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Article

Electrochemical Behavior of Unusual Dimeric Flavonoids Isolated from *Fridericia platyphylla*

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Brazil has the greatest plant diversity on the planet, distributed in different types of biomes. These plants are important sources of biologically active natural products, which are derived from various drugs marketed worldwide. This paper presents an electrochemical study of three unusual dimeric flavonoids, pharmacologically active, isolated and identified for the first time by our research group, in a Brazilian plant (*Fridericia platyphylla*). The results showed that oxidation processes are favored at higher pH, and mass transport was controlled by diffusion. Brachydins derivatives, Bra-A was oxidized at the lowest potential value (0.48 V *vs.* Ag/AgCl, $KCl_{(sat)}$) and Bra-B and Bra-C, presented the highest oxidation potentials (ca. 0.71 and ca. 0.57 V *vs.* Ag/AgCl, $KCl_{(sat)}$, respectively). This study shows that electrochemistry is one more tool that would help us focus on future bio-pharmacological investigations of these unusual compounds.

Keywords: brachydins, unusual flavonoids, differential pulse voltammetry, *Fridericia platyphylla*

Introduction

The Brazilian cerrado (neotropical savannah) is one of the most biogeographically diverse regions in the world, containing numerous native species of vascular plants.[1,2] Many of these plants are commonly used in traditional medicine to treat various diseases.[2] *Fridericia platyphylla*, whose publications in the literature are with one synonym *Arrabidaea brachypoda*, is a prominent representative of the Bignoniaceae family, known locally as "*cervejinha do campo*" and "*cipó una*". Moreover, it is widely used in traditional medicine to treat kidney stones and joint pain.[3-5]

Phytochemical investigation of the nonpolar fraction and the root extract of *Fridericia platyphylla* led to the targeted isolation of active constituents, including two glycosylated phenylethanoids derivatives, seven glycosylated dimeric flavonoids, and three rare dimeric flavonoids, first described in the Brazilian plant.[6,7] Three isolated dimeric flavonoids (brachydins) were similar to the substance dependensin, a natural product isolated from the plant *Uvaria dependens*, a member of the Annonaceae family.[8] The molecular structures of the three dimeric flavonoids (Scheme 1) are composed of four independent rings (labeled A, B, C, and D) and two fused benzopyran rings, with different substituent groups on the C ring.[7]

Recent studies,[7] published by our research group, have demonstrated the anti-*Trypanosoma cruzi* activity of

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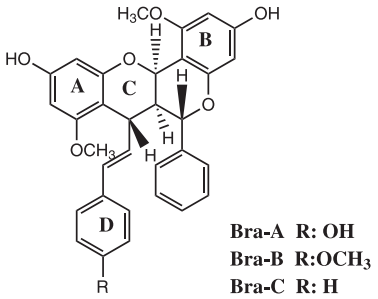

Scheme 1. Chemical structure of the brachydins isolated from *Fridericia platyphylla*.

brachydins in an *in vitro* and *in vivo* model of acute Chagas disease. The research revealed that brachydins inhibited the process of parasitemia and its intracellular development in host cells with values similar to the reference control for benznidazole.[7] The leishmanicidal activity of brachydins was also evaluated by measuring cell viability against the proliferation of promastigotes and amastigotes of *Leishmania amazonensis*. The dimeric flavonoids inhibited the ability of the parasite to invade, and Bra-B revealed greater activity against amastigote proliferation, the most severe form of the parasite, in addition to reducing the parasitism in macrophages, concerning the control group.[6]

Flavonoids are natural products known for their noticeable antioxidant, anticancer, and anti-inflammatory activities.[9] Such activities may be reflected in the electrochemical behaviors of these phenolic compounds. Electrochemical techniques have been recognized as essential tools for evaluation of the electrochemical oxidation mechanism, detection, and antioxidant activities of various flavonoids.[9-15] In addition, electrochemical techniques have advantages over other analytical methods, such as rapid response, sensitivity, and low limits of detection.[9]

Based on the biological importance that these dimeric flavonoids present, it is relevant to perform electrochemical studies to understand the redox behavior to support future studies with these compounds of great importance for the pharmaceutical area. The present work aimed to investigate the electrochemical behaviors of the three unusual dimeric flavonoids isolated from *Fridericia platyphylla*.

Experimental

Plant material

Fridericia platyphylla roots were collected in April 2017 at the Sant'Ana da Serra farm in João Pinheiro, Minas Gerais State, Brazil. The plant was identified at the José Badine Herbarium of the Federal University of Ouro Preto by the botanist Dr Maria Cristina Teixeira Braga Messias. A voucher (No. 17,935) was deposited at the herbarium. The plant was collected in agreement with the Brazilian laws concerning the protection of biodiversity (SisGen No. A451DE4).

The roots were dried at 50 °C in an oven for 72 h, followed by grinding in a knife mill. The powder obtained was extracted by exhaustive percolation using ethanol/water (7:3). After extraction, evaporation of the liquid was performed under reduced pressure at a temperature below 40 °C. The extract was transferred to glass vials and was subsequently lyophilized for the complete removal of the solvent. The crude hydroethanolic extract obtained was subjected to liquid/liquid partitioning using CH_2Cl_2 and H_2O/MeOH (7:3). The dichloromethane phase obtained after decanting was evaporated to dryness under vacuum at approximately 40 °C. This fraction was analyzed using high-performance liquid chromatography photodiode array detection method (HPLC-PDA), λ = 254 nm, (Shimadzu, Kyoto, Japan).

Dichloromethane phase fractionation

The dichloromethane phase (3.5 g) was first fractionated using a glass column filled with silica gel 60, (0.063-0.200 mm, Merck, Darmstadt, Germany) as a stationary phase. Hexane/ethyl acetate and ethyl acetate/methanol were added, using a linear polarity gradient, resulting in 19 fractions that were then analyzed by thin-layer chromatography (TLC) and HPLC-PDA. Fractions 14, 15, and 16 contained compounds denominated brachydins A, B, and C, respectively.

Chemicals and solutions

All reagents used in this work were of analytical purity and were prepared with high purity deionized water (resistivity ≤ 18 MΩ cm) obtained from a Milli-Q® Direct 8 water purification system (Millipore, Bedford, USA). The stock 0.4 mol L^{-1} Britton-Robinson (BR) buffer solution consisted of glacial acetic acid (Merck, Darmstadt, Germany), phosphoric acid (Merck, Darmstadt, Germany), boric acid (Merck, Darmstadt, Germany), and potassium chloride (Sigma-Aldrich, Saint Louis, USA).

Electrochemical measurements

Electrochemical analyses were performed using an Autolab PGSTAT 302N (Eco Chemie B.V., Utrecht, The Netherlands) coupled to a computer operating with GPES software for potential control, signal acquisition, and data processing. The electrochemical techniques used were cyclic voltammetry (CV) and differential pulse

voltammetry (DPV). The recorded data referred to the first cycle.

Sample preparation and measurement procedures

The brachydins stock solutions (Bra-A, Bra-B, and Bra-C) were prepared at 0.300 mmol L^{-1} in methanol and were kept refrigerated 6 °C temperature in amber flasks, where the solutions remained stable for at least 1 month. Before use, the stock solutions were diluted to the desired concentrations with the supporting electrolyte (0.04 mol L^{-1} BR buffer containing KCl 0.1 mol L^{-1}). Brachydins have low water solubility, so 20% methanol solution was used in the supporting electrolyte to ensure that the compounds were solubilized.

The analytical system consisted of a 5 mL capacity electrochemical cell made of Pyrex™ glass, with a Teflon™ cap and entries for the working electrode (glassy carbon, 0.07 cm^2 geometrical area), the reference electrode (Ag/AgCl, $KCl_{(sat)}$), and the auxiliary electrode (a single platinum wire). Before each experimental measurement, the glassy carbon electrode was polished on felt treated with an aqueous suspension of 0.05 μm alumina (Buehler, Chicago, USA). Before polishment, the electrode was immersed in methanol for 2 min in an ultrasonic bath (Unique, São Paulo, Brazil), followed by washing abundantly with deionized water. After polishing, the ultrasonication procedure was used to remove alumina particles attached to the electrode surface. Unless otherwise stated, the potential step of 2.5 mV, the interval time of 0.5 s (scan rate of 5 mV s^{-1}), modulation time of 70 ms and modulation amplitude of ± 50 mV were used in DPV. For CV, a scan rate of 50 mV s^{-1} was set.

Evaluation of the effect of the pH of the medium was performed by adjusting the pH of the solutions to values of 2.2, 4.0, 6.2, 7.2, 8.1, 10.1, and 12.1, by adding aliquots of 3 mol L^{-1} NaOH (Merck, Darmstadt, Germany), with the aid of a pH meter (827 pH Lab, Metrohm, São Paulo, Brazil). Cyclic voltammograms were obtained for the solutions containing brachydins at scanning speeds ranging from 10 to 100 mV s^{-1}.

Results and Discussion

Fractionation of the extract by liquid/liquid partitioning with dichloromethane revealed the presence of three significant compounds, using HPLC-PDA analysis. These compounds were identified by comparison with pure isolated standards (Figure 1). After confirming the presence of the compounds in the fraction, they were isolated after column chromatography.

Flavonoids are natural products known for their noticeable antioxidant, anticancer, and anti-inflammatory activities.[9] Such activities may be reflected in the electrochemical behaviors of these phenolic compounds. Electrochemical techniques have been recognized as essential tools for evaluation of the electrochemical oxidation mechanism, detection and antioxidant activities of various flavonoids,[9-15] making it possible to improve understanding of the structure-activity relationship by considering the effects that substituent groups and the numbers and positions of substituents on the flavan skeleton have on the oxidation potential.[16-18]

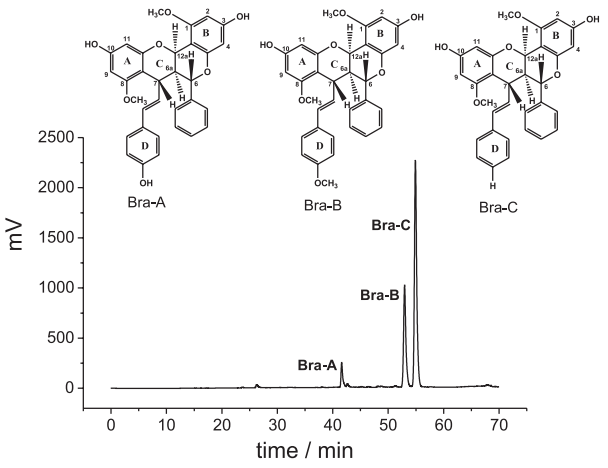

Figure 1. Chromatographic profile of the dichloromethane phase of the hydroethanolic extract of *Fridericia platyphylla* roots (λ = 254 nm), and chemical structure of the three unusual dimeric flavonoids.

These three compounds were previously characterized as unusual dimeric flavonoids, denoted brachydins (Bra) A, B, and C.[7]

Cyclic voltammetry was used as the first-choice technique to characterize the electrochemical behavior of these three unusual dimeric flavonoids. Figures 2a-2c show the cyclic voltammograms obtained for 0.3 mmol L^{-1} Bra (A, B, and C) solutions in BR buffer, at pH 7.0. Bra-A showed two main oxidation processes at peak potentials of around +0.48 and +0.80 V (Figure 2a), while Bra-B and Bra-C (Figures 2b and 2c) showed only one oxidation process, at +0.71 and +0.57 V, respectively. No cathodic processes were detected in the reverse scans for any of the compounds, demonstrating the irreversibility of the oxidation processes under the conditions used; this behavior was expected since the brachydins do not have a catechol group.[12] Furthermore, Bra-A presented a lower oxidation peak potential (+0.48 V), compared to Bra-B and Bra-C (+0.71 and +0.57 V, respectively), indicating that Bra-A was more easily oxidized, as a result of OH group located in ring D of Bra-A, which is more favorable to oxidation

than the D-ring substituents on other compounds (see the molecular structures in Figure 1).

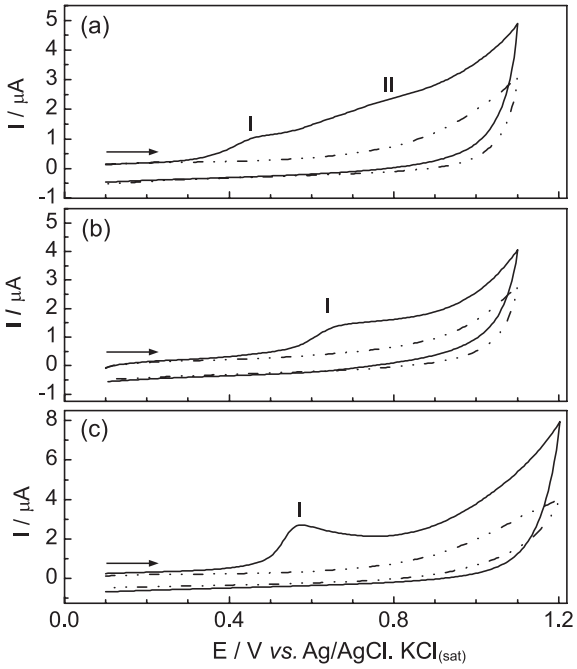

Figure 2. Cyclic voltammograms obtained with the glassy carbon electrode in 0.04 mol L^{-1} Britton Robinson buffer, pH 7.0 (dotted line), containing 0.3 mmol L^{-1} Bra-A (a), Bra-B (b), and Bra-C (c) (solids line). E_i = 0 V; E_f = +1.1 V (Bra-A and Bra-B); E_f = +1.2 V (Bra-C); scan rate = 50 mV s^{-1}.

In general, phenolic compounds containing several hydroxyl groups are more easily oxidized, due to their ability to donate protons. Gomes *et al.*[19] studied the electrochemical behaviors of flavones and 2-styrylchromones and concluded that an increase in the number of hydroxyl groups resulted in an anodic peak potential decrease of these compounds. This behavior does not occur with brachydins, as the –OH group of ring B is not in resonance with ring C.

Influence of the potential scan rate on the Bra-A, Bra-B, and Bra-C oxidation processes

Electrochemical methods are a powerful tool to understand oxidation or reduction of biological events involving endogenous or exogenous molecules.[20] The charge transfer reactions at electrode surfaces can simulate these processes, but how the results will be interpreted depends on the mass transport (diffusional or adsorption controlled) of the molecules from the solution at the electrode surface. This characterization is fundamental, principally for electrochemical systems, which has not been studied yet.

Thus, Figure 3 shows a sequence of voltammograms recorded at different potential scan rates in 0.04 mol L^{-1} BR buffer solutions containing 0.300 mmol L^{-1} of Bra-A, Bra-B, or Bra-C (Figures 3A, 3B, and 3C, respectively), which were used to determine the type of mass transport. For all the brachydins studied, the peak current increased linearly with the square root of the scan rate (Figure 3D), showing that mass transport of the analyte from the solution to the electrode surface was diffusion-controlled.[21,22]

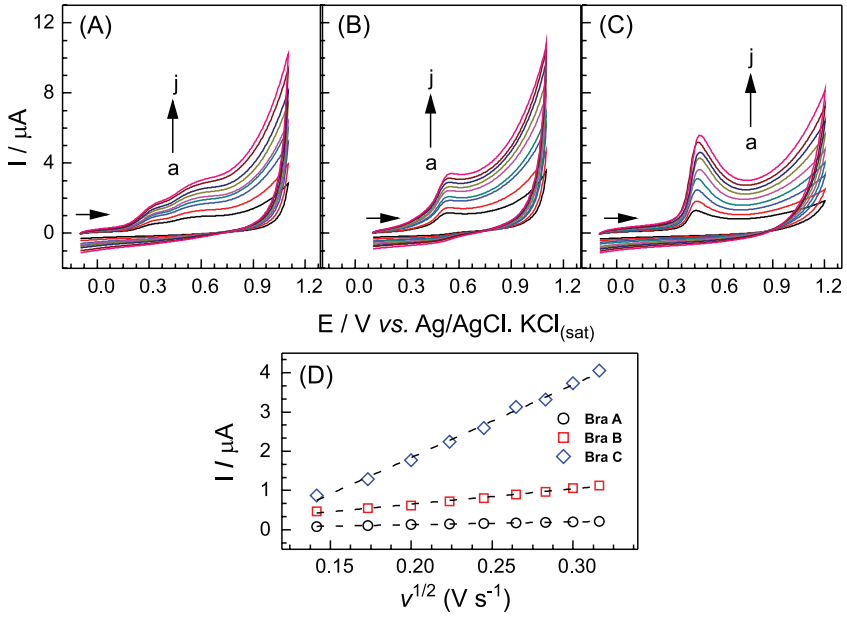

Figure 3. Cyclic voltammograms obtained with the glassy carbon electrode in 0.04 mol L^{-1} Britton Robinson buffer solution, pH 10.0, containing 0.3 mmol L^{-1} Bra-A (A), Bra-B (B), and Bra-C (C), at different potential scan rates from 20 to 100 mV s^{-1}. E_i = –0.1 V; E_f = +1.1 V. (D) I_p *vs.* $(v)^{1/2}$ plots in the range from 20 to 100 mV s^{-1} (a-j), and for Bra-A, I_p from the peak I was plotted.

Effect of pH on the Bra-A, Bra-B, and Bra-C oxidation processes

The influence of pH on the electrochemical oxidation processes was evaluated in the pH range from 2.0 to 12, using differential pulse voltammetry (DPV) with solutions containing 0.300 mmol L^{-1} of each compound in 0.04 mol L^{-1} BR buffer (Figures 4a-4g).

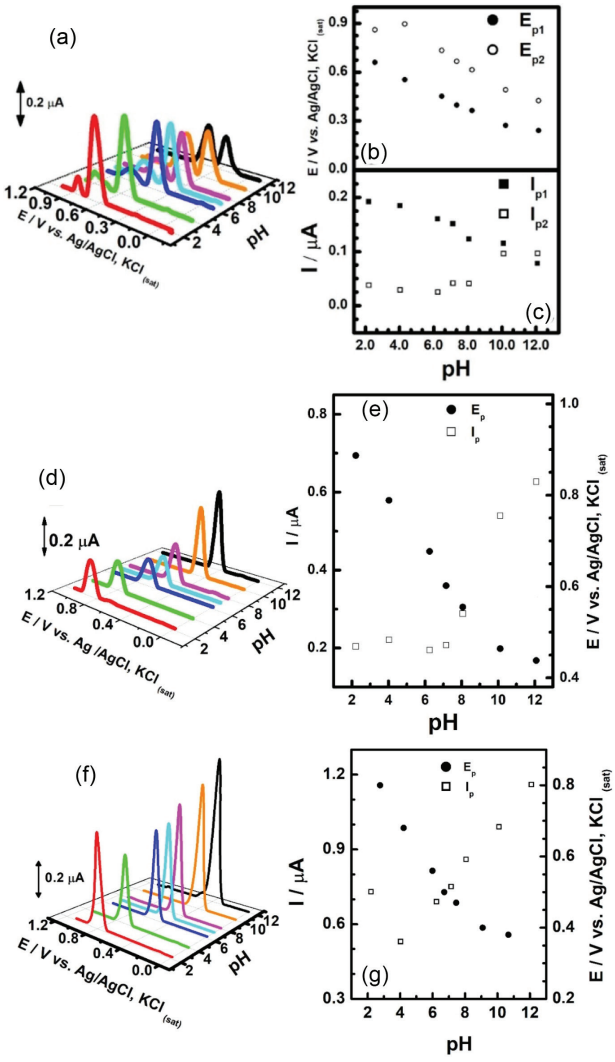

Figure 4. Differential pulse voltammograms (after baseline correction) obtained using the glassy carbon electrode in 0.04 mol L^{-1} Britton Robinson buffer solution containing 0.3 mmol L^{-1} Bra-A (a), Bra-B (d), and Bra-C (f), at different pH values (2.2, 4.0, 6.2, 7.2, 8.1, 10, and 12). E_i = 0 V; E_f = 1.1 V; scan rate = 5 mV s^{-1}. E_p (●) and I_p (▲) *versus* pH plots for (b), (c) Bra-A, (e) Bra-B, and (g) Bra-C.

The anodic peak potentials for Bra A, B, and C shifted to less positive values with increasing pH. It should also be noted that the peak potential (E_p in V) varies linearly with pH in the intervals from 4.0 to 12 for peak 1 of Bra-A, Bra-B, and Bra-C, and from 2.2 to 8.3 for Bra-A (peak 2), following the equations:

$$Ep1\ (Bra\text{-}A) = 0.75 - 0.050pH \quad (1)$$

$$Ep2\ (Bra\text{-}A) = 1.09 - 0.058pH \quad (2)$$

$$Ep1\ (Bra\text{-}B) = 1.00 - 0.056pH \quad (3)$$

$$Ep1\ (Bra\text{-}C) = 0.98 - 0.058pH \quad (4)$$

The slope values of about 59 mV *per* pH unit indicated that the same numbers of protons and electrons are involved in the electrode reactions.[23,24] Also, the numbers of electrons (n) involved in the reaction were estimated using the pulse width at half the current peak height ($W_{1/2}$) equation 5.[25]

$$W_{1/2} = 3.52RT/nF \quad (5)$$

where R is the gas constant, T is the temperature in Kelvin, and F is the Faraday constant. For Bra-A, one electron was estimated for each peak, resulting in n equal to 2, while for Bra-B and Bra-C, the values were very close to 1, indicating that the oxidation processes involved the transfer of one electron and, consequently, one proton.

The electron donor substituents make the oxidation process easier, whereas electron-withdrawing substituents shift the peak potential to high positive values. As is usual in the electrochemical oxidation of organic species, the redox process often involves the participation of protons, thus, the higher the pH, the easier the electron loss.

The plot of peak current *versus* pH (Figure 4b), shows that the peak current for Bra-A (peak 1) is much higher for 2.0 < pH < 5.0, due to the effect of pH on ionization of OH group of D ring. In acid media the OH group increase Bra-A hydrophobicity which produce a better interaction on the hydrophobic surface of the glassy carbon electrode. At neutral and alkaline pH, the OH groups are almost or fully ionized (deprotonated) increasing hydrophilicity and consequently affecting Bra-A interaction on the electrode surface. This is observed for the second peak of Bra-A (Figure 4c) and for the peaks of Bra-B (Figure 4e) and Bra-C (Figure 4g).

From the voltammetric data, electrochemical oxidation schemes were proposed for all the compounds (Figure 5). For Bra-A, the first oxidation process (I) occurs in the hydroxyl (**1a**) of the D ring (E_{p1} = 0.48 V). The removal of an electron would supply a cation radical. Upon the release of a proton, a radical is formed (**1b**), which can be delocalized by resonance, originating radical resonance structures (**1c**). The radicals may react with several of the components of the solution, including the original compounds. It can result in termination processes, with several possible products formed. However, the complete structural elucidation of the oxidized compounds was not possible in the present step of the work.

The hydrogen of the D ring hydroxyl is more acid, due to the olefinic portion, with the oxidation being facilitated at this point of the molecule, because after the oxidation, the electronic charge density in the D ring is in resonance, allowing its stabilization. The second oxidation (II) occurs in the –OH of the A ring (E_{p2} = 0.80 V). The influence of the inductive effect of ring D on the hydroxyl of ring A, makes its oxidation easier when compared to the hydroxyl of ring B. For Bra-B and Bra-C it is assumed that the oxidation process occurs in the hydroxyl group of the A ring. For Bra-B (E_p = 0.71 V) the inductive effect force of the methoxyl group (–OCH_3) of the D ring is lower than the carbonyl formed after the first oxidation in Bra-A. This effect is not observed for Bra-C (E_p = 0.57 V) which not presents substituent in the D ring and therefore, the –OH of the A ring is easily oxidized comparing to Bra-B. The absence of an electron removal group in the ring D facilitates the removal of proton from the hydroxyl group of the ring A. This can be observed in Figure 4 where the peak current increases with the increase of the pH, indicating that Bra-C suffers more easily the load transfer and consequently the oxidative process. The electrochemical

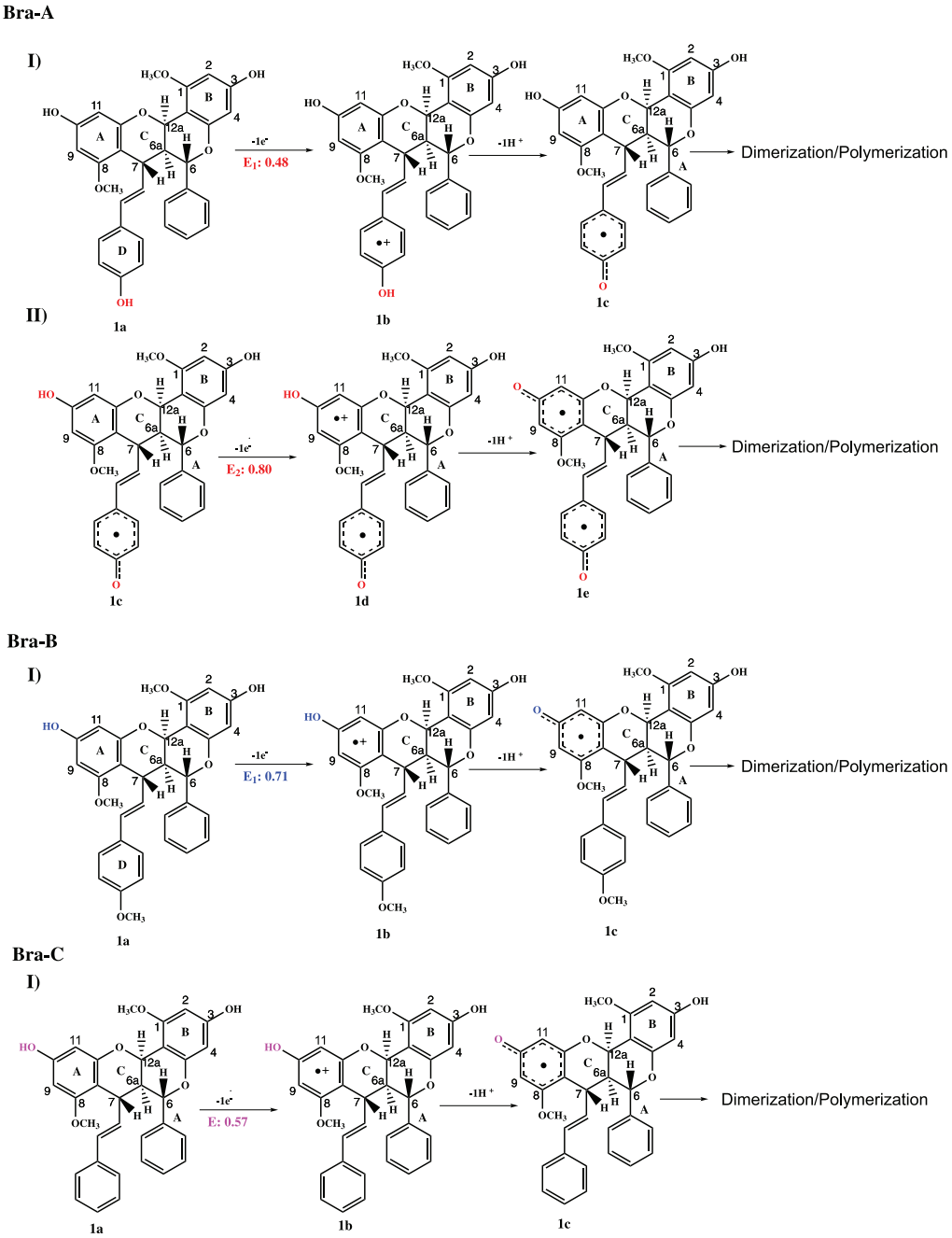

Figure 5. Proposed electrochemical oxidation scheme for the brachydin Bra-A, Bra-B, and Bra-C (adapted from reference 26).

oxidation of phenolic groups changes to more positive values, when the substituent presents higher Hammett's constants, that is, electron-withdrawing groups hamper electron loss, while electron-donor substituent may reduce the expected peak potentials.

It is possible that for all compounds, the hydroxyl groups of the B ring will be not oxidized, unlike what happens with the most flavonoids.[27] As shown, B ring does not have resonance with C ring; this makes oxidation of the OH group from B ring difficult. The absence of C2=C3 double bond and also the C3–OH group on C unity, the small effect of electronic dislocation, and the small stabilization of the phenoxyl radicals in the B ring justify the absence of oxidation processes in this ring for the three brachydins studied.

All polyphenols, especially flavonoids, present a common redox behavior, electrochemical oxidation occurring at the –OH groups, and influenced by the chemical substituents linked to the aromatic rings (–OCH_3, –OH, for example). Among other factors, the pH of the environment is the most important, directly affecting the polyphenol's antioxidant capacity, redox behavior, and oxidation product formation.[28] For brachydins, it was possible to observe the influence of the substitute on the D ring and greater oxidation at the higher pH. Chiorcea-Paquim *et al*.[28] report that in the electrochemical oxidation of organics species besides the participation of protons in the redox process, thus, the higher the pH, the easier the electron loss. The oxidation mechanism of Figure 5 was based on the proposal of Yamamura[26] for phenolic structures.

Conclusions

The voltammetric behavior of three unusual dimeric flavonoids, named brachydins A, B, and C, was evaluated and it was possible to propose electrochemical oxidation mechanisms for these compounds. To the best of our knowledge, this is the first study conducted with these unusual dimeric flavonoids isolated by our research group, from the Brazilian flora species. Future studies will be carried out by comparing the electrochemical potentials of these unusual dimeric flavonoids and glycosylated derivatives with their biological activities. This study shows that electrochemistry can be an important tool to evaluate the behavior of these flavonoids in several studies that our group has been developing.

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Author Contributions

Jessyane R. do Nascimento was responsible for data curation, investigation, formal analysis, writing original draft; Geyse A. C. Ribeiro for data curation, formal analysis; Auro A. Tanaka, Silvia H. P. Serrano and Roberto B. de Lima for visualization, writing-review and editing; Iranaldo S. da Silva for conceptualization, supervision, writing original draft, writing-review and editing; Cláudia Q. da Rocha for conceptualization, supervision, writing original draft, writing-review and editing, funding acquisition.

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