Novel Chemical Sensors Based on Boronic Acids for Glucose Detection

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Overview

• Background

• Project Aim

• Boronic Acids (BAs) for Sugar Recognition

• Direct Sensing in Solution

• Indirect Sensing
  • In Solution
  • In Ionogels

• Conclusions

• Future Work
Importance of Saccharide Sensing

- Disease: Diabetes and the consequential side effects
  - Stroke
  - Excessive Thirst
  - Blindness
  - Heart Attack
  - Kidney Damage
  - Difficultly Passing Urine
  - Weight Gain
  - Foot Ulcers
  - Peripheral Nerve Damage

- Monitoring glucose levels to prolong life expectancy
- Currently no non-invasive, continuous monitoring systems available
- Demonstrates a need for real-time, non-invasive monitoring

Current Monitoring Methods

Implanted Wearable Devices

Advantages:
• Real-time monitoring
• Continuous
• Coupled to insulin pump
• Elimates injections via syringe

Disadvantages:
• Invasive

Finger Pricking Method

Advantages:
• Minimally Invasive

Disadvantages:
• Not continuous
• Insulin injections required
• Miss episodes of hyper- and hypoglycaemia

https://www.accu-chek.co.uk/gb/products/
Electrochemical sensor in a wearable platform

Battery Powered

Interference from Electroactive Species in Ocular fluid

Use of Enzymes

Realistically....Not a Real Working Device

- Attached to a BASi Epsilon- EC Potentiostat +400 mV
- Sensing platform proposes glucose monitoring between 0.5-50 mM
- Ocular glucose range is 0.05-0.5 mM and up to 5 mM in diabetics
- Major shortcomings to meet immediate expectations

Project Aim
Boronic Acids (BAs) and Sugars

\[
\begin{align*}
\text{OH} & \quad \text{B}^- \quad \text{OH} \\
\text{R} & \quad \text{OH} \quad \text{OH} \\
\text{R} & \quad \text{OH} \quad \text{OH} \\
\text{R} & \quad \text{OH} \quad \text{OH} \\
\end{align*}
\]

\[\text{OH}^- \quad \text{pK}_a \, 9 \quad \text{OH}^- \quad \text{pK}_a \, 6 \]

\[
\begin{align*}
\text{OH} & \quad \text{OH} \quad = \text{Diol/Sugar}
\end{align*}
\]
Direct vs. Indirect Sensing

Direct Sensing

Indirect Sensing

Fluorescence Decrease

Fluorescence Increase

**Fluorophore**
Direct Sensing
(i) Addition of OH⁻ ions/glucose
(ii) Addition of water/removal of glucose
Successful synthesis of novel BA sensors were confirmed by NMR.

\[(i) \text{ Anhydrous dimethylformamide, } N_2, 80 \, ^\circ\text{C for 48h.}\]
Fluorescence Results

**Excitation and emission spectrum of m-COOHBA**
0.5 mM in pH 7.4 phosphate buffer.

**Excitation and emission spectrum of o-COOHBA**
0.5 mM in pH 7.4 phosphate buffer.
Glucose response for m-COOHBA and o-COOHBA (0.5 mM) in different pH buffer solutions ranging from pH 5-11.

α-D-Glucose binding to the BA derivatives forming 1,2-cis-boronic acid esters
Indirect Sensing
Two-Component Sensing

\[
\begin{align*}
\text{HO} & \quad \text{B} \\
\text{OH} & \quad \text{HO}
\end{align*}
\]
Indirect Sensing in Solution
Indirect Sensing in Solution – Sensor Synthesis

(i) \(PdCl_2(PPh_3)_2\), Cul, diethylamine, Ar, stirred at RT for 24h (66%).

(ii) anhydrous tetrahydrofuran, \(N_2\), reflux at 80 °C for 48h (21%).

Successful product formation confirmed by NMR.
Two-Component Sensing

Non-Fluorescent

Fluorescent
Two-Component Sensing in Solution – Fluorescence Quenching

Excitation and emission spectra of 4 μM 7HC in pH 8.12 buffer solution with increasing DBA1 concentrations up to 0.5 mM (125 eq.); Medium sensitivity; 2.5 nm bandwidth

Fluorescence OFF

\[ y = -11.125x + 5796.4 \]
\[ R^2 = 0.94975 \]
Two-Component Sensing in Solution – Fluorescence Recovery

Excitation and emission spectra of 7HC (4 μM) and DBA1 (700 μM) (1:175 eq.) in pH 8.12 buffer solution with increasing concentrations of glucose up to 5 mM; Medium sensitivity; 2.5 nm bandwidth
Two-Component Sensing in Solution – Fluorescence Quenching

Excitation and emission spectra of 4 μM 7HC in pH 7.4 with minimal MeOH (40 μL) with increasing DBA2 concentrations up to 0.3 mM (75 eq.); Medium sensitivity; 2.5 nm bandwidth

λ_{ex} = 328 nm

λ_{ex} = 366 nm

Fluorescence OFF

γ = -28.819x + 2924.2

R² = 0.97729
Two-Component Sensing in Solution – Fluorescence Quenching

Excitation and emission spectra of 4 μM 7HC in pH 7.4:MeOH (1:1) (pH 8.6) with increasing DBA2 concentrations up to 1.2 mM (300 eq.); Medium sensitivity; 2.5 nm bandwidth

Fluorescence OFF
Two-Component Sensing in Solution – Fluorescence Recovery

Excitation and emission spectra of 7HC (4 μM) and DBA2 (80 μM) (1:20 eq.) in pH 7.4:MeOH (1:1) (pH 8.6) with increasing concentrations of glucose up to 100 mM; Medium sensitivity; 2.5 nm bandwidth

Fluorescence ON
Indirect Sensing in Ionogels
Two-Component Sensing in Ionogel 1

Non-Fluorescent

Fluorescent
Two-Component Sensing in Ionogel 1

Excitation and emission spectrum of Ionogel 1 in pH 7.4 phosphate buffer solution.

Emission spectrum of Ionogel 1, when immersed in a BA (10 mM) solution (blue) over 12h and then in a glucose solution (10 mM) (yellow) over 12h.
Two-Component Sensing in Ionogel 1

Emission spectrum of Ionogel 1, when immersed in a BA solution (10 mM) over 4h.

Emission spectrum of Ionogel 1 when immersed in a glucose solution (44 mM) over 4h.
Two-Component Sensing in Ionogel 2
Fluorophore and BA immobilised inside non-fluorescent ionogel matrix

Emission spectrum of Ionogel 2, when immersed in a glucose solution (100 mM) over 4h.

Fluorescence quenching of Ionogel 2, when immersed in a glucose solution (100 mM) over 4h.
Direct Sensing

• Increased glucose concentrations causes fluorescence quenching in BA.
• -COOH substituent is desired for future anchoring possibilities.

Indirect Sensing

\textit{In Solution}

• Cationic BA derivative quenches fluorescence of anionic fluorophore and on glucose addition fluorescence can be restored.
• Two-Component Sensing depends on the pK\textsubscript{a} of the fluorophore and hence, the pH of the buffer solution.

\textit{In Ionogel 1}

• Both fluorescein and BA are electrostatically immobilised: fluorescence decreases on BA addition and is restored on glucose addition.
• EWGs attached to BA play a role in the quenching efficiency.

\textit{In Ionogel 2}

• Quenched fluorescence by 44\%, with increased concentrations of glucose (100 mM)
Future Work

Direct Sensing

- Immobilisation of the COOHBA sensors on to a lens-like platform.

Indirect Sensing

- The incorporation of the two component sensing ionogels in to a sensing platform, such as a hydrogel patch or contact lens, to allow for non-invasive and continuous monitoring of glucose levels in diabetic patients.
Other Presentations from the D. Diamond Group….

POSTER

Aishling Dunne

“Bipedal Hydrogels Walking in the Light”

ORAL PRESENTATION

Wayne Francis

“Droplets with Life-like Behaviour”
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Thank You for Your Attention!