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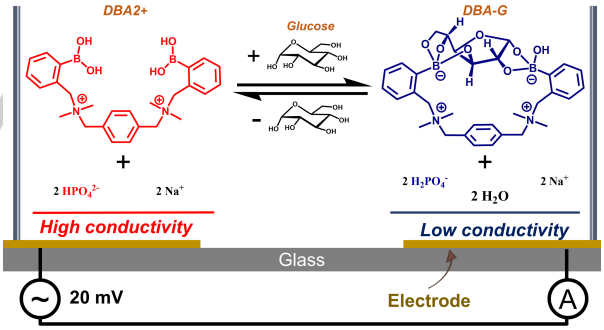
Molecular Design of a New Diboronic Acid for Electrohydrodynamic Monitoring of Glucose

Bing Wang,[a] Kuang-Hua Chou,[b] Bridget N. Queenan, [b,c] Sumita Pennathur *[b] and Guillermo C. Bazan* [a]

Abstract: A new dicationic diboronic acid structure, DBA2+, was designed to exhibit good affinity (K_d ≈ 1 mM) and selectivity toward glucose. Glucose binding changes the *pKa* of DBA2+ from 9.4 to 6.3, enabling opportunities for detection at physiological pH. Proton release from DBA2+ is firmly relative to glucose concentrations within the physiologically relevant range (0-30 mM), as verified by conductimetric monitoring. Neglectable interference from other sugars (e.g. maltose, fructose, sucrose, lactose, and galactose) was observed. These results demonstrate the potential of DBA2+ for selective, quantitative glucose sensing. The overall nonenzymatic strategy based on electrohydrohynamic effects may enable the development of stable, accurate and continuous glucose monitoring platforms.

Dysfunction of feedback regulations responsible for controlling glucose levels generally cause diabetes, leading to serious complications such as heart disease, kidney failure, and blindness.[1] Continuous glucose monitors (CGMs) are a class of on-body devices which track glucose levels. If the CGM provides stable, quantitative, real-time glucose measurements, it can be integrated with insulin-delivery systems to automate closed-loop control of glucose. Most commercially available CGMs employ enzymatic electrochemical glucose-sensing strategies. Due to enzyme instability and drift, these devices therefore suffer from delayed startup times (> two hours), short lifetimes (< two weeks) and the need for frequent calibration.[2] Non-enzymatic catalytic electrochemical sensors are a promising alternative, but traditionally have been challenged by selectivity and changes in electrode performance.[3] To develop a non-enzymatic and non-electrochemical glucose-sensing platform, we explored the molecular design of synthetic glucose-recognition moieties based on boronic acid (BA).[4]

BAs can form reversible covalent linkages to 1,2- and 1,3-diols, and in particular those present in sugars. In the process of binding diols, BAs become considerably more acidic, with *pKa* decreases of 2-4 units. The binding-induced change in BA acidity can induce changes in solution pH, electrostatic interactions and surface charge. These properties may ultimately be useful for optical, conductimetric, and field-effect transistor-based glucose sensing.[4a,4c,5] Mono boronic acids bind glucose, but also other sugars, especially fructose, galactose and ribose, which are considered interferents in practical glucose-detection platforms. Two strategies have evolved to confront this challenge: i) using glucose as a linker to change the aggregation of BA-functionalized hydrogels or fluorophores;[6] ii) the development of diboronic acids (DBAs) with molecular architectures that are more selective toward glucose.[7] Indeed, DBAs have now contributed to the first non-enzymatic commercial CGM.[7b,7c,8] However, DBAs have been primarily studied within the context of optical sensing of glucose, while the changes in *pKa* that take place upon glucose binding remain to be fully harnessed. It is therefore an opportune time to examine the design of DBA structures that open up different alternate detection strategies, while meeting requirements at physiological conditions. [7f,9]



Scheme 1. Schematic illustration of the binding of DBA2+ to glucose in PBS buffer solution and the anticipated changes to solution conductivity due to the difference in the composition of ions.

In this contribution, we report on a new DBA structure (DBA2+, see Scheme 1) that combines appropriate affinity toward and changes in *pKa* upon glucose binding. This combination of properties enables integration into a simple glucose-sensing assay based on solution conductivity, see Scheme 1. That DBA2+ contains two BAs at a relatively restricted distance was anticipated to provide the basis for glucose selectivity. Glucose binding causes DBA2+ to lower its *pKa* from 9.4 to 6.3, thus causing deprotonation at physiological pH. In phosphate buffer, released protons are neutralized by HPO_4^{2-}. Therefore, glucose mediates the conversion of DBA2+ and HPO_4^{2-} (higher ionic conductivity, left, red) to DBA2+/glucose complex (DBA-G) and $H_2PO_4^-$ (lower ionic

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conductivity, right, blue). The glucose sensing strategy is thus built around the reduction of *pKa* provided by the molecular structure DBA2+.

Successful operation of the assay in Scheme 1 requires DBA2+ to exhibit good solubility, high selectivity to glucose and a change of *pKa* upon glucose binding in an aqueous medium at pH = 7.4. Examination of the literature revealed the summary of typical DBA structures and properties summarized in Figure S1 and Table S1, respectively.[7b,7e-g] Our rationale for designing DBA2+ based on this previous body of work is provided in the Supporting Information.[10] Figure 1 shows the remarkably simple synthesis of DBA2+. Briefly, 1,4-dibromomethyl benzene was reacted with dimethyl amine in tetrahydrofuran; a subsequent reaction with 2-bromomethylphenyl boronic acid yields the target DBA2+ with bromide counter anions (DBA2+Br).

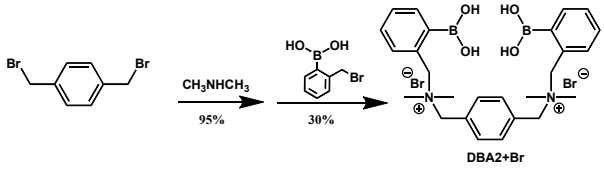

Figure 1. Synthesis route to DBA2+Br.

We first determined the *pKa* of DBA2+ before and after glucose binding. To do so, we took advantage of differences in absorption spectra upon formation of tetrahedral borate anion in high pH media.[11] Specifically, 1 mM DBA2+Br was dissolved with or without 200 mM glucose in a series of 50 mM buffers of pH 4 to 11.5. Absorbance at 280 nm was measured and *pKa* values were determined by curve fitting the changes in absorbance as a function of pH (Figure 2A). DBA2+ exhibits a *pKa* value of 9.4. In the presence of 200 mM glucose, conditions that provide DBA-G, one observes a shift in the plot, from which one derives a *pKa* value of 6.3. Importantly, the ~3 unit change in *pKa* for DBA2+ and DBA-G centers around pH = 7.4. These conditions were anticipated to provide the basis for the response toward glucose under physiologically relevant conditions.

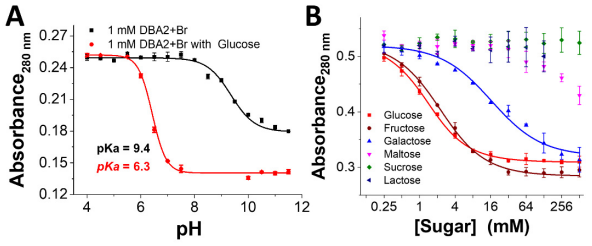

Figure 2. Chemical properties of DBA2+. (A) Glucose-dependent *pKa* of DBA2+ by measuring absorbance at 280 nm and fitting the curve as a function of pH. Absorbance of 100 µL of 1 mM DBA2+Br as a function of pH in buffer in the absence (black) or presence (red) of 200 mM glucose with calculated *pKa* indicated. (B) Absorbance of 200 µL of 1 mM DBA2+Br at 280 nm in 50 mM phosphate buffer at pH 7.4 in the presence of various concentrations of glucose and other sugars as indicated. Dissociation constants were determined by fitting curves as a function of [sugar].

We next determined the affinity and selectivity of DBA2+ to glucose compared to other sugars (fructose, galactose, maltose, sucrose and lactose) by measuring changes in UV-vis absorption at 280 nm with increasing sugar concentration Absorbance values of 1 mM DBA2+Br were measured in phosphate buffer (50 mM, pH = 7.4) containing various sugar species ([sugar] = 0 to 512 mM). The disassociation constant (K_d) of DBA2+ was calculated through non-linear curve fitting according to previous work (see Supporting Information for details).[12] The K_d value for glucose was found to be 0.9±0.1 mM (Figure 2B, red). K_d values for fructose and galactose were determined to be 1.7 mM and 16 mM, respectively (Figure 2B, brown and blue). The K_d values for maltose, sucrose and lactose could not be determined due to their low affinity towards DBA2+. DBA2+ therefore shows selectivity to glucose and fructose relative to other saccharides. Importantly, the maximum physiological or therapeutic plasma concentrations of fructose (0.13 mM) and galactose (0.28 mM) are well below those for glucose (normal range: 4-8 mM, diabetic range 0-30 mM). Due to the marked difference in absolute concentrations, any influence by the presence of fructose and/or galactose on the DBA2+ based system is predicted to be negligible.[8b]

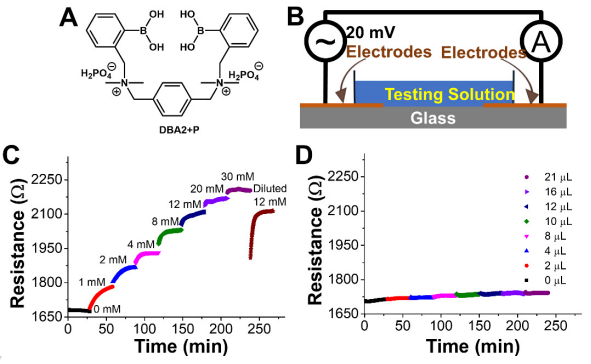

Figure 3. Measuring glucose concentration via monitoring solution resistance. (A) Structure of DBA2+P through anion exchange. (B) Schematic device architecture for impedance spectra and time resolution monitoring at high frequency. (C-D) Solution resistance (R) of 1mL of test solution changes with continues addition of 0.5 M or 2 M glucose concentration (C) or the same volume of water for control (D). After adding glucose to 30 mM, the testing solution was diluted to 12 mM (brown in C) to confirm repeatability.

Based on its properties, we concluded that DBA2+ could potentially support a conductivity-based glucose-sensing platform using low voltage AC impedance spectroscopy, which offers the promise of long-term stability and the potential for miniaturization.[13] Impedance spectra in the 1 kHz to 1 MHz range are dominated by the sum of the mobilities of individual ionic species. The conductivity of the ion species is determined by their solution concentration and molar conductivity under the assay conditions. Based on these considerations and the glucose-dependent changes in the nature and charge of ions in the medium (Scheme 1), a conductimetric assay based on solution resistance (R) was envisioned. From a practical perspective, we note that the accuracy of this approach is dependent on the influence of CO_2. CO_2 in solution may form

carbonic acid, which would decrease the pH and the background conductance.[13] It is critical to select a buffer that maintains pH and does not generate a large background conductance. For this purpose, we chose mM levels of $H_2PO_4^-$/HPO_4^{2-} (see Experimental Section for additional considerations).

To decrease background conductivity from spectator ions, the Br^- anions in DBA2+Br were replaced with $H_2PO_4^-$ through anion exchange, yielding DBA2+P (Figure 3A). A schematic of the device architecture for monitoring *R* is provided in Figure 3B. Changes in *R* of the initial solution (2 mM DBA2+P and 2.5 mM Na_3PO_4, pH = 7.6) as a function of glucose levels were tested. Typically, 1 mL of testing solution was included in the reservoir. The impedance vs. frequency response was monitored at 20 mV at frequency of 1×10^5 Hz. These conditions minimize contributions from capacitance and reactance, relative to the resistance (*R*) (Figure S2).

Using this strategy, changes in *R* of the solution over time as a function of glucose were measured (Figure 3C). Glucose solutions were added every 30 minutes with concentrations spanning the diabetes-relevant range, (i.e. [glucose] = 0-30 mM). An increase in solution resistance after each glucose addition over the full range of glucose concentrations was observed. In contrast, a control study that used water instead of glucose solution showed a much narrower range of *R* values (Figure 3D). Any non-specific effect by glucose on solutions *R* was evaluated in a DBA2+ free buffer.[14] These experiments show R changes on the order of 1-2% for up to [glucose] = 30 mM (Figure S3). After the addition of the maximum glucose concentration 1.5 mL of fresh testing solution was added to dilute the glucose concentration from 30 mM to 12 mM, and 1 mL of the mixture was left in the reservoir for continued test. After equilibration, the *R* value reaches almost the same value (*R* = 2115 Ω) as the previous test for 12 mM (*R* = 2109 Ω), which is shown in Figure 3C. This result demonstrates a reversible and repeatable response to glucose.

Table 1. Effect of Interfering Sugars on Performance of Conductimetric Sensor. Each interfering sugar at > 2.5x its MPC in the presence of physiological concentrations of glucose (5 mM) or pathophysiological concentrations of glucose (20 mM) experienced in diabetes.

Interfering Sugar	Max plasma [sugar] (mM)	Interference [sugar] (mM)	[Glucose] (mM)	Resistance increase (%)[a]
Fructose	0.133	1	5	2.9
			20	-0.3
Galactose	0.28	1	5	1.4
			20	0.6
Maltose	3.5	10	5	0.4
			20	1.6
Lactose	0.015	1	5	0.2
			20	1.6

[a] Resistance increase is based on the resistance value of testing solution with 5 mM Glucose or 20 mM glucose.

To assess reproducibility of the approach, quadruplicate measurements of *R* and conductance (σ) were carried out at room temperature. Examination of the plots of percentage change (*R* or σ) vs. [glucose] (Figure 4A) reveals good agreement between measurements, suggesting the accuracy and stability of the glucose sensing platform. It is highly likely that some of the statistical variations arise from changes in either solution volume or solution temperature (1-2% total conductance change per °C). These errors can be minimalized with membranes for glucose diffusion and temperature monitoring, among other strategies.

Lastly, we examined possible interference effects from other sugars, see Table 1. Tests were performed at two different glucose concentrations, 5 mM and 20 mM, in 1 mL of testing solution. In these tests, interferent concentrations were higher or equal to three times the maximum plasma concentration (MPC). To the testing solution containing glucose, 2 µL or 5 µL of interference solutions were added and the *R* was monitored. The interference by 1 mM fructose or galactose was tested due to the considerable high affinity compared to the other three disaccharides. As shown in Figure 4B, the addition of galactose had a negligible effect on solution resistance. The addition of fructose caused a 3% increase in resistance under low glucose (5 mM) conditions and only a transient increase under high glucose (20 mM) conditions. Maltose and lactose, which have been shown to influence other DBA-based assays, were also tested.[8b] Under our conditions, 10 mM maltose and 1 mM lactose show no significant change to *R*.

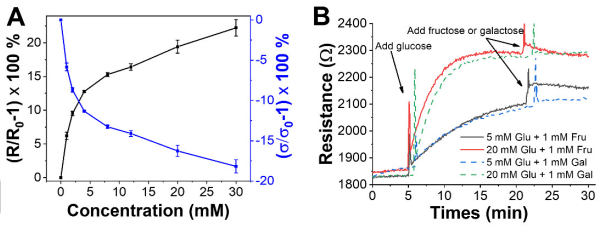

Figure 4. Robustness of glucose-sensing strategy. (A) Changes in solution resistance (*R*, left, black) or conductance (δ, right, blue) as a function of glucose concentration (n = 4 independent experiments at RT). Values are expressed as a percentage, normalized to the initial resistance (R_0) and conductance (δ_0) of the testing solution. (B) Changes in *R* upon addition of low (5 mM) or high (20 mM) glucose solutions (Glu), followed by addition of 1 mM fructose (Fru, solid lines) or galactose (Gal, dotted lines)

In conclusion, we report the design of DBA2+ for nonenzymatic and non-optical conductimetric determination of glucose concentrations. Despite a simple molecular structure, DBA2+ achieved relevant target properties, namely: 1) good affinity and selectivity to glucose; 2) ability to change *pKa* upon glucose binding at physiological pH; 3) sufficient water solubility; 4) ease of synthesis. Therefore, glucose binding to DBA2+ changes solution resistance, and monitoring of solution conductivity can be used to determine the concentration of glucose at physiological pH. Other sugars tested in this study show no substantial interference at relevant physiological concentrations. These findings suggest that DBA2+ and related

derivatives may be able to overcome (a) the lack of selectivity in synthetic small-molecule glucose-sensing methods and (b) the lack of stability in enzymatic glucose-sensing methods. The non-enzymatic, non-optical, non-electrochemical glucose-sensing strategy reported here may also ultimately be used to develop cheaper, more stable, and more quantitative CGMs for health monitoring. Surface immobilization of DBA2+ may also be envisioned to benefit ongoing approaches that require both selectivity to glucose and charge changing ability at physiological condition.[15]

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Keywords: • biosensors• diboronic acid • glucose monitoring • non-enzymatic •synthesis design

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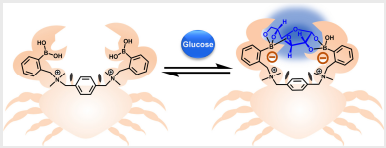

New diboronic acid, DBA2+, was prepared, which shows good affinity, selectivity toward glucose and changeable *pKa* centered physiological pH upon binding. DBA2+ realized non-enzymatic, conductimetric monitoring of glucose within diabetic range. With neglectable interference from other sugars, DBA2+ was demonstrated with the potential for selective, quantitative continuous glucose sensing.

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