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A molecularly imprinted polymer-based potentiometric sensor based on covalent recognition for the determination of dopamine†

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Polymeric membrane potentiometric sensors based on molecularly imprinted polymers (MIPs) have been successfully designed for the detection of organic compounds both in ionic and neutral forms. However, most of these sensors are based on the non-covalent recognition interactions between the functional groups of the MIP in the polymeric sensing membrane and the target. These weak non-covalent interactions are unfavorable for the detection of hydrophilic organic compounds (*e.g.*, dopamine). Herein novel MIP potentiometric sensor based covalent recognition for the determination of protonated dopamine is described. Uniform-sized boronate-based MIP beads are utilized as the recognition receptors. These receptors can covalently bind with dopamine with a *cis*-diol group to form a five-membered cyclic ester and thus provide a higher affinity because of the stronger nature of the covalent bonds. It has been found that the proposed electrode shows an excellent sensitivity towards dopamine with a detection limit of 2.1 μM, which could satisfy the needs for *in vivo* analysis of dopamine in the brain of living animals. We believe that the covalent recognition MIP-based sensing strategy provides an appealing way to design MIP-based electrochemical and optical sensors with excellent sensing properties.

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Introduction

In recent years, dopamine (DA) has received considerable attention due to its effects on renal, hormonal, and cardiovascular functions and the central nervous system.[1–3] More and more evidence has shown that DA detection for early diagnosis and treatment is essential for these diseases. Therefore, various typical analytical methods have been used to detect DA, including mass spectroscopy,[4] fluorescence,[5] chemiluminescence,[6] capillary electrophoresis[7] and high-performance liquid chromatography.[8] However, these well-established approaches have obvious drawbacks of complicated instrumentation, intensive labor and time-consuming procedures. Especially, these approaches usually cannot satisfy the requirement for on-site even *in-situ* measurements of DA (*e.g.*, *in-vivo* analysis of DA in the brain of living animals).

Nowadays, the emergence of chemical sensors exhibits great potential to dramatically change this situation owing to their low cost, simple operation and suitability for on-site monitoring.[9] As generic and highly successful chemical sensors, potentiometric ion-selective electrodes (ISEs)[10–13] which allow simple, rapid and selective detection of analytes would be a promising alternative for DA detection. In particular, recent improvements in the detection limits of polymeric membrane ISEs have yielded sensors for direct measurement in the sub-nanomolar concentration range.[14] Recently, these sensors have evolved to be an attractive tool for environmental trace analysis and potentiometric biosensing.[15,16] Inspired by this, a few polymeric membrane ISEs have been explored for the detection of DA.[17–19] However, it should be noted that these potentiometric sensors usually show unsatisfactory selectivity towards DA because these sensors are based on some universal receptors such as β-cyclodextrin and the electrode-active substance, rather than specific recognition receptors.

As highly specific receptors for organic molecules, molecularly imprinted polymers (MIPs) have attracted a lot of attention because such polymers exhibit affinities and selectivities comparable to natural receptors such as antibodies and enzymes.[20–24] Especially, they are more stable, less costly and easier to produce compared to their natural counterparts. MIPs are usually synthesized in the presence of template molecules, functional monomers and crosslinkers. After the removal of the template molecules, recognition cavities are formed in the MIPs, which can provide a comparable shape and size to the template. In recent years, several potentiometric sensors based on MIPs as receptors have been developed for the determination of DA.[25,26] However, the selective recognition interactions

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between DA and the MIP receptor in the ISE sensing membrane are mainly based on the weak non-covalent interactions such as hydrogen bonding and electrostatic interaction. Especially, the DA molecules with a log *P* of 0.12 are hydrophilic. In this case, DA cannot be easily extracted from the aqueous phase to the organic sensing membrane phase, thus resulting in a relatively poor potential response.

Herein, we describe a novel polymeric membrane ISE using a MIP as the receptor based on covalent recognition for the detection of protonated DA. Compared to the non-covalent interaction, the covalent one is more stable and more stoichiometric, which can lead to a higher selectivity and fewer non-specific binding sites. The stronger nature of the covalent bonds offers the possibility to obtain a MIP receptor with superior selectivity.[27] As a proof-of-concept experiment, a boronate-affinity MIP is incorporated into a polymeric ISE membrane as the sensing element. The proposed MIP receptor is synthesized by using 4-vinylphenylboronic acid (4-VPBA) as the functional monomer. The boronate-based MIP receptor can covalently bind with DA with a *cis*-diol group to form a five-membered cyclic ester between the boronic acid groups of the MIP and the *cis*-diol group of the template.[28,29] Note that, in this work, protonated DA was used as the target because the pK_a values of DA are 8.6 and 10.5, and DA molecules mainly exist in protonated or deprotonated forms rather than neutral forms. Additionally, deprotonated DA cannot form the above-mentioned five-membered cyclic ester. Therefore, protonated DA was selected as the target. It will be shown that the potentiometric MIP sensor based on covalent recognition could provide an effective way to achieve the selective and sensitive detection of DA. The results may encourage further development of potentiometric sensing systems for *in vivo* analysis of DA.

Experimental

Reagents and materials

4-VPBA was obtained from Macklin. 2,2-Azobis-isobutyronitrile (AIBN) and ethylene glycol dimethacrylate (EGDMA) were purchased from Aladdin. High molecular weight poly(vinyl chloride) (PVC), 2-nitrophenyl octyl ether (*o*-NPOE), bis(2-ethylhexyl)sebacate (DOS), dioctyl phthalate (DOP), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB), tetradodecylammonium tetrakis(4-chlorophenyl) borate (ETH 500) and DA were purchased from Sigma-Aldrich. Acetonitrile (ACN), methanol and tetrahydrofuran (THF) were obtained from Sinopharm Chemical Reagent Co., Ltd (China). Aqueous solutions were prepared with freshly deionized water (18.2 MΩ cm specific resistance) obtained with a Pall Cascada laboratory water system. THF was distilled prior to use.

Synthesis of the DA-MIP

The synthesis process of the DA-MIP is shown in Fig. 1. DA (0.5 mmol) and 4-VPBA (1 mmol) were firstly mixed in 15 mL of an ACN-phosphate buffer solution (PBS) solvent mixture with a pH of 7.8. Then, EGDMA (2.5 mmol) and AIBN (50 mg) were added to the solution mixture. The mixture was sonicated for 20 min to maintain homogeneity. The solution was purged with nitrogen for 10 min and sealed, and then polymerized in an oil bath at 70 °C for 16 h. After polymerization, the polymer particles were added to a mixture of methanol and acetic acid of pH 2.0, and heated at 40 °C with stirring for 4 h to remove the template. The non-imprinted polymer (NIP) was synthesized by similar procedures except for the omission of the template. The obtained DA-MIP and NIP were characterized by scanning electron microscopy (SEM, JSM 5600 LV, operating at 15 kV).

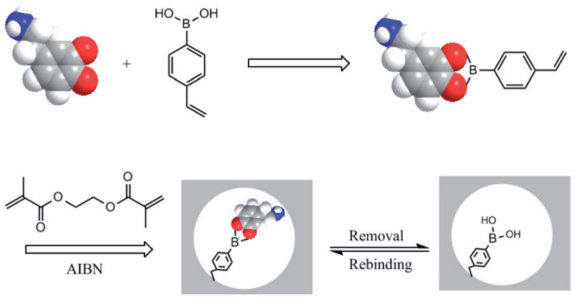

Fig. 1 Schematic illustration for the synthesis of the DA-MIP.

Fabrication of the membranes and the electrodes

The DA-MIP or NIP based-ISE membranes were prepared by dissolving 360 mg of the following components in 3 mL THF solution: DA-MIP or NIP (6.0 wt%), NaTFPB (1.0 wt%), ETH 500 (2.0 wt%), *o*-NPOE (60.7 wt%) and PVC (30.3 wt%), while the blank ISE membranes (only with borate) contained NaTFPB (1.0 wt%), ETH 500 (2.0 wt%), *o*-NPOE (64.7 wt%) and PVC (32.3 wt%). The reaction mixtures were stirred at room temperature for 2 h and transferred into a glass ring (36 mm i.d.) fixed on a glass plate. After overnight evaporation of the solvent, the membrane disks (4 mm i.d.) were cut from the membrane and glued to plasticized PVC tubes with THF/PVC slurry. 2 mM PBS of pH = 6.5 was used as the inner filling solution for each electrode. Before measurements, all the electrodes were conditioned overnight in a solution identical to the inner solution.

Electromotive force (EMF) measurements

All EMF measurements were carried out in 2 mM PBS of pH = 6.5 with stirring at room temperature using a PXSJ-216L pH meter (Leici, Shanghai, China) in a galvanic cell: saturated calomel electrode (SCE)//0.1 M LiOAC/sample solution/ISE membrane/inner filling solution/Ag, AgCl. Selectivity coefficients were determined by using Bakker's method.[30] The activity coefficient of ions, γ, was calculated from a modified Debye–Hükel equation:

$$\log \gamma = -0.511 z^2 \left[\sqrt{\mu} / \left(1 + 1.5\sqrt{\mu}\right) - 0.2\mu \right]$$

where μ is the ionic strength and z is the valence of the concerned ion.

Results and discussion

DA, an important neurotransmitter, plays a significant role in the function of the central nervous, renal and hormonal systems. In recent years, the potentiometric detection of DA has received considerable interest. Although a few potentiometric sensors using the MIPs as the receptors have been successfully developed for DA detection,[25,26] the weak non-covalent interactions, such as hydrogen bonds, dominate in the recognition of DA, which may lead to relatively poor response performance. Covalent interactions have been rarely taken advantage in the design of MIP receptors for DA recognition. Hence, in this work, a novel potentiometric sensor using a MIP based on covalent recognition of DA is described. A boronate-affinity MIP receptor which can covalently bind with DA is employed as the sensing element of the proposed sensor.

In addition, note that, in previous studies, quaternary ammonium salt (*e.g.*, tridodecylmethylammonium chloride, TDMACl)-doped polymeric sensing membranes were usually applied for the potentiometric detection of neutral phenols since undissociated neutral phenols and their derivatives can induce strong anionic potential responses on these anion-selective membranes.[31] In the present work, a NaTFPB based-cation-selective electrode is used to achieve the potentiometric determination of *cis*-diol-containing phenol, DA. The amine group of DA has a pK_a of 8.6 and is readily protonated in aqueous solution at pHs lower than 8.6. The protonated DA can thus be measured potentiometrically by the NaTFPB based-ISE.

Sensing mechanism of the proposed potentiometric sensor

The representation of the possible mechanism of the proposed sensor for the potentiometric detection of DA is illustrated in Fig. 2. At pH >5, the boronate-affinity MIP exhibits high affinity towards a *cis*-diol containing compound owing to the formation of a five or six-membered cyclic ester between the boronic acid groups of the MIP and the *cis*-diol group of the template.[28] Unlike the traditional ISEs, the MIP-based membrane electrode is conditioned in a solution of interfering ions (*e.g.*, Na^+) instead of primary ions (protonated DA). In this case, the ISE membrane is completely occupied by Na^+ and no protonated DA exists in the ISE membrane. When the electrode comes into contact with the sample solution containing protonated DA, hydrophilic DA ions can be favorably extracted from the aqueous phase into the membrane phase through the above mentioned strong covalent recognition interactions between DA and the MIP, thus causing the potential response.[32,33]

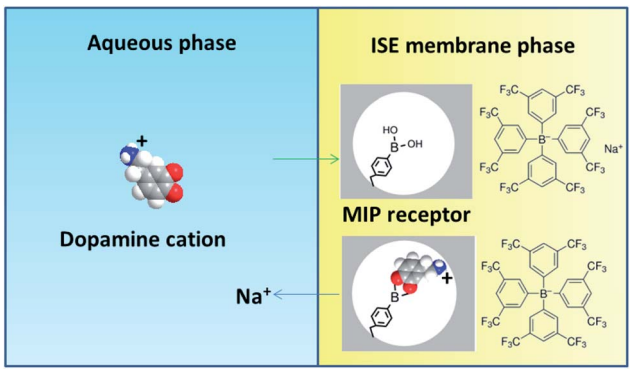

Fig. 2 Sensing mechanism of the proposed sensor based on the boronate-affinity MIP for the potentiometric detection of protonated DA.

Characterization of the DA-MIP

The surface morphology of the obtained covalent MIP was characterized by scanning electron microscopy (SEM). As shown in Fig. 3a, the MIP beads are spherical and uniform with a diameter distribution of 1–2 μm. Our previous studies have demonstrated that the uniform-sized beads could be well dispersed in the plasticized ISE membrane. In this case, more recognition sites available in the sensing membrane and lower membrane impedance could be generated.[22] Hence, it can be expected that the obtained MIP could function as well as the previous MIP receptors in the polymeric membrane. In addition, the SEM images also suggest that the NIP beads prepared with the same procedures have a similar morphological structure and particle size distribution (Fig. 3b).

Potentiometric responses of the DA-MIP-ISEs and NIP-ISEs

In order to illustrate the feasibility of using the proposed MIP as the recognition receptor for the sensitive and selective detection of DA, the responses of different polymeric membrane ISEs were firstly examined. To guarantee that DA exists in its protonated form, a PBS buffer with a pH of 6.5 was selected as the background solution. As shown in Fig. 4, the DA-MIP-ISE exhibits a larger cationic response than the NIP-based electrode. For the measurement of 10 μM DA in 2 mM PBS, the EMF change obtained by the NIP-based electrode is only less than one third of that by the electrode with the MIP beads as the sensing element. Note that, the NIP beads also have the boronic acid groups; however, the change obtained by the NIP electrode is still much smaller than that by the MIP electrode. Hence, it can be deduced that the specific interactions of the proposed sensor is not only from the formation of the covalent bonds between the boronic acid groups of the MIP and the *cis*-diol group of DA but also from the imprinting effects, such as the 3D shape matching between the well-fabricated imprinting cavities and the target molecules.

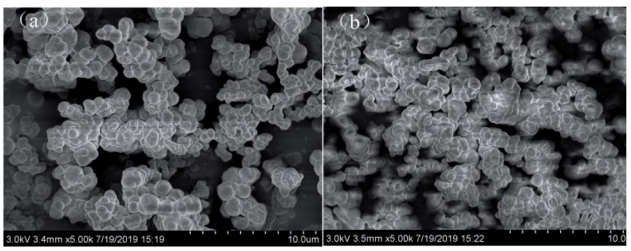

Fig. 3 SEM images of the obtained (a) DA-MIP and (b) NIP beads.

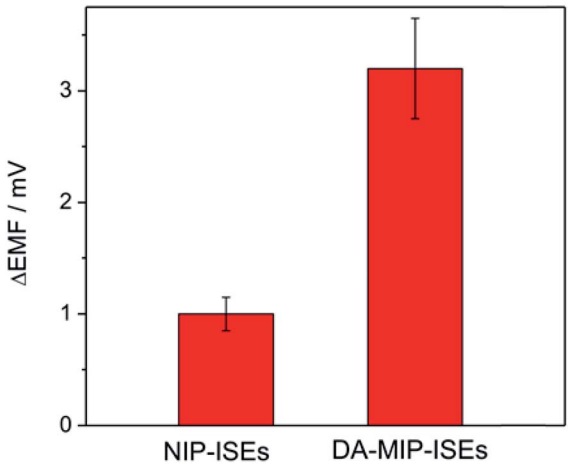

Fig. 4 Potentiometric responses of the DA-MIP-ISEs and NIP-ISEs to protonated DA at 10 μM. Each error bar represents one standard deviation for three measurements.

Optimization of the DA-MIP-ISE

In order to achieve the sensitive detection of protonated DA, experiments were further carried out to optimize the experimental parameters. It has been well established that the plasticizer influences the dielectric constant (ε_r) of the ISE membrane phase and the mobility of the ligands and their complexes, thus affecting the detection sensitivity.[34] The influence of the plasticizer on the potential response of the MIP-based ISE membrane was investigated and the results are shown in Fig. S1 in the ESI.† As can be seen, the electrode based on the polar plasticizer *o*-NPOE ($\varepsilon_r = 24.0$) exhibits larger potential responses than those based on the nonpolar plasticizers, DOP ($\varepsilon_r = 5.0$) and DOS ($\varepsilon_r = 4.8$). This is probably ascribed to the fact that DA could be favorably extracted into the membrane with the polar membrane solvent. Therefore, *o*-NPOE was chosen as the optimal membrane solvent.

Since the content of the plasticizer can affect the dispersion ability of the MIP receptors in the polymeric membrane, the effect of the plasticizer content was tested. As illustrated in Fig. S2 in the ESI,† when the weight ratio of *o*-NPOE to PVC is 1 : 1, relatively smaller cationic potential responses could be observed. By increasing the ratio to 2 : 1, larger cationic potential responses could be obtained. This improvement in the detection sensitivity could be probably due to the better dispersion of the MIP receptors in a polymeric matrix with a higher plasticizer content. However, upon further increasing the ratio to 3 : 1, no significant improvement in the detection sensitivity could be observed. In addition, a high plasticizer content may lead to the formation of a soft polymeric membrane, which is unfavorable for the construction of a liquid-contact ISE membrane.[35,36] Thus, the weight ratio of 2 : 1 was selected for the proposed electrode.

Performance of the DA-MIP-ISE

Under the optimized conditions, a calibration curve of the covalent recognition-based MIP potentiometric sensor was

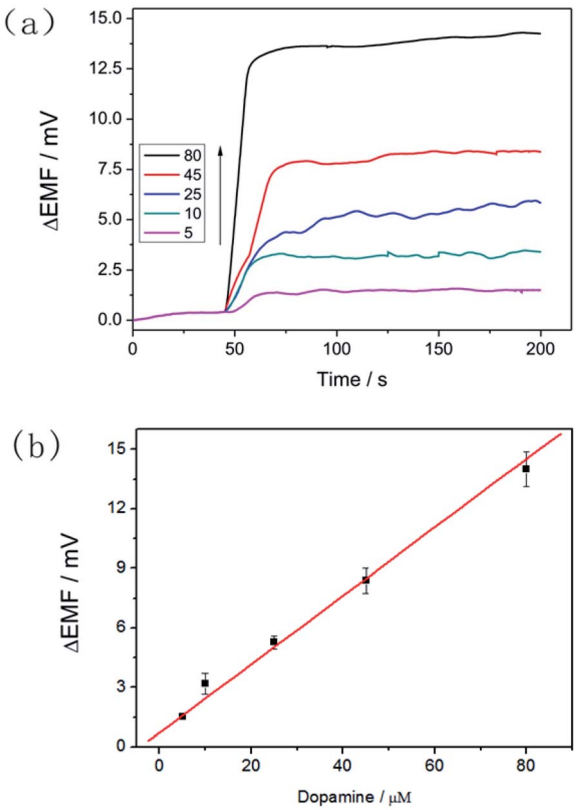

Fig. 5 (a) Typical dynamic potential responses of the DA-MIP-based membrane electrode upon additions of different concentrations of DA. (b) Corresponding calibration curve for DA detection. Experimental conditions: 2 mM PBS background with a pH of 6.5; DA-MIP-ISE membrane composition: DA-MIP (6.0 wt%), NaTFPB (1.0 wt%), ETH 500 (2.0 wt%), *o*-NPOE (60.7 wt%) and PVC (30.3 wt%).

obtained. Fig. 5a shows the typical potential response of the proposed electrode for measuring protonated DA with different concentrations of a 2 mM PBS buffer of pH 6.5. The potential difference between the baseline and the final equilibrium potential after DA addition is used for quantification. Further detailed analysis of the experimental results reveals that there is a linear dependence of the EMF change on the concentration of DA in the range of 5 to 80 μM ($R^2 = 0.996$) (Fig. 5b). In this case, a detection limit of 2.1 μM (3σ) could be obtained. Such a detection limit could allow the applications of the proposed sensor in the determination of DA in *in vivo* analysis in the brain of living animals.[37] In addition, the sensor was found to show excellent reproducibility and stability for DA detection. For 80 μM DA, the relative standard deviation (RSD%) of three electrodes is 6.2%. No significant change in the potential response was observed after being stored at 4 °C in the conditioning solution for two weeks. The reversibility of the proposed sensor was investigated. The results are shown in Fig. S3.† As illustrated, no obvious response decrease is observed after successive regeneration cycles for the proposed electrode regenerated by the 10 mM HCl solution, indicating that the proposed sensor is fully reversible.

Table 1 Potentiometric selectivity coefficients (log $K_{i,j}^{pot}$) obtained with the separate solution method for the DA-MIP-ISE

Ion J	log $K_{i,j}^{pota}$	Ion J	log $K_{i,j}^{pota}$
H^+	−2.6	Mg^{2+}	−4.1
Na^+	−2.7	Ca^{2+}	−3.4
K^+	−1.5	Aniline	−1.8

[a] Mean value obtained from three corresponding pairs of concentrations of protonate DA and the respective interfering cation in the Nernstian response range ± SD.

In order to validate its usefulness for real samples, the proposed sensor was used to analyze DA in human urine samples (Table S1†). As can be seen, the recoveries for the diluted urine samples vary from 90 to 107%, suggesting good feasibility for DA detection in real samples.

Selectivity coefficients

Bakker's method which can eliminate the influence of the inherent sensitivity limit on the ISE response toward interfering ions was used to evaluate the selectivity of the DA-MIP-ISE membrane electrode.[30] The potentiometric selectivity coefficients for protonated DA over a series of interfering cations are shown in Table 1. As can be seen, the DA-MIP-ISE shows a good selectivity to DA over other interfering inorganic cations (*e.g.*, Na^+, Mg^{2+} and Ca^{2+}) and organic cations (aniline cation). The high sensitivity and good selectivity of the proposed sensor offer promising potential for the potentiometric detection of DA in environmental and biological samples.

Conclusions

In this work, a novel potentiometric sensor for the determination of protonated DA has been demonstrated. A MIP with boronate groups which can covalently bind with DA to form a five-membered cyclic ester is employed as the sensing receptor. The response mechanism of the proposed MIP-based ISE is based on the diffusion of protonated DA cations at the membrane–sample interface. The proposed sensor based on covalent recognition could provide an effective way to achieve the sensitive and selective detection of DA. Since many covalent recognition-based MIPs have been extensively exploited in analytical chemistry, this methodology is promising to develop covalent MIP based potentiometric sensors for the measurements of various ionic species.

Author contributions

Chan Wang: conceptualization, methodology, and investigation; Longbin Qi: conceptualization, methodology, and review; Rongning Liang: conceptualization, methodology, writing-review & editing, and supervision.

Conflicts of interest

There are no conflicts to declare.

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