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Theoretical Study of Primary Antioxidant Action Thermodynamics

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Abstract

This paper presents a brief overview of our research focused on the thermodynamics of primary antioxidant action related mainly to (poly)phenolic compounds. Reaction enthalpies for three mechanisms of radical scavenging by primary (chain-breaking) antioxidants or model compounds have been investigated using quantum chemical calculations.

Keywords: primary antioxidant, substituted phenol, flavonoid, DFT, reaction enthalpy

1. Introduction

Oxidation represents the important part of aerobic life and the metabolism. It involves electron transfer between molecules or electron-rich species to an oxidizing agent. During this process, highly reactive free radicals may be formed. If these radicals are not effectively scavenged, their presence often leads to various diseases and ageing of organisms (Craft et al. 2012, Gülçin 2012). Autoxidation of lipids represents one of the most important oxidation processes in the food (Craft et al. 2012). In the case of synthetic polymers, (thermo)oxidation causes their degradation – the change in the molecular weight distribution, as well as changes in the chemical properties and mechanical behavior (Gugumus 1990). Oxidation generally involves a free radical chain reaction. During the initiation, the number of free radicals increases. In propagation step, the total number of radicals remains constant although the number of radical species may change. Termination reactions, representing the last step of oxidation, lead to the decay of free radicals (Craft et al. 2012, Gugumus 1990). In the oxidation process, chain branching, i.e. the formation of new radicals – new chain carriers, is often observed (Gugumus 1990). In general, there is no substantial difference in the oxidation of natural compounds and synthetic polymers (Gugumus 1990, Craft et al. 2012, Gülçin 2012).

An antioxidant is a substance that inhibits or prevents the oxidation of another molecule. Antioxidants are often classified either as primary, or secondary (Craft et al. 2012, Gülçin 2012, Ingold and Pratt 2014). Primary antioxidants, also known as chain-breaking or radical-trapping, inhibit oxidation processes. Secondary, i.e. preventive, antioxidants, inhibit oxidation indirectly, by the mechanisms such as oxygen-scavenging or pro-oxidants binding (Craft et al. 2012, Ingold and Pratt 2014). Secondary antioxidants also convert formed oxidation products, e.g. hydroperoxides, to more stable non-radical species (Gugumus 1990).

Non-toxicity represents one of the key properties of antioxidants. Therefore, recent research is strongly focused on naturally occurring compounds with antioxidant properties. Human diet also contains various substances showing antioxidant activity. Most important representatives of dietary antioxidants are vitamin C, tocopherols and tocotrienols (components of vitamin E), flavonoids, phenolic acids and carotenoids (Gülçin 2012). Phenolic compounds belong to the most important natural primary antioxidants. They can act through several mechanisms. Corresponding reaction enthalpies represent one of the significant characteristics of antioxidants. Ten years ago, most papers on antioxidant action of phenolic compounds (ArOH) were focused on the one-step hydrogen atom transfer (HAT) mechanism

$$\mathrm{ArOH} + \mathrm{R}\bullet \rightarrow \mathrm{ArO}\bullet + \mathrm{RH} \tag{1}$$

In Eq. 1, $\mathrm{R}^{\bullet}$ represents a scavenged radical. From the thermodynamics point of view, HAT is governed by the phenolic O–H bond dissociation enthalpy (BDE). However, two-step mechanisms of phenoxy radical, $\mathrm{ArO}^{\bullet}$, formation also take place. In the first step of Single Electron Transfer – Proton Transfer (SET-PT) mechanism, electron transfer to a radical, $\mathrm{R}^{\bullet}$, occurs

$$\mathrm{ArOH} + \mathrm{R}^{\bullet} \rightarrow \mathrm{ArOH}^{\bullet+} + \mathrm{R}^{-} \tag{2.1}$$

In the second step, proton is transferred to the formed R^{-} anion

$$\mathrm{ArOH}^{\bullet+} + \mathrm{R}^{-} \rightarrow \mathrm{ArO}^{\bullet} + \mathrm{RH} \tag{2.2}$$

This mechanism is described by ionization potential (IP) and proton dissociation enthalpy (PDE) from $\mathrm{ArOH}^{\bullet+}$ radical cation formed in the first step. However, low IP values also enhance the probability of superoxide radical anion formation through the direct electron transfer to present O_2 (Pratt et al. 2001, Wright et al. 2001).

In 2003–2004, another two-step mechanism, Sequential Proton-Loss Electron-Transfer (SPLET), has been discovered (Litwinienko and Ingold 2003, Foti et al. 2004, Litwinienko and Ingold 2004, Ingold and Litwinienko 2005, Ingold and Pratt 2014). Results of reaction kinetics experiments proved that vitamin E, flavonoids and other phenols can react with $\mathrm{dpph}^{\bullet}$ (2,2-diphenyl-1-picrylhydrazil radical) and other electron deficient radicals by two different and nonexclusive mechanisms, HAT and SPLET. SPLET can be described as follows

$$\mathrm{ArOH} \rightarrow \mathrm{ArO}^{-} + \mathrm{H}^{+} \tag{3.1}$$

$$\mathrm{ArO}^{-} + \mathrm{R}^{\bullet} \rightarrow \mathrm{ArO}^{\bullet} + \mathrm{R}^{-} \tag{3.2}$$

$$\mathrm{R}^{-} + \mathrm{H}^{+} \rightarrow \mathrm{RH} \tag{3.3}$$

The reaction enthalpy of the first step corresponds to the proton affinity (PA) of the phenoxide anion, ArO^{-}. The reaction enthalpy of the second step has been denoted as electron transfer enthalpy, ETE (Klein and Lukeš, 2006a). Flavonoids may also act as secondary antioxidants via chelation of copper and iron cations (Craft et al. 2012, Gülçin 2012, Galano et al. 2016, Dimitrić Marković et al. 2011, Leopoldini et al. 2011). These cations can significantly contribute to the acceleration of the oxidation.

In our research, the attention was paid first to the larger sets of primary antioxidants model compounds, such as anilines, phenols and thiophenols to assess the applicability and reliability of the chosen computational approach. All three mechanisms, i.e. HAT, SET-PT and SPLET, were studied for mono-substituted phenols, thiophenols, tocopherols, chromans and flavonoids. Because flavonoids and other polyphenols contain several phenolic OH groups with different acidities, their antioxidant action in aqueous solutions depends on pH, since their deprotonated forms show considerably different effect (Lemanska et al. 2001, Musialik et al. 2009, Álvarez-Diduk et al. 2013). Therefore, our recent work is devoted to the study of hydrogen atom transfer and deprotonation of flavonoid phenoxide anions. In the next sections, we present a brief review of our results obtained for above mentioned model compounds and naturally occurring phenolic antioxidants.

2. Quantum chemical calculations

All calculations were performed using Gaussian 03 or 09 program packages (Frisch et al. 2003 and 2010). The geometries of individual compounds, radicals or ions were optimized using DFT approach with B3LYP (Becke 1993) 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 sufficiently large, 6-311++G**, basis set (Binkley et al. 1980) allowing balanced treatment of all studied species. Computed total enthalpies were employed for the calculation of studied reaction enthalpies, i.e. BDE, IP, PDE, PA and ETE values. Integral Equation Formalism Polarized Continuum Model (IEF-PCM) method (Cances et al. 1997, Cances and Mennucci 1998) was used for the description of the solvent effect on studied reaction enthalpies. All enthalpies were calculated for 298.15 K.

The application of identical computational approach in all works related to model compounds and naturally occurring substances has two advantages: (*i*) Obtained results are fully compatible and can be mutually compared, because they are not influenced by the selection of computational method and/or basis-sets. (*ii*) Agreement between the available experimentally determined/estimated and computed reaction enthalpies for model compounds (anilines, phenols and thiophenols) indicates that used computational approach gives reliable predictions also for other compounds (such as tocopherols, polyphenols or phenolic acids). Despite the intensive experimental research of various antioxidants, the experimental values of corresponding reaction enthalpies, especially in solution-phase, are still missing.

3. Summary of selected results

3.1. Model compounds: phenols, thiophenols and anilines

For *para*- and *meta*-substituted phenols (Klein and Lukeš 2006a, 2006b, 2006c, Klein et al. 2009) and thiophenols (Rimarčík et al. 2011, Rottmannová et al. 2012), we have quantified the effect of various electron-donating and electron-withdrawing substituents on the enthalpies of the homolytic and heterolytic O–H and S–H bonds cleavage in the gas- and solution-phase. Usually, benzene and water were chosen as typical models of polar and non-polar solvent. Applied computational approach describes the effect of substituents in *para* and *meta* position reliably. Approximately linear Hammett-type dependences were found for investigated reaction enthalpies. These enable fast estimation of a reaction enthalpy from the Hammett constant of the substituent. Later, for *para* and *meta*-substituted benzeneselenols and benzenetellurols, we have investigated Se–H and Te–H BDEs (Škorňa et al. 2016a). For congener molecules, a decrease in BDEs is observed, i.e. with increasing volume of the atom from oxygen to tellurium, BDE values are decreasing. Besides, the substituent induced changes in X–H BDE (X = O, S, Se, Te) are decreasing from phenols to benzenetellurols, too.

For phenols and thiophenols, thermodynamically favored reaction pathway was determined in studied environments. In the gas-phase and non-polar benzene, HAT is preferred, while in polar solvents (such as ethanol, DMSO and water), SPLET is thermodynamically favored mechanism. Solvents attenuate substituent effect on IP, PDE, PA and ETE. On the contrary, substituent induced changes in O–H and S–H BDEs are in slightly wider ranges. In general, solvent exerts only small effect on BDEs (up to ca 10 kJ mol^{-1}) and the solution-phase BDE values are close to the gas-phase ones.

For the substituents placed in *meta* position, the linearity of Hammett-type dependence is worse in comparison to *para* position. It results in limited applicability of BDE = $f(\sigma_m)$ dependence for the prediction of BDE values using σ_m Hammett constants. This is especially the case of anilines (Vagánek et al. 2013). For *meta*-substituted anilines, BDE = $f(\sigma_m)$ dependence shows poor linearity. Therefore, we tried to identify a suitable structure-based descriptor of the substituent effect. We have found linear dependences of O–H BDE on the phenolic C–O bond length, R(C–O), and its shortening after hydrogen atom abstraction, ΔR(C–O) = R(C–O, molecule) – R(C–O, radical) (Klein and Lukeš 2006c). Analogous linear dependences were obtained also for thiophenols (Rottmannová et al. 2012). For large group of 21 substituents in *para* and *meta* positions, N–H BDE values can be correlated with aniline C–N bond length, R(C–N) or its shortening after hydrogen atom abstraction, ΔR(C–N), too (Vagánek et al. 2013). Moreover, in the case of thiophenols and anilines, one equation describes the substituent induced changes in BDEs for both, *para* and *meta*, positions satisfactorily. For phenols, *meta*- and *para*-substituted molecules have to be treated separately (Klein and Lukeš 2006c). Found dependences can be employed for fast estimation of BDEs from corresponding bond lengths. Recently, the applicability of this approach has been shown for various polyphenols (Bentz et al. 2017).

3.2. Tocopherols and chromans

Gas-phase reaction enthalpies related to the individual steps of HAT, SET-PT and SPLET were calculated for four tocopherols and seven naturally occurring chromans (Klein et al. 2007). Besides the gas-phase values, for α-tocopherol and one chroman, reaction enthalpies in water were computed. Analogously to phenols and thiophenols, it was found that water causes severe changes in the energetics of SET-PT and SPLET mechanisms, which include charged species ($ArOH^{\bullet+}$ radical cation or ArO^- anion). From the thermodynamics point of view, entering SPLET mechanism represents the most probable process in water. Again, it was confirmed that solvent does not influence phenolic O–H BDEs significantly.

3.3. Flavonoids

Numerous experimental reports on antioxidant action of flavonoids and other polyphenols have been published in last two decades (Craft et al. 2012, Gülçin 2012, Musialik et al. 2009, Rice-Evans et al. 1996, Procházková et al. 2011). However, experimental values of reaction enthalpies related to the three mechanisms of their primary antioxidant action are still not available. On the other hand, in last 15 years, many theoretical works focused on O–H BDE, IP, and PA values for smaller series of flavonoids appeared, see for example the overview in Table S1 in Vagánek et al. (2012). Since the authors employed different (semiempirical, DFT or *ab initio*) quantum chemical approaches, published results were not mutually compatible. Besides, used methods may provide more or less reliable results (Klein and Lukeš 2006b).

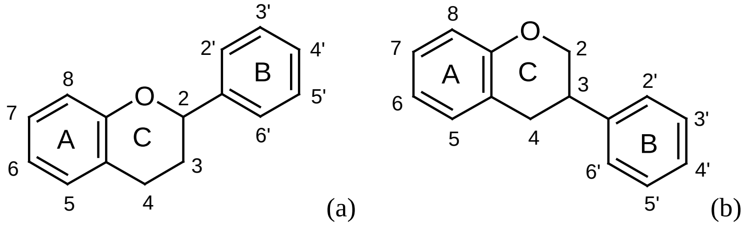

Fig. 1. Atom numbering and rings denotation in flavonoids and isoflavones.

For 10 flavonoids (apigenin, luteolin, fisetin, kaempferol, quercetin, epicatechin, taxifolin, tricetin, tricin and cyanidin) and 9 isoflavones (daidzein, formononetin, genistein, biochanin A, prunetin, 6-hydroxydaidzein, glycitein, orobol and santal), all three mechanisms of phenolic antioxidant action have been studied in the gas-phase, benzene and water (Vagánek et al. 2012 and 2014, Lengyel et al. 2013). Selected group of compounds enabled to evaluate the effects of various structural features, such as the presence of hydroxy groups in different positions (3’-OH, 3-OH, 5-OH), C2=C3 double bond or C4=O keto group in flavonoids, as well as the effect of 4’-OMe, 6-OMe, 7-OMe, 3’-OH, 5-OH and 6-OH groups in isoflavones on relevant reaction enthalpies, see carbon atoms numbering in Fig. 1. Moreover, the set of selected molecules allowed to assess the influence of the B ring connection point – in flavonoids B ring is connected to C2 carbon atom, while in isoflavones it is connected to the C3 carbon, Fig. 1. This structural change affects the antioxidant action, because isoflavones lack 3-OH group, which plays important role in free radical scavenging (Trouillas et al. 2006, Vagánek et al. 2012 and 2014, Klein et al. 2016).

Lowest O–H bond dissociation enthalpies (HAT) and proton affinities (SPLET) have been found usually for 4’-OH groups at ring B. In accordance to experimental reports (Heim et al. 2002, Rice-Evans et al. 1996, Procházková et al. 2011), we have found that for effectiveness of the HAT mechanism from thermodynamics point of view, the *ortho*-dihydroxy structure represents the most important structural feature in the two groups of the polyphenols. In case of molecules with only 4’-OH group at the B ring, obtained BDEs are higher. On the contrary, the presence of third OH group (5’-OH in tricetin) results in further decrease in 4’-OH BDE (Vagánek et al. 2014). With two exceptions, the lowest BDEs were found for 4’-OH groups in all studied environments. For kaempferol in benzene and water and cyanidin in gas-phase and benzene, lowest BDE values were obtained for 3-OH group. For the first step of SPLET mechanism, the situation in the case of flavonoids is not straightforward (Vagánek et al. 2014). For apigenin in water, the lowest PA value was calculated for two groups, 4’-OH and 7-OH. In taxifolin, deprotonation of 7-OH group is preferred in all studied environments. For kaempferol and tricin in the benzene and water, 7-OH PA is the lowest one, too. In several flavonoids, the differences between 4’-OH and 7-OH PAs are in aqueous solution relatively low, within ca 15 kJ mol^{-1}. These results are in accordance to the experimental work of Musialik et al. (2009), where the authors observed that in ionization supporting solvents, SPLET runs in ring A *via* deprotonation of 7-OH group of quercetin and HAT/SET-PT occurs from 3’,4’-dihydroxy moiety. In the case of isoflavones (Lengyel et al. 2013), the situation is very simple: in all environments, the lowest PA values were obtained exclusively for 7-OH groups. This indicates that ring A can play significant role in the SPLET reaction pathway.

Solvent affects the enthalpies of charged species involved in SET-PT and SPLET mechanisms significantly. In non-polar benzene, PAs are lower than IPs, but remain higher than BDEs. Therefore, HAT remains the thermodynamically preferred and SET-PT mechanism is the least preferred in benzene. In water, very large drop in PAs was observed, all values are considerably lower than BDEs. Therefore, in water, SPLET represents the thermodynamically preferred mechanism, followed by HAT and SET-PT (Vagánek et al. 2014, Lengyel et al. 2013). Here, one should keep in mind that these studies are focused on the thermodynamic preference of studied compounds to enter individual reaction pathways and the dominating process may depend on the type of scavenged free radical.

3.4 Deprotonated flavonoids and isoflavones

Because deprotonated polyphenolic compounds show different free radical scavenging action than parent molecules, our recent work (Klein et al. 2016) is focused on the hydrogen atom transfer from the mono-deprotonated forms (phenoxide anions) of 8 flavonoids and 8 isoflavones in terms of O–H bond dissociation enthalpies. For deprotonated species, these are denoted as BDE(A) according Lemanska et al. (2001). As in the previous reports (Vagánek et al. 2012 and 2014), cyanidin, which is a cation in native form, was also included in this work. Contrary to other studied molecules, its deprotonated forms are neutral and HAT mechanism results in the formation of neutral radical.

Obtained BDE(A) values are often considerably lower than BDEs of parent molecules. They are also usually lower than the reaction enthalpy of the second step of SPLET mechanism, ETE. Thus, our results indicate the thermodynamic preference of the formation of a radical anion to the electron transfer resulting in phenoxy radical formation. Radical anion formation was experimentally confirmed by Žemlička et al. (2014) for the luteolin-7-*O*-β-D-glucoside, where its formation was experimentally observed at B ring. We have confirmed the importance of mutual presence of C2=C3 double bond and 3-OH group in flavonoids – these are responsible for low B-ring O–H BDE(A) in 3-O⁻ anions. Although the attention was focused only on one selected reaction pathway, obtained results support the experimentally observed different antioxidant activity of deprotonated flavonoids in comparison to the parent species (Lemanska et al. 2001, Musialik et al. 2009, Álvarez-Diduk et al. 2013). For the studied environments, thermodynamically favored radical anions were identified.

For gallic acid carboxylate anion in aqueous solution, we have found that the deprotonation of the second OH group in molecule is still preferred to HAT (Škorňa et al. 2016b). Therefore, we have decided to calculate proton affinities, PA(A), of mono-deprotonated flavonoids. This study is under progress, but the first results indicate that PA(A) values are lower than BDE(A) values in aqueous solution (Klein et al. 2017), Table 1.

Anion	BDE(A)/kJ mol^{-1}					PA(A)/kJ mol^{-1}				
	3’-OH	4’-OH	3-OH	5-OH	7-OH	3’-OH	4’-OH	3-OH	5-OH	7-OH
3’-O^{-}		287	296	336	304		244	211	214	178
4’-O^{-}	302		283	333	300	259		218	220	182
3-O^{-}	279	251		320	278	194	186		246	192
5-O^{-}	306	288	307		326	184	175	233		214
7-O^{-}	308	290	300	360		182	172	214	249	

Table 1. B3LYP/6-311++G** O–H bond dissociation enthalpies, BDE(A)[a], and proton affinities, PA(A), of various anions of quercetin in water. [a] Data taken from (Klein et al. 2016).

4. Conclusion

We have shown that chosen computational approach, (IEF-PCM)B3LYP/6-311++G**, provides reliable results and describes observed experimental trends in corresponding reaction enthalpies correctly. It represents a rational compromise between the accuracy of found results and computational costs. In general, DFT methods are almost exclusively employed in this field of research. It can be expected, that newer functionals developed with the focus on the reaction thermodynamics will be used in larger extent in the next years.

Although studied reaction enthalpies are important characteristics of antioxidants, it should be noted that the activity of an antioxidant is also affected by the reaction kinetics, environment (e.g. polar/non-polar solvent or cellular environment, pH), its concentration and the presence of other compounds in the system.

Discovery of new and more effective antioxidants based on naturally occurring compounds remains one of the main aims of current research. Another important aim is to define optimum concentrations in individual systems, where the antioxidants are applied. These aspects clearly show that both, experimental and theoretical, investigations in this research field are inevitable.

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