A Diboronic Acid 'Glucose Cleft' and a Biscrown Ether 'Metal Sandwich' are Allosterically Coupled

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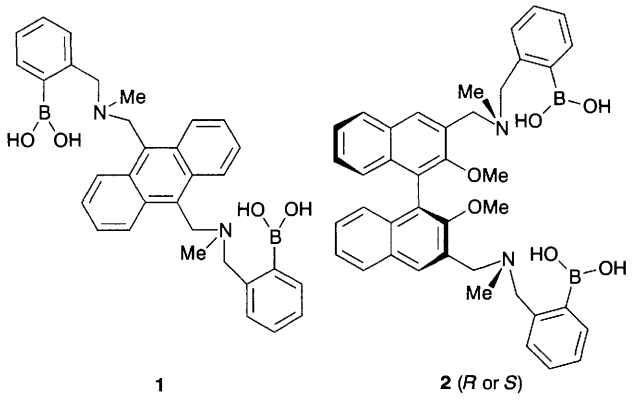
Glucose is released from the diboronic acid 'cleft' **3** when a metal 'sandwich' is formed by two 15-crown-5 rings; the binding events are sensitively monitored by changes in the fluorescence intensity.

The development of boronic acid receptors for saccharides has recently gained much attention.[1] One problem with many of these systems is that they only function in basic aqueous media. Wulff was the first to report that a neighbouring nitrogen enhances the formation of boronate esters even under netural pH conditions.[2] In a series of recent papers we employed the interaction of boronic acid and amine[3–5] to create photoinduced electron transfer (PET)[6,7] sensory systems for saccharides. 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. The strength of this acid–base interaction modulates 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 PET from nitrogen to anthracene on saccharide binding, a direct result of the stronger boron–nitrogen interaction.[3–5]

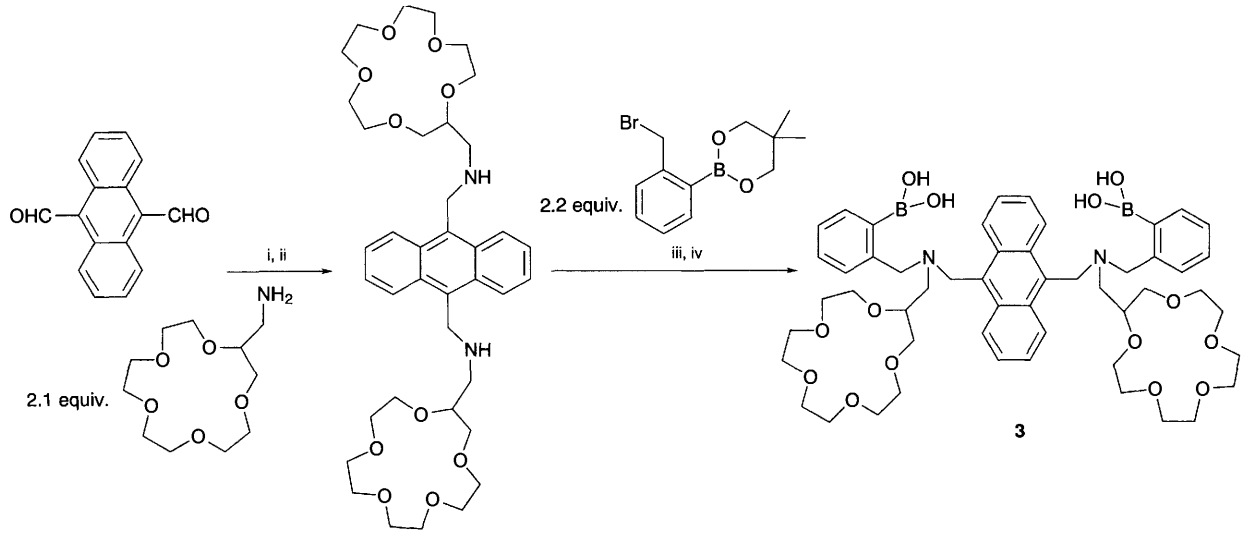
Our previous allosteric diboronic acid[1] has shown that boronate esters are just as useful as metal ion coordination or lipophilic interactions[9–14] in the construction of allosteric devices. With boronic acids **1** and **2**, by modifying the shape of the cleft we have been able to vary the inherent selectivity of the boronic acid. With compound **1** glucose selectivity[4] and with compound **2** chiral selectivity[5] was achieved (*NB.* in both these systems the formation of a 1 : 1 intramolecular complex was shown to be the important fluorescent species). With this work we take a step towards controlling the saccharide selectivity of our fluorescent saccharide cleft **1** by external stimuli. On examination of the CPK models for compound **3** we find that when the two 15-crown-5 rings form a metal ion sandwich, the distance between the two boronic acid moieties is lengthened, making the formation of the 1 : 1 fluorescent saccharide complex[4,5] impossible.



1 **2** (*R* or *S*)

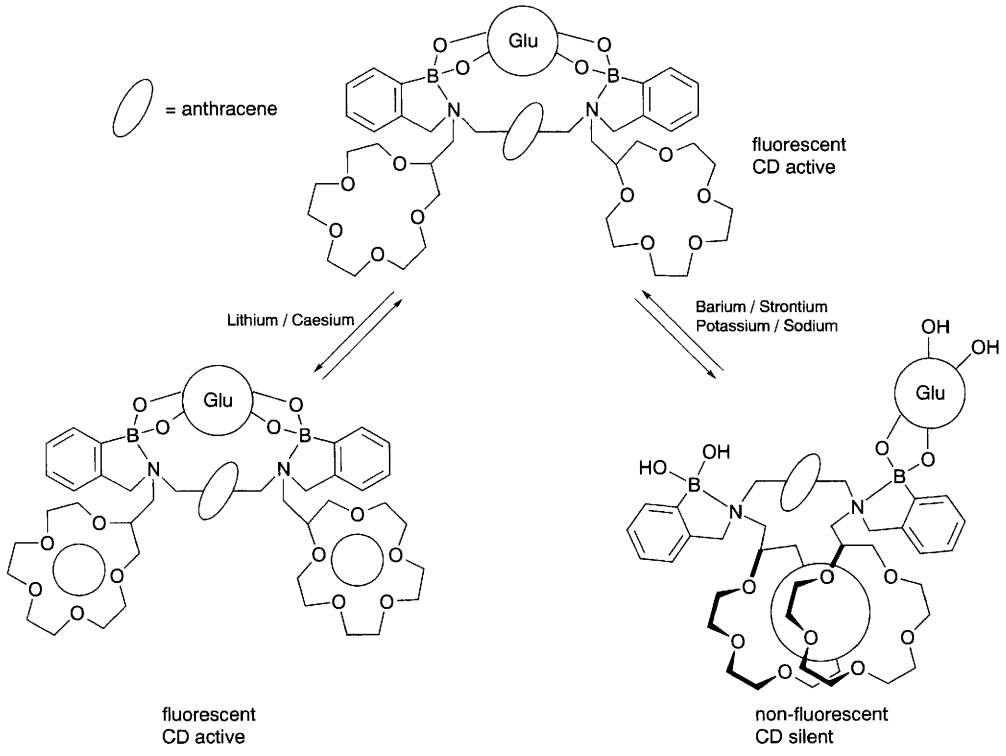
The synthesis of **3** was achieved according to Scheme 1 from readily available starting materials. The stability of the 1 : 1 intramolecular complex between **3** and D-glucose was determined from the titration curve of D-glucose with **3**. The sigmoidal curve was analysed using standard methods[15] to give a stability constant, log *K*, of 1.73 for D-glucose. Fig. 1 shows the normalized metal ion titration curves for compound **3** in the presence of 0.03 mol dm^{-3} D-glucose. Table 1 contains the stability constants (log *K*) for the metal complexes in the presence of 0.03 mol dm^{-3} D-glucose and the ionic diameter of the metal ions involved. From Table 1, metal ions with a diameter similar to potassium have the greatest affect on the 1 : 1 glucose complex. These metal ions are believed to have the largest contribution of a sandwich structure to metal ion binding.[16] Scheme 2 is indicative of the main species and reasonably explains the observed metal binding events.

Further confirmation that the 1 : 1 complex is the important fluorescent species involved in these measurements was given by circular dichromism (CD) spectroscopy. The CD spectra of compound **3** with 0.06 mol dm^{-3} D-glucose and 0.1 mol dm^{-3} sodium, potassium, strontium and barium are given in Fig. 2. The decrease in CD intensity at 258 nm for added metal ions is



3

Scheme 1 *Reagents and conditions* (yields): i, $CHCl_3$ (quant.); ii, $NaBH_4$, MeOH (95%); iii, K_2CO_3, MeCN, heat (35%); iv, 33.3% MeOH–H_2O, pH 7.77 (quant.)



Scheme 2 Possible complexes of **3** with glucose and metal ions

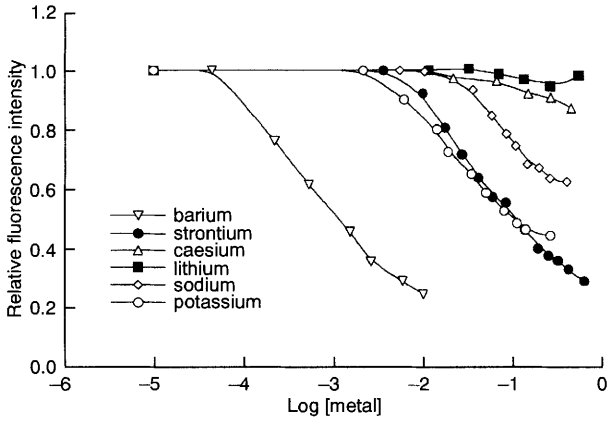


Fig. 1 Fluorescence intensity–log [metal ion] profile of **3** at 25 °C; 1.0 × 10^{-5} mol dm^{-3} **3** in 33.3% MeOH–H_2O and 0.03 mol dm^{-3} D-glucose (λ_{ex} 370, λ_{em} 423 nm)

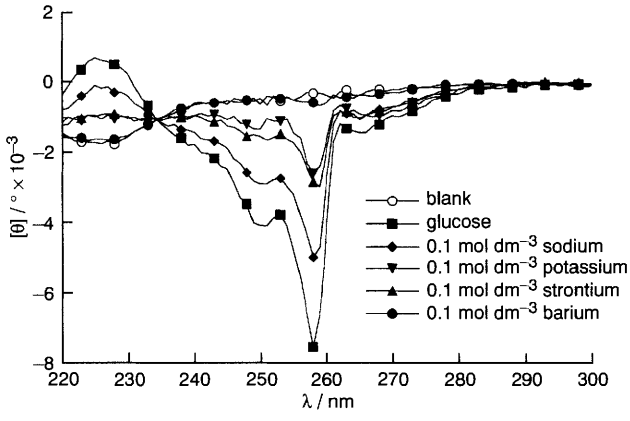


Fig. 2 Circular dichromism (CD) spectra of **3** at 25 °C; 1.4 × 10^{-3} mol dm^{-3} **3** in 33.3% MeOH–H_2O

Table 1 Metal ion stability constants in the presence of 0.03 mol dm^{-3} D-glucose and ionic diameter of metal cations

Metal cation	Stability constant log K (±0.05)	Ionic diameter/Å
Li^+	—	1.52
Na^+	1.28	2.04
K^+	1.80	2.76
Cs^+	—	3.40
Sr^{2+}	1.54	2.36
Ba^{2+}	3.39	2.70

proportional to the change in fluorescence intensity at 0.1 mol dm^{-3} metal ion. For sodium, 35%, potassium, 69%, strontium, 65% and barium, 96% decreases in CD intensity are observed and for sodium, 29%, potassium, 65%, strontium, 60% and barium, 100% decreases in fluorescence intensity are observed. Clearly, decomposition of the 1 : 1 complex is the cause of the decrease in the fluorescence intensity.

In conclusion, this is a novel allosteric system which mimics the action of the Na^+/D-glucose cotransport protein in nature. D-Glucose binds in the 'cleft' of **3** as a 1 : 1 complex in the presence of 0.03 mol dm^{-3} sodium and released from the 'cleft' at the same concentration of potassium. With this sytem we have moved one step closer to being able to specifically select and control saccharide binding in molecular sensors. We believe that such sensors will find many applications in biological systems for both the monitoring and mapping of biologically important saccharides.

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