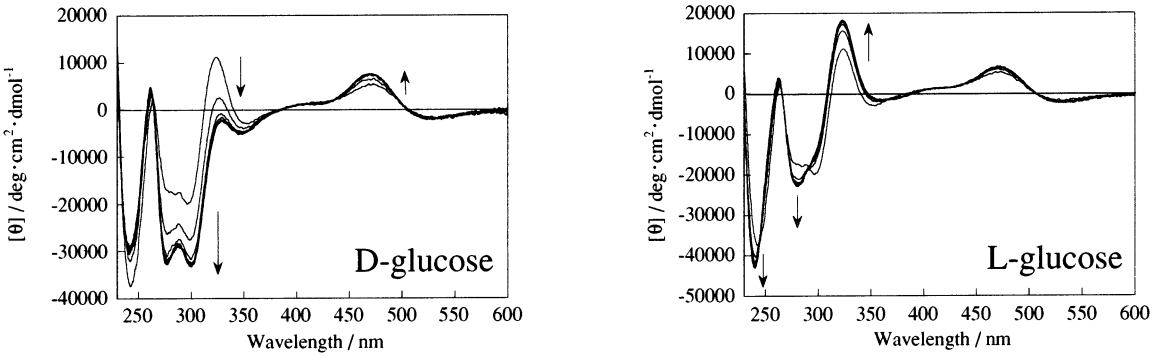


Figure 2. CD spectral changes of **(*R*)-9** (4.5×10^{-5} mol dm^{-3}) on addition of D- or L-glucose: 25°C, water (50 mmol dm^{-3} carbonate buffer, pH 10.5)/methanol = 1/1 (v/v)

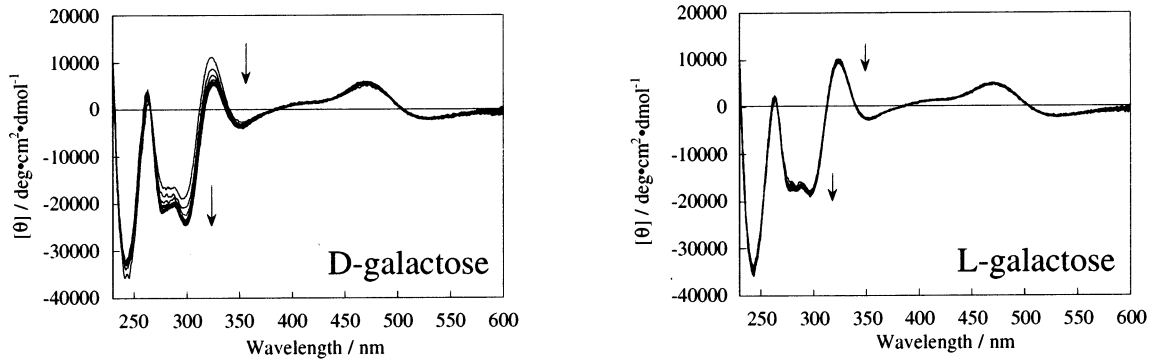


Figure 3. CD spectral changes of **(*R*)-9** (4.5×10^{-5} mol dm^{-3}) on addition of D- or L-galactose: 25°C, water (50 mmol dm^{-3} carbonate buffer, pH 10.5)/methanol = 1/1 (v/v)

Table 1
Comparison of the CD spectral changes induced by added D- and L-saccharide

Saccharide	$\Delta[\theta]_{324}$/deg cm^2 dmol^{-1}			$\Delta[\theta]_{280}$/deg cm^2 dmol^{-1}		
	D	L	D/L	D	L	D/L
Allose	−13 120	−1650	8.0	−9230	−7670	1.2
Glucose	−14 990	+7020	2.1	−14 460	−5320	2.7
Galactose	−6130	−880	7.0	−4320	−1770	2.4
Mannose	−1250	−5370	1/4.3	−6460	−4700	1.4
Xylose	−8760	+3650	2.4	−10 260	−2120	4.8
Arabinose	[a]	[a]		[a]	[a]	

[a] The change is too small to accurately estimate.

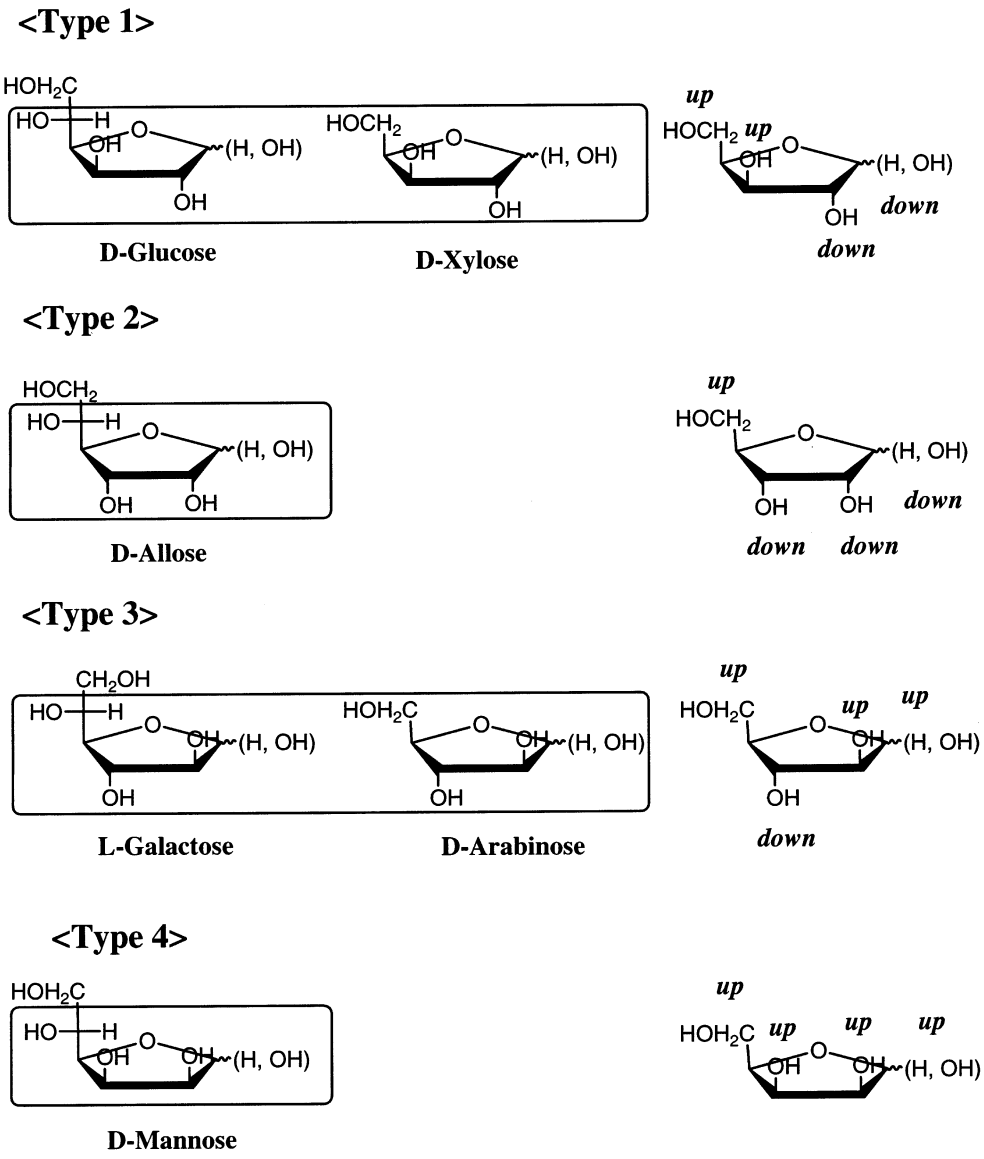
Then, is there any correlation between the CD sign and the saccharide structure? Recently, Norrild et al.[16] reported that saccharides tend to adopt the furanose form on complexation with diboronic acid compounds. Assuming that **(*R*)-9** also traps the furanose form, eight aldoses may be classified as in Scheme 3. It is known that boronic acid groups favorably complex with 1,2-*cis*-diol or 1,3-diol groups. In the furanose form the first binding-site is the 1,2-diol group. Taking the second binding-site into account, six monosaccharides tested herein may be classified into four different types. In type 1, including D-glucose and D-xylose, the OH groups useful as the second-binding site exist at the opposite side of the furanose ring with respect to the 1,2-diol group. This means that the distance between the two binding sites is relatively large. In other three types, in contrast, the OH groups useful as the second binding-site exist on totally (type 4) or partly (types 2 and 3) the same side of the furanose ring with respect to the 1,2-diol group. One may thus reach a conclusion that when the distance between the two binding sites is long, the CD intensity at 324 nm changes to the opposite direction, whereas when the distance is relatively short, it tends to change within the same direction. It is reasonable to consider, therefore, that the binding of D/L-glucoses or D/L-xyloses induces a large rotational change from free **(*R*)-9** and causes the CD change to the opposite direction.

3.3. Estimation of the association constants with saccharides

To obtain a quantitative insight into the saccharide affinity of **(*R*)-9**, we estimated the association constants (K_D and K_L) with D- and L-saccharides, respectively. Prior to this estimation, one has to corroborate whether **(*R*)-9** forms 1:1-stoichiometric complexes with these saccharides. The stoichiometry can be determined with the CD intensity changes by a Job plot, e.g., the typical example for D-xylose is shown in Fig. 4. It is seen from Fig. 4 that a maximum appears at [**(*R*)-9**]/([**(*R*)-9**]+[D-xylose])=0.5, indicating that, as shown in Scheme 4, the two boronic acids act cooperatively to bind one D-xylose molecule. The similar 1:1 stoichiometry was also confirmed for the complexes with the other five saccharides.

To determine K_D and K_L values, $\Delta[\theta]_{324}$ was plotted against saccharide concentrations, e.g., the typical example for D- and L-galactoses is shown in Fig. 5. A similar saturation curve was also observed for other five saccharides. By analysis of these plots by a Benesi–Hildebrand equation assuming the formation of 1:1 complexes, K_D and K_L values were obtained as summarized in Table 2. The CD spectral change induced by D- and L-arabinoses was so small (Table 1) that the K_D and K_L values were estimated by a substitution method: that is, to a solution containing **(*R*)-9** (4.5×10^{-5} mol dm^{-3}) and D-allose (2.1×10^{-3} mol dm^{-3}) was added D- or L-arabinose and the K_D or K_L was computed from the CD intensity change.

Examination of Table 2 reveals that the difference between K_D and K_L is not as large as that between the CD intensities. However, one can raise several interesting points characteristic of the saccharide binding to **(*R*)-9**. Firstly, **(*R*)-9** can scarcely discriminate between D- and L-enantiomers of glucose and xylose, which are classified into the type 1 group. Presumably, the distance between the two binding-sites is so long that complex formation induces a large conformational change in **(*R*)-9** and the slight energetic difference between D- and L-enantiomers is scarcely reflected by the total K_D and K_L values. Secondly, relatively large D/L discrimination is observed for galactose ($K_L/K_D=1/2.0$), arabinose ($K_L/K_D=1/2.4$), and mannose ($K_L/K_D=2.6$). These saccharides are classified into either type 3 (galactose and arabinose)



Scheme 3. Classification of six aldoses (in their furanose forms)

or type 4 (mannose) group. **(*R*)-9** also shows moderate discrimination ($K_L/K_D = 1.7$) for D-allose classified into type 2. The classification list thus suggests that only when the distance between the two binding-sites is relatively short can **(*R*)-9** significantly discriminate between D- and L-enantiomers. Thirdly, galactose and arabinose show a $K_D > K_L$ relationship, whereas other four saccharides show a $K_L > K_D$ relationship. To obtain a reasonable insight into D/L selectivity we compare the energy-minimized structures of **(*R*)-9**·saccharide complex and **(*R*)-9**·saccharide complex (Fig. 6). In the computational processes, sp^3-hybridization for boron atoms and furanose form for bound D- and L-saccharides are assumed. It can be clearly seen from Fig. 6

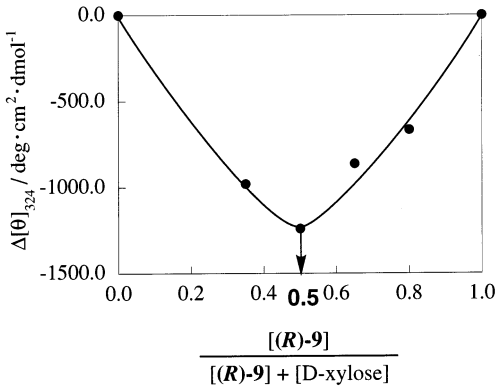
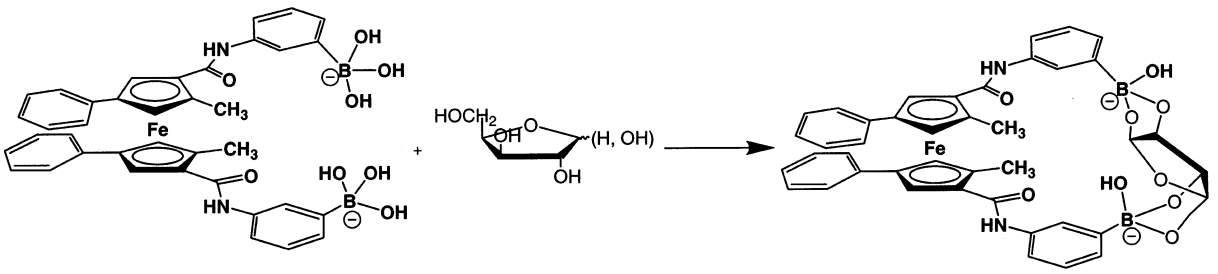


Figure 4. Job plot for complex formation between **(*R*)-9** and D-xylose: 25°C, [**(*R*)-9**]+[D-xylose] = 9.6×10^{-4} mol dm^{-3} (constant), water (pH 10.5 with 50 mmol dm^{-3} carbonate buffer)/methanol = 1:1 (v/v)



Scheme 4. 1:1 complex formation between **(*R*)-9** and D-xylose (assuming its furanose form)

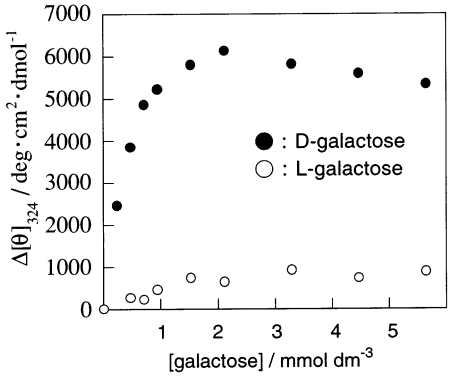


Figure 5. The $[\theta]_{324}$ changes of **(*R*)-9** on addition of D- and L-galactoses: [**(*R*)-9**] = 4.5×10^{-5} mol dm^{-3}, 25°C, water (50 mmol dm^{-3} buffer)/methanol = 1:1 (v/v)

Table 2
Association constants (dm^3 mol^{-1}) of **(*R*)-9** with D- and L-saccharides

Saccharide	K_D	K_L	K_L/K_D	Saccharide	K_D	K_L	K_L/K_D
Mannose	600	1560	2.6	Galactose	2320	1150	1/2.0
Allose	2920	4990	1.7	Arabinose	1600	660	1/2.4
Glucose	685	910	1.3				
Xylose	1780	2040	1.1				
	L-Saccharide selective				**D-Saccharide** selective		

that in the less stable **(*R*)-9**·saccharide complex (**(*R*)-9**·L-galactose and **(*R*)-9**·D-mannose complexes) two phenyl substituents overlapp each other, whereas in more stable **(*R*)-9**·saccharide complex [**(*R*)-9**·D-galactose and **(*R*)-9**·L-mannose complexes] they are relatively separated from each other. We thus believe that this steric crowding difference is the origin of the chiral discrimination in the present system

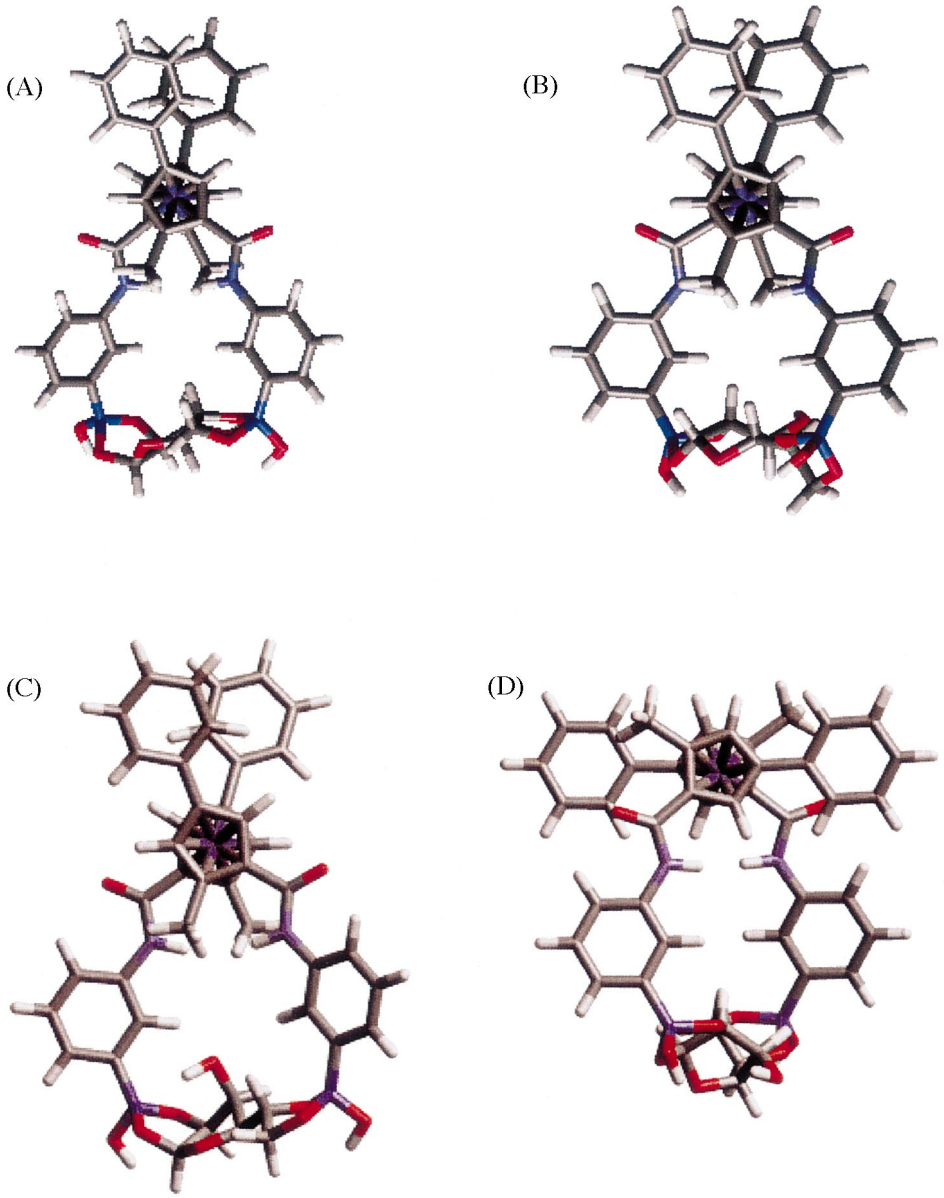


Figure 6. Energy-minimized structures of less stable **(*R*)-9**·L-galactose (A) and **(*R*)-9**·D-mannose (C) complexes and more stable **(*R*)-9**·D-galactose (B) and **(*R*)-9**·L-mannose (D) complexes

4. Conclusions

A boronic acid-appended chiral ferrocene derivative **(*R*)-9** was synthesized. The complexation processes between **(*R*)-9** and various saccharides were conveniently monitored by CD spectrometry, which established that a large difference (7–8 fold) exists in the CD intensity change between certain D- and L-saccharides. The association constants (K_D and K_L) could be determined from plots of the CD spectral changes against the saccharide concentrations. The moderate D/L difference of the association constants was observed for mannose ($K_L/K_D = 2.6$) and arabinose ($K_L/K_D = 1/2.4$). It is noteworthy that the chiral discrimination factors in the association constants are significantly large and those found in the CD spectral changes are highest among those achieved so far. These results consistently reveal that chiral ferrocene skeletons are very effectual as a scaffold, as already established in asymmetric syntheses,[15] to design chiroselective saccharide receptors. We are now planning to extend the present system to a novel redox-switched system utilizing ferrocene–ferrocenium redox interconversion.[17]

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