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Theoretical Investigation on Antioxidant Activity of Bromophenols from the Marine Red Alga *Rhodomela confervoides*: H-Atom vs Electron Transfer Mechanism

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Supporting Information

ABSTRACT: Bromophenols are known as antioxidant radical scavengers for some biomolecules such as those in marine red alga. Full understanding of the role played by bromophenols requires detailed knowledge of the radical scavenging activities in probable pathways, a focus of ongoing research. To gain detailed insight into two suggested pathways, H-atom transfer and electron transfer, theoretical studies employing first principle quantum mechanical calculations have been carried out on selected bromophenols. Detailed investigation of the aforementioned routes revealed that upon H-atom abstraction or the electron transfer process, bromophenols cause an increase in radical species in which the unpaired electron appears to be delocalized as much as possible over the whole aromatic ring, especially in the bromine substituent. The O−H bond dissociation energies (BDEs) and ionization potential energies (IPs) are reported at the B3LYP level of theory, providing the first complete series of BDEs and IPs for bromophenols. The observations are compared to those of other antioxidants for which BDEs and IPs have been previously obtained.

KEYWORDS: *bromophenol, radical scavenging activity, bond dissociation energy, DFT study, Rhodomela confervoides*

INTRODUCTION

Antioxidants can prevent biomolecules (such as proteins, nucleic acids, polyunsaturated lipids, and sugars) from undergoing oxidative damage through free radical-mediated reactions in low concentration.[1,2] Synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and tertiary butyl hydroquinone (TBHQ) are widely used to prevent the oxidation of oils and fats and extend the shelf life of lipid-containing foods. In recent years, their use in foods has suffered severe criticism regarding, for example, their carcinogenicity and toxicity.[3,4] These criticisms have led to an increasing interest in the search for naturally occurring antioxidants.

Interest in phenolic foods has grown greatly because of their antioxidant and free radical scavenging ability and potential health benefits. Attention has increased mostly toward finding naturally occurring antioxidants for use in foods or medicinal materials to replace synthetic antioxidants that, in some cases, have been reported to be carcinogenic.[3] The major antioxidant components of these common foods are the phenolic compounds. Their antioxidant activity seems to be related to their molecular structure, more precisely to the presence and number of hydroxyl groups, and to conjugation and resonance effects. Natural and synthetic phenolic compounds are the most abundant and widely used antioxidants by scavenging lipid radicals. It is believed that phenols may act as both radical scavengers and metal chelators related to their molecular structure and function through conjugation and resonance effects.[5]

In recent years, the continuous discovery of natural products with antioxidant activities from marine algae has attracted considerable attention due to the concerns about the toxic and carcinogenic effects of synthetic antioxidants.[6,7] Marine red algae from the *Rhodomelaceae* family (order Ceramiales) have proven to be rich sources of structurally novel and biologically active secondary metabolites.[8−18] Some of the isolated compounds from this family display significant radical scavenging activities,[8−12] such as α-glucosidase inhibition,[13] feeding deterrence,[14] and anti-inflammation.[15] Recently Li and co-workers identified and isolated 19 naturally occurring bromophenols, comprising 6 new and 13 known structures, from the methanolic extract of the marine red alga *Rhodomela confervoides*.[17,18] Each compound was evaluated for free radical scavenging activity against DPPH (α,α-diphenyl-β-dipicrylhydrazyl) and ABTS [2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt] radicals. Most of them exhibited potent activities slightly stronger than that of the positive control butylated hydroxytoluene (BHT) and ascorbic acid. The results of this study suggest that *R. confervoides* is an excellent source of natural antioxidants, and inclusion of these antioxidant-rich algal components would likely help to prevent the oxidative deterioration of food.

Two main mechanisms by which antioxidants can play their protective role have been proposed.[19] In the first mechanism (HAT: H-atom transfer), the free radical removes a hydrogen atom from the antioxidant (Ar−OH) to become a radical itself:

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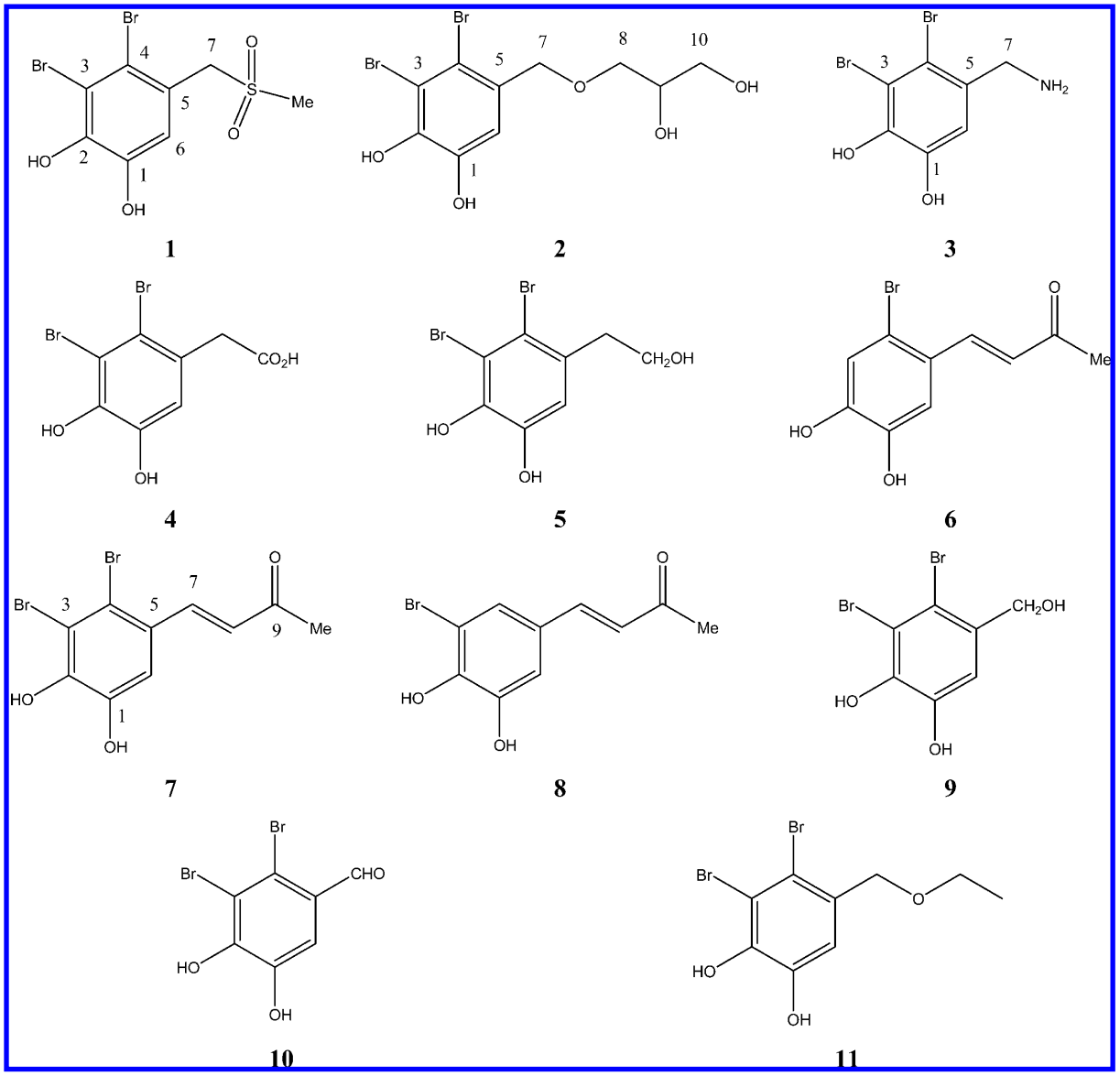

Figure 1. Chemical structures and numbering scheme for investigated bromophenols.

$$R^{\bullet} + Ar{-}OH \rightarrow RH + ArO^{\bullet}$$

In this mechanism, the bond dissociation energy (BDE) of the O−H bond is an important parameter in evaluating the antioxidant action, because the weaker the OH bond, the easier the H abstraction. The BDE thus influences the effectiveness of the H-atom transfer reaction from the antioxidant molecule to the reactive radical intermediates such as hydroxyl, alkoxyl, peroxyl, and hydroperoxyl radicals formed during degradation reactions.[20] Generally, electron-donating groups at the ortho- and para-positions relative to the phenolic O−H can weaken the O−H bond and thus enhance the reactivity of the O−H group.[21−27] This strategy has been proven to be the primary guideline for rational design of the novel and more effective antioxidants. In the second mechanism (ET: electron transfer), the antioxidant can give an electron to the free radical, becoming a radical cation itself:

$$R^{\bullet} + Ar{-}OH \rightarrow R^{-} + Ar{-}OH^{\bullet+}$$

The rapid development of quantum chemistry and computation methodologies allows the reliable calculation of BDEs and IPs with accuracy equivalent to or greater than those obtained from experiments. Therefore, theoretical calculations could be used as a cogent tool for predicting the relationship between the structure and activity of a compound and also for designing novel potential antioxidants. Up to now, there have been several successful examples of rational interpretation of structure−activity relationships of some natural antioxidants[28−30] and design of novel antioxidants[19,25−27,31,32] using the powerful and economical quantum chemical methods.

Quantum thermochemical calculation of the O−H bond dissociation enthalpy (BDE) is known to be successful for characterizing antioxidant activity for a large number of antioxidants.[19] There are many experimental methods developed for the determination of the O−H bond dissociation enthalpy (BDE) of phenols. Quantum calculations of the bond dissociation enthalpies can reproduce experimental BDEs to a good chemical accuracy. [19] Substituent additivity scales based on the bond dissociation enthalpies relative to phenol (ΔBDE) show that electron-donating groups introduced on the phenol ring enhance the antioxidant activity.

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Table 1. B3LYP/6-311++G (d,p) Absolute Energies (E in au), Relative Energies (ΔE in kcal/mol), Dipole Moments (μ in Debye), Bond Dissociation Energies (BDE in kcal/mol), Ionization Potentials (IP in kcal/mol), ΔBDE (in kcal/mol), ΔIP (in kcal/mol), and IC_{50} (μM) for Selected Bromophenols

structure	E	ΔE	μ	BDE	ΔBDE[a]	IP	ΔIP[a]	IC_{50}[b]
1-*raH1*	−6156.401129	2.6	2.92	79.9	−1.7	183.3	−18.4	9.52 ± 0.04
1-*raH2*	−6156.405344	0.0	2.43	77.3	−4.3			
2-*raH1*	−5912.047849	7.1	2.74	84.7	3.1	180.2	−21.5	7.43 ± 0.10
2-*raH2*	−5912.059045	0.0	6.30	77.6	−4.0			
3-*raH1*	−5623.812074	7.4	4.92	84.2	2.6	178.4	−23.3	20.47 ± 0.07
3-*raH2*	−5623.823604	0.0	4.55	76.8	−4.8			
4-*raH1*	−5757.078821	6.5	2.49	84.6	3.0	184.4	−17.4	19.84 ± 0.06
4-*raH2*	−5757.088991	0.0	3.96	78.1	−3.5			
5-*raH1*	−5682.992904	6.7	2.50	83.8	2.2	180.8	−20.9	30.91 ± 0.12
5-*raH2*	−5683.003347	0.0	3.91	77.1	−4.5			
6-*raH1*	−3185.657703	10.6	2.48	85.0	3.4	179.4	−22.3	8.72 ± 0.05
6-*raH2*	−3185.674462	0.0	2.91	76.1	−5.5			
7-*raH1*	−5759.204777	8.7	1.95	85.4	3.8	181.0	−20.7	7.62 ± 0.01
7-*raH2*	−5759.218596	0.0	3.44	74.3	−7.2			
8-*raH1*	−3185.661812	10.2	1.19	86.3	4.7	181.9	−19.8	9.40 ± 0.05
8-*raH2*	−3185.677797	0.0	3.22	76.6	−4.9			
9-*raH1*	−5643.696818	7.2	4.27	84.6	3.0	180.5	−21.2	42.33 ± 0.25
9-*raH2*	−5643.708067	0.0	2.80	77.4	−4.2			
10-*raH1*	−5642.504677	5.1	2.16	85.8	4.2	199.9	−1.9	32.01 ± 0.12
10-*raH2*	−5642.512666	0.0	2.45	80.7	−0.9			
11-*raH1*	−5722.280447	7.4	3.48	84.5	2.9	177.8	−23.9	38.42 ± 0.23
11-*raH2*	−5722.291997	0.0	4.23	77.1	−4.5			

[a]Relative to phenol. BDE and IP values for phenol at the same level are 81.6 and 201.7 kcal/mol. [b]DPPH radical scavenging activities were extracted from ref 17. Each value is presented as the mean ± standard deviation (n = 3).

A detailed knowledge of BDE and/or IP values of the aforementioned compounds bearing different substituents, which may lead to various inhibitory effects, is fundamental to understanding their functional roles. The aim of this investigation is to rationalize the correlation between molecular/electronic structure and scavenging activity of some bromophenols (Figure 1) extracted from the marine red alga *Rhodomela confervoides*, on the basis of BDE and IP values, and to establish a relative trend of reactivity among the compounds analyzed. To differentiate the reactivity of radicals formed in these molecules, several most probable atomic sites are arbitrarily chosen to generate radicals. From the correlation between the experimental data and those calculations, the role of each OH group and the contribution of the two mechanisms (HAT or ET) are discussed. Theoretical analysis of model systems leads to a deeper understanding of the mechanism than can be obtained by experiment. In all cases, thermochemical as well as structural data obtained by theoretical calculations can provide deeper insights into the proposed reaction mechanism that is supported by condensed phase experiments. This work may also encourage synthetic organic chemists to prepare differently substituted bromophenols and study their chemical behavior.

COMPUTATIONAL METHODS

All geometries of parent molecules (Ar−OH) and their radicals or cation radicals (Ar−O$^{\bullet}$ and Ar−OH$^{\bullet+}$) were optimized, employing the DFT/B3LYP method and the 6-311++G(d,p) basis set[33,34] as implemented in the Spartan program.[35] Cartesian coordinates for all these structures are provided as Supporting Information. Harmonic vibrational frequencies were computed at the same level of theory for all structures to characterize their conformation as minima or saddle points and to evaluate the zero-point energy (ZPE) corrections. The unrestricted open-shell formalism was used for optimization of radical species. Stability of the wave function has been checked. The natural bond orbital (NBO) analysis by means of DFT with B3LYP/6-311++G(d,p) orbital basis sets was used to characterize the electronic structures of these compounds. In this context, a study of hyperconjugative interaction has been completed. Hyperconjugation may be considered as a stabilizing effect that arises from an overlap between an occupied orbital and another neighboring electron-deficient orbital, when these orbitals are properly oriented. This noncovalent bonding−antibonding interaction can be quantitatively described by the NBO approach that is expressed by the second-order perturbation interaction energy ($E^{(2)}$).[36−39] It can be deduced from the second-order perturbation approach:[27]

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$$

where q_i is the donor orbital occupancy, ε_i; ε_j are diagonal elements (orbital energies), and F (i,j) is the off-diagonal NBO Fock matrix element. For radicals, spin densities were computed at B3LYP/6-311++G(d,p) level of theory and plotted to examine the extent of delocalization of the unpaired electron within the molecular framework.

RESULTS AND DISCUSSION

Structures and Radical Stabilities in the H-Atom Mechanism. To differentiate the reactivity of radical formations at investigated bromophenols, several atomic sites of following molecules are arbitrarily chosen for generating radicals: 3,4-dibromo-5-(methylsulfonylmethyl)benzene-1,2-diol (compound **1**),[40] 3,4-dibromo-5-((2,3-dihydroxypropoxy)-methyl)benzene-1,2-diol (compound **2**),[40] 5-(aminomethyl)-3,4-dibromobenzene-1,2-diol (compound **3**),[40] 2-(2,3-dibromo-4,5-dihydroxyphenyl)acetic acid (compound **4**),[40] 3,4-dibromo-5-(2-hydroxyethyl)benzene-1,2-diol (compound **5**),[41] 4-(2-bromo-4,5-dihydroxyphenyl)but-3-en-2-one (compound **6**),[40]

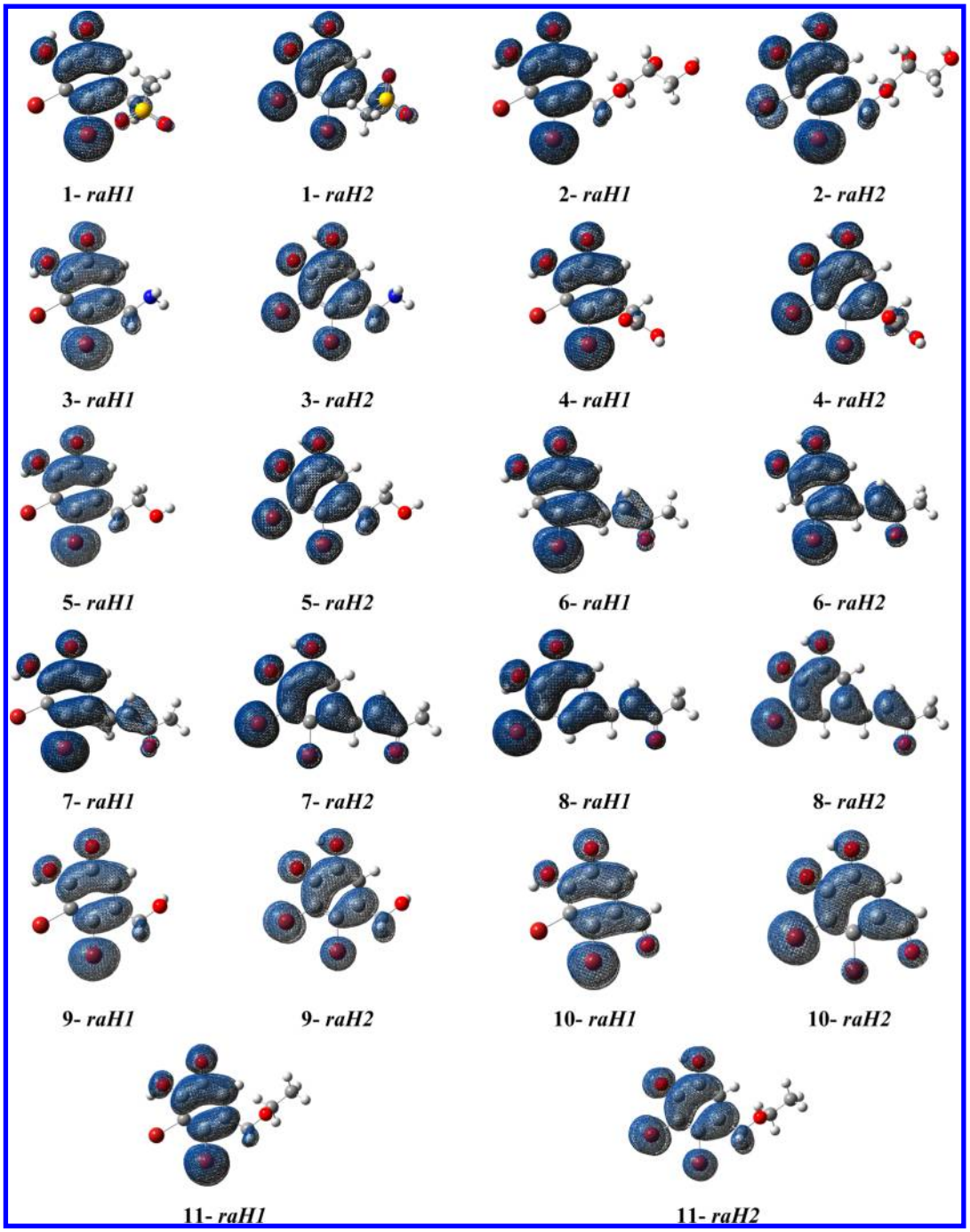

Figure 2. Plots of spin density for various hydrogen atom-abstracted radicals of selected bromophenols.

4-(2,3-dibromo-4,5-dihydroxyphenyl)but-3-en-2-one (compound **7**),[42] 4-(3-bromo-4,5-dihydroxyphenyl)but-3-en-2-one (compound **8**),[10] 3,4-dibromo-5-(hydroxymethyl)benzene-1,2-diol (compound **9**),[43] 2,3-dibromo-4,5-dihydroxybenzaldehyde (compound **10**),[44] and 3,4-dibromo-5-(ethoxymethyl)benzene-1,2-diol (compound **11**).[43]

By abstraction of a hydrogen atom from every aryl hydroxyl group presented in compounds **1**−**11**, two types of free radicals were found. For simplicity, ***raH1*** and ***raH2*** notations are adopted in this study to clarify geometries and energetic aspects of these radicals. These notations indicate that hydrogen atom abstraction in these molecules occurred through O1 and O2 atoms of the aromatic ring, respectively.

For an easier characterization of radical stability and geometrical change after radical formation, absolute energies (E in au), relative energies (ΔE in kcal/mol), dipole moments (μ in Debye), and bond dissociation energies (BDE in kcal/mol) of these structures are presented in Table 1. The calculated BDEs change from 79.9 to 86.3 kcal/mol for the hydroxyl group at C1 of the aromatic ring and from 77.1 to 80.7 kcal/mol for the hydroxyl group at C2 of the investigated bromophenols. The delocalization of the unpaired electron seems to stabilize further structures of radical centers in selected bromophenols. Even more direct evidence for the delocalization of the unpaired electron comes from the analysis of spin density plots. This analysis provides an electronic structure based on rationalization for the ionization capabilities

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of radicals. The spin density plots for investigated radicals are depicted in Figure 2.

The **1-*raH2*** radical, formed upon abstraction of a hydrogen atom from the OH group attached to the C2 atom of compound **1**, is more stable than **1-*raH1*** by 2.6 kcal/mol. This energy difference can be explained, considering that in **1-*raH2***, the electronic vacancy on the radical center is stabilized by the hyperconjugation of adjacent bonds occurring through $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.5 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 7.8 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 2.2 kcal/mol) orbital interactions. Moreover, the spin distribution observed in Figure 2 exhibits the involvement of the bromine atom in the ortho position of the **1-*raH2*** radical center in the delocalization of the unpaired electron.

Hydrogen atom abstraction in compound **2** leads to the formation of **2-*raH1*** and **2-*raH2*** radicals where **2-*raH2*** is more stable, lying 7.1 kcal/mol lower in energy than **2-*raH1***. The energy gap between these two radicals was determined through hyperconjugation stabilization interaction of the unpaired electron in the radical species. The **2-*raH2*** radical was stabilized by $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 9.3 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 8.8 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 2.4 kcal/mol) orbital interactions while in the **2-*raH1*** structure, delocalization of the odd electron occurred by $n_{O1} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 10.3 kcal/mol) and $n_{O1} \rightarrow \sigma^*_{C1-C6}$ ($E^{(2)}$ = 7.9 kcal/mol) interactions. **3-*raH1*** and **3-*raH2*** radicals obtained from hydrogen atom abstraction of hydroxyl groups in positions 1 and 2 of compound **3**. As seen in Table 1, **3-*raH2*** is 7.4 kcal/mol more stable than **3-*raH1***. The important delocalization interactions in **3-*raH2*** at the B3LYP level are $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.2 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 8.8 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 2.1 kcal/mol) whereas in **3-*raH1***, the unpaired electron was delocalized by $n_{O1} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 10.2 kcal/mol) and $n_{O2} \rightarrow \sigma^*_{C1-C6}$ ($E^{(2)}$ = 7.8 kcal/mol) orbital interactions.

Radicalization of hydroxyl group at C2 in compound **4** generates **4-*raH2***. Its major stability (by 6.5 kcal/mol) with respect to **4-*raH1*** can be explained by taking into account the resonance effects due to the delocalization over the aromatic ring especially at the bromine atom in the ortho position of radical center (see Figure 2 for more details). On the basis of the NBO analysis in **4-*raH2***, the half-filled orbital of the O2 atom participates as a donor and the BD* of C1−C2 and C2−C3 bonds as acceptors with second-order perturbation energies of 8.3 and 8.8 kcal/mol, respectively. Furthermore, this radical center is stabilized by the O2···H1−O1 intramolecular hydrogen bond with second-order perturbation energy of 2.0 kcal/mol. Radicalization of compound **5** yields **5-*raH1*** and **5-*raH2*** radicals, the latter being more stable by 6.7 kcal/mol. In this radical the unpaired electron appears to be delocalized over all atoms of the aromatic ring (see Figure 2). This radical is stabilized by $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.2 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 8.8 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 2.1 kcal/mol) orbital interactions.

The **6-*raH1*** and **6-*raH2*** radicals are obtained when a hydrogen atom is removed from one of the hydroxyl groups in compound **6**. The NBO calculation underscores the delocalization of the unpaired electron over the whole aromatic system possessing a conjugated CH═CH group, which allows complete delocalization over the whole molecule (Figure 2). As shown in Table 1, **6-*raH2*** is 10.6 kcal/mol more stable than **6-*raH1***. In **6-*raH2***, the radical center is stabilized by $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.5 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 8.2 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 2.8 kcal/mol) orbital interactions whereas in the case of **6- *raH1***, values of second-order perturbation energies for $n_{O1} \rightarrow \sigma^*_{C1-C2}$ and $n_{O1} \rightarrow \sigma^*_{C1-C6}$ orbital interactions are 9.7 and 8.0 kcal/mol, respectively. Radicalization of hydroxyl groups in compound **7** generates **7-*raH1*** and **7-*raH2*** radicals; as shown in Table 1, **7-*raH2*** is 8.7 kcal/mol more stable than **7-*raH1***. As shown in Figure 2, the presence of a CH═CH bridge between phenyl and the carbonyl group of compound **7** favored a resonance and conjugation effect in these radicals. NBO analysis revealed that the unpaired electron in **7-*raH2*** is stabilized by $n_{O1} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.6 kcal/mol) and $n_{O1} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 7.9 kcal/mol) orbital interactions. In addition, this radical is stabilized by O2···H1−O1 intramolecular hydrogen bond energy of 1.8 kcal/mol.

8-*raH2* is the most stable radical obtained during H-atom abstraction in compound **8** (Table 1). The electronic vacancy of this radical is compensated by the hyperconjugation interactions involving the overlap of the radical center with the neighboring σ bond orbitals ($n_{O2} \rightarrow \sigma^*_{C1-C2}$ and $n_{O2} \rightarrow \sigma^*_{C2-C3}$ interactions with $E^{(2)}$ energies of 8.7 and 8.8 kcal/mol), the intramolecular hydrogen bond formation with the adjacent OH group (O2···H1−O1 bond with energy of 1.8 kcal/mol), and delocalization of the unpaired electron to the CH═CHCOCH$_3$ group. On the other hand, the comparison of spin density plots of radicals obtained from compound **8** (Figure 2) with those of radicals **6** and **7** demonstrated that the number and position of bromine atoms play an important role in spin distribution of the radicals and antioxidant activities of these structures.

The radical formation of compound **9** gives two radicals, **9-*raH1*** and **9-*raH2***, and **9-*raH2*** was found to be 7.2 kcal/mol lower in energy. Looking at the spin density plots of these radicals (Figure 2), one can realize that the unpaired spin density is mainly found in the oxygen radical center, the neighboring C−C bonds, and the bromine atom in the ortho position of the radical center. The NBO analysis revealed that $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.3 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 8.8 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 2.0 kcal/mol) charge transfer interactions play important roles in stabilization of this radical.

The radical formation process in compound **10** yields **10-*raH1*** and **10-*raH2*** radicals, of which **10-*raH2*** shows the highest stability. This radical presents $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.5 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 8.9 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 1.9 kcal/mol) hyperconjugation interactions. Atomic spin density reported in Figure 2 shows that the unpaired electron in the **10-*raH2*** radical is mostly located on the O1, O2, and Br3 atoms of the aromatic ring and also partially on the CHO substituent (see Figure 1 for atom numbering). The radical formation process in compound **11** gives **11-*raH1*** and **11-*raH2*** radicals. The absolute minimum is **11-*raH2***, in which the relative energy value is mainly determined from $n_{O2} \rightarrow \sigma^*_{C1-C2}$ ($E^{(2)}$ = 8.2 kcal/mol), $n_{O2} \rightarrow \sigma^*_{C2-C3}$ ($E^{(2)}$ = 8.3 kcal/mol), and $n_{O2} \rightarrow \sigma^*_{O1-H1}$ ($E^{(2)}$ = 2.2 kcal/mol) orbital interactions. Spin density distribution for the **11-*raH2*** radical (Figure 2) involves all atoms of the aromatic ring, especially the two bromine atoms and an adjacent OH group.

Several studies focusing on the relationship between molecular structure and antioxidant activity of bromophenols from marine red algae have been reported.[12,45] The isolated bromophenol compounds were evaluated for DPPH radical

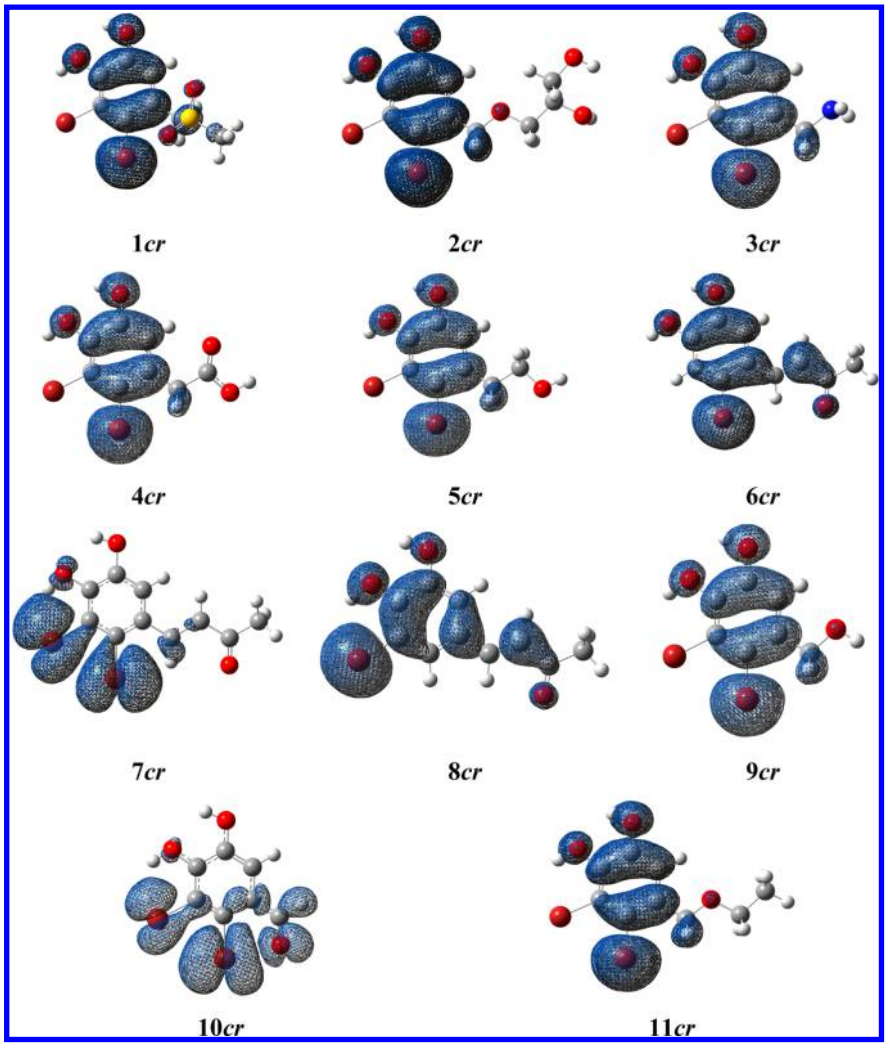

Figure 3. Plots of spin density for cation radicals of selected bromophenols obtained during ionization.

scavenging properties by Li and co-workers.[19] Analysis of the DPPH radical scavenging activity of investigated compounds demonstrated that the metabolites with *o*-dihydroxy groups on the aromatic ring generally display activity higher than that of compounds having a single free hydroxy group on the ring. This result is in accordance with the conclusions described by Chaillou and Nazareno.[46] As shown in Table 1, all compounds possessed the ability to scavenge DPPH radicals to various degrees. Comparing radical scavenging properties of these results demonstrated that compound **2** (IC_{50} = 7.43 μM)[19] and compounds with α,β-unsaturated carbonyl groups on the aromatic ring (i.e., compounds **6**, **7**, and **8** which gave IC_{50} values of 8.72, 7.62, and 9.40 μM, respectively)[19] generally display activity higher than that of the others. Overall, electron-donating groups decrease the BDE values while electron-withdrawing groups make hydrogen abstraction more energy demanding. As shown in Table 1, different substituents have little impact on the BDE values of O−H bonds in selected bromophenols. The most significant substituent effects were observed in compound **3** (CH_2NH_2 as an electron-donating group) and compound **10** (CHO as an electron-withdrawing group). Furthermore, as observed in Table 1, radicalization of the hydroxyl group in position 2 of selected bromophenols is more favorable than that in position 1. The comparison of ΔBDE values for these positions demonstrated that all investigated bromophenols have negative BDE values for the hydroxyl group at C2 of the aromatic ring while for the hydroxyl group at C1, the BDE values are positive. On the other hand, our results indicate that the presence of a bromine substituent on the phenol ring is the main factor influencing the stability of the radical and weakening of the O−H bond. As shown in Table 1, compound **7** indicated antioxidant activity (IC_{50} = 7.62 μM and BDE = 74.3 kcal/mol) higher than that of compounds **6** (IC_{50} = 8.72 μM and BDE = 76.1 kcal/mol) and **8** (IC_{50} = 9.40 μM and BDE = 76.6), suggesting that the number and position of the bromine atom(s) are also important factors contributing to the variation observed in the antioxidant activities of investigated compounds.

The One-Electron Transfer Mechanism. As mentioned in the introduction, antioxidants may also act according to the electron transfer mechanism, in which a radical cation $ArOH^{\bullet+}$ arises. The Cartesian coordinates of all optimized geometries are provided in Supporting Information. Figure 3 shows the spin density distribution for these radicals. The ionization potential (IP) in kcal/mol, which gives different trends of reactivity for investigated systems, is reported in Table 1. The compound exhibiting the lowest value for the gas-phase ionization potential is **11** (IP = 177.8 kcal/mol) followed by **3** (IP = 178.4 kcal/mol), **6** (IP = 179.4 kcal/mol), and **9** (IP = 180.5 kcal/mol). Furthermore, the ΔIP values of phenols given

in this table show a relative trend of reactivity that can be explained on the basis of molecular structure considerations. As shown in Table 1, the ΔIP of all investigated bromophenols are lower than that of phenols, suggesting that these compounds are efficient antioxidants.

Theoretical results show that in the case of the electron transfer mechanism, the main factors affecting the IP value are the extended delocalization and conjugation of the electrons enhanced by resonance phenomena, rather than the presence of a particular functional group. As seen in Figure 3, **1*cr***, **2*cr***, **3*cr***, **4*cr***, **5*cr***, **9*cr***, and **11*cr*** radical cations demonstrate spin density distribution mainly involved in the carbon atoms of the phenyl ring, the bromine atom in the C3 position, and hydroxyl groups. In **6*cr***, **7*cr***, and **8*cr*** radical cations, the spin density is mainly distributed in the carbon atoms of the phenyl ring, the bromine atoms, and the CH═CH substituent while in the **10*cr*** radical cation, the spin density distribution involves the bromine atoms and CHO as an electron-withdrawing group.

The comparison of ionization potential values with bond dissociation energies demonstrate that both H-atom abstraction and the electron transfer mechanism give the same trend of reactivity for investigated bromophenols. Computed radical scavenging activities of these compounds were compared to the experimental results obtained from scavenging activities against DPPH. Upon the removal of a hydrogen atom or the electron transfer process, investigated bromophenols gave rise to the radical species in which the unpaired electron appears to delocalize as much as possible over the whole aromatic ring and bromine atoms. Moreover, as far as the H-atom abstraction mechanism is concerned, the stability of radicals is enhanced by two factors (i.e., the possibility that establishes an intramolecular hydrogen bond between the oxygen radical center and its vicinal hydroxyl group and delocalization of its odd electron to bromine atoms).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional information as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS

DFT, density functional theory; B3LYP, Becke, three-parameter, Lee−Yang−Parr; BDE, bond dissociation energy; IP, ionization potential; ZPE, zero-point energy; NBO, natural bond orbital; BHT, butylated hydroxytoluene; BHA, butylated hydroxyanisole; TBHQ, tertiary butyl hydroquinone; DPPH, α,α-diphenyl-β-dipicrylhydrazyl; ABTS, 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; HAT, H-atom transfer; ET, electron transfer; IC_{50}, the half-maximal inhibitory concentration

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