The Synthesis and Properties of a Calixarene-based 'Sugar Bowl'

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A novel calix-diboronic acid **1** has been synthesised which can detect saccharides at neutral pH in aqueous media; the binding events are sensitively monitored by changes in the fluorescence intensity.

The development of receptors for saccharides has recently gained much attention. In particular several groups have demonstrated that boronic acids are promising functional groups for the binding of saccharides in aqueous systems.[1] One problem with many of these systems is that they only function at high pH in aqueous media. However, a neighbouring nitrogen enhances the formation of boronate esters even under neutral pH conditions.[2] Recently we employed such an interaction[3–5] to create photoinduced electron transfer (PET) sensors for saccharides.[6,7] When saccharides form cyclic boronate esters with boronic acids, the acidity of the boronic acid is enhanced[8] and therefore the Lewis acid–base interaction with the tertiary amine is strengthened thus modulating the PET from the amine (acting as a quencher) to anthracene (acting as a fluorophore). These compounds show increased fluorescence at pH 7.77 through suppression of the photoinduced electron transfer from nitrogen to anthracene on saccharide binding: a direct result of the stronger boron–nitrogen interaction.[3–5]

Earlier work has also demonstrated the versatility of boronic acid receptors in both the selective recognition of saccharides[1] and also the chiral recognition of saccharides.[2]

Our aim was to develop a 3-dimensional fluorescent diboronic acid capable of binding sugars at neutral pH in aqueous media. This was achieved by attaching two 2-aminomethylnaphthalene boronic acids to the upper rim of a tetraalkylated calixarene. The aminomethylnaphthalene boronic acid moieties act as a PET sensor on binding to saccharides. To our knowledge this is the first fluorescent saccharide-sensing calixarene 'sugar bowl.' Synthesis of the desired calix-diboronic acid was readily achieved (Scheme 1). The synthesis involved eight chromatography-free steps yielding **1** in 20% yield overall. The elegance of using calixarenes as building blocks for saccharide sensors stems from the multitude of latent functionality available to the synthetic chemist in comparison to non-functionalisable mono- and di-boronic acid saccharide sensors. Compound **1** possesses four propyl groups necessary to keep the calixarene in the cone conformation and two Ar–Br units used to block the 1,3-positions.

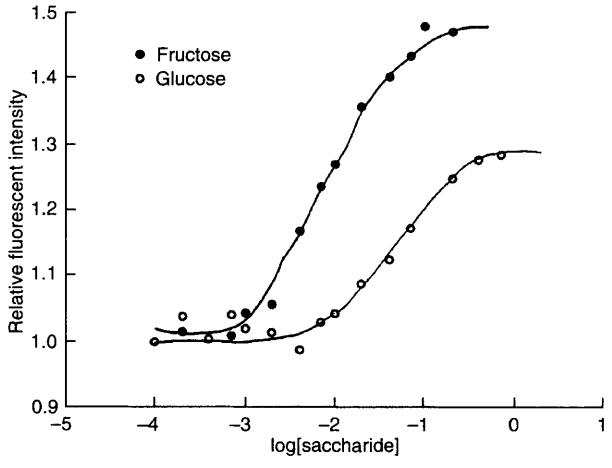
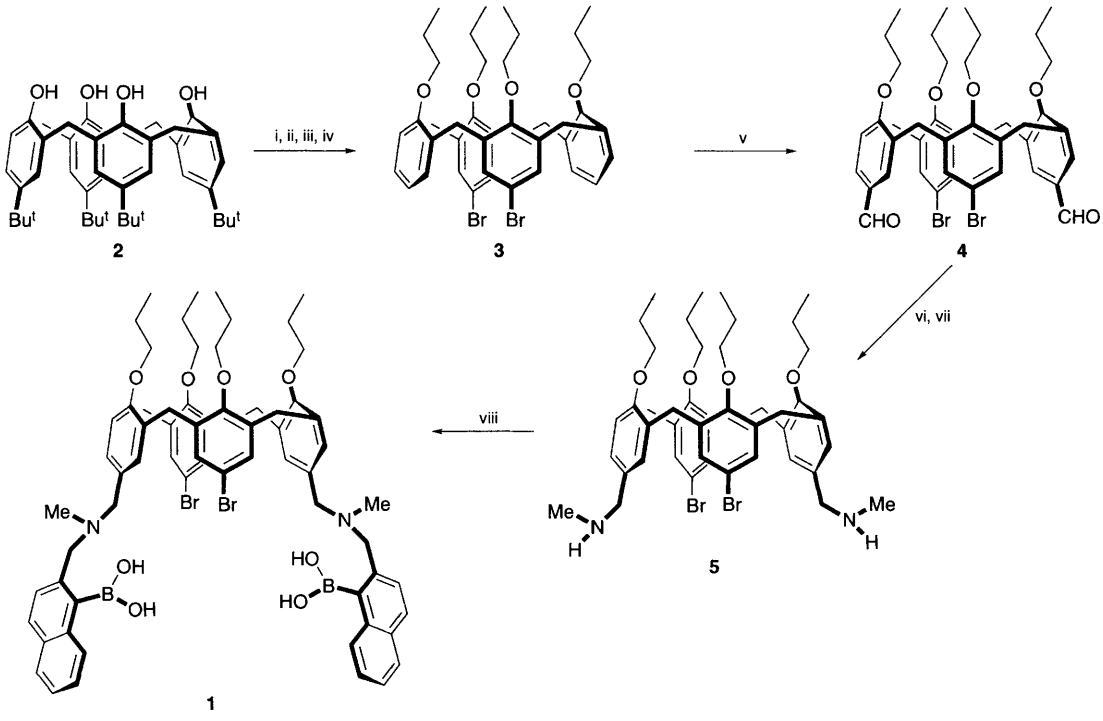
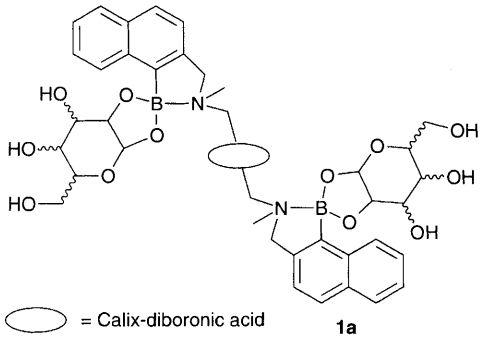


Fig. 1 Fluorescence intensity of **1** *vs.* log [D-fructose or D-glucose] at 25 °C; 1.0×10^{-5} mol l^{-1} of **1** in MeOH, λ_{ex} 279 nm, λ_{em} 337 nm

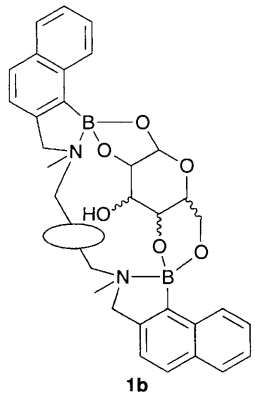


Scheme 1 Synthesis of calix-diboronic acid **1**. *Reagents* (yields): i, $AlCl_3$, toluene (70%); ii, PrI, K_2CO_3, MeCN, reflux, 6 h (80%); iii, Br_2, $CHCl_3$, 0 °C, 1 h (87%); iv, PrI, NaH, dimethylformamide (DMF), room temp. 12 h (76%); v, hexamethylenetetraamine (HMTA), trifluoroacetic acid, reflux, 24 h, (60%); vi, methylamine, MeOH, 1 h, (99%); vii, $NaBH_4$, MeOH, 1 h (95%); viii, 2-bromomethylnaphthalene boronic acid, K_2CO_3, MeCN, reflux, 16 h, (95%).

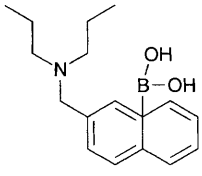
The saccharide fluorescence intensity titration curves for **1** at neutral pH (methanol–water, 33% *m/m*) are shown in Fig. 1. The stability constants are log K_a = 1.38 for D-glucose and log K_a = 2.06 for D-fructose. With **1** four main species exist under the experimental conditions: among them the fluorescent species are **1a** (a non-cyclic 2 : 1 intermolecular complex) and **1b** (a cyclic 1 : 1 intramolecular complex). Confirmation of the stoichiometry was mainly obtained by mass spectroscopy. The mass (SIMS positive) spectra of a 1 : 1 mixture of **1** with D-glucose contained the M^+ ion of **1b** and that with D-fructose contained the M^+ ion of **1a**. The results establish that the fluorescent-active species are **1a** for D-fructose and **1b** for D-glucose. Further verification of the stoichiometry of binding of D-glucose to **1** was obtained by comparing the stability constant of D-glucose and a monoboronic acid reference compound **6** with the stability constant of D-glucose mono-phosphate and **1**. One would expect the binding constants to decrease in both cases, mainly because monoboronic acid **6** can only form a 1 : 1 complex or a 2 : 1 complex, neither of which will be as strong as the suspected 1 : 1 intramolecular complex with **1**. What we actually see is a lower stability constant (log K_a = 0.0633) for D-glucose and **6** indicating that the stronger binding of D-glucose to **1** must be due to the intramolecular complex **1b**. The stability constant of D-glucose-1-monophosphate with **1** should be smaller than that of D-glucose with **1** because it can only form a 2 : 1 complex since one of its primary binding sites is blocked. Experimentally we found that D-glucose monophosphate does not bind to **1**, therefore a 2 : 1 complex can be ruled out for D-glucose. The stoichiometry of binding of D-fructose to **1** was verified by determining the binding constant of D-fructose to mono-boronic acid **6**. We would expect to see no change in the stability constant of D-fructose with **6** relative to **1** if a 2 : 1 intermolecular complex were to exist. Experimentally we found this to be true: both stability constants are similar (log K_a = 1.56 with **6** and 2.06 with **1**) indicating the intermolecular complex **1a** is the major complex formed while the complex **1b** may be formed to a minor extent.



1a



1b



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In conclusion it was possible to design a novel PET sensor based on a calix[4]arene core which showed saccharide selectivity for fructose. Considering the plethora of shapes and sizes of functionalised calixarenes available to us, it will not be long before precise saccharide sensors are developed employing calixarenes as building blocks.

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