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A New Saccharide Sensor Based on a Tetrathiafulvalene−Anthracene Dyad with a Boronic Acid Group

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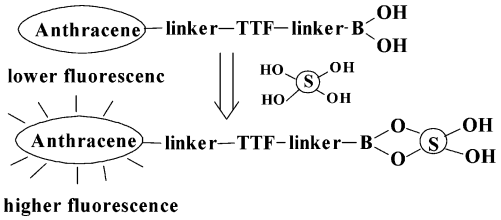
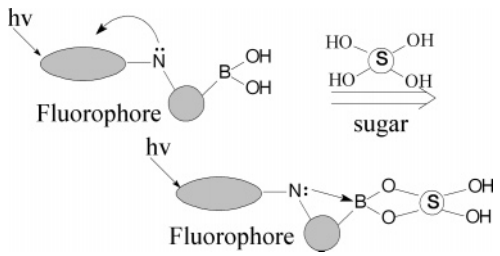


A new saccharide sensor based on a tetrathiafulvalene−anthracene dyad with a boronic acid group was designed and synthesized. Our study employed the tetrathiafulvalene (TTF) unit as the electron-rich group in the saccharide sensor instead of an amine group, and this new sensor detects fructose with good selectivity.

Saccharides play significant roles in biological processes. Development of new saccharide sensors is highly desired to understand cellular activities and diagnose diseases.[1] The boronic acid group can form cyclic esters with saccharides reversibly, and molecules featuring boronic acid groups have been investigated for saccharide recognition through various signal transduction mechanisms, such as CD,[2] absorption,[3] electrochemical property,[4] and fluorescence.[5] Two mechanisms have been employed to design effective saccharide sensors: the photoinduced electron-transfer mechanism (PET)[6a−g] and the internal charge-transfer mechanism (ICT).[6h−l] Shinkai and co-workers have studied extensively the saccharide sensors based on the PET mechanism containing three components: a fluorophore, an amine, and a boronic group (Scheme 1).[5,6a,b] As shown in Scheme 1, the nitrogen−boron interaction modulates the PET process and leads to fluorescence change before and after the bonding of the boronic acid group with saccharides. The interaction of the boronic acid and amine groups also confers a working pH of these saccharide sensors developed by Shinkai et al. close to physiological pH. To our best knowledge, however, only the amine group was used as the electron-rich center to design Shinkai's saccharide sensors.

SCHEME 1



Tetrathiafulvalene (TTF) derivatives, widely used as components of organic conductors and superconductors,[7] are good electron donors. In recent years, TTF derivatives have been employed to construct molecular shuttles[8] and redox fluorescence switches.[9] With this in mind, we studied the possible substitution of the amine group of

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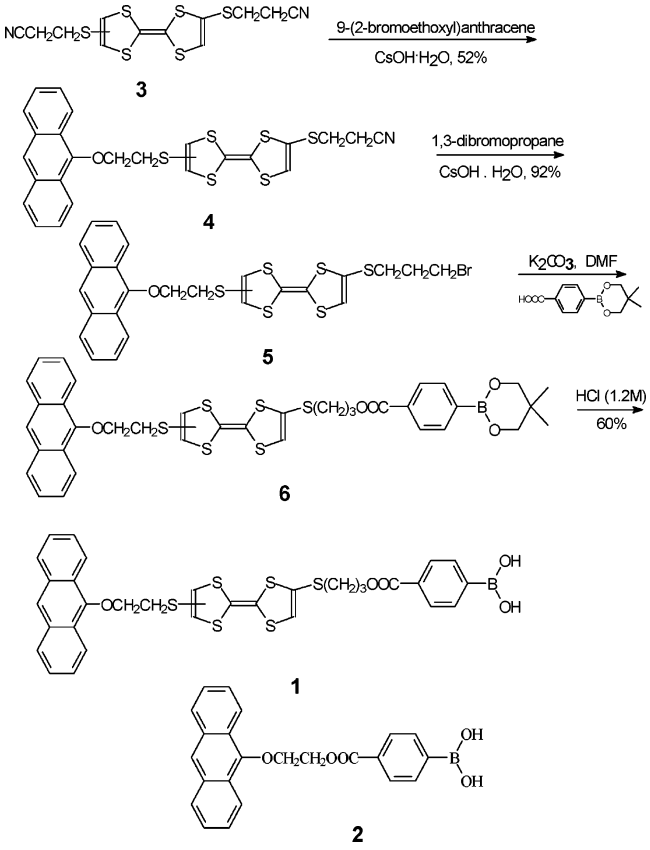
SCHEME 2



Shinkai's saccharide sensors with the TTF group for development of a new saccharide sensor as shown in our TTF−anthracene dyad **1** (Scheme 2). Herein we describe the synthesis and fluorescent spectral studies of **1** in the presence of saccharides. The results demonstrate that dyad **1** is a new saccharide sensor.

Synthesis of dyad **1** started from compound **3** (Scheme 2).[10] Selective deprotection of one of the 2-cyanoethyl groups in **3** with $CsOH{\cdot}H_2O$ and further reaction with 9-(2-bromoethoxyl)anthracene afforded compound **4**, from which compound **5** was yielded by similar procedures with 1,3-dibromopropane. Reaction of **5** and 2-(4-carboxyphenyl)-5, 5-dimethyl-1,3,2-dioxaborinane[11] in the presence of anhydrous potassium carbonate led to compound **6**. Dyad **1** was obtained by hydrolysis of **6** with hydrochloric acid solution (1.2 M) in a total 14% yield after purification with column chromatography.[12] The two isomers (cis and trans) of dyad **1** were not separable with column chromatography.[13] But, that would not affect the following fluorescent studies of dyad **1**.

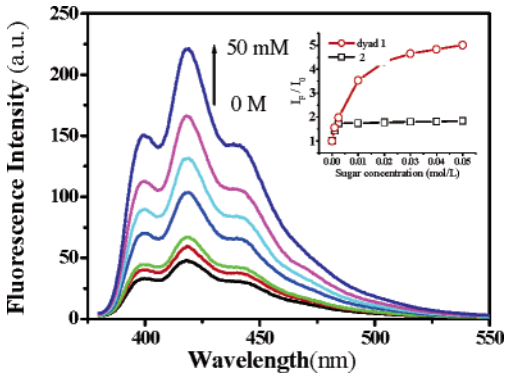


FIGURE 1. Fluorescence spectra of dyad **1** (5.0×10^{-5} M) with different concentrations of fructose (0−50 mM) at pH 7.3 adjusted by 0.033 M phosphate buffer in THF/H_2O (1:1, v/v); the excitation wavelength is 370 nm. The inset shows the relative fluorescence intensity profile of **1** and **2** vs fructose concentration.

Figure 1 shows the fluorescence spectra of dyad **1** in the presence of different concentrations of fructose at pH 7.3 in THF/H_2O (1:1, v/v). Before reaction with fructose, dyad **1** shows rather weak fluorescence. As for the anthracene−TTF−anthracene triad reported by us previously,[9b] the weak fluorescence of **1** could be attributed to the PET between the excited anthracene and TTF units.[14] The quenching effect of the boronic acid group,[15] which is a weak electron acceptor, may also contribute to the weak fluorescence of **1**. But, the TTF unit shows strong electron donating ability, and thus the weak fluorescence of **1** should be mainly due to the PET between the excited anthracene and TTF units. After addition of fructose, the fluorescence of the solution of dayd **1** was enhanced. A 5-fold fluorescence enhancement was observed when the concentration of fructose reached 50 mM (Figure 1). Compared to other fructose sensors reported previously under similar conditions, such fluorescence response of the solution of dyad **1** to fructose is relatively larger.[5]

Under identical conditions, the fluorescence spectra of dyad **1** in the presence of other saccharides such as

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(12) Characterization data for dyad **1**: ^{1}H NMR (400 MHz, $CDCl_3$, see Supporting Information) δ 2.12 (m, 2H), 2.93 (m, 2H), 3.36 (m, 2H), 4.35 (m, 4H), 4.63 (s, 1H), 4.66 (s, 1H), 6.41 (s, 1H), 6.48 (s, 1H), 7.48 (m, 4H), 7.79−8.25 (m, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 35.88, 63.08, 63.16, 73.33, 73.38, 122.14, 122.64, 122.76, 123.11, 124.47, 124.51, 124.55, 125.41, 125.49, 128.45, 128.82, 128.88, 132.24, 132.28, 132.32, 133.56, 133.44, 150.20, 166.31; ESI-MS $(M + 1)^+$, 695.2; HRMS Anal. Calcd for $(C_{32}H_{27}BO_5S_6{\cdot}CH_3OH + Na)^+$ 750.0532, found 750.0549; FT-IR (KBr, cm^{-1}) 3431, 3057, 2924, 1714, 1625, 1341, 1273, 1094, 881, 844.

(13) The ratio of the cis/trans isomers of dyad **1** should be 1:1 since that of the cis/trans isomers of the starting compound **3** is 1:1 (compound **3** was synthesized from 4-(2-cyanoethylthio)-1,3-dithiole-2-one in the presence of trialkyl phosphite). We could not determine the binding constants of the cis/trans isomers of **1** with saccharides as we could not separate them with column chromatography. But, it cannot be expected that there is a large difference between the cis/trans isomers of **1** in terms of binding saccharides. This is because it is the boronic acid group that reacts with saccharides and the influence of the anthracene group on the binding should be rather limited since the boronic acid and anthracene groups are separated by a relatively long distance.

(14) The first oxidation potential of dyad **1** was measured to be 0.54 V (vs Ag/AgCl) in THF, which was due to the oxidation of the TTF unit into the corresponding radical cation. The second oxidation potential (for $TTF^{\cdot+}$ to TTF^{2+}) and the irreversible oxidation peak due to the oxidation of the anthracene unit were measured to be 0.90 and 1.70 V, respectively. Besides, an irreversible reduction wave (−1.89 V) was observed for dyad **1**, and this was ascribed to the reduction of the anthracene unit. Accordingly, the free energy (ΔG_{PET}) for the PET from the TTF unit to the anthracene unit was estimated to be −0.83 eV with the Rehm−Weller equation: $\Delta G_{PET} = -E(\text{ox.}) - E(\text{red.}) + E(\text{ox.}) - e^2/\epsilon r$, with $E(\text{ox.}) = 0.54$ eV, $E(\text{red.}) = -1.89$ eV, $\lambda(\text{ex.}) = 370$ nm, and $e^2/\epsilon r = -0.1$ eV. See: (a) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259. (b) Grabowski, Z. R.; Dobkowski, J. *Pure Appl. Chem.* **1983**, *55*, 245.

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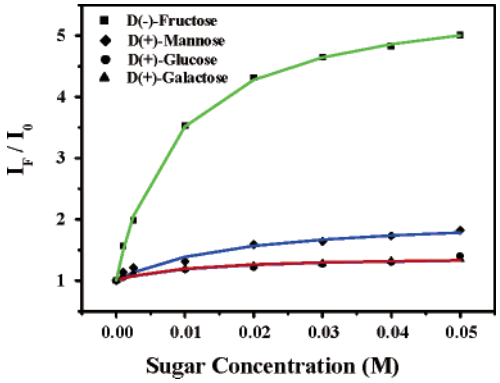

FIGURE 2. Fluorescence intensity change of dyad **1** (5.0×10^{-5} M) in 0.033 M phosphate buffer at pH 7.3 as a function of sugar concentration (fructose, gluctose, galactose, mannose); I_0 is the fluorescence intensity of the solution of dyad **1** in the absence of sugar; the solvent is THF/H_2O (1:1, v/v), and the excitation wavelength is 370 nm.

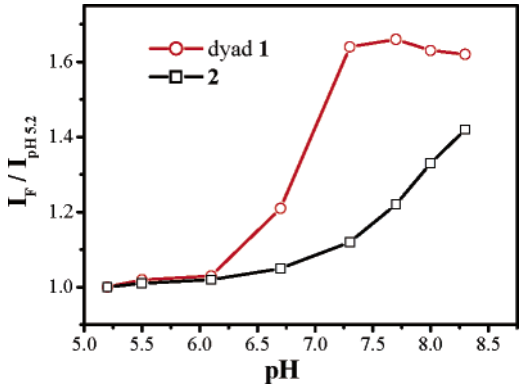

FIGURE 3. Relative fluorescence intensity profile vs pH for dyad **1** and **2** (5.0×10^{-5} M) in the presence of fructose (25 mM) in THF/H_2O (1:1, v/v) adjusted by 0.033 M phosphate buffer; $I_{pH5.2}$ is the fluorescence intensity of **1** or **2** at pH 5.2; the excitation wavelength is 370 nm.

TABLE 1. Association Constants (K_a) and Fluorescence Intensity Changes (I/I_0) of Dyad 1 with Different Sugars

sugar	K_a	I/I_0
fructose	115 ± 2 ($r^2 = 0.99$)	5.01
mannose	81 ± 8 ($r^2 = 0.98$)	1.82
glucose	70 ± 7 ($r^2 = 0.98$)	1.40
galactose	66 ± 7 ($r^2 = 0.98$)	1.35

mannose, glucose, and galactose were also investigated. Figure 2 shows the variation of the fluorescence intensity of dyad **1** with the concentration of fructose, mannose, glucose, and galactose. After the reaction of dyad **1** with mannose or glucose or galactose, the fluorescence of the solution of **1** does increase. But, compared to fructose, the degree of the fluorescence enhancement is relatively small for mannose, glucose, and galactose. By fitting the data shown in Figure 2, the association constants (K_a) of dyad **1** with fructose, mannose, glucose, and galactose were evaluated and the data are listed in Table 1.[16] These association constant data also show that dyad **1** binds more strongly with fructose.

The fluorescence response of dyad **1** to saccharides was also studied at different pH values. As an example, Figure 3 displays the relationship between fluorescence and pH of dyad **1** in solutions containing fructose (25 mM). Clearly, the fluorescence intensity increases very slightly when the pH of the solution is below 6.0, and it reaches maximum around pH 7.3, which is in the range of physiological pH. Similar phenomena were also seen for mannose, glucose, and galactose.

To study the role of the TTF unit on the fluorescence enhancement upon binding with saccharides, studies of the reference compound **2** (Scheme 2) under identical conditions were carried out. The inset of Figure 1 shows the fluorescence alteration of **2** upon reaction with fructose together with that of **1** for comparison. Obviously, compared with dyad **1** only slight fluorescence enhancement was observed for **2**. Besides, the fluorescence spectra of **2** in the presence of fructose were also measured in solutions at different pH values. The fluorescence intensity of **2** containing fructose (25 mM) was enhanced by increasing the pH values of the solution, which is different from that observed for dyad **1** (Figure 3). According to a previous report,[15] the observed fluorescence enhancement for **2** should be due to the transformation of the boronic acid group into the boronate anion (losing electron accepting ability).

Two conclusions can be drawn from the different behaviors of dyad **1** and **2** in terms of fluorescence increase upon reaction with saccharides: (1) the observed fluorescence enhancement for dyad **1** cannot be solely due to the transformation of the boronic acid into the boronate ion since dyad **1** shows a larger fluorescence increase compared with **2** under identical conditions and (2) the TTF unit in dyad **1** plays an important role in the fluorescence enhancement upon the binding of the boronic acid group with saccharides. The fluorescence enhancement observed for dyad **1** upon reaction with saccharides can be understood as follows: upon reaction with saccharides, the boronic acid group was converted to the boronate under the present conditions. According to previous studies,[5] the boronate is a stronger Lewis acid (i.e., stronger electron acceptor) than the corresponding boronic acid. As a result, the PET between the TTF unit and boronate would compete with that between the TTF and anthracene units of dyad **1**, which in turn would be prohibited to some extent, leading to the fluorescence enhancement of dyad **1**. Accordingly, we suppose that the mechanism of dyad **1** sensing saccharides is similar to that of Shinkai's saccharide sensors (Scheme 1).

In summary, a new TTF−anthracene dyad **1** with a boronic acid group was synthesized, and fluorescent spectral studies show that dyad **1** is a good saccharide (at least for fructose) sensor. Comparative studies with compound **2** indicate that the TTF group plays an important role for the observed fluorescence enhancement for dyad **1** after reaction with saccharides. The present studies suggest that the amine group in Shinkai's saccharide sensors can be replaced with other electron-rich centers such as the TTF group, extending the gamut of Shinkai's saccharide sensors. Moreover, the nature of the TTF/anthracene and TTF/boronic spacers may affect

(16) The K values shown in Table 1 were calculated from the plots of relative fluorescence intensity versus saccharide concentration by using the following equation: $I_F = (I_{F\min} + I_{F\max} K[\text{guest}])/(1 + K[\text{guest}])$. The standard errors obtained from the best fitting were also provided.

the sensitivity of dyad **1** to saccharides, adding new thoughts for designing effective saccharide sensors. Further investigations along this vein are in progress.

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Supporting Information Available: Synthesis and characterization of compounds **1**, **2**, **4**, **5**, **6**, and **7**; fluorescence spectra of **2** in the presence of fructose; ^{1}H NMR spectra of dyad **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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