Computational and Theoretical Chemistry 1110 (2017) 14–24

Contents lists available at ScienceDirect

Computational and Theoretical Chemistry

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

Donor-acceptor interactions as descriptors of the free radical scavenging ability of flavans and catechin

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ARTICLE INFO

Article history:
Received 17 February 2017
Received in revised form 16 March 2017
Accepted 22 March 2017
Available online 24 March 2017

Keywords:
(4α→6″, 2α → O → 1″)-phenylflavans
Catechin
Proanthocyanidins
Antioxidants
Density functional theory
Atoms in molecules
Natural bond orbital analysis
Bond dissociation enthalpies
Ionization potentials
Donor-acceptor interactions

ABSTRACT

Interest in food phenolics has increased in recent years largely due to their antioxidant capacity, free radical scavenging, and potential health benefits. In literature two main reaction mechanisms have been proposed for their role as free radical (FR) scavengers, i.e., the mechanism of a hydrogen atom transfer (HAT) governed by the O—H bond dissociation enthalpy (BDE), and the mechanism of single electron transfer (SET) governed by an electron transfer process, the ionization potential (IP) playing an important role.

Thirty nonplanar structures were analyzed. The study of (+)-catechin (CTQ) and (4α → 6″, 2α → *O* → 1″)-phenylflavans with a R′ = H, R = OH; R′ = OH, R = H, and R′ = OH, R = OH substitution is performed herein. Catechol, phenol, and resorcinol are also included as references. Results obtained with B3LYP hybrid functional with 6-311++G(d,p) and 6-31G(d,p) basis set are analyzed. Two new indicators arising from electron delocalizations are presented herein, thus showing that there is a different set of donor-acceptor interactions to explain FR scavenging mechanisms.

1. Introduction

Interest in food phenolics has increased in recent years largely due to their antioxidant capacity, free radical scavenging, and potential health benefits. Search for natural antioxidants for use in food or drugs is increasing to replace synthetics, some of them reported as carcinogenics [1].

Antioxidants are an important class of compounds that scavenge free radicals (FR), which arise as intermediates of oxidation reactions. Oxidative stress has been implicated in the development of neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington diseases, epileptic seizures, aging, in addition to promoting certain cancers [2–4].

The antioxidant efficiency of flavonoids has been related to the number of hydroxy groups in the molecule, conjugation, and resonance effects, as well as a hydrogen donor ability to reduce FR effects [5]. Moreover, the effectiveness of some flavonoids to inhibit FR depends on the structure (conformation), thermochemical properties, and also concentration and reaction rates (kinetic properties) [6].

Computational chemistry is one of the most powerful tools to make progress in this field, and several studies on this subject are reported in the literature [7–13]. Valuable information is provided lowering costs and time involved in experimental or clinical studies, and also inferring about the effects of different molecular characteristics on the properties of the flavonoids. Theoretical data may be used as a valid tool to predict the structure-activity relationships (SAR) of a compound and also for designing new potential antioxidants. The comparison of the theoretical and experimental data supports modern theoretical approaches able not only to explain controversial experimental facts but also to predict the chemical behavior and antioxidant activity of novel compounds [14].

In literature two main reaction mechanisms have been proposed, by which phenolic antioxidants can perform their role as FR scavengers, i.e., the mechanism of a hydrogen atom transfer (HAT), and the mechanism of single electron transfer (SET) [15–33]. Also recently an alternative mechanism including a complex formation has been demonstrated for glycerol and other polyols [34].

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http://dx.doi.org/10.1016/j.comptc.2017.03.028
2210-271X/

Both HAT and SET mechanisms of FR scavenging can be modeled by computational chemistry. HAT mechanism is governed by the O—H bond dissociation enthalpy (BDE), which is a molecular property used for assessing FR scavenger potential of a molecule. This is calculated as the difference between the formation heat of the molecule and its radicals, which accounts for the O—H bond breakage energy. The SET mechanism is governed by an electron transfer process, playing important roles both the ionization potential (IP) and $R'OH^{+\cdot}$ radical cation (RC) reactivity.

According to Wright et al. [29] to design an optimal synthetic antioxidant, i.e., for a given biological role, first BDE and IP must be known. This information will be also useful to elucidate SAR for natural antioxidants, such as catechol-containing flavonoids.

BDE thermochemical calculations are very useful for the characterization of the antioxidant activity of a large group of antioxidants [29,35], and can reproduce experimental values with good accuracy.

The reliability of the methods based on the Density Functional Theory (DFT) to predict the main antioxidant properties and reaction mechanisms involved in radical scavenging reactions of food chemicals is accepted in the community [17].

Currently is advanced in the determination of thermodynamic parameters, and other useful descriptors for analyzing the antioxidant action [36]. However, yet very few reports attempt to explain or rationalize such descriptor values and trends with *ab initio* calculations.

We have previously reported the analysis of the stereoelectronic effects induced by R = H, OH and OCH_3 substitution in *Z*-isomers of ($4\alpha \rightarrow 6''$, $2\alpha \rightarrow O \rightarrow 1''$)-phenylflavans [37]. In a more recent work, the study of ($4\alpha \rightarrow 6''$, $2\alpha \rightarrow O \rightarrow 1''$)-phenylflavans substituted with R′ = OH, R = OH showed the occurrence of cooperatively-acting charge delocalization mechanisms that define "delocalization routes", thus giving rise to interactions between different rings of the compound, even when not sharing the same plane [38]. The findings of both reports highlighted the key role played by hyperconjugative interactions in the stereoelectronic effects induced by substitution as a relevant factor for understanding the associated BDEs and IPs values.

The aim of this paper is to investigate the conformational and electronic properties of different flavonoids substituted with OH groups. These compounds were chosen to evaluate catechol and resorcinol effects on the antioxidant capacity of nonplanar flavonoids.

The effects of the basis quality on the calculation of the parameters of interest and description of the systems are also discussed. Minimal computational costs are necessary for the inclusion of different solvent effects, and for analyzing the reaction kinetics of interest for studies of other naturally-occurring antioxidants.

Accordingly, the study of (+)-catechin (CTQ) and ($4\alpha \rightarrow 6''$, $2\alpha \rightarrow O \rightarrow 1''$)-phenylflavans with R′ = H, R = OH (FFR′HROH); R′ = OH, R = H (FFR′OHRH), and R′ = OH, R = OH (FFR′ROH) substitution is performed herein. The selection has a methodological reason looking for a stepwise study with an increasing level of structural complexity. Catechol, phenol, and resorcinol are also included [39–41]. Phenol BDE is a reference value for all phenolic antioxidants. Its computational calculation is also a quality marker for theoretical results; the present calculation values are within experimental error, which validates the schemes followed.

Results according to three calculation schemes using density functionals and two different basis sets are studied. Electronic charge delocalizations that explain the thermodynamic parameter values associated with SET and HAT mechanisms are analyzed.

Descriptors to predict which structure of the parent molecule fit the best qualities as an antioxidant relative to BDE and IP values are searched. Electron delocalization routes and structural characteristics leading to the best BDE and IP values are defined.

The whole analysis is carried out taking into account our previous reports [37,42,43], thus studying the role of the substituents of both resorcinol and catechol rings in the initial description of the antioxidant capacity of this kind of compounds. This description is based on the study of electron distribution, and the corresponding electron delocalization effects. This paper deepens in this analysis with the hypothesis that there are different electron delocalization mechanisms to explain each proposed reaction.

The study of the in vacuum ("zero order") intrinsic characteristics of these compounds is relevant to measure the effects of different solvents in subsequent studies, and to contribute to modeling the effect of both polar and non-polar solvents on the antioxidant activity.

2. Methods

Calculations were carried out with the Gaussian 03 software package [44]. Geometries of the parent molecules were optimized by the Density Functional Theory using the B3LYP hybrid functional [45,46]. The suitability of this functional for studies of bond dissociation enthalpy involving natural isoflavonoids has already been reported elsewhere [11,17,20,23,47]. Two basis sets were used, i.e., 6-31G(d,p) (type of calculation hereinafter referred to as DZ), and 6-311++G(d,p) (type of calculation hereinafter referred to as TZ). At these same levels (DZ and TZ) zero point vibrational energy (ZPE) and enthalpy thermal contribution (ETC) were calculated, and AIM (atoms in molecules) and natural bond orbitals (NBO) analyses were performed.

Based on optimized geometries, ZPE and ETC corrections obtained with the 6-31G(d,p) basis set, set single-point calculations with the 6-311++G(d,p) basis set, and a further AIM/NBO analysis were carried out, which is the calculation scheme hereinafter called MIX. Restricted and unrestricted calculations were carried out for closed- and open-shell systems, respectively.

Both HAT and SET mechanisms were analyzed. In the HAT mechanism, the hydrogen atom transfer of the O—H bond is studied. The O—H bond dissociation energy (BDE) is associated with HAT mechanism, and is computed by the enthalpy (H) difference between the products and reactants of the reaction:

$$BDE(R'O{-}H) = H(R'O^{\cdot}) + H(H^{\cdot}) - H(R'OH)$$

where $H(R'O^{\cdot})$ is the enthalpy of the radical generated by H abstraction; $H(H^{\cdot})$ is the hydrogen atom enthalpy (−0.499897 Hartree at this level of theory); and H(R′OH) is the parent molecule enthalpy. BDE is an important theoretical descriptor that characterizes the radical scavenging activity of antioxidants.

The SET mechanism can occur in parallel to HAT. In this mechanism the antioxidant donates an electron to FR, turning itself in a CR. IP is associated with the SET mechanism, and is computed by the electronic energy difference of the reactants and products. The lower the IP value, the easier is the electron abstraction. IP values were determined as follows:

$$IP = Erc\text{-}Ep$$

where Ep and Erc indicate the electronic energy of the parent molecule, and that of the RC generated.

The calculated IP accounts for adiabatic IP, whereby the RC structure is fully optimized. At B3LYP/6-311++G(d,p) level the vibrational analysis for both parent molecules and radicals reaction products is performed. The values obtained are used to verify that the structures studied account for energy minima, and also to correct energy values by considering ZPE and ETC (which includes vibrational contributions and ZPE).

No spin contamination is found in the radicals, the $\langle S^2 \rangle$ values being not greater than 0.750 in all cases. Phenol, catechol, and