Selective fluorescence detection of fluoride using boronic acids

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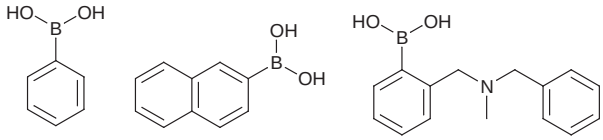
Fluorescent PET (photoinduced electron transfer) sensors 1,2 and 3 with boronic acid receptor units show F^- selective fluorescent quenching in aqueous solution at pH 5.5.

Neutral and ionic synthetic molecular receptors for anions are the focus of many research groups. Anion receptors can consist of protonated nitrogens, metal ions, hydrogen bonding sites and Lewis acid receptors.[1–6] The conversion of binding information between ions and synthetic molecular receptors into readable fluorescent outputs has attracted the attention of many research groups.[7–12] There is interest in following the uptake and metabolism of F^- in both plants and animals and in the analysis of drinking water. Fluoride concentrations are currently determined using electrodes prepared from LaF_3.[13] Electrodes for determining F^- concentrations are sensitive and selective, but, under certain circumstances a method for the direct visualisation of intracellular F^- would be of great advantage, especially to analytical biochemists.

The system presented here is based on the Lewis acid–base interaction between boron and anions. When boron binds with certain anions the hybridisation changes from sp^2 to sp^3.[14,15] Boron centred fluoride receptors were first studied by Katz, who trapped fluoride ions between two electron accepting boron atoms in 1,8-naphthalendiylbis(dimethylborane).[16,17] More recently Reetz combined a Lewis acid boron and crown ether to create a ditopic host for F^- and metal ions.[18] Paugam and Smith have used the tetrahedral fluoride adduct of phenyl boronic acid with fluoride to accelerate saccharide transport at neutral pH.[19] Shinkai and coworkers have recently developed a F^- receptor based on ferrocene boronic acids, the binding is measured electrochemically[20] or by the colour change of a redox coupled dye molecule.[21]

Work by the groups of Czarnik and Shinkai on saccharide sensors has shown that boronic acids exist as tetrahedral boronate anions at pH values above their pK_a, and that the tetrahedral boronate anion can quench the fluorescence of directly attached fluorophores by the mechanism of photoinduced electron transfer (PET).[22,23] With this work we decided to investigate whether F^- can also quench fluorescence on formation of a tetrahedral fluoride adduct.

When phenylboronic acid **1**‡ and 2-naphthylboronic acid **2**‡



1 **2** **3**

are titrated with KF in a 50% (w/w) methanol–water buffer at pH 5.5[24] the fluorescence of the phenyl and naphthyl fluorophores decreases with added KF. (λ_{ex} = 265 nm, λ_{em} = 295 nm and λ_{ex} = 268 nm, λ_{em} = 344 nm, respectively) (Fig. 1). The experimental curves are fitted best using eqn. (1) assuming

$$I = \frac{I_0 + I_\infty K_n[F^-]^n}{1 + K_n[F^-]^n} \quad (1)$$

with:

$$K_n = \frac{[RB(OH)_{3-n}F_n]}{[RB(OH)_2][F^-]^n}$$

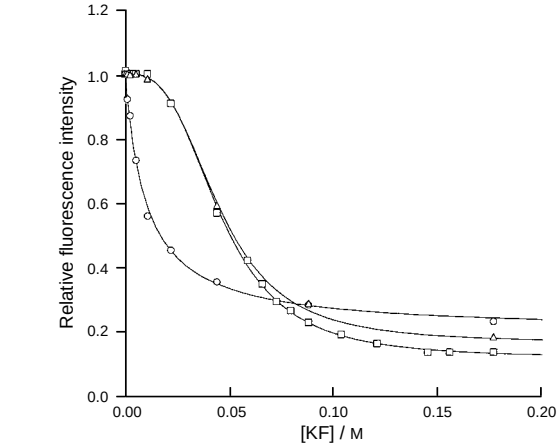
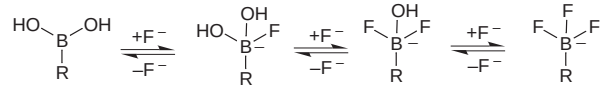


Fig. 1 Fluorescence intensity log [KF] profile of (□) **1**, (△) **2** and (○) **3** at 25 °C; 1.63×10^{-4} M **1** in 50% MeOH–H_2O, pH 5.5, λ_{ex} = 265 nm, λ_{em} = 295 nm; 1.16×10^{-4} M **2** in 50% MeOH–H_2O, pH 5.5, λ_{ex} = 268 nm, λ_{em} = 344 nm; 8.30×10^{-5} M **3** in 50% MeOH–H_2O, pH 5.5, λ_{ex} = 270 nm, λ_{em} = 309 nm

the formation of a trifluoro tetrahedral boronate (n = 3)[25] (Scheme 1). The stability constants K_3 determined from the best fit of these curves are 1.04×10^4 and 1.08×10^4 dm^9 mol^{-3} respectively. Compounds **1** and **2** can effectively detect concentrations of F^- in the range 50–70 mM. Compound **3** was prepared by alkylating 2-bromomethylphenylboronic acid with methyl aminomethylbenzene, an analytically pure sample was obtained by precipitation from $CHCl_3$ by hexane to give a 13% yield. Compound **3** was specifically designed to increase the strength of F^- binding relative to compound **1** by virtue of an additional hydrogen bonding site, which is available when the amine is protonated. The pK_a of the tertiary amine of compound **3** is 5.5, determined from a fluorescence pH titration. At a pH of 5.5 the amine is half protonated and can participate in hydrogen bonding with F^-.[8,10] Also at pH 5.5, **3** has a high fluorescence because PET from the nitrogen is reduced on protonation. When **3** is titrated with KF in a 50% (w/w) methanol–water buffer at pH 5.5[24] the fluorescence of the phenyl fluorophore decreases with added F^-. (λ_{ex} = 270 nm, λ_{em} = 309 nm) (Fig. 1). The experimental curve is fitted best using eqn. (1) and assuming the formation of monofluoro boronic acid derivative (n = 1)[25] (Scheme 1). The F^- stability constant K_1 determined from the best fit of this curve is 101 dm^3 mol^{-1}. Compound **3** can effectively detect concentrations of F^- in the range 5–30 mM. The single fluoride adduct of compound **1** is selectively stabilised by the additional hydrogen bonding from the protonated amine of compound **3** (Fig. 2). Titrations were also carried out using **1**, **2** and **3** with KCl and KBr but no change in fluorescence was observed until very high concentrations of



Scheme 1

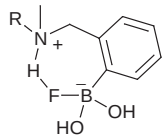


Fig. 2

these salts. A similar exclusive selectivity for F^- was observed by Shinkai and coworkers with ferrocene boronic acid.[20]

Both ^{11}B (128 MHz) and ^{19}F (376 MHz) NMR experiments were perfomed to confirm the presence of the F^- adducts depicted in Scheme 1. The ^{11}B NMR of compound **1** (0.205 M) in 33% (v/v) methanol-D_2O§ at 31 °C shows one boron signal at δ 13.2 relative to an external capillary of BMe_3 as reference. This signal shifted to δ 12.0 on addition of 1 equiv. of KF and to δ 7.4 on addition of 5 equiv. of KF. The ^{11}B NMR of **3** (0.137 M) in 70% (v/v) methanol–D_2O§ at 31 °C shows two boron signals at δ 14.5 and 2.5 corresponding to free boronic acid (sp^2) and nitrogen coordinated boronic acid (sp^3) respectively (At a pH of 5.5 the nitrogen atom of **3** is not fully protonated). On addition of 1 equiv. of KF the signal at high frequency moved to δ 13.5 while the other at low frequency remained at δ 2.5. On addition of 5 equiv. of KF only one signal at δ 2.5 was observed. The observed shifts from high to low frequency in the ^{11}B NMR are consistent with a shift from sp^2 to sp^3 boron on F^- binding.[26]

The ^{19}F NMR of compound **1** (0.205 M) in 33% (v/v) methanol–D_2O§ at 0 °C on the addition of 3 equiv. of KF shows signals at δ −126.9 [KF and $RB(OH)_2F^-$], −137.1 [$RB(OH)F_2^-$] and −147.5 [RBF_3^-] all relative to an external capillary of $CFCl_3$ as reference. The ^{19}F NMR of **3** (15.7 mM) in 50% (v/v) methanol–D_2O§ at 0 °C on addition of 3 equiv. of KF shows a signal at δ 131.6 [KF and $RB(OH)_2F$]. The species detected by ^{19}F NMR[27] are consistent with the F^- adducts depicted in Scheme 1 and the observed fluorescence behaviour. This work represents the first example where fluorescence has been used to detect F^- binding events. The use of these simple molecules has resulted in high F^- selectivity. We believe that with appropriate modifications of the Lewis acid and hydrogen bond donor, F^- selectivity can be fine tuned to any desired F^- concentration range. It is hoped that this work will lead to the development of fluorescent F^- sensors for a variety of industrial and medicinal applications.

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Notes and References

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‡ Compounds **1** and **2** were purchased from Lancaster Synthesis Ltd., Eastgate, White Lund, Morecambe, Lancashire, UK LA3 3DY, and used without further purification.

§ The pH was adjusted to 5.5 by the addition of HCl.

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