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Sugar Sensing Using Chiral Salen-Co(II) Complexes

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Abstract: Two chiral salen-Co(II) complexes, (*R*)-**7** and (*R*)-**8** bearing two boronic acid groups were synthesized. The saccharide-binding event was conveniently minitored by a spectral change in UV-vis absorption spectroscopy arising from saccharide-boronic acids complexation. Since the distance between the two boronic acid groups is shorter than other diboronic acid-based receptors, the saccharide selectivity is quite different from other systems: the largest association constant was observed for fructose and the next for talose. In addition, chiral recognition was achieved for certain saccharides: the largest discrimination was 2.1 observed for (*R*)-**7** with D/L-allose. These results indicate that the salen-metal complexes provide an excellent basic skeleton for designing the chiral sugar sensing systems.

INTRODUCTION

Molecular recognition of neutral and ionic species by synthetic receptors has been the fascination of many chemists for the last few decades. In many reported synthetic receptors hydrogen-bonding interactions play a central role.[1] It is shown, however, that the hydrogen-bonding interactions are effective in aprotic solvents but less effective for recognition of guests soluble only in aqueous media. We are currently investigating the recognition of saccharides which are soluble only in aqueous media. Covalent-bond formation between saccharide and boronic acid has been utilized for sugar recognition in affinity chromatography by Wulff *et al.*[2] Recently, Shinkai and coworkers[3] reported the formation of rigid, cyclic complexes of diboronic acids **1** and **2** with mono- and di-saccharides. The induced chirality upon formation of rigid, chiral complexes was monitored by circular dichroism (CD) spectroscopy. Yoon and Czarnic[4] also reported the fluorescence suppression of anthrylboronic acid 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, sugar sensing can be carried out only at basic pH region.[3-5] To detect saccharides at more useful neutral pH region we designed a diboronic-acid compound **3** which includes a fluorescent anthracene moiety and a photo-induced electron-transfer

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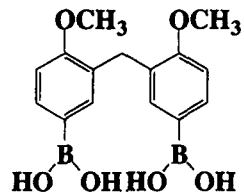
(PET) contrivance within a molecule.[6] This compound has enabled us to detect glucose with high selectivity and high sensitivity.[5,6]



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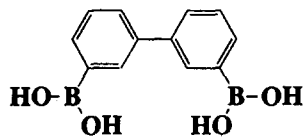

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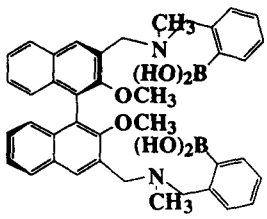
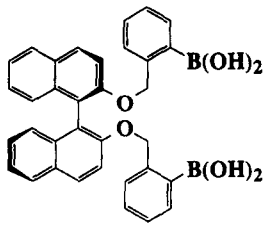
3

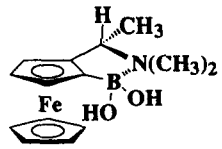
In spite of these efforts, successful examples for chiral discrimination in sugar sensing have still been very limited. To the best of our knowledge, there are only three precedents in which a significant level of chiral discrimination was observed. Compound **4** was the first artificial receptor designed 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 **5** which has a more rigid diboronic acid skeleton showed a chiral discrimination ability of 8.7-fold for D/L-xylose.[8] A chiral ferrocenylboronic acid **6** bearing an intramolecular tertiary amine can bind saccharides at ca. pH 7 and showed a chiral discrimination ability of D/L = 1.4 for certain linear saccharides.[9] Here, it occurred to us that salen-metal complexes would be applicable as a new scaffold for molecular design of sugar sensing systems related to chiral discrimination. For salen-metal complexes, for example, one can expect several intriguing abilities: *e.g.*, (i) various chiral scaffold can be readily prepared by using various commercially-available chiral diamines, (ii) sugar sensing becomes possible at visible wavelength region, (iii) the distance between two boronic acids is shorter than that in **4** or **5**, so that some saccharide different from those bound to **4** or **5** may be captured, (iv) the distance can be finely tuned by the coordination geometry of the central metal, and (v) the catalytic reaction mediated by the central metal would be controlled by the bound saccharide. With these expectations in mind we designed compounds **7** and **8**. As a central metal, Co(II) was chosen which is typical in salen-metal complexes, does not form the μ-oxo dimers, and may be applicable to the catalytic reactions[10] and to electrochemical sensing using interconversion between Co(II) and Co(III).[11, 12]



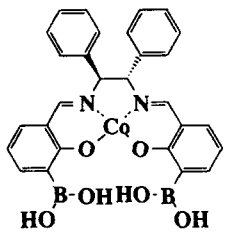
(*R*)-**4**



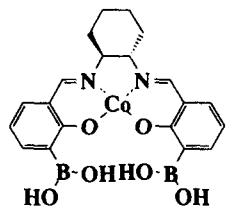
(*R*)-**5**



(*R*)-**6**



(*R*)-**7**

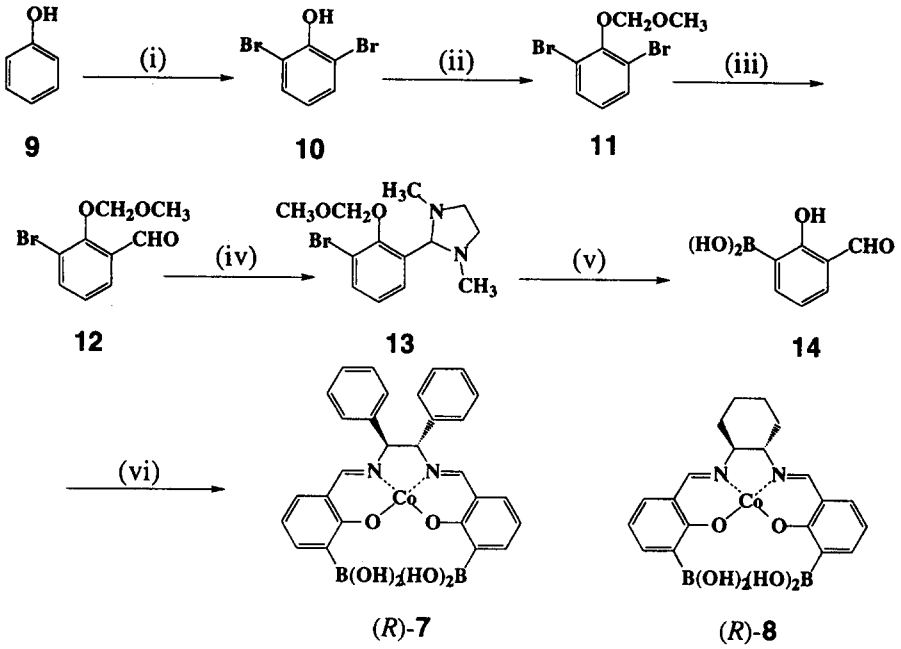


(*R*)-**8**

EXPERIMENTAL

Materials

Compounds (*R*)-**7** and (*R*)-**8** were synthesized from phenol according to Scheme1. In step (ii) the OH group was protected by the methoxymethyl group and then one bromo group was converted to the formyl group *via* lithiation (step(iii)). In step (iv) the formyl group was protected by *N*,*N*'-dimethylethylenediamine and then the residual bromo group was converted to the boronic acid group (step(v)). In this step, both the methoxymethyl group and the *N*,*N*'-dimethylethylenediamino group were deprotected by the treatment with sat. brine. The Co(II) complexes, (*R*)-**7** and (*R*)-**8** were obtained according to the conventional method.[13]



Scheme 1 (i) *t*-$BuNH_2$, Br_2, toluene, (ii) NaH, CH_3OCH_2Cl, THF, (iii) *n*-BuLi, DMF, THF, (iv) $CH_3NHCH_2CH_2NHCH_3$, toluene, (v) *n*-BuLi, $B(OMe)_3$, THF, (vi) $Co(OAc)_2$, (*R*)-1,2-diphenylethylenediamine for (*R*)-**7** and (*R*)-1,2-diaminocyclohexane for (*R*)-**8**, EtOH

2,6-Dibromophenol (10). This compound was synthesized according to Ref. 14: white solid, yield 73%; m.p. 49.8 - 50.2 °C (lit.[14] 55 - 56 °C); IR (KBr) ν_{O-H} 3414 cm^{-1}, $\nu_{C=C}$ 1570, 1438 cm^{-1}, δ_{Ar-H} 758 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$, 27°C) δ/ppm 6.70 (Ar-4H, s, 1H), 7.44 (Ar-3,5H, d, 2H).

***O*-Methoxymethyl-2,6-dibromophenol (11).** To a stirred solution of **10** in dry THF (150 ml) under N_2 at 0 °C NaH (7.00 g, 0.175 mol) was added in several portions. After 2 hr MOMCl (20.0 ml, 0.262 mol) was added and this solution was stirred for further 5 hr under N_2 at r.t. To this solution sat. brine was added and the aqueous layer was neutralized. The organic layer was separated and the aqueous layer was extracted with ether (100 ml X 3). Organic layers were combined and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by reduced-pressure distillation: colorless oil, yield 18.7 g (73 %); b.p. 118 - 121 °C (5 mmHg); IR (neat) ν_{C-H} 2927, 2827 cm^{-1}, $\nu_{C=C}$ 1556, 1448 cm^{-1}, δ_{Ar-Br} 1161 cm^{-1}, ν_{O-C-O} 932 cm^{-1}, δ_{Ar-H} 769 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$, 27°C) δ/ppm 3.73 (CH_3O, s, 3H), 5.18 (OCH_2O, s, 2H), 6.88 (Ar-4H, t, 1H), 7.52 (Ar-3,5H, d, 2H).

***O*-Methoxymethyl-3-bromosalicylaldehyde (12).** To a stirred solution of **11** in dry THF under N_2 at -78 °C *n*-BuLi (1.5 N hexane solution, 41.7 ml, 43.8 mmol) was added dropwise. After 1 hr a THF solution (10 ml) of DMF (7.30 ml, 43.8 mmol) was added dropwise and this solution was

stirred for further 2 hr at -78°C and was then allowed to warm to r. t. To this solution sat. brine was added and the aqueous layer was neutralized. The organic layer was separated and the aqueous layer was extracted with ether (100 ml X 3). Organic layers were combined and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica gel, $CHCl_3$): white solid, yield 7.7 g (50 %); m.p. 40.4 - 41.3 °C; IR (KBr) $\nu_{C\text{-}H}$ 2927, 2827 cm^{-1}, $\nu_{C=O}$ 1700 cm^{-1}, $\nu_{C=C}$ 1580, 1437 cm^{-1}, $\delta_{Ar\text{-}Br}$ 1161 cm^{-1}, $\nu_{O\text{-}C\text{-}O}$ 920 cm^{-1}, $\delta_{Ar\text{-}H}$ 750 cm^{-1}; ^{1}H-NMR (250 MHz, DMSO-d_6, 27°C) δ/ppm 3.73 (CH_3O, s, 3H), 5.18 (OCH_2O, s, 2H), 7.16 (Ar-5H, t, 1H), 7.81 (Ar-4,6H, d, 2H), 10.34 (CHO, s, 1H).

***O*-Methoxymethyl-2-(*N*,*N'*-dimethylimidazolyl)-6-bromophenol (13).** To a stirred solution of **12** in benzene *N*,*N'*-dimethylethylenediamine was added. This solution was refluxed for 2 hr with Dean-Stark trap equipped flask. This solution was dried with $MgSO_4$ and the solvent was removed *in vacuo*. We have tried to purify this compound with reduced-pressure distillation (2 mmHg, decomposed above 180°C) or chromatography (using silica gel, deprotection occured), but failed. We checked the residue with ^{1}H-NMR to confirm that **12** was quantitatively protected and could be used for the next reaction. So the residue was used for the next reaction without further purification: colorless oil; b.p. > 180°C (decomp.) (5 mmHg); ^{1}H-NMR (250 MHz, DMSO-d_6, 27°C) δ/ppm 2.22 (CH_3-N, s, 6H), 2.61, 3.38 (N-CH_2-, each m, each 2H), 3.67 (CH_3O, s, 3H), 3.99 (N-C<u>H</u>(-Ar)-N), 5.10 (OCH_2O, s, 2H), 7.07 (Ar-4H, t, 1H), 7.52 (Ar-3H, d, 1H), 7.68 (Ar-5H, d, 1H).

3-Boronylsalitylaldehyde (14). To a stirred solution of **13** (1.93 g, 6.13 mmol) in dry THF (50 ml) under N_2 at -78°C, *n*-BuLi (1.5 N hexane solution, 5.1 ml, 7.4 mmol) was added dropwise. After 1 hr $B(OMe)_3$ (2.5 ml, 21.5 mmol) was added and this solution was stirred for the further 1 hr at -78°C and was then allowed to warm to r. t. To this solution sat. brine was added and the aqueous layer was neutralized. The organic layer was separated and the aqueous layer was extracted with THF (100 ml X 3). Organic layers were combined and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by reprecipitation (THF / ether): white solid, yield 460 mg (46 %); m.p. > 220 °C (decomp.); IR (neat) $\nu_{O\text{-}H}$ 3371, 3103 cm^{-1}, $\nu_{C=O}$ 1699 cm^{-1}, $\nu_{C=C}$ 1580, 1437 cm^{-1}, $\nu_{B\text{-}O}$ 1346 cm^{-1}, $\delta_{Ar\text{-}H}$ 762 cm^{-1}; ^{1}H-NMR (250 MHz, DMSO-d_6, 27°C) δ/ppm 6.99 (Ar-5H, t, 1H), 7.76 (Ar-4,6H, m, 2H), 9.86 (B-OH, br, 2H), 10.34 (CHO, s, 1H).

[Co(bsalen)-(*R*)-dp] ((*R*)-7). To a stirred solution of (*R*)-1,2-diphenylethylenediamine in absolute ethanol (5 ml) at 50°C $Co(OAc)_2$ (53.3 mg, 0.300 mmol) was added. After 5 min. **9** (100 mg, 0.60 mmol) was added and the reaction mixture was stirred for further 15 min. at 50 °C and was then allowed to cool to r.t. The precipitate was collected and recrystallized from ethanol: orange solid, yield 118 mg (70 %); m.p. > 250 °C (decomp.); $[\alpha]_D^{25}$ = - 60.0 (c=1.0 in DMSO); IR(KBr) $\nu_{O\text{-}H}$ 3400, 3244 cm^{-1}, $\nu_{C=N}$ 1602 cm^{-1}, $\nu_{C=C}$ 1549, 1427 cm^{-1}, $\nu_{B\text{-}O}$ 1342 cm^{-1}, $\nu_{Ar\text{-}H}$ 760 cm^{-1}. Anal. Calcd for $C_{28}H_{24}O_6B_2N_2Co \cdot 1.0C_2H_6O$: C; 61.56, H; 5.24, N; 4.43%. Found: C; 61.12, H; 5.13, N; 4.75%.

[Co(bsalen)-(*R*)-ch] ((*R*)-8). This compound was synthesized by the same procedure as that used for (*R*)-**7**: orange solid, yield 28 %; m.p. > 250 °C (decomp.); $[\alpha]_D^{25}$ = - 105.0 (c=1.0 in DMSO); IR (KBr) $\nu_{O\text{-}H}$ 3400, 3244 cm^{-1}, $\nu_{C\text{-}H}$ 2927, 2907 cm^{-1}, $\nu_{C=N}$ 1603 cm^{-1}, $\nu_{C=C}$ 1549, 1427 cm^{-1}, $\nu_{B\text{-}O}$ 1342

cm^{-1}, ν_{Ar-H} 760 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6B_2N_2Co \cdot 1.0C_2H_6O$: C; 52.04, H; 5.13, N; 5.09%. Found: C; 51.69, H; 5.13, N; 4.70%.

Miscellaneous

Absorption spectra, ESR spectra, ^{1}H-NMR spectra and IR spectra were measured with Shimadzu 2500-PC, JEOL JES-FE1XG, BURUKER AC-250P, Shimadzu FTIR-8700, respectively, unless otherwise stated. The buffers used to adjust the medium pH were 50 mM acetate at pH < 5.8, 50 mM phosphate at pH 5.8-8.0 and 50 mM carbonate at pH 8.0 - 11.0.

RESULTS AND DISCUSSION

Solution Properties of (*R*)-7. Although the metal complexes were prepared by the reaction with $Co(OAc)_2$, it is ambiguous whether the central metal is Co(II) or Co(III). To specify this we measured the ESR spectrum of isolated (*R*)-**7** in DMSO at 25 °C. As shown in Fig. 1, the ESR spectrum could be analyzed as that of a typical square-planar Co(II) complex.[15] The parameters ($g_{//}$ = 1.902 and $g_\perp$ = 2.358) indicate that the Co(II) complex is not so distorted from the square-planar structure by the chiral (1*R*, 2*R*)-1,2-diphenylethylenediamine moiety.[15] In addition, the finding that the ^{1}H NMR spectrum in DMSO-d_6 is significantly broadened also supports the view that this is the paramagnetic Co(II) complex.

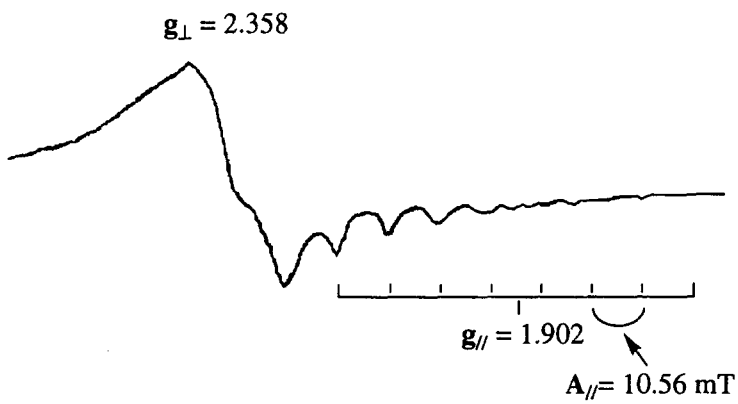


Fig. 1 ESR spectrum of (*R*)-**7** (6.0×10^{-4} mol dm^{-3}) in DMSO at 25 °C

Compounds (*R*)-**7** and (*R*)-**8** were not so soluble in water. Hence, we employed a water-methanol 1:1 (v/v) solution. The pH values indicated are those measured for the aqueous buffer solution before mixing with methanol. To confirm that these compounds are homogeneously solubilized into this mixed solvent, the absorption spectra were measured at various concentrations (~10^{-4} mol dm^{-3}) for more

hydrophobic (*R*)-**7**. The Lambert-Beer's plot of absorbance (λ_{max} 385 nm) vs. (*R*)-**7** concentration showed a satisfactory straight line [25 °C, water (pH 9.5 with 50 mmol dm^{-3} carbonate) - methanol = 1:1 (v/v)], indicating homogeneous solubilization of (*R*)-**7** into this mixed solvent (ε_{385}=1.50 X 10^4 mol^{-1} dm^3 cm).

pH Dependence of the Absorption Spectra. The pH-dependent absorption spectra of (*R*)-**7** is shown in Fig. 2. With increase in the medium pH the λ_{max} shifted from 383 nm to 392 nm. Careful examination of Fig. 2A reveals that two sets of isosbestic points exist, 297 and 415 nm for pH 6-9 and 395 nm for pH 9-11, suggesting the presence of two pK_a values. From the analysis of a plot of A_{380} *vs.* pH (Fig. 3) we obtained pK_{a1} = 8.6, and pK_{a2} = 10.5 for (*R*)-**7**. Another pK_a was observed in low pH region (3.5 - 6.5), but this pK_a was not affected by added saccharides. This means that the pK_{a3} is not concerned to adduct formation with the boronic acids but to dissociation of either phenol OH or Schiff base NH^+. On the other hand, the pK_{a1} and the pK_{a2} lie exactly in the pK_a range of boronic acids. One may consider, therefore, that as shown is Scheme 2, these two boronic acids are dissociated in a stepwise manner.

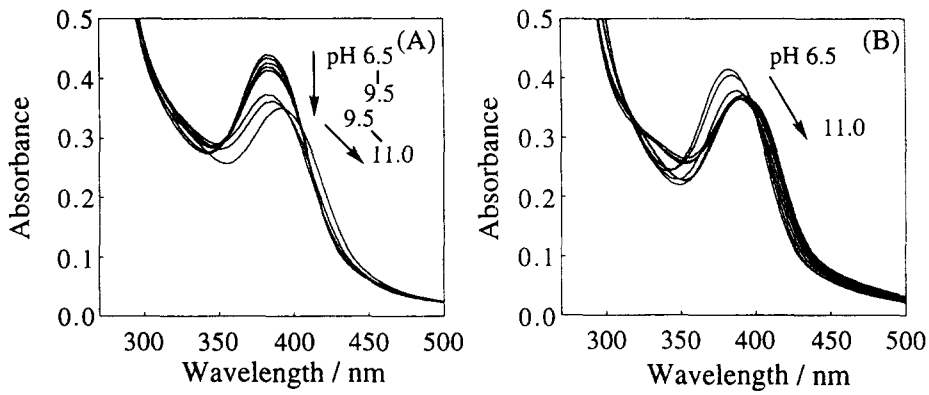


Fig. 2 pH dependence (6.5 - 11.0) of the absorption spectra of (*R*)-**7** (5.0 X 10^{-5} mol dm^{-3}) in the absence (A) and the presence (B) of D-fructose (0.10 mol dm^{-3}): 25 °C, water (50 mmol dm^{-3} buffer) - methanol = 1:1 (v/v)

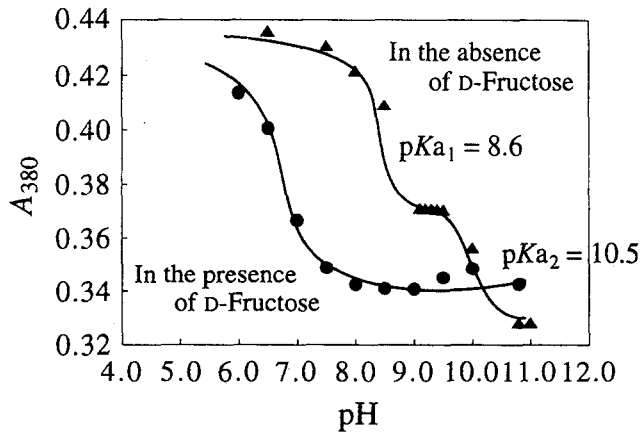
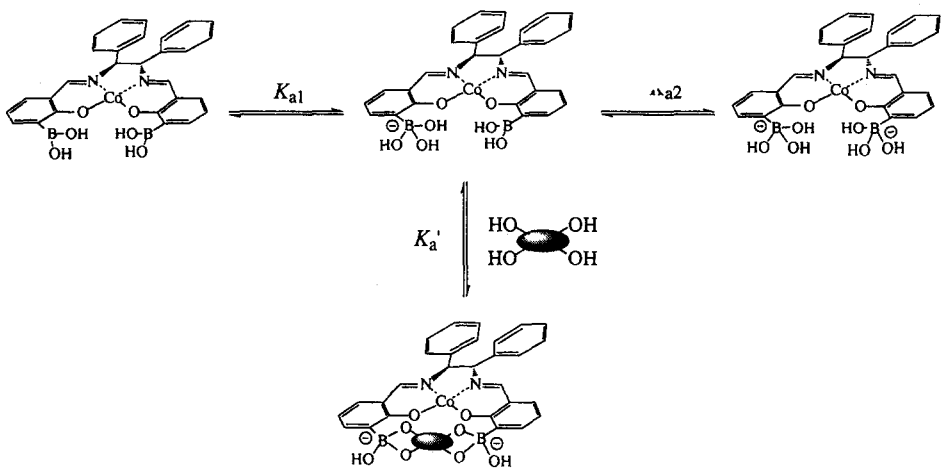


Fig. 3 Plots of A_{380} *vs.* pH in the absence and the presence of D-fructose



Scheme 2 Acid dissociation of (*R*)-**7** and complexation with D-fructose

The spectral change in the presence of D-fructose (which is known to show the highest affinity with monoboronic acids[3-5]) also featured a shift of the λ_{max} from 381 nm to 393nm (Fig. 2B). As shown in Fig. 3, however, the A_{380} vs. pH plot was quite different: it gave only one pK_a at 6.7 (pK_a'). This indicates that as shown in Scheme 2, the D-fructose complexation occurs in a one-step manner, lowering the pK_{a1}.[3-5,16] The pK_a in the presence of excess D-fructose was estimated to be 6.7.

To further corroborate the dissociation and complexation steps in Scheme 2, the stoichiometry of the complex between (*R*)-**7** and D-fructose was studied using a Job plot (Fig. 4). It is seen from Fig. 4 that a maximum appears at [(*R*)-**7**]/([(*R*)-**7**] + [D-fructose]) = 0.5, indicating that as shown in Scheme 2, the two boronic acids act cooperatively to bind one D-fructose molecule.

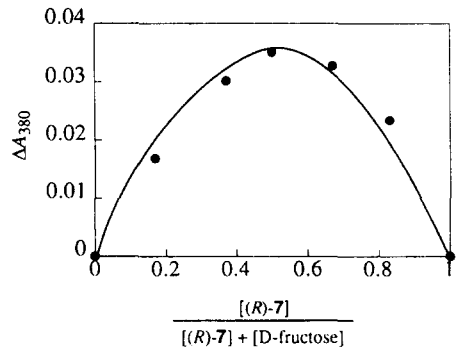


Fig. 4 Job plot for the complex formation from (*R*)-**7** and D-fructose: 25 °C, water (pH 9.5 with 50 mmol dm^{-3} carbonate buffer)-methanol = 1:1 (v/v).

Similarly, the pH-dependent absorption spectra were measured for (*R*)-**8** (Fig. 5A), from which the pK_{a1} and pK_{a2} values for the two boronic acids were estimated to be 8.7 and 10.2. In the presence of excess D-fructose (Fig. 5B), on the other hand, the pK_a appeared at 6.7, indicating a pK_a shift induced by complexation with D-fructose.

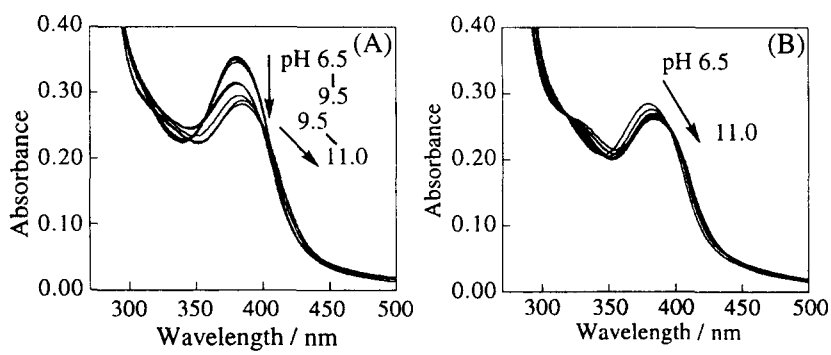
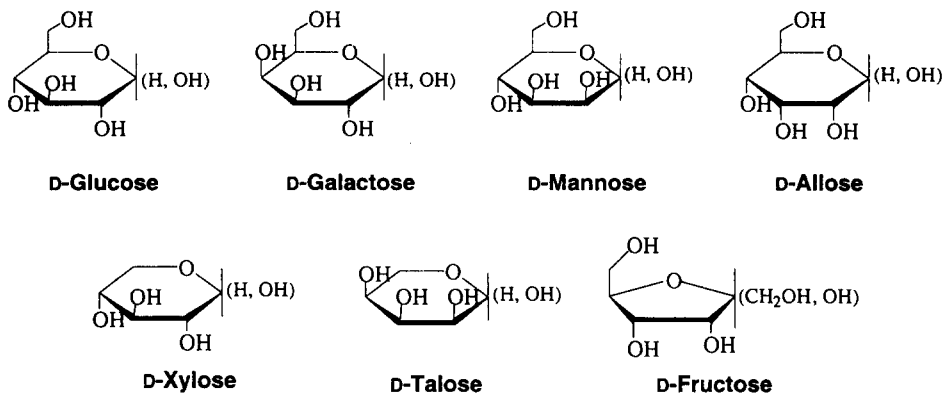


Fig. 5 pH dependence of the absorption spectra of (*R*)-**8** (5.0×10^{-5} mol dm^{-3}) in the absence (A) and the presence of D-fructose (0.1 mol dm^{-3}): 25 °C, water (50 mmol dm^{-3} buffer) - methanol = 1:1 (v/v).

Estimation of the Association Constants with Saccharides. As shown in Fig. 4, (*R*)-**7** forms a 1:1 complex with D-fructose with the aid of a cooperative action of the two boronic acids. Hence, the association constants (K_{ass}) were estimated for D- and L-isomers of seven saccharides assuming the formation of their 1:1 complexes. A typical spectral change is shown in Fig. 6 for D-allose. In Fig. 7, the absorbance increase at 385 nm is plotted against D- and L-allose concentrations. The analysis using a Benesi-Hildebrand equation provided a good linear relationship, supporting the formation of 1:1 complexes in this concentration range. The K_{ass} values thus obtained were 360 dm^3 mol^{-1} for D-allose and 780 dm^3 mol^{-1} for L-allose. Thus, (*R*)-**7** tends to bind L-allose in preference to D-allose and the chiral discrimination ability is estimated to be 2.1-fold.



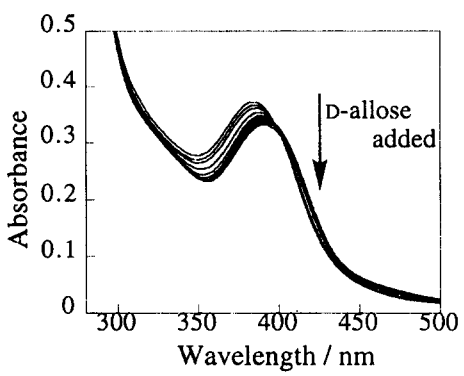


Fig. 6 Absorption spectral change in (*R*)-**7** (5.0 X 10^{-5} mol dm^{-3}) in the presence of D-allose (0 ~ 1.5 X 10^{-2} mol dm^{-3}): the measurement conditions are recorded in the caption to Fig. 5.

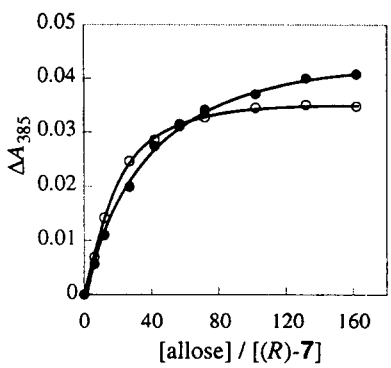


Fig. 7 Plots of ΔA_{385} vs. D-(●) or L-(○) allose concentrations(0 ~ 10 mmol dm^{-3}): the measurement conditions are recorded in the caption to Fig. 5.

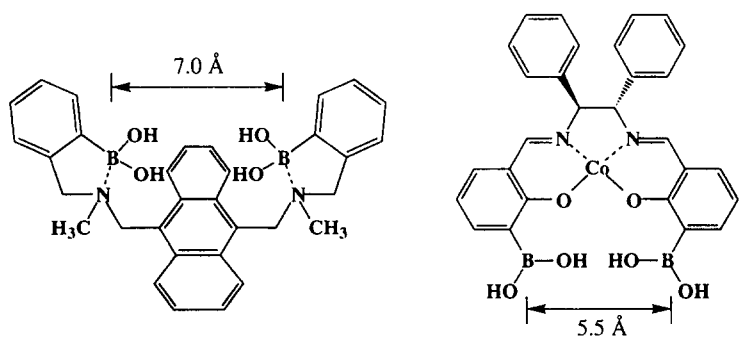
The K_{ass} values of (*R*)-**7** for other six saccharides were determined according to a similar manner. In addition, the K_{ass} values of (*R*)-**8** were also estimated by the same spectroscopic method. The results are summarized in Table 1.

Table 1 Association constants (K_{ass} / dm^3 mol^{-1}) of (*R*)-**7** and (*R*)-**8** with saccharides[a]

	(*R*)-**7**			(*R*)-**8**		
Saccharide	D	L	L / D	D	L	L / D
Glucose	240±20	250±10	1.0	170±10	210±20	1.2
Galactose	250±20	380±30	1.5	80±10	120±10	1.5
Mannose	580±40	920±60	1.6	---	---	---
Talose	1820±100	2380±60	1.6	1070±50	1550±100	1.4
Allose	360±30	780±50	2.1	200±30	320±50	1.6
Fructose	2760±200	2700±150	1.0	---	---	---
Xylose	950±60	960±50	1.0	340±20	560±30	1.7

[a] The mesurement conditions are recorded in the caption to Fig. 5.

Examination of Table 1 reveals that one can raise several interesting points characteristic of the saccharide binding to these bis(boronic acid) receptors.



3 (*R*)-**7**

Fig. 8 Distance between two boronic acid groups of **3** and (*R*)-**7**

Firstly,large K_{ass} values were observed for fructose and talose whereas those for glucose and galactose were relatively small. In diboronic acid derivatives previously studied, the distance between the two boronic acids was designed to *c.a.* 7.0 Å which is comparable with the size of monosaccharides.[5,6] As expected, these receptors showed a high affinity with glucose and galactose bearing 1,2-diol and 4,6-diol (for the pyranose-binding[6]; 5,6-diol for the furanose-binding[17]) useful for the cyclic ester formation with the two boronic acid groups. Compounds (*R*)-**7** and (*R*)-**8** feature the short distance (*c.a.* 5.5 Å) between the two boronic acids. As a result, they preferably bind fructose and talose which posses 1,2-diol and 3,5-diol (for fructose) or 3,4-diol (for talose) as the bindingsites. The results imply that the saccharide-binding selectivity can be controlled by the change in the distance between the two boronic acids.

Secondly, the significant chiral discrimination was observed for several saccharides: *e.g.*, D/L = 2.1 for (*R*)-**7** with D/L-allose, D/L = 1.7 for (*R*)-**8** with D/L-xylose, and D/L = 1.6 for (*R*)-**7** with D/L-mannose and D/L-talose and for (*R*)-**8** with D/L-allose. In contrast, a significant difference was not observed for (*R*)-**7** with D/L-glucose, D/L-fructose, and D/L-xylose. Although it is still difficult to explain why the significant chiral discrimination was observed for certain saccharides but not for other saccharides, we have noticed that L-isomers always give larger K_{ass} values than D-isomers whenever a significant D/L difference appears.

Thirdly, the K_{ass} values for (*R*)-**7** are always larger than those for (*R*)-**8**. Since the ethylene unit of diamine in (*R*)-**8** is a part of the cyclohexane ring, whereas that in (*R*)-**7** is not. It is expected, therefore, that the two boronic acid groups in (*R*)-**7** have more freedom than those in (*R*)-**8**. As mentioned above, the distance between the two boronic acid groups is slightly shorter than the size of monosaccharides. Hence, the steric flexibility remaining in (*R*)-**7** is advantageous to adjust the distance between the two boronic acids to monosaccharides.

CONCLUSION

The present study has shown that the salen skeleton is useful to design diboronic-acid-based receptors for certain saccharides such as talose and fructose and the complexation event can be readily detected by a spectroscopic change in the metal complexes. The chiral recognition, one of representative characteristics of salen-metal complexes, was observed although the D/L selectivity was not so high. These basic findings indicate that the chiral recognition ability of the present system will be further improved by optimized selection of chiral amines and metal ions. In addition, these improved systems will be fruitfully applied to catalytic reactions, the activity and selectivity of which are controlled by the saccharide-binding to the diboronic-acid-based receptor site. Further extension to these systems are currently continued in this laboratory.

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