Food Chemistry 210 (2016) 585–592

Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

Comparative study of the antioxidative activities of caffeoylquinic and caffeic acids

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ARTICLE INFO

Article history:
Received 14 October 2015
Received in revised form 1 April 2016
Accepted 2 May 2016
Available online 3 May 2016

Chemical compounds studied in this article:
Caffeic acid (PubChem CID: 689043)
Chlorogenic acid (PubChem CID: 1794427)
Cryptochlorogenic acid (PubChem CID: 9798666)
Neochlorogenic acid (PubChem CID: 5280633)

Keywords:
Antioxidative activity
Chlorogenic acid isomers
Caffeic acid
Thermodynamic parameters
HAT, SPLET, and SET-PT

ABSTRACT

A detailed conformational analysis was performed to determine the most stable conformers of chlorogenic, cryptochlorogenic, and neochlorogenic acids. The simulated and experimental NMR spectra of caffeoylquinic acids are in excellent agreement. The bond dissociation enthalpies, proton affinities, electron transfer enthalpies, ionisation potentials, and proton dissociation enthalpies for these compounds and caffeic acid in benzene, methanol, and water were used for thermodynamic consideration of the major antioxidative mechanisms: HAT (Hydrogen Atom Transfer), SPLET (Sequential Proton-Loss Electron-Transfer), and SET-PT (Single Electron Transfer – Proton Transfer). All compounds are characterised with very similar values of each enthalpy, suggesting that they will exhibit comparable antioxidative activities. This assumption is in perfect accord with the experimental findings. It was suggested that HAT may be the predominant mechanism in nonpolar solvents, while HAT and SPLET are competitive pathways in polar media. All calculations were performed using the B3LYP-D2/6-311++G(d,p) and M06-2X/6-311++G(d,p) levels of theory and CPCM solvation model.

1. Introduction

Caffeoylquinic acids are esters of caffeic acid (**CA**) with quinic acid. According to the difference in binding site, there are three isomers of these phenolic acids (Fig. 1): chlorogenic acid (5-O-caffeoylquinic acid, **5CQA**), cryptochlorogenic acid (4-O-caffeoylquinic acid, **4CQA**), and neochlorogenic acid (3-O-caffeoylquinic acid, **3CQA**).

5CQA is a constituent of various plants, where it acts as an antioxidant, and thus protects against lipid peroxidation (Kasai, Fukada, Yamaizumi, Sugie, & Mori, 2000; Ohnish et al., 1994). This compound is especially abundant in coffee, but it is also the major soluble polyphenol found in potato, tomato and eggplant, and it also accumulates to considerable levels in apples, pears, plums, and blueberries (Wang, Wang, & Yang, 2007). Green coffee extract is used for production of encapsulated food supplements, some beverages, and conventional coffee products (Farah, Monteiro, Donangelo, & Lafay, 2008). **3CQA** was found in the fresh and dried plum at significant concentration (Fang, Yu, & Prior, 2002), whereas the concentrations of **4CQA** and **5CQA** were smaller (Fang et al., 2002; Nakatani et al., 2000).

The studies on caffeoylquinic acids are mainly focused on experimental examinations of **5CQA** (Clifford, Wu, Kirkpatrick, & Kuhnert, 2007; Nakatani et al., 2000). This compound proved to exhibit anticarcinogenic, antimutagenic (Friedman, 1997), and glucose lowering effects (Thompson, Yoon, Jenkins, Wolever, & Jenkins, 1983), antioxidative activity for human low-density lipoprotein (Rice-Evans, Miller, & Paganga, 1996), as well as anti-obesity properties and ability to improve lipid metabolism (Cho et al., 2010). In addition, **5CQA** acts as a scavenger of reactive oxygen and nitrogen species (Kono et al., 1997). Surprisingly, theoretical investigations of caffeoylquinic acids have been initiated only recently, where **5CQA** was included in a set of twenty natural polyphenols whose structure-thermodynamics-antioxidant relationships were examined by means of the DPPH· scavenging assay, B3LYP/6-311++G(d,p) calculations, and quantitative structure-activity relationship modelling (Chen, Xiao, Zheng, & Liang, 2015). It is reasonable to expect that other two isomers, **3CQA** and **4CQA**, will also exhibit various biological effects, including

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http://dx.doi.org/10.1016/j.foodchem.2016.05.019
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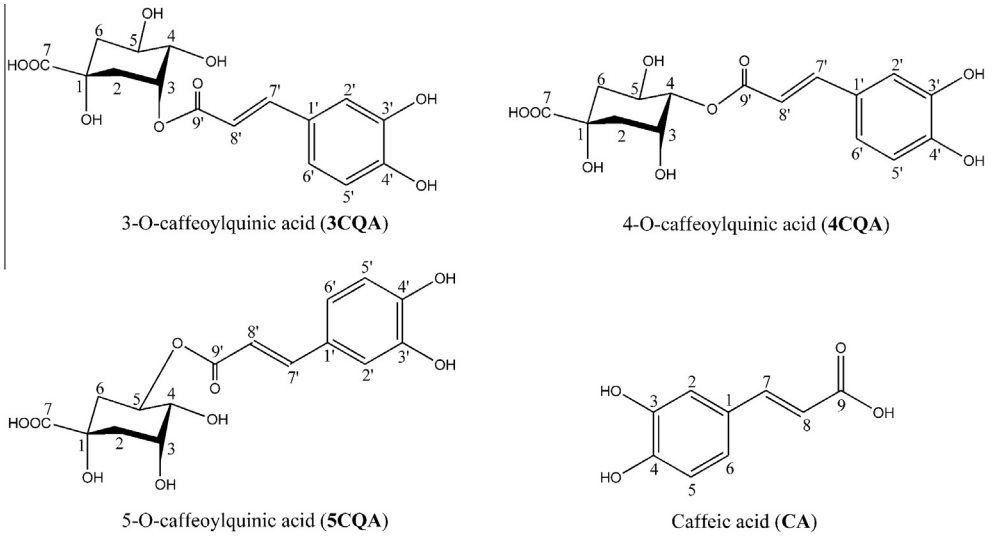

Fig. 1. Structural formulae of three isomeric caffeoylquinic acids and caffeic acid. The atom labelling schemes are remained throughout the manuscript.

antioxidative activity. Yet, the results regarding antioxidative activity of these two acids are scarce (Mullen et al., 2011; Nakatani et al., 2000). **5CQA** can isomerise through hydrolysis or extraction processes, and thus, change its bioactivity (Mullen et al., 2011). In addition, small quantity of **5CQA** is absorbed directly by the small intestine (Nardini, Cirillo, Natella, & Scaccini, 2002), but most of this compound is decomposed in the large intestine under the influence of the esterases of the gut microflora. This process yields **CA** which is easily absorbed and metabolically rather stable (Couteau, McCartney, Gibson, Williamson, & Faulds, 2001). It turns out that a comparison of the antioxidative activities of caffeoylquinic and caffeic acids is a significant task.

Phenolic acids (ArOH) realise their antioxidative activity via three major mechanistic pathways: HAT (Hydrogen Atom Transfer, Eq. (1)), SPLET (Sequential Proton-Loss Electron-Transfer, Eqs. (2) and (3)), and SET-PT (Single Electron Transfer – Proton Transfer, Eqs. (4) and (5)) (Klein, Lukeš, & Ilčin, 2007; Litwinienko & Ingold, 2007; Wright, Johnson, & DiLabio, 2001). These antioxidative mechanisms are commonly described by the following thermodynamic quantities: BDE (Bond Dissociation Enthalpy), PA and ETE (Proton Affinity and Electron Transfer Enthalpy), and IP and PDE (Ionisation Potential and Proton Dissociation Enthalpy).

$$ArOH \rightarrow ArO^{\cdot} + H^{\cdot} \quad (1)$$

$$ArOH \rightarrow ArO^{-} + H^{+} \quad (2)$$

$$ArO^{-} \rightarrow ArO^{\cdot} + e^{-} \quad (3)$$

$$ArOH \rightarrow ArOH^{+\cdot} + e^{-} \quad (4)$$

$$ArOH^{+\cdot} \rightarrow ArO^{\cdot} + H^{+} \quad (5)$$

The identity phenoxyl/phenol reactions ($ArO^{\cdot} + ArOH \rightarrow ArOH + ArO^{\cdot}$) can undergo the PCET (Proton-Coupled Electron Transfer) mechanism (Dawidowicz & Olszowy, 2012; Litwinienko & Ingold, 2007; Mayer, Hrovat, Thomas, & Borden, 2002). Here, a complex between an OH group of a phenol and a lone pair on $O^{\cdot}$ of the corresponding radical is formed. Then, the proton of the phenol is transferred to the lone pair of the radical, whereas an electron of the lone pair on the phenol is moved to the SOMO (singly occupied molecular orbital) of the radical. In addition, an antioxidant and radical can form an adduct ($ArOH + R^{\cdot} \rightarrow ArOH - R^{\cdot}$), thus obeying the RAF (Radical Adduct Formation) mechanism (Dawidowicz, Wianowska, & Olszowy, 2012; Leopoldini, Chiodo, Russo, & Toscano, 2011).

The aim of this work is to perform a comprehensive and comparative study of the antioxidative activity of all three caffeoylquinic acids and caffeic acid by focusing on the thermodynamics of three major antioxidative mechanisms: HAT, SPLET, and SET-PT.

2. Computational details

Within this work the calculations were performed by means of the Spartan'02 (Deppmeier et al., 2002) and Gaussian 09 (Frisch et al., 2010) program packages. Spartan was used to search the conformational space of caffeoylquinic acids by means of the Merck Molecular Force Field (MMFF) (Halgren, 1996) in combination with the Monte-Carlo method. Gaussian was used for all further calculations, implying that the MMFF structures of caffeoylquinic acids were subjected to a series of quantum mechanical calculations (see Section 3.1) to reveal the most stable conformer of each compound. These lowest-energy rotamers will be simply called the names of the parent acids: **3CQA**, **4CQA**, and **5CQA**. The structures of the parent molecules, as well as of the corresponding free radicals, anions, and radical cations in benzene (dielectric constant $\varepsilon = 2.2706$), methanol ($\varepsilon = 32.6130$), and water ($\varepsilon = 78.3553$) were achieved by full optimisations, including frequency calculations. For this purpose two DFT methods were applied: hybrid GGA B3LYP-D2 (Grimme, 2006) and hybrid meta-GGA M06-2X (Zhao & Truhlar, 2008), in combination with the 6-311++G(d,p) basis set (polarisation and diffuse functions added to all atoms), and CPCM polarisable continuum solvation model (Cossi, Rega, Scalmani, & Barone, 2003). These functionals were chosen because they proved to successfully describe short- and medium-range interatomic interactions. Bearing in mind that caffeoylquinic acids contain a number of hydrogen bonds it is expected that the parent molecules and all species issued from them will be described more reliably and accurately with the selected methods than with traditional density functionals. The restricted and unrestricted calculation schemes were used for the closed-shell and open-shell systems. The nature of all equilibrium geometries was confirmed by analysing the results of the frequency calculations: there were no imaginary vibrations. The natural bond orbital (NBO) analysis was performed for all molecules