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A Ditopic Fluorescence Sensor for Saccharides and Mercury Based on a Boronic-Acid Receptor and Desulfurisation Reaction

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Abstract: Two boron-contained fluorescent sensors, **1** and **2**, based on coumarin have been prepared. The fluorescence response of the two systems was investigated with addition of saccharide and mercury ions. Sensor **2** behaves as a bifunctional fluorescent switch with chemical inputs of D-fructose and mercury ions.

Keywords: boron · coumarin · fluorescence · mercury · saccharides

Introduction

The development of boronic-acid-based saccharide sensors that rely on the dynamic covalent interaction of boronic acids with diols has been extensively investigated.[1] Not only is the pair-wise interaction energy large enough to allow single-point molecular recognition, but also the primary interaction involves the reversible formation of a pair of covalent bonds (rather than non-covalent attractive forces). This interaction has been widely exploited in the development of fluorescent and colorimetric sensors.[2]

The design and construction of chemosensor systems which respond to chemical and/or photonic inputs by generating output signals to multiple guests have attracted considerable attention.[3] Most of the successful systems designed so far are based on photoinduced electron transfer (PET) mechanisms. Molecular systems combining binding ability with the initiation or inhibition of PET processes as a mode of signal transduction are in great demand for developing molecular-scale information processors.[4]

Mercury ions are potent toxins to humans, since accumulation in the blood–brain barrier results in severe neurological disorders.[5] Hence, the design and development of novel sensors for mercury ions is an important area of research.[6] Saccharides, on the other hand, are vital to human health through their use as building blocks and in the production of metabolic energy.[7]

Although these two species have opposing effects on human health, they are brought together in industrial food processing. In particular, food ingredients such as citric acid, sodium benzoate, and high-fructose corn syrup are produced using mercury-cell chlor-alkali. High-fructose corn syrup is extensively used in food products to enhance shelf life. Therefore, a substantial part of dietary exposure to mercury may originate from high-fructose corn syrup produced using mercury cells.[8]

The contamination of fructose corn syrup with mercury during its manufacture makes the development of a ditopic fluorescence sensor for mercury ions and fructose an important goal. However, there are few systems capable of selectively reporting the presence of saccharides and cationic guests. Herein, we present a fluorescence signaling system **2** which acts as a ditopic sensor[9] for Hg^{2+} ions and D-fructose.

Results and Discussion

The synthesis of compounds **1** and **2** are readily achieved in several steps. The fluorophore ethyl-7-(diethylamino)-2-oxo-2*H*-chromene-3-carboxylate (**4**) is prepared from 4-(diethylamino)-2-hydroxy-benzaldehyde and diethyl malonate in the presence of a catalytic amount of piperidine and acetic acid. Without further purification, the crude **4** is reacted

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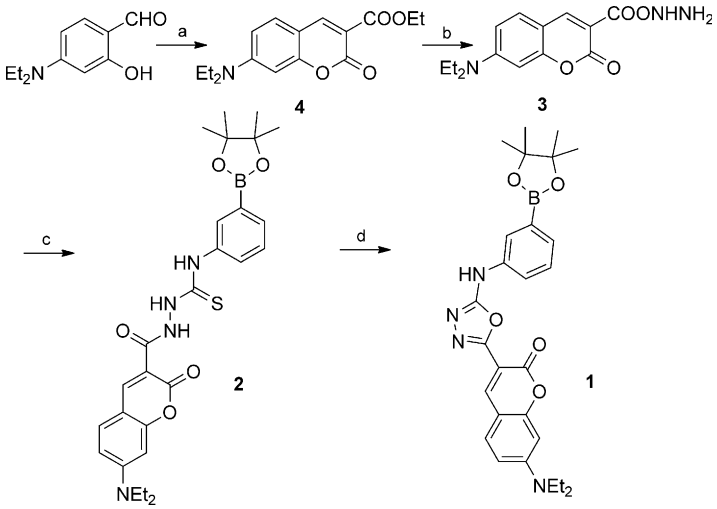
with hydrazine hydrate to afford **3** at room temperature in 12 minutes. Sensor **2** was then easily prepared by a condensation reaction of **3** with 3-isothiocyanophenyl boronic acid pinacol ester. Compound **1** was obtained directly from **2** using *N,N'*-dicyclohexylcarbodiimide (DCC) in 90% yield (see Scheme 1).



Scheme 1. Synthesis of sensors **1** and **2**. Reagents and conditions: a) diethyl malonate, piperidine, acetic acid, reflux, 3 h, 80% yield; b) hydrazine monohydrate, EtOH, 12 min, 52% yield; c) 3-isothiocyanophenyl boronic acid pinacol ester, CH_3CN, 2 h, 76% yield; d) DCC, toluene, reflux, 10 h, 90% yield.

The fluorescence titrations of **2** (3.7×10^{-7} mol dm^{-3}) and **1** (8.0×10^{-7} mol dm^{-3}) with different saccharides were carried out in a pH 8.21 buffer (52.1 wt% MeOH in H_2O with KCl, 0.01000 mol dm^{-3}; KH_2PO_4, 0.002752 mol dm^{-3}; Na_2HPO_4, 0.002757 mol dm^{-3}). The fluorescence intensity of receptor **1** decreased on the addition of saccharides, the expected behavior for directly integrated boronic acid fluorophore systems.[10] Conversely, we found that the fluorescent intensity of receptor **2** increased with the addition of saccharide; this result suggests that a d-PET (donor Photo-induced Electron Transfer)-type mechanism is operating.[11] The pH profile of receptor **2** (see the Supporting Information, Figure S1) confirms this assumption, where, at low pH, the fluorescence is switched "off" owing to PET from the fluorophore (as donor) to the boronic acid receptor unit, whilst at high pH the fluorescence is "on" and PET is switched "off". The fluorescence switch "on" is caused at high pH (or on saccharide binding) because PET from the fluorophore to the negatively charged boronate of the receptor is unfavorable.

Abstract in Chinese:

我们合成了两个含有硼酸和香豆素结构的荧光探针 1 和 2，并对这两个体系关于加糖和汞离子的荧光响应进行了研究。我们发现，探针 2 可以作为一种双功能的识别 D-果糖和汞离子的荧光传感器。

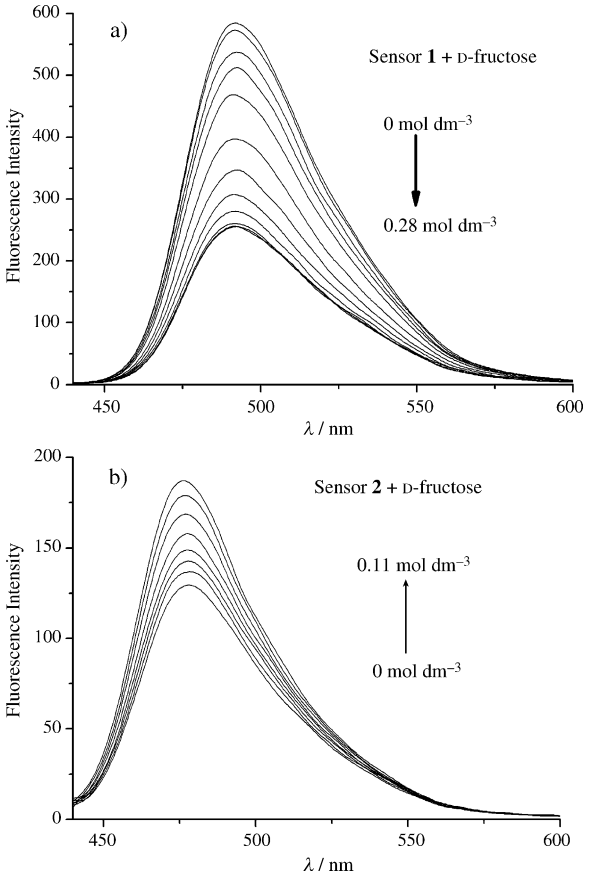


Figure 1. a) and b): Fluorescence spectra of **1** and **2** in the presence of increasing concentrations of D-fructose ($\lambda_{ex}=430$ nm).

The fluorescence spectra of **1** and **2** in the presence of D-fructose are shown in Figure 1a and Figure 1b; the analogous spectra for the addition of D-glucose and D-mannose are also available in the Supporting Information. The stability constants (K) of fluorescence receptors **1** and **2** with D-fructose, D-glucose, and D-mannose were calculated by fitting the emission intensity at 478 nm and 492 nm ($\lambda_{ex}=$ 430 nm) versus the concentration of saccharide (Figure 2a, and 2b). Minimal fluorescence response was observed for other saccharides, such as D-sucrose and D-xylose (see the Supporting Information, Figures S2 and S3). The stability constants calculated from these titrations are given in Table 1.[12] The stability order for receptors **1** and **2**, fructose > mannose > glucose, followed the "inherent stability order" observed for all simple boronic acids.[13]

Fluorescence chemosensors for the selective detection of Hg^{2+} ions are well known.[14] The mercury-desulfurization reaction has also been used to selectively detect Hg^{2+} ions by fluorescence[15] (Scheme 2). Therefore, we decided to investigate the "On-Off" switching behavior of receptor **2** with D-fructose and Hg^{2+} ions since it should produce optical responses towards added saccharides and Hg^{2+} ions. The reaction of **2** with Hg^{2+} ions to produce **1** proceeded to completion quickly and well within our set time interval (30 minutes) for our measurements (See the Supporting Information, Figure S4).

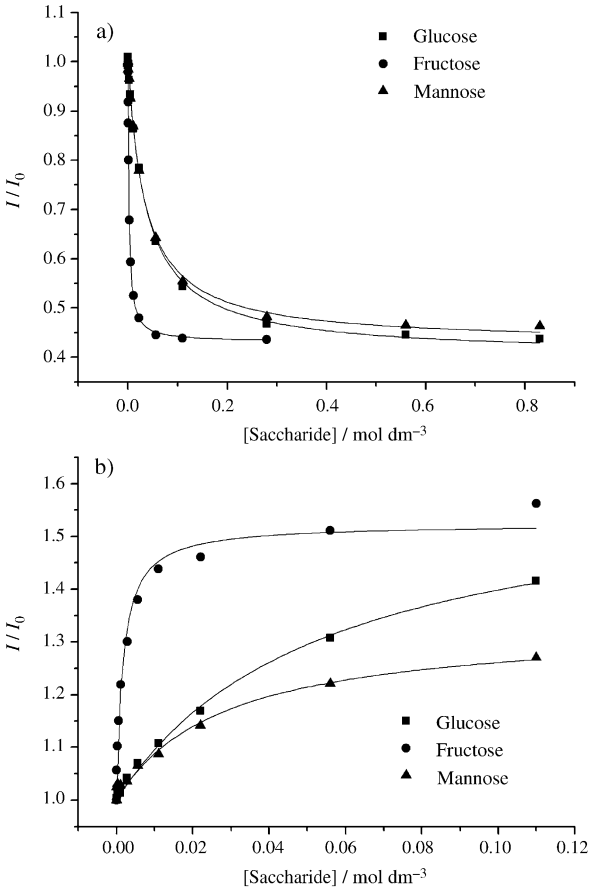
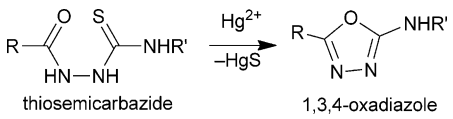


Figure 2. a) and b): binding curves for **1** (λ_{em} = 492 nm) and **2** (λ_{em} = 478 nm) in the presence of increasing concentrations of D-fructose, D-glucose, and D-mannose (λ_{ex} = 430 nm).

Table 1. Stability constant K (coefficient of determination, r^2) for the binding of receptors **1** and **2** with monosaccharides.

Saccharide	K **1** (r^2) [mol^{-1} dm^3]	K **2** (r^2) [mol^{-1} dm^3]
D-fructose	478.0 ± 14.5 (0.99)	587.4 ± 89.9 (0.98)
D-glucose	26.9 ± 1.2 (0.99)	18.6 ± 1.8 (0.99)
D-mannose	28.9 ± 1.1 (0.99)	36.1 ± 7.9 (0.97)



Scheme 2. Hg^{2+}-promoted formation of the 1,3,4-oxadiazole moiety.

This system can be compared to an AND gate that reports a HIGH output (1) only when two inputs are simultaneously applied. In this paper, the optical output signals of coumarin-based ditopic receptor **2** in response to saccharide and metal-ion binding behaves in an AND logic manner.

The fluorescence of receptor **2** (3.7×10^{-7} mol dm^{-3}) at 478 nm (Output) is significantly enhanced by 5.21 fold in the presence of both Hg^{2+} ions and D-fructose in pH 8.21 buffer (Figure 3, Table 2). Whilst a medium enhancement of 2.94 is obtained for the addition of only Hg^{2+} ions and a low enhancement of 1.44 is observed for the addition of D-fructose alone. We also investigated the effect of other metal ions: Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Mn^{2+}, Ca^{2+}, Cd^{2+}, and Mg^{2+} with receptor **2**. Of the metals investigated, only Hg^{2+} ions produced a significant fluorescence enhancement with receptor **2** at 478 nm (see the Supporting Information, Figure S10).

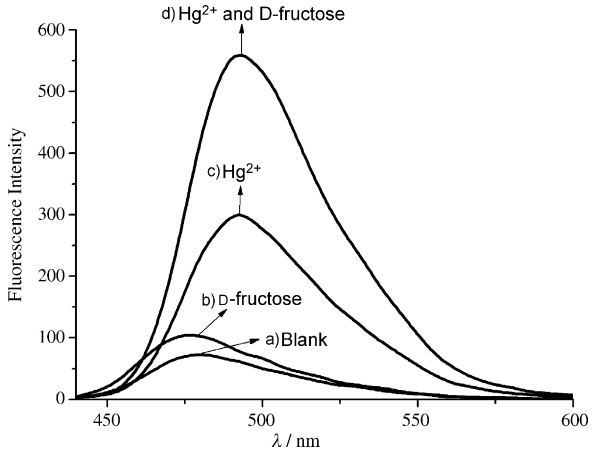


Figure 3. Fluorescence spectra of receptor **2** in the absence or presence of Hg^{2+} ions or D-fructose. Concentration of **2** was 0.37 mM, [Hg^{2+}] = 0.15 mM, [D-fructose] = 0.83 M. The solvent was methanol/H_2O buffer (52.1:47.9, 50 mM, pH 8.21) λ_{ex} = 430 nm: a) **2** alone, b) **2**+D-fructose, c) **2**+Hg^{2+}, and d) **2**+Hg^{2+}+D-fructose. All spectra were recorded after 30 min.

Table 2. Fluorescence truth table for receptor **2** with mercury and fructose as inputs.[a,b]

Input 1 (Hg^{2+})	Input 2 (D-fructose)	Output (normalized)
0	0	Low (1.00)
1	0	Medium (2.94)
0	1	Low (1.44)
1	1	High (5.21)

[a] Receptor **2** (0.37 *m*M), [Hg^{2+}] = 0.15 mM, [D-fructose] = 0.83 M emission in methanol/H_2O buffer (52.1:47.9, 50 mM, pH 8.21). λ_{ex} = 430 nm, and data of **2** (λ_{em} = 478 nm) were collected. AND logic requires that the signal is 1 only when both inputs are 1, and 0 in all other cases. [b] Relative emission intensities were normalized to the emission intensity of **2** alone at 0.37 mM concentration (λ_{em} = 478 nm).

Conclusions

In conclusion, receptor **2** is a ditopic fluorescent sensor for D-fructose and Hg^{2+} ions. This system simultaneously recognizes saccharides and the Hg^{2+} cation. We believe that our system will guide the design of new ditopic sensors with practical utility. We are currently working on developing saccharide-selective receptors based on the principles outlined in this preliminary report.

Experimental Section

General

Infra-red spectra were recorded between 4000 cm^{-1} and 600 cm^{-1}. Samples were either mixed with KBr in a mortar and pressed into a KBr pellet (KBr), or evaporated to dryness on a NaCl plate (film). All vibrations (ν) are given in cm^{-1}. Nuclear magnetic resonance spectra were run in either [D]chloroform or [D_6]dimethyl sulfoxide. ^1H NMR spectra were recorded at 300 MHz, ^{11}B {^1H} NMR spectra at 96 MHz, and ^{13}C {^1H} NMR spectra at 75 MHz. Chemical shifts (δ) are expressed in parts per million and are reported relative to the residual solvent peak or to tetramethylsilane as an internal standard in ^1H and ^{13}C {^1H} NMR spectra and boron trifluoride diethyl etherate as an external standard in ^{11}B {^1H} NMR spectra. The multiplicities and general assignments of the spectroscopic data are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt), unresolved multiplet (m), broad (br), and aryl (Ar). Coupling constants (J) are expressed in Hertz. Chemical shifts were assigned with consideration of the multiplicities and chemical shifts (^1H), ^{13}C {^1H} spectra are given as the sign of their pendant spectrum. Data acquisition and automated processing were controlled using Compass OpenAccess 1.3 software. The observed mass and isotope pattern perfectly matched the corresponding theoretical values as calculated from the expected elemental formula. Quartz cuvettes with 10 mm path lengths and four faces polished. All pH measurements taken during fluorescence experiments were on pH meter which was calibrated using standard buffer solutions. All solvents used in fluorescence measurements were HPLC or fluorescent grade and the water was deionized. All saccharides used in fluorescence measurements were certified as $\geq$99% pure. The fluorescence studies were carried out in an aqueous methanolic pH 8.21 buffer. The buffer was prepared in a 1 L volumetric flask according to a procedure laid out by Perrin and Dempsey and consisted of: 52.1 wt% HPLC grade methanol, in deionized water with KCl (0.7456 g, 0.01000 mol dm^{-3}), KH_2PO_4 (0.3745 g, 0.002752 mol dm^{-3}), and Na_2HPO_4 (0.3914 g, 0.002757 mol dm^{-3}).

Preparation of ***4****[16]*

A solution of 4-(diethylamino)-2-hydroxybenzaldehyde (1.93 g, 0.01 mol) and diethyl malonate (1.92 g, 0.012 mol) in glacial acetic acid was treated with piperidine (0.1 mL) and reflux for 3 h. To the reaction mixture was added 20 mL H_2O, and the mixture was cooled to 0 °C. The crystalline solid was filtered and washed with 50% cold ethanol (5 mL). Recrystallization from 50% EtOH gave **4** as a yellow crystalline solid: (2.30 g, 80%); m.p. 75–76 °C. ^1H NMR (300 MHz, $CDCl_3$): δ_H=1.22 (t, J=7.2 Hz, 6H), 1.37(t, J=7.2 Hz, 3H), 3.42 (q, J=7.2 Hz, 4H), 4.34 (q, J=7.2 Hz, 2H), 6.42 (d, J=2.2 Hz, 1H), 6.58 (dd, J=2.2 9.0 Hz, 1H), 7.33 (d, J=9.0 Hz, 1H), 8.40 ppm (s, 1H); ESI-MS: m/z: 312.33 ([M+Na]$^+$ $C_{16}H_{19}NO_4Na$ requires 312.15).

Preparation of ***3***

Hydrazine monohydrate (1.4 mL, 28 mmol) was added to a solution of **4** (2.0 g, 7 mmol) in EtOH (20 mL), and the reaction mixture was stirred at room temperature for 12 min, After cooling in an ice bath for 15 min, the precipitates were collected on a filter funnel to give **3** as orange needles: (0.92 g, 50%); m.p.: 160–165 °C. ^1H NMR (300 MHz, $CDCl_3$): δ_H=1.24 (t, J=7.2 Hz, 6H), 3.46 (q, J=7.2 Hz, 4H), 6.50 (d, J=2.4 Hz, 1H), 6.65 (dd, J=2.4 9.0 Hz, 1H), 7.51 (d, J=9.0 Hz, 1H), 8.68 (s, 1H), 9.74 ppm (s, 1H); TOF-MS: m/z 276.1 ([M+H]$^+$ $C_{15}H_{18}N_3O_3$ requires 276.13).

Preparation of ***2****[14d,17]*

3-isothiocyanophenyl boronic acid pinacol ester (0.26 g, 1 mmol) was added to solution of **3** (0.275 g, 1 mmol) in acetonitrile (30 mL).The reaction mixture was left to stand at room temperature for 2 h. The solid product which separated was filtered, washed with ether, dried, and recrystallized from dioxane to yield product **1** as light green solid: (0.40 g, 76%); m.p. 219–222 °C; IR: $\tilde{\nu}$=3283, 1697, 1610, 1573, 1510, 1462, 1416,1372, 1351,1304, 1275,1259, 1231, 1187, 1136 cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO): δ_H=1.12 (t, J=7.2 Hz, 6H), 1.26 (s, 12H), 3.46 (q, J=7.2 Hz, 4H), 6.61 (d, J=2.4 Hz, 1H), 6.80 (dd, J=2.4 9.0 Hz, 1H), 7.33–7.74 (m, 5H), 8.70 (s, 1H), 9.78 ppm (br, 2H); (75 MHz, [D_6]DMSO): δ_C=12.67, 25.02, 44.76, 84.06, 96.24, 107.97, 110.66, 132.16, 139.17, 148.43, 153.12, 157.75, 161.58 ppm; ESI-MS: m/z 537.2365 ([M+H]$^+$, $C_{27}H_{34}B_1N_4O_5S_1$ requires 537.2342).

Preparation of ***1***

A solution of **2** (0.27 g, 0.5 mmol) in toluene (5.0 mL) was stirred, and DCC (0.12 g, 0.6 mmol) was added and the mixture was heated to reflux for 10 h. After the solvent was evaporated under reduced pressure, the crude product was purified by column chromatography on silica gel to give **1** as a yellow solid (0.22 g, 90%); m.p. 249–250 °C; IR: $\tilde{\nu}$=3260, 1720, 1618, 1589, 1537, 1514, 1356,1236, 1220, 1191, 1135 cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO): δ_H=1.12 (t, J=7.2 Hz, 6H), 1.29 (s, 12H), 3.46 (q, J=7.2 Hz, 4H), 6.56 (d, J=2.4 Hz, 1H), 6.76 (dd, J=2.4 9.0 Hz, 1H), 7.31–7.79 (m, 5H), 8.40 (s, 1H), 10.59 ppm (br, 1H); (75 MHz, [D_6]DMSO): δ_C=12.68, 25.05, 44.66, 84.08, 96.53, 103.37, 107.63, 110.16, 120.41, 123.05, 125.65, 131.29, 144.21, 152.39, 155.65, 157.34, 157.42, 160.00 ppm; ESI-MS: m/z 503.2444 ([M+H]$^+$, $C_{27}H_{32}B_1N_4O_5$ requires 503.2465).

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