



Deprotonation of flavonoids severely alters the thermodynamics of the hydrogen atom transfer



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ABSTRACT

Deprotonated polyphenolics exhibit different free radical scavenging activity than parent molecules. Therefore, this study is focused on the hydrogen atom transfer (HAT) from mono-deprotonated forms (phenoxide anions) of 16 flavonoids in terms of O–H bond dissociation enthalpies, BDE(A), using B3LYP/6-311++G** approach. Solvent (benzene and water) contribution is computed using integral equation formalism polarized continuum model, IEF-PCM. Obtained BDE(A) values are usually lower than BDEs of the parent species. In general, from the thermodynamic point of view, HAT from a phenoxide anion is favored to the electron transfer, i.e. formation of the phenoxy radical. For the studied environments, preferred radical anions are identified. Obtained results can contribute to the explanation of experimentally observed pH dependent antioxidant effect of polyphenolics.

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1. Introduction

Flavonoids, Fl(OH)_n, represent a large class of plant polyphenolics consisting of ca 4.000 compounds possessing phenylchromane skeleton [1,2]. Interest in flavonoids research has been considerably grown after discovering their antioxidant and other important biological effects [1,2].

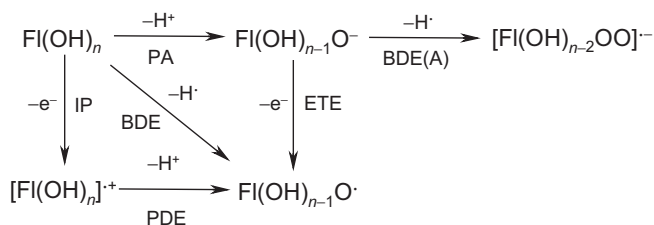
Reaction pathways of the antioxidant activity of phenolic compounds related to the radical scavenging are intensively investigated in last two decades [2–9]. In general, the phenolic antioxidants are able to trap damaging free radicals through three mechanisms shown in Scheme 1. Hydrogen atom transfer (HAT) contributes to the flavonoids primary antioxidant action (free radicals termination) via O–H bond homolytic splitting-off. This process is governed by the O–H bond dissociation enthalpy, BDE. In Scheme 1, two-step mechanisms of the antioxidant action, i.e. Single Electron Transfer–Proton Transfer (SET–PT) and Sequential Proton-Loss Electron-Transfer (SPLET) [2–9], are also depicted. Thermodynamics of SET–PT mechanism is characterized by the ionization potential (IP) and the proton dissociation enthalpy (PDE) of the formed radical cation. In the case of SPLET, deprotonation of the parent flavonoid, Fl(OH)_n, is followed by the electron transfer from Fl(OH)_{n-1}O⁻ anion.

The corresponding reaction enthalpies are proton affinity (PA) of the phenoxide anion and electron transfer enthalpy, ETE.

Experimental studies have shown that free radical scavenging capability of phenolic antioxidants in aqueous solutions is significantly affected by pH [6,7,10–15]. Depending on the acidity of individual OH groups, flavonoids may be partially or fully deprotonated in the solution and formed anions positively affect their antioxidant action. The higher the pH is, the higher the number of deprotonated sites is and the higher the contribution of SPLET is expected [7,8,14,16]. Besides the experimental determination of pK_a values and pH-dependent antioxidant activity assay (TEAC values) of various hydroxyflavones, Lemańska et al. [10,15] performed gas-phase calculations of deprotonation energies, ionization potentials and BDEs of the parent (neutral) molecules, as well as the calculations of electron transfer enthalpies, ETE, and BDE values for the most stable anions of the investigated hydroxyflavones. All reaction enthalpies were approximated from the total electronic energies. Authors suggested that upon deprotonation, the TEAC value increases because electron, not H⁺ donation, becomes considerably easier in comparison to the parent molecules. However, conclusions drawn from the gas-phase data may not hold for the processes in the solution-phase [17–25]. For anthocyanidins (flavonoids which are cations in the native form), Estévez et al. [17] found that HAT from the deprotonated species in solution-phase (water, methanol, cyclohexane) is always energetically favored over the second step of SPLET. For genistein, Zielonka et al. [26] estimated gas-phase

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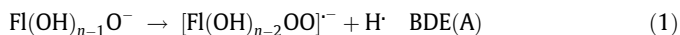
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Scheme 1. Reaction pathways of primary antioxidant action of phenolic antioxidants with denotations of corresponding reaction enthalpies: BDE – bond dissociation enthalpy, IP – ionization potential, PDE – proton dissociation enthalpy, PA – proton affinity, and ETE – electron transfer enthalpy.

5-OH and 4'-OH bond dissociation enthalpies of its 7-O⁻ anion from total electronic energies. The two values were lower than BDEs of the neutral parent form.

Despite the intensive theoretical study of flavonoids in terms of HAT, SET-PT and SPLET mechanisms [3,10,15–35], no systematic study of O–H BDEs (further denoted as BDE(A) according Refs. [10,15]) for the deprotonated forms, FI(OH)_{n-1}O⁻, is available. Therefore, the main aim of the present work is the study of the O–H BDE(A) values of phenoxide anions



in the gas-phase, benzene and water in order to determine whether BDE(A) values are lower than the corresponding O–H BDEs for parent species. Besides, these data enable to find, if the electron transfer or HAT is the thermodynamically preferred reaction pathway for the studied monoanions (see Scheme 1). We have chosen 16 flavonoids belonging to flavones (apigenin, luteolin, tricetin, tricrin), flavonols (fisetin, kaempferol, quercetin), flavanonols (taxifolin), anthocyanidins (cyanidin) and isoflavones (daidzein, genistein, biochanin A, prunetin, 6-hydroxydaidzein, glycitein, orobol and santal), Fig. 1. The selection of larger group of flavonoids also enables to investigate the influence of various structural features on BDE(A). Our previous studies [18,19,30] were focused on the reaction enthalpies related to HAT, SET-PT and SPLET mechanisms for these compounds in the same environments. Here, we have used identical computational approach allowing the correct comparison of the calculated reaction enthalpies. Our previous reports on model compounds (substituted phenols and thiophenols [36–38]) or naturally occurring phenolic antioxidants (tocopherols and chromans [39]) confirmed that chosen computational approach provides reliable trends and the found results are in accordance with the available experimental data. In Ref. [13], authors have also shown that B3LYP calculations with polarized continuum model (PCM) used for the description of solvent effect are able to provide reliable Gibbs free energies of deprotonation of flavonoids, as well as the acidity constants (pK_a) in aqueous solution. For pyridoxinic compounds [40] and quercetin [21], it was demonstrated that newer M05-2X and M06-2X functionals with SMD solvation model also provide identical trends in BDE, IP, PDE, PA and ETE, although a shift in the absolute values obtained using different functional and/or solvation model can be observed.

2. Computational details

All calculations were performed using Gaussian 09 program package [41]. The geometry of each compound, radical or anionic structure was optimized using DFT method with B3LYP [42,43] functional without any constraints (energy cut-off of 10⁻⁵ kJ mol⁻¹, final RMS energy gradient under 0.01 kJ mol⁻¹ Å⁻¹). Calculations were performed in 6-311+G** basis set [44], because the inclusion of the diffuse functions to the basis set is important for the proper

description of anions that have large electron density distributions. Optimized structures were confirmed to be real minima by the frequency analysis. Solvent contribution to the total enthalpies was computed employing integral equation formalism polarized continuum model, IEF-PCM [45,46].

From the calculated total enthalpies (*T* = 298.15 K) with not scaled zero-point energies (ZPE), we have determined O–H bond dissociation enthalpies, BDE(A), of studied anions

$$\text{BDE(A)} = H([\text{FI}(\text{OH})_{n-2}\text{OO}]^{\bullet-}) + H(\text{H}^{\bullet}) - H(\text{FI}(\text{OH})_{n-1}\text{O}^-) \quad (2)$$

Denotations used in Eqs. (1) and (2) have to be formally modified for cyanidin. In the native form, cyanidin is the cation [FI(OH)_n]⁺. Therefore, its mono-deprotonated forms, FI(OH)_{n-1}O, are neutral and HAT results in the formation of neutral [FI(OH)_{n-2}OO][•] radical.

The calculated gas-phase enthalpy of hydrogen atom is *H*(H[•], gas) = 1312.5 kJ mol⁻¹. Hydration enthalpy Δ_{hydr}*H*(H[•]) = -4.0 kJ mol⁻¹ [47] and the solvation enthalpy in benzene Δ_{solv}*H*(H[•], C₆H₆) = -6.4 kJ mol⁻¹ [48] were used in the determination of BDE(A) values in solution-phase, where the enthalpy of the hydrogen atom represents the sum of *H*(H[•], gas) and the solvation enthalpy.

Accuracy of the energy evaluation in the case of systems involving open-shell species is sensitive to the spin contamination. Spin contaminations of radical anions and radicals reached correct value of 0.75 after the annihilation of the first spin contaminant. Thus, spin contamination should not bias calculated enthalpies.

3. Results and discussion

In the first sections, gas-phase results are discussed in order to evaluate the influence of various structural features on BDE(A). Next part sheds light on the solvent induced changes in BDE(A) values. Finally, thermodynamically preferred radical anions are identified.

3.1. HAT in gas-phase

Reports on BDE(A) of studied compounds are still scarce. In Refs. [10,15,26], authors employed similar computational approaches. BDE(A) values were approximated from the B3LYP/6-311G**//B3LYP/6-31G(d) [10,15] or B3LYP/6-311+G**//B3LYP/6-31G(d) [26] total electronic energies, *E*₀. When the average shift (30 kJ mol⁻¹) between bond dissociation enthalpies approximated from the total electronic energies, *E*₀, and those obtained from the total enthalpies (Eq. 2) is taken into account [49], 7-OH BDE(A) = 308 kJ mol⁻¹ for 4'-O⁻ anion of quercetin, 4'-OH BDE(A) = 310 kJ mol⁻¹ for 7-O⁻ anion of kaempferol [10] and 7-OH BDE(A) = 337 kJ mol⁻¹ for 4'-O⁻ anion of luteolin [15] show good agreement with data in Table 1. For 7-O⁻ anion of genistein, 5-OH BDE(A) = 418 kJ mol⁻¹ and 4'-OH BDE(A) = 327 kJ mol⁻¹ [26] are in accordance with data in Table 2.

In general, B3LYP functional shows good performance in geometry optimization and bond energetics and it is widely employed in the theoretical investigation of phenolic antioxidants [3,10,13,15,17–20,24–27,30,34–39,49]. Therefore it is plausible to assume that obtained results represent reliable estimation of the studied O–H bond dissociation enthalpies which have not been determined experimentally yet. In further sections, results for flavonoids with the B ring attached to the C2 atom and isoflavones are discussed separately.

3.1.1. Flavonoids

Calculated BDE(A) values for deprotonated flavonoids are summarized in Table 1. For parent molecules, BDEs [30] are set in italic. In each line of the table, O–H BDE(A) values of the remaining OH

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