

Gallic acid: thermodynamics of the homolytic and heterolytic phenolic O—H bonds splitting-off

Peter Škornja, Martin Michalík, Erik Klein

*Institute of Physical Chemistry and Chemical Physics, Slovak University of Technology in Bratislava,
Radlinského 9, SK-812 37 Bratislava, Slovak Republic
peter.skorna@stuba.sk*

Abstract: The DFT study of primary antioxidant action of gallic acid and its carboxylic anion is presented in the gas-phase, benzene and water. Corresponding reaction enthalpies for three possible mechanisms was calculated using B3LYP/6-311++G** method. Bond dissociation enthalpy (BDE) and proton dissociation enthalpy (PDE) of 4-OH group was found to be the lowest in gas-phase as well as in both solvents approximated by IEF-PCM model. Ionization potentials (IPs) were higher than BDEs in all cases. Deprotonation of carboxylic group result in increased antioxidant potency as drop in BDE, proton affinities (PAs) and IPs was indicated in all environments.

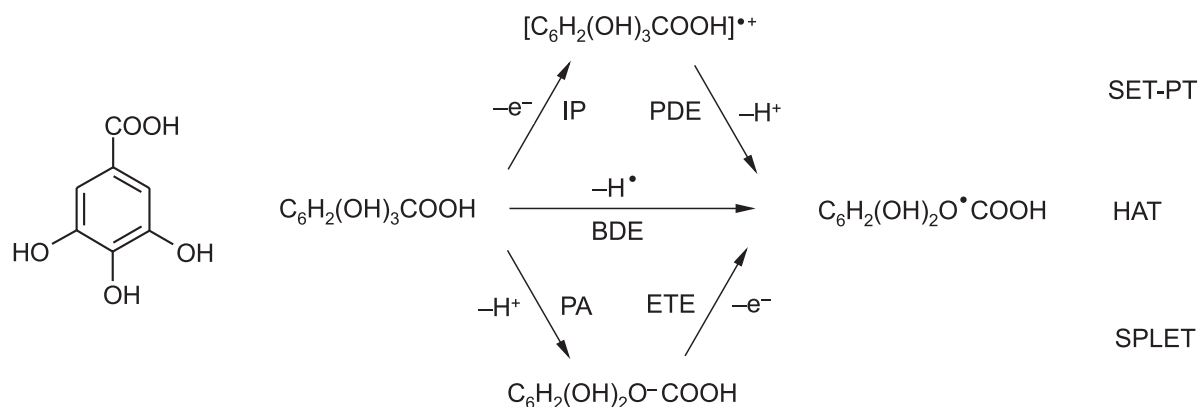
Keywords: hydrogen atom transfer, sequential proton-loss electron-transfer, deprotonation, bond dissociation enthalpy, proton affinity

Introduction

Gallic acid (3,4,5-trihydroxybenzoic acid) belongs to naturally occurring polyphenolic compounds. It is found in broad variety of plants and shows antioxidant, anticarcinogenic, antiviral, as well as neuroprotective effects. Therefore, it found biomedical and environmental applications. Gallic acid and its derivatives represent important additive in food technology, too (Gülçin, 2012; Huguenin, 2015). Phenolic antioxidants in general are able to react with free radicals *via* three mechanisms shown in Scheme 1 (Gülçin, 2012). From the thermodynamics point of view, Hydrogen Atom Transfer (HAT) is governed by the O—H bond dissociation enthalpy, BDE. The two-step Single Electron Transfer—Proton Transfer (SET-PT) is characterized by the ionization potential (IP) and the proton dissociation

enthalpy (PDE) of the formed radical cation. In the case of Sequential Proton-Loss Electron-Transfer (SPLET), deprotonation of an OH group is followed by the electron transfer from the formed phenoxide anion. The corresponding reaction enthalpies are proton affinity (PA) of the phenoxide anion and the electron transfer enthalpy, ETE.

In general, it is well known that physical, chemical and biological properties correlate with the acidity of phenolic acids or polyphenolics (Eslami, 2010; Ji, 2006; Marković, 2016; Yin, 2013). In the case of gallic acid, carboxylic group shows the highest acidity ($pK_a = 4.4$). Acidities of three phenolic groups were found in the range from $pK_a = 8.8$ (4-OH) to $pK_a = 11.4$ (5-OH) and these values determined using Raman spectroscopy are in accordance with previously published pK_a values (Huguenin, 2015). Electron paramagnetic resonance (EPR) study of



Scheme 1. Mechanisms of primary antioxidant action of gallic acid.

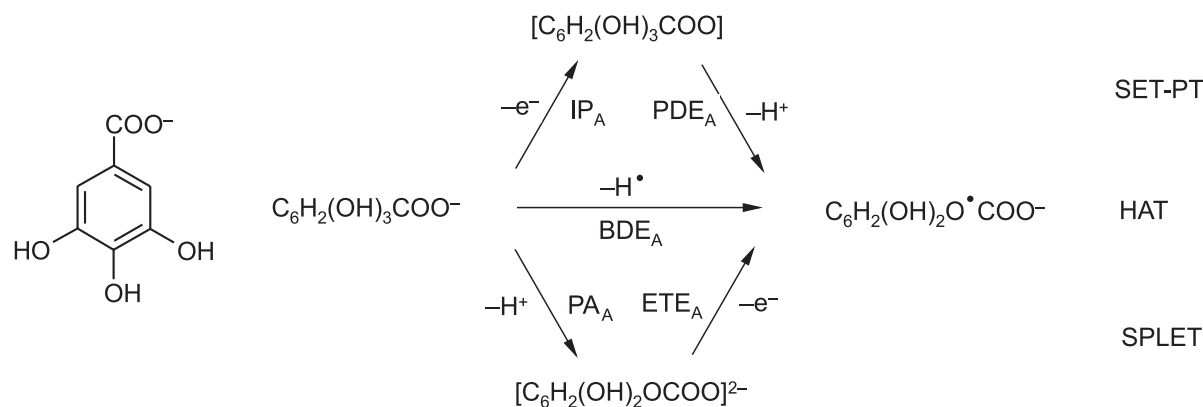
free radicals formed by the oxidation of gallic acid in water confirmed that at pH = 11, all remaining phenolic OH groups are ionized (Eslami, 2010). Already at physiological pH, the extent of deprotonation is significant (Ji, 2006; Marković, 2016). Thus, the study of antioxidant behavior of gallic acid requires the investigation of both, parent molecule and anions. For various flavonoids, it was experimentally, as well as theoretically shown that their antioxidant effect depends on pH, i.e. deprotonation severely alters antioxidant capacity of these compounds (Álvarez-Diduk, 2013; Klein, 2016; Lemańska 2001; Musialik, 2009).

Although several theoretical reports on parent gallic acid antioxidant action thermodynamics, depicted in Scheme 1, appeared in the last years (Chen, 2015; Ji, 2006; Koroleva, 2014; Leopoldini, 2004; Lu, 2006; Mohajeri, 2009; Saqib, 2015), a comprehensive study for the various anions formed from gallic acid is still missing. Therefore, the main aim of the present work is to study and mutually compare the reaction enthalpies related to the three mechanisms of primary antioxidant action of gallic acid (Scheme 1) and corresponding carboxylic anion (Scheme 2) in the gas-phase, benzene and water. Besides, this work is also focused on the investigation of HAT and SPLET mechanisms for species with one or two deprotonated OH groups that may be the main reaction pathways in water. Calculations are performed using B3LYP/6-311++G** method (Becke, 1993; Lee, 1988; Binkley, 1980) and integral equation formalism polarized continuum model (IEF-PCM) description of solvent effect (Cances, 1997 and 1998). This computational approach is identical to our previous papers (Lengyel, 2013; Klein, 2016; Vagánek, 2014) and allows the correct comparison of the calculated reaction enthalpies with data obtained for flavonoids. Chosen approach is widely used and provides reliable

trends – calculated geometries, EPR parameters (g-tensors, isotropic hyperfine coupling constants) and reaction enthalpies are in accordance with the available experimental data (Klein, 2016; Šolc, 2014; Toscano, 2016). In last years, newer M05-2X and M06-2X functional with SMD solvation model are also applied in the thermodynamics of antioxidant action works – including the reactions of gallic acid with various free radicals (Đorović, 2014). These 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 (Marković, 2013; Škorňa, 2016; Marković, 2016; Michalík, 2015). For *ortho*-, *meta*-, and *para*-substituted hydroxybenzoic acids, it was found that the shift in calculated proton affinities can be attributed mainly to the employed solvation model (Michalík, 2015) – values obtained using B3LYP and M06-2X functionals with the same solvation models were in very good mutual agreement, while application of SMD model led to PA values lower by ca 80 kJ mol⁻¹ in comparison to those obtained from IEF-PCM calculations. Analogous, very uniform shift was found also for IEF-PCM and SMD solution-phase proton affinities of 14 *para*-substituted benzoic acids with various electron-donating and electron-withdrawing substituents (Michalík, 2015).

Computational details

All calculations were performed employing Gaussian 09 program package (Gaussian, 2009). The geometry of each compound, radical or ion was optimized using DFT method with B3LYP 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. Optimized structures were



Scheme 2. Mechanisms of primary antioxidant action of gallic acid carboxylate anion.

confirmed to be real minima by frequency analysis. Solvent contribution to the total enthalpies was computed using IEF-PCM method. All IEF-PCM calculations (including geometry optimizations) were performed using default settings of Gaussian 09. Accuracy of the energy evaluation in the case of systems involving open-shell species is sensitive to the spin contamination. Spin contaminations of radical species reached correct value of 0.75 after the annihilation of the first spin contaminant. Thus, spin contamination should not bias calculated enthalpies.

From the calculated total enthalpies ($T = 298.15$ K) with not scaled zero-point energies (ZPE) we have determined following quantities

$$\text{BDE} = H(\text{ArO}^\bullet) + H(\text{H}^\bullet) - H(\text{ArOH}) \quad (1)$$

$$\text{IP} = H(\text{ArOH}^{\bullet+}) + H(e^-) - H(\text{ArOH}) \quad (2)$$

$$\text{PDE} = H(\text{ArO}^\bullet) + H(\text{H}^+) - H(\text{ArOH}^{\bullet+}) \quad (3)$$

$$\text{PA} = H(\text{ArO}^-) + H(\text{H}^+) - H(\text{ArOH}) \quad (4)$$

$$\text{ETE} = H(\text{ArO}^\bullet) + H(e^-) - H(\text{ArO}^-) \quad (5)$$

The calculated gas-phase enthalpy of proton, $H(\text{H}^+)$, is 6.197 kJ mol⁻¹ and gas-phase enthalpy of electron $H(e^-)$ is 3.145 kJ mol⁻¹ (Bartmess, 1994). Proton and electron solvation enthalpies were taken from Rimarčík (2010), where the employed computational approach was described in details. For carboxylate anions, the three mechanisms lead to formation of radical anion and the corresponding reaction enthalpies, denoted as BDE_A, IP_A, PDE_A, PA_A and ETE_A, can be defined analogously (Scheme 2).

Results and discussion

Reaction enthalpies for parent gallic acid

Although gallic acid and its antioxidant effect is intensively studied both, experimentally and theoretically, there is a lack of experimental data on the reaction enthalpies of its primary antioxidant action. From the rate constants of the reaction with the peroxy radicals (Denisova, 2008), O—H BDE = 347.7 kJ mol⁻¹ was determined in non-polar environment (methyl linoleate). Alberti et al. (2009) determined solution BDE = 339 kJ mol⁻¹ through the EPR experiment based on radical equilibration technique in acetonitrile/chlorobenzene. These values are slightly higher than those in Table 1 related to 4-OH group showing the lowest BDE. On the other hand, if we compare results compiled in Tables 1–3, with one exception, they are in accordance with B3LYP/6-311++G** values in work of Chen et al. (2015), differences do not exceed

5 kJ mol⁻¹. The only discrepancy we found in the case of PDE values in the benzene. The published values are roughly by 100 kJ mol⁻¹ larger. Since in all three mechanisms the final product, the phenoxy radical, is identical, using thermodynamic cycle we have verified that values in Table 2 are correct. Moreover, for tricetin (flavonoid with pyrogallol unit representing ring B), in benzene we found all three B ring PDEs in 62–100 kJ mol⁻¹ range (Vagánek, 2014). In general, obtained results are in agreement with other theoretical works (Ji, 2006; Koroleva, 2014; Leopoldini, 2004; Lu, 2006; Mohajeri, 2009; Saqib, 2015), too.

Tab. 1. B3LYP/6-311++G** O—H Bond Dissociation Enthalpies, BDE in kJ mol⁻¹, of Gallic Acid.

Group	gas	benzene	water
3-OH	354	349	341
4-OH	323	321	318
5-OH	326	327	329

Tab. 2. B3LYP/6-311++G** Proton Dissociation Enthalpies, PDE in kJ mol⁻¹, of Gallic Acid.

Group	gas	benzene	water
3-OH	885	84	30
4-OH	854	56	6
5-OH	856	62	18

Tab. 3. B3LYP/6-311++G** Proton Affinities and Electron Transfer Enthalpies, ETE in kJ mol⁻¹, of Gallic Acid.

Group	PA			ETE		
	gas	benzene	water	gas	benzene	water
3-OH	1430	416	191	246	344	336
4-OH	1373	369	156	272	363	347
5-OH	1373	373	165	275	366	351

Data in Table 1 reveal that in all environments, 4-OH BDE is the lowest. Although it requires disruption of the intramolecular hydrogen bond with the 5-OH oxygen atom, the hydrogen bond with 3-OH group stabilizes formed radical. On the other hand, 3-OH BDE is the highest, because it requires the hydrogen bond cancelling and resulting radical is not stabilized by a hydrogen bond. Solvent shows only a negligible effect on BDEs, found changes are within 5 kJ mol⁻¹ for 4-OH and 5-OH groups. For 3-OH group, BDEs are in 13 kJ mol⁻¹ range in the three environments. The lowest 3-OH BDE was found in water that may contribute to the stabiliza-

tion of formed radical and attenuates the effect of hydrogen bond (Lengyel, 2013).

Ionization potential value is the highest in gas-phase, 792 kJ mol⁻¹, and the lowest in the water, 497 kJ mol⁻¹. In benzene IP reached the value of 677 kJ mol⁻¹. These are higher than BDEs in Table 1, thus entering SET-PT mechanism is less probable from the thermodynamics point of view. In comparison to gas-phase, PDEs in benzene and water (Table 2) show considerable decrease that is in accordance with other works (Chen, 2015; Vagánek, 2014). Solvent stabilizes formed radical cation and large negative solvation enthalpy of proton results significant drop in PDEs. In agreement with BDEs, the lowest PDE was found for 4-OH group.

Analogously to SET-PT, SPLET is also relevant only in the solution-phase. In comparison to gas-phase, PA in benzene and water are lower by ca 1000 kJ mol⁻¹ and 1200 kJ mol⁻¹ (Table 3), respectively. Again, the lowest PA shows 4-OH group, in accordance with results for pyrogallol unit of tricetin (Vagánek, 2014). As it could be expected from previous works (Lengyel, 2013; Vagánek, 2014), the lowest ETE was found for 3-OH group showing the largest PA. Contrary to IP, PDE and PA, solution-phase ETEs are higher than the gas-phase ones, because solvent stabilizes the phenoxide anion formed in the first step of SPLET more than the phenoxy radical formed in the second step.

It can be concluded that in gas-phase and benzene, hydrogen atom transfer represents thermodynamically favored mechanism. In water, entering SPLET is thermodynamically preferred, because PA values are significantly lower than BDEs. SET-PT mechanism is the least preferred in the solution-phase.

Reaction enthalpies for carboxylate anion of gallic acid

In solution-phase, deprotonation of carboxylic group takes place. In benzene and water IEF-PCM/B3LYP/6-311++G** calculated enthalpy of carboxylic group deprotonation reached values of 393 kJ mol⁻¹ and 159 kJ mol⁻¹, respectively. In all investigated environments these values are very close to 4-OH and 5-OH PAs of parent gallic acid. In the case of *ortho*-, *meta*-, and *para*-substituted hydroxybenzoic acids studied at G3MP2 level, higher acidity of OH group in comparison to COOH one (in terms of PA values) was found only for *para*-hydroxybenzoic acid in the gas-phase (Galaverna, 2015). In CH₃CN and methanol, differences between COOH and OH groups PA values were not pronounced and did not exceed 19 kJ mol⁻¹. For COOH and 4-OH groups, we have also performed calculations using M06-2X functional (Zhao, 2008) and SMD solvation model

(Marenich, 2009) in the same basis set. This approach provided PA = 154 kJ mol⁻¹ for 4-OH group in agreement with IEF-PCM/B3LYP/6-311++G** result in Table 3 obtained for aqueous solution. For COOH group it gave lower value of 139 kJ mol⁻¹, which is in better agreement with experimental results.

Tab. 4. B3LYP/6-311++G** O—H Bond Dissociation Enthalpies, BDE_A in kJ mol⁻¹, of Gallic Acid Carboxylate Anion.

Group	gas	benzene	water
3-OH	319	323	327
4-OH	278	289	301
5-OH	288	300	313

The comparison of BDE_A values summarized in Table 4 with BDEs obtained for parent gallic acid (Table 1) indicates that carboxylate anion is better hydrogen atom donor from the thermodynamics point of view. In gas-phase, differences are from 35 (3-OH group) to 45 kJ mol⁻¹ (4-OH group). Solvents attenuate the differences between BDE_A and BDE values, in water they are from 14 to 17 kJ mol⁻¹ only. In all environments, the largest drop in bond dissociation enthalpies was found for 4-OH group. These results show that carboxylic group deprotonation may result in increased antioxidant potency of gallic acid. The similar results were also found for flavonoids, though the differences between BDEs and BDE_A values were more pronounced (Klein, 2016; Lemańska, 2001).

In each studied environment, ionization potential of carboxylate anion is significantly lower in comparison to gallic acid. The lowest value of IP_A = 261 kJ mol⁻¹ was obtained for gas-phase. In the two investigated solvents, IP_A values are practically identical: 367 kJ mol⁻¹ in benzene and 368 kJ mol⁻¹ in water. Compared to gallic acid, the largest drop in ionization potential was observed in the gas-phase (531 kJ mol⁻¹) and the lowest one in water (129 kJ mol⁻¹), because electron abstraction leads to neutral species. In the two solvents, calculated IP_A values are higher than BDE_A. In gas-phase, electron abstraction from the carboxylate anion is thermodynamically favored in comparison to hydrogen atom transfer.

Tab. 5. B3LYP/6-311++G** Proton Dissociation Enthalpies, PDE_A in kJ mol⁻¹, of Gallic Acid Carboxylate Anion.

Group	gas	benzene	water
3-OH	1380	368	145
4-OH	1371	361	142
5-OH	1378	366	143

For carboxylate anion, proton dissociation enthalpies (Table 5) reached considerably higher values in comparison to parent gallic acid, because heterolytic OH bond splitting off is not advantageous in the gas-phase. Found values are relatively close to PAs obtained for parent molecule. Again, the lowest values were found for 4-OH group, although PDEs of all three OH groups are close. In water, they lie within 3 kJ mol⁻¹.

Formation of a di-anion after one OH group deprotonation is highly improbable for the gas-phase. Because solvents considerably stabilize charged species, a decrease in PA_A values (Table 6) can be observed for benzene and water. However, found PA_A values are higher in comparison to gallic acid by ca 320 kJ mol⁻¹ in gas-phase and by ca 150 kJ mol⁻¹ in benzene. In benzene and benzene, PA_A values are higher than IP_A values. Thus, entering SPLET mechanism is the least probable process in the case of carboxylate anion in non-polar environment. On the other hand, water represents the polar solvent which is very good hydrogen bond donor, as well as acceptor. This results in PA_A values shifted only by 23–32 kJ mol⁻¹ in comparison to PAs. All three PA_A values are lower than BDE_A and IP_A values, therefore in water SPLET remains thermodynamically favored mechanism also for the carboxylate anion. In gas-phase, SET-PT mechanism is thermodynamically preferred due to low gas-phase IP.

Because the formation of di-anion is connected with considerably large reaction enthalpy in gas-phase, the second step of SPLET resulting in radical anion

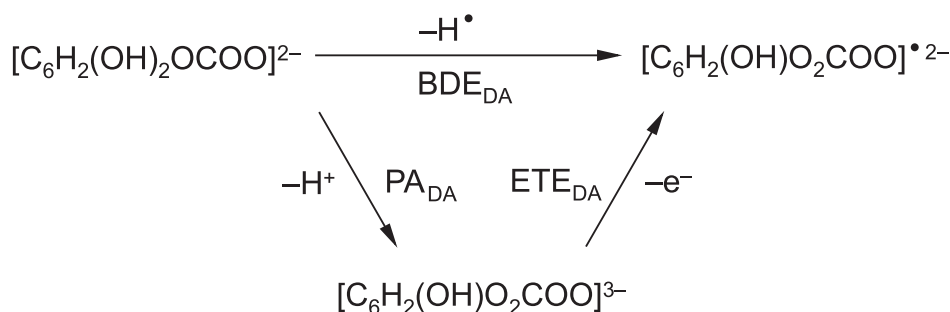
is exothermic. In solution-phase ETE_A values are positive. In both solvents, they are lower than ETE values for parent gallic acid. Larger differences (ca 170 kJ mol⁻¹) were found for benzene; in water they do not exceed 48 kJ mol⁻¹.

Tab. 6. B3LYP/6-311++G** Proton Affinities and Electron Transfer Enthalpies in kJ mol⁻¹ of Gallic Acid Carboxylate Anion.

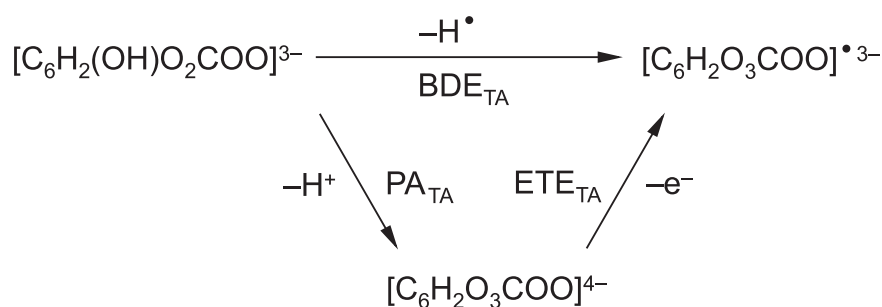
Group	PA _A			ETE _A		
	gas	benzene	water	gas	benzene	water
3-OH	1748	563	214	-106	172	300
4-OH	1699	522	188	-99	179	299
5-OH	1692	518	188	-82	194	311

HAT and SPLET mechanisms for di- and tri-anions

In aqueous solutions, full deprotonation may occur. At higher pH values (Eslami, 2010) occurrence of [C₆H₂O₃COO]^{•3-} radical tri-anion was observed. Because SPLET and HAT mechanisms can be considered plausible in this case, we decided to explore also processes depicted in Schemes 3 and 4. In Scheme 3, the radical di-anion is formed *via* HAT or SPLET mechanism from the di-anion with deprotonated COOH and one of the phenolic OH groups. The corresponding reaction enthalpies are denoted BDE_{DA}, PA_{DA} and ETE_{DA}. Analogous processes are studied in the case of tri-anion (a spe-



Scheme 3. HAT and SPLET mechanisms for di-anions of gallic acid.



Scheme 4. HAT and SPLET mechanisms for tri-anions of gallic acid.

Tab. 7. B3LYP/6-311++G** O—H Bond Dissociation Enthalpies, BDE_{DA} in kJ mol^{-1} , of Gallic Acid Carboxylate Anion with One Deprotonated OH Group.

Deprotonated OH group	BDE_{DA} , gas			BDE_{DA} , benzene			BDE_{DA} , water		
	3-OH	4-OH	5-OH	3-OH	4-OH	5-OH	3-OH	4-OH	5-OH
3-OH		235	227		244	247		260	279
4-OH	284		241	282		251	285		265
5-OH	283	249		292	253		305	263	

Tab. 8. B3LYP/6-311++G** Proton Affinities, PA_{DA} in kJ mol^{-1} , of Gallic Acid Carboxylate Anion with One Deprotonated OH Group.

Deprotonated OH group	PA_{DA} , gas			PA_{DA} , benzene			PA_{DA} , water		
	3-OH	4-OH	5-OH	3-OH	4-OH	5-OH	3-OH	4-OH	5-OH
3-OH		2135	2061		754	695		261	225
4-OH	2178		2120	795		746	284		256
5-OH	2117	2128		740	748		251	256	

cies with deprotonated COOH and two phenolic OH groups), Scheme 4. Here, the final product is radical tri-anion, $[\text{C}_6\text{H}_2\text{O}_3\text{COO}]^{\bullet 3-}$, and reaction enthalpies are BDE_{TA} , PA_{TA} and ETE_{TA} .

In Table 7, BDE_{DA} values are compiled. The first column indicates the phenolic OH group deprotonated prior to H-atom transfer studied. Values in individual columns represent BDE_{DA} values of remaining OH groups as shown in the column headings. Again, in all three environments, BDEs are similar, with one exception (3-OH BDE for deprotonated 5-OH group). These values are lower than 300 kJ mol^{-1} . In solution-phase, the lowest value reached 4-OH BDE for deprotonated 3-OH group. In the gas-phase, the lowest BDE_{DA} was found for 5-OH BDE in di-anion with deprotonated 3-OH group. This indicates that solvent is able to alter thermodynamically preferred HAT site through the stabilization of the formed product, although homolytic cleavage of the 4-OH group requires disruption of the intramolecular hydrogen bond with neighboring oxygen atom. If we compare BDE_{DA} values with corresponding ETE_A data from Table 6, one can see that BDE_{DA} values are usually lower than ETE_A values for the carboxylate anion after deprotonation of certain OH group in water. Thus, it may be anticipated that electron transfer is not the preferred reaction pathway for $[\text{C}_6\text{H}_2\text{O}(\text{OH})_2\text{COO}]^{2-}$ di-anions formed from carboxylate anion $\text{C}_6\text{H}_2(\text{OH})_3\text{COO}^-$. In gas-phase and benzene, the second step of SPLET is preferred, because all ETE_A values are considerably lower (for gas-phase electron transfer is even exothermic) than BDE_{DA} ones.

For SPLET, PA_{DA} values are summarized in Table 8, which has analogous structure as the Table 7. As it

could be expected on the basis of PA and PA_A values, the formation of tri-anion is from the thermodynamics point of view not probable in the gas-phase and benzene, where the values exceed 2000 and 690 kJ mol^{-1} , respectively. On the other hand, for di-anions, PA_{DA} values for remaining OH groups are, with one exception, lower than BDE_{DA} values in water, differences are in the range from 1 to 54 kJ mol^{-1} . For di-anion with deprotonated 3-OH group, 4-OH PA_{DA} is only by 1 kJ mol^{-1} higher than BDE_{DA} , for deprotonated 5-OH group 4-OH PA_{DA} is lower by 7 kJ mol^{-1} lower than BDE_{DA} . In these cases, one could suppose that the two mechanisms may be thermodynamically preferred equally. Again, PA_{DA} values can be confronted with ETE_A values from Table 6. The comparison of PA_{DA} and ETE_A indicates that further deprotonation of all possible $[\text{C}_6\text{H}_2\text{O}(\text{OH})_2\text{COO}]^{2-}$ di-anions is preferred to electron transfer in water.

Due to exceptionally large PA_{DA} values in gas-phase and benzene, corresponding ETE_{DA} values (Table 9) are negative. In water, all three ETE_{DA} values lie in $185\text{--}239 \text{ kJ mol}^{-1}$. In comparison with ETE and ETE_A values (Tables 3 and 6) that reached values of 300 kJ mol^{-1} or higher, these are considerably lower. Electron transfer from $[\text{C}_6\text{H}_2\text{O}_2(\text{OH})\text{COO}]^{3-}$ tri-anion can again compete with H-atom transfer from the last OH group. Corresponding BDE_{TA} values are compiled in Table 10. In water, they are higher than ETE_{DA} values. The values of PA_{TA} (Table 11), related to the deprotonation of the last phenolic OH group, are also higher than ETE_{DA} values in water. Therefore, electron transfer represents the thermodynamically favored pathway in the case of $[\text{C}_6\text{H}_2\text{O}_2(\text{OH})\text{COO}]^{3-}$ tri-anion (contrary to $[\text{C}_6\text{H}_2\text{O}(\text{OH})_2\text{COO}]^{2-}$ di-anion).

Tab. 9. B3LYP/6-311++G** Electron Transfer Enthalpies, ETE_{DA} in kJ mol^{-1} of Gallic Acid Carboxylate Anion with Two Deprotonated OH Group.

Deprotonated OH groups	gas	benzene	water
3-OH, 4-OH	-578	-98	185
3-OH, 5-OH	-512	-36	239
4-OH, 5-OH	-557	-83	195

Tab. 10. B3LYP/6-311++G** Bond Dissociation Enthalpies, BDE_{TA} in kJ mol^{-1} , of Gallic Acid Carboxylate Anion with Two Deprotonated OH Groups.

Deprotonated OH groups	gas	benzene	water
3-OH, 4-OH (5-OH)*	244	244	251
3-OH, 5-OH (4-OH)	254	254	256
4-OH, 5-OH (3-OH)	180	195	220

*In parenthesis dissociated OH group is indicated.

For tri-anions with two deprotonated OH groups, BDE_{TA} values for the last OH group (Table 10) in gas-phase and solution-phase values are similar. Here, the studied environments do not exert a considerable effect on the O—H bond homolytic cleavage. On the other hand, significant effect of environment is apparent in the case of PA_{TA} values. Data in Table 11 again confirm that SPLET mechanism can be relevant pathway only in water. However, PA_{TA} values are higher than corresponding BDE_{TA} ones. In contrast to carboxylate anion and studied di-anions, for all three tri-anions, the reaction enthalpy of H-atom transfer is lower than PA_{TA} characterizing the deprotonation of the last OH group. PA_{TA} values in gas-phase and benzene follow the observed trend: with each deprotonation, proton affinities significantly grow. In water, an increase in proton affinities is also observable; however it is in order of tens of kJ mol^{-1} . Table 11 contains only one ETE_{TA} value for each environment, because the last possible deprotonation of individual tri-anions leads to the same product, $[C_6H_2O_3COO]^{4-}$. Formation of $[C_6H_2O_3COO]^{3-}$ representing the final product after electron

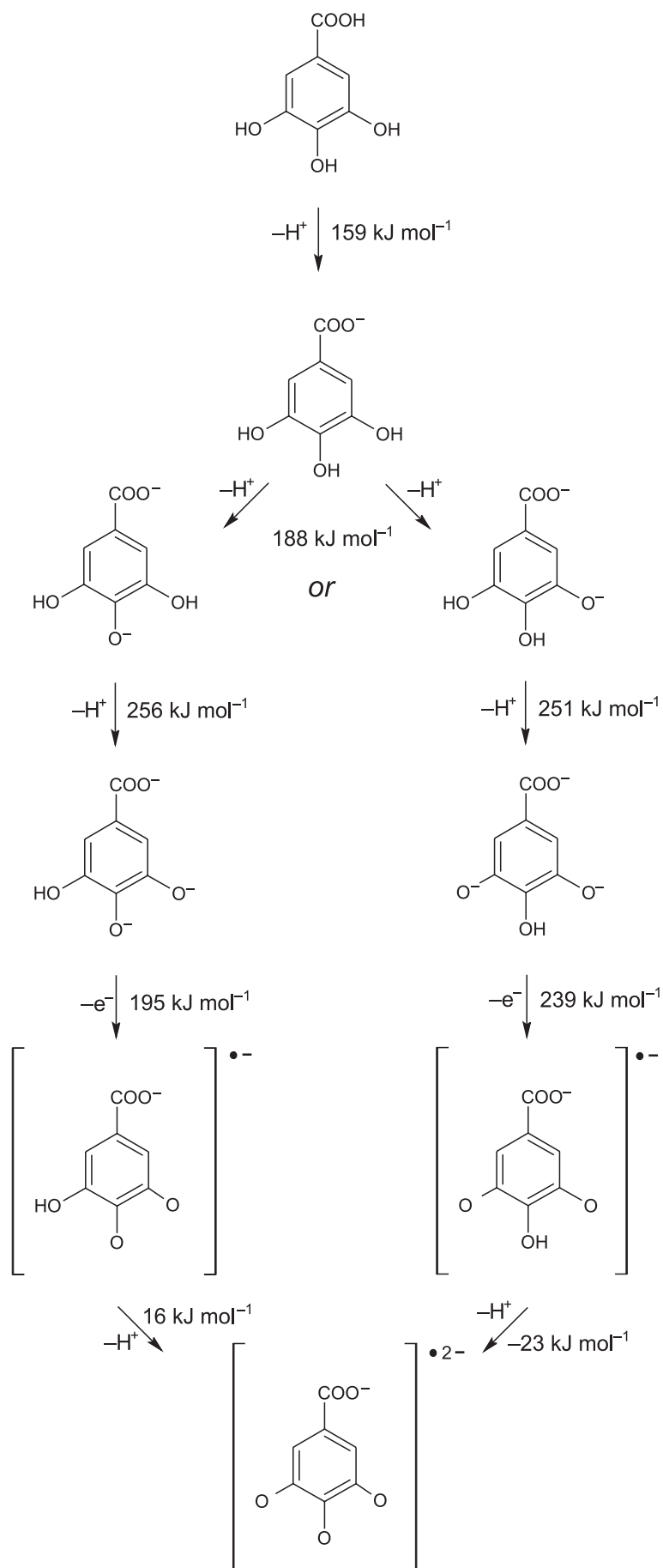
transfer was observed by EPR spectroscopy (Eslami, 2010). Obtained results predict that this process is in gas-phase and benzene exothermic, while in water it is endothermic, but ETE_{TA} is lower than all ETE , ETE_A and ETE_{DA} values.

On the basis of our calculations, as well as employing available experimental data on acidity of COOH and OH groups, we have proposed a reaction scheme for antioxidant action of gallic acid in aqueous solution. In each step of the Scheme 5, thermodynamically preferred process is shown. In the first step, deprotonation of COOH group occurs. According experimental reports on the acidities of three OH groups of gallic acid, 4-OH group should be the most acidic one (Huguenin, 2015). However, our calculations show identical PA for 5-OH group, too. On the other hand, various reported experimental pK_a values for the two OH groups are in the relatively wide range of 2 units (Huguenin, 2015), therefore similar acidities of the two OH groups cannot be excluded. In the next step, deprotonation of second OH group takes place, followed by electron transfer from the formed tri-anion. Then, the radical di-anions depicted in Scheme 5 can undergo HAT or SPLET pathway. In the case of HAT, the product can be non-radical (singlet state) or bi-radical (triplet state). Our calculations have confirmed that non-radical $[C_6H_2O_3COO]^{2-}$ product is more stable. For radical di-anion, where 3-OH group (as the last one) is dissociated, 3-OH BDE_{RDA} reached very low value of 46 kJ mol^{-1} . For the radical di-anion still possessing 4-OH group, the corresponding BDE_{RDA} reached very similar value of 48 kJ mol^{-1} . However, deprotonation of 3-OH group in the first radical di-anion shows PA_{RDA} value of 16 kJ mol^{-1} . It is lower than 3-OH BDE_{RDA} . For 4-OH in the second studied radical di-anion, we obtained negative PA_{RDA} value of -23 kJ mol^{-1} . Thus, the final $[C_6H_2O_3COO]^{3-}$ product is formed via deprotonation of the last OH group in corresponding radical di-anions. However, various competitive processes may play a role in the real systems, where all three mechanisms of primary antioxidant action can participate.

Tab. 11. B3LYP/6-311++G** Proton Affinities and Electron Transfer Enthalpies in kJ mol^{-1} of Gallic Acid Carboxylate Anion with Two Deprotonated OH Groups.

Deprotonated OH groups	PA_{TA}			ETE_{TA}		
	gas	benzene	water	gas	benzene	water
3-OH, 4-OH (5-OH)*	2483	930	294	-981	-323	112
3-OH, 5-OH (4-OH)	2557	989	329			
4-OH, 5-OH (3-OH)	2546	979	324			

*In parenthesis OH group undergoing deprotonation is indicated.



Scheme 5. Thermodynamically preferred pathway of $[\text{C}_6\text{H}_2\text{O}_3\text{COO}]^{\bullet 3-}$ formation in water.

Unfortunately, the chemical accuracy of the used method cannot be assessed directly, since experimental data for gallic acid are not available. However, for mono-substituted phenols and tocopherols, we have confirmed that employed computational approach provides results in agreement with available experimental data (Klein, 2006; Klein, 2007). Though individual BDE values may be slightly underestimated, the trends are in very good agreement with experimental data and theoretical results obtained using newer functionals developed for reaction energetics calculations (Đorović, 2014, Marković, 2012; Škorňa, 2016). For gas-phase PA values of mono-substituted phenols, employed computational method provided results in excellent agreement with experimental results (Klein, 2006).

Conclusion

In the case of parent gallic acid hydrogen atom transfer governed by BDE is thermodynamically favored in gas-phase and benzene. In all environments, 4-OH BDE is the lowest as hydrogen bond with 3-OH group stabilizes formed radical. On the other hand, 3-OH BDE is the highest, because it requires the hydrogen bond cancelling and resulting radical is not stabilized by a hydrogen bond. Minimal solvent effect on BDEs is observed. In water PA values are significantly lower than BDEs, therefore SPLET is thermodynamically preferred. SET-PT mechanism is the least preferred in the solution-phase.

In solution-phase, deprotonation of carboxylic group takes place. In benzene and water calculated enthalpy of carboxylic group deprotonation reached values very close to 4-OH and 5-OH PAs of parent gallic acid. Significant drop in bond dissociation enthalpies was found in all environments, especially in the case of 4-OH BDE. Thus, carboxylic group deprotonation may result in increased antioxidant potency of gallic acid. The similar results were also found for flavonoids. Although proton dissociation enthalpies of all three OH groups were close, their values were considerably higher in comparison to parent gallic acid.

Formation of a di-anion after one OH group deprotonation is highly improbable for the gas-phase. On the other hand, in water SPLET remains thermodynamically favored mechanism also for the carboxylate anion. SET-PT mechanism is preferred in gas-phase due to low ionization potential. Further deprotonation of di-anion is preferred to electron transfer in water.

Formation of tri-anion is from the thermodynamics point of view not probable in the gas-phase and ben-

zene. Nevertheless, BDE_{TA} values for the last OH group in gas-phase and solution-phase values are similar unlike PA_{TA} values showing significant effect of environment. Proton affinities in gas-phase and benzene follow the trend: with each deprotonation, proton affinities significantly grow. Despite only slight increase in proton affinities in water, electron transfer is the thermodynamically favored pathway in the case of tri-anion, contrary to di-anion.

Acknowledgements

This work was supported by the Slovak Research and Development Agency under the contract No. APVV-15-0053. This work was supported the Slovak Grant Agency (VEGA 1/0594/16 and 1/0307/14). We are grateful to the HPC centre at the Slovak University of Technology in Bratislava, which is a part of the Slovak Infrastructure of High Performance Computing (SIVVP project, ITMS code 26230120002, funded by the European region development funds, ERDF) for the computational time and resources made available.

References

- Alberti A, Amorati R, Campredon M, Lucarini M, Macciantelli D, Pedulli GF (2009) *Acta Alimentaria* 38: 427–436.
- Álvarez-Diduk R, Ramírez-Silva MT, Galano A, Merkoçi A (2013) *J. Phys. Chem. B* 117: 12347–12359.
- Bartmess JE (1994) *J. Phys. Chem.* 98: 6420–6424.
- Becke A (1993) *J. Chem. Phys.* 98: 5648–5652.
- Binkley JS, Pople JA, Hehre WJ (1980) *J. Am. Chem. Soc.* 102: 939–947.
- Cances E, Mennucci B, Tomasi J (1997) *J. Chem. Phys.* 107: 3032–3041.
- Cances E, Mennucci B (1998) *J. Math. Chem.* 23: 309–326.
- Chen Y, Xiao H, Zheng J, Liang G (2015) *PLoS ONE* 10(3): e0121276.
- Denisova TG, Denisov ET (2008) *Russ. Chem. Bull.* 57: 1858–1866.
- Đorović J, Dimitrić Marković JM, Stepanić V, Begović N, Amić D, Marković Z (2014) *J. Mol. Model.* (2014) 20: 2345.
- Eslami AC, Pasanphan W, Wagner BA, Buettner GR (2010) *Chemistry Central Journal* 4: 15.
- Galaverna RS, Bataglioni GA, Heerdt G, De Sa GF, Daroda R, Cunha VS, Morgon NH, Eberlin MN (2015) *Eur. J. Org. Chem.* 2015: 2189–2196.
- Gülçin İ (2012) *Arch. Toxicol.* 86: 345–391.
- Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery JA Jr., Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox

- JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ (2009) Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT
- Huguenin J, Hamadya SOS, Bourson P (2015) *J. Raman Spectrosc.* 46: 1062–1066.
- Ji H-F, Zhang H-Y, Shen L (2006) *Bioorg. Med. Chem. Lett.* 16: 4095–4098.
- Klein E, Lukeš V (2006) *J. Phys. Chem. A* 110: 12312–12320.
- Klein E, Lukes V, Ilčin M (2007) *Chem Phys.* 336: 51–57.
- Klein E, Rimarčík J, Senajová E, Vagánek A, Lengyel J (2016) *Comp. Theor. Chem.* 1085: 7–17.
- Koroleva O, Torkova A, Nikolaev I, Khrameeva E, Fedorova T, Tsentalovich M, Amarowicz R (2014) *Int. J. Mol. Sci.* 15: 16351–16380.
- Lee C, Yang W, Parr RG (1988) *Phys. Rev. B* 37: 785–789.
- Lemańska K, Szymusiak H, Tyrakowska B, Zieliński R, Soffers AEMF, Rietjens IMCM (2001) *Free Rad. Biol. Med.* 31: 869–881.
- Lengyel J, Rimarčík J, Vagánek A, Klein E (2013) *Phys. Chem. Chem. Phys.* 15: 10895–10903.
- Leopoldini M, Marino T, Russo N, Toscano M (2004) *J. Phys. Chem. A* 108: 4916–4922.
- Lu Z, Nie G, Belton PS, Tang H, Zhao B (2006) *Neurochemistry International* 48: 263–274.
- Marenich AV, Cramer CJ, Truhlar DG (2009) *J. Phys. Chem. B.* 113: 6378–6396.
- Marković Z, Amić D, Milenković D, Dimitrić-Marković JM, Marković S (2013) *Phys. Chem. Chem. Phys.* 15: 7370–7378.
- Marković Z, Đorović J, Dimitrić Marković JM, Biočanin R, Amić D (2016) *Turk. J. Chem.* 40: 499–509.
- Michalík M, Škorňa P, Lukeš V (2015) *Acta Chimica Slovaca* 8: 120–125.
- Mohajeri A, Asemani SS (2009) *J. Mol. Struct.* 930: 15–20.
- Musialik M, Kuzmich R, Pawlowski TS, Litwinienko G (2009) *J. Org. Chem.* 74: 2699–2709.
- Rimarčík J, Lukeš V, Klein E, Ilčin M (2010) *J. Mol. Struct. THEOCHEM* 952: 25–30.
- Saqib M, Mahmood A, Akram R, Khalid B, Afzal S, Kamal GM (2015) *J. Pharm. Appl. Chem.* 1: 65–71.
- Škorňa P, Rimarčík J, Poliak P, Lukeš V, Klein E (2016) *Comp. Theor. Chem.* 1077: 32–38.
- Šolc R, Gerzabek MH, Lischka H, Tunega D (2014) *Comp. Theor. Chem.* 1032: 42–49.
- Toscano M, Russo N (2016) *Comp. Theor. Chem.* 1077: 119–124.
- Vagánek A, Rimarčík J, Dropková K, Lengyel J, Klein E (2014) *Comp. Theor. Chem.* 1050: 31–38.
- Yin J, Andersen ML, Skibsted LH (2013) *J. Agric. Food Chem.* 61: 3159–3166.
- Zhao Y, Truhlar DG (2008) *Theor. Chem. Acc.* 120: 215–241.