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Density Functional Theory Studies on the Antioxidant Mechanism and Electronic Properties of Some Bioactive Marine Meroterpenoids: Sargahydroquionic Acid and Sargachromanol

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Cite This: *ACS Omega* 2020, 5, 20382−20390

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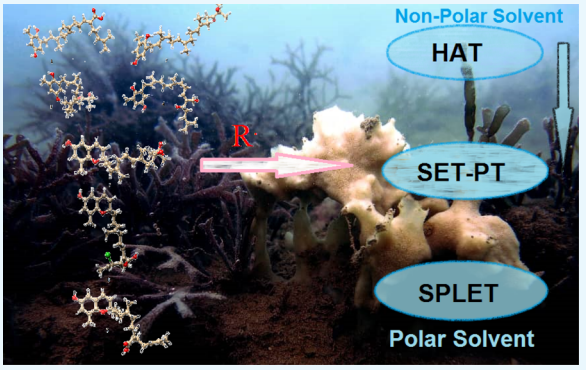
ABSTRACT: Certain meroterpenoids isolated from brown alga of the genus Sargassum are known to be antioxidant agents. Herein, density functional theory has been performed to analyze the preferred antioxidant mechanism of the two reactive antioxidant compounds derived from the Sargassum genus, that is, Sargahydroquinoic acid and Sargachromanol and some of their derivatives. Their global reactivity descriptors have been calculated to reveal their reactivity as an antioxidant. Molecule **1** is the most reactive antioxidant according to calculated descriptors. The results of molecule **1** are comparable to that of Trolox, suggesting their similar activity. The calculated descriptors are closely matched with experimental pieces of evidence. It has been found that hydrogen atom transfer (HAT) is more favored in gas media. Also, the effect of solvent polarity on the antioxidant activity has been explored for molecule **1**. The results disclose that the polarity of the solvent increases the contribution of two other mechanisms, that is, single-electron transfer, followed by proton transfer and sequential proton loss electron transfer.



1. INTRODUCTION

Excess formation of reactive free radicals in the body created from various enzymatic and nonenzymatic processes results in serious macromolecule damages such as in protein, DNA, membrane lipids, and carbohydrates causing cellular damage. The resulting oxidative stress is believed to play a key role in the development of aging and various degenerative diseases such as type 2 diabetes, inflammation, neurodegenerative diseases, and cancers.[1−6] Hence, there is an increasing attention to use therapeutically compounds with antioxidant activity that are able to inhibit these undesired oxidative reactions by trapping free-radical intermediates; which are created during oxidative reactions.[7−11]

Natural bioactive compounds have attracted researchers' attention because of their possible bioavailability and significant health-promoting properties. Among them, natural antioxidants are hoped to replace synthetic ones in order to prolong the shelf life of food and cosmetics. Besides, they may sufficiently avoid or at least reduce the oxidations of biomolecules by free radicals too.[12−16] Several compounds from marine sources have been known to have antioxidant activity via radical scavenging or inducing antioxidant enzyme levels.[17−21] Marine algae are one of the richest in various antioxidants,[22] and their derived compounds such as phlorotannins, meroterpenoids, carotenoids, and some of certain fatty acids are mostly studied from this point of view.[23−31]

Brown algae of the genus *Sargassum* (Sargassaceae, Fucales) contain structurally unique products such as plastoquinones and chromanols with different biological activities.[32,33] Recently, three isolated compounds from *Sargassum Serratifolium,* namely, Sargahydroquionic acid (SHQA), Sargaquionicacid (SQA), and Sargachromanol (SCM), have been reported with antioxidant activity,[34] whereas their different biological activities have been investigated both *in vitro* and *in vivo* by other researchers.[35−37] According to Lim et al. findings,[34] ethanol extract shows the highest levels of SHQA, SCM, and SQA. Their obtained results reveal that the SHQA and SCM exhibit stronger antioxidant activities than SQA. This different activity with respect to SQA indicates that antioxidant activities of isoprenoid quinones and chromanols strongly depend on their structural and electronic properties.

There are several mechanisms for free-radical scavenging action of phenolic antioxidants, and it has been reported that phenolic O−H bond dissociation enthalpy (BDE), adiabatic ionization potential (IP), proton dissociation enthalpy (PDE),

Received: May 19, 2020
Accepted: July 22, 2020
Published: August 6, 2020

https://dx.doi.org/10.1021/acsomega.0c02354
ACS Omega 2020, 5, 20382−20390

proton affinity (PA), and electron-transfer enthalpy (ETE) are important factors can determine thermodynamically preferred free-radical scavenging pathways.[38] Theoretical approaches, particularly, density functional theory (DFT), have been successfully applied in the aid to calculate these physicochemical descriptors related to different radical scavenging activity mechanisms[15,39−43] and also to find structure−activity relationships (SARs) for phenolic antioxidants.[44−47] However, to the best of our knowledge, there is no reported theoretical study regarding the antioxidant activities of SHQA and SCM or their derivatives so far.

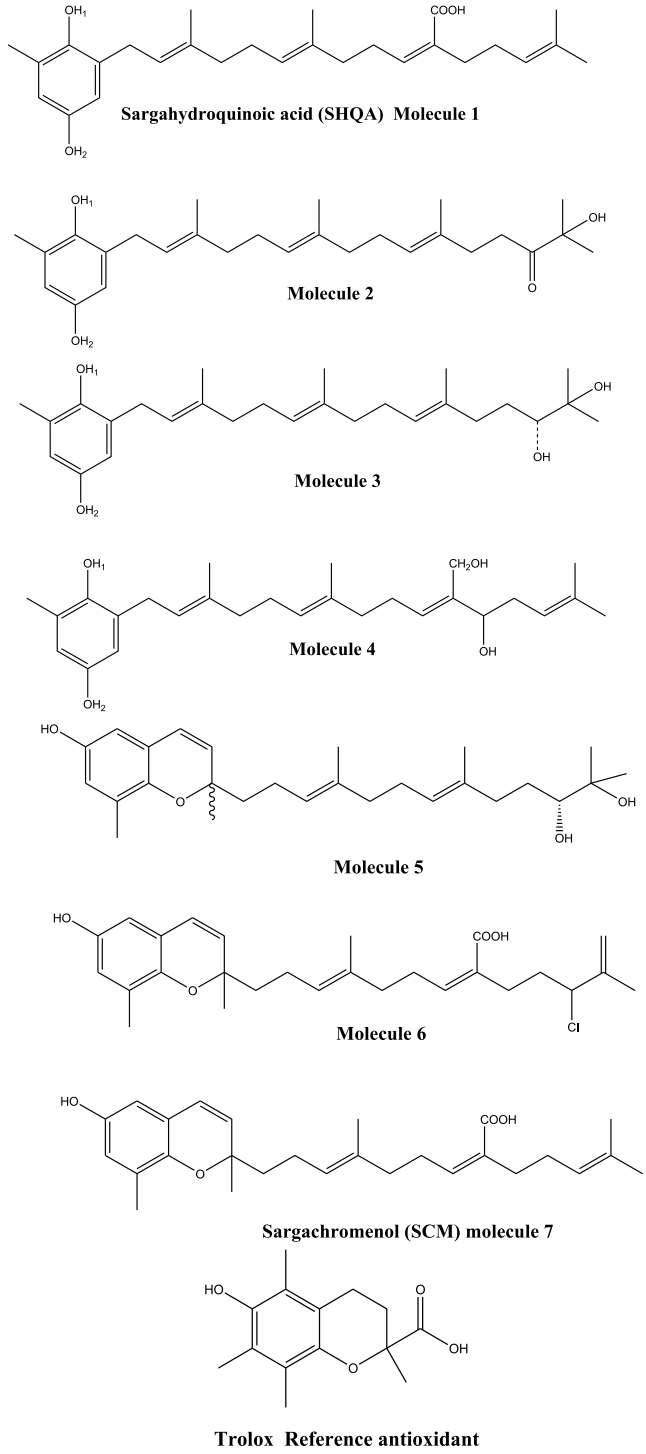
In the present study, the structural and electronic properties of four derivatives of SHQA and three SCM derivatives have been investigated by DFT, respectively. Their physicochemical descriptors characterizing the antioxidant ability, namely, BDE, IP, PDE, PA, and ETE of O−H, have been computed at the 6-311++g(2d,2p) level of theory. The preferred antioxidant mechanism has been also suggested in both gas and solution. Moreover, the global reactivity descriptors of neutral compounds have also been calculated in the framework of conceptual DFT. These calculations may illustrate the SAR and radical scavenging mechanism of these naturally occurring compounds, which is hoped to be useful for the development of marine-originated antioxidants.

2. RESULTS AND DISCUSSION

2.1. Optimized Geometries of Molecules and Their Radicals. Detailed knowledge of electronic and structural properties of antioxidant compounds is of great importance in describing their scavenging behavior. Hence, several initial geometries of investigated marine natural products[48] have been selected to undergo a full optimization. For this purpose, eight and six initial suggestions per molecule (**1**−**4**) and (**5**−**7**) have been considered, respectively. In the first step of this procedure, four and two possibilities of H_1, H_2, and H_{ring} orientation (i.e., it is oriented to the left or right side of O_1, O_2, or O_{ring}) have been selected. Then, the molecular mechanic optimization with MM + force field[49] implemented in the HyperChem program[50] has been performed on them and outputs used for further geometry optimization at the B3LYP/6-311++g (2d,2p) level of theory. Moreover, in parallel, the most stable geometries from force field optimization have been used for the new set of initial guesses in the second step, where the side-chain conformations have been changed in each molecule. At this time, four initial inputs have been chosen again. For better understanding, the initial input geometries for molecules **1**, **2**, and **7** have been illustrated in Figures S1−S3. Consequently, eight and six optimized geometries have been obtained for molecules **1**−**4** and **5**−**7**, respectively. Finally, the most stable geometries have been selected for preparing input geometries of radicals and further study. The schematic structures of all studied compounds are reported in Scheme 1, and the most stable optimized geometries are presented in Figure 1. Because of the presence of isopernoid chains with high mobility linked to hydroquinone or chromanol moieties of the investigated molecules, they finally achieve completely different stereochemical geometries because the intramolecular interactions between their several parts differ significantly. Several hydrophobic interactions in the side chain are also responsible in the final stabilities of molecules.

2.2. Global Reactivity Descriptors. A quantitative analysis of the investigated molecule reactivity has been performed by determining the global reactivity descriptors. Hence, vertical IP and electron affinities have been calculated. The values of global

Scheme 1. Schematic Representations of Molecules 1−7 and Reference Antioxidant Trolox



reactivity descriptors by the vertical IPs and EAs are reported in Table 1 (all reported data are in atomic unit). The hardness parameter (η) is directly correlated with the molecule stability, whereas softness (S) gives an insight into molecule chemical reactivity. The calculated chemical hardness (η) of molecules **1** and **5** is lower than that of other molecules in the gas phase reflecting their lower stabilities. The order of softness parameter for these two different series is **1** > **2** > **3** > **4** and **5** > **6** = **7**, revealing that molecules **1** and **5** are more favorable in the charge-transfer mechanism than other coseries molecules. The

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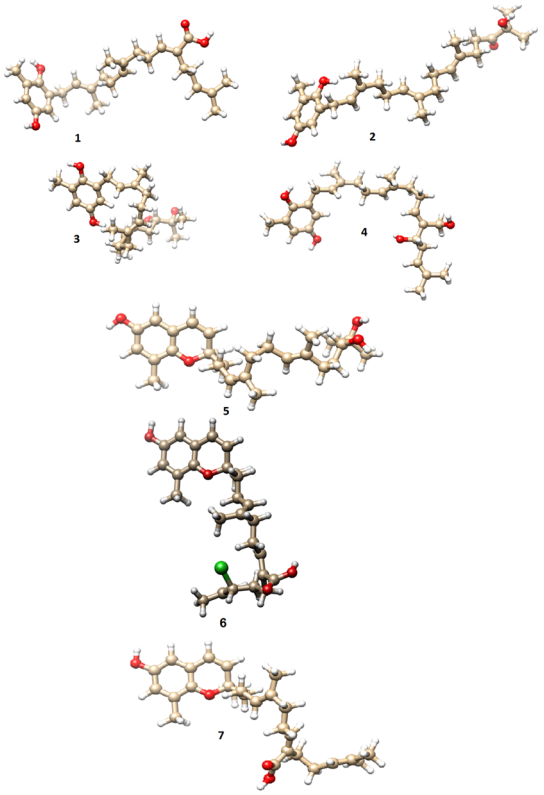

Figure 1. Optimized geometries of the most stable structures **1**−**7** at B3lyp/6-311++g(2d,2p).

common feature of electron-scavenging mechanisms is attracting electrons. For better understanding of the charge-transfer reaction, electronegativity (χ) should be considered. The negative of electronic chemical potential, μ, represents the ability of molecules to attract electrons. In accordance with results, lower electronegativity belongs to molecule **1**, which shows that it is more proficient in giving electron rather than capturing, which is an indication of its more antioxidant ability. On the other hand, the chemical potential measures a tendency of an electron to escape. As it becomes more negative, it is difficult to donate an electron, but it is more favored to gain. Hence, the lower μ of molecule **1** shows that it has more tendency to lose an electron. These chemical reactivity descriptors suggest that molecules **1** and **5** are somewhat more promising targets for electron-scavenging reactions, which is supported by the recent experimental study of Lim et al.[34] The values of dipole moments have been reported in Table 1. It is evident that all compounds are highly polarized and confirm their solubility in the polar solvents, and it also shows that the effect of environment polarity on their scavenging electron reaction will be considerable.

Finally, in the last column of Table 1, the values of mean polarizability have been presented, and in Table S1, the polarizability tensors of molecules **1**−**7** have been reported. The polarizability of molecules measures the relative tendency of charge distribution. In other words, system electronic cloud can be distorted from its normal shape in the presence of a weak external electric field.[51] This parameter relates to how the susceptibility of system electrons can be influenced by approaching of a charge, whereas several factors have an effect on it, such as compound complexity, size of molecular systems, and number of electrons. The higher polarizability means greater amount of polarization of the system in the same applied field. Herein, the order of mean polarizability**1** > **2** > **4** > **3** suggests that molecule **1** is more polarizable; however, their differences are not very considerable; on the other hand, the order in **6** > **5** > **7** points out the influence of system complexity and electron numbers on polarizability, which shows that molecule **6** is the most polarizable compound because of the presence of chlorine atoms.

2.3. Frontier Molecular Orbitals. The gas-phase electron density distribution of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) is given in Figure 2 for studied natural marine products. The plots of HOMOs show that in all investigated systems, HOMOs are localized on the ring as well as OH_1 and OH_2 (in molecules **1**−**4**) and OH_{ring} for molecules **5**−**7**. Hence, these OH groups would be the most probable reaction sites which can be attacked by free radicals, removing an electron. In contrast, the distribution of LUMOs reveals that carbons of phenol and isoprenoid chain are highly contributed, and there is no contribution of OH_1, OH_2, and OH_{ring}. These regions can be of interest for molecular reactions with nucleophiles. Consequently, molecules with a lower Frontier molecular orbital gap are more polarized. In this case, a significant degree of intermolecular charge transfer between electron donors and electron acceptors can occur, which may have an influence on the molecule biological activity.[52] According to the results in Table 1, molecule **1** has a lower HOMO−LUMO gap, suggesting its high polarizability. Moreover, these values are the same for molecules **5**−**7**, suggesting their similar biological activity.

2.4. Molecular Electrostatic Potential: Electrostatic Potential Isosurface. The molecular electrostatic potential (MEP) is an important descriptor to validate the pieces of evidence related to the reactivity of a molecular system. The three-dimensional MEP surface gives us an indication about position, shape, and size of the positive, negative, and the neutral electrostatic potentials. These information directed us to better

Table 1. Global Reactivity Descriptors, Dipole Moment, and Mean Polarizability at the B3lyp/6-311++g(2d,2p) Level of Theory[a]

molecule	ε_{HOMO}	ε_{LUMO}	$\Delta E_{HOMO-LUMO}$	η	S	μ	χ	dipole moment	$\langle a \rangle$
1	−0.293	−0.179	0.114	0.057	17.543	−0.236	0.236	2.946	356.153
2	−0.306	−0.170	0.136	0.068	14.705	−0.238	0.238	3.961	353.36
3	−0.318	−0.173	0.145	0.072	13.793	−0.246	0.246	3.020	336.520
4	−0.321	−0.166	0.155	0.078	12.903	−0.244	0.244	2.913	346.924
5	−0.299	−0.194	0.105	0.052	19.047	−0.247	0.247	3.387	351.526
6	−0.300	−0.195	0.105	0.053	18.868	−0.248	0.248	5.884	360.614
7	−0.299	−0.194	0.105	0.053	18.868	−0.247	0.247	3.708	347.262

[a]All parameters are in atomic unit

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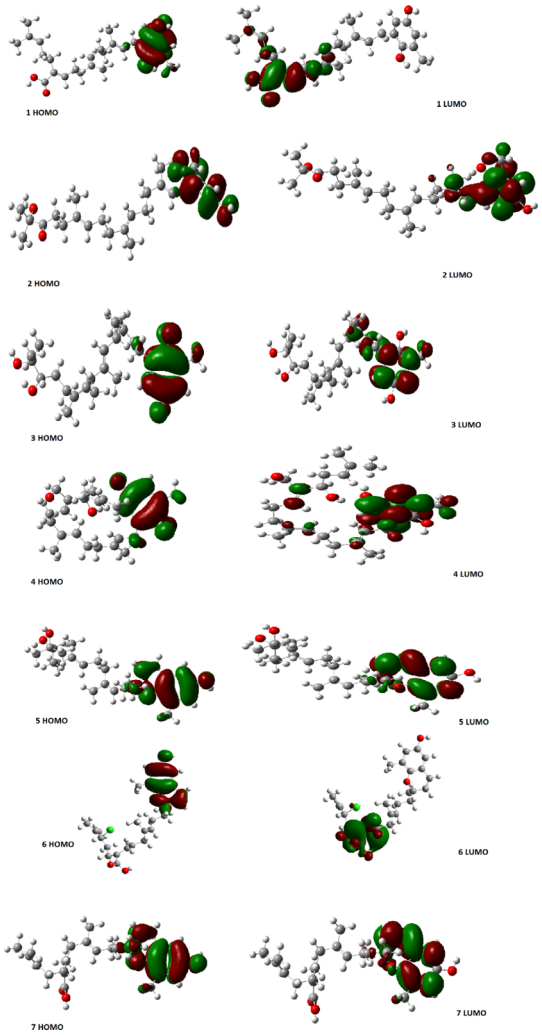

Figure 2. Frontier molecular orbital plots (HOMO and LUMO) in molecules **1**−**7** in the gas phase.

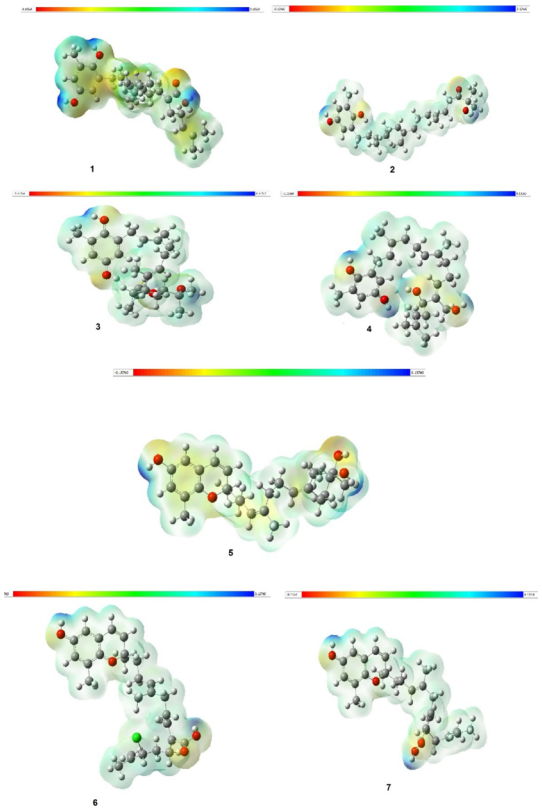

Figure 3. MEP isosurfaces of molecules **1**−**7**.

Table 2. O−H BDE, IP, PDE, PA, and ETE at the B3LYP/6-311++g(2d,2p) Level of Theory in the Gas Phase[a]

system	BDE	IP	PDE	PA	ETE
1-OH_1	70.66	180.85	192.67	326.25	47.27
1-OH_2	74.06	180.85	194.68	327.82	47.71
2-OH_1	72.26	179.60	194.14	327.69	46.05
2-OH_2	72.67	179.60	194.54	329.39	44.75
3-OH_1	72.17	174.32	199.32	325.85	47.79
3-OH_2	74.94	174.32	202.09	329.16	47.25
4-OH_1	72.63	180.95	193.15	328.71	45.39
4-OH_2	73.66	180.95	194.18	330.49	44.64
5-OH_{ring}	74.07	177.07	198.47	329.49	46.05
6-OH_{ring}	73.24	178.73	195.98	327.36	47.34
7-OH_{ring}	73.23	177.34	197.36	328.54	46.16
trolox	73.00	159.1	229.87	347.10	41.90

[a]All values are in kcal/mol.

understanding of system physicochemical properties and their relationship with molecular structure and reactivity toward electrophilic and nucleophilic attacks. In Figure 3, the maximum negative electronic potential is the preferred site for electrophilic attack, which is shown in red, while the positive electrostatic potential indicated in blue color will be attracted by the charged molecules or radicals. According to the results in Figure 3, high electrostatic potential regions are observed in the vicinity of the oxygen of hydroxyl groups 1 and 2 and H_{ring}, while a low electropositive potential is mainly found on H1 and H2. Comparing the value of blue color codes, (+0.162 a.u. in **1**, +0.124 in **2**,+0.117 in **3** and +0.133 in **4**) suggesting that H_1 and H_2 in molecule **1** are the most preferable sites for nucleophilic attacks, while in **5**−**7**, these codes are +0.157 (H_{ring} in **5**), +0.137 (H_{ring} in **6**), and +0.132 (H_{ring} in **7**) that indicate that H_{ring} is the preferable site for nucleophilic interactions and the intense electrostatic potential region in the vicinity of oxygen of ring makes it as a good radical trap. Finally, the hydrogen atoms of hydroxyl groups in the side chains are a suitable site for nucleophiles, while the oxygen is preferable for electrophiles.

2.5. Descriptors of the Antioxidant Properties. The antioxidant activity properties of all compounds are reported in Table 2. The results show that the parameters put into play three mentioned mechanisms are of a very different magnitude. This evidence can be a primary indication of which radical scavenging route is favored over another. In the following parts, each parameter and its related mechanism will be discussed.

2.5.1. HAT Mechanism. The BDE is the best reliable thermodynamic parameter to describe the HAT mechanism. Because this route involves in the H atom transferring from a hydroxyl group of antioxidant compound to the free radical, the weakest O−H bond with lowest BDE is expected to be abstracted easier, revealing its higher antiradical (antioxidant) activity. Hence, the computed BDE values in the gas phase, for O−Hs of ring, are reported in Table 2. The results disclose that O−H_1 of molecule **1** has the least BDE value and it shows its higher radical scavenging reactivity than other molecules, in agreement with the experimental evidence of Lim et al.'s study.[34] On the other hand, in molecules **1**−**4**, there are two O−H

https://dx.doi.org/10.1021/acsomega.0c02354
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groups in **1** and **4** situations (O−H_1 and O−H_2). In all cases, an abstraction of the H atom in **1** situation results in lower BDE value than abstraction of the H atom in **4** position. Although this difference is of only 0.41 kcal/mol for molecule **2**, it significantly relates to semiquinone radical species stability generated after H_1 atom abstraction, where methyl and isoprenoid chains in ortho positions can stabilize the intermediate radicals. Moreover, the O−H_2 BDE value reveals that the second HAT action is also possible; however, it will be with slightly reduced tendency because of lower stabilization of its radicals.

In molecules **5**−**7**, the BDE values are close to each other, which demonstrate that the side chain has no sensible effect on H-atom abstraction. Nevertheless, molecule **5** shows to some extent smaller activity than two other molecules. Generally, these calculated BDEs of two OHs in a one molecule are close to each other (the maximum difference is in molecule **1**, 3.4 kcal/mol), and all data are very close to the value of Trolox (as a reference antioxidant); this means that all investigated systems have the H-donating ability similar to that of Trolox.

2.5.2. SET-PT Mechanism. Apart from the HAT mechanism, another possible pathway for antioxidant molecules is single-electron transfer followed by proton transfer (SET-PT). In this route, an electron is transferred from the antioxidant to the free radical, leading to the radical cation formation, which it deprotonates subsequently. Hence, adiabatic ionization proton (IP) and PDE are the most important parameters in describing the feasibility of the mechanism. In Table 2, the calculated IPs and PDEs are presented. The IP amount required for the first step is lower than that needed to accomplish the second step of the SET-PT mechanism. Thus, the second step is the most probable one to limit the reaction rate of such a mechanism in a polar solvent. In general, lower IPs are more subject to ionization and easier in electron-transfer rate between free radicals and antioxidants. By comparison, **1** and **4** have close IP to each other, the order is Trolox < **3** < **5** < **7** < **6** < **2** < **1** < **4**, and they are higher than required BDE obtained from their different radical sites. This order reveals that molecule **3** is the most active antioxidant, and all the obtained IPs are larger than reference compound Trolox, suggesting their lower activity than Trolox. In the second step of the mechanism, the important parameter, PDE, measures the tendency of deprotonation of radical cations formed in the first step. The lowest PDE is for OH_1 in molecule **1**, which indicates its higher tendency to deprotonation. Although the IP trend appears to be slightly different from that of BDE, the PDE value and the sum of these two step energies (IPs + PDEs) obey the same trend as BDE energies and molecule **1** shows lower energies than others, even lower than that of the reference molecule, confirming that it is similar to higher activities with respect to other derivatives particularly chromonol ones **5**−**7** (in agreement with experiment). Moreover, the PDE values of O−H_1 are less than O−H_2 in all four studied compounds (**1**−**4**) in agreement with BDA findings presents that this hydroxyl group loses the proton from radical cation easier than other ones. Anyhow, although this result is also in agreement with experimental pieces of evidence,[34] the energies needed to undertake the whole SET-PT reaction are too higher than that of the HAT mechanism, and it suggests that this is not the preferred path by neither of these marine natural compounds in the gas phase.

2.5.3. SPLET Mechanism. This sequential proton loss electron transfer (SPLET) path has been suggested as a possible route to trap radical particularly in polar environments.[53] In Table 2, reported PA and ETEs show that the first step (PA) extremely requires much more energy to perform than the second step (ETE). This indicates that the first step is the slowest one and rate-determining step. It is evident that O−H_1 (molecules **1**−**4**) presents the smallest PAs. This means that transfer of proton from O−H_1 seems to be more probable than O−H_2. Similar to SET-PT path, the overall energies of both steps seem to exclude that the mentioned mechanism can occur in the gas phase too compared to HAT.

By analyzing both SET-PT and SPLET reaction mechanisms, it is evident that both pathways involve greater energies required to occur with respect to the HAT one. On the other hand, molecule **1** is almost the most active antioxidant in accordance with the above-mentioned calculated descriptors and all investigated natural products obey the same trends in the three proposed mechanisms, which indicate that HAT is preferred for them in the gas phase. Because the amounts of energies for all molecules (in each mechanism) are close to each other and there is no significant difference between them, molecule **1** has been selected as the model for analyzing solvent effects on its activity.

2.6. Solvent Effects on Antioxidant Activity. In Table 3, the BDE, IP, PA, PDE, and ETE of molecule **1** in three different solvents have been reported. Moreover, Trolox parameters are presented here for the sake of comparison. Compared with the gas phase, BDE values slightly changed in the solvent because there is no charge species in the HAT process stabilized by polar solvents or destabilized by nonpolar ones. However, the effect of polar solvents has been more than that of benzene and the lowest BDE belongs to the aqueous phase 69.90 kcal/mol for O−H_1. Again similar to the gas phase, O−H_1 is the more favored group for H-donation (giving an electron). Furthermore, the magnitude of the solvent effect on the BDE values is the same as that of Trolox. On the other hand, the IP values have been decreased in three solvents. However, this reduction is extremely more in polar ones. It can be due to the stabilization of charged systems created in the first step of the SET-PT mechanism by polar solvents. Additionally, the delocalization and conjugation of the π-electrons are more in the polar media. The second important parameter of the SET-PT route is PDE. Because this step is probably the rate-limiting ones in the gas phase, a notable solvent effect on PDEs is interesting. According to results, PDEs have been dramatically reduced in solvents because there are two charged species, namely, proton and radical cation, which can be stabilized by polar solvents. These pieces of evidence confirm the easier proton dissociation in solvents, particularly, polar media such as ethanol and water. Moreover, the values of

Table 3. O−H BDE, IP, PDE, PA, and ETE for System 1 at the B3LYP/6-311++g(2d,2p) Level of Theory in Different Solvents (Water, Ethanol, and Benzene)[a]

system	solvent	BDE	IP	PDE	PA	ETE
1-OH_1	water	69.90	117.4	20.9	69.80	68.5
1-lOH_2		72.96		22.3	70.00	69.7
1-OH_1	ethanol	70.16	130.4	15.04	67.44	78.00
1-OH_2		73.23		17.64	68.61	79.43
1-OH_1	benzene	71.18	159.47	30.56	118.05	71.98
1-OH_2		75.20		33.95	120.77	72.65
trolox	water	70.70	98.10	21.20	56.82	62.48
	ethanol	72.60	106.03	13.80	52.03	67.80
	benzene	73.01	136.85	37.03	109.43	64.45

[a]All values are in kcal/mol.

https://dx.doi.org/10.1021/acsomega.0c02354
ACS Omega 2020, 5, 20382−20390

IP are nearly similar to the reference molecule Trolox, suggesting that these studied marine natural products have slimier electron donating to Trolox in polar and nonpolar solvents too.

Finally, calculated PAs and ETEs indicate the solvent effect on the SPLET mechanism. First, PA values similar to the case of PDEs have experienced high reduction that is much notable for polar solvents. As an example, the PAs of O−H_1 decrease from 326.25 to 69.80 kcal/mol and 67.44 in water and ethanol, respectively. Thus, polar solvents can speed up the rate-determining step of SPLET and make the deprotonation easier than nonpolar solvents. Also, the ETEs are much lower than the corresponding IPs, indicating that deprotonated molecule **1** (probably this is the case for its other derivatives) is more feasible to extract an electron in comparison with its neutral form.

Generally, according to these data, although BDEs are much lower than IP, PDE, and PAs in the gas phase, suggesting HAT preference in gaseous media, the trends change in solvents. It is clear that polar solvents dramatically influence PDE and PAs. This discloses that the HAT process can be more probable in gas and benzene solution (nonpolar solvent in general), where IPs and PAs are still more than BDEs for both O−H bonds. However, it should be mentioned that, in spite of significant decrease of IPs in polar solvents, their values are still larger than PAs, PDEs, and BDEs, indicating that the SET-PT mechanism is not the preferred ones for our studied systems irrespective of the solvent. On the other hand, the solvent effects are remarkable for PAs in a way their values become much smaller than IPs and close to BDEs in polar solvents. Therefore, it is reasonable to suggest the SPLET path as a more favorable/competitive one in polar media.

3. CONCLUSIONS

The radical scavenging activity of seven naturally occurring compounds derived from brown alga of the genus *Sargassum* was investigated theoretically at the B3LYP/6-311++g (2d,2p) level of theory. On comparing the computed global reactivity descriptors in the gas phase, it is found that the order of reactivity is **1** > **2** > **3** > **4** and **5** > **6** = **7**, suggesting that molecules **1** and **5** are slightly more favorable in the charge-transfer mechanism. The molecule dipole moments and mean polarizabilities of all investigated compounds show their highly polarized nature, which would be more affected by polar media. Frontier molecular orbital plots along with molecular potential maps of studied compounds illustrate that phenolic OH groups would be the most probable reaction sites that can be attacked by free radicals.

Based on the most stable optimized geometry of all neutral compounds and their corresponding ionic and radical species, reaction enthalpies (BDE, IP, PDE, PA, and ETE) have been calculated related to three mechanisms: HAT, SET-PT, and SPLET. It should be mentioned that side-chain geometry sounds to have no significant influence on the radical scavenging activity of compounds because the antioxidant descriptor differences are not very considerable, although the mobility of side chains resulted in dissimilar orientation as it is evident in molecules **1** and **3**. It is clear that their antioxidant activities are more or less in the same range in spite of their side chains having different stereochemical geometries. Furthermore, the results confirm experimental pieces of evidence that SHQA is slightly more potent in radical scavenging than SCM; however, their difference is not too much (e.g., 2.34 kcal/mol for BDE). It has been found that the HAT mechanism is the preferred one in the gas phase. The effect of the solvent on the proposed mechanism has been investigated for SHQA (molecule **1**) in three different media, namely, water, ethanol, and benzene. Result shows that the HAT mechanism is absolutely the most energetically favored route mechanism in nonpolar and gaseous media, whereas by increasing the polarity of solvent, those reactions which involve charged species such as proton, anion, and radical cation would be more stabilized by the polar solvent. This is resulted because of the reduction of IP, PDE, and PA. In spite of a high decrease of IPs, their values are still more than BDEs in both polar media, which reveals that SET-PT is not preferred in ethanol and water. However, a dramatic decrease of PAs suggests that the SPLET path may be more expected in the polar solvent in competition with the HAT mechanism.

4. THEORETICAL AND COMPUTATIONAL DETAILS

4.1. Theoretical Background. *4.1.1. Radical Scavenging Pathways.* Three main mechanisms have been proposed to explain the radical scavenging ability of phenolic antioxidants. Therefore, free radicals can be deactivated by antioxidants according to the following mechanisms.[38,44,54]

1. Hydrogen atom transfer (HAT, eq 1) from antioxidant molecules (ArOH) to radicals ($R^\bullet$)

$$ArOH + R^\bullet \rightarrow ArO^\bullet + RH \quad (1)$$

2. Two-step reaction: single-electron transfer followed by proton transfer (SET-PT, eq 2)

$$ArOH + R^\bullet \rightarrow ArOH^{\bullet+} + R^- \rightarrow RH + ArO^\bullet \quad (2)$$

3. Two-step reaction: sequential proton loss electron transfer (SPLET, eq 3)

$$ArOH \rightarrow ArO^- + H^+; \qquad ArO^- + R^\bullet \rightarrow ArO^\bullet + R^-; \qquad R^- + H^+ \rightarrow RH \quad (3)$$

These mechanisms may occur in parallel with different rates and priorities. The numerical parameters related with three mechanisms including BDE, IP, PDE, PA, and ETE can be estimated by theoretical methods. In the following equations, these parameters are described.

$$BDE = H^\bullet_{ArO} + H^\bullet_H - H_{ArOH} \quad (4)$$

$$IP = H_{ArOH}{}^{\bullet+} + H_e - H_{ArOH} \quad (5)$$

$$PDE = H^\bullet_{ArO} + H_H{}^+ - H_{ArOH}{}^{\bullet+} \quad (6)$$

$$PA = H_{ArO}{}^- + H_H{}^+ - H_{ArOH} \quad (7)$$

$$ETE = H^\bullet_{ArO} + H_e - H_{ArO}{}^- \quad (8)$$

where H is molecular enthalpy of different species. In the HAT pathway, the BDE parameter (eq 4) can be applied to reveal the reactivity of ArOH; the lower the BDE value, the higher expected activity is. The SET-PET mechanism is defined by IP and PDE from $ArOH^{\bullet+}$. Compounds with lower IP and PDE values are defined as more potent antioxidants. Finally, in the SPLET mechanism, the first step reaction enthalpy, PA, and reaction enthalpy of electron abstraction, ETE, are two important factors to disclose the radical scavenging activity.

4.1.2. Global Reactivity Descriptors. The conceptual DFT offers a perspective to predict or analyze the chemical reactivity of molecules in terms of their global reactivity descriptors.[55−57]

https://dx.doi.org/10.1021/acsomega.0c02354
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The global hardness, η, is given as the second derivative of the energy, E, with respect to the number of electrons, N, at constant external potential, $v(\vec{r})$ defines the opposition of a chemical species to changing its electronic number. Parr and Pearson[58] proposed the following quantitative definition of hardness (η) within DFT

$$\eta = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})} \tag{9}$$

where μ is the electronic chemical potential of an N electron system in the presence of an external potential $v(\vec{r})$.

The expression for μ[59] is given by

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \tag{10}$$

The hardness has been used as an important reactivity descriptor of a molecule[60] by measuring the resistance to changes in the electron distribution of the system, namely, molecules with larger values of η are interpreted as being less reactive. Originally, the factor 1/2 in eq 9 has been applied to make the hardness definition symmetrical with regard to the chemical potential in eq 10, but it has been deleted. Using finite-difference approximation, eqs 11 and 12 would be

$$\eta = \frac{E_{N+1} - 2E_N + E_{N-1}}{2} = (\mathrm{IP} - \mathrm{EA})/2 \tag{11}$$

$$\chi = -\mu \approx \frac{E_{N-1} - E_{N+1}}{2} = (\mathrm{IP} + \mathrm{EA})/2 \tag{12}$$

where E_N, E_{N-1}, and E_{N+1} are the energies of N, $(N-1)$, and $(N+1)$ electron systems, respectively. By applying "Koopmans" theorem,[61] IP $\approx -\varepsilon_{\mathrm{HOMO}}$ and EA $\approx -\varepsilon_{\mathrm{LUMO}}$ are the vertical IP and electron affinity (EA), respectively. Thus, eqs 11 and 12 can be written as

$$\eta \approx (\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}})/2 \tag{13}$$

$$\mu \approx (\varepsilon_{\mathrm{HOMO}} + \varepsilon_{\mathrm{LUMO}})/2 \tag{14}$$

where ε denotes the corresponding Frontier molecular orbital energy and μ measures the "intrinsic strength" of a Lewis acid or base and χ is electronegativity.[62] The global softness, S,[63] is simply the multiplicative inverse of the global hardness, η

$$S = \eta^{-1} = \left(\frac{\delta N}{\delta \mu}\right)_{v(\vec{r})} \tag{15}$$

4.2. Computational Details. All calculations presented here have been carried out using Gaussian 09 program package.[64] Geometry optimization and frequency analysis of all naturally occurring systems including neutrals, radicals, radical cations, and anions have been done in vacuum. They have been fully optimized in their electronic ground states at the B3LYP/6-311++g(2d,2p)[65,66] level of theory, which was confirmed by the absence of imaginary frequencies. Unrestricted calculations have been applied for open shell systems such as radicals and radical cations with no spin contaminations. The $\langle S^2 \rangle$ value, in all cases, was about 0.750. The Frontier molecular orbitals HOMO and LUMO have been illustrated for neutral molecules at the same level of that structural optimization, and global reactivity descriptors have been calculated.

The solvent effect, at the single point level on the optimized geometries of the gas phase, has been explored in polar (H_2O, dielectric constant = 78.35 and ethanol, dielectric constant = 24.85) and nonpolar (benzene, dielectric constant = 2.27) solvents by the self-consistent reaction field polarizable continuum method theory (SCRF-PCM).[67] This study has been done just for the compound with the highest antioxidant activity. The molecular enthalpies have been calculated at 298.15 K. The $H(H^+)$, $H(H^\bullet)$, and $H(e^-)$ enthalpies in the gas phase and solvents have been used from the literature.[68−73] Trolox has been selected as an antioxidant reference molecule.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c02354.

Initial inputs for geometry optimization of molecules **1**, **2**, and **7** and polarizability tensors of molecules **1**−**7** in atomic unit (PDF)

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Notes

The author declares no competing financial interest.

■ ACKNOWLEDGMENTS

The author would like to show her gratitude to the Prof. Iraj Nabipour, Head of the "Persian Gulf Biomedical Sciences Research Institute" for sharing his pearls of wisdom with her during the course of this research. The author also thanks Reshad Moradi for taking the background photo of TOC graphic, the amazing underwater of Persian Gulf. Last, the author thanks three "anonymous" reviewers for their comments that improved the quality of manuscript.

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