



Study of the oxidation mechanisms associated to new dimeric and trimeric esters of ferulic acid



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ABSTRACT

The electrochemical behaviour of new ferulic acid derivatives, three dimeric and one tripodal esters as well as the monomeric benzylic ester, is described. All of them follow an ECE (electrochemical–chemical–electrochemical) oxidation mechanism. Electrografting processes were observed too, except in the case of the monomeric ester. Interestingly, topology seems to play an important role in their capacity of being adsorbed by the electrode, which suggest that a greater reactivity of the *bi*- and *tri*- radicals, probably generated during the first steps of electrochemical oxidation of this type of compounds or an increase of the van der Waals interactions between huge molecules and the electrode surface, could be the main responsible. In addition, electrodonating power, as that defined within the density functional theory, was estimated for the benzylic ester, one dimeric ester, the tripodal ester, and the ferulic acid. This quantity was compared with the corresponding experimental values of the oxidation potential. Results show that monomers are more effective for the process of donating electrons; however, a higher number of ferulic units increases the ability of the *bis* and *tris* structures to increase their electrodonating power.

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1. Introduction

Phenolic compounds have attracted the attention of numerous research groups during the last years, since it is believed that they contribute to prevent the oxidative damage caused by free radicals and reactive oxygen species (ROS) [1–3]. They belong to a huge family of compounds that include phenolic acids derived from benzoic or cinnamic acids and extend to flavonoids or tannins, all of them secondary metabolites ubiquitous in plants [4], such as the bioactives caffeic acid (CA), sinapic acid (SA), and ferulic acid (FA), three members of hydroxycinnamic acids group (Fig. 1).

FA occurs in vegetables, some fruits, sweet corn, rice bran, and coffee [5,6], and exhibits a wide range of therapeutic properties like neuroprotective, hepatoprotective, radioprotective, antidiabetes, antiapoptotic, antiageing, and antiinflammatory effects, which could be related to its antioxidant capacity [5]. FA dimeric derivatives are present in nature too, for example covalent diferulates cross-linked between polysaccharides (structure 1 in Fig. 2) are

found in plant tissues [7]. On the other hand, compounds 2 and 3 were found in *Ficus foveolata* [8], which is employed to prepare a rejuvenating agent and a tonic to enhance the sexual performance by the people of the North and North-eastern part of Thailand. Compound 2 was also isolated from *Pachycentria formosana* [9], an endemic creeping shrub from the forests of Taiwan, whereas a mixture of 4 and 5 was found in *Stereospermum acuminatissimum* [10], a tall tree from the forest of west tropical Africa, whose leaves and barks are used for antiinflammatory purposes in the Cameroonian traditional medicine. Another symmetrical derivative that contains two ferulyl moieties into its structure is the curcumin (diferuloylmethane, compound 6 in Fig. 2), the principal component of turmeric, one of the most important ingredients in curry powder [11], which has received the attention of numerous research groups due to their high medicinal potential, probably associated to its antioxidant capacity [12–16].

The interesting therapeutic properties of FA have motivated the design of new synthetic derivatives of this hydroxycinnamic acid [17–19], in order to understand the structure–activity relationship and to enhance its beneficial contributions to human health. On the other hand, electrochemistry has become an important tool in the study of antioxidant properties of organic compounds

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[17,18,20,21], since their oxidation potentials can be used to study its electron donating capacity, and also as an indicator of its radical scavenging ability. It has been shown that there is a relationship between less positive oxidation potential (or a higher susceptibility to electrochemical oxidation) and higher radical scavenging activities [17,18,21]. Electrochemical behaviour of **FA** has been described extensively in the literature [22–25], nevertheless the interest in the study of electrochemical oxidation of new derivatives of this acid still continues.

Recently, we have undertaken the study of the oxidation mechanisms of new hydroxycinnamic acid derivatives with dimeric topology through electrochemical and theoretical chemistry methods. Our interest in this type of compounds arise from the fact that similar structures are found in natural products with medicinal potential, and even synthetic analogues have been prepared in order to explore their therapeutic properties [26,27]. In a previous report [28], we found that the electrochemical oxidation in aprotic medium of three symmetrical *bis*-amides derived from **FA** involves the lost of an electron followed by a deprotonation reaction, and the subsequent delocalization of the radical toward the carbon to the carbonyl group, at the lateral chain of feruloyl moieties, which react in a very efficient way with the surface of the glassy carbon electrode (GCE). Theoretical calculations and electrochemical experiments confirmed the proposed mechanism. Although adsorption phenomena were observed previously by our group in monomeric ferulic amides too [25], dimeric topology seems to increase the blocking effect of the electrode surface in a significant way. In contrast, during the electrochemical oxidation of analogous CA amides, similar electrografting processes were not observed [29]. In addition, we found interesting differences in the electrochemical behaviour of dimeric ester derivatives and amide derivatives of CA, nevertheless that all of them contained two caffeoyl electroactive moieties, which suggests that small differences in the structure result in interesting changes in the electrochemical responses of this type of compounds.

In the present work, we report the electrochemical oxidation in aprotic medium of new three dimeric esters **7–9** derived from **FA** (Fig. 3). Cyclic voltammetry of analogous CA dimeric esters was carried out in DMSO by our group before [29]. In order to compare the effect of the topology in the electrochemical behaviour of **7–9**, the anodic oxidation of monomeric benzylic ester of **FA**, compound **10**, is also discussed here. On the other hand, inspired by Leontopodic acid (a natural triester derived from **CA** with interesting antioxidant and protective DNA properties) [30], we prepared the new tripodal ester **11**, whose conformational preferences were previously analysed *in silico* by our group [31]. Its electrochemical behaviour is also presented here through cyclic voltammetry results. In addition, Density Functional Theory (DFT) calculations of compounds **7**, **10**, **11**, as well **FA**, were performed in order to evaluate the electrodonating power (ω^-), as described by Gázquez et al. [32], therefore, we have estimated the corresponding ionisation potentials (IP), adiabatic and vertical, in gas phase and applying solvent effect. Comparison of the obtained theoretical (IP and ω^-) and experimental (oxidation potential) trends is discussed, as well.

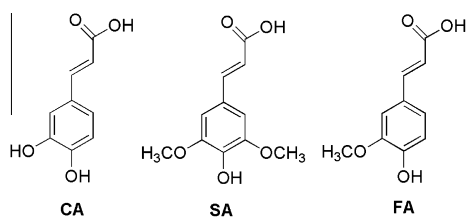


Fig. 1. Caffeic acid (**CA**), sinapic acid (**SA**), and ferulic acid (**FA**).

2. Experimental

2.1. Instrumentation

Melting points were determined with Melt-Temp apparatus and are not corrected. ^1H and ^{13}C spectra were recorded on a JEOL GSX-270 and an Agilent Technologies 400/54 Premium Shielded spectrometers, using deuterated chloroform (CDCl_3) or acetone ($\text{C}_3\text{D}_6\text{O}$) as solvents. Chemical shifts were recorded in δ (ppm) values downfield from TMS as internal standard. Coupling constants (J) are given in Hertz. HR-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

Ferulic acid (99%), 1,2-dibromoethane (98%), 1,5-dibromopentane (97%), 1,8-dibromooctane (98%), 1,3,5-*tris*(bromomethyl)benzene (97%), benzyl bromide (98%), tetrabutylammonium hydroxide in methanol (1.0 M) and tetrabutylammonium hexafluorophosphate 98% ($n\text{-Bu}_4\text{NPF}_6$) were purchased from Sigma–Aldrich and were used without purification. Acetonitrile (AN) (content of $\text{H}_2\text{O} < 0.1\%$, CROMASOLV[®] Plus) was used as solvent in the preparation of compounds **7–9** and **11** and during the electrochemical experiments too. Dimethylformamide (DMF) reagent grade, was employed in the synthesis of compound **10** after distillation. Products were purified by flash column chromatography on silica gel 230–400 mesh using as eluent mixtures of EtOAc/hexanes.

2.3. Synthesis

Procedure to obtain 7–9 and 11. In a 250 mL flask provided with a stir bar, were placed: 5.21 mmol (1.01 g) of **FA**, 50 mL of AN, and 5.14 mmol (5.2 mL) of a solution 1 M of tetrabutylammonium hydroxide in methanol. The resulting mixture was allowed to stir for 30 minutes at room temperature, after that, 2.50 or 1.70 mmol (in the case of **7–9** or **11**, respectively) of the corresponding halide were added directly to the solution. The reactions proceeded at room temperature for 52 h, after which the crude of reaction was dried under vacuum. Then 50 mL of CH_2Cl_2 were added, the solution was washed several times with water and the organic layer was dried over magnesium sulphate. The solvent was removed in a rotary evaporator and the residue was chromatographed on silica gel. Yields are given for isolated products.

Compound **10** was prepared in agreement to the procedure reported by Son et al. [33].

2.3.1. Benzylic ester of ferulic acid (**10**)

The product was a pale yellow liquid. Isolated yield: 40%. ^1H NMR (270 MHz, CDCl_3) δ (ppm): 3.92 (s, 3H), 5.25 (s, 2H), 5.93 (s, OH), 6.32 (d, $^3J_{\text{HH}} = 16.0$ Hz, 1H), 6.90 (d, $^3J_{\text{HH}} = 8.0$ Hz, 1H), 7.02 (d, $^4J_{\text{HH}} = 2.0$ Hz, 1H), 7.06 (dd, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{HH}} = 2.0$ Hz, 1H), 7.34–7.43 (m, 5H). 7.64 (d, $^3J_{\text{HH}} = 16.0$ Hz, 1H), ^{13}C NMR (100.5 MHz, CDCl_3) δ (ppm): 56.0, 63.3, 109.3, 114.8, 115.2, 123.2, 127.0, 128.3, 128.4, 128.7, 136.2, 145.3, 146.8, 148.1, 167.2.

2.3.2. 1,2-Di-O-feruloyl ethanediol (**7**)

M.p. 103 °C. Isolated yield: 15%. ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ (ppm): 3.91 (s, 6H), 4.44 (s, 4H), 6.43 (d, $^3J_{\text{HH}} = 15.9$ Hz, 2H), 6.87 (d, $^3J_{\text{HH}} = 8.1$ Hz, 2H), 7.15 (dd, $^3J_{\text{HH}} = 8.1$ Hz, $^3J_{\text{HH}} = 2.0$ Hz, 2H), 7.36 (d, $^4J_{\text{HH}} = 2.0$ Hz, 2H), 7.64 (d, $^3J_{\text{HH}} = 16.0$ Hz, 2H), 8.15 (broad signal, 2H, OH). ^{13}C NMR (100.5 MHz, CDCl_3) δ (ppm): 56.3, 62.5, 111.3, 115.3, 116.0, 124.2, 127.4, 146.2, 148.8, 150.2, 167.4. MS

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