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Electrochemical Oxidation of Symmetrical Amides of Ferulic Acid in Aprotic Medium

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ABSTRACT

The electrochemical behavior of three symmetrical amides derived from ferulic acid (FA) is reported. Strong adsorption processes of all compounds to the carbon electrode surface were observed. Experimental and theoretical results provide evidence that carbon radicals, located at the alpha position with respect to the carbonyl group of the ferulic moieties, are generated during the oxidation process and react with the electrode surface. The identity of the diamine connectors does not exert an influence on the global oxidation mechanism and has a very modest impact on the efficiency of the observed adsorption process. The dimeric topology of the three diamides also favors the blocking of the electrode surface compared with monomeric analogues studied before.

1. Introduction

Hydroxycinnamic acids and their derivatives are widely found in the plant kingdom, mainly in cereals, fruits and also in propolis from diverse geographic regions [1–6]. They have been recognized as potential therapeutic agents against the prevention of a wide range of free radical-related illnesses, including cancer, diabetes, neurodegenerative disorders, cardiovascular dysfunction and inflammatory and skin diseases [7–15]. Among them, ferulic acid (FA) is a natural antioxidant that arises from the metabolism of phenylalanine and tyrosine [4,16]. It is found in vegetables, leaves and seeds, especially artichokes, eggplants, rice bran, and in some Chinese medicinal herbs also, such as *Angelica sinensis*, *Cimicifuga heracleifolia* and *Lignsticum chuangxiong* [17]. The biological properties of this acid and its natural or synthetic monomeric derivatives have been investigated by numerous research groups during recent years [18–20]. On the other hand, dimeric compounds derived from FA have also been found recently in plants employed in the traditional medicine of some countries to treat ailments associated with damage caused by reactive oxygen species (ROS) [21,22].

Even though the electrochemical behavior of FA is well documented in the literature [23–25], the interest in the oxidation mechanisms of new [26,27] derivatives continue, in order to improve the understanding of the structure-activity relationship. On the other hand, electrochemical methods have been an invaluable tool to investigate the oxidation mechanism of curcumine (diferuloylmethane) [28–30], the principal component of turmeric (curry spice), whose potential therapeutic properties could be related to the antioxidant capacity of this symmetrical FA derivative [31].

Recently, we reported the anodic oxidation of a series of esters and amides derivatives of caffeic acid (CA) and FA [32]. From those hydroxycinnamic compounds, caffeic acid benzyl amide (CABzA) showed the lowest oxidation potential value, even lower than the value obtained for caffeic acid phenethyl ester (CAPE), which has been recognized as an efficient antioxidant. In that study we found that radical scavenging capacity, evaluated through 2,2'-diphenyl-1-pycrilhydrazyl (DPPH) assay, of the completed series showed a good relationship with the oxidation potentials. In addition, blocking of the electrode surface phenomenon was observed only during the electrochemical oxidation of ferulic acid amides. Our interest in this subject stems from our desire to understand the precise mechanisms that underlie the electrochemical oxidation processes of new hydroxycinnamic acid derivatives.

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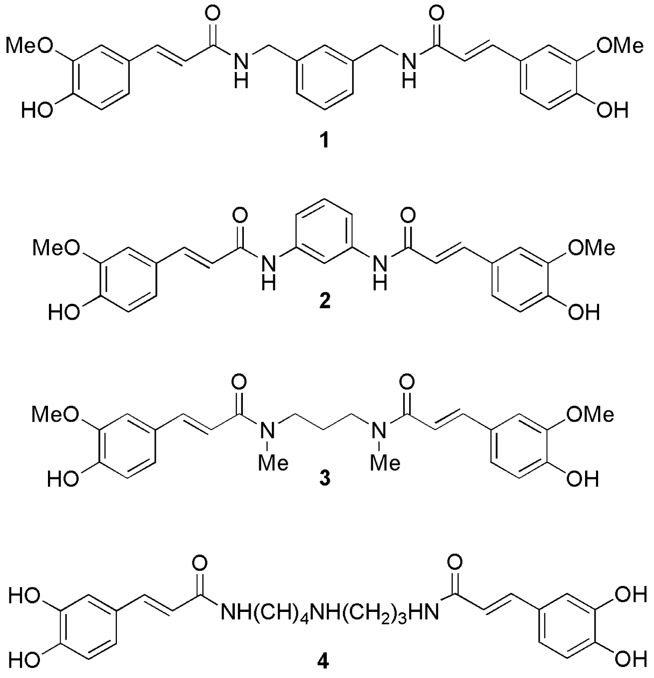

Fig. 1. Symmetrical amides synthetized and studied in the present work (**1**-**3**) and the dimeric amide identified in eggplant by Withaker *et al.* (compound **4**, ref 33).

In the present work, we report the electrochemical oxidation in an aprotic medium of three symmetrical amides structurally based on FA, which are shown in Fig. 1 (compounds **1**-**3**). Related compounds have also been found in natural products, and synthetic analogues have attracted the attention of several authors as potential therapeutic agents. For example, compound **4** (Fig. 1) was identified by Whitaker in eggplant, one of the top 10 vegetables in oxygen radical scavenger capacity [33], whereas, the cytotoxic activity of similar FA amides was evaluated by Palop *et al.* [34]. Interestingly, the results revealed that the nature of the amine used as connector of the ferulyl type moieties could be decisive between cytotoxic activity or inactivity against some cell lines. In addition, the amyloid beta-aggregation inhibition capacities of **1** and related compounds have been evaluated before by other authors [35]. However, to the best of our knowledge, the details of the oxidation mechanism of dimeric hydroxycinnamic acid amides have not been reported before. Complementary information was obtained from electronic structure calculations and it is also discussed here.

2. Experimental

2.1. Instrumentation

Melting points were determined with Melt-Temp apparatus and are not corrected. ^{1}H and ^{13}C spectra were recorded on a Varian Mercury Plus (300 MHz) and an Agilent Technologies 400/54 Premium Shielded (400 MHz) spectrometers, using deuterated methanol (CD$_3$OD) as solvent. Chemical shifts were recorded in δ (ppm) values downfield from TMS as internal standard. Coupling constants (J) are given in Hertz. ESI-TOF MS spectra were measured on a Gi969A Agilent spectrometer. Cyclic voltammetry experiments were performed in a potentiostat PGZ-301 (Radiometer Copenhagen) with positive feedback resistance compensation.

2.2. Chemicals

All chemical reagents and tetrabutylamonium hexafluorophosphate 99% (n-Bu$_4$NP$_6$) were purchased from Sigma-Aldrich and were used without purification. DMF and CH$_2$Cl$_2$ were of reagent grade and were distilled before use. Acetonitrile (AN) (CROMASOLV® Plus content of H$_2$O <0.1%) was used as solvent during the electrochemical experiments. Products were purified by flash column chromatography on silica gel 230-400 mesh using EtOAc/hexanes as eluent mixtures.

2.3. General procedure for the synthesis of compounds ***1***-***3***

In a 250 mL flask provided with stir bar and rubber septa, 5.25 mmol (1.01 g) of ferulic acid, 20 mL of DMF, and 5.25 mmol (0.73 mL) of Et$_3$N were placed. The solution was stirred for 10 minutes at 0 °C in an ice bath, after that, 2.5 mmol of either m-xylylenediamine, 1,3-phenylenediamine or N,N'-dimethyl-1,3-propanediamine were directly added to the solution. About 5.25 mmol (2.32 g) of (benzotriazol-1-yloxy)*tris*(dimethylamino)phosphonium hexafluorophosphate (BOP) dissolved in 20 mL of CH$_2$Cl$_2$ were added via syringe and the mixture was stirred at 0 °C for a further 30 minutes. The reactions then proceeded at room temperature for 24 h, after which CH$_2$Cl$_2$ was removed under reduced pressure and the resulting solution was diluted in 150 mL of cold water. The product was extracted three times with 150 mL of EtOAc, and the organic layer was washed with 100 mL of HCl 1 N, 100 mL of water and then with 100 mL of an aqueous solution of NaHCO$_3$ 1 M. Finally, it was dried over sodium sulfate. The solvent was removed in a rotary evaporator until dry and the residue was chromatographed on silica gel employing mixtures of hexanes/EtOAc as eluents with a gradient from 80:20 to 50:50. Yields are given for isolated products.

Compound **1**: (2*E*,2'*E*)-*N*,*N'*-(1,3-phenylenebis(methylene))*bis*(3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide) M.p. 144-145 °C. Isolated yield (9.09%)

^{1}H NMR (300 MHz, CD$_3$OD) δ (ppm): 3.85 (s, 6H) 4.50 (s, 4H) 6.45 (d, $^3J_{HH}$= 15.7 Hz, 2H) 6.77 (d, $^3J_{HH}$= 8.2 Hz, 2H) 7.03 (dd, $^3J_{HH}$= 8.2 Hz, $^4J_{HH}$ = 1.9 Hz, 2H) 7.1 (d, $^4J_{HH}$= 1.9 Hz, 2H) 7.20-7.32 (m, 4H) 7.46 (d, $^3J_{HH}$= 15.7 Hz, 2H). ^{13}C NMR (75.5 MHz, CD$_3$OD) δ (ppm): 44.3, 56.5, 111.5, 116.5, 118.5, 123.3, 127.4, 127.5, 128.2, 129.8, 140.4, 142.5, 149.2, 149.9, 169.0. MS (ESI-TOF) calculated for [C$_{28}$H$_{29}$N$_2$O$_6$]$^+$ 489.20, found [M + H]$^+$ 489.20.

Compound **2**: (2*E*,2'*E*)-*N*,*N'*-(1,3-phenylene)*bis*(3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide) M.p. 121-122 °C. Isolated yield (5.7%)

^{1}H NMR (300 MHz, CD$_3$OD) δ (ppm): 3.88 (s, 6H) 6.61 (d, $^3J_{HH}$= 15.7 Hz, 2H) 6.81 (d, $^3J_{HH}$= 8.0 Hz, 2H) 7.06 (d, $^3J_{HH}$ = 8.2 Hz, 2H) 7.12 (s, 2H) 7.23-7.41 (m, 4H) 7.55 (d, $^3J_{HH}$ = 15.7 Hz, 2H). ^{13}C RMN (75.5 MHz, CD$_3$OD) δ (ppm): 56.5, 111.7, 113.0, 116.5, 117.0, 119.1, 123.5, 128.2, 130.2, 140.6, 143.3, 149.2, 150.0, 167.2. MS (ESI-TOF) calculated for [C$_{26}$H$_{25}$N$_2$O$_6$]$^+$ 461.17, found [M + H]$^+$ 461.17

Compound **3**: (2*E*,2'*E*)-*N*,*N'*-dimethyl-(propane-1,3-diyl)*bis*(3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide) M.p. 150-151 °C. Isolated yield (9.45%)

^{1}H RMN (400 MHz, CD$_3$OD) δ (ppm): 1.95 (m, 2H), 2.90 (s, 6H), 3.40-3.60 (m, 4H) 3.81 (s,6H) 6.81 (d, $^2J_{HH}$= 7.6 Hz, 2H) 6.99 (d, $^3J_{HH}$= 15.2 Hz, 2H) 7.10 (d, $^2J_{HH}$= 7.6, 2H) 7.27 (s, 2H) 7.50 (d, $^3J_{HH}$= 15.2 Hz, 2H) 8.06 (s, 2H). ^{13}C RMN (100.5 MHz, CD$_3$OD) δ (ppm): 27.0, 34.9, 45.5, 55.7, 111.5, 115.9, 122.7, 127.0, 128.3, 143.1, 148.6, 149.4, 167.2. MS (ESI-TOF) calculated for [C$_{25}$H$_{31}$N$_2$O$_6$]$^+$ 455.22, found [M + H]$^+$ 455.22

2.4. Voltammetry measurements

A Pyrex glass three-electrode cell was used in the electrochemical experiments. The working electrode was a 3 mm diameter glassy carbon disk (Sigradur G from HTW, Germany). This electrode was polished with 1 µm alumina powder and rinsed in an ultrasound bath with distilled water and ethanol before each