**Electrochemical Cleavage of the Carbon–Boron Bond in p-Acetamidophenylboronic Acid at Neutral pH Conditions**

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Herein, it is reported that p-acetamidophenylboronic acid can be electrolytic cleavage of the carbon–boron bond to p-acetamidophenol at an electric potential of 1.2 V vs. Ag/AgCl in 100 mM phosphate buffer of pH 7.4 (containing 10% acetonitrile). The electrochemical reaction was investigated by HPLC, LC with tandem mass spectrometry, and cyclic voltammetry. This electrochemical reaction could be useful in the development of electrical controlled drug delivery systems under neutral pH conditions.

**Key words** phenylboronic acid; p-acetamidophenylboronic acid; electrochemical cleavage; drug delivery system

**Introduction**

Phenylboronic acid (PBA) and its derivatives have been studied extensively and are widely used as reaction substrates for the Suzuki–Miyaura coupling.1–3 They also attracting increased attention as functional molecules. PBA and its derivatives spontaneously form boronate esters with diols, and because this bond formation is reversible, it competes with other diols such as sugars.4–6 This unique property has been utilized in systems that depend on responses from sugars. Such systems include functional dyes-based,7 fluorescence-based,8 electrochemical9–11 and electrochemical12,13 glucose detection systems. Microgels, nanoparticles and thin films formed by the boronate ester bond between PBA and diol were used for drug delivery systems.14–16 The competitive action of the sugars cleaves the ester bonds and these materials decompose. As a result, the internally stored drug is released. In addition, PBA and its derivatives are oxidized to hydrogen peroxide and converted to phenolic derivatives.17 This reaction proceeds rapidly and with high sensitivity under physiological conditions. Thus, PBA oxidation reaction has been utilized to develop various functional materials that are based on the detection of reactive oxygen species18,19 and hydrogen peroxide response gels and nanoparticles.20–24 They have also been used for the development of glucose and lactate degrading thin films, in combination with oxidases.25–27

Herein, we report the electrolysis of p-acetamidophenylboronic acid as a new functionality of PBA (Fig. 1). The carbon–boron bond in p-acetamidophenylboronic acid cleaved by the applied electric potential to form a corresponding phenolic derivative (p-acetamidophenol). Under the influence of negative electric potential in organic solvents, some of the PBA derivatives with specific structures could be converted to phenolic derivatives in organic solvents in the presence of oxygen.28,29 In aqueous solution, PBA derivatives were converted to phenol and aniline derivatives upon catalysis by ammonia and copper electrode.30 However, these electrolytic reactions in organic solvents or requiring copper catalysts condition were not proceed under neutral pH conditions. In contrast, the electrolytic reaction reported herein proceeds in neutral aqueous solutions at a carbon electrode. A number of drug delivery systems have been developed using the competitive reaction of PBA with sugars and carbon–boron bond cleavage by hydrogen peroxide as key reactions. Similarly, the use of p-acetamidophenylboronic acid can be expected to control drug release by electrical stimulation, which could be a key reaction in the development of electrical controlled drug delivery systems under neutral pH conditions.

**Results and Discussion**

In this study, p-acetamidophenylboronic acid was subjected to electrolysis on an electrochemical analyzer (ECstat-400, ec-frontier.co.jp, Kyoto, Japan), with a glassy carbon plate (10 × 10 mm) or glassy carbon disk electrode (diameter: 3 mm) as the working electrode, a platinum plate (10 × 10 mm) as the counter electrode, and a Ag/AgCl (3 M KCl) wire as a reference electrode. A glassy carbon electrode was immersed in a 1 mM solution of p-acetamidophenylboronic acid (prepared in 100 mM phosphate buffer containing 10% acetonitrile, pH 7.4) and applied electrolytic potential at 1.2 V vs. Ag/AgCl. This electrolyzed solution was sampled after 0, 0.5, and 1.0 h and then subjected to HPLC analyses. Signals were detected at 230 nm to obtain the HPLC-UV chromatograms of the electrolytic solutions collected at each time point (Fig. 2). The peak at a retention time (tR) of 10 min in every chromatogram corresponds to p-acetamidophenylboronic acid. In the chromatogram of the sample collected at 0.5 h, a new peak appeared at 230 nm. This new peak could be identified as p-acetamidophenol on the basis of its UV spectrum. The peak areas of p-acetamidophenol increased with time, whereas the area of p-acetamidophenol decreased. This indicates that p-acetamidophenol is the main product of the electrolytic reaction.

**Fig. 1. Electrolysis of p-Acetamidophenylboronic Acid**

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a $t_R$ of 9 min. The relative abundance of this compound in the chromatogram of the sample collected at 1.0 h was higher than that at 0.5 h, suggesting that the peak at a $t_R$ of 9 min corresponded to the electrolytic product.

Next, the electrolytic solution was fractionated in the HPLC-UV set-up and analyzed using LC electrospray ionization tandem mass spectrometry (LC/ESI-MS) for structure identification. Typical mass spectra of the electrolytic product and $p$-acetamidophenylboronic acid in positive mode are shown in Supplementary Figs. S1 and S2. These species generated protonated ion $[M+H]^+$ peaks at $m/z$ 152.10 and $m/z$ 180.33, respectively. In the MS of $p$-acetamidophenylboronic acid (Supplementary Fig. S2), relative abundance of the species corresponding to $m/z$ 152.1 was less than 5%, suggesting that $m/z$ 152.1 is not a fragment ion of $p$-acetamidophenylboronic acid.

Tandem MS of the electrolytic product is shown in Fig. 3a; the fragmentation pattern is same as that of the $p$-acetamidophenol standard (Supplementary Fig. S3). The relative abundance of the compound in 5 µL electrolytic solution was $6.98 \times 10^5$ which is comparable to the 47% abundance of the $p$-acetamidophenol standard (relative abundance: $1.49 \times 10^7$ approx. 7.6 ng/on column).

The cyclic voltammetry (CV) of $p$-acetamidophenylboronic acid was performed from $-0.1$ to $1.5$ V in three cycles (Fig. 4). The scan was initiated at an applied electric potential of $-0.1$ V, which was further increased toward a positive potential and finally reverted to a negative charge at 1.5 V. In the first cycle, oxidation current and reduction current were observed at $+1.2$ and $+0.15$ V, respectively. In the second cycle, new oxidation current was observed at $0.45$ V, and reversible cyclic voltammograms were obtained in the second and third sweep. Oxidation and reduction peaks increased in the third cycle (Supplementary Fig. S4). On the other hand, no new oxidation and reduction peaks appeared when CV was performed in the sweep range of $-0.1$ to $0.7$ V (Supplementary Fig. S5). The cyclic voltammograms suggested that a new redox compound was produced from $p$-acetamidophenylboronic acid upon the application of an electric potential of around 1.2 V.

The cyclic voltammogram of $p$-acetamidophenol is shown in Supplementary Fig. S6. The oxidation and reduction peaks were observed around $0.45$ and $0.20$ V, respectively and were approximately the same as in the second and third cycles shown in Fig. 4. The electrochemical redox reaction of $p$-acetamidophenol is shown in Supplementary Fig. S7. HPLC, MS/MS, and CV results suggest that $p$-acetamidophenol was produced upon the electrolysis of $p$-acetamidophenyl-
boronic acid upon the application of an electric potential of 1.2 V. In contrast, the cyclic voltammograms of \( p \)-(N-propylaminocarboxyl)phenylboronic acid and PBA did not show any high-potential oxidation and reversible peaks (Supplementary Fig. S8), suggesting that the acetamide structure is related to the electrolytic reaction. In the electrolysis of \( p \)-acetamidophenylboronic acid using a divided cell (H-Cell), the production of \( p \)-acetamidophenol was also observed (Supplementary Figs. S9–S11).

Conclusion

We have demonstrated that the electrolysis of \( p \)-acetamidophenylboronic acid proceeds at a carbon electrode in a neutral pH conditions. This electrolytic reaction scheme is unknown and is currently under investigation. It is possible to develop functional polymers, gels, thin films, microparticles and capsules that can be decomposed by electrical stimulation under neutral pH conditions by using \( p \)-acetamidophenylboronic acid. These functional materials could be applied to electrical controlled drug delivery systems.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains supplementary materials (Experimental section, Figure S1–S11).

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