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# Phenylboronic acid-functionalized TTFAQ: modular synthesis and electrochemical recognition for saccharides

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ABSTRACT

A phenylboronic acid-functionalized π-extended tetrathiafulvalene (TTFAQ) derivative was prepared through an efficient Cu-catalyzed alkyne-azide [3+2] cycloaddition reaction (click reaction). This boronic acid-TTFAQ hybrid system shows different electrochemical redox behavior upon titration with various saccharides in DMSO/$H_2O$ at pH 8.75, suggesting potential use in saccharide sensing and recognition.



The development of biosensors to detect saccharides has been a topical research in the past decade, driven by the growing need for understanding the crucial roles that various saccharide species play in numerous biologically important events ranging from protein targeting, cell recognition, and production of metabolic energy to disease diagnosis and management.[1,2] A general design architecture for a saccharide biosensor contains three essential components: receptor, reporter (i.e., read-out unit), and linkage group. Phenylboronic acid, ever since the discovery of its ability to rapidly form cyclic ester with *cis* 1,2- or 1,3-diols in aqueous media, has been extensively explored as saccharide receptors.[2–5] A major advantage of using phenylboronic acid for saccharide sensing lies in the possibility to achieve selectivity for a range of saccharides. Organic chromophores, fluorophores, and electrophores are commonly employed read-out units to be associated with phenylboronic acid in the design of saccharide sensors, which lead to various types of colorimetric,[6–8] fluorimetric,[9–14] and electrochemical saccharide sensors.[15–18]

In recent years, boronic acid-based electrochemical sensors have emerged as an appealing alternative to the conventionally used enzymatic electrochemical sensors for saccharides.[19,20] Molecular components with excellent redox reversibility and stability, such as ferrocene[15,17] and polyanilines,[16,18] have been exploited within this context. Tetrathiafulvalene (TTF) and π-extended TTF analogues (exTTFs) are well-known organic electronic materials for their remarkable redox activities and unique properties of forming charge-transfer complexes to show metallic conductance.[21,22] In the field of sensor design, the application of TTF components in constructing chemosensors for anion detection has made a significant progress in the past few years. Little attention, on the other hand, has been given to TTF-based saccharide sensors bearing boronic acid functionality. Recently, the Zhu group devised a TTF-anthracene-boronic acid triad system, in which the TTF unit was enlisted to modulate photoinduced electron transfer (PeT) to attain fluorescence-sensing function toward saccharides.[23,24] Nonetheless, boronic acid-based electrochemical sensors for saccharides using TTF as the electrochemical reporter still remain an uncharted territory awaiting further exploration.

To shed light on this issue, a molecular array involving diphenylboronic acids and a central exTTF unit was designed and tested by us as a prototypical sensor system for electrochemical recognition of saccharides. A proposed working principle for this type of electrochemical sensors is depicted in Scheme 1. Basically, the binding of boronic acid groups with the diols of saccharides under aqueous conditions is expected to alter the oxidation potential of the central exTTF donor unit. As such, it may render recognition of saccharides via certain electrochemical (e.g., potentiometric or voltammetric) means. Moreover, the incorporation of two boronic acid groups was anticipated to deliver a twofold benefit: (1) to increase the affinity for saccharides and (2) to afford enhanced selectivity to particular saccharides through chelate complexation.

We chose an anthraquinodimethane-type exTTF (TTFAQ) as the electrochemical reporter, in view of the strong electron-donating ability and redox activity of this type of molecules.[22] The synthetic step linking boronic acid groups to TTFAQ was planned to proceed

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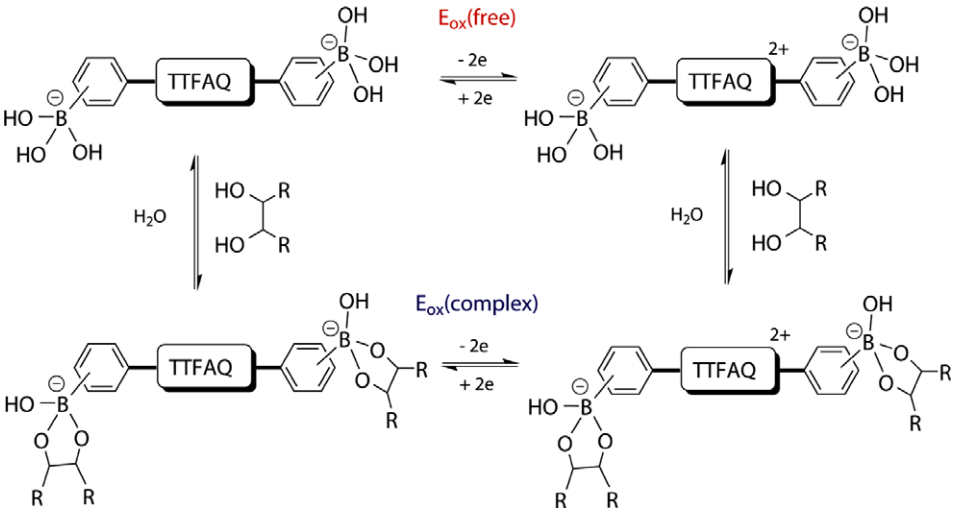



**Scheme 1.** Proposed working principle for saccharide sensing by a TTFAQ-diboronic acid triad.

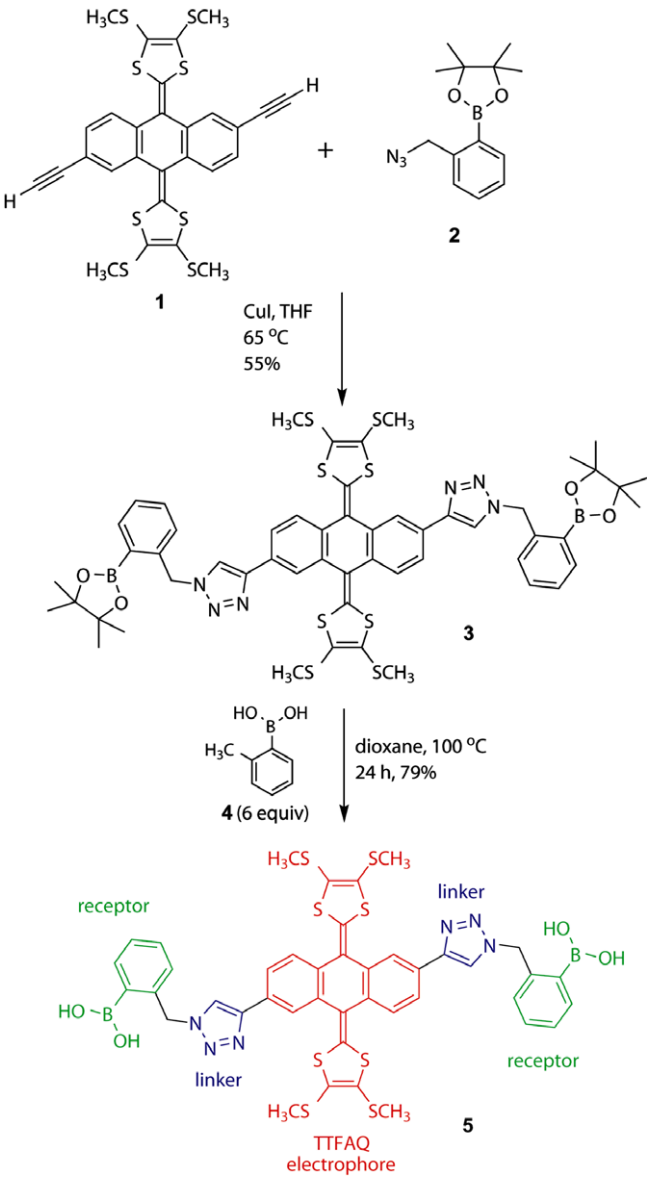
in a modular manner by using a well-documented click reaction, namely Cu-catalyzed alkyne-azide cycloaddition (CAAC) reaction.[25–28] The detailed synthetic route is shown in Scheme 2. A 2,6-dialkynylated TTFAQ building block **1**, which was previously developed by our group,[29,30] was expected to react with azido-appended pinacol boronate **2**[31] under the catalysis of CuI in THF to afford diboronate ester-functionalized TTFAQ **3**. Our initial attempts at this reaction under room temperature conditions were not successful, due to very slow reaction rate. Increasing the reaction temperature to 65 °C and the amount of CuI (0.89 M equiv relative to **1**) greatly sped up the reaction, giving compound **3** in 55% yield.[32]

Boronate ester **3** was then subjected to an ester exchange reaction with excess *o*-tolueneboronic acid (6 equiv) in dioxane at 100 °C to yield the desired product, TTFAQ-diboronic acid **5**, in 79% yield, while the byproduct pinacol *o*-tolueneboronic ester was recovered as a precursor to the starting material **2**. TTFAQ-diboronic acid **5** appears as a dark brown solid, showing good solubility in DMSO. The structure and purity of compound **5** were verified by $^1$H NMR, IR, and MS analyses.[33]

To test the sensing function of **5** toward saccharides, four different saccharide species—glucose, fructose, ribose, and rinose—were titrated, respectively, into a solution of **5** in DMSO/$H_2O$ (3:2, v/v). A buffer system (KCl 2.08 M, $KH_2PO_4$ 0.022 M, $Na_2HPO_4$ 0.022 M) was added to the solution of **5** to keep the pH at ca. 8.75 as well as to function as the electrolytes for voltammetric experiments. The binding of saccharide molecules with **5** was monitored by differential pulse (DP) voltammetry, and the detailed titration voltammograms are given in Figure 1.

The employment of DMSO/$H_2O$ (3:2, v/v) as the medium for the titration experiments was due to the poor solubility of compound **5** in $H_2O$. With the assistance of DMSO, compound **5** could be coaxed into aqueous solvents with a sufficient concentration (2.56 mM) for electrochemical analysis. The DP voltammogram of **5** (see Fig. 1A) before titration with saccharides showed rather weak current signals, likely as a result of significant viscosity and diminutive diffusion coefficient. Nonetheless, a noticeable oxidation peak is discernible at +0.62 V, which coincides with a two-electron quasi-reversible process as revealed by cyclic voltammetric analysis.[34]

Upon titration of **5** with fructose, the solution appeared to be less viscous and the current intensity increased steadily with increasing addition of fructose. Of significance in the voltammogram of **5** is the observation of a new oxidation peak that emerged at ca. +0.36 V besides the original peak at +0.62 V upon titration of




**Scheme 2.** Synthesis of diboronic acid-TTFAQ **5** via click chemistry.

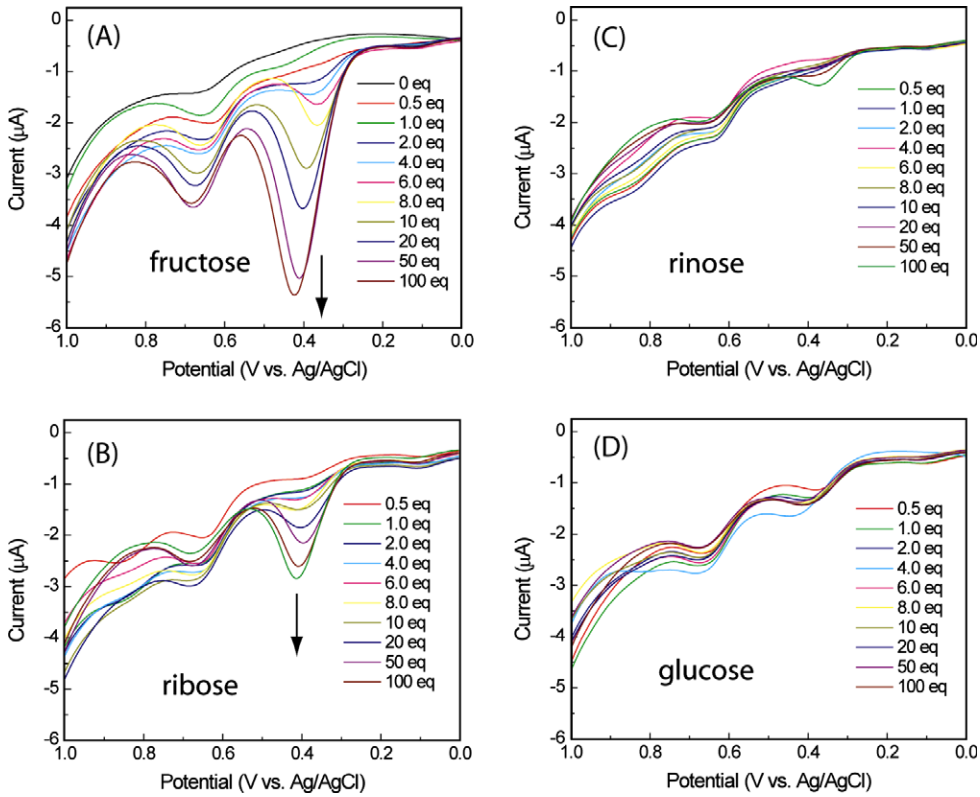



**Figure 1.** Differential pulse voltammograms of **5** (2.56 mM) obtained during titration with various saccharides at pH 8.75 in DMSO/$H_2O$ (3:2, v/v). Electrolytes: KCl (2.08 M), $KH_2PO_4$ (0.022 M), $Na_2HPO_4$ (0.022 M); Working electrode: glassy carbon; Counter: Pt wire; Reference: Ag/AgCl; Scan rate: 20 mV/s; Pulse width: 50 mV; Step: 4 mV; Pulse period: 200 ms.

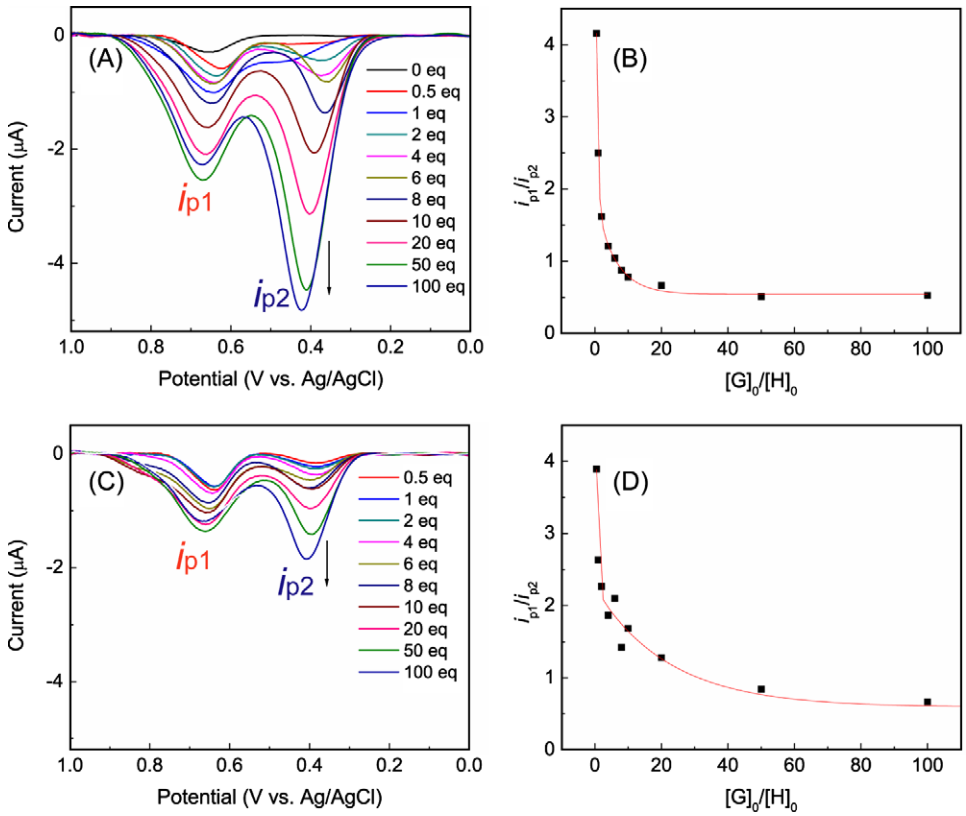



**Figure 2.** (A) Baseline-corrected differential pulse voltammograms of **5** upon titration with fructose. (B) Correlation of $i_{p1}/i_{p2}$ with $[G]_0/[H]_0$ upon titration with fructose. (C) Baseline-corrected differential pulse voltammograms of **5** upon titration with ribose. (D) Correlation of $i_{p1}/i_{p2}$ with $[G]_0/[H]_0$ upon titration with ribose. Baseline corrections in (A) and (C) were done using a non-linear curve-fitting program *Fityk* 0.90, and the data in (B) and (D) were fitted using a biexponential function.

fructose. This oxidation peak presumably arises from the complex of compound **5** with sugar. Obviously, the binding of boronic acid with sugar enhanced the electron-donating ability of the central TTFAQ core, causing an anodic shift of its oxidation potential. In a previous report by James and co-workers, a similar anodic shift was observed when a ferrocene-boronic acid sensor was complexed with sugars.[17] As the titration proceeded, the two oxidation peaks were observed to slightly drift from +0.62 to +0.68 V and from +0.36 to +0.42 V, respectively. To clearly visualize the changes of the two current peaks, the voltammograms were subjected to baseline correction, and the results are shown in Figure 2.

Of note in this figure is that, in titration of fructose from 0.5 to 20 M equiv, the ratio of the intensities of two oxidation current peaks ($i_{p1}/i_{p2}$) varied considerably in relation to the ratio of $[G]_0/[H]_0$, where $[G]_0$ refers to the initial concentration of sugar (guest) and $[H]_0$ to the initial concentration of **5** (host). When the ratio $[G]_0/[H]_0$ was further increased, the current peak ratio $i_{p1}/i_{p2}$ remained virtually constant (ca. 0.52), indicating that the titration reached saturation.

The titration experiment of **5** with ribose gives a similar pattern of DP voltammograms (see Fig. 1B); however, the degree of current variation in response to ribose titration appears to be less significant in comparison with the result of fructose (see Fig. 2C and D). This observation suggests that compound **5** has a relatively weaker affinity for ribose than fructose. The voltammograms of **5** upon titration with rinose and glucose under the same conditions showed rather insignificant changes (see Fig. 1C and D), indicating low binding affinities between compound **5** and these two saccharide species.

In summary, we have developed the modular synthesis of a boronic acid-functionalized TTFAQ derivative **5** using the Cu-catalyzed alkyne-azide cycloaddition (click) reaction as the key ligation step. Compound **5** was found to show pronounced electrochemical responses selectively toward fructose and ribose. To the best of our knowledge, this is the first example demonstrating selective saccharide-sensing function for a TTFAQ-boronic acid hybrid. Determination of the stoichiometry and exact binding constants for the complexation of **5** with various saccharides is not attainable at this stage, due to the limited solubility of **5** in aqueous media and viscosity effects. Efforts to modify the structure of **5** with water-soluble functionalities are currently under way, and it is anticipated that with improved water solubility the TTFAQ-boronic acid system may find applicability in the field of saccharide recognition and quantification.

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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.2010.02.171.

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32. *Synthesis and characterization of compound* **3**: To a 100 mL round-bottomed flask were charged compound **1** (0.18 g, 0.29 mM), **2** (0.23 g, 0.88 mM), CuI (0.05 g, 0.26 mM), and THF (60 mL). The mixture was heated to 65 °C for 24 h, and then cooled to room temperature. The solvent was removed in vacuo, and the residue was redissolved in $CH_2Cl_2$, washed by saturated brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was purified through flash column chromatography (EtOAc/hexanes, 1:4) to give compound **3** (0.18 g, 0.16 mM, 55%) as an orange solid. Mp 138–140 °C; IR (neat) 2976, 2921, 1601, 1532, 1495, 1455, 1382, 1348, 1144, 1069, 1045 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.92 (d, $J$ = 8.34 Hz, 2H), 7.81 (s, 2H, triazole-H), 7.76 (dd, $J$ = 8.02, 1.60 Hz, 2H), 7.57 (d, $J$ = 8.34 Hz, 2H), 7.45 (t, $J$ = 7.69 Hz, 2H), 7.36 (t, $J$ = 7.05 Hz, 2H), 7.29 (d, $J$ = 7.69 Hz, 2H), 5.92 (s, 4H, $CH_2$), 2.38 (s, 6H, $SCH_3$), 2.34 (s, 6H, $SCH_3$), 1.39 (s, 24H, pinacol ester $CH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 140.9, 136.7, 135.0, 134.1, 131.9, 131.6, 129.3, 129.0, 127.9, 126.5, 125.9, 125.4, 123.5, 123.3, 122.5, 120.0 (two $sp^2$ carbon signals not observed due to coincidental overlap), 84.3, 53.5, 25.0, 19.2, 19.1; HR-MALDI-TOF MS (dithranol) $m/z$ calcd for $C_{54}H_{56}B_2N_6O_4S_8$ 1130.2315, found 1130.2339.
33. *Synthesis and characterization of compound* **5**: To a 100 mL round-bottomed flask were charged compound **3** (0.27 g, 0.24 mM), phenylboronic acid **4** (0.20 g, 1.44 mM), dioxane (12 mL), and aq HCl (5 M, 4 mL). The mixture was heated at 100 °C for 24 h. After cooling to room temperature, the solvent was removed in vacuo. The residual solid was sequentially washed with EtOAc, acetonitrile, and then $Et_2O$, affording compound **5** (0.18 g, 0.19 mM, 79%) as a brown solid. Mp 230–232 °C; IR (neat) 3386 (OH), 2919, 1560, 1530, 1492, 1445, 1367, 1076; $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.59 (s, 2H), 8.05 (s, 2H), 7.83 (d, $J$ = 9.62 Hz, 2H), 7.66 (d, $J$ = 6.41 Hz, 2H), 7.63 (d, $J$ = 8.34 Hz, 2H), 7.37 (t, $J$ = 7.37 Hz, 2H), 7.31 (t, $J$ = 7.05 Hz, 2H), 7.11 (d, $J$ = 7.69 Hz, 2H), 5.87 (s, 4H, $CH_2$), 2.42 (s, 6H, $SCH_3$), 2.37 (s, 6H, $SCH_3$) ($B(OH)_2$ signal not observed due to rapid proton exchange); HR-MALDI-TOF MS (dithranol) $m/z$ calcd for $C_{42}H_{36}B_2N_6O_4S_8$ 966.0750, found 966.0751.
34. A quasi-reversible redox wave pair was observed at $E_{1/2}$ = +0.62 V in the cyclic voltammogram of **5** measured in DMSO. For details, see the Supplementary data.