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Potentiometric detection of glucose based on oligomerization with a diboronic acid using polycation as an indicator†

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A novel potentiometric sensor for D-glucose (Glu) using 4,4'-biphenyldiboronic acid as a receptor and polyion (poly-*N*-(3-aminopropyl) methacrylamide, PAPMA) as an indicator is described. The diboronic acid condenses with Glu via its two *cis*-diol units to form cyclic or linear oligomeric polyanions which can interact electrostatically with PAPMA, thus efficiently decreasing its potentiometric response on a polycation-sensitive membrane electrode. Although D-fructose (Fru), D-galactose (Gal) and D-mannose (Man) show even higher binding affinities to the diboronic acid as compared to Glu, these monosaccharides with only one *cis*-diol unit cannot oligomerize with the receptor, which efficiently excludes the interferences from the Glu's stereoisomers. The results obtained from blood sample analysis indicate that the proposed sensor is promising for detection of Glu in real-world applications.

1. Introduction

Specific target sensing is of great importance in clinical diagnostics, environmental monitoring and industrial process measurements.¹ Conventionally, the difference between the binding affinity of a receptor to a target and that to a non-target species dominates the selectivity of an affinity-dependent sensor. Highly affinitive receptors such as antibodies, aptamers, molecularly imprinted polymers, and ionophores have been

screened or synthesized as recognition elements in construction of sensors with various kinds of readout strategies.^{2–12} It is very challenging to achieve selective detection when specific receptors are unavailable, especially for those target molecules which have structurally similar stereoisomers.¹³ Therefore, developing affinity-independent methods for selective target sensing is highly desired.

D-glucose (Glu) is the most important carbohydrate in human metabolism and used as a source of energy for the body's cells.¹⁴ Diabetes and some cancers are correlated with abnormal Glu levels in human blood.^{14–16} Enzyme-based Glu monitoring systems are commercially available, in which immobilized Glu oxidase are usually employed for catalyzing the hydrolysis of Glu.^{17,18} Despite their high sensitivity, however, disadvantages such as poor long-term stability are observed for these methods, and thus considerable efforts have been made to develop new receptors for enzyme-free Glu sensors.^{14,19} Studies on alcohol-affinitive molecules show that boronic acids (BAs), which tightly and reversibly react with *cis*-diol units in aqueous media,^{20,21} can be employed for constructing binding sites for *cis*-diol containing species with high affinities. In recent years, many BA-based receptors with preferential bindings to Glu have been prepared^{22,23} and used to develop Glu sensors with various signal transductions such as UV-vis absorption,²⁴ fluorescence,²⁵ SPR (surface plasmon resonance),²⁶ and electrochemistry.²⁷ However, most of these compounds exhibit rather limited selectivities due to the high binding affinities of the BA moiety to other monosaccharides such as D-fructose (Fru), D-galactose (Gal), and D-mannose (Man).²⁸

Interestingly, Glu has a unique structure in which a pair of *cis*-diol units exist at the 1,2- and 5,6-positions, while its isomers such as Fru, Gal and Man have only one *cis*-diol unit. This property allows Glu to be analyzed selectively as a mediator for molecular assembly of BA modified species. Based on the oligomerization of a tetraphenylethene (TPE)-cored diboronic acid and the aggregation of boron-doped graphene quantum dots (GQDs) via esterification of the boronic acid groups with the two

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cis-diol units of Glu, novel optical Glu sensors have been developed.^{15,16} The luminescence from the TPE core or GQDs can be greatly boosted due to restriction of the intramolecular rotation. Although the oligomerization/aggregation sensing strategies largely improve the selectivity for Glu detection, structurally complicated probes are required and the “end-capping reactions” induced by other monosaccharides may still deteriorate the sensing selectivity.

With attractive features of portability, low cost and resistance to interferences from color and turbidity, potentiometric polymeric membrane electrodes have gained great successes in biological and environmental analyses.^{29–33} However, those membrane electrodes for highly specific Glu detection have rarely been reported, probably due to the inability of Glu to induce potential response directly and unavailability of potentiometric reporters to specially recognize Glu and transduce the target-binding events.^{34,35} Herein, based on the specific polycondensation reaction between Glu and a diboronic acid and the subsequent electrostatic interactions between the formed oligomeric anionic species and polycation poly-*N*-(3-aminopropyl)methacrylamide (PAPMA), a novel potentiometric sensor for Glu is proposed.

2. Experimental

2.1. Reagents and materials

High molecular weight poly(vinyl chloride) (PVC), 2-nitrophenyl octyl ether (*o*-NPOE), tetradodecylammonium tetrakis(4-chlorophenyl)-borate (ETH 500), and dinonylnaphthalene sulfonic acid (DNNS[−]H⁺) as a 50 wt% solution in heptane were purchased from Sigma. 4,4'-Biphenyldiboronic acid was purchased from J&K chemical. PAPMA with a molecular weight of *ca.* 3000 was purchased from Shanghai Boka Chemical. Other reagents were purchased from Sinopharm Group Co., Ltd. All chemicals were of selectophore or analytical reagent grade. Aqueous solutions were prepared with freshly deionized water (18.2 MΩ cm specific resistance) obtained with a Pall Cascada laboratory water system.

2.2. Electrode preparation and EMF measurements

Polymeric liquid membranes containing (in wt%) *o*-NPOE (48), PVC (48), the cation exchanger DNNS[−]H⁺ (3), and ETH 500 (1) were prepared by using a solvent-casting technique with tetrahydrofuran as the casting solvent. After transferring the membrane cocktail to a glass ring fixed on a glass plate and evaporation of the tetrahydrofuran overnight, a uniform polymeric liquid membrane (*ca.* 200 μm in thickness) was obtained. Disks of 5 mm in diameter were punched from the parent polymeric liquid membrane and glued to plasticized PVC tubes (o.d. 5 mm, i.d. 3 mm) to fabricate the membrane electrodes. For all the measurements, 0.12 M NaCl was used as the conditioning and inner filling solutions. Before use, all the electrodes were conditioned in 0.12 M NaCl overnight.

A rotating silver disk electrode (ATA-1B, Jiangsu Jiangfen Electroanalytical Instrument Co., Ltd., China) with a diameter of 3 mm was used as internal reference electrode as described

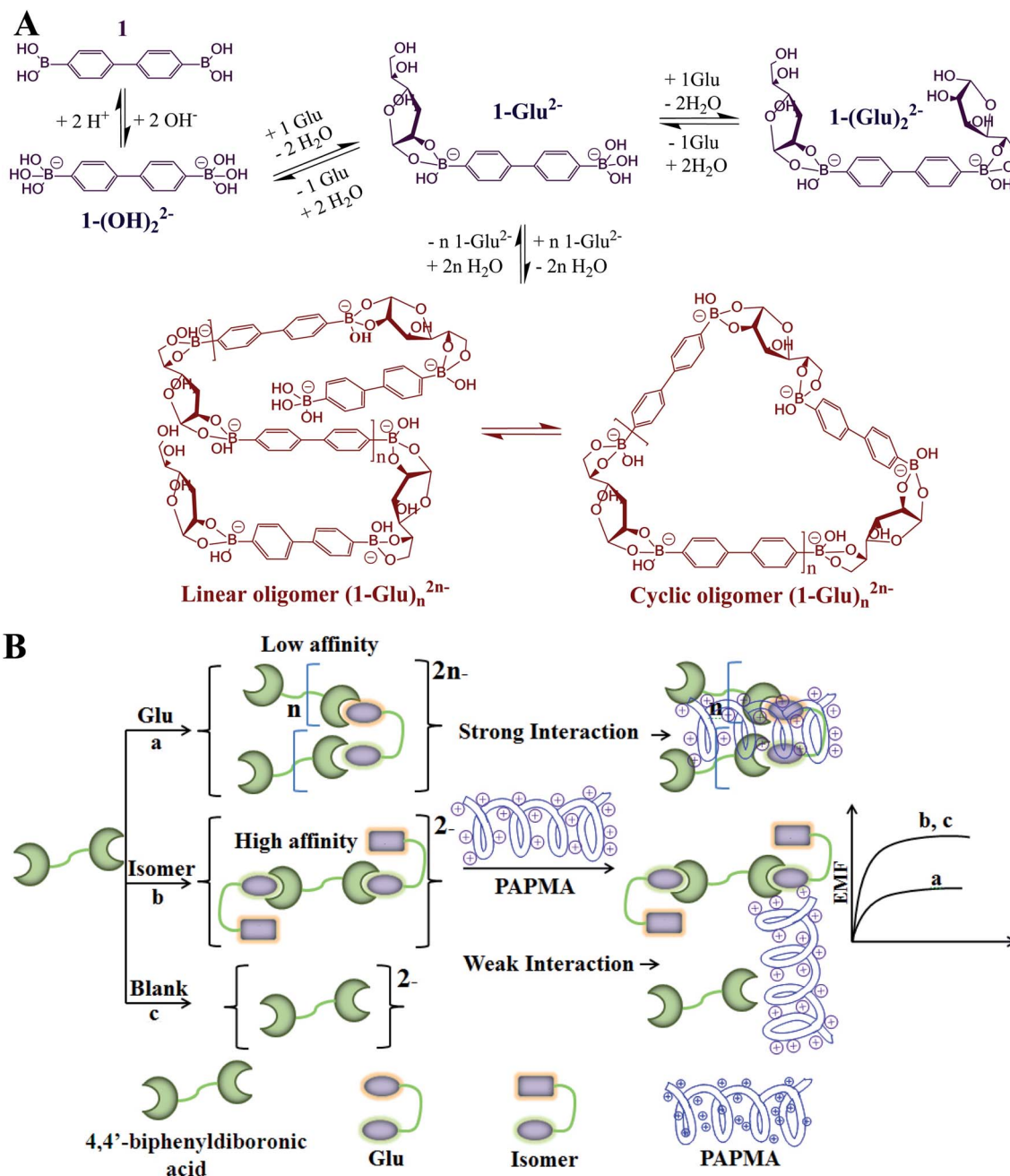
before to obtain more stable and reproducible potential responses.³⁶ All experiments were performed with a rotating mode configuration (at 3000 rpm). All electromotive force (EMF) values were measured using a Model CHI 760C electrochemical workstation (Shanghai Chenhua Apparatus Corporation, China) in a Faraday cage in the following galvanic cell: saturated calomel electrode (SCE)/0.1 M LiOAc/sample solution/sensing membrane/inner filling solution/AgCl/Ag.

2.3. Determination of Glu *via* the proposed sensor

100 μM of the diboronic acid was mixed with Glu at different concentrations in 20 mM carbonate buffer solution (pH = 10.5) containing 0.12 M NaCl with a total volume of 5.0 mL. After incubation at room temperature for 10 min, 1.0 μg mL^{−1} of PAPMA was added into the solution. The potential responses of the DNNS-doped polymeric membrane electrode were recorded. The potential difference (ΔE) between the potentials measured with and without Glu was used as the signal for Glu quantification. By plotting ΔE versus C_{Glu} , the calibration curve for Glu detection was obtained. Blood samples were taken two hours after meal from healthy volunteers. After 10-fold dilution of the blood samples with the 20 mM carbonate buffer solution, the standard addition method was employed for detection of the blood glucose levels. For comparison, the blood samples were measured in parallel by using a commercial glucose meter (Cambridge Health Care Limited, Nanjing, China). The author claimed that all experiments were performed in compliance with the relevant laws and institutional guidelines of China. The committee of Qingdao University of Science and Technology has approved all the experiments. We stated that informed consent was obtained for any experimentation with human subjects.

3. Results and discussion

The working mechanism for specific Glu detection is shown in Scheme 1. In an alkaline aqueous solution, the diboronic acid (*i.e.*, 4,4'-biphenyldiboronic acid, (1) can be ionized and transformed to 1-(OH)₂^{2−}. The presence of Glu induces the polycondensation reactions between 1-(OH)₂^{2−} and Glu, and the cyclic or linear oligomers (1-Glu)_{*n*}^{2*n*−} can be formed *via* the boronate binding with the two *cis*-diol units of Glu (Scheme 1A).^{15,16,37} In this case, the positive potential response to the polycation PAPMA of a cation exchanger doped polymeric membrane electrode can be reduced significantly owing to the strong electrostatic interactions between the produced polyanions (1-Glu)_{*n*}^{2*n*+} and PAPMA (Scheme 1B(a)). In contrast, the condensation reactions between 1-(OH)₂^{2−} and the Glu's stereoisomers with only one *cis*-diol unit in their molecular structures produce monoadducts (1-Glu^{2−}) and bisadducts (1-(Glu)₂^{2−}) as shown in Scheme 1A, but not the polyanion species. These monosaccharides would have negligible influences on the potential response of PAPMA since the singly and doubly charged anion products cannot bind PAPMA tightly (Scheme 1B(b)). As a control, the probe 1-(OH)₂^{2−} itself has a little influence on the potential response to PAPMA owing to the



Scheme 1 (A) Reaction processes of 1 and Glu, referring to ref. 15. (B) Response mechanism of the potentiometric assay.

weak electrostatic interaction between PAPMA and $1-(\text{OH})_2^{2-}$ (Scheme 1B(c)). It is clear that the incapability of hexoses with only one *cis*-diol unit to form cyclic or linear oligomers establishes the basis for specific Glu detection.

In our preliminary design, an anion exchanger (tridodecylmethylammonium chloride, TDMACl) doped membrane electrode for polyanion was employed to indicate the condensation reaction between 1 and Glu. Unfortunately, rather poor responses were observed for the produced oligomers since the high hydrophilicities of $(1-\text{Glu})_n^{2n-}$ prevent them from being extracted into the membrane phase.³⁸ Actually, protamine has been used as an indicator in our preliminary experiments

considering its significant potential response on the membrane electrode. However, the results were not satisfying owing to the fact that protamine- $(1-\text{Glu})_n^{2n-}$ complexes could actually possess an overall positive charge, and deteriorate the detection results. Based on the strong electrostatic interactions between PAPMA and the oligomer polyanions, a polycation-sensitive electrode with a cation exchanger (dinonylnaphthalene sulfonate, DNNS) doped membrane was used in this study to probe the Glu sensing events. To investigate whether PAPMA (whose monomer is *N*-(3-aminopropyl)methacrylamide with a pK_a of 9.81, calculated with ACD Labs 14.0) can induce significant potential responses under alkaline conditions which are

favorable for the condensation reaction, potential responses to $1.0 \mu\text{g mL}^{-1}$ PAPMA in carbonate buffer solutions at different pH values were tested (Fig. S1, ESI†). The results show that PAPMA can induce large potential changes in alkaline solutions at pH of 9.0–10.5.

To validate the mechanism of the potentiometric assay, potentiometric responses to $1.0 \mu\text{g mL}^{-1}$ PAPMA were recorded in the presence of the receptor and different monosaccharide (Fig. S2A, ESI†). As illustrated, the potential response to PAPMA can be reduced significantly when **1** and Glu are both involved. Those monosaccharides with one *cis*-diol group (such as Fru) show negligible influence on the potential response of PAPMA. These results indicate that the polycondensation reaction between **1** and Glu and thus the formed oligomers are crucial for the reduction in the potential response to PAPMA. Potentiometric titrations were employed to gain further insights into the sensing mechanism. As shown in Fig. S2B (ESI†), the response curve was shifted to a higher mass concentration in the presence of Glu compared to those of the blank and Fru titrations. The mass shift can be attributed to electrostatic interactions between the positively charged protonated amine groups of PAPMA and the negatively charged boronate groups of the oligomers. The quantitative stoichiometry information for the interactions between the oligomer and PAPMA may be useful for deeply understanding the response mechanism. Unfortunately, the generated oligomers do not have a defined polycondensation number n , although the condensation reaction between boronate and the *cis*-diol unit is strictly stoichiometric.

The experiments parameters including the sample pH, amounts of the indicator and receptor, and incubation time were optimized for higher sensitivity (Fig. 1). It has been shown that alkaline conditions are favorable for the borate ester formation.¹⁵ However, PAPMA may deprotonate in highly alkaline solutions as mentioned before, which may deteriorate the performance of the proposed sensor. As shown in Fig. 1A, a higher sensitivity can be obtained at pH 10.5. PAPMA is used as indicator to transduce the Glu induced oligomerization. As illustrated in Fig. 1B, the maximum potential change can be obtained when using $1.0 \mu\text{g mL}^{-1}$ PAPMA for detection of 5 mM Glu. PAPMA at lower concentrations may cause lower potential changes which is probably due to the smaller potential responses to PAPMA of the polymeric membrane electrode. However, on the other hand, PAPMA at concentrations higher than $1.0 \mu\text{g mL}^{-1}$ may become insensitive to the formed oligomers, thus reducing the potential change. The diboronic acid works as the receptor and is essential for the specific polycondensation reaction with Glu. As shown in Fig. 1C, higher voltage changes can be obtained by using the diboronic acid at concentrations ranging from 50 to 100 μM . Lower levels of the receptor could induce inefficient polycondensation reaction with Glu, while higher levels could cause the end-capping reaction preferentially forming the bisadduct $(1\text{-Glu-1})^{4-}$ over the cyclic or linear oligomers $(1\text{-Glu})_n^{2n-}$.^{15,16} Indeed, $(1\text{-Glu-1})^{4-}$ with a low valence interacts rather weakly with PAPMA as compared to the polyanion oligomers thus inducing lower potential change. 100 μM of the diboronic acid could be used

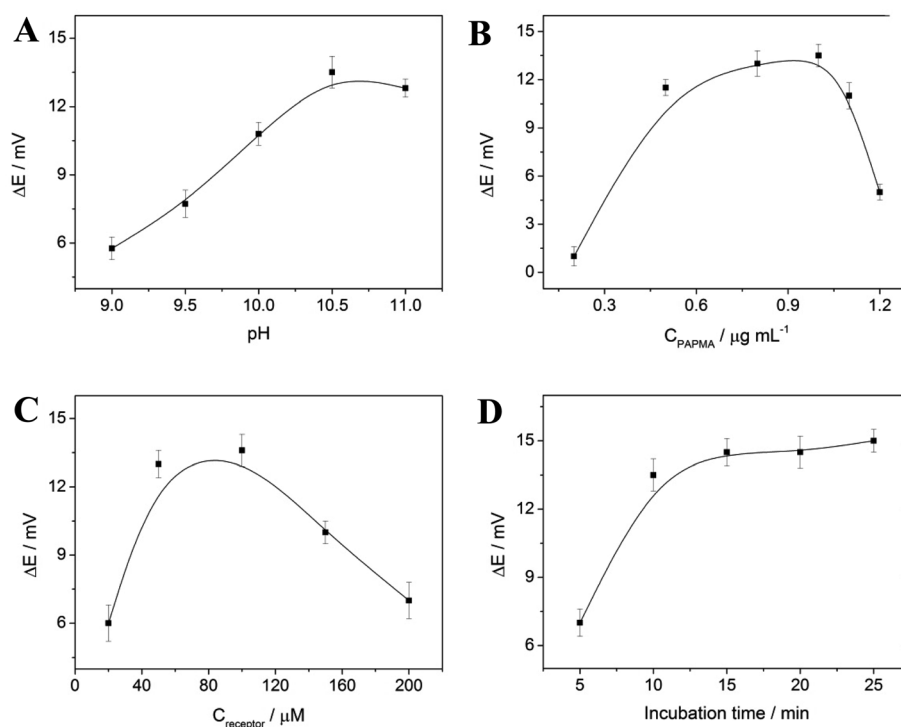


Fig. 1 Effects of the sample pH (A), concentrations of PAPMA (B) and the receptor (C), and incubation time (D) on the potential response of the DNNS-doped polymeric membrane electrode. Unless stated otherwise, experiments were performed under the following conditions: pH, 10.5; PAPMA, $1.0 \mu\text{g mL}^{-1}$; receptor, 100 μM ; incubation time, 10 min; Glu, 5 mM. The sample medium was 20 mM carbonate buffer solution containing 120 mM NaCl. Each error bar represents one standard deviation of 3 replications.

for a relatively higher sensitivity and wider linear response range (see below). Experiments also show that an incubation time of 10 min is required for high-efficiency oligomerization between the diboronic acid and Glu (Fig. 1D).

The potential responses to PAPMA in the presence of Glu at different concentrations under the optimized conditions are shown in Fig. 2. It can be seen that the potential response to PAPMA is effectively inhibited by Glu *via* the formation of the oligomer polyanions. The calibration curve for potentiometric glucose detection shown in Fig. S3 (ESI†) indicates that the voltage change is linear with the Glu concentration in the range of 0.5–13 mM with a detection limit of 0.3 mM (3σ). However, a reversal effect was observed for Glu at concentrations higher than 15 mM. As shown in Fig. S4A (ESI†), the potential change induced by Glu in the polymeric membrane response to PAPMA could be much less pronounced at a rather high Glu concentration of 20 mM. This effect may be due to the fact that high levels of Glu could induce the end-capping reaction forming the bisadduct $1-(\text{Glu})_2^{2-}$.^{15,16} As discussed above, $1-(\text{Glu})_2^{2-}$ interacts weakly with PAPMA as compared to the oligomers, and thus the potential response to PAPMA could be recovered (Fig. S4A, ESI†). Such a reversal effect was also observed for the potentiometric titrations as illustrated in Fig. S4B (ESI†). It should be noted that the dynamic response range of the proposed sensor could be shifted down to 0.2–8 mM or up to 2–18 mM by simply adjusting the amount of the receptor **1** (using 50 or 150 μM of **1**, as shown in Fig. S5, ESI†). Receptors with different affinities to *cis*-diol such as fluoro-substituted diboronic acids and benzo-boroxole can also be used for tuning the response range.³⁹

To examine the selectivity for Glu detection, the proposed sensor was challenged with non-target monosaccharides such as Fru, Gal, and Man, which have similar structures and coexist with Glu in real samples. Although C_{Glu} in human blood (3.6–

5.8 mM) is much higher than C_{Fru} , C_{Gal} , and C_{Man} (<0.1 mM), the binding affinities of these three monosaccharides to **1** should be much larger than that of Glu, considering that the association constants reported for phenylboronic acid binding with Fru, Gal, Man and Glu are 160 M^{-1} , 15 M^{-1} , 13 M^{-1} , and 4.6 M^{-1} (0.1 M PBS, pH = 7.4), respectively.^{14,15,19} As shown in Fig. 3, Fru, Gal and Man have little influence on the potential response to PAPMA when they are individually present in the sample solutions, demonstrating a high degree of specificity for the proposed sensing system. However, when Fru, Gal or Man coexists with Glu in the solution, the potential change in the PAPMA response induced by Glu would be reduced slightly, owing to the competition between these monosaccharides and Glu for binding to **1**.

The proposed potentiometric sensor is more robust compared to the previous fluorescent sensors using the oligomerization sensing strategy, since the end-capping reactions by other monosaccharides with one *cis*-diol group can still induce relatively high fluorescence interferences.¹⁶ Indeed, it was found that 0.1 mM Fru could cause *ca.* 14% reduction when measuring 5 mM Glu for the present sensor, but 60% for previous fluorescence sensor.¹⁶ These results indicate that the proposed polymeric membrane electrode works well as a Glu-specific sensor and suggest that the binding affinity is not a decisive factor in determining the sensor's selectivity. To give more detailed demonstration of selectivity, a calibration curve for potentiometric sensing of glucose in the presence of 0.1 mM Fru, 0.1 mM Gal, 0.1 mM Man, and 1.5 mM lactate is displayed in Fig. S6.† Obviously, little influence on the response curves and detection limit are observed from the background, demonstrating the superior selectivity and robust of the proposed method.

The feasibility of the proposed sensor was evaluated for detection of Glu in human blood. Previous studies show that the polycation-sensitive membrane electrodes are rather subject to the blood matrix effect. The high viscosity of blood and the

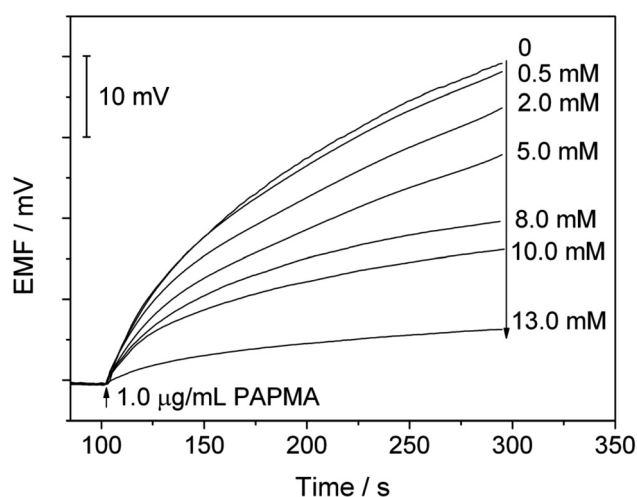


Fig. 2 Potential responses to $1.0\text{ }\mu\text{g mL}^{-1}$ PAPMA of a DNNS-doped polymeric membrane electrode in the presence of $100\text{ }\mu\text{M}$ **1** and Glu at different concentrations with an incubation time of 10 min. The sample medium was 20 mM carbonate buffer solution (pH = 10.5) containing 120 mM NaCl. See Fig. S3 in the ESI† for the calibration curve.

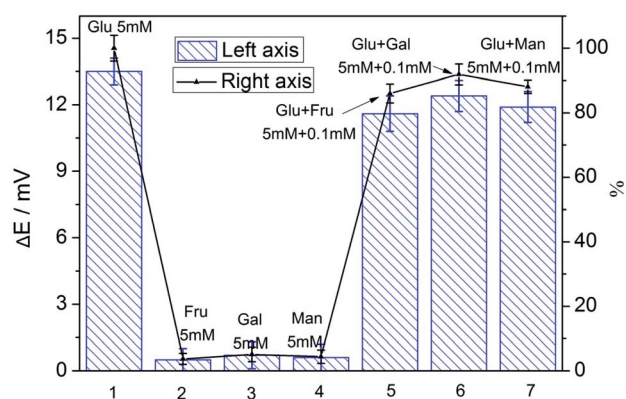


Fig. 3 Selectivity of the proposed potentiometric Glu sensor. The bar graph indicates the potential change of PAPMA in the presence of monosaccharides, while the line curve shows the ratio of potential signal obtained in the same system over that from 5 mM Glu. Each error bar represents one standard deviation of 3 replications. Inset shows the calibration curve for detection of Glu.

nonspecific adsorption of proteins on the surface of the polymeric membrane can deteriorate the potential response to PAPMA.^{40,41} To eliminate such sample matrix effect, blood samples which were taken two hours after meal from healthy volunteers were diluted by a factor of 10 with the carbonate buffer, and the standard addition method was used to detect the Glu levels. As shown in Table S1 (ESI[†]), the results obtained by the present potentiometric sensor are in good accordance with those obtained by a commercial Glu meter, thus implying that the proposed sensing strategy is promising for detection of Glu in real-world applications.

4. Conclusions

In conclusion, a Glu-specific potentiometric sensor based on a conceptually new mechanism has been developed. The poly-anionic oligomers (1-Glu)_n²ⁿ⁻ generated by the specific Glu binding event can inhibit the potential response to PAPMA of a DNNS-doped polymeric membrane *via* the electrostatic interactions between PAPMA and the oligomer polyanions. Although Fru, Gal, and Man show even higher binding affinities to the diboronic acid as compared to Glu, these monosaccharides with only one *cis*-diol unit cannot oligomerize with the receptor. This sensing mechanism efficiently excludes the interferences from monosaccharides with only one *cis*-diol unit. Compared to the enzyme-free fluorescent counterparts, the present potentiometric sensor shows a higher selectivity over the Glu's stereoisomers. Moreover, unlike the complicatedly synthesized fluorophores, the receptor used in this work is structurally simple and commercially available.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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