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ORIGINAL PAPER

A strategy for the electro-organic synthesis of new hydrocaffeic acid derivatives

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Abstract Electrochemical treatment processes can significantly contribute to the protection of the environment through the minimization of waste and toxic materials in effluents. From a pharmaceutical point of view and due to the existing resemblance between the electrochemical and biological reactions, it can be assumed that the oxidation mechanisms on the electrode and in the body share similar principles. In this paper, the application of electrochemical studies in the design of an environmentally friendly method was delineated for the new hydrocaffeic acid (HCA, 3,4-dihydroxy hydrocinnamic acid) derivatives synthesis at carbon electrodes in an undivided cell. In this cell, the EC mechanism reaction was involved, comprising two steps alternatively; (1) electrochemical oxidation and (2) chemical reaction. In particular, the electro-organic reactions of HCA, an important biological molecule, were studied in a water–acetonitrile (90:10 v/v) mixture in the presence of benzenesulfinic acid (**3**) and *p*-toluenesulfinic acid (**4**). The research included the use of a variety of experimental techniques, such as cyclic voltammetry, controlled-potential electrolysis and product spectroscopic identification.

Keywords Hydrocaffeic acid · Bulk electrolysis · Electro-organic synthesis · EC and ECE mechanism · Sulfinic acids

1 Introduction

Phenolic compounds are important constituents of apple base products, because they greatly contribute to their sensory properties and other attributes. In particular, poly phenolic compounds have antioxidant activity, free-radical scavenging capacity, coronary heart disease prevention and anticarcinogenic properties [1–4]. Furthermore, phenolics are associated with bitterness, astringency, color stability and some of them have been used for detecting adulterations in apple products and could be inhibitors for microbiological growth-avoiding process spoilages [5, 6].

In addition, hydroxycinnamic acid compounds are widely distributed in the plant kingdom. They usually exist as esters of organic acid or glycosides or they are bound to protein and other cell wall polymers. Hydroxycinnamic acid and other hydroquinones are abundant in nature and also process some biological activities [7–11]. Caffeic acid (3,4-dihydroxy cinnamic acid) esters, such as caffeic acid phenethyl ester (CAPE) and benzyl esters, display selective antiproliferative activity against some types of cancer cells [12]. CAPE, which is a component of propolis from honeybee hives, has exhibited anticarcinogenic and immunomodulatory properties [13]. It was proposed that the molecular basis of this action may be connected to the inhibition of the nuclear transcription factor NK-kappa B [14].

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Moreover, the electrochemical method is rapid and inexpensive for the study of biologically important molecules. The dihydroxybenzenes electro-oxidation in aqueous solutions [15–25] involves the transfer of two electrons and two protons for the provision of the associated quinone.

It had been considered that the synthesis of new hydrocaffeic acid (HCA) derivatives would be efficient from a pharmaceutical viewpoint. This idea generated the prompt development of a facile and environmentally friendly reagentless electrochemical method for the synthesis of some new HCA derivatives (**7**, **8**) in aqueous solutions in an undivided cell, using carbon electrodes. Following a literature survey, this is the first research concerning the HCA electro-organic reactions, also extending to the electro-organic synthesis of new HCA derivatives (Fig. 1).

2 Experimental

2.1 Apparatus

All electrochemical experiments were performed with the Autolab potentiostat PGSTAT 30 (Eco Chemie B.V., Utrecht, Netherlands), equipped with GPES 4.9 software. A three-electrode cell was also employed, comprising a glassy-carbon electrode as working electrode (WE). In the controlled-potential macroscale electrolysis (bulk electrolysis), an assembly of three carbon rods (8 mm in diameter and 7 cm in length) was used as the WE, while a platinum wire was used as the counter electrode and Ag|AgCl|KCl (sat.) as the reference electrode. All potentials were reported with respect to this reference.

The NMR spectra were recorded on a Bruker FT-NMR-500 (Germany), the IR spectra were recorded on a Perkin-Elmer IR Spectrophotometer (USA). The melting point of the products was measured with the help of an electrothermal melting point model 9200.

2.2 Reagents

The Aldrich Chemical Co. supplied the reagent grade materials of HCA, benzenesulfinic acid sodium salt, *p*-toluenesulfinic acid sodium salt hydrate, not being further purified. The used salts for preparation of the acetate buffer (CH_3COOH/CH_3COONa, 0.15 mol L^{-1}) were reagent grade materials from Merck and were not purified. All solutions were prepared with acetonitrile (Merck) and deionized water.

2.3 Products characteristics

3-(4,5-dihydroxy-2-(phenylsulfonyl)phenyl)propanoic acid ($C_{15}H_{14}O_6S$, **7**): M.p. > 210 °C. FT-IR (KBr) (ν_{max}/cm^{-1}): 3,500–2,750 (OH, br), 1,690 (C = O), 1,610, 1,520, 1,458, 1,240, 1,160, 1,070, 753, 715, 690, 645, 560. ^1H NMR (500 MHz, DMSO-d_6 solution) δ 2.22 (t, 2H, J = 7.64 and 8.07 Hz, $–CH_2–$), 2.79 (t, 2H, J = 8.10 and 7.49 Hz, $–CH_2–$), 6.87 (s, 1H, HCA ring proton), 7.35 (d, 2H, J = 8.10 Hz, sulfinic acid ring proton), 7.58 (s, 1H, HCA ring proton), 7.75 (m, 3H, sulfinic acid ring proton), 10.33 (br, 2H, hydroxyl protons), 12.36 (br, 1H, carboxylic acid proton). ^{13}C NMR (500 MHz, DMSO-d_6 solution) δ 23.06 ($–CH_2–$), 30.4 ($–CH_2–$), 117.15, 120.60, 127.55, 128.87, 131.50, 133.05, 143.54, 143.67, 146.72, 151.60, 172.61 (–COOH).

3-(4,5-dihydroxy-2-tosylphenyl)propanoic acid ($C_{16}H_{16}O_6S$, **8**) M.p. > 210 °C (dec.). FT-IR (KBr) (ν_{max}/cm^{-1}): 3,500–2,800 (OH, br), 1,695 (C = O), 1,605, 1,535, 1,490, 1,475, 1,285, 1,150, 1,125, 1,078, 755, 640, 590. ^1H NMR (500 MHz, DMSO-d_6 solution) δ 2.24 (t, 2H, J = 7.66 and 8.09 Hz, $–CH_2–$), 2.36 (s, 3H, $–CH_3$), 2.82 (t, 2H, J = 8.20 and 7.52 Hz, $–CH_2–$), 6.74 (s, 1H, HCA ring proton), 7.39 (d, 2H, J = 8.20 Hz, sulfinic acid ring protons), 7.51 (s, 1H, HCA ring proton), 7.64 (d, 2H, J = 8.28 Hz, sulfinic acid ring protons), 10.25 (br, 2H, hydroxyl protons), 12.38 (br,

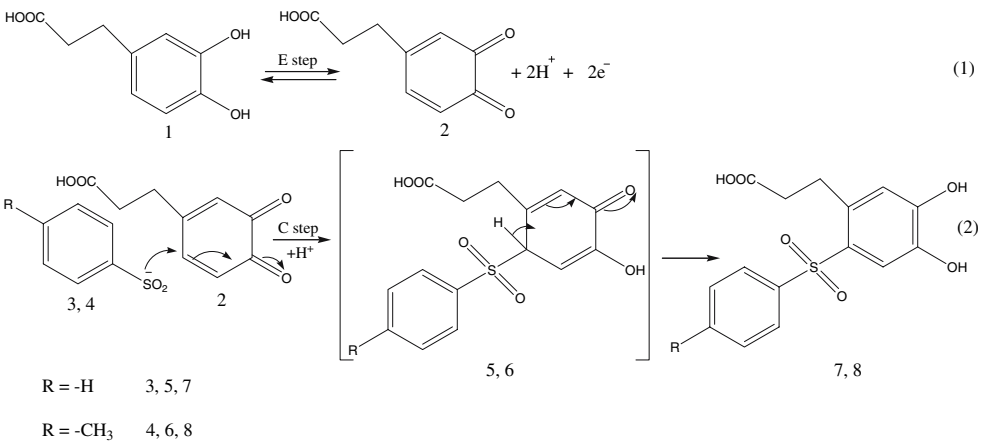

Fig. 1 Reaction mechanism for electro-organic synthesis of the products (**7** and **8**)

1H, carboxylic acid proton). ^{13}C NMR (500 MHz, DMSO-d_6 solution) δ 21.84 (–CH_3), 27.58 (–CH_2–), 36.04 (–CH_2–), 117.33, 119.19, 127.48, 128.82, 130.75, 133.15, 140.34, 144.39, 144.50, 151.36, 174.32 (–COOH).

3 Results and discussion

3.1 Electro-organic reactions of HCA

From a pharmaceutical aspect, it can be stated that the oxidation mechanisms on the electrode and in the body obey similar principles, since electrochemical reactions resemble the biological ones [26]. For this reason, the HCA cyclic voltammograms were obtained. Figure 2 displays the typical successive cyclic voltammogram (CV *a*) of 0.25 mmol L^{-1} HCA in acetate buffer, 0.15 mol L^{-1} (pH 4.5):acetonitrile (90:10 v/v). This CV demonstrates one anodic peak (I*a*) (at 0.315 V) and one respective cathodic peak (I*c*) (at 0.245 V). These peaks corresponding to the HCA (**1**) transformation to 3-(3,4-dioxocyclohexa-1,5-dienyl)propanoic acid (**2**) and vice versa within a two-electron and two-proton process ($\Delta Ep = 0.070$ V). The CV *b* presents the cyclic voltammogram obtained for a 0.25 mmol L^{-1} solution of **1** in the presence of 0.25 mmol L^{-1} benzenesulfinic acid (**3**), which exhibits two anodic peaks at 0.323 V (I*a*) and 0.489 V (II*a*). In this voltammogram, the cathodic counterpart of the anodic peak I*a* decreases, because of the reaction between **2** and **3**, leading to the product formation (**7**, Fig. 1). The anodic peak I*a* is associated with the HCA electro-oxidation (CV *b* of Fig. 2 in comparison with that of CV *a*) and II*a* is attributed to the product (**7**) electro-oxidation. In this condition, CV *c* of Fig. 2 is related to the electrochemical behavior of benzenesulfinic acid (**3**). Cyclic voltammograms were scanned at different rates between 20 and 250 mV s^{-1}. The I*c* peak height raises with the scan rate increase (Fig. 3). In this figure, II*c* is the cathodic counterpart of anodic peak II*a*. The plotting of the peak current ratio (i_{Ia}/i_{Ic}) *vs.* the scan rate confirms reactivity of **2** toward **3** (with the EC mechanism), appearing as an increase in the height of the i_{Ic} at higher scan rates (Fig. 3, inset).

For the determination of transferred electrons number, controlled-potential coulometry was performed in aqueous solution, containing 0.25 mmol of **1** and 0.25 mmol of **3** at 0.34 V. The consumption of about $2e^-$ per molecule of **1** was demonstrated. Figure 4 illustrates the CVs of 0.25 mmol L^{-1} HCA (**1**) in the absence (CV *a*) and presence (CV *b*) of *p*-toluenesulfinic acid (**4**). The anodic peak (II*a*, 0.473 V) in CV *b* of Fig. 4 is related to the product electro-oxidation (**8**). In this figure, CV *c* is associated to the electro-oxidation of **4**. The electro-organic reactions of **1** in the presence of *p*-toluenesulfinic acid (**4**) proceed in a way similar to that of **3**. This can be inferred from Fig. 4, compared with Fig. 2. In Fig. 5, CVs were scanned at different rates between 20 and 3,000 mV s^{-1}. It is evident that at low scan rates (Fig. 5, I) the height of I*a* anodic peak (related to the HCA electro-oxidation) is lower than II*a* anodic peak (related to the product (**8**) electro-oxidation), because at these scan rates the time scale for reaction of **2** with **4** is longer. On the contrary, at higher scan rates (Fig. 5, II), this phenomenon occurs vice versa, owing to the shorter time for reaction and product formation in the course of potential cycling. As a consequence, the product (**8**) formation diminishes during the scan rate increase. A similar behavior can be assumed from Fig. 3 for HCA

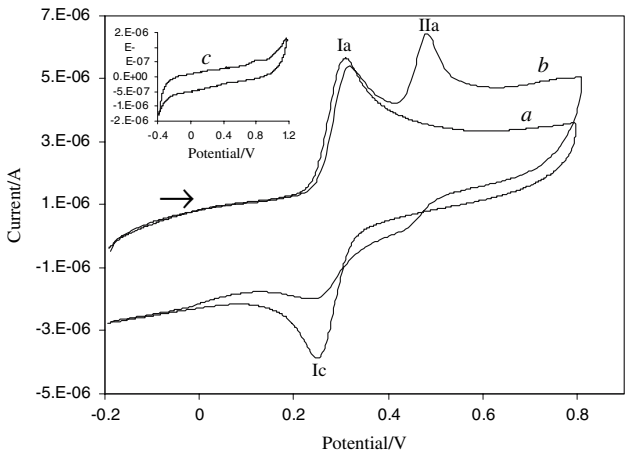

Fig. 2 Comparative cyclic voltammograms of 0.25 mmol L^{-1} HCA without (**a**), with (**b**) benzenesulfinic acid and **c** 0.25 mmol L^{-1} benzenesulfinic acid, at a glassy-carbon electrode in acetate buffer, 0.15 mol L^{-1} (pH 4.5): acetonitrile (90:10 v/v). Scan rate: 80 mV s^{-1}

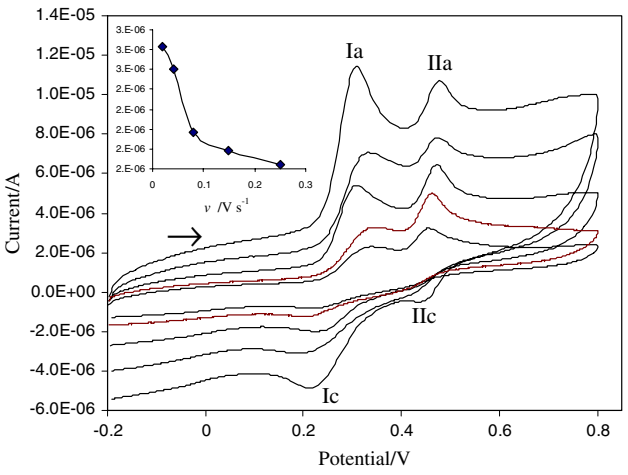

Fig. 3 Typical cyclic voltammograms of 0.25 mmol L^{-1} HCA in the presence of 0.25 mmol L^{-1} benzenesulfinic acid at different scan rates, from inner to outer: 20, 40, 80, 150 and 250 mV s^{-1}, other conditions as in Fig. 2

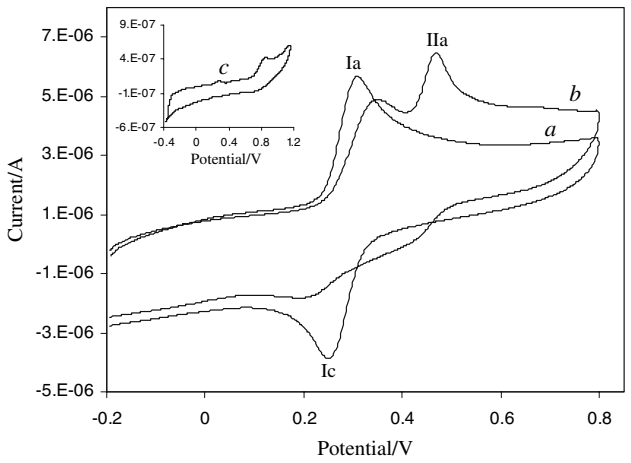

Fig. 4 Comparative cyclic voltammograms of 0.25 mmol L^{-1} HCA without (**a**), with (**b**) *p*-toluenesulfinic acid and **c** 0.25 mmol L^{-1} *p*-toluenesulfinic acid. Scan rate: 80 mV s^{-1}, other conditions as in Fig. 2

electro-organic reactions in the presence of benzenesulfinic acid (**3**).

3.2 Controlled-potential bulk electrolysis for electro-organic synthesis of the products

In this procedure, 200 mL mixture of water–acetonitrile (90:10, v/v), containing acetate buffer (pH 4.5, 0.15 M), 1.5 mmol HCA (**1**) and sulfinic acid (**3** or **4**) (in equal concentration), were electrolyzed at the chosen potential (0.34 V) in an undivided cell. For the minimum acetonitrile consumption (as a nonaqueous solvent), the high cell volume (200 mL) was employed in controlled-potential bulk electrolysis. The electrolysis time duration for electro-organic synthesis of the products (**7**, **8**) are 22 h and 17 h, respectively. Because the *p*-toluenesulfinic acid is a stronger nucleophile than benzenesulfinic acid, owing to methyl group presence in *p*-toluenesulfinic acid structure, required electrolysis time for production of **8** is less than that of **7**. The long electrolysis time can be attributed to the increase of reaction yield and decrease in the separation process. The electrolysis stopped when thin layer chromatography (TLC, with ethyl acetate) monitored the low amounts of starting materials. The process was interrupted several times during the electrolysis and the carbon electrodes were washed in acetone each 0.5 h in order to reactivate the electrode surface. Afterwards, the products were extracted by washing with dichloromethane. This procedure was repeated for several times. Both aqueous and nonaqueous media were controlled for product extraction by TLC. In the end, dichloromethane was air-dried at room temperature and characterized by means of FT-IR, ^{1}H NMR and ^{13}C NMR. The yield for the **7** and **8** products were 45% and 57%, respectively.

At the end of this section, a brief discussion about HCA anodic oxidation (**1**) during the electrolysis progress seems to be interesting. However, it should be taken into consideration that both HCA and its products (**7**, **8**) have an oxidation peak (Figs 2, 3, 4 and 5). As a conclusion, the ECE mechanism for HCA electro-oxidation is illustrated in the presence of **3** and **4**. All the same, the EC part of this mechanism was used with controlled-potential electrolysis being chosen at the potential value of 0.34 V.

Following these observations, a certain pathway was suggested for the electro-organic reactions of HCA (**1**) in the presence of **3** and **4**. According to these results, it appears that the 1,4-(Michael) addition reaction of **3** and **4** to **2** (Fig. 1, Eq. 2) is much faster than that of the other secondary reactions, leading to the products (**7**, **8**).

Thus, the present resulting data demonstrated the HCA anodic oxidation in the presence of nucleophile agents (**3**, **4**). In the first step of this process, the HCA was electrochemically oxidized to 3-(3,4-dioxocyclohexa-1, 5-dienyl)propanoic acid (**2**). Then, the **2** was attacked by nucleophilic agents (**3**, **4**) to form the products (**7**, **8**). The electro-organic reaction mechanism for oxidation of **1** is

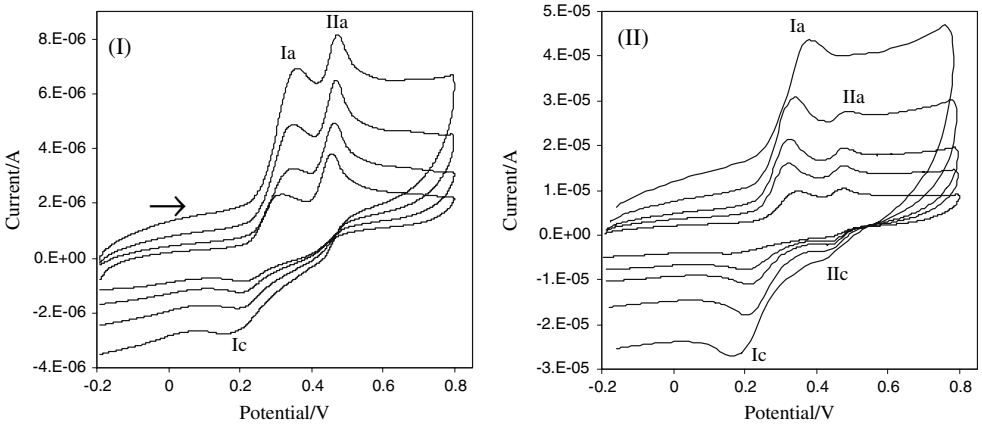

Fig. 5 Typical cyclic voltammograms of 0.25 mmol L^{-1} HCA in the presence of 0.25 mmol L^{-1} *p*-toluenesulfinic acid at different scan rates, from inner to outer: (I) 20, 40, 80, 150; (II) 250, 500, 750, 1,500, 3,000 mV s^{-1}, other conditions as in Fig. 2

displayed in Fig. 1 in the presence of **3** and **4**. Despite the fact that HCA dimerization reaction rate increases with the pH values increase (because of the **3** and **4** anionic formation demand through acid dissociation reaction), the **7** and **8** electro-organic synthesis was carried out at pH = 4.5. This work provided a better comprehension of HCA electrochemical behavior in the electro-organic reactions.

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