Pergamon

Tetrahedron 56 (2000) 6193–6198

TETRAHEDRON

Sugar 'Chirality' Sensing Using a 'Prochiral' Salen–Co(II) Complex

Toshihisa Mizuno, Masashi Yamamoto, Masayuki Takeuchi and Seiji Shinkai*

Department of Chemistry & Biochemistry, Graduate School of Engineering, Kyushu University, Fukuoka 812-8581, Japan

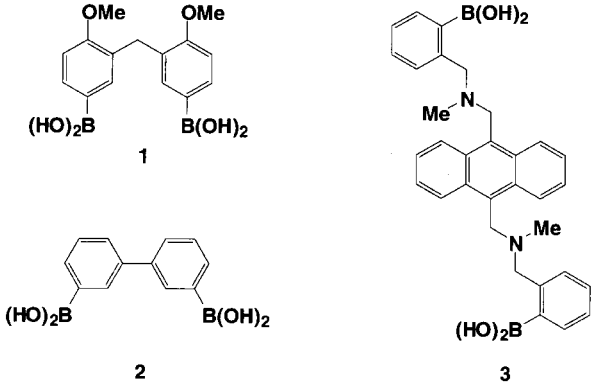
Received 26 May 2000; accepted 21 June 2000

Abstract—A prochiral salen–Co(II) complex (**6**) bearing two boronic acid groups was synthesized. The saccharide-binding event was conveniently monitored by a circular dichroism (CD) spectral change. The exciton-coupling-type CD spectra thus obtained were compared with those of chiral salen–Co(II) complexes, (*R*)-**4** and (*R*)-**5**. Very interestingly, monosaccharides which are selectively bound to (*R*)-**4** and (*R*)-**5** with *P* helicity generate the *P* helicity CD spectra in prochiral **6**. This means that the two boronic acid groups in (*R*)-**4** and (*R*)-**5** are chirally preorganized suitable to the binding of these monosaccharides. Reflecting the short distance between the two boronic acid groups, **6** shows the very high selectivity for talose which has all OH groups arranged on the same side of the pyranose ring. These results indicate that **6** is useful for sugar 'chirality' sensing at visible wavelength region and prediction of D/L selectivity for (*R*)-**4** and (*R*)-**5**.

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] More recently, we demonstrated that this concept is applicable to reversible saccharide sensing in aqueous media: that is, diboronic acids **1** and **2** form rigid, cyclic complexes with mono- and di-saccharides to give the CD-active species.[3] The induced chirality upon formation of rigid, chiral complexes was monitored by circular dichroism (CD) spectroscopy at UV wavelength region. Yoon and Czarnik[4] also reported the 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. 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 (PET) contrivance within a molecule.[6] Compound **3** not only generates CD-active saccharide complexes but also induces a large fluorescence change upon saccharide complexation.[6] This compound has enabled us for the first time to detect glucose with high selectivity and high sensitivity (Scheme 1).[5,6]

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.[7–9] For salen–metal complexes, for example, one can expect several intriguing abilities: e.g. (i) various chiral scaffolds 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 can be made shorter, so that some saccharide different from those bound to **1**–**3** may be captured, (iv) the

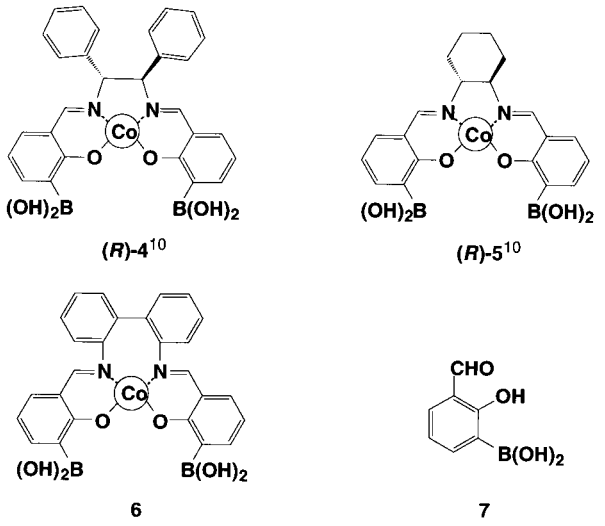


Scheme 1.

Keywords: sugar; chirality; salen–Co(II) complex.

* Corresponding author. Tel.: +81-92-642-3583; fax: +81-92-632-3611; e-mail: seijitcm@mbox.nc.kushu-u.ac.jp

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00578-0



Scheme 2.

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 previously designed compounds (*R*)-**4** and (*R*)-**5**.[10] 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[11] and to electrochemical sensing using interconversion between Co(II) and Co(III).[12,13] In (*R*)-**4** and (*R*)-**5** the distance between the two boronic acid groups is shorter than other diboronic acid-based receptors, so that the saccharide selectivity is quite different from other systems: the particularly large association constant was observed for fructose and talose.[10] In addition, chiral recognition was achieved for certain saccharides: the largest discrimination was 2.1 observed for (*R*)-**4** with D/L-allose.[10] These findings imply that when a 'prochiral' salen–Co(II) complex is used as a saccharide receptor, the saccharide binding should induce the 'chiral' twisting of the salen–Co(II) complex, which should be readily read out as a change in the CD spectra. This means that saccharide 'chirality' sensing is possible with a 'prochiral' salen–Co(II) complex. Taking these lines of expectation into account, we newly synthesized compound **6** (Scheme 2).

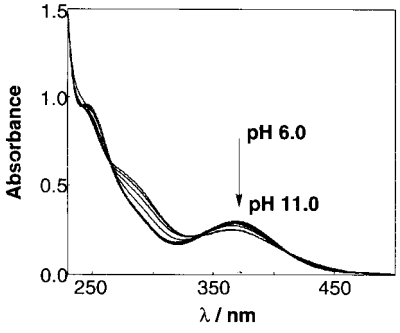


Figure 1. pH dependence (6.0–11.0) of the absorption spectra of **6** (5.0×10^{-5} mol dm^{-3}): 25°C, water (5.0×10^{-2} mol dm^{-3} buffer)–methanol= 1:1 (v/v).

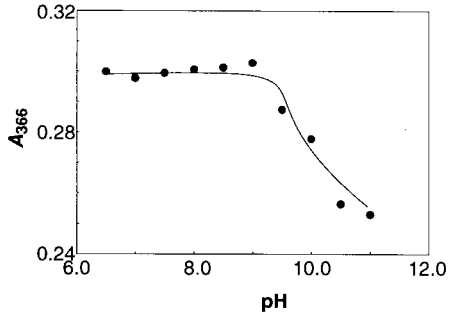


Figure 2. Plots of A_{366} vs. pH for **6**.

Results and Discussion

Estimation of pK_a

Compound **6** was 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 water buffer solution before mixing with methanol. To confirm that this compound is homogeneously solubilized into this mixed solvent, the absorption spectra were measured at the various concentrations ($\sim10^{-4}$ mol dm^{-3}). The Lambert–Beer's plot of an absorbance (λ_{max} 366 nm) vs. **6** concentration showed a satisfactory straight line [25°C, water (pH 9.5 with 50 mmol dm^{-3} carbonate)–methanol= 1:1 (v/v)], indicating the homogeneous solubilization of **6** into this mixed solvent.

The pH-dependent absorption spectral change is shown in Fig. 1. With increase in the medium pH the λ_{max} shifted from 383 to 392 nm with several tight isosbestic points. In (*R*)-**4** and (*R*)-**5** the stepwise titration curves were observed, indicating that the two boronic acid groups are dissociated separately.[10] In contrast, Fig. 1 supports the view that the two boronic acid groups are dissociated simultaneously. From a plot of A_{366} vs. pH (Fig. 2) the pK_a was estimated to be 9.7. Presumably, in (*R*)-**4** and (*R*)-**5** in which the framework is rigidified by chiral amines, electrostatic repulsion between the two boronic acid groups cannot be relaxed by the appropriate molecular motion. As a result, the dissociation of the first boronic acid group affects that of the second one. On the other hand, **6** bearing a prochiral 2,2′-biphenyldiamine is more flexible, so that electrostatic repulsion can be relaxed by the appropriate molecular motion. This situation results in the simultaneous dissociation of the two boronic acid groups in **6**.

CD spectral change in the 6·saccharide complexes

It has been established that both (*R*)-**4** and (*R*)-**5** form 1:1 stoichiometric cyclic complexes with most monosaccharides.[10] Since their basic skeleton is not much different from that of **6**, it is undoubted that **6** also forms 1:1 stoichiometric complexes. According to the theoretical calculations (for the method see Experimental), two phenyl rings in the biphenyl moiety are twisted with a dihedral angle of 47.7° which results in either *P* or *M* helicity in the Co(II) complex moiety. As expected, addition of D-galactose induces a shift of this *P*–*M* equilibrium and results in the exciton-coupling-type CD spectra (Fig. 3). Of course, addition of L-galactose

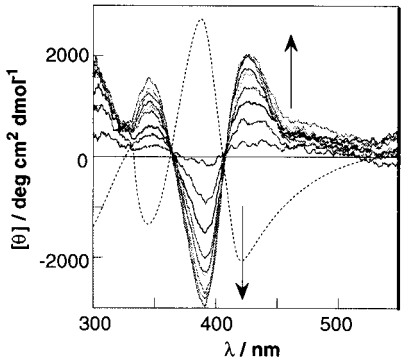


Figure 3. CD spectra of **6** (5.0×10^{-5} mol dm^{-3}): 25°C, water (pH 10.5 with 5.0×10^{-2} mol dm^{-3} carbonate)–methanol=1:1 (v/v). Solid line: [D-galactose=0.0–1.8×10^{-2} mol dm^{-3}; dotted line: [L-galactose]=1.8×10^{-2} mol dm^{-3}.

results in the CD spectrum symmetrical to this (Fig. 3). On the other hand, Fig. 4 shows the CD spectrum of (*R*)-**4** which generates the *P* helicity in the Co(II) complex moiety owing to the chirality of the (1*R*,2*R*)-1,2-diphenylethylenediamine moiety. Comparison of these two figures indicates that the exciton-coupling bands of (*R*)-**4** are similar to those of the **6**·L-galactose complex while symmetrical to those of the **6**·D-galactose complex. The results clearly establish that the salen plane of **6** is twisted into the *P* helicity by complexation with L-galactose while it is twisted into the *M* helicity by complexation with D-galactose.

Very interestingly, we previously found that (*R*)-**4** has the higher affinity with L-galactose than with D-galactose (Table 1).[10] One may consider, therefore, that the two diboronic acid groups in (*R*)-**4** are chirally preorganized so that they can favorably bind L-galactose in preference to D-galactose. The similar exciton-coupling-type CD bands as **6**·D-galactose complex were also induced by addition of D-glucose or D-xylose. Although these saccharides are not chirally discriminated by (*R*)-**4**, it is known that (*R*)-**5** which has the similar chiral plane as (*R*)-**4** shows the L>D selectivity for these saccharides (Table 1).[10] These results support the view that from a CD spectral change induced for prochiral **6** one can reasonably predict L/D selectivity of (*R*)-**4** and (*R*)-**5**. The CD spectral change induced by addition of D-mannose is somewhat different from others and cannot be used to evaluate the above correlation relationship (Fig. 5). On the other hand, addition of D-fructose or D-talose induced the CD spectral change in **6** similar to (*R*)-**4** (Fig. 6). This trend

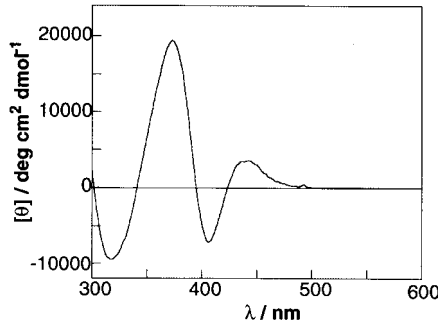


Figure 4. CD spectrum of (*R*)-**4**: the measurement conditions are the same as those in Fig. 3.

Table 1. Ratios of association constants of (*R*)-**4** and (*R*)-**5** and D-saccharide-induced helicity of **6**

Saccharide	L/D Selectivity ratio[a]		Induced helicity in **6** by D-saccharide
	(*R*)-**4** with *P* helicity	(*R*)-**5** with *P* helicity	
D-Galactose	1.5	1.5	*M*
D-Glucose	1.0	1.2	*M*
D-Xylose	1.0	1.7	*M*
D-Mannose	1.6	–	?
D-Fructose	1.0	–	*P*
D-Talose	1.6	1.4	*P*

[a] Ratios of association constants cited from Ref. 10.

suggests that (*R*)-**4** and (*R*)-**5** would show D selectivity for these saccharides. For fructose L/D selectivity was not clearly observed whereas for talose both (*R*)-**4** and (*R*)-**5** still showed L selectivity (Table 1).[10] As illustrated in Scheme 3, D-talose has a unique absolute configuration which features all OH groups situated on the pyranose ring. The distance between two boronic acid groups in **6** (ca. 5.5 Å)[10] is shorter than those in other diboronic-acid-based receptors with glucose or galactose selectivity (ca. 7–8 Å).[3,5–7] Hence, **6** should show the high affinity with D-talose. As discussed later, the association constant (*K*) for D-talose is greater by about two orders of magnitude than those for other saccharides. Presumably, D-talose employs the different binding mode (e.g. using the different

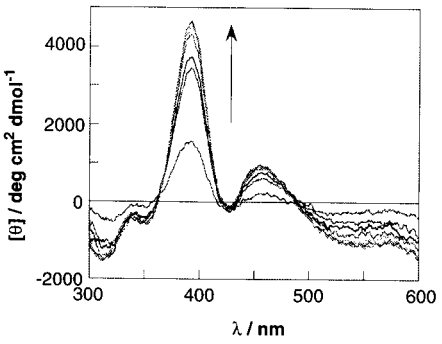


Figure 5. CD spectra of **6** (5.0×10^{-5} mol dm^{-3}) in the presence of D-mannose (0.0–1.8×10^{-2} mol dm^{-3}).

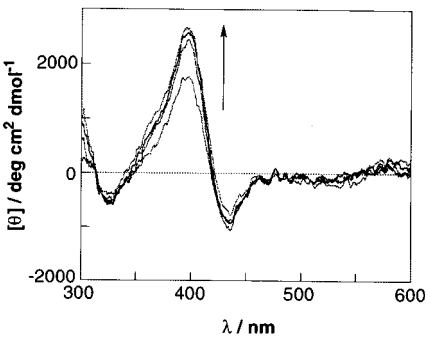
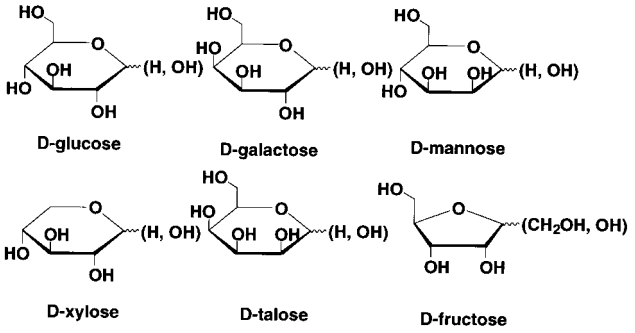


Figure 6. CD spectra of **6** (5.0×10^{-5} mol dm^{-3}) in the presence of D-talose (0.0–1.8×10^{-2} mol dm^{-3}).



Scheme 3.

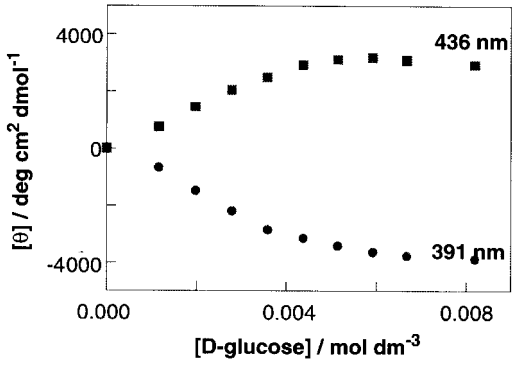


Figure 7. Plots of θ_{min} (at 391 nm) and θ_{max} (436 nm) vs. [D-glucose]: [**6**]=5.0×10^{-5} mol dm^{-3}.

OH groups) from other saccharides, which results in an exception in the L/D selectivity-CD sign correlation relationship.

Determination of *K* values

Since one can regard that **6**, as well as (*R*)-**4** and (*R*)-**5**, forms 1:1 cyclic complexes with monosaccharides[10] and the resultant complexes are CD-active, the *K* values can be readily estimated by analysis of θ vs. [saccharide] plots according to Benesi–Hildebrand equation.[14] Fig. 7 shows typical plots for D-glucose at θ_{min} (391 nm) and θ_{max} (436 nm). From these plots the *K* for D-glucose was estimated to be 2.4×10^2 dm^3 mol^{-1}. The *K* values for other saccharides were also determined in a similar manner. The results are summarized in Table 2, together with θ_{min} and θ_{max} of the CD spectra at the intensity-saturated region.

Examination of Table 2 reveals that one can raise several interesting characteristics of the salen-based saccharide receptor **6**. Firstly, the particularly large *K* was observed for D-talose and the next *K* for D-fructose. On the other hand, the *K* values for typical monosaccharide such as D-glucose and D-galactose were relatively small. The most likely binding sites with the two boronic acid groups are 1,2-diol and 3,4- or 4,6-diol in the pyranose form (or 3,5- or 5,6-diol in the furanose form) in D-talose. This short binding sites meet the characteristic short distance between the two boronic acid groups in **6**. The similar steric situation is also adapted to D-fructose. On the other hand, D-glucose uses 1,2-diol and 4,6-diol in the pyranose form (or 5,6-diol in the furanose form) and D-galactose uses 1,2-diol and 3,4- or 4,6-diol in the pyranose form (or 3,5-diol or 5,6-diol in the furanose form) as the binding sites and the distance is too long to fit the diboronic acid cleft of **6**. Thus, saccharide selectivity can be basically rationalized in terms of host/guest distance selectivity.

Table 2. Association constants (*K*) and CD parameters

Saccharide	K/dm^{-3} mol^{-1}	$\theta(\lambda)$/deg cm^{-2} dmol^{-2} (nm)	
D-Galactose	2.6×10^2	−2970 (388)	2010 (443)
D-Glucose	2.4×10^2	−3880 (391)	3190 (436)
D-Xylose	4.5×10^2	−2960 (391)	2030 (425)
D-Mannose	3.9×10^2	4640 (392)	940 (456)
D-Fructose	8.0×10^2	3013 (394)	−1692 (440)
D-Talose	1.0×10^4	2650 (398)	−860 (429)

Secondly, one may recognize some correlation between the CD sign and the saccharide absolute configuration. D-Galactose, D-glucose, and D-xylose give the *M* helicity for the CD spectra: these saccharides commonly have 2-OH directed downward the pyranose ring. This configurational characteristic allows them to be bound to two boronic acid groups in an extended, *anti*-like structure. On the other hand, D-talose has 2-OH directed upward the pyranose ring. This configurational characteristic allows it to be bound to two boronic acid groups in a folded, *syn*-like structure. This difference should twist the salen plane into the opposite direction.

Thirdly, there is no significant correlation between the *K* and the CD intensity: the CD intensity for D-talose is not particularly strong and the strong CD intensity is observed for D-glucose and D-mannose with the medium to small *K* values.

Computational evaluation of *P*/*M* preference

To obtain an insight into the *P*/*M* preference of **6** we evaluated by a computational method whether typical L-saccharides really induce the molecular twist into the *P* helicity. The energy-minimization was carried out according to the following processes. Firstly, **6** including both the biphenyl moiety and the Co(II) complex moiety is enforced to adopt a coplanar conformation and keeping this conformation, L-galactose is bound to the two boronic acid groups (where the two B atoms employ OH^- adduct sp^3-hybridization) (Fig. 8A). Secondly, this enforced coplanarity is released so that the **6**·L-galactose complex can be twisted into either *P* or *M* helicity. Thirdly, this preferable twisted molecule is finely energy-minimized (Fig. 8B).

It is clearly seen from Fig. 8B that complexation with L-galactose induces the twist of the Co(II) complex plane into *P* helicity. The result is exactly complementary to our previous finding that both (*R*)-**4** and (*R*)-**5** with *P* helicity bind L-saccharides in preference to D-saccharides.[10] In fact, the energy-minimized structure for (*R*)-**4** (Fig. 8C) shows the molecular twist into *P* helicity, which provides the same helicity for the chiral orientation of the two boronic acid groups in the energy-minimized **6**·L-galactose complex.

The foregoing results thus establish that the D/L preference of the diboronic acid receptor designed on a salen–Co(II)

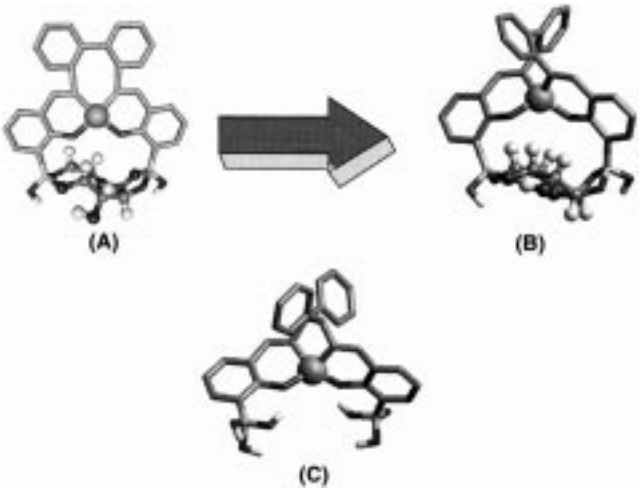


Figure 8. (A) **6**·L-galactose complex where the **6** moiety is still enforced to keep coplanarity, (B) energy-minimized structure of **6**·L-galactose complex with *P* helicity, (C) energy-minimized structure of (*R*)-**4** with *P* helicity.

complex scaffold is readily estimated by a saccharide-induced CD sign in prochiral **6**.

Conclusion

The present study has shown that the salen skeleton is useful to design diboronic-acid-based receptors with the particularly large *K* value for D-talose and with the moderate *K* values for other saccharides and the complexation event can be readily detected by a CD spectroscopic change in the metal complexes. Furthermore, the CD sign is useful to predict D/L selectivity of chiral salen–Co(II) complexes. These basic findings indicate that the chiral recognition ability of the present system will be further improved by optimized selection of 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.

Experimental

Materials

The synthesis of 3-boronylsalicylaldehyde (**7**) was reported previously.[10]

Compound 6. To a stirred solution of 2,2′-bipheyldiamine in absolute ethanol (5 ml) at 50 °C $Co(OAc)_2$ (53.3 mg, 0.300 mmol) was added. After 5 min **7** (100 mg, 0.60 mmol) was added. The mixture was stirred for 15 min at 50°C and then allowed to cool to room temperature. The solution was evaporated to dryness and the solid residue was dissolved in chloroform. This solution was washed with water and then dried over Na_2SO_4. The solution was again evaporated to dryness, the solid residue being purified by reprecipitation from chloroform to *n*-hexane: yellow powder, yield 40 mg (25 %); mp>220°C (decomp.); IR (KBr) ν_{O-H} 3400, 3244 cm^{-1}, $\nu_{C=N}$ 1602 cm^{-1}, $\nu_{C=C}$ 1549, 1427 cm^{-1}, ν_{B-O} 1342 cm^{-1}. Anal. Calcd for $C_{26}H_{20}O_6B_2N_2Co$: C, 58.15; H, 3.75; N, 4.03 %. Found: C, 58.30; H, 3.80; N, 4.13%.

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.

Miscellaneous

Absorption spectra, ^1H NMR spectra, IR spectra were measured with Shimadzu 2500-PC, Bruker AC-250P, Shimadzu FTIR-8700, respectively, unless otherwise stated. CD spectra were performed using a JASCO J-720WI spectrophotometer. The buffers used to adjust the medium pH were 50 mmol dm^{-3} acetate at pH<5.8, 50 mmol dm^{-3} phosphate at pH 5.8–8.0, 50 mmol dm^{-3} carbonate at pH 8.0–11.0.

References

1. (a) Rebek, Jr. *J. Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (b) Goswam, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1989**, *111*, 3425. (c) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 3744. (d) Etter, M. C.; Adsmond, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 4549. (e) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673. (f) Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 634. (g) Kano, K.; Yoshiyasu, K.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1988**, 801. (h) Inouye, M.; Takahashi, K.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 341(i) Mazik, M.; Bandmann, H.; Sicking, W. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 551. (j) Davis, A. P.; Wareham, R. S. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2270. (k) Neidlein, U.; Diedrich, F. *Chem. Commun.* **1996**, 1493.

2. (a) Wulff, G.; Vietmeier, J.; Poll, H. G. *Makromol. Chem.* **1987**, *188*, 731. (b) Wulff, G.; Poll, H. G. *Makromol. Chem.* **1987**, *188*, 741.

3. (a) Kondo, K.; Shiomi, Y.; Saisho, M.; Harada, T.; Shinkai, S. *Tetrahedron* **1992**, *48*, 8239. (b) Tsukagoshi, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4089. (c) Shiomi, Y.; Saisho, M.; Tsukagoshi, K.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2111. (d) Shiomi, Y.; Kondo, K.; Saisho, M.; Harada, T.; Tsukagoshi, K.; Shinkai, S. *Supramol. Chem.* **1993**, *2*, 11.

4. Yoon, J.; Czarnik, A.; W *J. Am. Chem. Soc.* **1992**, *114*, 5874.

5. For comprehensive reviews on boronic-acid-based sugar receptors see (a) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Supramol. Chem.* **1995**, *6*, 141. (b) James, T. D.; Linnane, P.; Shinkai, S. *Chem. Commun.* **1996**, 281. (c) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1910.

6. (a) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2207. (b) James, T. D.; Sandanayake, K. R. A. S.; Iguchi, R.; Shinkai, S. *J. Am. Chem. Soc.* **1995**, *117*, 8982.

7. James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Nature* **1995**, *374*, 345.

8. Takeuchi, M.; Yoda, S.; Imada, T.; Shinkai, S. *Tetrahedron* **1997**, *53*, 8335.

9. Ori, A.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1771.

10. Mizuno, T.; Takeuchi, M.; Shinkai, S. *Tetrahedron* **1999**, *55*, 9455. In this reference, the configurations for (*R*)-**7** and (*R*)-**8** (*R*)-**4** and (*R*)-**5**, respectively, in the present paper) were not correctly illustrated.
11. For recent reviews for the catalytic reactions mediated by salen–Co(II) complexes, see (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2012. (c) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. (d) Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1997**, *38*, 3435. (e) Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201. (f) Yamashita, Y.; Katsuki, T. *Synlett* **1995**, 825. (g) Das, B. C.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 2903. (h) Föster, S.; Rieker, A. *J. Org. Chem.* **1996**, *61*, 3320 and cited therein.
12. For an example of electrochemical sensing, see Ref. 9.
13. For Co(II)–Co(III) interconversion coupled to sugar sensing, see (a) Mizuno, T.; Takeuchi, M.; Hamachi, I.; Nakashima, K.; Shinkai, S. *Chem. Commun.* **1997**, 1793. (b) Mizuno, T.; Takeuchi, M.; Hamachi, I.; Nakashima, K.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2281.
14. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.