A saccharide 'sponge'. Synthesis and properties of a dendritic boronic acid

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Very low concentrations of D-galactose and D-fructose are bound to a dendrimer containing eight boronic acids and eight anthracene units; the binding events are sensitively monitored by changes in the fluorescence intensity.

Recently we developed a photoinduced electron transfer (PET) fluorescence sensor for saccharides based on the interaction of a tertiary amine and a boronic acid.[1] When this system is extended to diboronic acids, the resulting cleft like molecules are saccharide selective.[2,3] Furthermore, if a chiral core is introduced into the cleft, even chiral discrimination of saccharides can be achieved.[4] Also, when the boronic acid–saccharide binding is coupled with metal ion binding interesting allosteric systems ensue.[5] We have also incorporated this fluorescence reporting system into calixarenes which are precursors of more complex devices.[6]

Starburst dendrimers are highly ordered polymers with extraordinary physical properties which look set to provide solutions to a wide variety of technological and ecological problems, from the removal of heavy metal pollutants (*e.g.* lead and cadmium) from industrial waste to their use as highly efficient drug delivery systems and even the formation of artificial chemical cells and tissues.[7]

These unique properties prompted us to explore possible combinations of our saccharide detection system with dendrimers. Since amino PAMAM starburst dendrimers are commercially available, they offered a convenient starting point in the construction of dendritic saccharide sensors. The synthesis was both short and simple and gave the desired boronic acid starburst dendrimer **1** in 27% overall yield (Scheme 1).

Saccharide titrations with the dendrimer **1** were carried out in 100% methanol at 25 °C (Fig. 1), for when water was used as the solvent an excimer emission due to the aggregation of the anthracene moiety was observed. The saccharide titration curves of compound **2** were determined at the same concentration per boronic acid moiety as **1** in 100% methanol (Fig. 2). The stability constants (K) for **2** can be easily determined from the analysis of the titration curves assuming the formation of a 1 : 1 boron–saccharide complex (because this is acceptable under [**2**] ≪ [saccharide]).[8] On the other hand, the saccharide-binding to **1** is more complicated because it may behave as a monoboronic acid to form a 1 : 1 boron–saccharide complex or as a diboronic acid to form a 2 : 1 boron–saccharide complex. The stoichiometry is usually estimated by a continuous variation plot. We found, however, that this method cannot be simply applied to **1** including eight saccharide-binding boronic acids. Thus, we tried to solve this problem by comparing the saccharide-binding abilities of 2 : 1-complex-forming D-galactose and D-glucose[2–5] with those of 1 : 1-complex-forming D-fucose (or 1-methyl-D-galactopyranoside) and D-xylose, respectively. It is clearly seen from Fig. 1 that D-galactose and D-glucose have K values much greater than their deoxy-, deoxymethyl- or partially-protected-derivatives. The results support the view that the enhanced binding ability in **1** is primarily ascribed to the cooperative action of two boronic acids to form an intramolecular 2 : 1 complex. Also, the fact that D-fucose has K greater than 1-methyl-D-galactopyranoside suggests that the primary binding to D-galactose occurs at the 1,2-diol site.

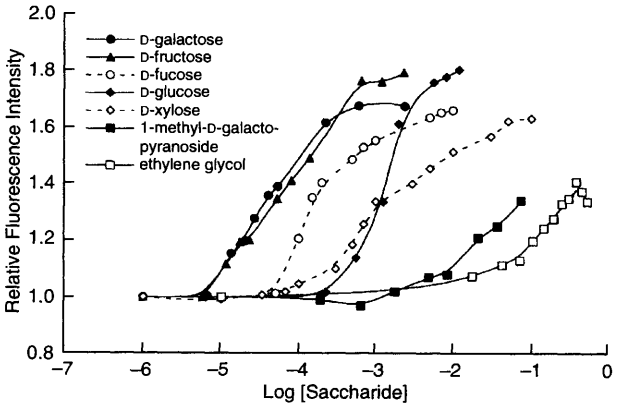


Fig. 1 Fluorescence intensity *vs.* log [saccharide] profile of **1** at 25 °C; 3.18 × 10^{-6} mol dm^{-3} of **1** in 100% MeOH, λ_{ex} 370 nm, λ_{em} 423 nm

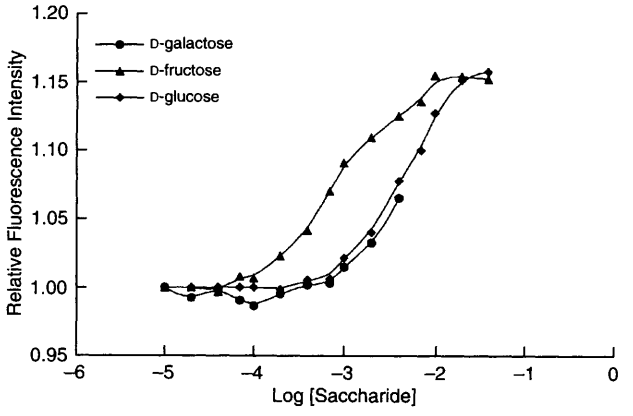
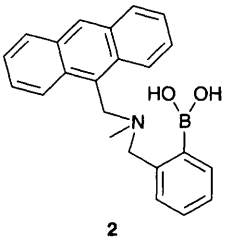


Fig 2 Fluorescence intensity *vs.* log [saccharide] profile of **2** at 25 °C; 2.55 × 10^{-5} mol dm^{-3} of **2** in 100% MeOH, λ_{ex} 370 nm, λ_{em} 423 nm



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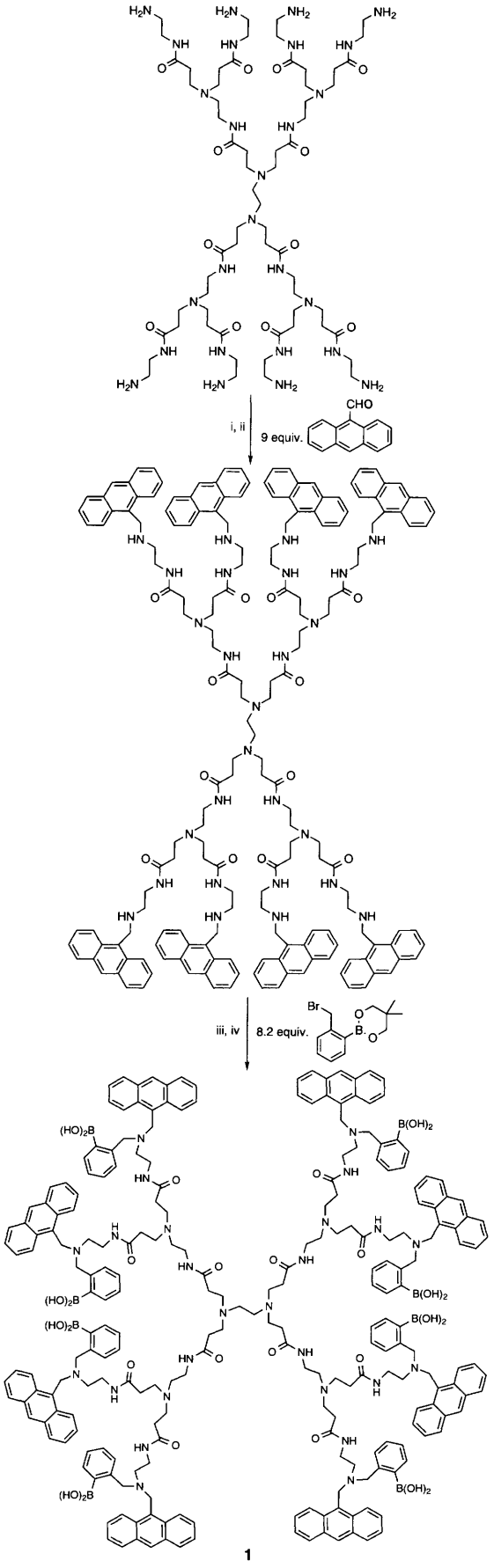

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Scheme 1 Synthesis of boronic acid derivative **1**. *Reagents and conditions*: i, MeOH (70%); ii, $NaBH_4$, $CHCl_3$/MeOH (quant); iii, K_2CO_3, MeCN, heat (38%); iv, 100% MeOH (quant).

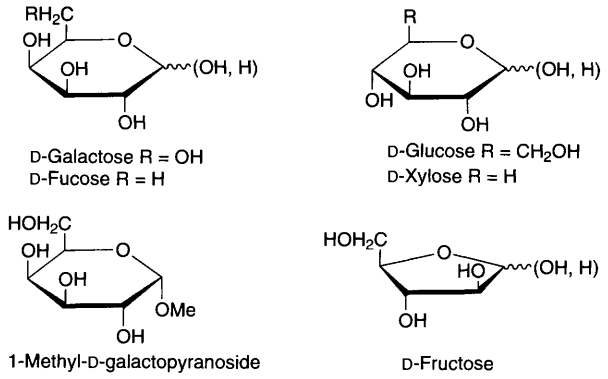

Table 1 Stability constants for compounds **1** and **2** in 100% methanol at 25 °C

Saccharide	Compound **1** log K	Compound **2**[b] log K
D-Galactose	4.43[c]	2.32[a]
D-Fructose	4.23[c]	2.86
D-Glucose	2.87[c]	2.31
D-Fucose	3.70[b]	—
D-Xylose	2.48[b]	—
1-Methyl-D-galacto-pyranoside	1.60[b]	—
Ethylene glycol	0.83[b]	—

[a] Determined assuming the same saturation value as D-glucose. [b] Determined assuming the formation of a 1 : 1 boron–saccharide complex. [c] Determined assuming the formation of a 2 : 1 boron–saccharide complex.

Taking the above binding modes into consideration, we estimated K values for **1**. The plots according to ref. 8 showed good linear relationships ($r > 0.98$), indicating the propriety of the above assumption. The results are summarized in Table 1.

Our previous work has shown that diboronic acid 'clefts' can strongly and selectively bind saccharides.[2,3] With flexible diboronic acids there is little preorganization in the host, resulting in a less stable saccharide complex. Dendritic boronic acid **1** is flexible yet forms very stable complexes with D-fructose, D-galactose and D-glucose (Table 1). This apparent contradiction may be explained by the increased number of binding sites: when one boronic acid binds a saccharide any one of seven remaining boronic acids can complex the second saccharide binding site.

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