JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

Density Functional Theory (B3LYP) Study of Substituent Effects on O–H Bond Dissociation Enthalpies of *trans*-Resveratrol Derivatives and the Role of Intramolecular Hydrogen Bonds

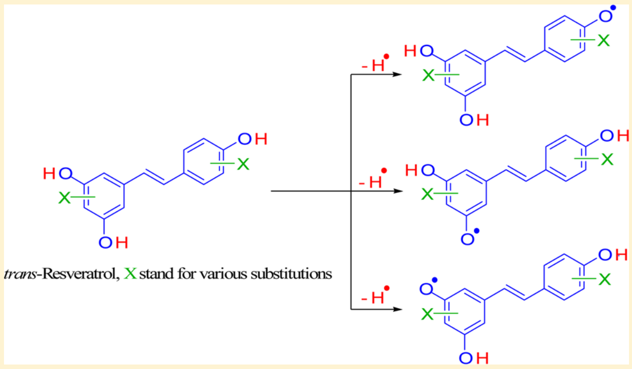
Elyas Nazarparvar,[†] Mansour Zahedi,*[,†] and Erik Klein*[,‡]

[†]Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, G.C., Evin, 19839-6313, Tehran, Iran

[‡]Department of Physical Chemistry, Slovak University of Technology, Radlinského 9, SK–812 37 Bratislava, Slovak Republic

Supporting Information

ABSTRACT: In this paper, 23 substituents with various electron-donating and electron-withdrawing characters were placed in available positions of *trans*-resveratrol in order to study their effect on the three O–H bond dissociation enthalpies (BDEs) via density functional theory (DFT) with Becke three-parameter exchange and Lee–Yang–Parr correlation (B3LYP). It has been found that the mutual positions of substituents and OH groups affect investigated BDEs substantially. Formation of strong intramolecular hydrogen bonds and suitable spin density distributions in several radicals result in low BDEs. Calculated BDEs have been correlated with Hammett constants, selected geometry parameters, and charge on phenoxy radical oxygen $q(O)$. Found dependences are satisfactorily linear.



1. INTRODUCTION

Nowadays, there is growing attention to selecting efficient and safe antioxidants stemming from natural sources, such as flavonoids, vitamin E, and other phenols.[1] One of the most closely considered compounds, *trans*-3,4′,5-trihydroxystilbene, resveratrol, found in red wine, grape products, berries, and peanuts, has established a wide variety of effectual biological properties.[2,3] Resveratrol, as a kind of phytoalexin, is broadly reported for its antioxidant and anticancer activity, protection against cardiovascular disease, etc.[4,5] The antioxidant activity of resveratrol is related to its hydroxyl groups, which can scavenge free radicals produced in vivo.[6,7] Its antioxidant activity is lost after the replacement of the hydrogens from phenolic OH groups by CH_3 groups.[8]

It is well-established that phenolic antioxidants (ArOH) scavenge free radicals according to two possible reducing pathways,[9−12] namely, hydrogen atom transfer (HAT) and single-electron transfer followed by proton transfer (SETPT). A few years ago, a new mechanism, sequential proton loss electron transfer (SPLET), was discovered.[12,13] All these mechanisms have the same net result: formation of phenoxy radical, $ArO^\bullet$, and the termination of free radicals. Under certain conditions, HAT mechanism ($ArOH \rightarrow ArO^\bullet + H^\bullet$) may represent the main pathway through which phenolic antioxidants play their protective role.[11,12]

From the thermodynamics point of view, HAT is governed by O–H bond dissociation enthalpy (BDE). Moreover, BDEs associate also with the rate constants of free radicals termination.[14,15] Linear dependence between BDEs and reaction barriers (activation energies) for hydroperoxyl radicals was found by Mohajeri and Asemani.[16] Therefore, the O–H BDE is a vital parameter in evaluating the action of phenolic antioxidants. Knowledge of BDEs has accumulated substantially for the past 20 years, owing to the recent development of both experimental and quantum chemical techniques.[17,18]

The BDEs for resveratrol, its structural subunits, and derivatives with different numbers of OH groups have been calculated by Queiroz et al.[19] They have found that resveratrol is a potential antioxidant because its radical cations or semiquinone radicals have several resonance structures where the unpaired electron is mainly distributed on the 4′-hydroxystilbene. Queiroz et al.[19] have also manifested that the antioxidant activity of *trans*-resveratrol is related to the stabilization energy of 4′-hydroxystilbene in *trans*-resveratrol hydroxylated derivatives. In addition, the radical scavenging activity of *trans*-resveratrol analogues and *cis*-resveratrol has been investigated by Mikulski et al.[20] Their results have proved that the most favorable mechanism for radical scavenging is through hydrogen atom donation from the antioxidants studied, and the activity can be related to the planar and semiquinone structure of the phenoxy free radicals stabilized by resonance and the presence of the vinyl bond. Growing evidence suggesting that resveratrol plays an important role in

Received: August 2, 2012
Published: October 18, 2012

dx.doi.org/10.1021/jo301612a | J. Org. Chem. 2012, 77, 10093−10104

the prevention of human pathological processes prompted our interest in investigating its antioxidant activity. In the present work, different electron-withdrawing groups (EWG) and electron-donating groups (EDG) were placed in available positions, denoted as X_1, X_2, X_3, and X_4, of the two aromatic rings (A- and B-ring) of *trans*-resveratrol (Figure 1) in order to study effect of substituents on 3-, 5-, and 4′-OH BDEs. Because the intramolecular hydrogen bonds between certain substituents and OH groups can substantially alter the stability of the parent molecules[21] and/or formed radical species, it is inevitable to investigate the influence of these interactions on BDEs, too. In general, hydrogen bonds are usually formed in molecules and radicals, where a hydrogen atom is located between two electronegative atoms as a result of the interaction between the proton-donating bond D—H and proton acceptor A (D and A are electronegative atoms such as O, N, etc).[22] O—H···O, O—H···N, N—H···O, and N—H···N represent typical systems forming hydrogen bonds. The geometry of the hydrogen bond, D—H···A, may be defined by following parameters:[23] D—H, proton−donor bond length; H···A, hydrogen-bond length; D---A, heavy atom distance; and D—H···A, hydrogen-bond angle. Short H···A length, significant D—H elongation, and linearity of the D—H···A hydrogen bond are preconditions leading to the formation of strong hydrogen bonds. Three OH groups in resveratrol may play a proton-donating role. Moreover, in the case of hydrogen bonds formed in phenoxy radicals, phenoxy radical oxygen can act as a proton acceptor in the presence of substituent that can serve as proton donor.

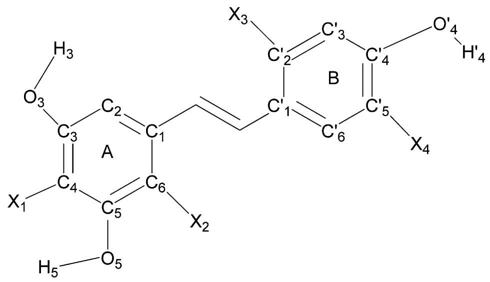


Figure 1. (A) $X_1 = X_2 = X_3 = X_4$ = H (*trans*-resveratrol). (B) $X_2 = X_3 = X_4$ = H and X_1 = various substitutions. (C) $X_1 = X_3 = X_4$ = H and X_2 = various substitutions. (D) $X_1 = X_2 = X_4$ = H and X_3 = various substitutions. (E) $X_1 = X_2 = X_3$ = H and X_4 = various substitutions.

Thus, the main aims of this work are (i) to identify the position showing the largest substituent effect on BDE; (ii) to find the molecule with the lowest BDE; (iii) to assess which aromatic ring in the molecule is more important from the BDE point of view; (iv) to explore the possibility and conditions for the formation of short and exceptionally strong intramolecular hydrogen bonds in parent molecules and corresponding phenoxy radicals; and (v) to describe the geometrical parameters and strengths of important intramolecular hydrogen bonds by natural bond orbital (NBO) analysis. In order to determine appropriate descriptors of substituent-induced changes in BDEs, Hammett constants as well as some structural parameters, such as C−O and O−H bond lengths and partial charge on phenoxy radical oxygen, *q*(O), have been examined.

2. COMPUTATIONAL DETAILS

The density functional theory (DFT) method with Becke three-parameter exchange and Lee−Yang−Parr correlation (B3LYP) functional[24,25] and the 6-31G(d,p) basis set[24,26] were used for geometry optimization of each compound and respective radical structures in the gas phase. Single-point calculations have been carried out with the 6-311++G(2d, 2p) basis set.[27,28] All enthalpies reported

Table 1. Calculated BDEs and ΔBDEs of 5-, 3-, and 4′-OH Related to X_1 Position

	5-OH		3-OH		4′-OH	
substituent	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})
none	353.6	0.0	348.2	0.0	325.7	0.0
NMe_2	337.9	−15.7	338.1	−10.1	324.2	−1.5
NHMe	311.2	−42.5	317.3	−30.9	323.5	−2.2
NH_2	302.6	−51.0	314.4	−33.8	321.8	−3.9
OH	326.8	−26.8	313.1	−35.1	324.8	−0.9
OMe	330.5	−23.2	326.3	−22.0	323.7	−2.0
t-Bu	338.8	−14.8	339.3	−9.0	323.6	−2.1
Me	343.2	−10.5	340.9	−7.3	324.2	−1.5
ethyl	344.1	−9.6	341.8	−6.4	325.2	−0.5
$CH{=}CH_2$	336.4	−17.2	338.1	−10.1	321.8	−3.9
Ph	345.9	−7.7	343.9	−4.3	324.0	−1.7
F	351.0	−2.7	348.4	0.2	327.3	1.6
CCH	351.8	−1.9	352.1	3.9	326.1	0.3
Cl	351.0	−2.6	348.9	0.7	332.5	6.8
Br	348.2	−5.4	350.5	2.2	331.2	5.4
COH	336.8	−16.8	403.0	54.8	327.3	1.6
COOH	368.7	15.0	394.0	45.7	329.7	4.0
$CONH_2$	309.0	−44.6	389.1	40.9	327.2	1.5
CF_3	347.2	−6.5	349.3	1.1	330.8	5.1
CN	355.0	1.4	356.6	8.4	332.5	6.8
NO	353.6	0.0	369.8	21.6	336.2	10.5
NO_2	393.7	40.0	393.1	45.5	335.9	10.2
POH_2	393.4	39.7	339.3	−9.0	333.4	7.7
SO_2H	360.7	7.1	361.1	12.9	330.1	4.4

were zero-point (ZPE) corrected with unscaled frequencies. To confirm the optimized structures to be in real minima, frequency calculation was done. For the species having more conformers, all conformers were investigated. The conformer with the lowest electronic energy was used in this work. Obtained total energy of the hydrogen atom in gas phase, −0.499 897E_h, was used in the BDE calculations. On the basis of the DFT-optimized geometries, the partial NBO charges were obtained with the 6-311G(2d,2p) basis set.[24,26] All calculations were performed with the Gaussian 09 program package.[29] The hydrogen-bond analysis has been obtained by use of Weinhold's natural population analysis and NBO.[30] Spin densities and atomic charges were also obtained via the natural population analysis of Weinhold and Carpenter.[31] All BDEs were calculated at 298.15 K and 1.0 atm pressure.

3. RESULTS AND DISCUSSION

From the calculated total enthalpies, we have determined O−H bond dissociation enthalpies:

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

Total enthalpies of species X, $H(X)$, at temperature T are usually estimated from[9,10,32,33]

$$H(X) = E_0 + ZPE + \Delta H_{trans} + \Delta H_{rot} + \Delta H_{vib} + RT \quad (2)$$

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

3.1. O−H Bond Dissociation Enthalpy Values of Nonsubstituted Resveratrol. First, 3-, 5-, and 4′-OH BDEs for nonsubstituted resveratrol have been computed. The results in the first row of Table 1 show that the 4′-OH BDE is lower by 22.5 and 27.9 kJ·mol^{-1} than 3- and 5-OH BDEs, respectively. These two OH groups are mutually placed in meta positions. OH group in meta position shows an electron-withdrawing effect[19] and causes the increase in BDE. Figure 2 is an illustration of the positive spin densities of formed radicals after hydrogen abstraction. To avoid a complicated picture, just positive spin densities are reported. As revealed from Figure 2A,B, the positive spin densities of 3- and 5-ArO$^\bullet$ are distributed mainly in A-ring. Thus, in these two species the unpaired electron cannot be delocalized to the B-ring. Low 4′-OH BDE indicates that hydrogen abstraction from the OH group in para position to the rest of molecule is facilitated by the existence of the π-delocalized system between B- and A-rings (see positive spin density in Figure 2C). In the case of hydrogen abstraction from 3- and 5-OH groups, no π-delocalized system between A- and B-rings was observed.

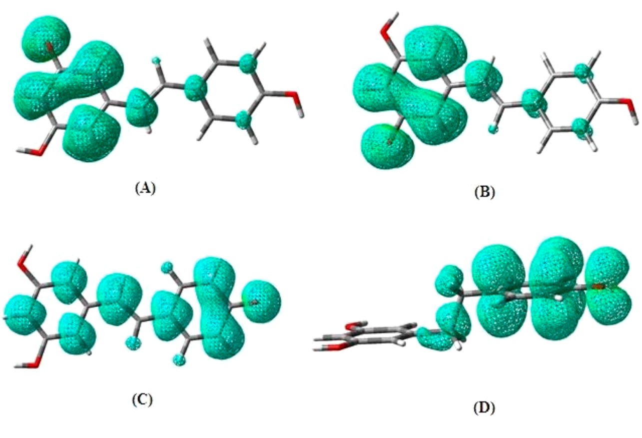


Figure 2. Positive spin density and unpaired electron distribution of (A) 3-ArO$^\bullet$, (B) 5-ArO$^\bullet$, (C) 4′-ArO$^\bullet$, and (D) 4′-ArO$^\bullet$ with saturated C═C bond between A- and B-rings.

In 4′-ArO$^\bullet$ radical, the positive spin density is distributed between B- and A-rings, and this prevalent spin density is the determinant factor for the highest stability of 4′-ArO$^\bullet$. In order to confirm the contribution of delocalization to the 4′-ArO$^\bullet$ radical stability, a conjugated (C═C) bond between A- and B-rings has been saturated. The spin density distribution of corresponding 4′-ArO$^\bullet$ radical shows that delocalization occurs just in B-ring (see Figure 2D) and 3-, 5-, and 4′-OH BDEs are within 9 kJ·mol^{-1}. It can be concluded that hydrogen abstraction is thermodynamically preferred from the 4′-OH group in the B-ring, because in the case of 4′-ArO$^\bullet$ radical, the conjugation through C═C bond provides electron delocalization from the B-ring.

3.2. O−H Bond Dissociation Enthalpy Values for Molecules with Substituent in X_1 Position. The computed 3-, 5-, and 4′-OH BDEs and ΔBDEs, where ΔBDE represents the difference between substituted and nonsubstituted resveratrol BDEs, are reported in Table 1. Highest 3-OH BDE values are found for COH (403.0 kJ·mol^{-1}) and NO_2 (393.1 kJ·mol^{-1}), while lowest ones are found for OH (313.1 kJ·mol^{-1}) and NH_2 (314.4 kJ·mol^{-1}). Highest 5-OH BDEs are achieved for NO_2 (393.7 kJ·mol^{-1}) and POH_2 (393.4 kJ·mol^{-1}), while lowest 5-OH BDE values are found for NH_2 (302.6 kJ·mol^{-1}) and $CONH_2$ (309.0 kJ·mol^{-1}). The difference between highest and lowest BDE values is 89.9 kJ·mol^{-1} for 3-OH and 91.1 kJ·mol^{-1} for 5-OH. All 4′-OH BDEs lie within a considerably narrower range of 14.4 kJ·mol^{-1}. The highest 4′-OH BDE is found for NO_2 group (336.2 kJ·mol^{-1}); the lowest values are found for NH_2 and CH═CH_2 groups (321.8 kJ·mol^{-1}). These BDE shifts are caused by the resonance between the two rings, although the X_1 position is very far from the 4′-OH group.

X_1 lies between 3- and 5-OH groups, which are therefore in ortho positions. In parent molecules with alkyl substituents, both OH groups are oriented away from the substituent because of steric effect. When substituents containing N or O atoms with low hydrogen−hydrogen repulsion, such as NO_2, COOH, CN, and NO, are placed in X_1 position, the OH groups of resveratrol prefer to be oriented toward the substituent (Figure 3). In the case of NH_2, NHMe, NMe_2, POH_2, and OH substituents, one OH group is oriented toward while the second one is away, because of hydrogen−hydrogen repulsion and/or formation of hydrogen bonds (Figure S1 in Supporting Information).

Symmetric substituents should exert identical effect on both 5- and 3-OH BDEs. For instance, when NO_2 is placed in X_1 position, difference between 3- and 5-OH BDEs can be neglected. On the other hand, for substituents that are able to form intramolecular hydrogen bonds (for example, $CONH_2$, COH, and POH_2 group), differences between 3- and 5-OH BDEs may differ on the order of tens of kilojoules per mole. Steric effects of substituents also influence BDE values. Values in Table 1 show that, for studied substituents, differences between 3- and 5-OH BDEs lie in the range 0.3−80.1 kJ·mol^{-1}. The largest difference was found for $CONH_2$ substituent. When the H atom of 5-OH is abstracted from the parent molecule, a new intramolecular hydrogen bond between NH_2 group and oxygen results in a more stable radical (Figure 4).

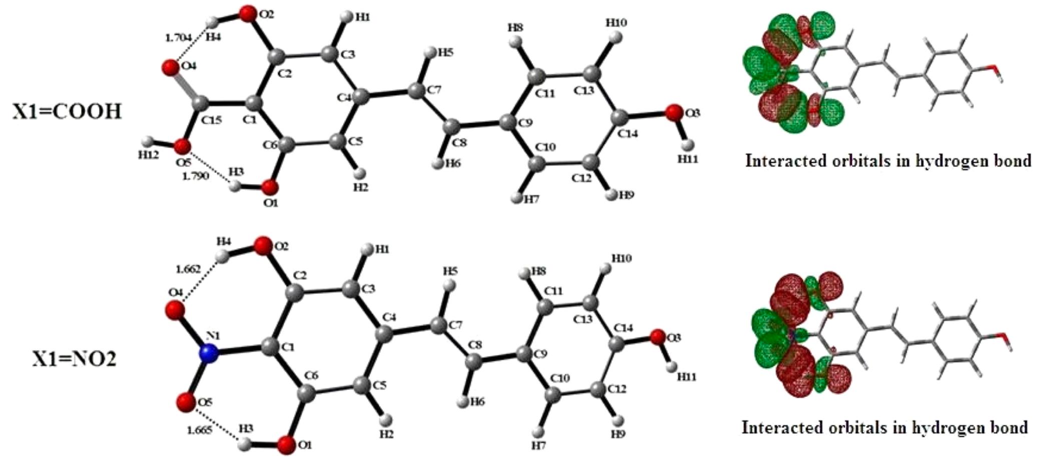


Figure 3. Interaction between the lone pair (LP) and antibonding (BD*) orbitals, involved in hydrogen bonding of NO_2 and COOH substitutions related to X_1 position.

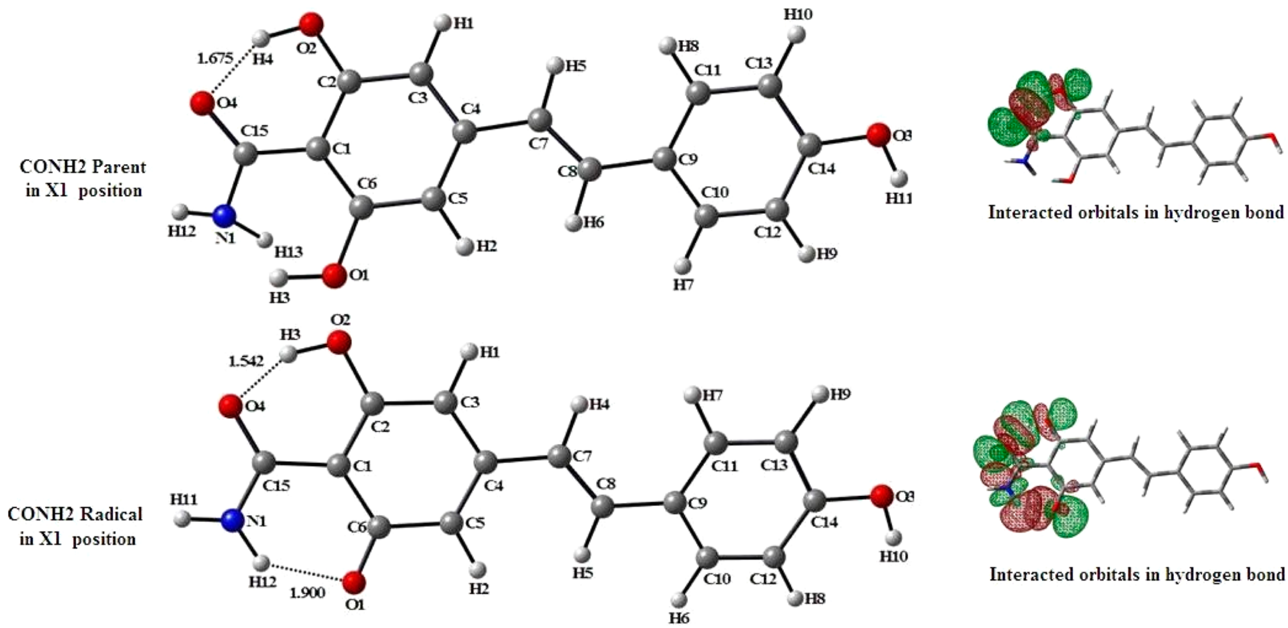


Figure 4. Interaction between lone pair (LP) and antibonding (BD*) orbitals involved in hydrogen bonding of $CONH_2$-substituted parent molecule and 5-ArO• radical.

When the hydrogen atom is detached from the 3-OH group in the parent molecule, a hydrogen bond has to be broken and the resulting radical will not be more stable unless the substituent rotates to form a new intramolecular hydrogen bond. Calculated results show that the presence of an intramolecular hydrogen bond in the parent molecule causes an increase in BDE because additional energy is required to break it. On the other hand, formation of an intramolecular hydrogen bond in a radical causes higher stability and leads to a decrease in BDE. We can conclude that the lowest BDE value was found for 5-OH group (302.6 kJ·mol^{-1}) in the molecule with NH_2 group in the X_1 position. The NH_2, NHMe, and NMe_2 groups are considered to be good electron-donating groups and these substitutions could stabilize the molecule due to resonance. In addition, the order of electron-donating effect is as follows: NMe_2 > NHMe > NH_2. However, since the methyl groups are bulky, repulsion may cause NMe_2 to be twisted out of the plane of the rings. This may result in weaker resonance with the aromatic rings. Thus, 4′-OH BDE (321.8 kJ·mol^{-1}) in the presence of NH_2 is lower than those for NHMe and NMe_2 groups.

3.3. O–H Bond Dissociation Enthalpy Values for Molecules with Substituent in X_2 Position. A substituent in X_2 position is ortho to the 5-OH group and para to the 3-OH group. Computed BDEs and ΔBDEs are reported in Table 2. The substituent effect on 5-OH group in the ortho position is more significant: changes in 5-OH BDE lie in the range from −54.6 to 88.4 kJ·mol^{-1}. Changes in 3-OH BDE (para position to X_2) are in the range from −35.9 to 24.6 kJ·mol^{-1}. Again, highest BDE values are related to strong electron-withdrawing groups such as NO_2, CN, and CF_3, and the lowest values are related to strong electron-donating groups, such as NH_2 and NMe_2. Halogens (F, Cl, and Br) have opposite effects on the parent molecule and radical. They may destabilize the parent molecule by raising its energy and stabilize the radical moiety by resonance effect.[34] These two opposite effects result in a reduced BDE values in the presence of halogen atoms in comparison with other electron-withdrawing groups.

Table 2. Calculated BDEs and ΔBDEs of 5-, 3-, and 4′-OH Related to X_2 Position

	5-OH		3-OH		4′-OH	
substituent	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})
none	353.1	0.0	346.4	0.0	325.7	0.0
NMe_2	323.7	−29.4	340.7	−5.7	327.3	1.6
NHMe	310.5	−42.6	335.0	−11.4	326.9	1.2
NH_2	298.5	−54.6	310.5	−35.9	323.2	−2.5
OH	347.5	−5.6	329.9	−16.5	329.8	4.1
OMe	335.6	−17.5	341.8	−4.6	326.4	0.7
t-Bu	336.8	−16.2	342.8	−3.6	327.6	1.9
Me	340.8	−12.3	339.7	−6.7	327.0	1.2
ethyl	340.7	−12.4	339.7	−6.6	328.3	2.6
$CH{=}CH_2$	346.5	−6.5	347.9	1.5	328.5	2.7
Ph	355.3	2.2	349.1	2.7	325.7	−0.1
F	354.1	1.0	344.8	−1.6	328.1	2.4
CCH	362.7	9.7	349.6	3.2	325.3	−0.4
Cl	356.5	3.4	350.7	4.3	329.8	4.1
COMe	383.8	30.7	363.9	17.5	333.0	7.3
Br	354.7	1.7	352.0	5.6	330.4	4.7
COH	412.0	59.0	369.5	23.1	334.6	8.9
COOH	385.9	32.9	367.7	21.3	330.0	4.3
$CONH_2$	441.4	88.4	361.8	15.4	333.3	7.6
CF_3	366.0	12.9	367.2	20.8	331.8	6.1
CN	369.0	15.9	364.4	18.0	333.0	7.3
NO	332.0	−21.1	342.8	−3.6	332.3	6.6
NO_2	380.8	27.8	371.1	24.7	332.5	6.8
POH_2	394.7	41.6	366.4	20.0	335.6	9.9
SO_2H	390.9	37.8	371.0	24.6	337.6	11.9

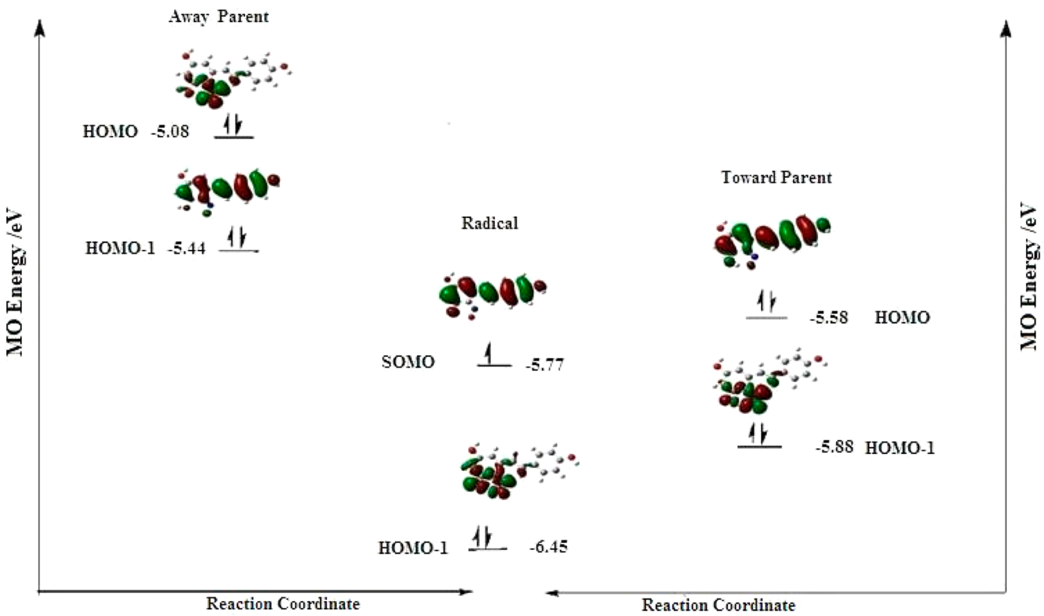


Figure 5. Molecular orbitals HOMO, HOMO − 1, and SOMO energies (in electronvolts) for toward and away structures of NO-substituted parents and radical, related to X_2 position.

The effect of substituents in X_2 position on 4′-OH BDE ranges from −2.5 to 11.9 kJ·mol^{-1}. Groups placed in X_1 and X_2 positions induce similar changes in 4′-OH BDE, and resonance with the B-ring may take place.

For the strongly electron-withdrawing NO group in X_2 position, obtained results indicate the strong influence of a hydrogen bond on 5-OH BDE. A decrease in BDE, in comparison to the nonsubstituted molecule, was found also for 3-OH group. The molecular orbital (MO) and NBO analysis results show that the intramolecular hydrogen bond stabilizes the parent molecule and radical significantly. In Figure 5, the highest occupied (HOMO), singly occupied (SOMO), and HOMO − 1 molecular orbitals for toward and away orientations of NO group in the parent molecule and the formed radical are presented. In the case of the toward parent structure, the energies and shapes of these orbitals are similar.

Table 3. Calculated BDEs and ΔBDEs of 5-, 3-, and 4′-OH Related to X_3 Position

	5-OH		3-OH		4′-OH	
substituent	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})
none	353.1	0.0	346.4	0.0	325.7	0.0
NMe_2	352.1	−1.0	345.8	−0.5	323.7	−2.0
NHMe	352.3	−0.8	345.8	−0.6	324.3	−1.4
NH_2	352.6	−0.4	346.6	0.3	326.3	0.6
OH	352.2	−0.8	345.2	−1.2	318.5	−7.2
OMe	351.7	−1.4	344.9	−1.5	316.2	−9.5
t-Bu	352.8	−0.3	347.0	0.6	328.6	2.9
Me	352.8	−0.3	346.7	0.3	324.9	−0.8
ethyl	352.7	−0.3	346.8	0.4	324.2	−1.5
$CH{=}CH_2$	353.4	0.4	347.0	0.6	329.1	3.4
Ph	352.9	−0.2	346.0	−0.4	327.8	2.1
F	351.7	−1.3	346.4	0.1	325.4	−0.3
CCH	353.7	0.6	346.4	0.0	329.3	3.6
Cl	354.3	1.2	346.9	0.5	327.2	1.5
COMe	355.5	2.4	348.8	2.4	336.8	11.1
Br	354.4	1.4	347.0	0.6	327.2	1.5
COH	356.0	3.0	349.0	2.6	341.5	15.8
COOH	353.9	0.9	345.6	−0.7	330	4.3
$CONH_2$	353.9	0.8	344.9	−1.5	324.4	−1.3
CF_3	355.4	2.3	347.4	1.0	331.2	5.5
CN	357.1	4.0	347.5	1.2	333.1	7.4
NO	356.6	3.6	347.7	1.3	340.7	15.0
NO_2	356.2	3.1	347.6	1.2	336.5	10.8
POH_2	356.3	3.2	349.6	3.3	338.4	12.7
SO_2H	357.5	4.4	348.3	2.0	338.6	12.9

Table 4. Calculated BDEs and ΔBDEs of 5-, 3-, and 4′-OH Related to X_4 Position

	5-OH		3-OH		4′-OH	
substituent	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})	BDE (kJ·mol^{-1})	ΔBDE (kJ·mol^{-1})
none	353.1	0.0	346.4	0.0	325.7	0.0
NMe_2	350.2	−2.9	346.3	−0.1	308.5	−17.2
NHMe	352.1	−1.0	344.9	−1.5	279.2	−45.5
NH_2	352.8	−0.3	346.4	0.0	286.0	−39.7
OH	350.5	−2.6	346.8	0.4	287.1	−37.6
OMe	352.6	−0.4	346.5	0.1	325.7	0.0
t-Bu	346.2	−6.8	339.5	−6.9	312.5	−12.2
Me	350.3	−2.8	346.0	−0.4	317.4	−7.3
ethyl	352.8	−0.3	346.0	−0.4	316.7	−8.0
$CH{=}CH_2$	353.3	0.2	346.5	0.2	314.5	−11.2
Ph	352.9	−0.1	346.2	−0.1	324.7	−1.0
F	354.4	1.4	347.4	1.0	330.3	4.6
CCH	354.0	0.9	347.0	0.6	335.4	9.7
Cl	354.6	1.5	347.4	1.1	333.4	7.7
COMe	354.3	1.3	347.8	1.4	362.0	36.3
Br	352.1	−0.9	347.5	1.1	333.8	8.1
COH	355.1	2.0	348.1	1.7	359.5	33.7
COOH	354.4	1.4	347.5	1.1	374.0	48.3
$CONH_2$	353.9	0.9	347.8	1.4	336.9	11.1
CF_3	355.3	2.3	348.0	1.7	333.7	8.0
CN	356.2	3.1	348.6	2.2	337.5	11.8
NO	356.4	3.3	348.6	2.2	330.9	5.2
NO_2	356.8	3.7	348.9	2.5	374.3	48.6
POH_2	354.7	1.6	348.1	1.8	356.8	31.0
SO_2H	360.3	7.3	352.6	6.3	369.8	44.1

This causes a higher BDE value. In the case of the away structure, due to instability of the parent molecule, the energy difference between the molecule and radical is lower and causes a drop in BDE. NBO analysis shows a strong intramolecular hydrogen bond in the toward structure (Figure S2 in Supporting Information), which is in agreement with the

Table 5. Experimental BDEs and ΔBDE of Substituted Phenols Compared to Calculated Values of Resveratrol[a]

substituent	exptl phenol BDE ($kJ\cdot mol^{-1}$)	BDE(E_0) ($kJ\cdot mol^{-1}$)	BDE(g) ($kJ\cdot mol^{-1}$)	exptl ΔBDE ($kJ\cdot mol^{-1}$)	ΔBDE(E_0) ($kJ\cdot mol^{-1}$)	ΔBDE(g) ($kJ\cdot mol^{-1}$)
none	376	376	346	0	0	0
			Para-Substituted Structures[b]			
p-NMe_2	336	369	335	−40	−7	−11
p-NH_2	323	338	310	−53	−38	−36
p-OH	341	358	330	−35	−18	−17
p-MeO	354	371	342	−22	−5	−5
p-*t*-Bu	371	372	343	−5	−4	−4
p-Me	371	369	340	−5	−7	−7
p-Ph	366	378	349	−10	3	3
p-Cl	377	380	351	1	5	4
p-Br	379	382	352	3	6	6
p-COMe	388	394	364	12	18	18
p-CF_3	398	397	367	22	22	21
p-CN	394	395	364	18	19	18
p-NO_2	396	401	371	20	26	25
			Meta-Substituted Structures[c]			
m-H	376	354	326	0	0	0
m-NH_2	368	355	326	−8	0	1
m-NMe_2	367	352	324	−9	−2	−2
m-Me	374	353	325	−2	−1	−1
m-OMe	377	345	316	1	−10	−10
m-Cl	384	356	327	8	2	2
m-COMe	384	366	337	8	12	11
m-CF_3	392	360	331	16	5	5
m-CN	393	362	333	17	7	7
m-NO_2	394	365	336	18	11	11

[a]Experimental phenol BDE values are from ref 36. BDE(g) stands for calculated gas-phase values, and BDE(E_0) indicates BDEs approximated from the total electronic energies. [b]Experimental values are compared to calculated BDEs and ΔBDEs of 3-OH in X_2 position for para-substituted structures. [c]Experimental values are compared to calculated BDEs and ΔBDEs of 4′-OH in X_3 position for meta-substituted structures.

above-mentioned statements. The NBO analysis shows that the interaction between the lone pair of O3 and the antibonding orbital of O1−H2 results in stabilization energy of 91.7 $kJ\cdot mol^{-1}$. This observation is in good agreement with HOMO and HOMO−1 energy difference between toward and away NO-substituted parents.

3.4. O−H Bond Dissociation Enthalpy Values for Molecules with Substituent in X_3 Position. X_3 is the meta position to 4′-OH group in the B-ring. The effect of EWG and EDG substituents on 3-, 5-, and 4′-OH BDE values is reported in Table 3. The highest 4′-OH BDE was found for CHO (341.5 $kJ\cdot mol^{-1}$) and the lowest value was found for OMe (316.2 $kJ\cdot mol^{-1}$). Thus, the difference between highest and lowest 4′OH BDE values is just 22.4 $kJ\cdot mol^{-1}$. In the ortho and para positions, both resonance and inductive effects affect BDEs considerably, while inductive effect in the meta position changes them to a significantly lower extent. Moreover, resonance and inductive effects are stronger in ortho position in comparison to para position. X_3 substitutions cause almost negligible effect on 3- and 5-OH BDEs, because these groups in A-ring are in meta positions to the rest of the molecule. It could be concluded that, if resonance exists between the two rings (A and B), the radical could be stabilized and BDE value is decreased, and vice versa. The computed 3- and 5-OH BDEs in Table 3 confirm the very weak effect of substituents in X_3 position. 3-OH BDEs lie within a 4.8 $kJ\cdot mol^{-1}$ range, while 5-OH BDEs are in a 5.8 $kJ\cdot mol^{-1}$ range. We can conclude that substitution in X_3 position is less effective.

3.5. O−H Bond Dissociation Enthalpy Values for Molecules with Substituent in X_4 Position. The X_4 position is ortho to the 4′-OH group, and substituents placed here are able to show a significant effect on 4′-OH BDE. The largest decrease in 4′-OH BDE, −45.5 $kJ\cdot mol^{-1}$, was found the for strongly electron-donating NHMe group (BDE = 279.2 $kJ\cdot mol^{-1}$). Low 4′-OH BDEs were found for NH_2 and OH groups, too. Highest 4′-OH BDEs were found for electron-withdrawing NO_2 and COOH groups. The difference between the highest and lowest 4′-OH BDE values is 95.1 $kJ\cdot mol^{-1}$. X_4 substitution has a weak effect on 3- and 5-OH BDE values (see Table 4) because X_4 is in meta position to the rest of the molecule. 3- and 5-OH BDEs lie within 13.2 and 14.1 $kJ\cdot mol^{-1}$ ranges.

Data compiled in Tables 1−4 show that B-ring is of greater importance since the 4′-OH group is in para position to the rest of the molecule and the formed radical can be resonance-stabilized. X_4 is the most suitable position in *trans*-resveratrol from the BDE point of view: the lowest BDEs were found for electron-donating substituents in this position. In organic chemistry, it is generally accepted that electron-withdrawing substituents stabilize the parent molecule and destabilize formed radicals, which results in increased BDE. Electron-donating groups have an opposite effect and their presence leads to a decrease in BDE.

3.5.1. Differences in Bond Dissociation Enthalpies between Toward and Away Conformations for Substituents in X_4 Position. The differences in BDEs between toward and away conformations demonstrate the importance of intramolecular hydrogen bonding on parent molecules and formed radical species stability. For the vast majority of studied structures, the isomer with the hydrogen pointing toward the

Table 6. Second-Order Perturbation Energies, Hydrogen-Bond Lengths, Distance between Heavy Atoms,[a] and Hydrogen-Bond Angles

substitution	NBO donor (lone pair)	NBO acceptor (antibonding orbital)	energy (kJ·mol^{-1})	R(H···A) (Å)	R(D—H) (Å)	R(D---A) (Å)	D—H···A (deg)
NO_2	O4	O2−H4	47.9	1.662	0.988	2.650	145.7
NO_2	O5	O1−H3	47.2	1.665	0.987	2.652	145.8
COOH	O4	O2−H4	34.9	1.704	0.987	2.691	147.3
COOH	O5	O1−H3	19.7	1.790	0.971	2.761	142.4
COH	O4	O2−H4	43.2	1.685	0.992	2.677	148.8
$CONH_2$	O4	O2−H4	40.0	1.675	0.991	2.666	148.4
NO	O4	O1−H3	57.2	1.656	0.999	2.655	148.0
NH_2	N1	O1−H3	12.0	2.051	0.980	3.031	121.5
NHMe	N1	O1−H3	10.6	2.056	0.980	3.036	121.0
NMe_2	N1	O1−H3	13.1	2.011	0.983	2.994	123.0
POH_2	O4	O1−H3	35.5	1.727	0.992	2.719	156.5
SO_2H	O4	O2−H4	17.8	1.799	0.978	2.777	149.6
SO_2H	O5	O1−H3	17.8	1.809	0.978	2.787	149.4
NO_2-subst 3-ArO$^•$	O5	O1−H3	79.0	1.558	1.009	2.567	148.6
NO_2-subst 5-ArO$^•$	O4	O2−H3	79.3	1.558	1.009	2.567	148.6
$CONH_2$-subst 5-ArO$^•$	O4	O2−H3	81.8	1.542	1.020	2.562	152.0
$CONH_2$-subst 5-ArO$^•$	O1	N1−H12	15.4	1.900	1.017	2.917	133.6
$CONH_2$-subst 3-ArO$^•$	N1	O1−H3	19.7	1.959	0.979	2.938	139.0
COOH-subst 5-ArO$^•$	O4	O2−H3	54.9	1.616	1.001	2.617	148.8
COOH-subst 3-ArO$^•$	O5	O1−H3	30.1	1.709	0.978	2.687	142.7
POH_2-subst 3ArO$^•$	O4	O1−H3	42.3	1.693	1.001	2.694	156.0
SO_2H-subst 5-ArO$^•$	O5	O1−H3	31.0	1.739	0.989	2.728	150.1
SO_2H-subst 3-ArO$^•$	O4	O2−H3	31.6	1.736	0.989	2.725	150.2

[a]D and A = O or N.

substituent is found to be energetically favored. However, the results show that the most stable parent conformer for alkyl (Me, ethyl, *t*-Bu) and NH_2 groups is the away one. BDE differences between toward and away conformations for studied substituents are in the range 0.0−45 kJ·mol^{-1} (see Table S1 in Supporting Information). In the case of one oxygen from NO_2 group, a strong hydrogen bond with OH group is formed, increasing the energy difference to 45.6 kJ·mol^{-1}. For OMe substituent, the toward conformer is more stable due to the hydrogen-bond presence, whereas in away conformer, OMe group has to be twisted out of plane and a hydrogen bond cannot form. In the case of CF_3, the nonbonding electron pair of halogen forms a hydrogen bond with the OH-group hydrogen in the toward isomer. BDE difference between the away and toward isomers is 28.4 kJ·mol^{-1} in favor of the toward structure. For NMe_2 group, in the two conformers, the substituent rotates out of the plane due to repulsion between the methyl group and the phenolic oxygen. Hydrogen bond in the toward structure can be formed between the nonbonding electron pair of N atom and the OH group, while for the away conformer it is impossible. BDE for the toward isomer is higher by 21.4 kJ·mol^{-1}. In the case of NHMe group, the toward isomer is again more stable than the away one, and the difference in BDEs reached 17.8 kJ·mol^{-1}.

3.6. Comparison of Computed and Experimental Bond Dissociation Enthalpies. Since there are no experimental BDE data for substituted *trans*-resveratrols, the calculated BDEs have been compared with those of substituted phenols (Table 5), as has been done elsewhere.[35] In this table, BDE(g) stands for calculated gas-phase values and BDE(E_0) for BDEs approximated from the total electronic energies. Interestingly, not only is there good agreement between the calculated BDE values and experimental ones,[36] but trends in BDE changes are also similar for various substituted groups.

3.7. Analysis of Intramolecular Hydrogen Bonds in X_1 Position. It should be mentioned that the energy ranges for various types of H-bonds are different, and they have been often discussed in the literature and review articles on hydrogen bonding. For example, Emsley[37] has separated hydrogen bonds into two categories: weak or normal hydrogen bonds, and strong or very strong hydrogen bonds. The normal hydrogen bonds are regarded as those with strengths of about 12−20 kJ·mol^{-1} and generally less than 50 kJ·mol^{-1}. Strong hydrogen bonds may have energies larger than 50 kJ·mol^{-1}. Alkorta et al.[38] have established another classification of hydrogen bonds: namely, interaction energies up to 20 kJ·mol^{-1} have been considered as weak, those with energies between 20 and 42 kJ·mol^{-1} have been defined as medium, while energy values exceeding 42 kJ·mol^{-1} have been assumed as strong or very strong hydrogen bonds. Hence, a compromise between different classifications of energy ranges for different H-bond types was given by Kaplan.[39] He distinguishes weak H-bonds as those for which the range is 2−16 kJ·mol^{-1}. For moderate H-bonds these energies are about 16−62 kJ·mol^{-1}, with values of 62−250 kJ·mol^{-1} for strong hydrogen bonds. There is no restricted border between H-bonds and covalent bonds as discussed in the literature from time to time.[40] The nature of the intramolecular hydrogen bonds has been analyzed within the framework of the NBO procedure. Results of the NBO analysis of second-order perturbation energies corresponding to hydrogen-bonding interactions are variously interpreted. NBO results for some parent molecules and radicals from Table 6 allow us to make the following comments. In the case of $CONH_2$-substituted 5-ArO$^•$, there are two different intramolecular hydrogen-bonding interactions, as can be seen in

Table 6. The strong hydrogen bond with stabilization energy of 81.8 kJ·mol^{-1} is caused by interaction between the lone pair of O4 and the antibonding orbital of O2−H3 (see Figure 4), whereas the interaction of lone pair of O1 with the antibonding orbital of N1−H12 yields 15.4 kJ·mol^{-1}. However, in $CONH_2$-substituted 3-ArO$^•$, there is just one weak hydrogen bond between the lone pair of N1 and the antibonding orbital of O1−H3, with stabilization energy about 19.7 kJ·mol^{-1}, and the strong hydrogen bonding is canceled. Therefore, the $CONH_2$-substituted 5-ArO$^•$ radical is more stable than the $CONH_2$-substituted 3-ArO$^•$ one, which causes a BDE difference of 80.1 kJ·mol^{-1}. In the case of NO_2, two hydrogen bonds are formed simultaneously between oxygens of NO_2 group and 3- and 5-OH hydroxyl groups. Oxygens in NO_2 act as a proton acceptor and OH groups as proton donors. The stabilization energies stemming from the interaction between the lone pair of O4 and the antibonding orbital of O2−H4 and the interaction between the lone pair of O5 and the antibonding orbital of O1−H3 (see Figure 3) are 47.9 and 47.2 kJ·mol^{-1}, respectively. The strong and short hydrogen bonds are also found in NO_2-substituted 3- and 5-ArO$^•$ radicals with 79.0 and 79.3 kJ·mol^{-1} stabilization energies, respectively. In the case of the COOH group, two hydrogen bonds are formed with different stabilization energies. The proton acceptor role of carbonyl oxygen is better than that of oxygen from a hydroxyl group. Such fact favors the former's hydrogen bond with strength of ca. 15 kJ·mol^{-1}. For the radicals, the COOH-substituted 3-ArO$^•$ hydrogen-bonding interaction energy was lower by 20.8 kJ·mol^{-1} than that for COOH-substituted 5-ArO$^•$, and there is good agreement between the 3- and 5-OH BDE values and aforementioned stability. In the case of POH_2-substituted 3-ArO$^•$, the stabilization energy stemming from the interaction between the lone pair of O4 and the antibonding orbital of O1−H3 is 42.3 kJ·mol^{-1}.

The results of NBO analysis also confirm the differences in BDEs in the presence of other substitutions such as POH_2, NO_2, etc. (see Table 6). It can be concluded that certain hydrogen bonds have significant consequence on BDEs: the strong hydrogen bonds formed in radical structures induce significant decreases in BDEs.

Several geometrical parameters, such as the distance between the heavy atoms involved in hydrogen bonding, bond angle, hydrogen-bond length, and proton−donor bond length, are reported in Table 6. Computed data confirm that the bond angle and hydrogen interaction energy are mutually dependent: the lower the deviation from 180°, the stronger the interaction energy. There is a good correlation between hydrogen-bond length, distance between the heavy atoms, and bond angle with the energy.

We can conclude that the symmetric groups such as NO_2 and SO_2H have identical 3- and 5-OH BDE values due to similar geometry conditions. As vivid evidence, when NO_2-substituted 3- and 5-ArO$^•$ radicals as well as SO_2H-substituted 3- and 5-ArO$^•$ radicals with identical bond lengths and bond angles are considered, the difference between the interaction energies reached negligible values of 0.3 kJ·mol^{-1} for NO_2-substituted 3- and 5-ArO$^•$ and 0.6 kJ·mol^{-1} for SO_2H-substituted 3- and 5-ArO$^•$.

There is a good correlation between the hydrogen-bond energy and the geometry parameters such as proton−donor bond length, hydrogen-bond length, heavy atom distance, and hydrogen-bond angle. The strongest hydrogen bond, with 81.8 kJ·mol^{-1} stabilization energy, in $CONH_2$-substituted 5ArO$^•$ results from elongation of the proton−donor bond (1.020 Å), shortening of the hydrogen bond (1.542 Å), small distance between the heavy atoms (2.562 Å), and linearity of the corresponding bond angle (152.0°).

On the other hand, for NHMe with a low proton−donor bond length (0.980 Å), the longest hydrogen bond (2.056 Å), distance between the heavy atoms of 3.036 Å, and the highest deviation from linearity (121.0°), the computed energy is only 10.6 kJ·mol^{-1}. Calculated hydrogen-bond energies were plotted against proton−donor bond length, hydrogen-bond length, heavy atom distance, and hydrogen-bond angle (Figures S3−S5 in Supporting Information). With increased hydrogen-bond energy, elongation of the proton−donor bond, shortening of the hydrogen-bond length, shortening of heavy atom distance, and linearity of the hydrogen bond in the molecule were found. However, the linearity of $E_{HB} = f(\text{angle})$ dependence is very poor, while the correlation coefficients of $E_{HB} = f(\text{D—H})$, $E_{HB} = f(\text{A}\cdots\text{H})$, and $E_{HB} = f(\text{D---A})$ dependences reached 0.92, 0.88, and 0.85, respectively. The linearity of $R(\text{D—H})$ was also examined against $R(\text{D---A})$, and the plotted results show very good correlation between these parameters with 0.997 correlation coefficient (Figure S6 in Supporting Information).

Analogous results and trends were also observed for substituents placed in X_4 position, which is ortho to the 4′-OH group.

3.8. Dependence of 3-OH BDEs on Hammett Constants for Groups in X_2 Position. The Hammett equation (and its extended forms) has been one of the most commonly used ways to study and explain organic reactions and their mechanisms. Hansch et al.[41] presented Hammett constants σ_m (for substituents in meta position) and σ_p (for substituents in para position) from the ionization of organic acids in solutions. These substituent effect descriptors can successfully predict equilibrium and rate constants for a large variety of reactions.[41,42] Hammett constants also correlate very well with the changes in BDE in the case of anilines, phenols, or thiophenols.[32,34,36,43] Pratt and DiLabio and co-workers[44,45,43] found linear dependence between BDE values of para-substituted phenols, 6-substituted 3-pyridinols, and 2-substituted 5-pyrimidinols and Hammett constants σ_p. Klein and Lukeš[46,35] also found linear dependence between BDE values of para- and meta-substituted phenols and Hammett constants σ_p and σ_m. In the present work, BDE values for 22 para-substituted *trans*-resveratrols were plotted against Hammett constants (Figure S7 in Supporting Information). Equation 3 obtained from the linear regression is as follows:

$$\text{BDE} = 35.14\sigma_p + 346.8 \tag{3}$$

where BDE is given in kilojoules per mole. It is worth mentioning that in the case of NMe_2 group, published σ_p values lie in a very wide range from −0.24 to −0.83.[42,47] Moreover, in the case of NMe_2 and NO groups, it was found that there exists exceptionally large charge transfer between NMe_2 and NO substituents and OH group, which is the reaction site in studied species in comparison to the vast majority of substituents.[48] If the points for NMe_2 and NO were omitted, the correlation coefficient value reached 0.93. 3-OH BDE values correlate with Hammett constants σ_p relatively well, if we consider the large number of substituents. We can conclude that the employed computational method describes the expected linear BDE versus Hammett constant dependence satisfactorily.

3.9. Correlations of 3-OH Bond Dissociation Enthalpies with Phenolic C–O and O–H Bond Lengths for

Groups in X_2 Position. Klein and Lukeš[35] found that BDE and ΔBDE values of para- and meta-substituted phenols are linearly dependent on the calculated length of the phenolic C−O bond and ΔR(C−O) = [R(C−O, molecule) − R(C−O, radical)]. In the present work, ΔR(C−O) has been investigated to analyze the effect of resonance on the stability of the formed radical. Satisfactory correlation between ΔR(C−O) and O−H bond lengths with BDE values was found. The values of C−O, ΔR(C−O), and O−H bond lengths corresponding to non-substituted resveratrol and structures with substituents in para (X_2) position to 3-OH group are tabulated in Table S2 in Supporting Information. The 3-OH BDE values are plotted against ΔR(C−O) and R(O−H) in Figures S8 and S9 (in Supporting Information), respectively. Equations 4 and 5 obtained from the linear regression are as follows:

$$\text{BDE} = -2522[\Delta R(\text{C}-\text{O})] + 621.9 \quad (4)$$

$$\text{BDE} = 53\,397[R(\text{O}-\text{H})] - 51\,244.0 \quad (5)$$

where BDE is given in kilojoules per mole and ΔR(C−O) and R(O−H) are given in angstroms. The correlation coefficients of these two dependences are 0.98 and 0.90, respectively.

Thus, it can be concluded that ΔR(C−O) correlates with BDE satisfactorily for all substituents, if the point for NO is omitted. For NO group, ΔR(C−O) is significantly larger in comparison to all other values. While all ΔR(C−O) are decreasing with the increase in electron-withdrawing effect of substituents, for NO group, ΔR(C−O) is considerably larger than values for the strongest electron-donating groups (NMe_2, NH_2). Obtained data show that the presence of NO group causes a large charge transfer with the O atom of the resulting radical after H atom abstraction. It has been found that the resulting OCCN dihedral angle is almost 180° and the NO moiety resides in the adjacent ring's plane. Due to the above-mentioned charge transfer, CN bond length is considerably decreased. These observations justify NO "misbehavior" as an electron-withdrawing group relative to others and thereby the need to omit it from the regression analysis. The obtained correlation is exceptionally good, if we consider the large number of studied groups. Therefore, the shortening of C−O bond length is a more suitable descriptor of substituent effect than Hammett constants, and it may be applied as a criterion of a resonance effect of substitutions with the benzene ring since it is related to BDE (one of the antioxidant potency descriptors). The computed C−O and O−H bond lengths related to 3-OH group for the structures substituted in X_2 position were also plotted against Hammett constants σ_p (Figures S10 and S11 in Supporting Information). With the increase in Hammett constant, elongation of the O−H bond and shortening of the C−O bond in the molecule were found. However, the linearity of R(C−O) = $f(\sigma_p)$ dependence is very poor, and the correlation coefficient of R(O−H) = $f(\sigma_p)$ dependence reached only 0.82. In the case of ΔR(C−O) = $f(\sigma_p)$, individual points are less scattered along the regression line and the correlation coefficient reached a value of 0.90.

Phenolic C−O bond length shortening, ΔR(C−O), may be also applied as a criterion of proposed compound suitability, since it correlates with BDE well.

For 5-OH group, which is located in ortho position to X_2, no dependence of BDEs on C−O, ΔR(C−O), and O−H bond lengths was apparent, due to the steric effects and/or formation of intramolecular hydrogen bonds that strongly affect 5-OH BDE values.

3.10. Correlation of Calculated 3-OH Bond Dissociation Enthalpies with Partial Charge on Phenoxy Oxygen, q(O), for Substituents in X_2 Position. Klein and Lukeš[46,35] showed that BDE and ΔBDE values of para- and meta-substituted phenols are linearly dependent on calculated partial charge, q(O), on oxygen atom in phenoxy radical formed after hydrogen atom abstraction. Current results show that there exists a correlation between BDEs and q(O) in corresponding radicals. In the presence of electron-donating groups, partial charge on oxygen becomes more negative. The computed 3-OH BDEs for X_2-substituted structures are plotted against q(O) in Figure S12 in Supporting Information. The correlation coefficient for 23 substituents reached 0.99; the equation obtained from linear regression is as follows:

$$\text{BDE} = 614.4q(\text{O}) + 658.6 \quad (6)$$

where BDE is given in kilojoules per mole.

We found that the calculated BDEs grow with increasing q(O). It can be concluded that the partial charge on oxygen atom in 3-ArO$^\bullet$ radical is another suitable substituent effect descriptor.

The relationship between q(O) and Hammett constants has been examined, too. The increase in Hammett constant is accompanied by an increase in q(O) (Figure S13 in Supporting Information). The equation obtained from linear regression is as follows:

$$q(\text{O}) = 0.053\sigma_p - 0.506 \quad (7)$$

with a correlation coefficient value of 0.95.

3.11. Correlations of 4′-OH Bond Dissociation Enthalpies with Hammett Constants and Phenolic C−O and O−H Bond Lengths for Substituents in X_3 Position. The computed 4′-OH BDEs for substituents in X_3 position have been plotted against Hammett σ_m constants; however, no linear trend was found (the correlation coefficient was about 0.62). The C−O, ΔR(C−O), and O−H bond lengths for these molecules are tabulated in Table S3 (Supporting Information). The 4′-OH BDEs plotted against ΔR(C−O) and R(O−H) are shown in Figures S14 and S15 in Supporting Information. The following equations were obtained from the linear regression:

$$\text{BDE} = -3359[\Delta R(\text{C}-\text{O})] + 715.7 \quad (8)$$

$$\text{BDE} = 30\,177[R(\text{O}-\text{H})] - 28\,835 \quad (9)$$

where BDE is given in kilojoules per mole and ΔR(C−O) and R(O−H) are given in angstroms, with correlation coefficients 0.94 (eq 8) and 0.90 (eq 9). Thus, ΔR(C−O) and R(O−H) are better substituent effect descriptors than Hammett constants.

Finally, we should note that BDEs were also correlated with available σ^+ and $\sigma^\bullet$ constants.[41,49−51] However, the linearity of obtained dependences was worse in comparison with Hammett σ constants.

4. CONCLUSIONS

Electron-donating and electron-withdrawing groups have been placed in four available positions of *trans*-resveratrol, and their effects on the three O−H BDEs were investigated. The B-ring is more important than A-ring from the BDE point of view, because the radical structure formed after H-atom abstraction from the 4′-OH group can be stabilized by the resonance between the two rings. To some extent, this OH group is also affected by the substitutions in A-ring. Moreover, for strong electron-donating groups placed in X_4 position (the ortho position to 4′-OH), the lowest BDEs were obtained. Computed BDEs show that the *trans*-resveratrol derivatives with suitable spin density distribution have the lowest BDEs. The results show that intramolecular hydrogen bonds and steric effects are able to considerably stabilize the parents and radicals. When substituents and neighboring OH groups are oriented in such a way that intramolecular hydrogen-bond formation is possible, the BDE values are shifted substantially. NBO analysis results also confirmed the intramolecular hydrogen-bond stabilization. The results show that there are linear correlations between BDEs and ΔR(C−O), R(O−H), and the charge on phenoxy radical oxygen, q(O). 3-OH BDE values for substituents in X_2 position also correlate with Hammett constants well. In the case of studied O−H BDEs, ΔR(C−O) and the charge on phenoxy radical oxygen q(O) may be considered better substituent effect descriptors than Hammett constants.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Three tables and 15 figures showing calculated BDEs of 4′-ArO−H in X_4 position and BDE differences between conformers; geometry parameters, partial charge on phenoxy radical oxygen, and Hammett constants related to 3-OH in X_2 position and 4′-ArO−H in X_3 position; hydrogen-bonding of POH_2- and NH_2-substituted parent related to X_1 position; hydrogen-bonding of toward NO-substituted parent related to X_2 position; and hydrogen-bond energies, Hammett constants, and geometry parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*(M.Z.) E-mail m-zahedi@sbu.ac.ir, phone ++982122431661, fax ++982122431661; (E.K.) e-mail erik.klein@stuba.sk, phone ++421259325535, fax ++421252493198.
*

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Professor S. W. Ng for providing us the software (G09W suite of programs) and hardware (machine time) facilities and also making available the opportunity to access some new features of Gaussian products. We acknowledge financial support from the Research Council of Shahid Beheshti University. Also, technical support of the Chemistry Computational Center at Shahid Beheshti University is gratefully acknowledged.

■ ABBREVIATIONS

DFT, density functional theory; ZPE, zero point energy; BDE, bond dissociation enthalpy; HAT, hydrogen atom transfer; B3LYP, (Becke three-parameter (exchange), Lee, Yang, and Parr (correlation; density functional theory); EDG, electron-donating group; EWG, electron-withdrawing group; HOMO, highest occupied molecular orbital; NBO, natural bond orbital; SOMO, singly occupied molecular orbital

■ REFERENCES

(1) Halliwell, B.; Aeschbach, R.; Löliger, J.; Aruoma, O. *Food Chem. Toxicol.* **1995**, *33*, 601−617.
(2) Saiko, P.; Szakmary, A.; Jaeger, W.; Szekeres, T. *Mutat. Res., Rev. Mutat. Res.* **2008**, *658*, 68−94.
(3) Baur, J. A.; Sinclair, D. A. *Nat. Rev. Drug Discovery* **2006**, *5*, 493−506.
(4) Frankel, E.; Waterhouse, A.; Kinsella, J. E. *Lancet* **1993**, *341*, 1103−1104.
(5) Abou-Zeid, L. A.; El-Mowafy, A. M. *J. Mol. Struct.: THEOCHEM* **2002**, *593*, 39−48.
(6) Wang, M.; Li, J.; Rangarajan, M.; Shao, Y.; LaVoie, E. J.; Huang, T.; Ho, C. *J. Agric. Food. Chem.* **1998**, *46*, 4869−4873.
(7) Fang, J.-G.; Lu, M.; Chen, Z.-H.; Zhu, H.-H.; Li, Y.; Yang, L.; Wu, L.-M.; Liu, Z.-L. *Chem.—Eur. J.* **2002**, *8*, 4191−4198.
(8) Stivala, L. A. S. M.; Carafoli, F.; Perucca, P.; Bianchi, L.; Maga, G. F. L.; Pagnoni, U. M.; Albini, A.; Prosperi, A.; Vannini, V. *J. Biol. Chem.* **2001**, *276*, 22586−22594.
(9) Vafiadis, A. P.; Bakalbassis, E. G. *Chem. Phys.* **2005**, *316*, 195−204.
(10) Navarrete, M.; Rangel, C.; Corchado, J. C.; Espinosa-García, J. *J. Phys. Chem. A* **2005**, *109*, 4777−4784.
(11) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173−1183.
(12) Musialik, M.; Litwinienko, G. *Org. Lett.* **2005**, *7*, 4951−4954.
(13) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2005**, *70*, 8982−8990.
(14) Burton, G. W.; Doba, T.; Gabe, E.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053−7065.
(15) Zhang, H. Y. *J. Am. Oil Chem. Soc.* **1998**, *75*, 1705−1709.
(16) Mohajeri, A.; Asemani, S. S. *J. Mol. Struct.* **2009**, *930* (1), 15−20.
(17) Zhu, Q.; Zhang, X. M.; Fry, A. J. *Polym. Degrad. Stab.* **1997**, *57*, 43−50.
(18) Berry, R. J.; Wilson, A. L.; Schwartz, M. *J. Mol. Struct.: THEOCHEM* **2000**, *496*, 121−129.
(19) Queiroz, A. N.; Gomes, B. A. Q.; Moraes, W. M., Jr.; Borges, R. S. *Eur. J. Med. Chem.* **2009**, *44*, 1644−1649.
(20) Mikulski, D.; Gorniak, R.; Molski, M. *Eur. J. Med. Chem.* **2010**, *45*, 1015−1027.
(21) Chen, J.; McAllister, M. A.; Lee, J. K.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 4611−4619.
(22) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; Freeman: San Francisco, CA, 1960.
(23) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.
(24) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(25) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(26) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100.
(27) Davidson, E. R.; Feller, D. *Chem. Rev.* **1986**, *86*, 681−696.
(28) Radom, L.; Schleyer, P. R.; Pople, J. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.1*; Gaussian, Inc., Wallingford CT, 2009.
(30) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.

(31) Weinhold, F.; Carpenter, J. In *The Structure of Small Molecules and Ions*; Naaman, R., Vager, Z., Eds.; Plenum: New York, 1988; pp 227−236.
(32) Chandra, A. K.; Uchimaru, T. *Int. J. Mol. Sci.* **2002**, *3*, 407−422.
(33) Zhang, H.-Y.; Ji, H.-F. *J. Mol. Struct.: THEOCHEM* **2003**, *663*, 167−174.
(34) Bordwell, F. G.; Zhang, X.-M.; Satish, A. V.; Cheng, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 6605−6610.
(35) Klein, E.; Lukeš, V. *J. Mol. Struct.: THEOCHEM* **2006**, *767*, 43−50.
(36) Bordwell, F. G.; Cheng, J. *J. Am. Chem. Soc.* **1991**, *113*, 1736−1743.
(37) Emsley, J. *Chem. Soc. Rev.* **1980**, *9*, 91−124.
(38) Alkorta, I.; Rozas, I.; Elguero, J. *Chem. Soc. Rev.* **1998**, *27*, 163−170.
(39) Kaplan, I. G. *Theory of Molecular Interactions* ; Studies in Physical and Theoretical Chemistry, Vol. *42*; Elsevier: Amsterdam, 1986.
(40) Desiraju, G. R. *Acc. Chem. Res.* **2002**, *35*, 565−573.
(41) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(42) Krygowski, T. M.; Stepień, B. T. *Chem. Rev.* **2005**, *105*, 3482−3512.
(43) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334−340.
(44) Pratt, D. A.; DiLabio, G. A.; Brigati, G.; Pedulli, G. F.; Valgimigli, L. *J. Am. Chem. Soc.* **2001**, *123*, 4625−4626.
(45) DiLabio, G. A.; Pratt, D. A.; LoFaro, A. D.; Wright, J. S. *J. Phys. Chem. A* **1999**, *103* (11), 1653−1661.
(46) Klein, E.; Lukeš, V. *Chem. Phys.* **2006**, *330* (3), 515−525.
(47) Pytela, O. *Collect. Czech. Chem. Commun.* **1994**, *59*, 381−390.
(48) Krygowski, T. M.; Sadlej-Sosnowska, N. *Struct. Chem.* **2011**, *22*, 17−22.
(49) Creary, X. *Acc. Chem. Res.* **2006**, *39*, 761−771.
(50) Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S. *J. Org. Chem.* **1987**, *52*, 3254−3263.
(51) Creary, X.; Engel, P. S.; Kavaluskas, N.; Pan, L.; Wolf, A. *J. Org. Chem.* **1999**, *64*, 5634−5643.