Electrochemical Detection of Saccharides by the Redox Cycle of a Chiral Ferrocenylboronic Acid Derivative: a Novel Method for Sugar Sensing

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A chiral ferrocenylboronic acid **1** bearing an intramolecular tertiary amine binds saccharides at *ca.* pH 7, the complexation event, which can be conveniently detected by an electrochemical method, shows chiral discrimination for certain linear saccharides.

Boronic acids can form cyclic esters with diols rapidly and reversibly in basic aqueous solution. It has been shown that the boronic acid–diol interaction is very useful as a potential method to *touch* sugars and *selectively* recognize them.[1] In certain fluorescent boronic acids the fluorescence intensity is sensitively affected by the complexation event and the fluorescence change is readily applicable to practical sugar sensing.[2] The finding suggests that the redox potential of the aromatic moiety covalently linked to the boronic acid would be also affected by complexation with saccharides and the event would be read out by an electrochemical method. With these objects in mind, we designed compound **1**: the ferrocene moiety serves as a redox centre for the reading-out and the intramolecular amine coordinates to the boron atom to change its sp^2-orbital to sp^3-orbital and makes the sugar-binding boronic acid chiral. Ferrocenylboronic acid without the intramolecular amine can bind saccharides only at high pH region with an OH^--mediated sp^2-to-sp^3 orbital change whereas **1** can bind saccharides even at neutral pH region because of its pre-organized sp^3-orbital.

Compound **1** was synthesized and optically resolved as shown in Scheme 1. The absolute configuration of **5** has been established.[3] As the regioselectivity in the subsequent lithiation process is entirely controlled by the configuration of the *N,N*-dimethyl-1-aminoethyl group,[3] (*R*)-(+)-**5** affords (−)-**1** whereas (*S*)-(−)-**5** affords (+)-**1**. In this step, the point chirality in **5** creates the molecular chirality in **1**. The molecular chirality in **1** is useful to estimate the association constants (K_1) by CD spectroscopy and leads to the hope that **1** may show chiral discrimination ability.

Fig. 1 shows the CD spectral change of (−)-**1** in the presence of D-sorbitol. From a plot of [θ] *vs.* [D-sorbitol] we obtained the association constant (K_1) = 67 ± 6 dm^3 mol^{-1}. The voltammograms were recorded at 25 °C with a BAS-100B/W electrochemical analyser using a single-compartment cell fitted with a glassy carbon working electrode, a platinum wire counter electrode and a Ag/AgCl reference electrode. Each measurement was repeated at least three times and the average value and the error range were determined. The differentiation curves of the normal pulse voltammetry (NPV)† for a (−)-**1** plus D-sorbitol system are shown in Fig. 2. From plots of $\Delta I_f/(\Delta I_f + \Delta I_c)$ (where ΔI_f and ΔI_c are the differentiation values at the halfwave potential of free (−)-**1**H^+ and (−)-**1**·D-sorbitol complex, respectively) *vs.* [D-sorbitol] we estimated K_1 for

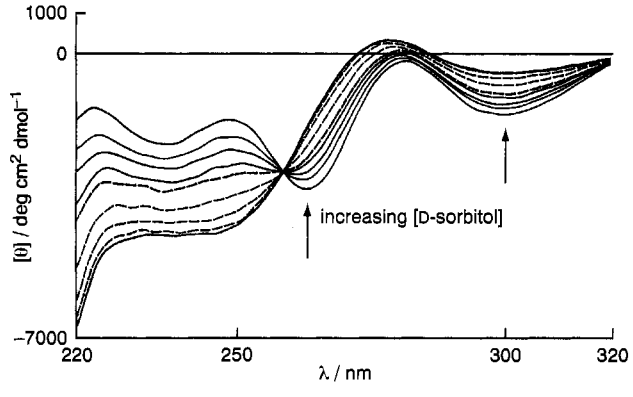


Fig. 1 CD spectral change of (−)-**1** (1.0×10^{-3} mol dm^{-3}) in the presence of D-sorbitol (0–7.0×10^{-2} mol dm^{-3}): 25 °C, pH 7.0 with 0.1 mol dm^{-3} phosphate buffer.

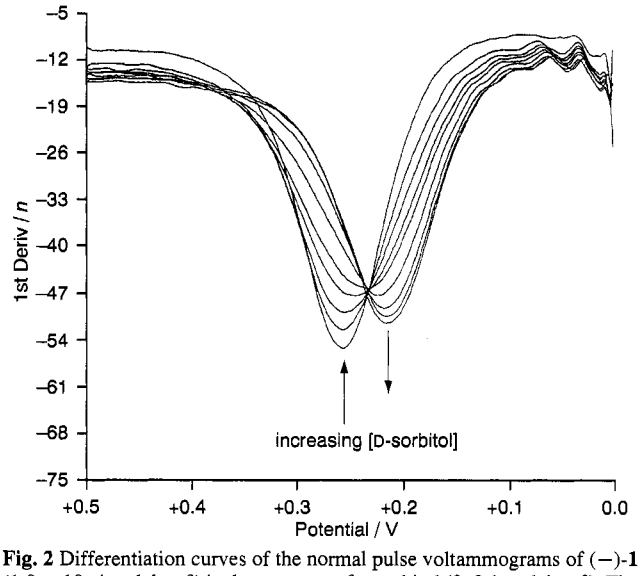
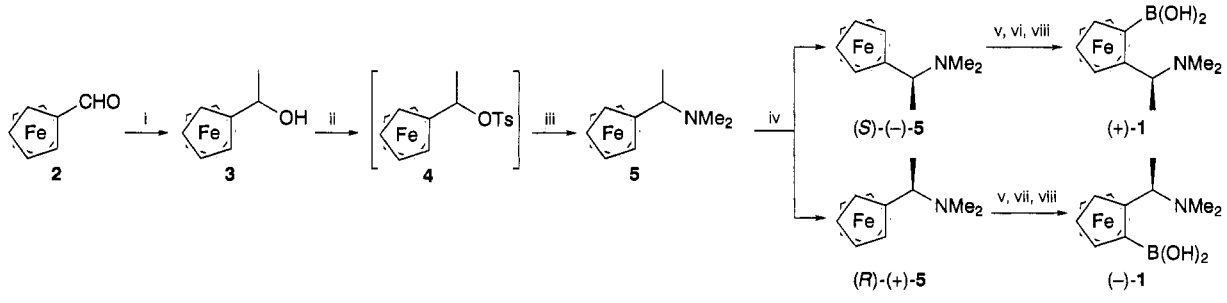


Fig. 2 Differentiation curves of the normal pulse voltammograms of (−)-**1** (1.0×10^{-4} mol dm^{-3}) in the presence of D-sorbitol (0–0.1 mol dm^{-3}). The measurement conditions are similar to those in Fig. 1. The area of the glassy carbon electrode is 0.07 cm^2. Voltammetric parameters are as follows: scan rates, 2 mVs^{-1}; pulse width, 50 ms; pulse period, 500 ms.



Scheme 1 *Reagents and conditions*: i, MeMgI, Et_2O, reflux, 85.3%; ii, *p*-TsCl, Pyridine, 0 °C; iii, Me_2NH, Pr^iOH, room temp., 85.2%; iv, (*R*)-(+)-tartaric acid, 60%; v, BuLi, Et_2O, room temp.; vi, $(PrO)_3B$, Et_2O, −78 °C, 40.7%; vii, $(Pr^iO)_3B$, Et_2O, −78 °C, 31.7%; viii, H_2O

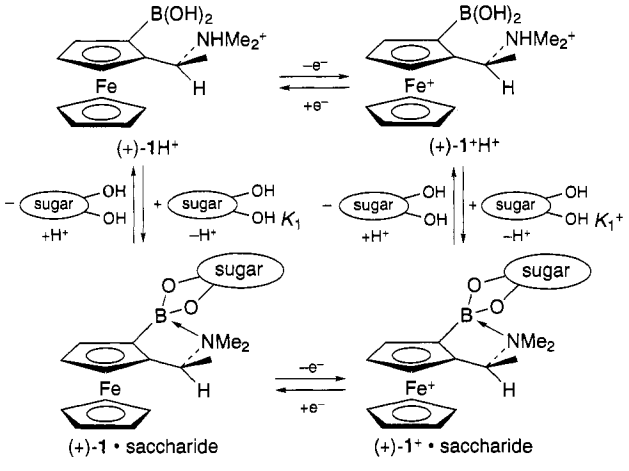
ferrocene species and K_1^+ for ferricinium species: $K_1 = 70 \pm 7$ dm^3 mol^{-1} and $K_1^+ = 500 \pm 40$ dm^3 mol^{-1}. The coincidence of the K_1 values determined by two different methods supports that the 'true' association constant is obtained by the electrochemical method. The K_1 and K_1^+ values for several saccharides are summarized in Table 1.

Examination of Table 1 raises several interesting features of the present electrochemical method. First, the saccharide-induced redox potential change was observed only at *ca.* pH 7: that is, the simple boronic acid-saccharide complexation is not responsible for the redox potential change in the ferrocene moiety. This means that in Scheme 2 the process measurable as the redox potential change corresponds to conversion of $\mathbf{1}H^+$ to **1**·saccharide complex (or $\mathbf{1}^+H^+$ to $\mathbf{1}^+$·saccharide complex). Secondly, the K_1^+ values are greater by about one order of magnitude than the K_1 values. The boronic acid in cationic $\mathbf{1}^+$ is more acidic than that in neutral **1** and therefore shows the higher affinity with saccharides. In D-glucose the K_1 was too small to determine by the present method but $K_1^+ = 6$ dm^3 mol^{-1} could be estimated. Thirdly, and most importantly, the significant chiral discrimination was observed for linear, noncyclic saccharides but not for cyclic saccharides. The largest enantiomeric selectivity was that observed for **1** plus sorbitol [for example, D/L = 1.4 for (+)-**1**]. It is not yet clear why the significant chiral discrimination is confined to linear saccharides. Examination of CPK molecular models suggests that in the complexes with linear saccharides remaining OH groups can enjoy the interaction with Fe^{II} or Fe^{III} whereas it is not the case in the complexes with cyclic saccharides. Although we do not have further evidence to justify this rationale, the iron–OH interaction possible only in linear saccharides seems reasonable to explain the chiral discrimination ability.

Table 1 Association constants (K_1 and K_1^+)[a]

	K_1		K_1^+	
Saccharide	(+)-**1**	(−)-**1**	(+)-$\mathbf{1}^+$	(−)-$\mathbf{1}^+$
D-Fructose	15 ± 2	14 ± 2	190 ± 20	220 ± 20
D-Glucose	—[b]	—[b]	6 ± 2	6 ± 2
D-Mannitol	28 ± 3	27 ± 4	170 ± 20	150 ± 20
D-Sorbitol	110 ± 10	70 ± 7	720 ± 50	500 ± 40
L-Sorbitol	76 ± 7	120 ± 10	500 ± 40	710 ± 50
L-Iditol			500 ± 50	390 ± 40
Pentaerythritol		13 ± 2		44 ± 3

[a] 25 °C, pH 7.0 with 0.1 mol dm^{-3} phosphate buffer. The association constants were determined by the analysis of plots of [saccharide] *vs.* $\Delta I_f/(\Delta I_f + \Delta I_c)$ according to Benesi–Hildebrand equation.[4] [b] The perceptible change in NPV was not observed.



(+)-**1** • saccharide (+)-$\mathbf{1}^+$ • saccharide

Scheme 2

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Footnote

† We also tested CV, differential pulse voltammetry (DPV) and Osteryoung square wave voltammetry (OSWV) in addition to NPV. Among them NPV afforded the best data in the sensitivity and the reproducibility. The voltammogram was very reproducible (for more than five scans) indicating that decomposition of ferricinium ion is not induced.

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