Electrochemical detection of catechol and dopamine as their phenylboronate ester derivatives

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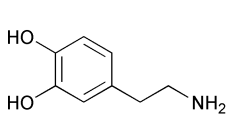
By virtue of its reaction with phenylboronic acid to form a boronate ester, dopamine can be detected electrochemically in aqueous solutions, at physiological pH, in the presence of excess ascorbic acid.

It is well known that, in aqueous media, certain diols and boronic acids react together to form boronate esters, to an extent dependent upon the pH of the solution.[1] Such reactions have previously been used in the detection of sugars both by fluorescence spectroscopy[2] and, as part of recent progress in the electrochemical sensing of organic molecules,[3] by electrochemical measurements.[4] Here, we show that boronate esters, formed by the reaction of the aromatic diol 1,2-dihydroxybenzene (catechol) with phenylboronic acids, are electrochemically oxidised at potentials considerably more positive (by *ca*. 0.5 V) than that necessary to oxidise catechol itself, at a given value of pH. This positive shift indicates that, while formation of the neutral ester is thermodynamically favourable, the oxidised ester tends to revert back to (oxidised) catechol and the phenylboronic acid; cyclic voltammograms of these systems are consistent with such a mechanism. These properties extend to the boronate ester formed by reacting phenylboronic acid (PBA) with the catecholamine neurotransmitter dopamine **1**.



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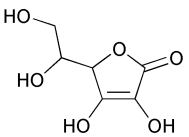

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This has allowed us to electrochemically detect dopamine in the presence, as would be the case in any human sample, of excess ascorbic acid **2**. Detection is achieved *via* oxidation of the ester, which occurs at a potential positive enough of the values for dopamine and ascorbic acid oxidation to allow resolution by voltammetry (the values for dopamine and ascorbic acid are too close to allow their resolution). Other electrochemical approaches to the problem of dopamine detection, including the use of electrodes modified with ion-exchange membranes,[5] polypyrrole films,[6] templated silicate films,[7] and self-assembled monolayers[8] have met with varying degrees of success but there is presently no direct method, electrochemical or other, of measuring the level of dopamine in human samples; abnormal levels of dopamine have been linked to brain disorders such as Parkinson's disease[9] and schizophrenia.[10]

As aliquots of phenylboronic acid were added to a 1 mM solution of catechol in phosphate buffer at pH = 8, the form of cyclic voltammograms, recorded in this solution using a glassy carbon working electrode, was found to change from the typical form for the quasi-reversible electrode reaction of the catechol itself.[11] With each addition of PBA, a diminution of the catechol oxidation peak was accompanied by the growth of a more positive oxidation peak. Fig. 1 shows voltammograms recorded for catechol alone and for catechol in the presence of 20 equivalents of PBA; the latter clearly shows a new oxidation peak (b) at E_{pa} ('anodic peak potential') = 619 mV *vs*. Ag/AgCl. Since PBA is not electroactive in the potential window

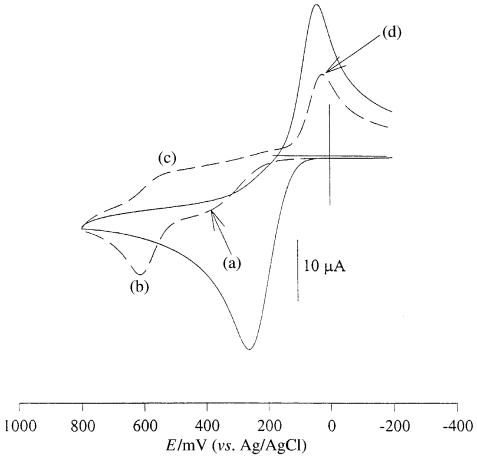
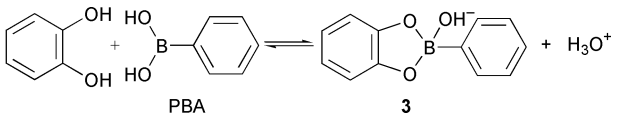


Fig. 1 Cyclic voltammograms, recorded using a glassy carbon working electrode in aqueous buffer at pH = 8 and 298 K, of 1 mM catechol (——) and 1 mM catechol plus 20 molar equiv. of PBA (- - -). Sweep rate 100 mV s^{-1}.

examined, the new oxidation peak is attributed to the oxidation of the boronate ester **3**, the presence of which in equilibrium with PBA and catechol accounts for the positive shift of the remaining catechol oxidation to peak (a). The formation of **3** (Scheme 1) was evidenced by ^{1}H NMR studies conducted over the pH range 6–8 (phosphate buffer, 10% d_4-methanol in H_2O), where the spectra of an equimolar mixture of PBA and catechol (each at 0.05 M) contained signals in the aromatic region consistent with the formation of a 1 : 1 adduct between the two reactants.



PBA **3**

Scheme 1

The peak (b) associated with the oxidation of **3** appears as for an electrochemically quasi-reversible, two-electron reaction ($E_{pa} - E_{pa/2} \approx 50$ mV; $E_{pa/2}$ is the half-peak potential). The somewhat smaller return peak (c) for reduction of the oxidised ester ($i_{pa}/i_{pc} \approx 0.34$; i_{pa} and i_{pc} are the anodic and cathodic peak currents, respectively), suggests that it is removed by a homogeneous reaction. Given that the second reduction peak (d) is at the potential observed previously for the reduction of oxidised catechol (benzoquinone) and was largely removed by reversal of the voltammogram at 400 mV (*i.e.* just short of oxidising **3**), we conclude that the oxidation of **3** leads to its cleavage to yield benzoquinone and (presumably) PBA.

With a view to obtaining fine control over the oxidation peak potential for the boronate ester, additional voltammetric studies were performed replacing PBA with the *meta*-substituted phenylboronic acids **4** and **5**. Only a slight effect was observed. The oxidation peaks for the esters formed from catechol with **4** and **5** were, respectively, coincident with and only 16 mV

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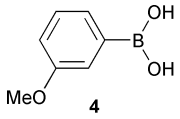

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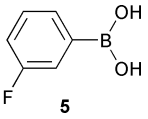

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positive of that for the oxidation of **3** (results independent of pH over the range 6–8). ^{1}H NMR studies (pH = 7.5, phosphate buffer, 10% d_4-methanol in H_2O, reactants each at 0.05 M) revealed a similar trend in the ratio of boronate ester to boronic acid, following the order **5** > PBA ≈ **4**. The same trend was also observed using ^{11}B NMR (128 MHz, using BF_3:OEt_2 as an external standard), where each spectrum contained a boron signal corresponding to the boronate ester at *ca*. 18 ppm upfield from the signal corresponding to the boronic acid. The trend observed broadly reflects that for esters formed by reacting boronic acid with aliphatic diols,[1c] and is consistent with boronate ester formation being more favourable as the pK_a of the boronic acid decreases.[12] This is expected since electron withdrawing groups on the phenyl ring would tend to stabilise the product.

To demonstrate the possible use of these phenylboronic acid–catechol systems for the detection of biologically important catecholamines, differential pulse voltammetry was performed, using a glassy carbon electrode in pH = 7.5 phosphate buffer solution, to show how the neurotransmitter dopamine **1** could be detected in the presence of excess ascorbic acid **2**. Fig. 2 shows how the oxidation peak for 0.5 mM dopamine [voltammogram (a)] was obscured by that for oxidation of an added 5 mM of ascorbic acid [voltammogram (b)]. Then, after addition of 10 mM of PBA [voltammogram (c)], a new peak emerged at around 600 mV *vs*. Ag/AgCl, which (by analogy to the catechol/PBA case†) is for oxidation of an ester formed between dopamine and PBA, thus allowing the otherwise hidden dopamine to be detected. The figure inset confirms that the new peak recorded in voltammogram (c) does not indicate ester formation between PBA and ascorbic acid. Voltammogram (d) is that for 0.5 mM ascorbic acid in the presence of 10 mM of PBA and shows no peak for oxidation of an ester (the ascorbic acid voltammogram was unchanged by the addition of PBA and we conclude that no significant ester formation occurs). In voltammogram (e), where ascorbic acid was replaced by dopamine, a peak for oxidation of the boronate ester appeared at around 600 mV just as in voltammogram (c) in the main figure.

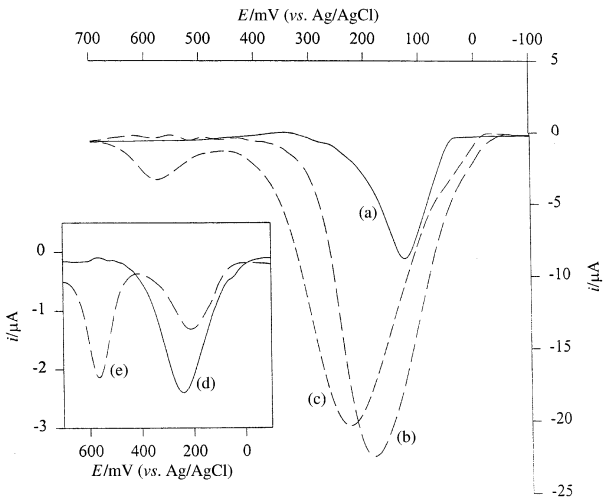

Fig. 2 Differential pulse voltammograms, recorded using a glassy carbon working electrode in aqueous buffer at pH = 7.5 and 298 K, of (a) dopamine **1** (0.5 mM), (b) **1** (0.5 mM) plus ascorbic acid **2** (5 mM), (c) **1** (0.5 mM) plus **2** (5 mM) plus PBA (10 mM), (d) **2** (0.5 mM) plus PBA (10 mM), and (e) **1** (0.5 mM) plus PBA (10 mM). Sweep rate 20 mV s^{-1}; pulse amplitude 50 mV.

Dopamine can thus be detected electrochemically in solutions, at physiological pH, containing an excess of ascorbic acid (we found the limit to be an excess of around 20-fold). We believe that this approach can readily be applied to the development of electrochemical sensors for dopamine and related catecholamines, especially since, once oxidised, the esters formed tend to revert back to the initial reactants, making the sensor re-useable.

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Notes and references

† The cyclic voltammetry of dopamine/PBA resembles that of catechol/PBA.

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