DFT/B3LYP Study of the Substituent Effects on the Reaction Enthalpies of the Antioxidant Mechanisms of Magnolol Derivatives in the Gas-Phase and Water

Meysam Najafi,[*] **Mohammad Najafi, and Houshang Najafi**

Department of physiology, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
[*]*E-mail: meysamnajafi2012@yahoo.com*
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In this paper, the study of various *ortho-* and *meta*-substituted Magnolol derivatives is presented. The reaction enthalpies related to three antioxidant action mechanisms HAT, SET-PT and SPLET for substituted Magnolols have been calculated using DFT/B3LYP method in gas-phase and water. Calculated results show that electron-withdrawing substituents increase the bond dissociation enthalpy (BDE), ionization potential (IP) and oxidation/reduction enthalpy (O/RE), while electron-donating ones cause a rise in the proton dissociation enthalpy (PDE) and proton affinity (PA). In *ortho-* position, substituents show larger effect on reaction enthalpies than in *meta*-position. In comparison to gas-phase, water attenuates the substituent effect on all reaction enthalpies. In 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. Results show that calculated enthalpies can be successfully correlated with Hammett constants (σ_m) of the substituted Magnolols. Furthermore, calculated IP and PA values for substituted Magnolols show linear dependence on the energy of the highest occupied molecular orbital (E_{HOMO}).
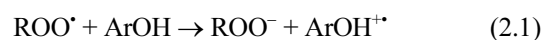
Key Words : Antioxidant, Magnolol, Solvent effect, Substituent effect

Introduction

In recent years, the border between chemistry and biochemistry has become even more diffuse. The role of natural antioxidants has lately received much attention because they can avoid or at least significantly reduce the peroxidation of lipids by free radicals, which are related to a variety of disorders and diseases.[1,2] Magnolol is phenolic compound obtained from the bark and seed cones of Magnolia officinal are which has been used in traditional Chinese medicine.[3] Magnolol has number of biological properties such as antioxidant anticancer.[4-6] Magnolol has been reported to have strong antioxidant ability against lipid peroxidation and DNA damage induced by many oxidant systems.[7,8] Magnolol scavenges hydroxyl radical, peroxynitrite, singlet oxygen, hydrogen peroxide, and possibly peroxyl radical, which are generated during the oxidation of unsaturated lipids and lead to the propagation of lipid peroxidation.[9,10] The phenolic antioxidants (ArOH) inhibit oxidation by transferring their phenolic H atom to a chain-carrying peroxyl radical (ROO·) at a rate much faster than that of chain propagation.[11] This yields a nonradical product (ROOH) that cannot propagate the chain reaction

Abbreviations: Density Functional Theory (DFT), Bond Dissociation Enthalpy (BDE), Ionization Potential (IP), Proton Dissociation Enthalpy (PDE), Proton Affinity (PA), Oxidation/Reduction Enthalpy (O/RE), 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).

$$ROO^· + ArOH \rightarrow ROOH + ArO^· \qquad (1)$$

It is proposed[11-13] that chain-breaking antioxidants can play their protective role *via* two major mechanisms. In the first one, H-atom transfer (HAT) mechanism, the phenolic H atom is transferred in one step, as shown in Eq. (1). In the HAT mechanism, the bond dissociation enthalpy (BDE) of the phenolic O-H bond is one of the important parameters in evaluating the antioxidant action; 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
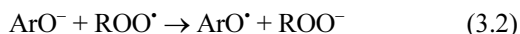
$$ROO^· + ArOH \rightarrow ROO^- + ArOH^{+·} \qquad (2.1)$$

$$ArOH^{+·} \rightarrow ArO + H^+ \qquad (2.2)$$

In the first step, cation radical is formed (Eq. 2.1). In the second one, deprotonation of $ArOH^{+·}$ occurs (Eq. 2.2), followed by the protonation of ROO^-

$$ROO^- + H^+ \rightarrow ROOH \qquad (2.3)$$

Ionization potential (IP) and proton dissociation enthalpy (PDE)[14,15] represent enthalpies of the SET-PT process. In the SET-PT mechanism, the ionization potential (IP) is the most significant parameter; the lower the IP value, the easier the electron abstraction. However, low IP values are favorable to raise the electron-transfer reactivity, they enhance the chance of generating a superoxide anion radical through the transfer of the electron directly to surrounding O_2.[11,16,17] Recently, another mechanism has been discovered.[18-21] This was named sequential proton loss electron transfer (SPLET), taking place in two steps (Eqs. 3.1 and 3.2)

$$ArOH \rightarrow ArO^- + H^+ \qquad (3.1)$$

$$ArO^- + ROO^\bullet \rightarrow ArO^\bullet + ROO^- \qquad (3.2)$$

$$ROO^- + H^+ \rightarrow ROOH \qquad (3.3)$$

The reaction enthalpy of the first step (Eq. 3.1) corresponds to the proton affinity, PA, of the phenoxide anion (ArO$^-$).[22-24] In the second step (Eq. 3.2), electron transfer from phenoxide anion to ROO$^\bullet$ occurs and the phenoxy radical is formed. The reaction enthalpy of this step is denoted as oxidation/reduction enthalpy, O/RE. From the antioxidant action viewpoint, the net result of SPLET is the same as in the two previously mentioned mechanisms, the transfer of 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.[25] The biological implications and the great potential of Magnolols 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.[26,27] Because in chemistry one often needs to compare a group of reactions differing only in the substitution, it is also important to study the effect of substituents on the reaction enthalpy. Substituent effects are among the most important concepts of structural effects influencing the chemical, physicochemical, and biochemical properties of chemical species.[35,36] In recent years many previous experimental[22-24,37-42] and theoretical[12,22,33,43-50] investigations have been carried out on phenol and mono-substituted phenols in gas and solvent environment. Theoretical study of substituent effect can be utilized in the synthesis of substances with enhanced antioxidant properties. In the present paper, we investigate the effect of various substituents on reaction enthalpies related to HAT, SPLET and SPT-ET mechanisms of Magnolol derivations. Understanding the role of different structural features and preparation of new compounds with enhanced antioxidant property is of great interest. Therefore, Magnolol molecule (Figure 1(a)) represents the Magnolol. Various substituents such as electron-withdrawing groups (EWG) and electron-donating groups (EDG) were located in *ortho* and *meta* position on the aromatic ring (Figure 1(b)). For Magnolol and mono-substituted Magnolols, energetic of the antioxidant action has not been studied, yet. Therefore, we have systematically investigated 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 Magnolols in gas phase and water. Correlations of calculated enthalpies with Hammett constants of substituents were investigated. According to our knowledge, no attempt to find a relationship between structural parameters and reaction enthalpies related to HAT, SPLET and SET-PT mechanisms in the case of Magnolols has been made previously. This work also shows linear dependence between calculated enthalpies and the energy of the highest occupied molecular orbital (E_{HOMO})
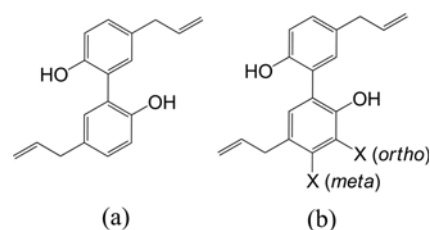

Figure 1. (a) Structure of Magnolol, (b) Studied Magnolols: X=Br, Ethyl, CH=CH$_2$, CCH, CF$_3$, Me, Cl, CN, COMe, CHO, COOH, F, NMe$_2$, NHMe, NH$_2$, NO$_2$, OMe, OH, Ph, *t*-Bu.

of studied molecules in the two environments. Because SET-PT and SPLET mechanisms are of importance in solvated media,[18-21,33,41,70] it is interesting to explore how the solvent alters the reaction enthalpies of individual steps of the two mechanisms. Because Magnolol is a powerful water-soluble antioxidant, water as the main cell environment was chosen in order to assess the substituent effect on above mentioned enthalpies in solution-phase. To shed light on the solvent effect, PCM (polarized continuum model) calculations have been performed for studied molecules in water.

Computational Details

The geometries of the molecules and respective radicals, radical cations and anions were optimized using DFT method with B3LYP functional[71-73] and the 6–31G (d,p) basis set[71,72] in the gas-phase and solution phase. Single point calculations were performed using 6–311++G (2d,2p) basis set.[74,75] The ground-state geometries of molecules were optimized at restricted B3LYP level and the geometry of the radicals, radical cations, anions were optimized at the restricted B3LYP open shell (half electron) level. 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 energy (ZPE) corrected with un-scaled frequencies. On the basis of the DFT optimized geometries, the partial charges were obtained using 6–31(d,p) basis set.[71,72] Solvent contribution to the total enthalpies was computed employing PCM method.[76,77] All calculations were performed using Gaussian 98 program package.[78] 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 Eq. (4).[14,42]

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

where E_0 is the calculated total electronic energy, ZPE stands for zero-point energy, ΔH_{trans}, ΔH_{rot}, and ΔH_{vib} are the translational, rotational, and vibrational contributions to the enthalpy, respectively. Finally, RT represents PV-work term and is added to convert the energy to enthalpy. From the

calculated total enthalpies we have determined following quantities:

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

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

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

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

$$O/RE = H(ArO^\bullet) + H(e^-) - H(ArO^-) \quad (9)$$

The calculated gas-–phase enthalpy of proton, H (H⁺), and electron, H (e⁻), is 6.197 and 3.145 kJ mol⁻¹,[79] respectively. Obtained results reveal that water causes considerable changes of the total enthalpies of molecule, radical, anion and the radical cation of studied compounds. Enthalpy of H⁺ hydration is −1090 kJ mol⁻¹.[80] It severely affects PAs and PDEs. Since the enthalpy of electron hydratation, $\Delta_{hydr}H(e^-)$, could not be found in the literature, B3LYP/6–311++G** computed electron hydration enthalpy, $\Delta_{hydr}H(e^-)$ = −105 kJ mol⁻¹, was employed.[81]

Bond Dissociation Enthalpies in Gas Phase and Water. Knowledge of BDEs has been accumulating substantially for the past 15-20 years owing to the development of both experimental and quantum chemical techniques.[38,39,41,45,47,69,70,82-94] In this study, all conformers have been optimized and the conformer with higher stability has been used in each case. The calculated BDE for the basic structure, Magnolol, in gas-phase reached 375 kJ mol⁻¹. The computed gas-phase BDE and BDE values, where BDE = BDE (X-ArOH) −

BDE (ArOH), for substituents placed in *ortho-* and *meta-* position (Figure 1(b)) are reported in Table 1. The O-H BDE of structure with NO₂ substituent in *ortho-* and *meta-* position was higher *ca.* 53 and 18.3 kJ mol⁻¹ in comparison to BDE value of Magnolol, respectively. For *ortho-* substituted Magnolols with NMe₂, NH₂ and NHMe the BDE values are by 43.1, 45.7 and 39.4 kJ mol⁻¹ lower in comparison to the Magnolol, respectively. For *ortho-* substituted Magnolols with halogens the BDE values are almost by 19 kJ mol⁻¹ higher in comparison to the Magnolol. For *ortho-* substituted Magnolols with CHO, COOH and COMe the BDE values are *ca.* 19.6, 20 and 15.8 kJ mol⁻¹ higher than BDE value of Magnolol, respectively. The O-H BDE of structure with OH substituent in *ortho-* and *meta-* position was lower *ca.* 27.8 and 5.6 kJ mol⁻¹ in comparison to BDE value of Magnolol, respectively. For *meta-* substituted Magnolols with NMe₂, NH₂ and NHMe the BDE values are by 14.1, 12.6 and 13 kJ mol⁻¹ lower in comparison to the Magnolol, respectively. For *ortho-* and *meta-* substituted Magnolols with OMe the BDE values are by 23.1 and 5.6 kJ mol⁻¹ lower in comparison to BDE value of Magnolol, respectively. The difference between the highest and lowest BDE values for *ortho-* and *meta-* substituent Magnolols were 91.4 and 32.6 kJ mol⁻¹, respectively. Obtained result can be interpreted with a known fact that electron-withdrawing groups in *ortho-* and *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

Table 1. Calculated BDEs and BDEs in (kJ mol⁻¹) of *ortho* and *meta* substituted Magnolols in gas-phase and water, and Hammett constants of substituents σ_m[36]

| Substituent | gas | | | | water | | | | |
| | *ortho* | | *meta* | | *ortho* | | *meta* | | |
	BDE	ΔBDE	BDE	ΔBDE	BDE	ΔBDE	BDE	ΔBDE	σ_m
NMe₂	331.9	−43.1	361.9	−14.1	328.0	−27.6	348.2	−7.4	−0.24
NHMe	329.3	−45.7	363.0	−13.0	314.4	−41.2	350.1	−5.5	−0.24
NH₂	335.6	−39.4	363.4	−12.6	323.0	−32.6	348.1	−7.5	−0.16
t-Bu	358.9	−16.1	374.0	−2.0	329.6	−26.0	352.7	−2.9	−0.10
Ethyl	358.2	−16.8	373.6	−2.4	347.4	−8.2	353.3	−2.3	−0.07
Me	363.9	−11.1	372.9	−3.1	349.3	−6.3	352.8	−2.8	−0.07
Ph	367.5	−7.5	378.6	2.6	350.5	−5.1	359.0	3.4	0.06
CH=CH₂	367.4	−7.6	379.2	3.2	351.0	−4.6	359.0	3.4	0.06
OH	347.2	−27.8	370.4	−5.6	350.1	−5.5	353.3	−2.3	0.12
OMe	351.9	−23.1	370.4	−5.6	353.7	−1.9	352.6	−3.0	0.12
CCH	381.3	6.3	379.3	3.3	355.0	−0.6	363.2	7.6	0.21
F	391.8	16.8	379.0	3.0	377.4	21.8	359.4	3.8	0.34
CHO	394.6	19.6	384.5	8.5	382.4	26.8	364.7	9.1	0.35
COOH	395.0	20.0	381.5	5.5	378.9	23.3	366.5	10.9	0.37
Cl	394.3	19.3	379.5	3.5	386.1	30.5	361.6	6.0	0.37
COMe	390.8	15.8	380.3	4.3	391.8	36.2	363.0	7.4	0.38
Br	396.0	21.0	379.6	3.6	391.2	35.6	361.5	5.9	0.39
CF₃	416.4	41.4	386.9	10.9	387.3	31.7	366.2	10.6	0.43
CN	420.7	45.7	389.5	13.5	392.4	36.8	371.5	15.9	0.56
NO₂	428.0	53.0	388.3	12.3	394.8	39.2	372.8	17.2	0.71

presence leads to a decrease in the O-H BDE. The calculated BDE for the Magnolol is 355.6 kJ mol^{-1} in water phase that is lower than gas-phase BDE by 20 kJ mol^{-1}. In previous studies,[41,45,47,70,91] the solvent and substituent effect on O-H BDEs substituted phenols have been investigated with PCM method. Fu *et al.*[86] and Guerra *et al.*[87] determined solvation effect of water on ΔBDEs of *para* substituted phenols *via* PCM method and in these studies reaction enthalpies were calculated with B3LYP method and 6-31G* basis set. Russo *et al.*[57] have investigated solvent effect on BDE value of several phenolic antioxidants *via* PCM method. Klein *et al.*[70] indicated that PCM method could describe substituent effect in very good agreement with experimental data[40] for O-H BDEs of substituted phenols in water. No systematic study of solvent effect on BDEs and ΔBDEs of substituted Magnolols have been published, yet. The computed BDEs and ΔBDEs in the water for *ortho-* and *meta*-substituted Magnolols are reported in Table 1. For *ortho*-substituted Magnolols with NMe$_2$, NH$_2$ and NHMe the BDE values are by 27.6, 32.6 and 41.2 kJ mol^{-1} lower in comparison to the Magnolol, respectively. For *ortho*-substituted Magnolols with halogens the BDE values are by 13 kJ mol^{-1} higher in comparison to the Magnolol. For *meta*-substituted Magnolols with halogens the BDE values are by 4.5 kJ mol^{-1} higher than BDE value of Magnolol, respectively. For *ortho-* and *meta*-substituted Magnolols with CHO, COOH and COMe the BDE values are *ca.* 25 and 9 kJ mol^{-1} higher than BDE value of Magnolol, respectively. An inspection of the O-H BDE values appearing in Table 1 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 considerable changes in enthalpies of molecule and radical of studied structures. In water, electron-donating substituents decrease BDE values, whereas electron-withdrawing groups increase BDE values similar to founded results for the gas phase. The difference between the highest and lowest BDE values in water for *ortho-* and *meta*-positions were 80 and 23.5 kJ mol^{-1}, respectively. In comparison to gas-phase, the effects of various substituents which include EDG and EWG on the BDEs in *ortho-* and *meta*-positions were decreased in water phase. Therefore we can conclude that in comparison to gas-phase, effect of EDG-substituents and EWG-substituents on BDE in *ortho-* and *meta*-positions decreases in water. 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 ΔBDEs) for EDG-substituted Magnolols is the combined results of the radical stabilization and the parent molecules destabilization. However, increased BDEs (positive ΔBDEs) for EWG-substituted Magnolols seem to be the combination of both the parents and the radicals destabilization. The overall results of the calculations of O-H BDE can be summarized by the fact that EWG-substituted Magnolols with higher BDEs may exhibit weaker antioxidant activity in comparison to EDG ones in gas phase and water. In present study computed results for substituted
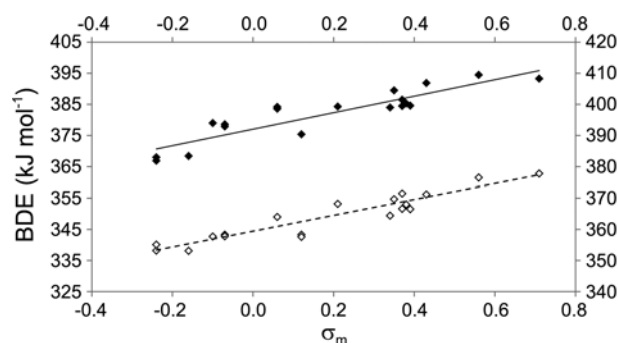

Figure 2. Dependence of BDE on σ_m for *meta*-substituted Magnolols in gas-phase (solid squares, solid line, bottom *x*-axis, left *y*-axis) and water (open squares, dashed line, top *x*-axis, right *y*-axis).

Magnolols show that substituents in *ortho*-positions exert significantly stronger influence on O-H BDE than substituents in *meta*- position in gas phase and water. These results are in agreement with previous studies on the *meta-* and *ortho*-substituted phenols and chromans.[11,41,49,63,69] 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 σ_m (for substituent in *meta*-position) and σ_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.[35,36] Hammett constants correlate very well with the changes in BDE in the case of anilines, phenols or thiophenols.[39,42,83,93] DiLabio *et al.*[16,88,95] found that BDE and ΔBDE values of *para*-substituted phenols, 6-substituted-3-pyridinols, 2-substituted-5-pyrimidinols, and anilines are linearly dependent on Hammett constants σ_p. Klein *et al.*[37,48] found that BDE and ΔBDE values of *para*-substituted and *meta*-substituted phenols are linearly dependent on Hammett constants σ_p and σ_m. Klein *et al.*[69] have shown that BDE values of *meta*-substituted chromans are linearly dependent on Hammett constants σ_m in the gas phase and water. BDE values computed for the *meta*-substituted Magnolols in gas phase and water are plotted against Hammett constants in Figure 2. The correlation coefficients in gas and water reached 0.92 and 0.93 respectively. Equations obtained from the linear regression are as follows:

$$BDE\ (kJ\ mol^{-1}) = 26.5 \times \sigma_m + 375.1\ (gas) \qquad (10)$$

$$BDE\ (kJ\ mol^{-1}) = 25.4 \times \sigma_m + 355.6\ (water) \qquad (11)$$

Linear regressions show that DFT method describes the expected linear BDE *vs* Hammett constant dependence satisfactorily. It is very important because can be utilized in the synthesis of novel Magnolol derivatives with enhanced antioxidant properties.

Ionization Potentials in Gas Phase and Water. This paper represents the first theoretical systematic study of substituted Magnolols IP values. In previous studies[41,47] the substituent effect on IPs of *para-* and *meta*-substituted phenols

Table 2. Calculated IPs and ΔIPs in (kJ mol^{-1}) of *ortho* and *meta* substituted Magnolols in gas-phase and water

Substituent	gas				water			
	ortho		*meta*		*ortho*		*meta*	
	IP	ΔIP	IP	ΔIP	IP	ΔIP	IP	ΔIP
NMe$_2$	670.0	−55.5	653.2	−72.3	230.0	−49.4	225.4	−54.1
NHMe	670.3	−55.2	656.3	−69.2	228.8	−50.6	224.2	−55.3
NH$_2$	677.1	−48.4	672.1	−53.4	236.8	−42.6	234.5	−45.0
t-Bu	705.4	−20.1	702.7	−22.8	269.6	−9.8	267.7	−11.8
Ethyl	709.7	−15.8	708.2	−17.3	271.1	−8.3	269.7	−9.8
Me	711.2	−14.3	709.7	−15.8	270.7	−8.7	269.1	−10.4
Ph	700.8	−24.7	701.5	−24.0	276.6	−2.8	276.8	−2.7
CH=CH$_2$	715.3	−10.2	709.9	−15.6	275.0	−4.4	276.0	−3.5
OH	699.2	−26.3	706.6	−18.9	258.6	−20.8	267.6	−11.9
OMe	701.0	−24.5	703.5	−22.0	260.9	−18.5	266.1	−13.4
CCH	729.0	3.5	720.2	−5.3	292.4	13.0	290.5	11.0
F	744.6	19.1	742.9	17.4	294.5	15.1	292.8	13.3
CHO	753.2	27.7	753.4	27.9	305.2	25.8	304.8	25.3
COOH	751.4	25.9	743.2	17.7	301.2	21.8	302.2	22.7
Cl	742.5	17.0	739.1	13.6	296.3	16.9	294.5	15.0
COMe	737.2	11.7	737.4	11.9	295.6	16.2	294.2	14.7
Br	740.2	14.7	737.7	12.2	296.1	16.7	294.6	15.1
CF$_3$	762.9	37.4	761.2	35.7	311.6	32.2	316.0	36.5
CN	778.4	52.9	775.4	49.9	319.5	40.1	317.9	38.4
NO$_2$	784.9	59.4	782.9	57.4	325.8	46.4	327.1	47.6

have been investigated in gas-phase employing B3LYP approach. Chandra *et al.*[82] calculated IP values for substituted pyridinethiols in gas-phase. In this paper, the calculated IP for the Magnolol in gas-phase reached 725.5 kJ mol^{-1}. The computed gas-phase IPs and ΔIP = IP(X-ArOH) − IP(ArOH) for substituents in *ortho*- and *meta*-position are reported in Table 2. In *ortho*- and *meta*-position, highest IP values were found for strong EWG substituents (NO$_2$, CF$_3$ and CN); lowest IPs was obtained for strong EDG substituents (NMe$_2$, NH$_2$, and NHMe). For halogens in *ortho*-positions, the IP values are by 17 kJ mol^{-1} higher in comparison to the Magnolol. For *ortho*- and *meta*-substituted Magnolols with strong EDGs-NMe$_2$, NH$_2$ and NHMe, IP values are by 72 and 54 kJ mol^{-1} lower in comparison to Magnolol, respectively. Decrease in IP of the molecules with OH group in *ortho*- and *meta*-positions are *ca.* 26 and 18 kJ mol^{-1}, respectively. For *ortho*- and *meta*-substituted Magnolols with OMe, decrease in IP reached 24 and 22 kJ mol^{-1}, respectively. Halogens in *ortho*- and *meta*-positions induce 19 and 15 kJ mol^{-1} rise in IP, respectively. For *ortho*- and *meta*-substituted Magnolols with CHO, COOH and COMe, IP values are by *ca.* 22 and 17 kJ mol^{-1} higher, respectively. The IP values of Magnolols with the strongest electron-withdrawing NO$_2$ group in *ortho*- and *meta*-positions were higher by *ca.* 60 and 40 kJ mol^{-1} in comparison to non-substituted Magnolol, respectively. The difference between the highest and lowest IP values for *ortho*- and *meta*-position was 130 and 96 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 subsitutents have an opposite effect. Therefore, their presence in the molecule leads to a decrease in IP. The decrease in IPs (negative ΔIPs) of EDG-substituted Magnolols is the combined result of the cation radical stabilization and the parent molecules destabilization. However, the increased IPs (positive ΔIPs) of EWG-substituted Magnolols 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.[41,47,82-85] The computed IPs using above mentioned calculated $\Delta_{hydr}H(e^-)$ value[81] in the water for molecules substituted in *meta*- and *ortho*-positions are reported in Table 2. Table 2 summarizes ΔIP values, too. Water causes considerable changes in the enthalpies of molecule and cation radical of studied Magnolols. Calculated IP related to Magnolol in water is lower than that in gas-phase by 280 kJ mol^{-1}. Mainly, due to the negative enthalpy of electron hydration in water, IP is significantly lower than that in gas-phase. For strong EDGs, *i.e.* NMe$_2$, NH$_2$ and NHMe, in *ortho*- and *meta*-positions, found drops in IP values are 50 and 40 kJ mol^{-1}, respectively. For OH group in *ortho*- and *meta*-positions, decrease in IP reached *ca.* 20 and 11 kJ mol^{-1}, respectively. For halogens in *ortho*- and *meta*-position increase in IP reached 15 and 13 kJ mol^{-1}, respectively. For *ortho*- and *meta*-substituted Magnolols with strong electron-withdrawing NO$_2$ group, the rise in IP value is *ca.* 46 and 35 kJ mol^{-1}, respectively. 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
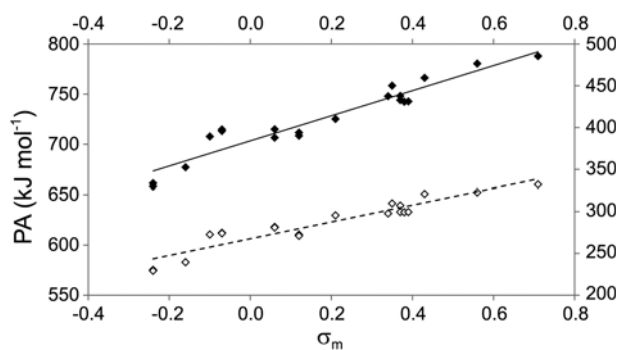
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Figure 3. Dependence of IP on σ_m for *meta*-substituted Magnolols in gas-phase (solid squares, solid line, bottom *x*-axis, left *y*-axis) and water (open squares, dashed line, top *x*-axis, right *y*-axis).

Table 3. Calculated E_{HOMO} in (eV) of *ortho* and *meta* substituted Magnolols in gas-phase and water

Substituent	gas		water	
	ortho	*meta*	*ortho*	*meta*
NMe$_2$	−5.92	−5.96	−6.16	−6.07
NHMe	−5.94	−5.88	−6.18	−6.11
NH$_2$	−5.87	−5.74	−6.09	−6.01
t-Bu	−5.96	−5.96	−6.25	−6.31
Ethyl	−5.92	−6.06	−6.23	−6.31
Me	−6.11	−6.13	−6.39	−6.35
Ph	−6.10	−6.11	−6.38	−6.36
CH=CH$_2$	−6.10	−6.09	−6.38	−6.35
OH	−6.15	−6.11	−6.53	−6.38
OMe	−6.14	−6.27	−6.42	−6.48
CCH	−6.27	−6.41	−6.51	−6.58
F	−6.27	−6.37	−6.54	−6.59
CHO	−6.40	−6.52	−6.62	−6.66
COOH	−6.40	−6.50	−6.61	−6.66
Cl	−6.59	−6.53	−6.77	−6.64
COMe	−6.49	−6.60	−6.72	−6.74
Br	−6.47	−6.57	−6.69	−6.71
CF$_3$	−6.57	−6.64	−6.73	−6.73
CN	−6.74	−6.80	−6.83	−6.73
NO$_2$	−6.89	−6.89	−7.00	−6.91

opposite effect. Water causes *ca.* 15 kJ mol^{-1} attenuation of substituent effect in terms of narrower ΔIP range. Again, substituents in *ortho*-positions exert stronger influence upon IP than the same substituents in *meta*-position. Values in Table 3 also reveal that IPs in water are considerably lower than corresponding gas-phase ones.

Klein *et al.*[41] confirmed that there are linear relations between IPs of substituted phenols and Hammett constants σ_p and σ_m in gas-phase. Here, the IP values computed for the *meta*-substituted Magnolols in gas-phase and water are plotted against Hammett constants in Figure 3. The correlation coefficients in gas-phase and water reached 0.95 and 0.94, respectively. Equations obtained from the linear regression are as follows:

$$IP\ (kJ\ mol^{-1}) = 125.1 \times \sigma_m + 725\ (gas) \quad (12)$$

$$IP\ (kJ\ mol^{-1}) = 100.1 \times \sigma_m + 280\ (water) \quad (13)$$

We can conclude that DFT method describes the expected linear IP *vs* Hammett constant dependence satisfactorily.

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 DFT computational approach are sufficiently accurate to characterize the electron-donating ability of antioxidants.[96,97] The energy of the highest occupied molecular orbital (E_{HOMO}) represents an alternative parameter to assess the electron-donating ability of antioxidants. This is widely used in anti-oxidant study[98,99] because of the simple calculation procedure, where only calculation for parent molecule is required. Besides, according the Koopmans' theorem [100], vertical IP_v value can be estimated from E_{HOMO}, $IP_v = -E_{HOMO}$. Therefore, HOMO energy represents an applicable parameter for prediction of antioxidant activity[101,102] and oxidant scavenging ability[103] *via* SET-PT mechanism. In this paper, found E_{HOMO} for Magnolol in gas-phase and water are −6.17 and −6.30 eV, respectively. As a general rule, the higher the E_{HOMO}, the more active the compound is as an antioxidant.[103,104] The computed E_{HOMO} values of investigated Magnolols in gas-phase and water are summarized in Table 3. These reveal

that in the case of EWG-substituents, E_{HOMO} values become more negative, while the presence EDG-substituents results in less negative E_{HOMO} values. Therefore, Magnolols with strong electron-donating groups are better electron donors, *i.e.* they enter SET-PT mechanism more easily. In previous study show that B3LYP/6–311+G(2d,2p) method significantly underestimates vertical gas-phase ionization potentials obtained from E_{HOMO} according to Koopmans' theorem for mono-substituted anilines, phenols and thiophenols.[93] However, the trends in ionization potentials, in terms of ΔIPs, are described reliably. Therefore, we decided to find expected linear dependence between calculated IPs and corresponding E_{HOMO} values (Figure 4). For *meta*-substituted Magnolols, correlation coefficients in gas-phase and water reached 0.95 and 0.96, respectively. Obtained equations are as follows:
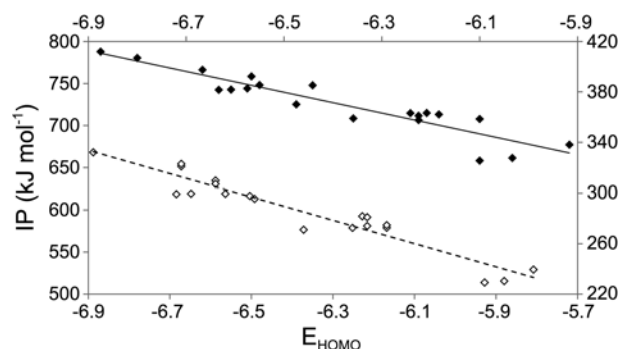

Figure 4. Dependence of IP on E_{HOMO} for *meta*-substituted Magnolols in gas-phase (solid squares, solid line, bottom *x*-axis, left *y*-axis) and water (open squares, dashed line, top *x*-axis, right *y*-axis).

$$IP \ (kJ \ mol^{-1}) = -103.2 \times E_{HOMO} \ (eV) + 77.1 \ (gas) \qquad (14)$$

$$IP \ (kJ \ mol^{-1}) = -110.4 \times E_{HOMO} \ (eV) - 428 \ (water) \qquad (15)$$

Obtained equations enable fast IP estimations for mono-substituted Magnolols from the computed E_{HOMO} values. This can be useful in the selection of suitable candidates for the synthesis of novel Magnolol derivatives with enhanced antioxidant properties.

Proton Affinities in Gas-Phase and Water. PA represents the reaction enthalpy of the first step in SPLET mechanism (Eq. 3.1). PAs of substituted Magnolols have not been obtained by theoretical calculations previously. In previous studies[22-24,41,42] the substituent effect on PAs of *para*- and *meta*-substituted phenols have been investigated by DFT using B3LYP functional in gas-phase. Chandra *et al.*[82] calculated PA values for substituted pyridinethiols in gas-phase, too. Calculated gas-phase PA for Magnolol reached 1490 kJ mol⁻¹. The computed PAs and ΔPAs for the various substituents in *ortho*- and *meta*-positions in gas-phase are reported in Table 4. The highest values of PA for *ortho*- and *meta*-positions were found for NMe₂, NH₂, and NHMe groups. The lowest PA values for thes positions were found in the case of NO₂, CF₃ and CN groups. Compared to non-substituted Magnolol, for Magnolols with NMe₂, NH₂ and NHMe groups in *ortho*- and *meta*-positions, PA values are by 14 and 7.5 kJ mol⁻¹ higher, respectively. Halogens in *ortho*- and *meta*-positions cause decrease in PA by 19 and 15 kJ mol⁻¹, respectively. For *ortho*- and *meta*-substituted Magnolols with CHO, COOH and COMe PAs are by 35 and 18 kJ mol⁻¹ lower than PA of Magnolol, respectively. For

strong electron-withdrawing NO₂ substituent in *ortho*- and *meta*-positions, drops in PA reached largest values: *ca.* 64 and 44 kJ mol⁻¹, respectively. The differences between the highest and lowest gas-phase PA values for *ortho*- and *meta*-substituents were 80 and 53 kJ mol⁻¹, respectively. In agreement with previous studies on substituted phenols,[22-24,42] 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 ArO⁻ but destabilize the parent phenol. Electron donating groups have an opposite effect.[15,39,84,85] The present calculated PA for the Magnolol reached 51 kJ mol⁻¹ in water. For Magnolols substituted in *meta*- and *ortho*-positions, computed PAs and ΔPAs in the water are reported in Table 4. Water causes considerable changes in the enthalpies of anions. Calculated PA for Magnolol in water is lower than gas-phase value by 1440 kJ mol⁻¹. Mainly, due to the large negative enthalpy of H⁺ hydration, PAs in the water are significantly lower than gas-phase values. Again, EWG substituents decrease PAs, whereas EDG groups increase PAs in agreement with results for substituted phenols in water.[70] Again, strong electron-donating NMe₂, NH₂ and NHMe cause an increase in PA. For *ortho*- and *meta*-substituted Magnolols, PA values are by 11 and 5 kJ mol⁻¹ higher in comparison to the Magnolol, respectively. The presence of OH group in *ortho*- and *meta*-positions results in 7 and 2.5 kJ mol⁻¹ PA growth, respectively. For halogens in *ortho*- and *meta*-positions, the drops in PAs reached 15 and 12 kJ mol⁻¹, respectively. The largest decrease in PA shows Magnolol with NO₂ group in *ortho*-

Table 4. Calculated PAs and ΔPAs in (kJ mol⁻¹) of *ortho*- and *meta*-substituted Magnolols in gas-phase and water

| Substituent | gas | | | | water | | | |
| | *ortho* | | *meta* | | *ortho* | | *meta* | |
	PA	ΔPA	PA	ΔPA	PA	ΔPA	PA	ΔPA
NMe₂	1507.2	15.9	1499.3	8.0	63.1	11.4	55.8	4.3
NHMe	1504.5	13.2	1498.8	7.5	64.8	13.1	56.1	4.6
NH₂	1506.4	15.1	1498.1	6.8	61.1	9.4	56.6	5.1
t-Bu	1498.1	6.8	1493.8	2.5	60.0	8.3	54.7	3.2
Ethyl	1498.7	7.4	1493.4	2.1	58.8	7.1	54.5	3.0
Me	1495.1	3.8	1492.3	1.0	56.3	4.6	54.3	2.8
Ph	1496.1	4.8	1482.7	−8.6	55.4	3.7	53.6	2.1
CH=CH₂	1495.3	4.0	1483.6	−7.7	54.9	3.2	50.9	−0.6
OH	1500.9	9.6	1494.8	3.5	59.0	7.3	50.0	−1.5
OMe	1496.8	5.5	1494.5	3.2	56.9	5.2	50.2	−1.3
CCH	1495.7	4.4	1476.7	−14.6	55.3	3.6	50.4	−1.1
F	1480.7	−10.6	1476.7	−14.6	39.1	−12.6	40.2	−11.3
CHO	1454.6	−36.7	1471.2	−20.1	40.3	−11.4	37.7	−13.8
COOH	1444.6	−46.7	1473.6	−17.7	36.1	−15.6	41.4	−10.1
Cl	1472.8	−18.5	1473.4	−17.9	36.7	−15.0	38.9	−12.6
COMe	1456.3	−35.0	1464.2	−27.1	38.0	−13.7	42.9	−8.6
Br	1468.5	−22.8	1476.2	−15.1	36.0	−15.7	40.3	−11.2
CF₃	1444.6	−46.7	1453.6	−37.7	23.3	−28.4	35.6	−15.9
CN	1434.2	−57.1	1452.4	−38.9	10.7	−41.0	32.4	−19.1
NO₂	1427.2	−64.1	1446.7	−44.6	14.0	−37.7	29.6	−21.9

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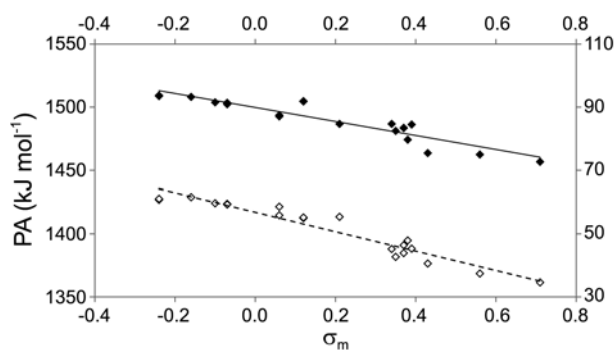
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Figure 5. Dependence of PA on σ_m for *meta*-substituted Magnolols in gas-phase (solid squares, solid line, bottom *x*-axis, left *y*-axis) and water (open squares, dashed line, top *x*-axis, right *y*-axis).

Figure 6. Dependence of PA on E_{HOMO} for *meta*-substituted Magnolols in gas-phase (solid squares, solid line, bottom *x*-axis, left *y*-axis) and water (open squares, dashed line, top *x*-axis, right *y*-axis).

(38 kJ mol^{-1}) or *meta* (22 kJ mol^{-1}) positions. Differences between the highest and lowest PA values for three studied positions were 50 (*ortho*) and 27 kJ mol^{-1} (*meta*). It confirms that water attenuates substituent induced changes. Klein *et al.*[41,70] found a linear dependence between PAs of substituted phenols and Hammett constants in gas-phase and water. There is a linear relation between PAs substituted pyridinethiols with Hammett constants,[82] too. For the *meta*-substituted Magnolols in gas-phase and water, computed PAs are plotted against Hammett constants in Figure 5. The correlation coefficients in gas-phase and water reached 0.94 and 0.95, respectively. Equations obtained from the linear regression are as follows

$$PA \ (kJ \ mol^{-1}) = -55.6 \times \sigma_m + 1490 \ (gas) \qquad (16)$$

$$PA \ (kJ \ mol^{-1}) = -30.8 \times \sigma_m + 51 \ (water) \qquad (17)$$

These results show good linearity of found PA = f(σ_m) dependences. We have also performed linear correlation of PA values with E_{HOMO} in the two environments. In this paper also we try to find expected linear dependence between calculated PAs and corresponding E_{HOMO} values (Figure 5). Obtained dependences for substituents in *meta*-position are shown in Figure 5. Correlation coefficients reached 0.95 (gas-phase) and 0.94 (water). Following regression lines were obtained

$$PA \ (kJ \ mol^{-1}) = 47.3 \times E_{HOMO} \ (eV) + 1787 \ (gas) \qquad (18)$$

$$PA \ (kJ \ mol^{-1}) = 31.7 \times E_{HOMO} \ (eV) + 256 \ (water) \qquad (19)$$

The positive line slopes reflect the fact that the EDG-substituents increase PA, as well as absolute value of E_{HOMO}. On the other hand, EWG-substituents cause decrease in PAs and absolute E_{HOMO} values. Obtained equations may be used to predict PAs for *meta*-substituted Magnolols from their E_{HOMO}. We can conclude that E_{HOMO} can be employed for fast estimations of reaction enthalpies for the first steps of both investigated two-step SET-PT and SPLET mechanisms.

Proton Dissociation Enthalpies and Oxidation/Reduction Enthalpies in Gas-Phase and Water. PDE and O/RE 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
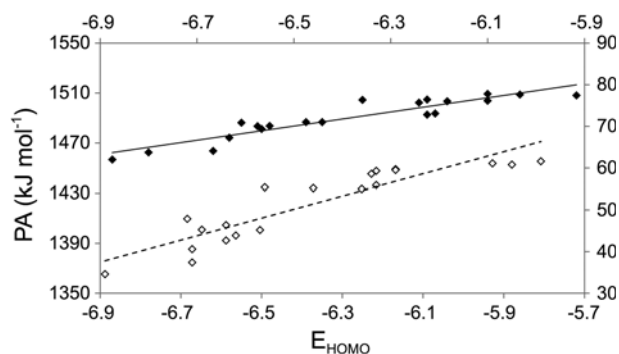
study PDEs and O/REs and to investigate the solvent and substituent effects on these reaction enthalpies. In previous papers[12,15,41,69,105] the substituent effect on PDEs for substituted phenols have been theoretically investigated by DFT using B3LYP functional. In recent papers,[69,105] the PDE and O/RE values of *ortho*- and *meta*-substituted Magnolols have been calculated in gas and water. There are no experimental PDEs available yet. PDE values for amine type antioxidants have not been studied previously. Calculated PDEs for the Magnolol reached 1035 kJ mol^{-1} in gas-phase and 145 kJ mol^{-1} in water. PDE of Magnolol in water is lower by 890 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. Computed PDE values for the substituents in *ortho*- and *meta*-position in gas-phase and water are reported in Table 5. Highest PDEs were found for strong EDG substituents (NMe$_2$, NH$_2$, and NHMe), whereas lowest PDEs were obtained for strong EWG substituents (NO$_2$, CF$_3$ and CN). This trend is opposite to that observed for PAs. It is known that electron-donating groups stabilize ArOH$^{+\bullet}$ but destabilize the parent structure, while electron-withdrawing groups have an opposite effect [15,39,94]. These results are in agreement with previous papers on substituted phenols and chromans.[12,15,41,44,69,105] For substituted Magnolol, O/REs were not studied previously. In literature, only DFT/B3LYP O/REs of substituted phenols and chromans[41,69,33,105] are available. Calculated O/RE values for Magnolol reached 243 kJ mol^{-1} in gas-phase and 325 kJ mol^{-1} in water. The computed O/REs values for Magnolol with substituents in *ortho*- and *meta*-position are compiled in Table 5. In gas-phase and water, highest O/REs were found for strong EWG substituents (NO$_2$, CF$_3$ and CN). Lowest O/REs were found in the case of strong EDG substituents (NMe$_2$, NH$_2$, NHMe). This trend corroborates to that observed for BDEs and IPs. It is known that electron withdrawing groups are favorable to stabilize ArO$^-$. Electron donating groups have an opposite effect. Therefore, electron withdrawing groups increase O/RE values, while electron donating groups decrease O/REs.[15,39,85,94,106]

Thermodynamically Preferred Mechanism. In general,

Table 5. Calculated PDEs and O/REs in (kJ mol^{-1}) of *ortho* and *meta* substituted Magnolols in gas-phase and water

Substituent	gas				water			
	ortho		meta		*ortho*		*meta*	
	PDE	O/RE	PDE	O/RE	PDE	O/RE	PDE	O/RE
NMe$_2$	1070.6	220.1	1103.6	238.0	170.0	295.3	191.7	313.8
NHMe	1060.8	217.8	1101.6	236.9	165.7	294.6	194.9	315.4
NH$_2$	1058.2	216.9	1094.2	233.1	161.2	294.5	182.9	312.9
t-Bu	1045.3	240.6	1057.4	241.5	149.7	311.7	154.2	317.4
Ethyl	1044.5	242.2	1052.3	241.1	149.9	314.6	154.7	319.3
Me	1043.0	238.6	1050.1	241.4	149.8	316.6	157.7	318.9
Ph	1049.9	260.0	1051.0	257.8	149.0	324.5	151.2	326.8
CH=CH$_2$	1038.6	260.5	1052.6	256.7	145.1	329.4	152.0	329.4
OH	1047.0	227.8	1049.7	246.5	157.2	306.0	164.7	324.7
OMe	1044.0	232.0	1053.7	238.7	153.5	309.0	163.5	319.2
CCH	1044.5	272.6	1040.8	267.3	138.0	345.0	141.6	341.1
F	1023.4	261.1	1021.0	266.1	130.5	342.4	127.6	340.6
CHO	1023.9	282.3	1016.0	277.2	150.9	358.2	131.8	351.4
COOH	1028.1	286.8	1023.2	276.7	134.1	361.1	131.2	346.5
Cl	1028.8	272.5	1023.3	273.9	132.1	344.1	126.0	344.2
COMe	1028.5	276.8	1027.7	274.9	140.6	354.6	127.8	341.5
Br	1031.6	277.2	1021.8	277.2	132.9	345.4	125.9	344.6
CF$_3$	1016.2	298.4	1006.6	304.0	123.8	364.4	115.2	354.1
CN	999.1	317.1	996.0	304.9	114.8	372.1	109.5	360.5
NO$_2$	996.7	319.4	990.3	310.4	121.1	382.3	107.6	366.6

free energy represents the criterion of the thermodynamically preferred process. However, in the case of studied reactions the absolute values of the entropic term $-T\Delta_r S$ reach few tens of kJ mol^{-1}[81,48,95,106,107] and all free energies, $\Delta_r G = \Delta_r H - T\Delta_r S$, are only shifted in comparison to corresponding enthalpies. Therefore, comparison of BDEs, PAs and IPs can indicate which mechanism is thermodynamically preferred. Calculated gas-phase IPs and PAs of mono-substituted Magnolols are significantly higher, by 85-100 and 1000-1200 kJ mol^{-1}, 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 70-100 and 160-320 kJ mol^{-1}, respectively. In water, IP values remain still higher than BDEs by *ca.* 85-100 kJ mol^{-1}, respectively. Significantly lower PAs indicate that SPLET represents the thermodynamically preferred reaction pathway in water.

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 Magnolols were calculated in gas-phase and water. Obtained results indicate that electron-withdrawing substituents increase the bond dissociation enthalpy (BDE), ionization potential (IP) and oxidation/reduction enthalpy (O/RE), while electron-donating ones cause a rise in the proton dissociation enthalpy (PDE) and proton affinity (PA). Water attenuates the substituent effect on all reaction enthalpies. In 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. Results show that calculated enthalpies can be successfully correlated with Hammett constants (σ_m) of the substituted Magnolols. It has been also found that PA and IP values for substituted Magnolols can be estimated from their E_{HOMO} values. This fact may be useful for the development of new Magnolol based antioxidants.

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