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A sorbitol-selective fluorescence sensor

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Abstract—A new anthracene derivative bearing two phenylboronic acid groups at the 1,8-positions was prepared and its binding properties towards sorbitol, xylitol, fructose, glucose and galactose have been studied using fluorescence analysis.

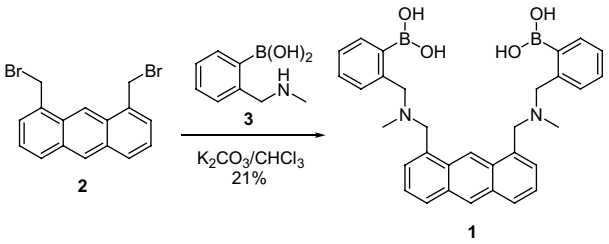
A great amount of attention has been devoted to the development of fluorescent chemosensors to recognize ions.[1] On the other hand, detection of neutral species by a real-time fluorescence analysis in aqueous media has been one of the major challenges in fluorescent chemosensor-related research. Recently, by applying boronic acid–saccharides interaction to the fluorescent PET (photo-induced electron transfer) sensor, many successful results have been reported during last decade.[2]

Even though boronic acid has been known for almost 50 years to have high affinity for diol-containing compounds such as carbohydrates,[3] Yoon and Czarnik reported[4] 2-anthrylboronic acid as the first example of fluorescent chemosensor in 1992, which displayed chelation-enhanced fluorescent quenching (CHEQ) effects upon the addition of polyols.

Most noticeably, the Sinkai group[5] and James group[6] have been leading the field in many regards. Sinkai and his co-workers have reported new series of PET sensors for saccharides bearing boronic acid unite as well as benzyl amine unit.[5] Recently, James group also reported many noticeable results regarding boronic acid-based fluorescent receptors for saccharides.[6]

We report herein a new fluorescent PET sensor for saccharides, which bears two phenylboronic groups at the 1,8-positions of anthracene. While 9,10-isomer (**4**) is reported to recognize glucose,[5b,c] host **1** selectively senses D-sorbitol in aqueous solution at physiological pH.

We prepared the host **1** by reaction of the 2-methylaminomethylphenylboronic acid **3**[7] with 1,8-bis(bromomethyl)anthracene **2** as shown in Scheme 1. Our synthesis began with 1,8-bis(hydroxymethyl)anthracene, which was then transformed to 1,8-bis(bromomethyl) anthracene **2** using the procedures of Nakagawa and co-workers.[8] 2-Methylaminomethylphenylboronic acid **3** was obtained from the treatment of 2-formylphenyl boronic acid and methylamine followed by the reduction with sodium borohydride. Compound **1** was synthesized by the addition of **3** to a mixture of **2**, K_2CO_3 and $CHCl_3$ at room temperature (see Supporting Information).



Scheme 1. Synthesis of compound **1**.

Keywords: Fluorescent chemosensor; Carbohydrate sensing; Boronic acid; Anthracene; Sorbitol detection.
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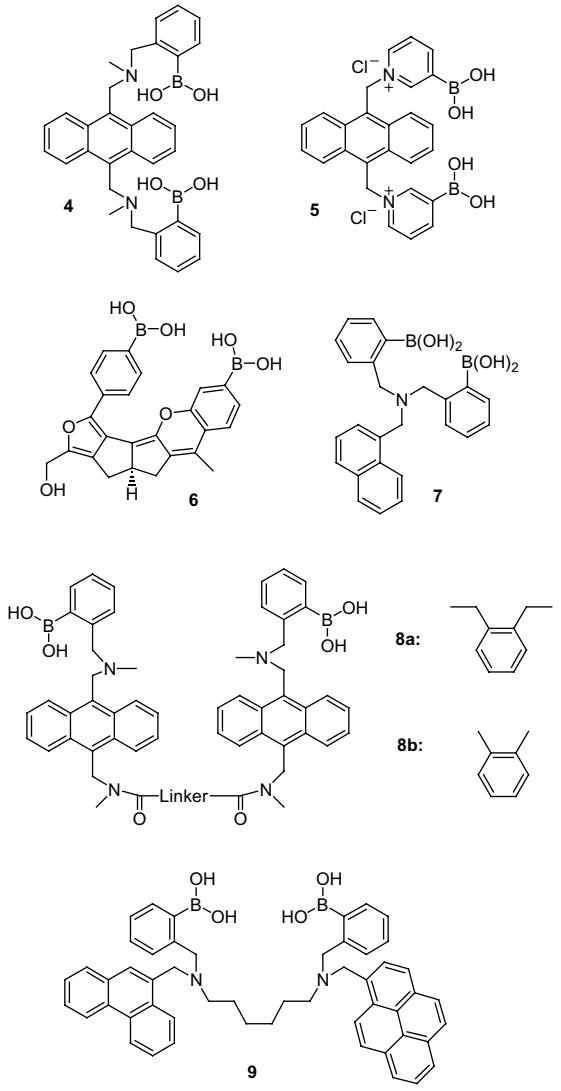

Figure 1. Diboronic acid sensors for saccharides reported in the literature.

As shown in Figure 1, few receptors as the diboronic acid sensors have been reported by Shinkai and co-workers (**4**),[5b,c] Norrild and co-workers (**5**),[9] Drueckhammer and co-workers (**6**),[10] Wang and co-workers (**8**)[11] and James and co-workers (**7**,[6a] **9**[6f]). These receptors display selective binding for glucose over other carbohydrates. For example, sensor **4** exhibited a 12- and 25-fold selectivity for glucose over fructose and galactose, respectively. Wang and co-workers reported that **8a** also shows 43-fold selectivity for glucose over fructose.[11] On the other hand, the binding constants of sensor **8b** for glucose, fructose and galactose were determined as 178, 283 and 33 M^{-1}, respectively. These compounds differ in linker length and flexibility, which might be the reason for the opposite selectivity of the two sensors. On the other hand, host **7** is reported to show a selectivity towards small saccharides such as D-sorbitol, D-fructose, dulcitol, etc.[6a]

We have recently reported various anthracene derivatives bearing binding units at the 1,8-positions as fluorescent sensors for anions and cations.[12] Introduction of ligands onto 1,8-positions of anthracene provided a unique preorganized and rigid binding site compared to 9,10-anthracene derivatives. Indeed, our host **1** displayed quite different binding properties towards saccharides compared to host **4**.

From the pH–fluorescence profile in unbuffered aqueous media, pK_a of compound **1** in the presence of 0.1 mM of fructose, galactose and glucose were calculated as 4.22, 4.26 and 4.47, respectively. An observed fluorescence dependence on pH is in keeping with the intramolecular amine quenching mechanism.[5a]

In host **1**, the interaction of boronic acid and benzyl amine moiety can only partially inhibit the photo-induced electron transfer (PET), however, this inhibition of PET can be maximized upon the addition of saccharides because the complexed form of boronic acid–saccharide can lower the pK_a of boronic ester. Consequently, the anionic form of boronate can make a stronger interaction with adjacent benzylic amine moiety, which resulted in the fluorescent chelation-enhanced fluorescent (CHEF) effect by blocking the PET efficiently.[5a]

All titration studies were conducted in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4 and using a 6 μM concentration of compound **1**. Excitation wavelength was 365 nm. From the fluorescent titrations, the association constants for sorbitol, xylitol, fructose, galactose and glucose were calculated as 1060, 440, 200, 81 and 12 M^{-1} (errors <10%), respectively (Figs. 2–6).[13] Unlike host **4**, host **1** displayed a selectivity for sorbitol among the saccharides examined. The selectivity for sorbitol is almost 100 times that for glucose. To confirm the selectivity, the association constant for sorbitol was redetermined in the presence of 1 mM glucose (K_a = 1080 M^{-1}): no decrease in observed association constant resulted (see Supporting Information). The fluorescence enhancements of chemosensor **1** with sorbitol, xylitol, fructose, galactose and glucose were 2.2-, 1.9-, 3.9-, 2.9- and 2.3-fold, respectively.

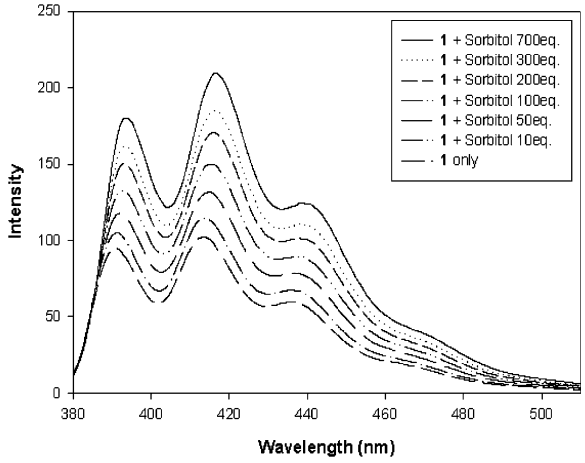

Figure 2. Fluorescence spectra of **1** (6 μM) upon the addition of D-sorbitol in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4.

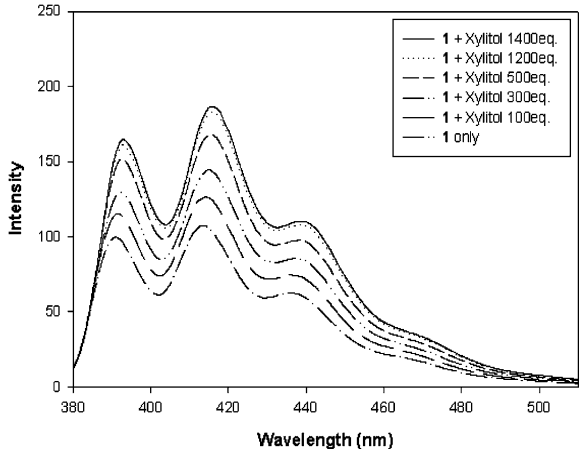

Figure 3. Fluorescence spectra of **1** (6 μM) upon the addition of xylitol in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4.

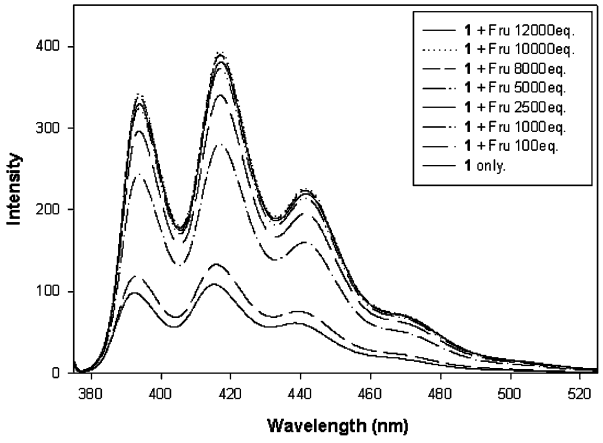

Figure 4. Fluorescence spectra of **1** (6 μM) upon the addition of D-fructose in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4.

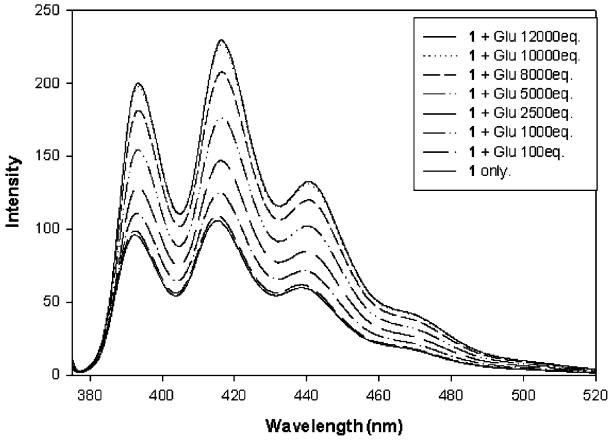

Figure 5. Fluorescence spectra of **1** (6 μM) upon the addition of D-gulcose in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4.

D-Sorbitol is an important food additive, usually added to prevent dehydration of food and other materials on exposure to air because it binds with water strongly. Our synthetic saccharide sensor **1** displayed a sufficient selectivity for sorbitol, which can be productively compared to the selectivity of chemosensor **4**.

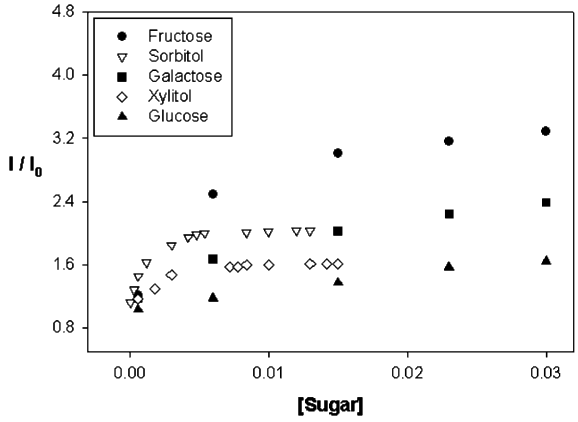

Figure 6. Fluorescence titrations of **1** (6 μM) in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4 as a function of sugar concentration.

In conclusion, new anthracene derivative **1**, which contains two boronic acid groups at 1,8-positions of anthracene was prepared. The fluorescent chemosensor **1** displayed a selective binding with D-sorbitol at pH 7.4 among the saccharides examined. This work illustrates that the selectivity of chemosensor bearing diboronic acid groups can be modified by controlling the spacing unit between two boronic acid groups and the rigidity of this binding site. This result also demonstrated the possibility of monitoring the concentration of biologically important saccharides, which are less abundant than D-glucose, in a variety of industrial and biological applications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.121. Experimental Sections including characterizations of **1** are available.

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