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# Polymeric membrane sensors with boronic acid functionalized boron dipyrromethene for selective measurement of dopamine

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ABSTRACT

Boronic acid functionalized boron dipyrromethene (BABDP) was studied as a new fluorescent probe for the detection of catechols and catecholamines. Dopamine (DA) and catechol induced a strong fluorescence quenching effect due to the photoinduced electron transfer (PET) process. In homogeneous assay, the fluorescence changes were observed in the solutions with dopamine concentration from $10^{-8}$ M to $10^{-2}$ M at pH 7.4, and the catechol induced less but still significant response. The selectivity toward dopamine was greatly improved by using hydrophobic polymer films containing BABDP and cation exchanger. Positively charged dopamine was exchanged into the membrane and interacted with BABDP to produce the signal change, while the interference from neutral catechol was eliminated. The results measured from both optical and electrochemical sensors confirmed the selective measurement of dopamine in the range of $10^{-4}$ M to $10^{-2}$ M at physiological pH.



## 1. Introduction

Dopamine (DA) is one of the naturally occurring catecholamines that are an important class of neurotransmitters [1,2]. It plays an essential role in the central nervous system, and its lack in biological fluids may lead to neurological disorders such as Parkinsonism [3]. The level of DA reflects the biodegradation efficiency of other biological molecules, such as tyrosine, therefore the measurement of dopamine is important in clinical diagnosis [4,5]. There are various methodologies having been reported for detecting DA, including fluorescence [6,7], electrochemistry [8,9], chromatography [10,11]. Electrochemical methods can detect DA as low as $6.0 \times 10^{-8}$ M in plasma, but there are ascorbic acid (AA) usually coexists with DA in physiological samples that the oxidation potentials of them are too close to be determined separately [8,9,12]. Besides, the electrode has poor selectivity and reproducibility due to the adsorption of oxidation products. The common instrumental techniques like high performance liquid chromatography (HPLC) have been widely used for the determination of DA. Such methods of detection are often complicated and very expensive [13,14]. The fluorescence methods for dopamine have recently gained much attention due to its simplicity and high sensitivity. However, the reported selectivity toward catecholamine is limited [15], therefore development of fluorescence probes for DA is of great importance.

Boronic acid is a well-known functional group for selective recognition of 1,2-diol or 1,3-diol with formation of five- or six-membered cyclic esters. Yoon and Czarnik have utilized the fluorescence probe with boronic acid to detect sugar in 1992 [16]. Since then, there have been numerous reports about fluorescent chemosensors with boronic acid group for saccharides [17,18]. However, the studies on boronic acid based sensors for dihydroxyl benzene derivatives are rarely found. Seckin et al. reported the FIA method utilizing m-dansylaminophenyl boronic acid (DAPB) to determine DA in pharmaceutical injections [6]. Wang's group reported a boronic acid appended quinoline derivative as a fluorescent probe for catechol [15]. Jun et al. reported the fluorescent receptor composed of imidazolium, pyrene and boronic acid groups for the recognition of dihydroxyphenylacetic acid [19].

Boron dipyrromethene (BODIPY) dyes are well-known to be highly fluorescent, very stable, having narrow emission bandwidths and amenable to structure modification. We recently reported the preparation of boronic acid functionalized BODIPY derivatives and their applications as saccharides sensors [20]. In this work, we studied the response of BABDP toward different dihydroxyphenyl compounds.

## 2. Experimental

### 2.1. Reagents and instrumentation

High molecular weight poly(vinyl chloride) (PVC), sodium tetrakis (4-fluorophenyl) borate dihydrate (NaTFPB), 2-nitrophenyl

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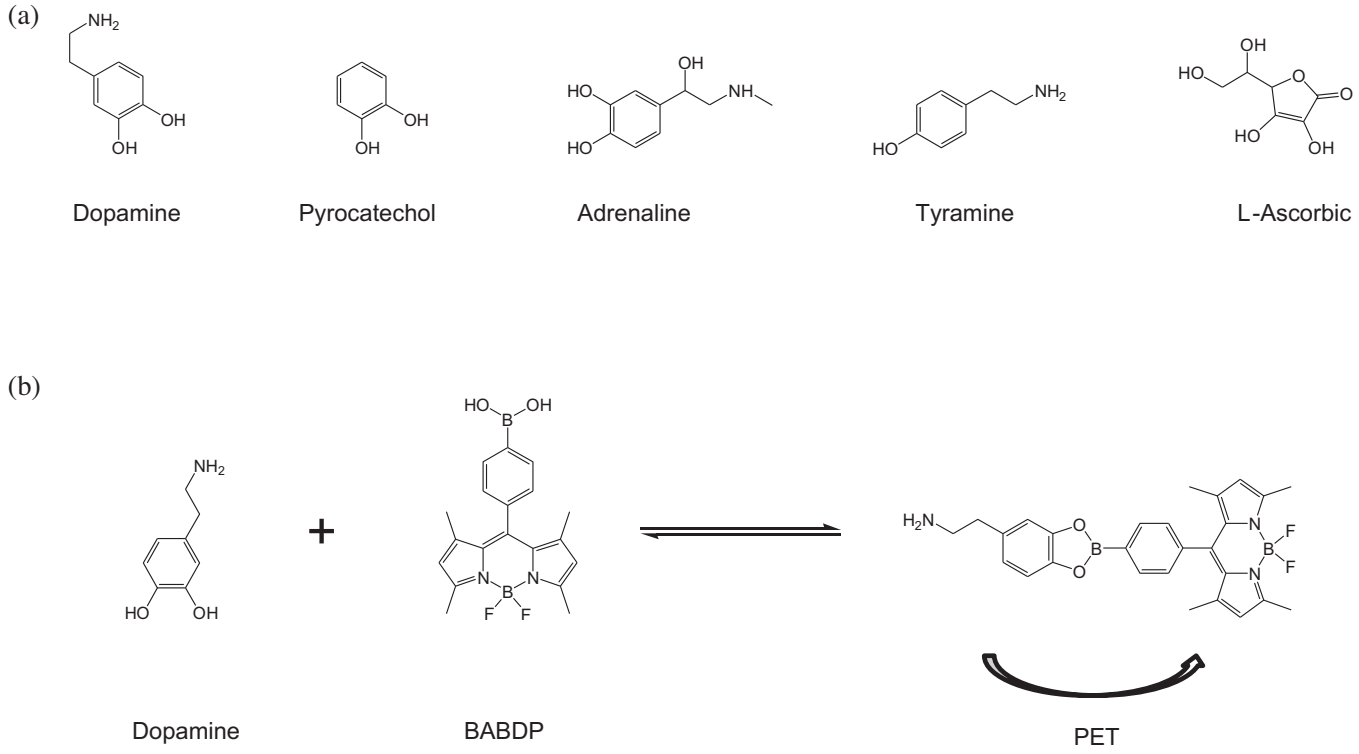


**Fig. 1.** (a) The chemical structures of dopamine, pyrocatechol, tyramine, adrenaline and ascorbic acid; (b) the quenching mechanism of BABDP after adding DA.

octyl ether (NPOE), bis(2-ethylhexyl) sebacate (DOS), and tetrahydrofuran (THF) were purchased from Fluka (Switzerland). BABDP (structure is shown in Fig. 1) was synthesized according to the literature [18].

HEPES, sodium hydroxide, dopamine hydrochloride, L-ascorbic acid were obtained from Sangon (Shanghai, China), pyrocatechol, tyramine, and adrenaline were obtained from Sigma–Aldrich (Switzerland), adrenalone hydrochloride monohydrate was obtained from Alfa Aeesar. Plasma was obtained from Nanjing clinical biological technology company. All aqueous solutions were prepared by dissolving the appropriate salts or diluting standard solutions as specified in nanopure-purified (18.2 MΩ cm) deionized water.pH 7.4 buffer was prepared with HEPES (10 mmol) adjusted with 1 M NaOH. Dopamine hydrochloride, pyrocatechol, L-ascorbic acid, tyramine, and adrenaline were dissolved in HEPES buffer solution.

A Shimadzu RF-5301PC fluorescence spectrometer and Thermo Scientific Varioskan Flash spectral scanning multimode reader were used for fluorescence measurements in homogeneous assay and membrane phase. The maximum excitation and emission wavelengths of BABDP are $\lambda_{ex}$ = 493 nm, $\lambda_{em}$ = 510 nm (excitation slit width, 3 nm; emission slit width, 1.5 nm; scanning speed, 3000 nm/min). The pH was monitored with a calibrated glass pH electrode (Sartorius PB-10).

### 2.2. Homogeneous measurements

For the pH response, DA was diluted by different pH values of phosphate buffer solutions to obtain $10^{-3}$ M DA solution, and then these solutions were used to dilute $10^{-4}$ M BABDP which was dissolved in ethanol to get the solutions with 1 μM BABDP and $10^{-3}$ M DA. Each of the solutions were transferred to the cuvettes and measured with fluorescence spectrometer.

For measuring the dopamine and other interfering species, 10 μL $10^{-4}$ M BABDP ethanol solutions mixed with 1 mL HEPES buffer solutions (pH 7.4) with different concentration of dopamine, pyrocatechol, L-ascorbic acid, tyramine or adrenaline. 200 μL of the solution was transferred into the wells of the microplate for fluorescence detection. Each concentration was measured by six identical wells.

### 2.3. Preparation and measurements of polymeric optodes

A total 100 mg of mixture containing 5 mmol/kg BABDP, 50 mmol/kg NaTFPB, PVC, and the plasticizer DOS or NPOE (1:2 by weight) was prepared and dissolved in 1 mL of THF. After complete dissolution, these cocktails were then uniformly dispensed (5 μL/well) into each U-bottomed microwell of polypropylene plate. The plates were air-dried in a dust-free vessel for at least 4 h prior to use. The film thickness was calculated to be 5 μm. All membranes inside the wells were conditioned with pH 7.4 buffer solution until the polymer film-coated wells had stable fluorescence intensity. Different concentration ($10^{-2}$ to $10^{-8}$ M) dopamine solutions were prepared by diluting the $10^{-1}$ M stock solution with pH 7.4 HEPES buffer. The 200 μL solutions were added into each well and each concentration was measured with six identical wells. The equilibrium time of the sensor is 20 min before the fluorescence measurement. In all measurements, the excitation wavelength was chosen at 450 nm and the emission wavelength was at 515 nm.

### 2.4. Preparation of potentiometric sensors and EMF measurements

For EMF measurements, the ion-selective membranes were cast by dissolving the BABDP (10 mmol/kg) and the lipophilic ion-exchanger salt NaTFPB (2 mmol/kg), together with PVC and the plasticizer DOS or NPOE (1:2 by weight) to give a total cocktail mass of 140 mg, in 1.5 mL of THF and pouring it into a glass ring (22 mm i.d.) fixed onto a glass slide with rubber bands. The solvent THF