Theoretical investigation of stereochemistry and solvent influence on antioxidant activity of ferulic acid

Alicja Urbaniak [a,*], Małgorzata Szeląg [b], Marcin Molski [c]

[a] Department of Bioorganic Chemistry, Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland
[b] Department of Human Molecular Genetics, Faculty of Biology, Adam Mickiewicz University, Umultowska 89, 61-614 Poznań, Poland
[c] Department of Theoretical Chemistry, Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

ABSTRACT

In this paper, we present a summary of structure – antioxidant activity relation of ferulic acid's stereoisomers. We have analyzed four antioxidant mechanisms important in free radicals scavenging: hydrogen atom transfer (HAT), sequential proton loss electron transfer (SPLET), single electron transfer – proton transfer (SET-PT) and transition metal chelation (TMC) by calculation of antioxidant descriptors and other related parameters. All calculations have been performed with B3LYP/6-311++G(2d,2p) level of theory in vacuum and in ethanol, water and dimethyl sulfoxide media, based on conductor-like polarizable continuum solvation model. The results have shown that *cis*-ferulic acid and *trans*-ferulic acid (including less energetic rotamers) display similar reactivity and, in comparison to previously published results for phenols and polyphenols, may be considered as a good antioxidants. It has been determined that planar structure of ferulic acid (FA) supported by π-electron delocalization positively influences the ability of this compound to neutralize free radicals. Moreover, we have shown that for FA HAT is the most preferable in gas-phase and SPLET is more preferable in all polar media studied. FA might be also considered as a potential transition metals chelating agent.

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1. Introduction

Ferulic acid (FA, 4-hydroxy-5-methoxycinnamic acid) belongs to the cinnamic acid derivatives (Fig. 1(1)). It occurs in form of two stereoisomers: *trans*-ferulic acid (*t*-FA, Fig. 1(2)) and *cis*-ferulic acid (*c*-FA, Fig. 1(3)). Ferulic acid esters (γ-oryzanols) are active ingredients of wild rice. FA occurs in natural environment in cell walls of grains, vegetables and fruits, where is a part of the complex structure of lignins, hydrolyzing tannins and as esters or glycosides (e.g. mono-, di-, or polysaccharides). As a single form (not connected with other compounds) it is present in small quantities in plants, and its concentration depends on the species and maturity of the plant. Under heating plants and vegetables (especially in an acidic environment) the concentration of free FA increases due to hydrolysis of ester and glycosidic bonds.

The specific biological function of FA is the antioxidant activity, namely the ability to eliminate reactive forms of oxygen and free radicals (mostly superoxide, hydroxyl and hydroxy peroxides). Its antioxidant properties have been confirmed by many experimental studies [1–6]. It is believed that free radicals are involved in aging process and are responsible for many diseases as cancer, cardiovascular disorders, atherosclerosis, asthma, arthritis, neurodegenerative disorders: Alzheimer's, Parkinson's disease and dementia. Observed toxicity of synthetic antioxidants [7–11] caused the increased interest in natural compounds showing this property. Ability to counter the effects of oxidative stress to the skin caused by UV radiation and the presence of nitric oxide with connection to the radical scavenging properties makes the FA a very effective compound in fight with ROS (reactive oxygen species) [12].

Free radicals can be deactivated in reactions with phenolic antioxidants according to the following mechanisms [13–29] (Fig. 2):
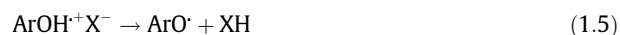
1. Hydrogen atom transfer (HAT)

$$ArOH + X^{\bullet} \rightarrow ArO^{\bullet} + XH \tag{1.1}$$

2. Sequential proton loss electron transfer (SPLET)

$$ArOH \rightarrow ArO^{-} + H^{+} \tag{1.2}$$

$$ArO^{-} + X^{\bullet} + H^{+} \rightarrow ArO^{\bullet} + XH \tag{1.3}$$
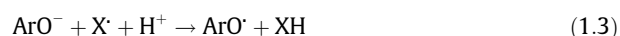
3. Single electron transfer followed by proton transfer (SET-PT)

$$ArOH + X^{\bullet} \rightarrow ArOH^{\bullet+} + X^{-} \tag{1.4}$$

$$ArOH^{\bullet+}X^{-} \rightarrow ArO^{\bullet} + XH \tag{1.5}$$

* Corresponding author. Address: Department of Bioorganic Chemistry, Grunwaldzka 6, 60-780 Poznań, Poland. Tel.: +48 507468651.
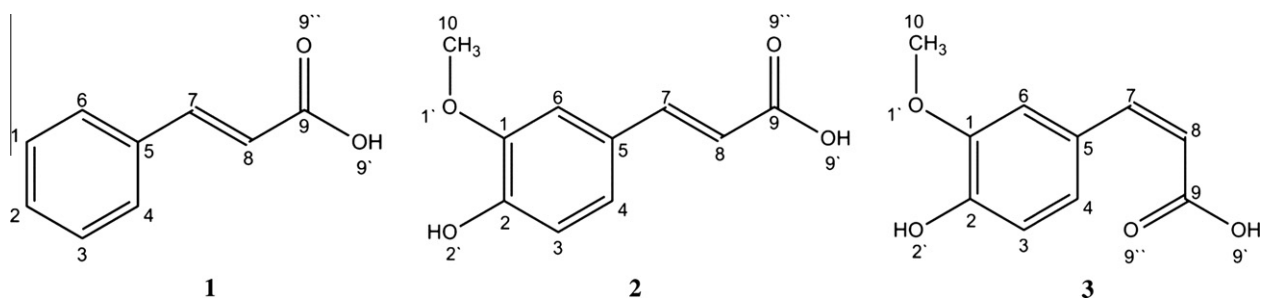*E-mail address:* au50380@st.amu.edu.pl (A. Urbaniak).

Fig. 1. Molecular geometry of (1) *trans*-cinnamic acid, (2) *trans*-ferulic acid and (3) *cis*-ferulic acid.

Moreover, phenolic antioxidants pose the ability to chelate the ions of transition metals, according to Transition Metals Chelation (TMC) mechanism [13,25], which is connected to the Fenton reaction (1.6). According to TMC each molecule which may dissociate giving anion and proton has the ability to chelate heavy metals. Because chelation often occurs through deprotonated hydroxyls in the polyphenols, the ability of a molecule to give the proton is calculated (1.7).

$$H_2O_2 + M^{n+} \rightarrow HO^- + HO^· + M^{(n+1)+} \quad (1.6)$$

$$ArOH \rightarrow ArO^- + H^+ \quad (1.7)$$
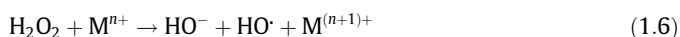
Antioxidant abilities are also related with distribution of HOMO, distribution of LUMO and spin density (SD) of molecules. The lower HOMO energy is the weaker are the abilities of molecule to proton donation. Knowing HOMO distribution we can conclude about the groups in molecule which can be easily attacked by free radicals. From the difference between HOMO and LUMO energy we can conclude about chemical activity of the molecule. The lower ΔE(LUMO–HOMO) is the more active the molecule investigated, what

was proved in scientific studies for *trans*-ferulic acid in vacuum [41], but was never described for both stereoisomers in polar media such as water, ethanol and DMSO. SD parameter characterizes the distribution of non-paired electron and the stability of radical form of the molecule.

In this work we provide a comprehensive analysis of structure – antioxidant activity relation for *trans*-ferulic acid and *cis*-ferulic acid. We present a review of currently analyzed antioxidant parameters for ferulic acid supported by the comparison of our results with available computational data published in the last decade.

2. Computational details

All quantum-chemical calculations were performed using Gaussian 03W computational package [30]. To find the starting geometries and structures with minimum energy a conformational analysis was performed. Through the scanning of dihedral angles: $\alpha = H_{2'} - O_{2'} - C_2 - C_3$ (describing the rotation of 2'-OH group around $O_{2'}$—C_2 single bond) and $\theta = C_{10} - O_{1'} - C_1 - C_6$ (describing
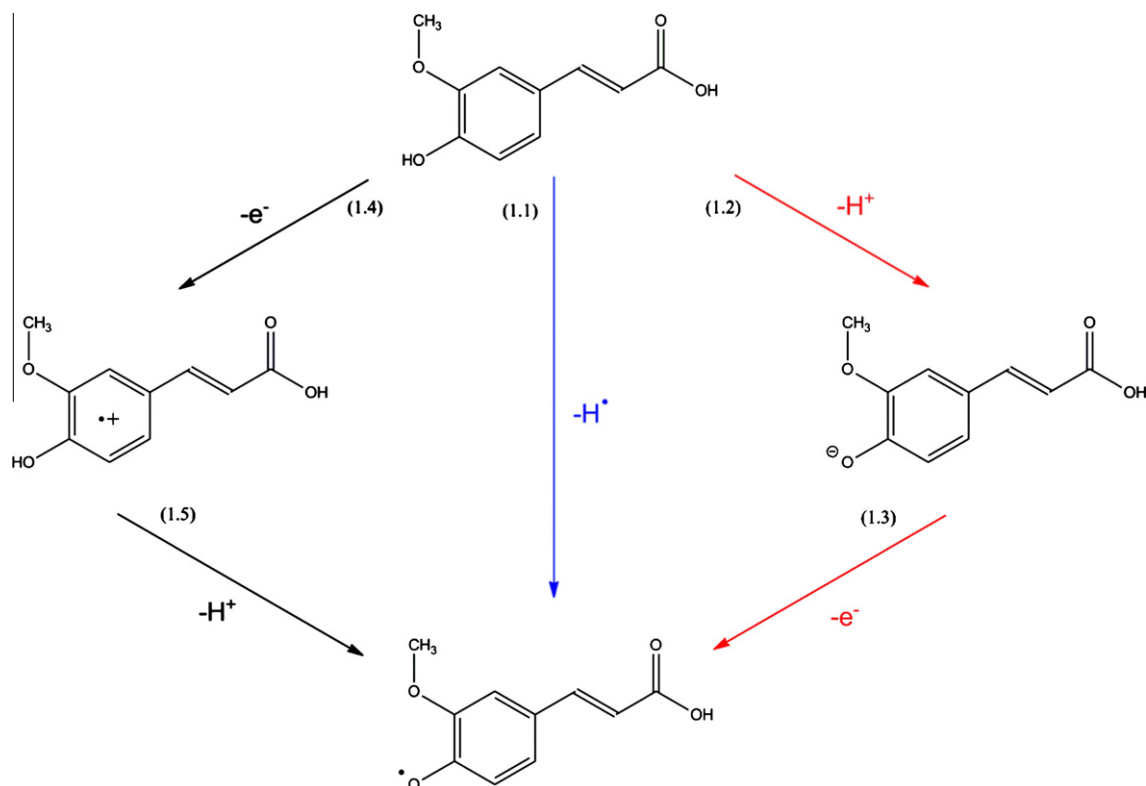

Fig. 2. Antioxidant properties of ferulic acid (1.1) – HAT, (1.2) and (1.3) – SPLET, (1.4) and (1.5) – SET-PT mechanisms.