

# On the Antioxidant Activity of the *Ortho* and *Meta* Substituted Daidzein Derivatives in the Gas Phase and Solvent Environment

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**Abstract.** The antioxidant activities of substituted Daidzein derivatives have been investigated. The electron withdrawing substituents increase the bond dissociation enthalpy, ionization potential, while electron donating groups cause a rise in the proton affinity. The Daidzein derivatives with the lowest bond dissociation enthalpy, ionization potential and proton affinity values were identified as the compounds with high antioxidant activity. The Daidzein derivatives can process their protective role via hydrogen atom transfer and sequential proton loss electron transfer mechanism in gas phase and solvent, respectively.

**Key words:** Antioxidant, Daidzein, substituent effect, DFT,  $E_{\text{HOMO}}$ .

**Resumen.** Se ha investigado la actividad antioxidante de derivados de la daidzeína sustituida. Los sustituyentes electroattractores incrementan la entalpía de disociación de enlace y el potencial de ionización, mientras que los grupos electrodonadores provocan un aumento en la afinidad protónica. Los derivados de la daidzeína con las menores entalpía de disociación de enlace, potencial de ionización y afinidad protónica se identificaron como los compuestos con actividad antioxidante alta. En fase gaseosa y en presencia de solvente, los derivados de la daidzeína pueden desarrollar su papel protector vía la transferencia de un átomo de hidrógeno y por un mecanismo secuencial de pérdida de protón-transferencia electrónica, respectivamente.

**Palabras Clave:** Antioxidante, daidzeína, efecto del sustituyente, TFD,  $E_{\text{HOMO}}$ .

## Abbreviations:

Density Functional Theory (DFT), Bond Dissociation Enthalpy (BDE), Ionization Potential (IP), Proton Affinity (PA), Single Electron Transfer followed by Proton Transfer (SET-PT), Sequential Proton Loss Electron Transfer (SPLET), Hydrogen Atom Transfer (HAT), Polarized Continuum Model (PCM), EDG-substituent (Electron Donating Group), EWG-substituent (Electron Withdrawing Group).

## Introduction

Excess formation of reactive oxygen species (ROS) by various enzymatic and nonenzymatic processes in living organisms has been associated with the oxidation of DNA, proteins and lipids. The ROS have been found to play an important role in the initiation and progression of various diseases such as atherosclerosis, cancer, cardiovascular disease, neurodegenerative disease and aging [1]. Antioxidant helps cells to cope with oxidative stress by effectively quenching free radicals.

Daidzein (7-Hydroxy-3-(4-hydroxyphenyl) chromen-4-one) and its derivatives represent one of the most active classes of compound possessing a wide spectrum of biological activity. Many of these compounds have proven to be active as antioxidant and antitumor agents [2]. Daidzein (Fig. 1.) and its derivatives have been effectively used as antioxidants for the treatment of disorders in which there is excessive or undesirable clotting, such as thrombophlebitis, pulmonary embolism, and certain cardiac conditions [3]. Daidzein has been shown to impose protective effects in oxidant stress mediated tissue injury in vivo. Daidzein as hydrophilic antioxidant possesses high capacity to modulate the inflammatory cascade triggered by oxidative stress and to improve altered angiogenesis that pervades the management of diabetic foot ulcer [4]. Daidzein

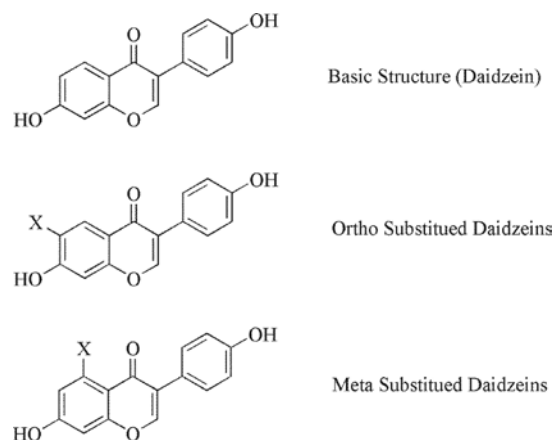


Fig. 1. Structure of Daidzein (7-Hydroxy-3-(4-hydroxyphenyl) chromen-4-one) and Studied the ortho and meta substituted Daidzeins: X=Br, Ethyl, CH=CH<sub>2</sub>, CCH, CF<sub>3</sub>, Cl, CN, COMe, COH, COOH, F, NMe<sub>2</sub>, NHMe, NH<sub>2</sub>, NO<sub>2</sub>, OMe, OH, Ph, t-Bu.

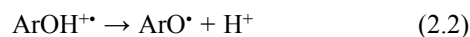
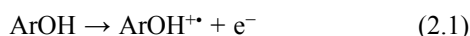
has been reported to act by different modes such as: protection and inhibition of LDL lipid peroxidation, reduction of myocardial infarction as a promising drug for cardiac ischemia and reperfusion, stimulation of wound healing in genetically diabetic mice, reduction of the glutamate-induced oxidative effects, and anti proliferative effects in the rat aortic smooth muscle cells in vivo [5].

The phenolic antioxidants (ArOH) inhibit oxidation by transferring their phenolic H atom to a chain-carrying peroxy radical (ROO<sup>•</sup>) at a rate much faster than that of chain propagation [6]. This yields a non-radical product (ROOH) that cannot propagate the chain reaction. It is proposed that chain-breaking antioxidants can play their protective role via two major mecha-

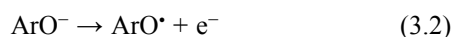
nisms. In the first one, H-atom transfer (HAT) mechanism, the phenolic H atom is transferred in one step. The bond dissociation enthalpy (BDE) represents reaction enthalpy of the HAT mechanism; the lower the BDE, the easier the dissociation of the phenolic O–H bond.



The second mechanism, single electron transfer followed by proton transfer (SET-PT), takes place in two steps. In the first step, cation radical is formed. In the second one, deprotonation of  $\text{ArOH}^{+\bullet}$  occurs, followed by the protonation of  $\text{ROO}^-$ . Ionization potential (Eq. 2.1) and proton dissociation enthalpy (Eq. 2.2) represent enthalpies of the SET-PT process [7].



Recently, another mechanism has been discovered. This was named sequential proton loss electron transfer (SPLET), taking place in two steps. The reaction enthalpy of the first step corresponds to the proton affinity (Eq. 3.1) of the phenoxide anion ( $\text{ArO}^-$ ). In the second step, electron transfer from phenoxide anion to  $\text{ROO}^\bullet$  occurs and the phenoxy radical is formed. The reaction enthalpy of this step is denoted as electron transfer enthalpy (Eq. 3.2) [8, 9].



From the antioxidant action viewpoint, the net result of SPLET is the same as in the two previously mentioned mechanisms, the transfer of the hydrogen atom to the free radicals. Although, reaction enthalpies (BDE, IP, PA) related to three mechanisms is of importance in evaluating the antioxidant action, other criteria, including solubility, bioavailability, and nontoxicity must also be considered when designing an effective and safe antioxidant.

The biological implications and the great potential of Daidzeins as antioxidant aroused our interest in elucidating its antioxidant activity by means of DFT/B3LYP calculations, which have been successfully used for a variety of antioxidants [10, 11]. The substituent effects are among the most important concepts of structural effects influencing the chemical, physicochemical, and biochemical properties of chemical species [12, 13]. In recent years many previous experimental and theoretical investigations have been carried out on phenol and mono-substituted phenols in gas phase and the solvent environment [14–17]. Theoretical study of the substituent effect on antioxidant activity of Daidzein can be utilized in the synthesis of substances with enhanced antioxidant properties. Various substituents such as electron-withdrawing groups (EWG) and electron-donating groups (EDG) were located in ortho and meta position on the aromatic ring of Daidzein (Fig. 1.). In present paper the substituent effect on reaction enthalpies of

homolytic (HAT mechanism) and heterolytic two-step (SPLET and SET-PT) mechanisms of O–H bond cleavage for mono-substituted Daidzeins were investigated in gas phase and water. The Daidzein is a powerful water soluble antioxidant therefore in this study the water as the main cell environment was chosen in order to assess the substituent effect on above mentioned enthalpies in solution phase. Also the correlations of calculated enthalpies with corresponding  $E_{\text{HOMO}}$  values and Hammett constants of substituents were investigated.

Thus, the main aims of this work are (i) To find the novel Daidzein derivatives with high antioxidant activity from the theoretical point of view; (ii) To identify the substituents that are the most effective in reducing the BDE, IP and PA; (iii) To compare the difference of same substituent effect in ortho and meta positions on reaction enthalpies; (iv) To explore how the polar solvents alter the reaction enthalpies of three mechanisms of studied derivatives; (v) To find which mechanism is preferred from the thermodynamic point of view in gas phase and solvent; (vi) To identify the dependencies between reaction enthalpies and structural parameters for the studied derivatives.

## Computational details

The geometries of the derivations (at the restricted B3LYP level) and corresponding systems involving open-shell species (at the unrestricted B3LYP level) were optimized using the DFT and the 6-31G (d,p) basis set in the gas phase and solution phase. Single point calculations for derivations (at the restricted B3LYP level) and for systems involving open-shell species (at the restricted B3LYP open shell (half electron) level) were performed using 6-311++G (2d,2p) basis set [18]. The optimized structures were confirmed to be real minima by frequency calculation. For the species having more conformers, all conformers were investigated. The conformer with the lowest electronic energy was used in this work. All reported enthalpies were zero-point (ZPE) corrected with un-scaled frequencies. Solvent contribution to the total enthalpies was computed employing the PCM method [19, 20]. All calculations were performed using Gaussian 98 program package [21]. All enthalpies were calculated for 298.15 K and 1.0 atmosphere pressure.

## Results and Discussion

Total enthalpies of the studied species X,  $H(X)$ , at the temperature T are usually estimated from the expression (4).

$$H(X) = E_0 + \text{ZPE} + \Delta H_{\text{trans}} + \Delta H_{\text{rot}} + \Delta H_{\text{vib}} + RT \quad (4)$$

From the calculated total enthalpies we have determined following quantities:

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

$$\text{IP} = H(\text{ArOH}^{+\bullet}) + H(e^-) - H(\text{ArOH}) \quad (6)$$

$$\text{PDE} = \text{H}(\text{ArO}^{\bullet}) + \text{H}(\text{H}^+) - \text{H}(\text{ArOH}^{+\bullet}) \quad (7)$$

$$\text{PA} = \text{H}(\text{ArO}^-) + \text{H}(\text{H}^+) - \text{H}(\text{ArOH}) \quad (8)$$

$$\text{ETE} = \text{H}(\text{ArO}^{\bullet}) + \text{H}(\text{e}^-) - \text{H}(\text{ArO}^-) \quad (9)$$

The calculated gas phase enthalpy of proton,  $\text{H}(\text{H}^+)$ , and electron,  $\text{H}(\text{e}^-)$ , is 6.197 and 3.145  $\text{kJ mol}^{-1}$ , respectively. The enthalpy of  $\text{H}^+$  hydration is  $-1090 \text{ kJ mol}^{-1}$ . The B3LYP/6-311++G\*\* computed electron hydration enthalpy,  $\Delta_{\text{hydr}}H(\text{e}^-) = -105 \text{ kJ mol}^{-1}$ , has been employed in this paper [22-24]. It is known that, potential inaccuracies related to computed solvation enthalpies of electron, proton and hydrogen atom will be cancelled when the substituent effect is studied as the difference in the reaction enthalpies of substituted and Daidzein, i.e. in terms of  $\Delta\text{BDE}$ ,  $\Delta\text{PA}$  and  $\Delta\text{IP}$ . On the other hand, BDE, PA and IP values allow determination of the preferred reaction pathway in the studied solvent and gas phase [25-30]. The previous studies on the antioxidant activity of natural and synthesized phenolic antioxidant show that B3LYP functional describes the substituent effect in very good agreement with available experimental results. Also in previous studies the B3LYP method provided the BDE, IP and PA values of various substituted phenols that these values are in very high agreement with published experimental values [8, 27, 31-34].

## Ionization Potentials in Gas Phase and Water

This paper represents the first theoretical systematic study of substituted Daidzeins IP values. In previous studies [17, 26] the substituent effect on IPs of para and meta substituted phenols and pyridinethiols have been investigated in gas phase employing B3LYP approach. No systematic study of solvent effect on IPs and  $\Delta\text{IPs}$  of substituted Daidzeins have been published, yet. In this paper, the calculated IP for the Daidzein in gas phase reached 667  $\text{kJ mol}^{-1}$ . The computed gas phase IPs and  $\Delta\text{IP} = \text{IP}(\text{X-ArOH}) - \text{IP}(\text{ArOH})$  for substituents in ortho and meta position are reported in Table 1.

In ortho and meta position, highest IP values were found for strong EWG substituents ( $\text{NO}_2$ ,  $\text{CF}_3$  and  $\text{CN}$ ); the lowest IPs were obtained for strong EDG substituents ( $\text{NMe}_2$ ,  $\text{NH}_2$ , and  $\text{NHMe}$ ). For F, Cl and Br in ortho and meta positions, the IP values are higher in comparison to the Daidzein. For meta and ortho substituted Daidzeins with OH and OMe, IP values are lower in comparison to Daidzein. For meta and ortho substituted Daidzeins with COH, COOH and COMe, IP values are higher in comparison to Daidzein. The difference between the highest and the lowest IP values for meta and ortho positions was 92.1 and 141.9  $\text{kJ mol}^{-1}$ , respectively.

As a known fact in organic chemistry, the EWG substituents stabilize the parent molecule and destabilize the radical and radical cation. It results in the increase in IP. However, EDG

**Table 1.** Calculated IPs and  $\Delta\text{IPs}$  in ( $\text{kJ mol}^{-1}$ ) of ortho, meta and non-substituted Daidzeins in gas phase and water.

Substituent	Gas				Water			
	ortho		meta		ortho		meta	
	IP	$\Delta\text{IP}$	IP	$\Delta\text{IP}$	IP	$\Delta\text{IP}$	IP	$\Delta\text{IP}$
Non	667.0	0.0	667.0	0.0	442.0	0.0	442.0	0.0
$\text{NMe}_2$	592.0	-75.0	622.5	-44.5	387.3	-54.7	406.3	-35.7
$\text{NHMe}$	595.1	-71.9	625.8	-41.2	389.1	-52.9	409.6	-32.4
$\text{NH}_2$	596.9	-70.1	626.6	-40.4	391.4	-50.6	412.1	-29.9
t-Bu	631.5	-35.5	645.9	-21.1	417.6	-24.4	429.9	-12.1
Ethyl	634.0	-33.0	649.2	-17.8	419.6	-22.4	428.4	-13.6
Ph	630.3	-36.7	647.3	-19.7	419.7	-22.3	427.9	-14.1
$\text{CH}=\text{CH}_2$	638.7	-28.3	647.8	-19.2	415.9	-26.1	426.3	-15.7
OH	616.4	-50.6	639.7	-27.3	407.5	-34.5	422.9	-19.1
OMe	620.3	-46.7	642.5	-24.5	406.0	-36.0	423.2	-18.8
CCH	685.8	18.8	681.7	14.7	455.6	13.6	452.9	10.9
F	707.9	40.9	692.3	25.3	472.9	30.9	461.0	19.0
COH	706.4	39.4	688.9	21.9	469.9	27.9	459.7	17.7
COOH	705.2	38.2	690.1	23.1	469.3	27.3	458.7	16.7
Cl	702.1	35.1	690.2	23.2	471.6	29.6	456.8	14.8
COMe	702.4	35.4	687.9	20.9	469.3	27.3	456.1	14.1
Br	706.7	39.7	690.9	23.9	474.7	32.7	454.6	12.6
$\text{CF}_3$	722.2	55.2	699.6	32.6	480.1	38.1	467.1	25.1
CN	728.4	61.4	708.1	41.1	488.0	46.0	476.0	34.0
$\text{NO}_2$	733.9	66.9	714.6	47.6	495.2	53.2	481.2	39.2

substituents have an opposite effect. Therefore, their presence in the molecule leads to a decrease in IP. The decrease in IPs (negative  $\Delta$ IPs) of EDG-substituted Daidzeins is the combined result of the cation radical stabilization and the parent molecules destabilization. However, the increased IPs (positive  $\Delta$ IPs) of EWG-substituted Daidzeins may stem from the combination of both the parents and the cation radical destabilization. These results are in accordance with data published for substituent phenols [17, 24].

The computed IPs using above mentioned calculated  $\Delta_{\text{hydr}}H(e^-)$  value in the water for substituted Daidzeins in meta and ortho positions are reported in Table 1. Table 1 summarizes  $\Delta$ IP values, too. In water, determination of IP requires the value of electron hydration enthalpy,  $\Delta_{\text{hydr}}H(e^-)$ . The B3LYP/6-311++G\*\* computed electron hydration enthalpy,  $\Delta_{\text{hydr}}H(e^-) = -105 \text{ kJ mol}^{-1}$ , has been employed in this paper [24]. Potential inaccuracies related to employed electron hydration enthalpy value will be canceled when the substituent effect is expressed in terms of  $\Delta$ IPs. Water causes considerable changes in the enthalpies of parent molecules and cation radical of substituted Daidzeins. In this paper, the calculated IP for the Daidzein in the water reached  $442 \text{ kJ mol}^{-1}$ .

For strong EDGs, i.e.  $\text{NMe}_2$ ,  $\text{NH}_2$  and  $\text{NHMe}$ , in meta and ortho positions, found the drop in IP values. For meta and ortho substituted Daidzeins with  $\text{NO}_2$  group the IP value is higher than corresponding value of Daidzein. In water, substituent induced changes are lower than those observed in the gas phase. The EWG-substituents stabilize the parent molecule and destabilize the radical cation. On the other hand, EDG-substituents have an opposite effect. Water causes attenuation of substituent effects in terms of narrower  $\Delta$ IP range. Again, substituents in ortho position exert stronger influence upon IP than the same substituents in meta position. Calculated IPs related to substituted Daidzeins in water are lower than the corresponding values in the gas phase. Mainly, due to the negative enthalpy of electron hydration in water, IP is significantly lower than that in the gas phase.

For substituted Daidzeins in ortho position substituents exert significantly stronger influence upon IP than in the meta position in gas phase and water. These results stem from the fact that the radical cation derived from the electron abstraction from any of ortho substituted Daidzeins can be stabilized by the electron donating power of the ortho hydroxyl and the intramolecular hydrogen bond formed (for example  $\text{NH}_2$ ,  $\text{NHMe}$ , halogen groups). Alternatively, if the substituent can act as hydrogen bond donors to the phenolic oxygen atom the corresponding phenoxyl radical cation may be stabilized relative to basic structure with a consequent decrease in its IP. Therefore cause that forming the hydrogen bond in ortho position; substituents in ortho position have stronger influence upon IP ca  $10\text{--}30 \text{ kJ mol}^{-1}$  in comparison to same substituent with meta position. The overall results of the calculations of IP can be summarized by the fact that EWG-substituted Daidzeins with higher IPs may exhibit weaker antioxidant activity in comparison to EDG ones in gas phase and water. The obtained results in this work are in agreement with previous studies on

the substituted phenols (reported data in Table 2) and chromans [17,18,24].

## Proton Affinities in Gas phase and Water

PA represents the reaction enthalpy of the first step in SPLET mechanism. PAs of substituted Daidzeins have not been obtained by theoretical calculations previously. In previous studies [25, 26] the substituent effect on PAs of para and meta substituted phenols and pyridinethiols have been investigated by DFT using B3LYP functional in the gas phase.

The present calculated PA for the Daidzein reached  $1444 \text{ kJ mol}^{-1}$  in gas phase. The computed PAs and  $\Delta$ PAs for the various substituents in ortho and meta positions of Daidzein in the gas phase are reported in Table 3. The highest values of PA for ortho and meta positions were found for  $\text{NMe}_2$ ,  $\text{NH}_2$ , and  $\text{NHMe}$  groups. The lowest PA values of these positions were found in the case of  $\text{NO}_2$ ,  $\text{CF}_3$  and  $\text{CN}$  groups. The F, Cl and Br groups in ortho and meta position cause decrease in PA in comparison to Daidzein. For Daidzeins with COH, COOH and COME groups in meta and ortho positions, PA values are lower than PA value of Daidzein.

The differences between the highest and the lowest gas phase PA values for ortho and meta-substituents were  $128.8$  and  $70 \text{ kJ mol}^{-1}$ , respectively. In agreement with previous studies on substituted phenols (reported data in Table 2) [15-17] it can be concluded that EDG substituents increase PA, whereas EWG ones decrease PA. It is known that a charged molecule is more sensitive to the effect of substituent than its neutral counterpart. EWG substituents stabilize  $\text{ArO}^-$  but destabilize the parent structures. Electron donating groups have an opposite effect [27-29].

For PA calculations in water, proton hydration enthalpy,  $\Delta_{\text{hydr}}H(H^+)$ , is inevitable. Therefore, we have utilized  $\Delta_{\text{hydr}}H(H^+) = -1022 \text{ kJ mol}^{-1}$  value [24]. The present calculated PA for the Daidzein reached  $253 \text{ kJ mol}^{-1}$  in water. For Daidzeins substituted in meta and ortho positions, computed PAs and  $\Delta$ PAs in the water are reported in Table 3.

Again, EWG substituents decrease PAs, whereas EDG groups increase PAs in agreement with results from substituted phenols in water [17]. Again, strong electron-donating  $\text{NMe}_2$ ,  $\text{NH}_2$  and  $\text{NHMe}$  cause an increase in PA. The presence of COH, COOH and COME group in ortho and meta positions results in PA decrease. For halogens in ortho and meta positions, we have the drops in PAs. The largest decrease in PA shows Daidzein with  $\text{NO}_2$  group in ortho or meta positions. Differences between the highest and lowest PA values for two studied positions were  $85.9$  (ortho) and  $58.3 \text{ kJ mol}^{-1}$  (meta).

Water causes considerable changes in the enthalpies of anions. Calculated PAs related to substituted Daidzeins in water are lower than the corresponding values in the gas phase. Mainly, due to the large negative enthalpy of proton hydration, PAs in the water are significantly lower than gas phase values.

It confirms that water attenuates substituent induced changes. For substituted Daidzeins in ortho position substituents exert

**Table 2.** Experimental and theoretical (in DFT/B3LYP method, 6-31G (d,p) and 6-311++G (2d,2p) basis sets)  $\Delta$ BDEs,  $\Delta$ IPs and  $\Delta$ PAs of various substituted phenols ( $\text{kJ mol}^{-1}$ ) in gas phase and water.

Substituent	$\Delta$ BDE			$\Delta$ IP			$\Delta$ PA		
	Exp <sup>[a]</sup>	Gas <sup>[b]</sup>	Water <sup>[c]</sup>	Exp <sup>[d]</sup>	Gas <sup>[e]</sup>	Water <sup>[f]</sup>	Exp <sup>[g]</sup>	Gas <sup>[f]</sup>	Water <sup>[e]</sup>
NMe <sub>2</sub>	-40	-43	-31	-67	-71	-66	22	26	18
NHMe	-35	-38	-23	-74	-79	-74	22	24	19
NH <sub>2</sub>	-35	-38	-22	-68	-72	-63	24	24	20
OH	-20	-24	-21	-45	-48	-40	17	20	15
OMe	-13	-16	-17	-22	-23	-29	18	16	9
t-Bu	-5	-7	-2	-10	-12	-8	-	7	8
Me	-2	-4	-4	-8	-10	-8	11	9	7
Ethyl	-2	-3	-1	-15	-17	-5	8	6	6
CH=CH <sub>2</sub>	-2	-3	3	-7	-6	-11	-10	-12	-3
Ph	-4	-5	-8	-20	-21	-5	-	-14	-9
F	-7	-8	-9	22	24	18	-21	-24	-21
CCH	-	-6	3	-	13	14	-22	-27	-18
Cl	-6	-8	-9	20	23	16	-24	-23	-18
Br	-7	-8	-7	20	22	16	-28	-22	-18
COH	13	16	11	-	24	21	-33	-33	-17
COOH	16	19	12	30	31	19	-25	-27	-15
COMe	16	17	13	25	28	16	-	-31	-16
CF <sub>3</sub>	14	16	12	49	52	32	-46	-48	-30
CN	16	18	12	63	68	35	-53	-55	-38
NO <sub>2</sub>	23	25	19	70	74	41	-66	-69	-41

<sup>a</sup>From Ref. [23].<sup>b</sup>From Ref. [31].<sup>c</sup>From Ref. [32].<sup>d</sup>From Ref. [33].<sup>e</sup>From Ref. [8].<sup>f</sup>From Ref. [34].<sup>g</sup>From Ref. [7].

significantly stronger influence upon PA than in the meta position in gas phase and water. These results stem from this fact that the anion derived from the proton abstraction from any of ortho substituted Daidzeins can be stabilized by the electron withdrawing substituent. Alternatively, if the substituent can act as hydrogen bond donors to the phenolic oxygen atom the corresponding phenoxyl anion may be stabilized relative to basic structure with a consequent decrease in its PA.

Therefore cause that forming the hydrogen bond in ortho position; substituents in ortho position have stronger influence upon PA ca 10-25  $\text{kJ mol}^{-1}$  in comparison to same substituent in meta position. The obtained results of this work are in agreement with previous studies on the substituted phenols and chromans [17, 28, 29].

### Bond Dissociation Enthalpies in Gas Phase and Water

In previous studies [15-17] the solvent and substituent effects on O-H BDEs substituted phenols have been investigated.

No systematic study of solvent effect on BDEs and  $\Delta$ BDEs of substituted Daidzeins have been published, yet. The O-H BDE value of Daidzein is ca 381 and 367  $\text{kJ mol}^{-1}$  in gas phase and water, respectively. In this section we investigated the substituent and solvent effects on BDE of Daidzein. The computed gas phase BDE and  $\Delta$ BDE values, where  $\Delta$ BDE = BDE (X-ArOH) - BDE (ArOH), for substituents placed in ortho and meta position (Fig. 1.) are reported in Table 4. The electron-donating substituents decrease BDE values, whereas electron-withdrawing groups increase BDE values. The O-H BDE of structure with NO<sub>2</sub>, COH, COOH and COMe substituent in ortho and meta position was higher than BDE value of Daidzein. For ortho and meta substituted Daidzeins with NMe<sub>2</sub>, NH<sub>2</sub> and NHMe the BDE values are lower than BDE value Daidzein. For ortho and meta substituted Daidzeins with halogen substituents the BDE values are higher than BDE value of Daidzein. For ortho and meta substituted Daidzeins with OMe and OH substituent the BDE values are lower in comparison to the BDE value of Daidzein. The difference between the highest

**Table 3.** Calculated PAs and  $\Delta$ PAs in ( $\text{kJ mol}^{-1}$ ) of ortho, meta and non-substituted Daidzeins in gas phase and water.

Substituent	Gas				Water			
	ortho		meta		ortho		meta	
	PA	$\Delta$ PA	PA	$\Delta$ PA	PA	$\Delta$ PA	PA	$\Delta$ PA
Non	1444.0	0.0	1444.0	0.0	253.0	0.0	253.0	0.0
NMe <sub>2</sub>	1498.0	54.0	1469.2	25.2	288.8	35.8	272.8	19.8
NHMe	1495.3	51.3	1469.7	25.7	290.8	37.8	273.2	20.2
NH <sub>2</sub>	1497.2	53.2	1472.0	28.0	290.1	37.1	275.0	22.0
t-Bu	1474.9	30.9	1462.7	18.7	275.0	22.0	267.7	14.7
Ethyl	1477.5	33.5	1461.3	17.3	272.8	19.8	265.8	12.8
Ph	1473.9	29.9	1459.8	15.8	272.4	19.4	264.9	11.9
CH=CH <sub>2</sub>	1471.1	27.1	1460.9	16.9	272.9	19.9	263.5	10.5
OH	1481.7	37.7	1464.7	20.7	285.0	32.0	267.0	14.0
OMe	1477.6	33.6	1467.0	23.0	282.9	29.9	268.0	15.0
CCH	1470.5	26.5	1462.8	18.8	271.3	18.3	266.7	13.7
F	1412.7	-31.3	1422.0	-22.0	228.3	-24.7	235.3	-17.7
COH	1406.6	-37.4	1416.5	-27.5	224.5	-28.5	232.8	-20.2
COOH	1403.6	-40.4	1418.9	-25.1	224.3	-28.7	236.5	-16.5
Cl	1409.8	-34.2	1418.7	-25.3	222.9	-30.1	234.0	-19.0
COMe	1406.3	-37.7	1419.5	-24.5	225.2	-27.8	238.0	-15.0
Br	1410.5	-33.5	1421.5	-22.5	230.2	-22.8	235.4	-17.6
CF <sub>3</sub>	1386.6	-57.4	1408.9	-35.1	217.5	-35.5	226.7	-26.3
CN	1376.2	-67.8	1407.7	-36.3	204.9	-48.1	223.5	-29.5
NO <sub>2</sub>	1369.2	-74.8	1402.0	-42.0	201.2	-51.8	216.7	-36.3

and lowest BDE values for ortho and meta substituent Daidzeins were 89.5 and 51.4  $\text{kJ mol}^{-1}$ , respectively. The obtained results can be interpreted with a known fact that electron-withdrawing groups in ortho and the meta position stabilize the parent molecule and destabilize the radical; hence, it increases the O–H BDE. However, electron-donating groups in ortho and meta position have an opposite effect, and therefore, their presence lead to a decrease in the O–H BDE.

Klein *et al.* [17] indicated that the PCM method could describe the substituent effect in very good agreement with experimental data for O–H BDEs of substituted phenols in water (reported data in Table 2). The calculated BDE for the Daidzein in water is lower than corresponding value in gas phase by 14  $\text{kJ mol}^{-1}$ . The computed BDEs and  $\Delta$ BDEs in the water for ortho and meta-substituted Daidzeins are reported in Table 4. For ortho and meta substituted Daidzeins with NMe<sub>2</sub>, NH<sub>2</sub> and NHMe the BDE values are lower in comparison to the Daidzein. For meta and ortho substituted Daidzeins with halogen substituents the BDE values are higher in comparison to the Daidzein. For ortho and meta substituted Daidzeins with COH, COOH and COMe the BDE values are higher than the BDE value of Daidzein. The difference between the highest and the lowest BDE values in the water for ortho and meta positions were 78.4 and 32.6  $\text{kJ mol}^{-1}$ , respectively. In water, electron-donating substituents decrease BDE values, whereas electron-withdrawing groups increase BDE values similar to

found results for the gas phase. In comparison to the gas phase, the effects of various substituents which include EDG and EWG on the BDEs in ortho and meta positions were decreased in the water phase. Therefore we can conclude that in comparison to the gas phase, the effect of EDG-substituents and EWG-substituents on BDE in ortho and meta positions decreases in water.

An inspection of the O–H BDE values appearing in Table 4 shows that in water calculated BDE values were lower than gas phase ones. Overall results reveal weak dependence of BDEs values on the solvent polarity. Water causes changes in enthalpies of molecule and radical of studied structures. Since water causes unequal stabilization/destabilization of the parent molecule and the respective radical this can be a fundamental reason for obtained results.

Therefore decrease in BDEs (negative  $\Delta$ BDEs) for EDG-substituted Daidzeins is the combined results of the radical stabilization and the parent molecules destabilization. However, increased BDEs (positive  $\Delta$ BDEs) for EWG-substituted Daidzeins seem to be the combination of both the parents and the radicals destabilization.

In the present study computed results for substituted Daidzeins show that substituents in ortho position exert significantly stronger influence on O–H BDE than substituents in the meta position in gas phase and water. It can be concluded some of ortho substituted Daidzein can form hydrogen bonding. The

**Table 4.** Calculated BDEs and  $\Delta$ BDEs in ( $\text{kJ mol}^{-1}$ ) of *ortho*, *meta* and non-substituted Daidzeins in gas phase and water, and Hammett constants of substituents  $\sigma_m$  [13].

Substituent	Gas				Water				$\sigma_m$
	<i>ortho</i>		<i>meta</i>		<i>ortho</i>		<i>meta</i>		
	BDE	$\Delta$ BDE	BDE	$\Delta$ BDE	BDE	$\Delta$ BDE	BDE	$\Delta$ BDE	
Non	381.0	0.0	381.0	0.0	367.0	0.0	367.0	0.0	—
NMe <sub>2</sub>	333.6	-47.4	355.3	-25.7	326.2	-40.8	350.7	-16.3	-0.24
NHMe	334.0	-47.0	356.4	-24.6	325.6	-41.4	351.6	-15.4	-0.24
NH <sub>2</sub>	334.5	-46.5	356.8	-24.2	327.2	-39.8	352.6	-14.4	-0.16
<i>t</i> -Bu	363.6	-17.4	370.4	-10.6	352.8	-14.2	359.2	-7.8	-0.10
Ethyl	362.9	-18.1	371.0	-10.0	353.6	-13.4	358.8	-8.2	-0.07
Ph	365.2	-15.8	371.8	-9.2	354.7	-12.3	359.7	-7.3	0.06
CH=CH <sub>2</sub>	369.1	-11.9	374.2	-6.8	355.2	-11.8	358.7	-8.3	0.06
OH	351.9	-29.1	363.8	-17.2	344.3	-22.7	355.8	-11.2	0.12
OMe	356.6	-24.4	363.8	-17.2	347.9	-19.1	356.1	-10.9	0.12
CCH	393.0	12.0	390.7	9.7	376.2	9.2	373.7	6.7	0.21
F	400.5	19.5	393.4	12.4	381.6	14.6	372.9	5.9	0.34
COH	401.3	20.3	392.9	11.9	380.6	13.6	375.2	8.2	0.35
COOH	398.7	17.7	393.6	12.6	381.1	14.1	377.0	10.0	0.37
Cl	398.0	17.0	393.1	12.1	380.3	13.3	372.1	5.1	0.37
COMe	395.5	14.5	392.7	11.7	379.0	12.0	373.5	6.5	0.38
Br	396.7	15.7	395.0	14.0	379.4	12.4	372.0	5.0	0.39
CF <sub>3</sub>	415.1	34.1	399.3	18.3	394.5	27.5	376.7	9.7	0.43
CN	418.4	37.4	402.9	21.9	398.6	31.6	382.0	15.0	0.56
NO <sub>2</sub>	423.1	42.1	406.7	25.7	404.0	37.0	383.3	16.3	0.71

forming hydrogen bonds can high effect on reaction enthalpies of *ortho* substituted Daidzein markedly. The substituent can act as hydrogen bond donors to the phenolic oxygen atom (for example *o*-NH<sub>2</sub> group) the corresponding phenoxyl radical may be stabilized relative to basic structure with a consequent decrease in its O-H BDE. Therefore cause that forming the hydrogen bond in *ortho* position; substituents in *ortho* position have stronger influence upon BDE ca 8-40  $\text{kJ mol}^{-1}$  in comparison to same substituent in *meta* position. The overall results of the calculations of O-H BDE can be summarized by the fact that EWG-substituted Daidzeins with higher BDEs may exhibit weaker antioxidant activity in comparison to EDG ones in gas phase and water. The obtained results in this work are in agreement with previous studies on the substituted phenols, chromans and other natural phenolic antioxidants [16, 25].

#### Proton Dissociation Enthalpies and Electron Transfer Enthalpies in Gas phase and Water

PDE and ETE represent the reaction enthalpies of the second steps in SET-PT and SPLET mechanisms, respectively. For the whole SET-PT and SPLET energetics knowledge, it is also important to study PDEs and ETEs and to investigate the solvent and substituent effects on these reaction enthalpies. In previous papers the substituent effect on PDEs of substituted phenols have been theoretically investigated by DFT using

B3LYP functional [35-37]. In recent papers the PDE and ETE values of *ortho* and *meta* substituted chromans have been calculated in gas and water [25, 38]. There are no experimental PDEs available yet. The PDE value for Daidzein as antioxidant has not been studied previously. The Calculated O-H PDE in for Daidzein reached 1032  $\text{kJ mol}^{-1}$  in the gas phase and 147  $\text{kJ mol}^{-1}$  in water. Calculated PDEs for the substituted Daidzeins in the gas phase and water were summarized in Table 5. PDE of Daidzein in water was lower than the corresponding value in the gas phase by 885  $\text{kJ mol}^{-1}$ . Mainly, due to the large enthalpy of proton hydration, PDEs in water are significantly lower than gas phase values. Water also causes considerable changes in the enthalpies of radicals and radical cations of studied structures. Highest PDEs were found for strong EDG substituents (NMe<sub>2</sub>, NH<sub>2</sub>, and NHMe), whereas lowest PDEs were obtained for strong EWG substituents (NO<sub>2</sub>, CF<sub>3</sub> and CN). This trend is opposite to that observed for PAs. It is known that electron-donating groups stabilize ArOH<sup>•+</sup> but destabilize the parent structure, while electron-withdrawing groups have an opposite effect [35-38]. The obtained results of this work are in agreement with previous studies on the substituted phenols and chromans [35-38].

For substituted Daidzein, ETEs were not studied previously. In literature, only DFT/B3LYP ETEs of substituted phenols and chromans are available [36-40]. The calculated O-H ETE for Daidzein reached 324  $\text{kJ mol}^{-1}$  in the gas phase and

**Table 5.** Calculated PDEs and ETEs in (kJ mol<sup>-1</sup>) of *ortho*, *meta* and non-substituted Daidzeins in gas phase and water.

Substituent	Gas				Water			
	<i>ortho</i>		<i>meta</i>		<i>ortho</i>		<i>meta</i>	
	PDE	ETE	PDE	ETE	PDE	ETE	PDE	ETE
Non	1032.0	324.0	1032.0	324.0	147.0	256.0	147.0	256.0
NMe <sub>2</sub>	1100.6	294.3	1067.6	312.8	193.7	233.1	172.0	251.0
NHMe	1098.6	293.6	1057.8	314.4	196.9	230.8	167.7	249.9
NH <sub>2</sub>	1091.2	293.5	1055.2	311.9	184.9	229.9	163.2	246.1
t-Bu	1054.4	310.7	1042.3	316.4	156.2	253.6	151.7	254.5
Ethyl	1049.3	313.6	1041.5	318.3	156.7	255.2	151.9	254.1
Ph	1048.0	323.5	1046.9	325.8	153.2	273.0	151.0	270.8
CH=CH <sub>2</sub>	1049.6	328.4	1035.6	328.4	154.0	273.5	147.1	269.7
OH	1046.7	305.0	1044.0	323.7	166.7	240.8	159.2	259.5
OMe	1050.7	308.0	1041.0	318.2	165.5	245.0	155.5	251.7
CCH	1037.8	344.0	1041.5	340.1	143.6	285.6	140.0	280.3
F	1018.0	341.4	1020.4	339.6	129.6	274.1	132.5	279.1
COH	1013.0	357.2	1020.9	350.4	133.8	295.3	152.9	290.2
COOH	1020.2	360.1	1025.1	345.5	133.2	299.8	136.1	289.7
Cl	1020.3	343.1	1025.8	343.2	128.0	285.5	134.1	286.9
COMe	1024.7	353.6	1025.5	340.5	129.8	289.8	142.6	287.9
Br	1018.8	344.4	1028.6	343.6	127.9	290.2	134.9	290.2
CF <sub>3</sub>	1003.6	363.4	1013.2	353.1	117.2	311.4	125.8	317.0
CN	993.0	371.1	996.1	359.5	111.5	330.1	116.8	317.9
NO <sub>2</sub>	987.3	381.3	993.7	365.6	109.6	332.4	123.1	323.4

256 kJ mol<sup>-1</sup> in water. The computed ETEs values for Daidzein with substituents in *ortho* and *meta* position are compiled in Table 5. In gas phase and water, highest ETEs were found for strong EWG substituents (NO<sub>2</sub>, CF<sub>3</sub> and CN). Lowest ETEs were found in the case of strong EDG substituents (NMe<sub>2</sub>, NH<sub>2</sub>, NHMe). The ETE values of substituted Daidzeins in the gas phase are higher than ca 35-70 kJ mol<sup>-1</sup> in comparison to corresponding values in water. It is known that electron withdrawing groups are favourable to stabilize ArO<sup>-</sup>. Electron donating groups have an opposite effect. Therefore, electron withdrawing groups increase ETE values, while electron donating groups decrease ETEs [36-40]. This trend corroborates with that observed for BDEs and IPs. The obtained results of this work are in agreement with previous studies on the substituted phenols and chromans [36-40].

### Thermodynamically preferred mechanism

In general, free energy represents the criterion of the thermodynamically preferred process. However, in the case of studied reactions the absolute values of the entropic term  $-T\Delta_rS$  reach few tens of kJ mol<sup>-1</sup> and all free energies,  $\Delta_rG = \Delta_rH - T\Delta_rS$ , are only shifted in comparison to corresponding enthalpies [24]. Therefore, comparison of BDEs, PAs and IPs can indicate which mechanism is thermodynamically preferred. Calculated gas phase IPs and PAs of mono-substituted Daidzeins are significantly higher, by 292 and 1057 kJ mol<sup>-1</sup>, than BDEs,

respectively. Therefore, HAT mechanism represents the most anticipated process in the gas phase from the thermodynamic point of view. In water, PA values are lower than BDE and IP values by 117 and 191 kJ mol<sup>-1</sup>, respectively. In water, IP values remain still lower than BDEs by ca 76 kJ mol<sup>-1</sup>, respectively. Significantly lower PAs indicate that SPLET represents the thermodynamically preferred reaction pathway in water.

### Dependence of calculated reaction enthalpies of Daidzein derivatives on the Hammett constants

The Hammett equation (and its extended forms) has been one of the most widely used means for the study and interpretation of organic reactions and their mechanisms. Hammett constants  $\sigma_m$  (for substituent in *meta* position) and  $\sigma_p$  (for substituent in *para* position) obtained from the ionization of organic acids in solutions can frequently successfully predict equilibrium and rate constants for a variety of families of reactions [12, 13]. Hammett constants correlate very well with the changes in BDE, IP and PA values in the case of anilines, phenols, chromans and thiophenols [17, 27]. In present paper we investigated the dependences between reaction enthalpies of *meta* substituted Daidzeins and corresponding Hammett constant values. Presence of linear dependences can be utilized in the synthesis of novel Daidzein derivatives with high antioxidant activity. The BDE values computed for the *meta* substituted Daidzeins in the gas phase and water are corrected against Hammett constants.



The correlation coefficients in gas and water reached 0.95 and 0.94 respectively. Equations obtained from the linear regression are as follows:

$$\text{BDE (kJ mol}^{-1}\text{)} = 25.4 \times \sigma_m + 381 \text{ (gas)} \quad (10)$$

$$\text{BDE (kJ mol}^{-1}\text{)} = 22.1 \times \sigma_m + 367 \text{ (water)} \quad (11)$$

Also the linear dependences between computed IP and PA values for the meta substituted Daidzeins in the gas phase and water were investigated. For IP values the correlation coefficients in gas phase and water reached 0.93 and 0.92, respectively. Equations obtained from the linear regression are as follows:

$$\text{IP (kJ mol}^{-1}\text{)} = 134.8 \times \sigma_m + 667 \text{ (gas)} \quad (12)$$

$$\text{IP (kJ mol}^{-1}\text{)} = 111.7 \times \sigma_m + 442 \text{ (water)} \quad (13)$$

For PA values the correlation coefficients in gas phase and water reached 0.92 and 0.93, respectively. Equations obtained from the linear regression are as follows

$$\text{PA (kJ mol}^{-1}\text{)} = -48.5 \times \sigma_m + 1444 \text{ (gas)} \quad (14)$$

$$\text{PA (kJ mol}^{-1}\text{)} = -37.3 \times \sigma_m + 253 \text{ (water)} \quad (15)$$

We can conclude that the DFT method describes the expected linear BDE, IP and PA values vs. Hammett constant dependence satisfactorily. These results show good linearity of BDE, IP and PA =  $f(\sigma_m)$  dependences. Obtained equations enable fast BDE, IP and PA estimations for meta substituted Daidzeins from the corresponding Hammett constants values. This can be useful in the selection of suitable candidates for the synthesis of novel Daidzein derivatives with enhanced antioxidant properties.

#### Dependence of calculated reaction enthalpies of Daidzein derivatives on corresponding $E_{\text{HOMO}}$

To accelerate the discovery of novel antioxidants, considerable effort has been devoted to investigating the structure activity relationships (SARs) for antioxidants. Furthermore, rational design strategies for antioxidants have been proposed and applied in research. It was shown that IPs determined using the DFT computational approaches are sufficiently accurate to characterize the electron donating ability of antioxidants [30]. The energy of the highest occupied molecular orbital ( $E_{\text{HOMO}}$ ) represents an alternative parameter to assess the electron donating ability of antioxidants. This is widely used in the antioxidant study because of the simple calculation procedure, where the only calculation for parent molecule is required. In this paper, found  $E_{\text{HOMO}}$  for Daidzein in the gas phase and water are  $-5.72$  and  $-6.24$  eV, respectively. As a general rule, the higher the  $E_{\text{HOMO}}$ , the more active the compound is as an antioxidant. The computed  $E_{\text{HOMO}}$  values of investigating Daidzeins in the gas phase and water are summarized in Table 6. These reveal that in the case of EWG-substituents,  $E_{\text{HOMO}}$  values become more negative, while the presence EDG-substituents results in

less negative  $E_{\text{HOMO}}$  values. Therefore, Daidzeins with strong electron-donating groups are better electron donors, i.e. they enter SET-PT mechanism more easily. In the previous study it showed that B3LYP/6-311+G (2d,2p) method significantly underestimates vertical gas phase ionization potentials obtained from  $E_{\text{HOMO}}$  for mono-substituted anilines, phenols and thiophenols [30]. However, the trends in ionization potentials, in terms of  $\Delta\text{IPs}$ , are described reliably. Therefore, we decided to find expected linear dependence between calculated IPs and corresponding  $E_{\text{HOMO}}$  values. For meta-substituted Daidzeins, correlation coefficients in gas phase and water reached 0.94 and 0.95, respectively. Obtained equations are as follows:

$$\text{IP (kJ mol}^{-1}\text{)} = -1.23 \times E_{\text{HOMO}} \text{ (kJ mol}^{-1}\text{)} + 69 \text{ (gas)} \quad (16)$$

$$\text{IP (kJ mol}^{-1}\text{)} = -1.27 \times E_{\text{HOMO}} \text{ (kJ mol}^{-1}\text{)} - 365 \text{ (water)} \quad (17)$$

Also, dependences between calculated IP values and corresponding  $E_{\text{HOMO}}$  values for substituents in ortho position were investigated. Correlation coefficients reached 0.93 (gas phase) and 0.96 (water). Following regression lines were obtained

$$\text{IP (kJ mol}^{-1}\text{)} = -1.38 \times E_{\text{HOMO}} \text{ (kJ mol}^{-1}\text{)} + 75 \text{ (gas)} \quad (18)$$

$$\text{IP (kJ mol}^{-1}\text{)} = -1.56 \times E_{\text{HOMO}} \text{ (kJ mol}^{-1}\text{)} - 335 \text{ (water)} \quad (19)$$

From the obtained equations we can conclude that  $E_{\text{HOMO}}$  can be employed for fast estimations of reaction enthalpies for

**Table 6.** Calculated  $E_{\text{HOMO}}$  in (eV) of *ortho*, *meta* and non-substituted Daidzeins in gas phase and water.

Substituent	gas		water	
	<i>ortho</i>	<i>meta</i>	<i>ortho</i>	<i>meta</i>
Non	-5.72	-5.72	-6.24	-6.24
NMe <sub>2</sub>	-5.49	-5.50	-6.14	-6.07
NHMe	-5.46	-5.50	-6.09	-6.03
NH <sub>2</sub>	-5.48	-5.41	-6.11	-6.05
<i>t</i> -Bu	-5.41	-5.28	-6.10	-5.95
Ethyl	-5.49	-5.50	-6.18	-6.23
Ph	-5.48	-5.63	-6.16	-6.27
CH=CH <sub>2</sub>	-5.67	-5.67	-6.28	-6.30
OH	-5.66	-5.65	-6.29	-6.29
OMe	-5.70	-5.68	-6.46	-6.32
CCH	-5.68	-5.79	-6.39	-6.39
F	-5.81	-5.97	-6.47	-6.52
COH	-5.83	-5.89	-6.50	-6.54
COOH	-5.94	-6.08	-6.55	-6.56
Cl	-5.96	-6.06	-6.57	-6.60
COMe	-6.15	-6.06	-6.69	-6.58
Br	-6.07	-6.19	-6.65	-6.65
CF <sub>3</sub>	-6.00	-6.13	-6.64	-6.64
CN	-6.11	-6.17	-6.69	-6.68

the first of SET-PT mechanism. These linear dependences can be utilized in the selection of suitable substituents for the synthesis of novel Daidzein derivatives with enhanced antioxidant activity.

## Conclusions

In this article, the reaction enthalpies of the individual steps of three antioxidant action mechanisms, HAT, SET-PT and SPLET, for various *ortho* and *meta* substituted Daidzeins were calculated in gas phase and water. Obtained results indicate that electron-withdrawing substituents increase the bond dissociation enthalpy (BDE) and ionization potential (IP), while electron-donating ones cause a rise in the proton affinity (PA). Water attenuates the substituent effect on all reaction enthalpies. Results show that the substituents in *ortho* position have high potential for synthesis of novel Daidzein derivatives. In the gas phase, BDEs are lower than PAs and IPs, i.e. HAT represents the thermodynamically preferred pathway. On the other hand, SPLET mechanism represents the thermodynamically favored process in water. The antioxidant structures act in solvent (water) certainly, therefore it can be concluded that EWG group increase the antioxidant activity of Daidzein derivatives. Results show that calculated enthalpies can be successfully corrected with Hammett constants ( $\sigma_m$ ) of the substituted Daidzeins. It has been also found that IP values for substituted Daidzeins can be estimated from their  $E_{\text{HOMO}}$  values. This fact may be useful for the development of novel Daidzein based antioxidants.

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