

Novel Molecular Sensors for Saccharides Based on the Interaction of Boronic Acid and Amines: Saccharide Sensing in Neutral Water

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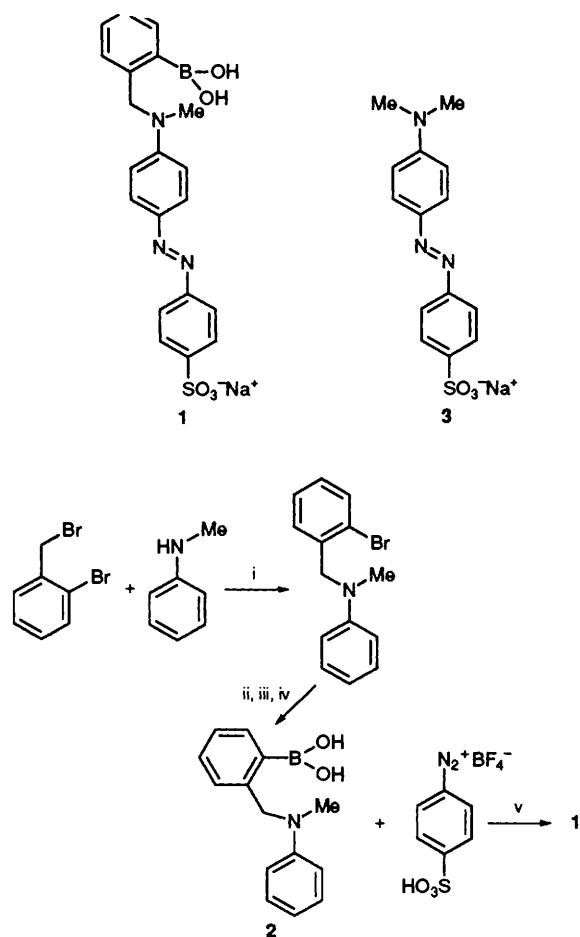
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The first known synthetic molecular colour sensor for saccharides is designed utilizing the boronic acid–amine interaction and visible colour changes were observed upon interaction with saccharides in neutral aqueous solutions.

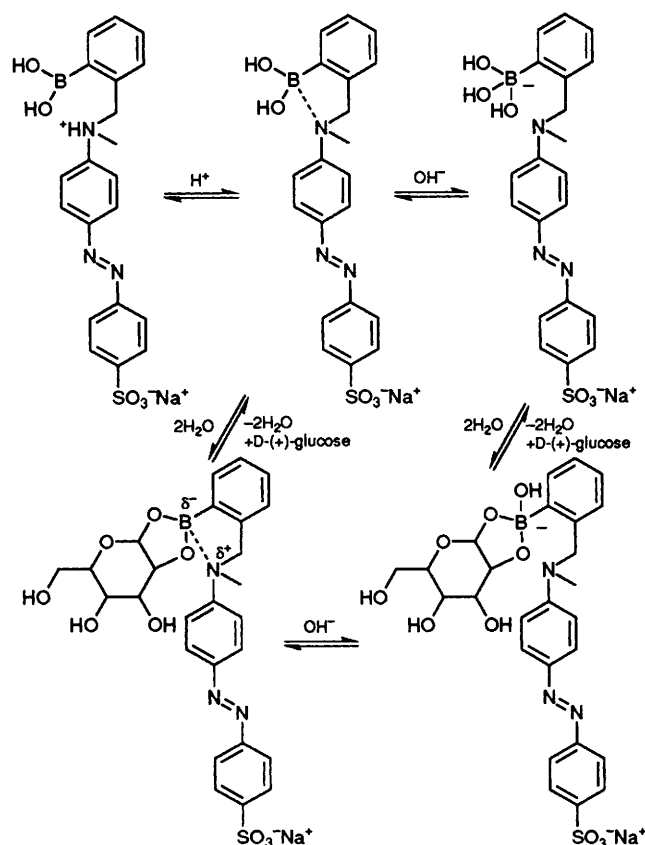
Recognition of neutral organic species by synthetic molecular receptors has been of interest to many chemists. Most of the known synthetic molecular receptors utilise hydrogen-bonding interactions in order to recognise and bind with guest molecules.¹ However, these interactions are less effective in aqueous media when the guest species is well solvated. On the other hand, covalent interactions found in the binding between boronic acid and saccharides in aqueous media are stronger than such hydrogen-bonding interactions. Phenylboronic acid complexation with saccharides *via* two covalent bonds creates five- or six-membered rings. The usefulness of the boronic acid moiety as a saccharide receptor has been demonstrated in saccharide recognition in rigid matrices,^{2,3} CD detection of saccharides⁴ and also recently in fluorescence detection of saccharides.^{5,6} Two problems associated with the boronic acid moiety are the requirement of basic conditions and the absence of electronic changes on the phenylboronic moiety upon saccharide binding. We have addressed these problems and rationally designed a molecular sensor which responds to saccharides in neutral aqueous media.

Here we report the first known colour sensor for saccharides based on the interaction found between boronic acid and a neighbouring amine group. The amine interaction makes the boronic acid moiety more acidic hence lowering the working pH of the sensor molecule.^{3,6} The electron rich amine creates an electron rich centre compared to the electron deficient boron centre. The rationally designed molecule **1** utilizes these effects. The anilinic electron donor moiety of the ICT (internal charge transfer) chromophore is assembled as the neighbouring group participant to the boronic acid–saccharide interaction. It is well known that the pK_a of the boronic acid is increased by saccharide interaction.^{3,5,7} The electronic changes associated with this pK_a change could be directly transmitted to the neighbouring amine moiety creating a spectral change in the ICT chromophore. The complexation process can be measured by the spectral change.

The synthesis of **1** was readily achieved by the route outlined in Scheme 1. The boronic acid precursor **2** was prepared from the corresponding bromide *via* lithiation in 60% yield. The diazonium coupling was carried out in acetic acid at room temperature using 4-sulfonylphenyldiazonium tetrafluoroborate. The required product was purified by cationic ion-exchange column chromatography and was isolated as its sodium salt.[†]



Scheme 1 Reagents (yields): i, K_2CO_3 , MeCN, reflux (90%); ii, *n*-butyllithium, THF, $-78^\circ C$; iii, $B(OMe)_3$, THF, $-78^\circ C$; iv, H_2O room temp. (60%); v, $MeCO_2H$, room temp.



Scheme 2

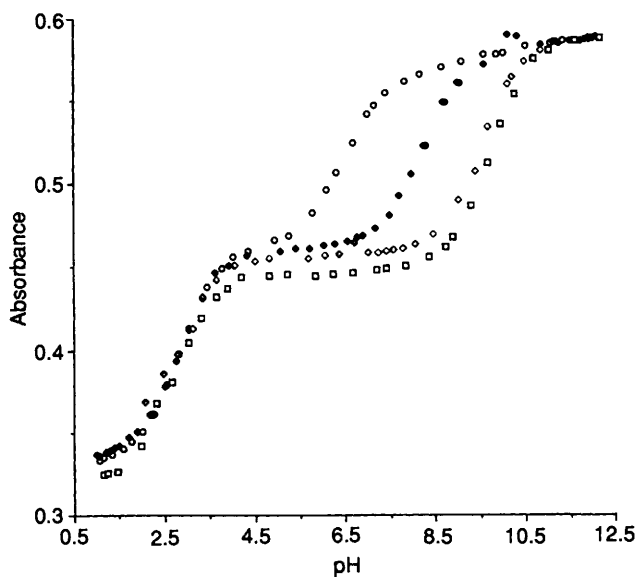


Fig. 1 Absorption-pH profile of **1** with saccharides, 0.05 mol dm^{-3} saccharide and 0.05 mol dm^{-3} NaCl; (\square) no saccharide; (\circ) D-(-)-fructose; (\blacklozenge) D-(+)-glucose; (\diamond) ethylene glycol. (Absorbance at 468 nm.)

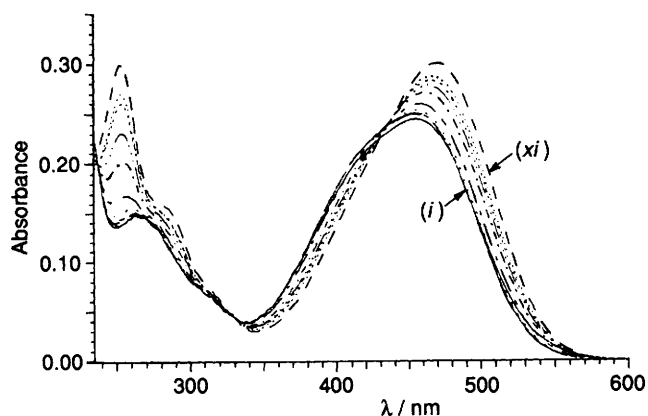


Fig. 2 Absorption spectral changes of **1** at different pH with 0.05 mol dm^{-3} D-(+)-glucose and 0.05 mol dm^{-3} NaCl; pH = 4.34 (i), 5.39 (ii), 6.49 (iii), 6.98 (iv), 7.41 (v), 7.88 (vi), 8.39 (vii), 8.71 (viii), 9.07 (ix), 9.23 (x), 10.64 (xi)

Table 1 The influence of saccharides on the pK_a values of **1** in aqueous media with 0.05 mol dm^{-3} NaCl

	pK_{a1}	ΔpK_{a1}	pK_{a2}	ΔpK_{a2}
D-(-)-Fructose	6.45	3.31	2.88	0.28
D-(+)-Glucose	8.29	1.47	2.78	0.18
Ethylene glycol	9.54	0.22	2.75	0.15
No saccharide	9.76	—	2.60	—

The absorption pH profile for the molecular sensor **1** in aqueous media with different saccharides is given in Figs. 1 and 2. The step found at low pH range ($pK_{a2} = 2.60$) is due to protonation of the anilinic moiety. The boronic acid-amine interaction has shifted this equilibrium towards lower pH compared to the parent chromophoric molecule **3** ($pK_a = 3.7$). The second step ($pK_{a1} = 9.76$) is believed to be due to the association equilibrium of the boronic acid with the amine moiety. The most important species involved and the equilibrium process is given in Scheme 2. The introduction of D-(-)-fructose into the solution shifts the second equilibrium (pK_{a2}) by $0.28 pK_a$ units and more importantly the first equilibrium (pK_{a1}) by $3.31 pK_a$ units (Table 1 and Fig. 1). D-(+)-Glucose gave a relatively small shift and ethylene glycol which is less prearranged (as a *cis*-diol) gave almost no change. The saccharide titration at pH 7.6 gave a small absorption spectral change and a very low stability constant for glucose, and ethylene glycol did not give any measurable spectral changes. D-(-)-Fructose gave good spectral changes ($\log K = 2.14$) as expected from the pH titration curve. Saccharide binding to boronic acid is expected to be at the 1,2-diol sites in the case of glucose and the 1,3-diol sites in the case of fructose, creating five- and six-membered rings, respectively.⁶ However, it is not clear why fructose with a possible six-membered ring gave higher pK_a shifts. The more flexible, hence less prearranged ethylene glycol, which can create a five-membered ring, gave no measurable shift of pK_a .

In conclusion, we have rationally designed the first known synthetic receptor for saccharides which gives a visible colour change in neutral aqueous media. The molecular sensor **1** exhibits relatively small shifts in its absorption bands upon interaction with saccharides but we believe that the molecule could be altered to give larger spectral shifts and hence a more accurate method of saccharide detection. Since saccharides are not so stable in basic aqueous media under which conditions boronic acids can bind saccharides efficiently, the present system, which works at neutral pH region, should lead to the development of new saccharide sensing methods.

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Footnote

† All new compounds gave satisfactory analytical data.

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