Retraction for *Organic & Biomolecular Chemistry*:

Recognition of D-fructose based on tetra-boronic functionalized viologen in aqueous solution

Liheng Feng, Fei Liang, Yue Wang, Guofeng Wang and Xiaoju Wang

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We, the named authors, hereby wholly retract this *Organic & Biomolecular Chemistry* article, due to insufficient experimental data being available to explain the results.

Signed: Liheng Feng, Fei Liang, Yue Wang, Guofeng Wang and Xiaoju Wang, September 2011

Retraction endorsed by Richard Kelly, Editor, *Organic & Biomolecular Chemistry*

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PAPER

Recognition of D-fructose based on tetra-boronic functionalized viologen in aqueous solution†

Liheng Feng,*[a] Fei Liang,[a] Yue Wang,[a] Guofeng Wang[a] and Xiaoju Wang*[b]

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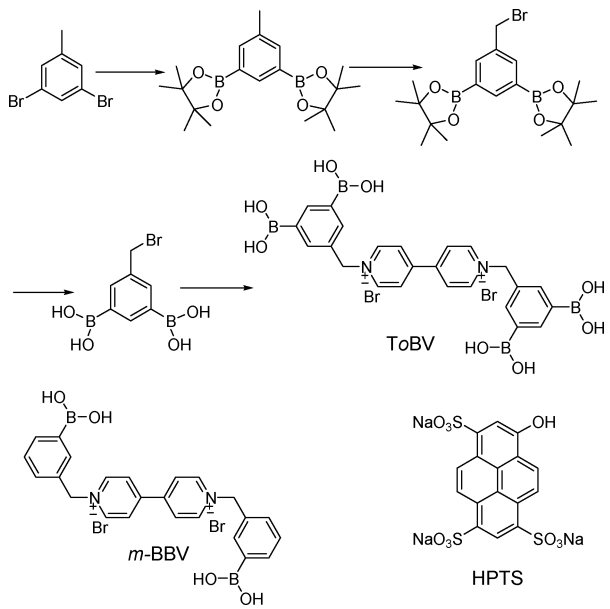
A highly selective and sensitive switch for D-fructose is formed by 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS) fluorescent dye and the tetra-boronic acid viologen receptor T*o*BV. The sensing system can not only recognize D-fructose among seven natural D-monosaccharides but also may distinguish the enantiomer of D/L-fructose. The research rationale and results will offer a new strategy for the development of saccharides recognition.

Introduction

Molecular recognition of monosaccharides has always attracted extensive attention because of their important transportation and metabolic actions in living organisms.[1] However, due to monosaccharides having only one kind of functional group (hydroxyl) and many variable configurations in aqueous solution,[2] it is rather difficult to obtain highly sensitive and selective receptors for monosaccharides, especially for enantioselectivity.[3] Despite the large and diverse set of fluorescence-based sensing systems for monosaccharides, no methods for monosaccharides detection that have authentic specificity have been reported.[4] The two-component sensing systems that were developed by Singaram and his co-workers displayed rather high sensitivity for monosaccharide detection.[5] However, it is a pity that these two-component systems had not ideal specificity for monosaccharides. Judging from the current findings, it is feasible to develop highly specific receptors of monosaccharides through providing suitably spaced boronic groups. The two-component system is promising for monosaccharides recognition because of its considerable flexibility in the choice of the quencher and fluorophore. Given the importance of fructose to the food and beverage industry, development of a promising detection system for D-fructose is urgent.[6] Due to fructose possessing a high affinity for boronic acid receptors,[7] our purpose is to develop a highly specific two-component D-fructose sensing system with suitable boronic acids spaced in a viologen receptor.

Based on the idea, we synthesized tetra-boronic substituted benzyl viologen (T*o*BV) and combined it with 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS) to form a facile sensing switch for D-fructose (Scheme 1). Anionic fluorescent dye



Scheme 1 Synthesis and structures of positively charged quenchers T*o*BV, *m*-BBV and fluorescent dye HPTS.

HPTS was the optical signal reporter section and its fluorescence was modulated by electron transfer from HPTS to T*o*BV. Cationic viologen T*o*BV was both a quencher and receptor in the system. We think the recognition system should have high selectivity and sensitivity for D-fructose based on the suitably spaced positions of the boronic groups in the same benzene ring and the facile two-component system.

Results and discussion

Quencher/receptor T*o*BV was synthesized in four steps from the commercially available 1,3-dibromo-5-methylbenzene.[8] Firstly, the C–B coupling reaction between 1,3-dibromo-5-methylbenzene

[a]*School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan, 030006, China. E-mail: lhfeng@sxu.edu.cn; Tel: +86 3517011600*
[b]*Institute of Molecular Science, Key Laboratory of Chemical Biology and Molecular Engineering of Ministry of Education, Shanxi University, Taiyuan, 030006, China*

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and bis(pinacolato)diboron gave 3,5-bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)toluene. Then 5-(bromomethyl)phenyl-1,3-diboronic acid was obtained by bromination with NBS and deesterification with sodium periodate. Lastly, *N*,*N*′-4,4′-bis(benzyl-3,5-diboronic acid)-bipyridinium dibromide (T*o*BV) was synthesized by quaternization of commercially available 4,4′-dipyridyl with 5-(bromomethyl)phenyl-1,3-diboronic acid in 78.3%.

To verify our idea, the recognition response of the two-component sensing system for D-fructose was determined in an aqueous solution at pH 7.4 (Fig. 1). Obviously, the ground-state complex between anionic dye HPTS and cationic T*o*BV was formed by electron transfer from HPTS to T*o*BV, resulting in a great reduction in the HPTS fluorescence intensity (see Fig. S1 and Fig. S2†). Upon introduction of D-fructose to the sensing system, an apparent recovery of the HPTS fluorescence was observed due to the formation of the negatively charged borate ester between T*o*BV and D-fructose. The fluorescence recovery of HPTS was dependent on the D-fructose concentration. A 150-fold increase in fluorescent intensity was observed by adding 10 mM D-fructose to the HPTS/T*o*BV (1/150) system, which showed rather high sensitivity for D-fructose detection. Additionally, we investigated the sigmoidal curve of the sensing system with D-fructose at pH 7.4 (see Fig. S3†). The binding constant of the sensing system to D-fructose was 167.29 ± 20.4 M^2 based on the sigmoidal curve.

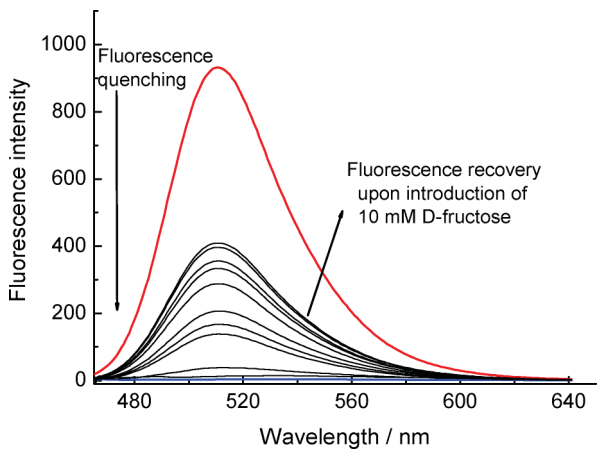

Fig. 1 Characteristic fluorescence response by introduction of the quencher followed by D-fructose to an HPTS solution (4.0×10^{-6} M) at pH 7.4. The T*o*BV/HPTS ratio for this data was 150/1 and the final D-fructose concentration was 10.0 mM. The red line indicates unquenched fluorescence; the blue line indicates fluorescence after introduction of quencher T*o*BV.

The selectivity of the sensing system for seven usual D-monosaccharides was determined by titration experiments in aqueous solution at pH 7.4 (Fig. 2). As expected, only with introduction of D-fructose to the sensing system was a significant fluorescent recovery of HPTS observed. Few fluorescent recoveries of HPTS were observed by adding other D-monosaccharides to the sensing system, respectively. To the best of our knowledge, the selectivity of the sensing system for D-fructose is the highest ever recorded. The ratios of relative intensities (D-fructose/D-monosaccharides) that were obtained by adding 10 mM D-fructose and other D-monosaccharides were about 34–71 fold. Such high

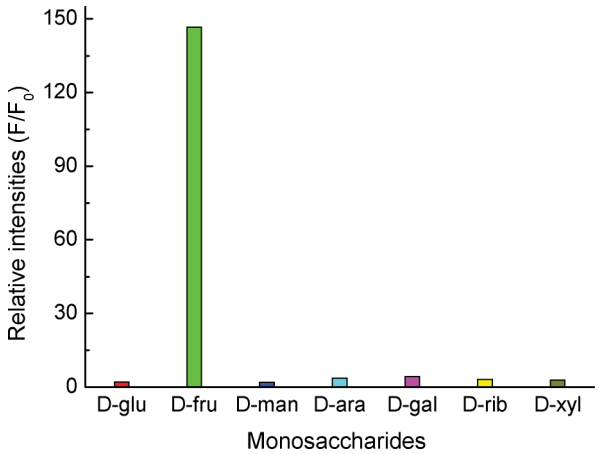

Fig. 2 The binding characteristics of HPTS (4.0×10^{-6} M) and T*o*BV (6.0×10^{-4} M) with different D-monosaccharides (10 mM, respectively) in pH 7.4 phosphate buffer solutions.

selectivity of the sensing system for D-fructose was easily understandable. Firstly, it is well known that the affinity of the boronic group to D-fructose is stronger than that to other monosaccharides. However, the stronger affinity between T*o*BV and D-fructose alone does not explain such high selectivity. Therefore, we think that it was mainly dependent on the suitably spaced positions of the boronic groups in same benzene ring. The above hypothesis can be confirmed by another two-component system comprising *N*,*N*′-4,4′-bis(benzyl-2-boronic acid)bipyridinium dibromide (*m*-BBV) and HPTS (Scheme 1). The sensing system had been developed by Singaram and the results showed fluorescent recovery of the sensing system for D-fructose was still stronger than that for other monosaccharides. Regrettably, the selectivity of the sensing system for D-monosaccharides was poor.[5g,8d] It was obvious that *m*-BBV can not provide the suitable space for D-fructose to forming pyranose (Scheme S1†) because it had only one boronic group in the same benzene ring.

In order to broaden the recognition properties of HPTS/T*o*BV, the enantioselectivity of the sensing system for D-fructose and L-fructose also was very important and was determined in aqueous solution at pH 7.4 (Fig. 3). Surprisingly, only a few fluorescent recoveries of HPTS were observed by adding L-fructose to the sensing system. The relative intensities of fluorescence in the presence of 5 mM D-fructose was 57-fold of that in the presence of 5 mM L-fructose. The quenching action of T*o*BV to HPTS had a slight influence in the presence of L-fructose, however, a large reduction in quenching efficiency of T*o*BV to HPTS was observed in the presence of D-fructose (see Fig. S4†), which indicated the borate between T*o*BV and D-fructose was easily formed and can prevent further quenching of T*o*BV to HPTS. Moreover, the selectivity and sensitivity of the sensing system with the mixtures of D-fructose and L-fructose (total 10.0 mM) were determined by titration experiments (see Fig. S5 and Fig. S6†). The titration curve was considerably dependent on D-fructose and showed highly enantioselectivity.

Remarkably, when the detection solution was irradiated by 365 nm UV-Vis light, the specificity of the sensing system for D-fructose was observable by the naked eye (Fig. 4). The color changes of the solutions from light-green to colorless came from the ground-state complex formation between HPTS and

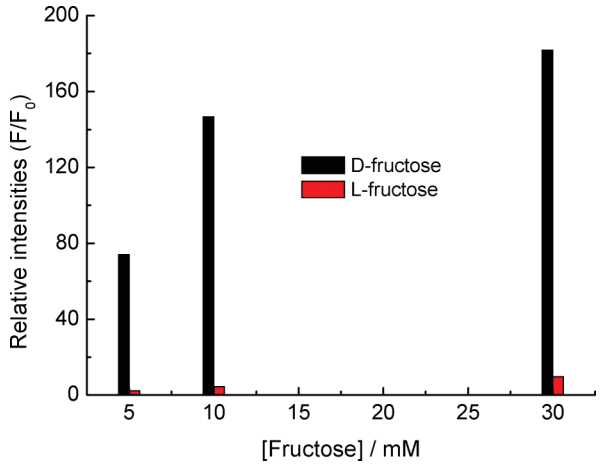

Fig. 3 The binding characteristics of HPTS (4.0×10^{-6} M) and T*o*BV (6.0×10^{-4} M) with D-fructose and L-fructose in pH 7.4 phosphate buffer solutions.

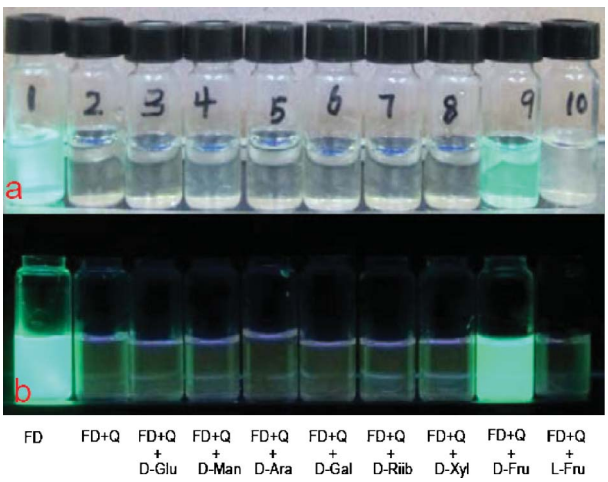

Fig. 4 The color changes of the HPTS fluorescent dye (FD, 4.0×10^{-6} M) solutions by introduction of T*o*BV quencher (4.0×10^{-4} M) followed by 2.0 mM of monosaccharide in pH 7.4 phosphate buffer solution, respectively. The solutions were irradiated by λ_{365} nm UV-Vis light. a was in the presence of λ_{365} nm UV-Vis light and a daylight lamp, b was only in the presence of λ_{365} nm UV-Vis light.

T*o*BV. The rather large recovery of the solution color was only displayed by adding D-fructose. Additionally, the obvious change of the solution color was in the presence of 2 mM D-fructose, which showed the sensing system had rather high sensitivity and selectivity for D-fructose. We believe the obvious color change of the sensing system is valuable and may provide a simple and convenient detection method for D-fructose in practical samples.

Conclusions

In summary, we have developed a highly selective and sensitive D-fructose sensing system based on water soluble HPTS and the tetra-boronic acid receptor T*o*BV. The sensing system can not only recognize D-fructose among seven natural D-monosaccharides but also may distinguish the enantiomer of D/L-fructose. We believe that the research rationale and results will offer a new strategy for the development of saccharides recognition. The specific combining ways of the HPTS/T*o*BV sensing system with different saccharides are currently under way.

Experimental section

Materials and instruments

Unless otherwise stated, all chemical reagents were obtained from commercial suppliers and used without further purification. Solvents used were purified and dried by standard methods prior to use. *N*,*N*′-4,4′-Bis(3-diboronic acid benzyl)-bipyridinium dibromide (*m*-BBV) was prepared according to the previous literature.[5g] Bis-(pinacolato)diboron, 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS), *N*,*N*′-4,4′-bipyridyl, Pd(dppf)Cl_2 and 1,3-dibromo-5-methylbenzene were purchased from Aldrich (Steinheim, Germany). D-Monosaccharides were purchased from Alfa Aesar (Tianjin, China), L-fructose was provided by Shanghai DEMO Medical Tech. Co.ld (China). pH Measurements were carried out on a Mettler Toledo MP 220 pH meter. ^{1}H NMR and ^{13}C NMR were measured on a Bruker ARX400 spectrometer with chemical shifts reported as ppm (TMS as an internal standard). ^{11}B NMR spectra were recorded on a Bruker at 80 MHz and are reported in ppm with respect to $BF_3{\cdot}OEt_2$ ($\delta = 0$). The IR spectra were determined on a PE-1700 IR spectrophotometer by dispersing samples in KBr disks. Elemental analyses were performed on a Vario EL elemental analysis instrument (Elementar Co.). High-resolution mass spectra (HRMS) were acquired on an Agilent 6510 Q-TOF LC/MS instrument (Agilent Technologies, Palo Alto, CA) equipped with an electrospray ionization (ESI) source.

Solution preparation and spectra measurement

All experiments with water used distilled water. All of the working solutions were buffered at pH 7.4 ± 0.1 using a phosphate (the mixture system of Na_2HPO_4 (0.2 M, 61.0 mL) and NaH_2PO_4 (0.2 M, 39.0 mL)) buffer solution. The stock solution (4.0×10^{-3} M) of HPTS was diluted in a 1.0 L measuring flask with pH 7.4 buffer solution to afford the working solution (4.0×10^{-6} M). The stock solution of T*o*BV was 0.04 M. The stock solution of monosaccharides was 1.0 M in a 10.0 mL measuring flask. The standard stock solutions of lower concentration were prepared by suitable dilution of the stock solution with pH 7.4 buffer solution. All spectra analysis studies were carried out at pH = 7.4 in buffer solution and the working solutions were placed in a quartz cuvette with a 1 cm path. The total volume of working solutions was 2.0 mL. The studies of fluorescence quenching and sensing of monosaccharides used titration experiments and the volume added did not exceed 3% of the total. After the mixture solution was shaken for 30 s, the new spectra were measured. Fluorescence spectra were acquired with a Varian Cary Eclipse fluorescence spectrophotometer, the excitation and emission slit widths were 2.5 nm and 5.0 nm respectively. The excitation wavelength was set at 450 nm according to experimental requirements. All of the experiments were performed at barometric pressure and room temperature.

Synthesis of T*o*BV

3,5-Bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)toluene. A mixture of 10.0 g (0.04 mol) 1,3-dibromo-5-methylbenzene, 22.4 g (0.088 mol) diborane pinacol ester, 1.5 g (2.0 mmol) Pd(dppf)Cl_2, 23.52 g (0.24 mmol) KOAc and 80 mL DMSO was heated to 80 °C for 4 h. After the mixture was cooled, 500 mL water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed by vacuum distillation. The crude product was purified by column chromatography on silica gel with ethyl acetate : petroleum ether (1 : 20) as the eluant to afford a white power (11.32 g, 82.3%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, 1H), 7.73 (s, 2H), 2.35 (s, 3H), 1.33 (s, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.09, 24.89, 83.77, 136.32, 138.42; IR (KBr) cm^{-1}: 2955, 2871, 1674, 1559, 1502, 1496, 1381, 1353, 1202, 1062, 937, 835, 628, 536; Element Analysis for $C_{19}H_{30}B_2O_4$ (Mol. Wt.: 344.06) calcd.: C 66.33; H 8.79; O 18.60; found: C 66.41; H 8.85; O 18.55%; HRMS-ESI for $C_{19}H_{30}B_2O_4$ (*m*/*z*) 345 [M + 1], 344 [M], 189 [M – 155].

***N*,*N*′-4,4′-Bis(benzyl-3,5-diboronic acid)-bipyridinium dibromide (T*o*BV).** A mixture of 10.32 g (30.0 mmol) 3,5-bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)toluene, 6.23 g (35.0 mmol) NBS, 0.35 g (1.4 mmol) benzoyl peroxide and 250 mL CCl_4 was refluxed for 7 h under a N_2 atmosphere. The resulting solution was filtered while it was cooled to room temperature. The filtrate was washed with saturated sodium hyposulfite solution (3 × 100 mL) then brine (2 × 100 mL), dried over Na_2SO_4 and concentrated by vacuum distillation to afford a yellow-white precipitate. The precipitate was recrystallized with CCl_4 to give 3,5-bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-1-bromomethylbenzene (white solid, 9.46 g, 74.5%). Next, a mixture of 8.46 g (20.0 mmol) 3,5-bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-1-bromomethylbenzene, 12.84 g (60.0 mmol) sodium periodate and 50 mL THF/H_2O (4 : 1) was stirred until homogeneous at room temperature, and then 2 N HCl (0.2 mL) was added. After 48 h, the reaction mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was recrystallized two times with CCl_4 to give 5-(bromomethyl)phenyl-1,3-diboronic acid (white solid, 1.99 g, 38.6%). Lastly, to a solution of 1.94 g (7.5 mmol) 5-(bromomethyl)phenyl-1,3-diboronic acid in 20 mL DMF was added 0.585 g (3.75 mmol) 4,4′-dipyridyl, and the reaction mixture was stirred at 80 °C for 48 h under nitrogen. The orange precipitate was collected by filtration, washed with DMF, acetone, then ether and dried under a stream of nitrogen to yield T*o*BV (1.21 g, 47.8%). ^{1}H NMR (D_2O, 400 MHz) δ 9.50 (d, J = 10.0 Hz, 4H), 8.76 (d, J = 7.2 Hz, 4H), 8.07 (s, 6H), 5.95 (s, 4H); ^{13}C NMR (D_2O, 100 MHz) δ 64.52, 99.98, 127.67, 132.52, 136.58, 146.12, 149.68, 151.44; IR (KBr) cm^{-1}: 3405, 3008, 2954, 2876, 1616, 1602, 1535, 1489, 1352, 1264, 1145, 1037, 912, 845, 715, 656; ^{11}B NMR (80 MHz, D_2O) δ 25.4; HRMS-ESI for $C_{24}H_{24}B_2Br_2N_2O_4$ (*m*/*z*) HRMS-ESI (*m*/*z*) 513.24 [M – 2Br].

Acknowledgements

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