Synthesis of Novel One-Walled \textit{meso}-Phenylboronic Acid-Functionalized Calix[4]pyrrole: A Highly Sensitive Electrochemical Sensor for Dopamine

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Cite This: ACS Omega 2022, 7, 15082−15089

ABSTRACT: Facile access to new one-walled \textit{meso}-substituted phenylboronic acid-functionalized calix[4]pyrrole (C4P) has been revealed for the first time, starting from cost-effective and easily accessible materials. The structures of both the intermediate dipyrromethane (DPM) and the targeted functionalized C4P have been confirmed by means of $^1$H-NMR, $^{13}$C-NMR, IR, and HRMS spectral data. The voltammetric investigations of the functionalized C4P films cast over a glassy carbon electrode (C4P-GCE) clearly establish the redox stability and redox accessibility of the boronic acid functional moiety present in the C4P framework. We demonstrate that the presence of the unique boronic acid functionality in the C4P endows it with an excellent potential for the highly sensitive electrochemical sensing of the neurotransmitter dopamine (DA). A linear correlation between the strength of the Faradaic signals corresponding to the electro-oxidation of DA over C4P-GCE and the concentration of DA was observed in a concentration range as wide as 0.165−2.302 μM. The C4P-GCE has revealed exceptional stability and reproducibility in the electrochemical sensing of DA, with a nanomolar level limit of detection as low as 15 nM.

INTRODUCTION

Towards the advancement of chemical, biological, industrial, environmental, pharmaceutical, and agricultural sciences, intelligent devices known as supramolecular sensory materials occupy a central place by virtue of their ability to detect diverse analytes in real-world applications.\textsuperscript{1,2} Basically, in the design of supramolecular sensors, the overarching goal is to develop selective and sensitive sensors with the ability to execute potential tasks in multiple environments.\textsuperscript{3} For the design and construction of such versatile sensors, supramolecular chemists mimic and exploit highly specific nature-oriented host−guest interactions.\textsuperscript{4} Among the various available supramolecular sensors, an appealing nonaromatic tetrapyrrolic supramolecular receptor or sensor commonly known as calix[4]pyrrole (C4P) is highly inspired by host−guest interactions.\textsuperscript{5} Within the arena of molecular recognition, C4P either in its simple form or modified at the \textit{meso}- or \textit{β}-position has great promise in ion/ion pair/neutral substrate binding, biomembrane ion transport, drug delivery, molecular switches, catalysis, and potential therapeutics in general and selective as well as sensitive ion/molecule sensing in particular.\textsuperscript{6−11} Keeping in mind the handy role of C4Ps as a selective and sensitive supramolecular sensors, researchers across the globe are putting their efforts time-to-time to design and construct diverse C4P-based architectures for the sensing of the anticipated analytes.\textsuperscript{12−17} To our best knowledge, the sensing of desired analytes utilizing C4P-based systems has been successfully accomplished mostly by virtue of optical techniques (e.g., colorimetry, UV−Vis, fluorescence, etc.). However, only limited studies have been published where the sensitive and selective sensing of charged or neutral species was carried out using electrochemical techniques.\textsuperscript{18−22} Needless to say, the electrochemical sensing of target analytes by supramolecular sensors has attracted significant interest over the past two decades, owing to its simplicity, high sensitivity, low operational cost, and rapidity.\textsuperscript{23,24} Thus, there is an urgent need to design and develop new C4P-based electrochemical sensors for the detection and discrimination of vital analytes of biological significance.

Dopamine (DA) is a chemical messenger of paramount clinical significance, as it play a decisive role in the communication of the central nervous system and thus physical, psychological and physiological health.\textsuperscript{25,26} The

Received: February 15, 2022
Accepted: April 12, 2022
Published: April 25, 2022
imbalance of DA levels in bodily fluids can lead to neurological disorders like Parkinson’s disease, Alzheimer’s disease, schizophrenia, dementia, depression, and addiction.27,28 Therefore, the very accurate, rapid, reliable, selective, and sensitive estimation of the DA concentration (in the nanomolar range) in body fluids especially brain has promising implications in clinical diagnostics.29−36 A well-known fact with a thorough literature background is that the boronic acid functional group is redox-active and has an inherent capacity to bind reversibly with diol molecules, thereby forming cyclic boronate ester linkage.37,38 Keeping this fact in mind, and taking into consideration the potential sensing applications of C4P systems, we envisioned that one meso-position of the C4P framework could be functionalized with the phenylboronic acid moiety. The so-crafted phenylboronic acid-functionalized C4P is demonstrated to exhibit potential towards the electrochemical sensing of DA, with a nanomolar-level limit of detection as low as 15 nM. Most importantly, and to our best knowledge, this is the first ever boronic acid-based C4P system that has been constructed and studied.

**RESULTS AND DISCUSSION**

Considering the relevance of boronic acid chemistry in the design and development of diverse supramolecular sensors for vital analytes, we intended to design and construct one-walled *meso*-phenylboronic acid-functionalized C4P (1) from simple and commercially available starting materials, for instance, pyrrole, 4-acetylphenylboronic acid, and acetone. The retrosynthetic approach clearly revealed the fact that the *meso*-substituted one-walled C4P (1) could be obtained from DPM (2), which in turn could be assembled from pyrrole and 4-acetylphenylboronic acid (3) (Scheme 1). Thus, with an appropriate knowledge of the retrosynthetic pathway, the phenylboronic acid-based DPM (2) was first prepared in a decent yield via a green method recently reported by our own group.11 The freshly distilled pyrrole was treated with 4-acetylphenylboronic acid utilizing a deep eutectic solvent of DMU:L-(+)-TA (7:3) (Scheme 2). The formed DPM (2) was then treated with the proper equivalents of acetone and pyrrole, undergoing acid-mediated cyclization to afford the desired one-walled *meso*-phenylboronic acid-functionalized C4P (1) in moderate yield (Scheme 2). These compounds were fully characterized by 1H-NMR, 13C-NMR, IR, and HRMS spectroscopic techniques. The 1H-NMR spectrum of C4P (1) taken in DMSO-<i>d</i><sub>6</sub> (Figure S5) displayed two broad singlets at 9.58 and 9.39 ppm that corresponded to the four pyrrolic NH-protons, whereas the peaks at 7.96 and 7.70 ppm corresponded to the four phenyl ring protons of the
phenylboronic acid subunit. The peak that appeared at 6.82 ppm was attributed to the two protons of $\text{B(OH)}_2$ functionality, and the eight $\beta$-pyrrolic CH-protons appeared at 5.81 (two protons) and 5.72–5.74 ppm (six protons). Finally, 21 aliphatic protons of the seven methyl groups present at the meso-positions appeared between 1.41 and 1.73 ppm. The peaks that appeared in the $^{13}$C-NMR (DMSO-$d_6$) spectrum of C4P (1) were 153.05, 141.29, 140.72, 139.30, 137.85, 136.12, 135.09, 128.29, 105.30, 102.81, 101.55, 45.67, 35.49, 35.11, 31.13, 28.33, and 25.27 ppm (Figure S6). Finally, the desired C4P (1) was confirmed by the mass spectral data, which showed the peak at $m/z$ [M + Na]$^+$ = 557.3050 (C$_{33}$H$_{39}$BN$_4$NaO$_2$, Figure S7).

To assess the redox accessibility of the redox center of the so-crafted functionalized C4P (1) and its potential utility for electrochemical sensing, we carried detailed voltammetric investigations over a glassy carbon electrode modified with the functionalized C4P (1) in a three electrode setup. Prior to the experiment, the electrode (GCE, 2 mm diameter) was polished with an alumina slurry (0.5–0.05 mm), then washed with copious amounts of triple-distilled water and finally ethanol. A catalyst ink was prepared by dissolving 3 mg/mL C4P (1) in DMF. To the mixture was added 4 mL of 25% nafion as a binder, and the mixture was sonicated for 1 h at 25 °C. An appropriate volume of this catalyst ink was drop cast onto the GCE disk and allowed to dry under ambient conditions for 12 h. Before the electrochemical measurements, the electroanalyte solutions were purged with argon gas for 10 min. The solutions were kept covered with an Ar blanket during the measurements on modified GCE electrodes in a three-electrode setup. The redox properties of the synthesized C4P-based sensor (1) were examined on a modified GCE working electrode in a PBS (pH 7.2) electrolyte system. As depicted in Figure 1, while no Faradaic response was observed for the bare GCE, a feeble oxidation peak and a broad diffuse cathodic peak were observed in the voltammetric scans of the one-walled phenylboronic acid-functionalized C4P (1) modified GCE. An increase in potential scan rate was observed to enhance the peak currents with almost no shift in peak positions. The peak currents of these redox responses exhibited a linear dependence over the square root of the scan rate, with a statistical correlation ≥ 0.99. This suggests a diffusion-controlled redox response for C4P (1) as a film over the GCE. The addition of dopamine to the inert electrolytic solution of PBS was observed to significantly modify the redox response of the C4P (1) modified GCE. As depicted in Figure 1 B, the presence of DA results in a significant enhancement in the C4P (1) specific redox peaks. Two oxidation peaks for the C4P (1) modified GCE, one with broad hump centered around ~0.1 V and another with a prominent oxidation peak at +0.9 V, were noticed (Figure 1). Similarly, three prominent reduction peaks centered at −0.1, −0.6, and −0.96 V could be observed for C4P (1) modified GCE in the presence of DA (Figure 1). The shift in the positions of the oxidation and reduction peaks and the emergence of new peaks with the addition of dopamine suggest that dopamine can be sensed directly by the C4P (1) modified GCE. In view of these findings related to the obvious advantages of the C4P (1) mediated electrochemical sensing of dopamine and to confirm the existence of a cyclic boronate ester linkage, we assessed the activity of the C4P (1) modified GCE toward the electro-oxidation of the diol molecule catechol. The voltammetric investigations performed in an Ar-purged 7.2 PBS solution in the presence of catechol revealed clear Faradaic responses in both the forward and backward scans. These almost similar electrocatalytic responses for both dopamine and catechol infer that C4P (1) interacts...
with both of these molecules via the diol linkage to form cyclic boronate ester. The same was followed through differential pulse voltammetry studies.

In view of our observations vis-à-vis the higher sensitivity and lower detection limit possible with DPV in comparison to CV for DA and catechol sensing, we chose the former approach for the quantitative investigations pertaining to the DA and catechol sensing potential of the meso-substituted one-walled phenylboronic acid C4P (1) modified GCE (C4P(1)/GCE). DPV was performed at changing concentrations of DA and catechol in 0.1 M PBS (pH 7.2), and the differential pulse voltammograms are illustrated in Figure 2A and C, respectively. The DA oxidation peak current ($I_{pa}$) values clearly increased as the concentration of dopamine increased. Additionally, the oxidation peak current varied with the increasing concentration of catechol. The oxidation peak in the DPV curves recorded for C4P(1)/GCE increased, when the accumulation or deposition time was increased from 5 to 10 s and reached the maximum value of the peak current at an accumulation time of 10 s, with no change in the peak current for further increases in the deposition time. The electro-oxidation current of dopamine and catechol was found to be at a maximum at a modulation amplitude of 0.050 V during this deposition time. The DPV signals plotted as a function of the DA concentration versus the day current suggested a linear correlation between the two. Similar findings were revealed in the case of catechol. The linear dependence of DPV signals over the concentration of dopamine in the range of 0.165–2.302 $\mu$M was analyzed through a calibration plot of $I_{pa}$ versus [DA], as displayed in Figure 2B. The linear fit of $I_{pa}$ versus the concentration of dopamine fits to a linear regression equation, viz. $I_{pa} = 0.3867[D\text{A}] + 0.6324$ ($R^2=0.99$). The calibration plot was used to estimate the limit of detection (LOD) based on triple signal-to-noise ratio ($S/N = 3$) using the equation LOD $= 3\sigma/S$, where $\sigma$ is the standard deviation of the error of the intercept and $S$ is the slope of the calibration plot. The LOD was thus obtained as 0.015 $\mu$M (15 nM). Similarly, the DPV signals for the catechol oxidation peak exhibited a linear correlation. The linear concentration correlation was found to be in the range of 0.5–4 $\mu$M. The linear fit for the oxidation peak current of catechol follows the equation $I_{pa} = 35.5654[\text{catechol}] - 1.1074$ in the lower concentration range and $I_{pa} = 4.5276 [\text{catechol}] + 0.16339$ in the higher concentration range (Figure 2D). The calibration plot therefore reveals two detection limits of 13 and 18 nM in the lower and higher concentration ranges, respectively. The high sensitivity and low detection limits observed for DA and catechol sensing over the C4P (1) modified GCE are in accordance with the established fact that the latter, which possesses a redox-active phenylboronic acid functional group, has the ability to reversibly bind diol molecules like dopamine and catechol through the cyclic boronate ester linkage (Scheme 3). The reusability of the C4P (1) modified GCE was checked in the presence of 0.8 $\mu$M DA for five consecutive days, and it was found that the corresponding peak currents were remained at about 97% efficiency on day five on the same electrode (Figure 3A and B). A quantitative comparison of the DA sensing performance of the C4P-based electrochemical sensor (1) with those of other chemical electrodes recently reported in the literature is presented in Table 1. As evident from the entries of Table 1, the electrochemical sensing performance of C4P-based electrochemical sensor (1) crafted in our present work is comparable to or even better than the already reported state-of-art materials for DA sensing.

To reveal the role of the C4P framework in DA sensing, we observed satisfactory shifts in the $^1$H-NMR (DMSO-d$_6$) peaks of 1:1 C4P (1)/DA. As can be seen from the $^1$H NMR spectra (Figure 4), quite large upfield shifts occurred in the pyrrolic NH protons and phenyl protons, while a small upfield shift was noticed in case of $\beta$-pyrrolic protons. Moreover, the formation...
of the complex was also confirmed by the disappearance of two phenolic protons of dopamine. To further establish the sensing of DA, an UV–Vis titration was also performed by successively adding a 17 mM solution of DA in CH₃OH to C4P (0.05 mM in CH₃OH) (Figure S10). Although very little blue-shifting was noticed for the initial additions of dopamine to C4P (1), a blue shift of about 3.64 nm to the dopamine absorption spectrum was observed after the addition of 230 μL of DA, indicating complex formation.

■ CONCLUSIONS

In summary, a novel one-walled meso-phenylboronic acid-functionalized C4P-based sensor has been revealed for the potential electrochemical sensing of dopamine and catechol. To the best of our knowledge, the presented work is first of its kind. Boronic acid chemistry has been employed to tune and exploit the electrochemical sensing potential of C4P for the sensing of dopamine, a neurotransmitter whose quantification is extremely useful for the clinical diagnosis of a variety of ailments. We are of the opinion that the present study might open a new gateway in the design of economical and reliable sensors for the early clinical diagnosis of deadly neurodegenerative diseases, which arise from elevated or decreased levels of neurotransmitters in bodily fluids. Sensing studies of the newly developed C4P-based electrochemical sensor (1) with other diol molecules and neurotransmitters are underway in our laboratory and will be published in due time. Moreover, the synthesis and intensive study of two-walled phenylboronic acid-based C4P systems are also under investigation.

■ EXPERIMENTAL SECTION

Materials, Methods, And Instrumentation. All chemicals and solvents required for the synthesis of our target molecules (functionalized C4Ps) were purchased either from the Sigma-Aldrich or some other companies such as Spectrochem Pvt. Ltd., Alfa Aesar, TCI Chemicals Pvt. Ltd., GLR Innovations, etc. Nafion, N,N-dimethylformamide, and dopamine hydrochloride, which were used for electrochemical measurements, were purchased from Sigma-Aldrich. Pyrrole was distilled before use, and the acetone used was of HPLC purity.

Table 1. Electrochemical Sensing (Using DPV) Comparison of the Present Work with Already Available Electrochemical Dopamine Biosensors Based On Different Combinations of Materials Modified on a GCE

| Electrode Material                  | Linear Range (μM) | LOD (nM) | Ref. |
|-------------------------------------|-------------------|----------|------|
| Pt-Ag/Gr/GCE                        | 0.1–60            | 12       | 39   |
| GQDs@MWCNTs/GCE                     | 0.25–250          | 95       | 40   |
| Ag-doped PANI/GCE                   | 10–90             | 1900     | 41   |
| C60-gCN/GCE                         | 100–1000          | 29       | 42   |
| N,P-Mo2C@C/PB/GF                    | 0.18–30           | 11       | 43   |
| AuNBP/MWCNT/GCE                     | 0.05–2.7          | 15       | 44   |
| AgAu-MWCNT                          | 3–2.3             | 0.23     | 45   |
| graphene-MWCNT                      | 5–100             | 0.87     | 46   |
| GNP/GO                              | 0.9–70            | 56       | 47   |
| boron-doped diamond                 | 400–600000        | 100      | 48   |
| AuNP@NBSAC                          | 1–50              | 50       | 49   |
| β-CD/Se-CQDs                        | 60–1000           | 20       | 50   |
| Pt-Co@rGO                           | 35–1500           | 51       | 51   |
| CuTRZMoO4@PPy-n                     | 1–100             | 800      | 52   |
| MWCNT-NH2/diazirine/Tyr             | 5–90              | 200      | 53   |
| Au-E/bisSeDTSi/Pox                  | 0.1–200           | 73       | 54   |
| meso-substituted one-walled phenylboronic acid C4P (1)/GCE | 0.165–2.302 | 15 | This work |

Figure 4. 1H-NMR spectral changes of C4P (1) observed upon the addition of proper equivalents of DA. Asterisks (*) represents peaks of ethyl acetate, water, and DMSO.

Figure 4.
grade. Analytical thin layer chromatography (TLC) was performed on pre-made silica gel-coated aluminum plates, and an appropriate ratio of ethyl acetate to hexane was used for TLC development. Column chromatography was carried with silica gel (100–200 mesh) using a suitable solvent mixture of ethyl acetate and hexane. A Bruker spectrometer was used to record 1H-NMR spectra (400 and 500 MHz) and 13C-NMR spectra in CDCl3. Asterisks (*) in the spectra signify the residual solvent peak. High-resolution mass spectrometric (HRMS) measurements were performed using an electrospray ionization (ESI, Q-ToF) spectrometer. Electrochemical measurements were performed on a Metrohm Autolab potentiostat and galvanostat (PGSTAT-100N). A three-electrode set-up with a glassy carbon electrode (GCE, 2 mm diameter) or a GCE modified with functionalized C4P as the working electrode, platinum wire as the counter electrode, and Ag/AgCl 3M KCl as the reference electrode was used for the presented electrochemical investigations, and all devices were from Metrohm.

**Synthetic Procedure for Phenylboronic Acid-Functionalized DPM (2).** Freshly distilled pyrrole (10.15 mL, 146.37 mmol, 12 equiv) and 4-acetylphenylboronic acid 2 (2 g, 12.20 mmol, 1 equiv) were added to a clear low-melting mixture (5 g) of DMU and t-(+)-TA in a 7:3 ratio at 70 °C. The reaction mixture was allowed to stir at 70 °C for 1 h and was monitored by TLC. After the reaction was complete, water (20 mL) was added to the warm reaction mixture. After the reaction mixture was cooled to room temperature, the organic contents were extracted with DCM, dried over Na2SO4, 2:8 followed by 4:6 ethyl acetate/hexane) to get pure DPM (2.56g, 75% yield).

Phenylboronic Acid-Functionalized DPM (2). White solid; yield 75%; 1H-NMR (400 MHz, CDCl3) δ 8.14–8.10 (m, 2H), 7.86–7.66 (m, 3H), 7.30–7.19 (m, 3H), 6.73–6.70 (m, 2H), 6.69–6.23–6.21 (m, 2H), 6.03–6.0 (s, 2H), 2.13 (s, 3H); 13C-NMR (126 MHz, CDCl3) δ 137.08, 135.54, 127.16, 117.74, 117.18, 108.33, 108.19, 106.49, 45.08, 28.68; IR (KBr) 3434, 2962, 1762, 1608, 1463, 1380 cm−1; HRMS (ESI, Q-ToF) m/z calculated for C18H17BN2O2 [M + H]+ 281.1460, found 281.1460.

**Synthetic Procedure for Phenylboronic Acid-Functionalized One-Walled C4P (1).** To a stirred solution of 2 (1g, 3.57 mmol, 1 equiv), freshly distilled pyrrole (1.24 mL, 17.85 mmol, 5 equiv), and dry acetonitrile (2.64 mL 35.70 mmol, 10 equiv) in dry CH2Cl2 (50 mL) was added TFA (0.547 mL, 7.14 mmol, 2 equiv) dropwise under an inert nitrogen atmosphere at 0 °C. The reaction mixture was allowed to come at room temperature and stirred for 3 h. After the completion of the reaction, the reaction mixture was neutralized using 1 M NaOH and extracted with CH2Cl2. The organic phase was dried over Na2SO4 filtered, and concentrated under vacuum. The crude residue was then subjected to column chromatography (SiO2, 2.8 followed by 4:6 ethyl acetate/hexane) to get pure DPM 2 (2.56g, 75% yield).

Phenylboronic Acid-Functionalized One-Walled C4P (1). White solid; yield 75%; 1H-NMR (500 MHz, DMSO-d6) δ 8.98 (s, 2H), 9.39 (s, 2H), 7.96 (s, 2H), 7.70 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 5.81 (t, J = 3.0 Hz, 2H), 5.72–5.74 (m, 6H), 1.73 (s, 3H), 1.60 (s, 6H), 1.52 (s, 4H), 1.48 (s, 6H), 1.41 (s, 2H) 13C-NMR (126 MHz, DMSO-d6) δ 153.05, 141.29, 140.72, 139.30, 137.85, 136.12, 135.09, 128.29, 105.30, 102.81, 101.55, 45.67, 35.49, 35.11, 31.13, 28.33, 25.27; IR (KBr) 959, 1396, 1512, 3138 cm−1; HRMS (ESI, Q-ToF) m/z calculated for C8H18BN2Na2O2 [M + Na]+ 557.3058, found 555.3050.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c00926.

Copies of 1H-NMR, 13C-NMR, HRMS, and IR spectra of phenylboronic acid-functionalized DPM (2) and phenylboronic acid-functionalized one-walled C4P (1) and 1H-NMR and UV–Vis titration data (PDF)

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**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

The authors are grateful for the financial support from DST-SERB, New Delhi (project file no. ECR/2017/000821) and are also thankful to Jamia Millia Islamia for providing the wonderful infrastructure. I.A.R. specially thanks CSIR, New Delhi, for the SRF fellowship.

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