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Micro-band Boron-doped Diamond Electrode in Capillary Electrophoresis for Simultaneous Detection of AMP, ADP, and ATP

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Abstract. A micro-band boron-doped diamond (BDD) electrode was prepared by sealing a piece of BDD film with an area of 1.11×10^{-7} m² between two insulating plates, one Teflon and one silicon rubber, to form sandwich-like layers, so the surface area could be investigated. The micro-band BDD was combined with capillary zone electrophoresis as an electrode for the simultaneous detection of adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP) in a solution. These adenosine phosphates can be separated with a 0.3 m-long fused silica capillary using Britton–Robinson buffers at pH 2.0. Current in the concentration range of 0.1 to 2.0 mM were linear with the limits of detection of 0.004 μ M, 0.006 μ M, and 0.011 μ M for AMP, ADP, and ATP, respectively. A comparison with an unmodified BDD as the detector in the same electrophoresis system showed that the micro-band generated better limits of detection (LODs) than the macroelectrode. This method was successfully applied to human urine samples injected with three adenosine phosphates, as well as adenine and guanine, which can be well-separated with recovery percentages of adenine, guanine, AMP, ADP, and ATP of 99.2%, 102.5%, 107.4%, 107.7%, and 105.4%, respectively.

Keywords: Adenosine phosphates; Boron-doped diamond; Capillary zone electrophoresis; Electrochemical detection; Micro-band electrode

1. Introduction

Adenosine triphosphate (ATP) is an important small package of energy in a cell. Its hydrolysis reaction to adenosine diphosphate (ADP) and adenosine monophosphate (AMP) is sufficient to promote unfavorable processes required by the cell (Yadav et al., 2017). These adenosine phosphates (APs) are also important as extracellular signaling agents (Giuliani et al., 2019). As signaling agents, the alteration of APs can cause diseases such as epilepsy, Alzheimer's disease, Parkinson's disease, and stroke, and it can lead to drug abuse

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(Effendi et al., 2020). Moreover, the presence of these compounds in urine or blood plasma could be indicators of liver disease (Staufner et al., 2016; Wang et al., 2020). Therefore, detailed and sensitive detection of these compounds is highly important.

Numerous conventional measurements have been reported on APs detectors using liquid chromatography (Zhu et al., 2017; Andries et al., 2018; Menegollo et al., 2019). However, this method is time-consuming and expensive, and it requires an expert to operate the instruments. Aptamer-based sensors also have been reported (Zhang et al., 2017; Zhou et al., 2020). However, they failed to distinguish ATP from ADP and AMP, as they show a similar affinity (Li and Liu, 2020). Other efforts used carbon fiber in electrophoresis for amperometric detection (Gunawardhana and Lunte, 2018) and electroanalytical detection using a pencil graphite electrode (Krishnan et al., 2020). Previously, electrochemical detection of adenosine phosphates with an unmodified boron-doped diamond (BDD) was successfully reported (Asai et al., 2016). BDD is known as an electrode that exhibits interesting electrochemical properties, such as low background current and wide potential window. These are excellent characteristics of sensor applications (Wahyuni et al., 2015; Hayat et al., 2019). The wide potential window in aqueous media has also been reported and proven to suppress the evolution of H₂ in applications of CO₂ reduction (Natsui et al., 2018; Jiwanti et al., 2020). In addition, high chemical and physical stability also are very useful for applications in extreme conditions (Dettlaff et al., 2019; Muharam et al., 2019; Miao et al., 2020).

On the other hand, lamination is a widely applied technique for fabricating microelectrodes by insulating the electrode between two insulator plates, forming sandwich-like layers. The advantage of lamination compared to other techniques on the substrate is the availability of an electrode surface that can be renewed simply by cutting off the ends. This differs from the lithography method, in which the electrode cannot be polished (Zhuang et al., 2015; Baluchová et al., 2019). Moreover, lamination is an inexpensive, alternative fabrication of microelectrodes, and it provides a voltammetric response with a value similar to theoretical predictions (Macpherson, 2015). Hence, modification of BDD as a micro-band electrode promises to make the electrodes achieve more than unmodified ones (Prayikaputri et al., 2017). In this report, the BDD electrode was fabricated through lamination as a microband. Then its electrochemical properties were determined by using a capillary electrophoresis system for the simultaneous detection of the three adenosine phosphates (AMP, ADP, and ATP) together in a solution.

2. Methods

2.1. Chemicals

AMP, ADP, ATP, dipotassium hydrogen orthophosphate (K₂HPO₄), and potassium dihydrogen phosphate (KH₂PO₄) were purchased from Wako Pure Chemical Industries (Osaka, Japan), while phosphoric acid (H₃PO₄), acetic acid (CH₃COOH), boric acid (H₃BO₄), and methanol were obtained from Merck (Darmstadt, Germany). All chemicals were used without further purification. Ultrapure water was produced by the Millipore Direct-Q[©] 5 UV Water Purification System for preparing aqueous solutions.

2.2. Preparation and Characterization of Micro-band BDD Electrode

Polycrystalline BDD was prepared in the Einaga Laboratory, Keio University, using a microwave plasma-assisted chemical vapor deposition system (MPCVD, CORNES Technologies/ASTeX-5400). Polycrystalline film was deposited on a Si (100) plate from a methanol solution containing boron with a B to C ratio of 1% (1% BDD). The average polycrystalline film was approximately 5 μ m, and it was made of sp³ carbon in the absence

of sp² fraction, based on Raman characterization. Details of the preparation and characterization were described elsewhere (Ivandini et al., 2019). Prior to modification as the micro-band, the silicon substrate was removed from the BDD by immersing the polycrystalline film of BDD in a mixture of HF (48%) and HNO₃ (60%) (1:1) for 12 h. The micro-band electrode was then prepared using lamination according to the method used by (Prayikaputri et al., 2017). Both the BDD and silicon rubber were cut into squares of 1 cm × 1 cm. Then, with the support of Teflon, sandwich-like layers 4 mm wide formed in this order: Teflon-silicone-BDD-silicone-Teflon. A copper wire was inserted to provide electrical contact.

2.3. Electrochemical Measurement of Adenosine Phosphates

Electrochemical measurements were performed using cyclic voltammetry at a potential range of –1.6 V to +2.0 V to study the electrochemical behavior of APs. The fabricated micro-band BDD and an Ag/AgCl system were used as the working and reference electrodes, respectively, while a platinum electrode was used as the counter electrode. Various concentrations of single and mixed solutions of adenosine phosphates (AMP, ADP, and ATP) were prepared in phosphate buffer solutions (PBS) at pH 6.8. The pH influence was studied in a Britton–Robinson buffer containing 0.04 M H₃PO₄, 0.04 M CH₃COOH, and 0.04 M H₃BO₄. To adjust the pH, 0.02 M NaOH was used. Then, applications using a capillary electrophoresis system were conducted by coupling the capillary electrophoresis system with a potentiostat (Figure 1). Amperometry was applied at various separation voltages from 5 kV to 25 kV and with various concentrations of APs (0.1 mM to 2 mM) in solution.



Figure 1 The capillary electrophoresis system

2.4. Using Capillary Electrophoresis to Sample Human Urine

As a practical application, an analysis was conducted on a sample of human urine. The sample, which was freshly collected from the Laboratory of Organic Chemistry and Biochemistry, Department of Chemistry, Universitas Indonesia, was initially filtered using a 0.45 μ m nylon filter. The sample was then mixed with PBS pH 6.8 at a ratio of 1:1. Measurements were performed using capillary electrophoresis to analyze the composition of adenosine phosphate compounds in human urine by amperometric methods.

3. Results and Discussion

3.1. Characterization of the Micro-band Boron-doped Diamond Electrode

The quality of the polycrystalline BDD was examined using Raman spectroscopy. Figure 2a displays the Raman spectra of the BDD electrode. The relative intensity around 1332 cm⁻¹ corresponded to high-crystallinity diamond film with C-C structure in sp³ hybridization. The absence of a peak around 1500 cm⁻¹ indicates that the polycrystalline layer of BDD was free from impurities caused by the C-C structure in sp² hybridization. Finally, two small peaks at 500 cm⁻¹ and 1000 cm⁻¹ imply the presence of disordered sp³ hybridization between C-C bonds on the formed diamond because of the non-uniform usage of trimethyl borate as the doping agent in BDD synthesis (Watanabe et al., 2014). In addition, characterization using X-ray Photoelectron Spectroscopy (XPS) was performed to reaffirm the formation of the BDD electrode. Figure 2b shows the result of the XPS spectrum of the BDD electrode. A peak was observed at 284.5 eV, which suggests the presence of C (1s) atoms. A second peak occurred at 532.5 eV. This implied the presence of 0 (1s) atoms from the formation of 0-H bonds on the BDD surface.



Figure 2 Raman (a) and XPS (b) spectra of the BDD electrode

Figure 3 shows the SEM image of the micro-band BDD electrode. Figure 3a displays the longitudinal section of the electrode. The thickness of the BDD film in the micro-band electrode is around 10 μ m. The homogeneous particle grains on the BDD surface were observed to be ±4-5 μ m in size, as shown in the inset of Figure 3a. The layer of the BDD micro-band electrode is shown in Figure 3b. The figure shows some dark sides as a gap from the delamination defects in processes like washing and drying, and during the experiments.



Figure 3 SEM images of micro-band BDD electrode, before (a) and after (b) fabrication. The inset on (a) shows the grains of the BDD polycrystalline film

3.2. Electrochemistry of AMP, ADP, and ATP at the Micro-band BDD Electrode

The electrochemical properties of APs were investigated by using cyclic voltammetry in a PBS buffer solution at pH 6.8. Cyclic voltammograms (CVs) of AMP, ADP, and ATP are shown in Figures 4a, 4b, and 4c, respectively. The CVs show that the oxidation peak of adenosine phosphate is typically around +0.9 V. Accordingly, a potential of +1.0 V is selected as the optimal current in this study, assuming that all adenosines have been completely oxidized at this potential.

It was previously proposed that oxidation of APs occurred at the adenosine moiety (Asai et al., 2016). Furthermore, current differences of the oxidation peak were observed in the three APs. The higher the phosphate number, the lower the oxidation kinetics of the APs, as reported by Asai et al. (2016). It is presumed that more phosphate group numbers bound to the adenosine means there is a repulsion between the AP molecule and the electrode surface.

Cyclic voltammetry also was performed on AMP, ADP, and ATP by applying scans that ranged from 25 mV/s to 250 mV/s. The linear correlation between currents and the square roots of the scan rate. These results indicated that the oxidation of APs is controlled by a diffusion process, as stated by the Randles–Sevcik equation. The diffusion coefficient of ATP also was measured by the amperometric technique at +0.9 V for 5 min in a PBS buffer at pH 6.8. The amperometric measurement determined the diffusion coefficient to be 0.0874 m²/s, based on the Cottrell equation. The diffusion coefficient was then used to calculate the effective surface area of the BDD electrode, which was 1.11×10^{-7} m².



Figure 4 Cyclic voltammograms of phosphate buffer solution pH 6.8 in the absence and in the presence of AMP (a); ADP (b); and ATP (c), together with the plot dependences of current (d) and potential (e) vs. pH of AM, ADP, and AMP

The influence of pH was further examined using Britton–Robinson buffers with a pH that ranged from 2.0 to 10.0. Figure 4c shows that the change in pH affects the potential of

APs oxidation as well as the change in the peak current. From a pH of 2 to a pH of 4, the oxidation potential decreased, and it was saturated until pH 10. A slope of around -59 mV/pH from pH 2 to pH 4 for all APs confirms the previous results. This means that the oxidation process involved an equal number of electrons and protons, as stated by the Nernst equation. Furthermore, the highest oxidation currents of APs were observed at pH 2, as the presence of one or more phosphate groups from AMP, ADP, and ATP resulted in negative charges and affected the interaction with the electrodes in acidic solution. Therefore, pH 2 was selected for the next experiments.

3.3. Separation of AMP, ADP, and ATP in Capillary Electrophoresis

Capillary electrophoresis is a separation method for chemicals that is based on the movement of ions or charged particles in a solution when an electric current is applied. Capillary electrophoresis is a high-performance separation method because of the differential electrophoretic migration of electrically charged particles, which is affected by their size and charge (Ramos-Payán et al., 2018). Connecting capillary electrophoresis with a detector can be used for a high-performance analytical method. The system used a high-voltage power supply with two poles. At the positive pole was a detector system, and at the negative pole, a sample holder was placed. Therefore, the negatively charged ions were attracted to the detector. The more negative the ions, the faster their movement to the detector. Oxygen atoms in phosphate groups of the APs are known to provide negative charges. Accordingly, ATP, which has three phosphate moieties, moves faster, followed by ADP and AMP.

The effect of separation voltage in capillary electrophoresis was examined by applying various separation voltages from 5 kV to 25 kV for 30 min with amperometry at +1.0 V employed in the detector. Figure 5a shows that no peak appeared when 5 kV was applied. This means that more time is needed to attract the AP. A higher separation voltage is needed to achieve shorter migration times, as shown by the electropherogram using 10 k separation voltage in Figure 5b. There, three peaks at 110 s, 1500 s, and 1800 s are observed. However, a separation voltage above 10 kV resulted in an incomplete separation (Figures 5c to 5f). Therefore, 10 kV was selected for the next experiments.



Figure 5 The effect of separation voltage of: (a) 5 kV; (b) 10 kV; (c) 12 kV; (d) 15 kV; (e) 20 kV; and (f) 25 kV in capillary electrophoresis on individual solutions of 0.1 M for ATP, ADP, and AMP in Britton–Robinson buffer pH 2.0. The micro-band BDD electrode was used as the detector with amperometric detection at +1.0 V (vs. Ag/AgCl)

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The effect of various concentrations in capillary electrophoresis by applying a separation voltage of 10 kV was studied using individual solutions of AMP, ADP, and ATP as well as solutions of the three APs at concentrations that ranged from 0.1 mM to 2 mM. Figure 6 and Table 1 show the good linearity of the currents, measured in the capillary electrophoresis system with r^2 around 0.99. Furthermore, capillary electrophoresis of the solution of AMP, ADP, and ATP showed that the three APs were well separated with good linearity. The limit of detection (LOD) of each AP estimated by the system were 0.04 μ M, 0.06 μ M, and 0.011 μ M, respectively, for AMP, ADP, and ATP in the solution. Meanwhile, the sensitivity of systems that use micro-band electrodes and normal (macro) BDD electrodes was compared. The sensitivity was determined by the gradient of the calibration curve for AMP, ADP, and ATP. It showed that the micro-band BDD electrode was more sensitive than the BDD macro electrode (Figure 7).



Figure 6 Amperometric detection of capillary electrolysis with 10 kV separation voltage in solutions with various concentrations of: (a) AMP; (b) ADP; (c) ATP; and (d) a mixture of AMP, ADP, and ATP



Figure 7 Calibration curves of AMP, ADP, and ATP extracted by capillary electrolysis using a 10 kV separation voltage on: (a) micro-band BDD; and (b) macro BDD electrode

The sensitivity of the microelectrode can be explained by the diffusion processes that occur from the bulk solution to the electrode surface. The macroelectrode has linear diffusion, while the microelectrode has radial diffusion (Moussa and Mauzeroll, 2019). With the macroelectrode, the current decreases over time because of its linear diffusion process. Hence, it takes more time for the molecules to diffuse to the electrode surface. As a result, the steady-state condition becomes more difficult to achieve. On the other hand, with a microelectrode, since the diffusion layer moves outward toward the bulk solution and enlarges the area of the diffusion layer boundary, the rate and flux of the current generated by the electrode increases drastically (Moussa and Mauzeroll, 2019). Thus, it can be concluded that the microelectrode is much more sensitive than the macroelectrode.

Table	1 A	nalyt	ical performanc	es of t	he develope	ed cap	oilla	ry electroph	oresis	for the	ATP,
ADP,	and	ATP	measurements	using	microband	BDD	in	comparison	with	normal	BDD
macro	belec	trode									

		Concentration range	Linear Equation	R ²	Limit of detection
	ATP	0.1 mM-2.0 mM	5.96x –0.18	0.997	0.01 µM
Microband BDD	ADP	0.1 mM-2.0 mM	7.59x –0.61	0.997	0.06 µM
	AMP	0.1 mM-2.0 mM	8.80x –0.09	0.999	0.04 µM
	ATP	0.1 mM-2.0 mM	0.78x +0.01	0.996	0.02 µM
Macroelectrode BDD	ADP	0.1 mM-2.0 mM	2.47x +0.03	0.995	0.09 µM
	AMP	0.1 mM-2.0 mM	7.29x +0.05	0.999	0.07 µM

3.4. Applications for a Real Sample Analysis

Real samples analysis was carried out with a sample of human urine spiked with 0.1 mM concentrations of AMP, ADP, and ATP to study the electrochemical responses. Adenine and guanine at the same concentrations also were added. Figure 8 shows that the system detected several peaks at around 500 s, 670 s, 1100 s, 1300 s, and 1600 s. These were defined as adenine, guanine, ATP, ADP, and AMP, respectively. Furthermore, the recovery percentage of adenine, guanine, AMP, ADP, and ATP was calculated at 99.2%, 102.5%, 107.4%, 107.7%, and 105.4%, respectively. The results indicated that the system can be used for real applications.



Figure 8 Electrophoretogram of the human urine sample

4. Conclusions

Micro-band BDD electrodes with an effective surface of 1.11×10^{-7} m² were successfully fabricated by lamination that used Teflon and silicon as the insulating plates. Cyclic voltametric studies of AMP, ADP, and ATP showed that the optimal parameters for electrochemical detection were at a potential of +0.9 V and a pH of 2.0. Employing the

electrode for capillary electrophoresis can be conducted simultaneously on a solution of AMP, ADP, and ATP with linear correlations between the oxidation currents and the concentrations. The results showed that the system shows promise for a real application for simultaneous detection of adenosine phosphates. Hence, further investigations on the fabrication processes of the micro-band BDD electrode, as well as the optimal parameters used in the CE system, are crucial to increase the effectiveness of the modified BDD electrode as an adenosine detector.

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