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REGULAR ARTICLE

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Structural and electronic characterization of antioxidants from marine organisms

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Abstract Density functional theory was employed to investigate the molecular properties of new systems that serve as antioxidants in the marine environment. The B3LYP/6-311++G** protocol was used for all computations. Investigation, performed in gas phase and in solvent, was devoted mainly to the determination of the O–H bond dissociation enthalpies and the ionization potentials of examined compounds, since these quantities represent the most important parameters on which the biological activity can be rationalized. The results, interpreted in terms of conjugation and delocalization effects acting on molecules and all their possible radicals, showed that between the studied systems the hydroquinone derivatives have the greatest potentiality as antioxidants.

Keywords Antioxidants · Bond dissociation enthalpies · Ionization potentials · Density functional theory

1 Introduction

Marine organisms, particularly marine fungi, are well-known for their production of unique biologically active metabolites [1]. Among marine fungi, those living in association with algae, represent a rich source of novel antioxidant products. The association between algae and fungi is called “Algicolous” [1].

Antioxidants protect cells against the damaging effects of reactive oxygen species (singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite) and help us to fight diseases like artherosclerosis, dementia and cancer. In addition, they may be useful as therapeutics or food additives.

The natural antioxidants considered here (see scheme 1) are: two novel hydroquinone derivatives (**1** and **2**), two dihydronaphthalenones (**3** and **4**), and three known fungal metabolites (**5–7**) [2]. For these systems the trivial name “Acremonins” was adopted [1], because all the afore mentioned compounds are produced from algicolous marine fungus Acremonium species isolated from the tissue of a brown algae present in Mediterranean sea.

Two main mechanisms by which antioxidants can play their protective role were proposed in literature [3]. In the first one, referred to as H-atom transfer, the free radical removes a hydrogen atom from the antioxidant ArOH that becomes itself a radical:

$$R^\bullet + ArOH \Rightarrow RH + ArO^\bullet$$

A greater stability of the $ArO^\bullet$ radical with respect to $R^\bullet$ is required for a good efficiency of ArOH.

The evaluation of the bond dissociation enthalpy (BDE) of the O–H bonds of an antioxidant can give information about the easiness with which it forms the radical species; that is, because of their stability, they should react with the substrate molecules more slowly than $R^\bullet$.

In the second mechanism, referred as one-electron transfer, the antioxidant gives an electron to the free radical becoming itself a radical cation:

$$R^\bullet + ArOH \Rightarrow R^- + ArOH^{+\bullet}$$

The radical cation arising from the electron transfer must be stable. In this case the ionization potential (IP) is the most significant energetic factor for scavenging activity evaluation. The lower the IP, the easier is the electron abstraction.

The aim of our investigation is to rationalize the correlation between molecular/electronic structure and scavenging activity, on the basis of BDE and IP values, and to establish a relative trend of reactivity among the compounds analyzed.

BDE and IP values were computed in gas phase and in aqueous solution.

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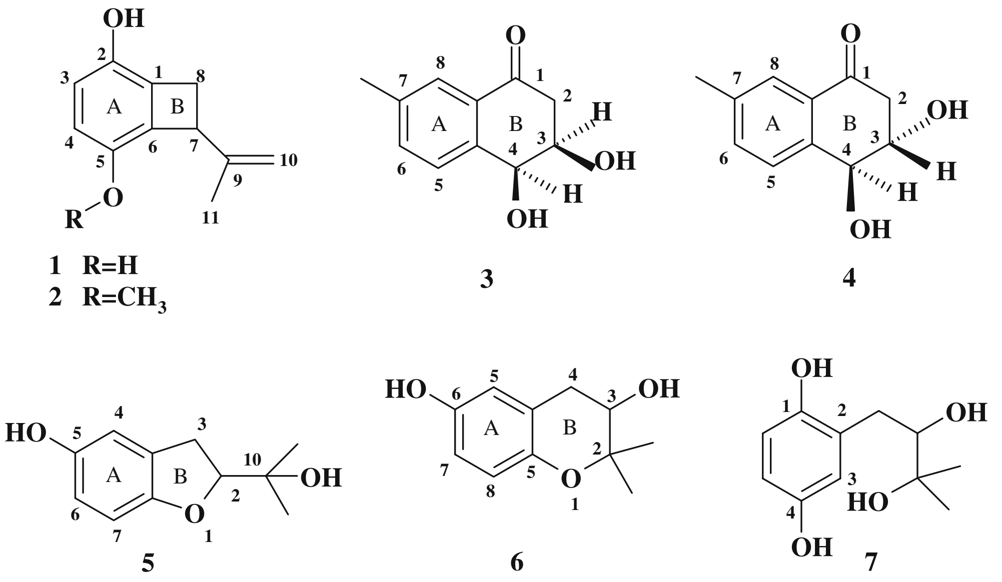


Scheme 1

2 Computational details

All calculations were performed by the Gaussian 03 code [4]. The Becke [5] hybrid (B3) exchange, together with the Lee–Yang–Parr [6] (LYP) correlation potentials were used for optimizing geometries in connection with the 6-311++G** basis set [7,8]. The unrestricted open-shell approach was used for computations of radical species. Harmonic vibrational frequencies were computed for both parent (ArOH) molecule and radicals (ArO$^{\bullet}$ and ArOH$^{+\bullet}$) in order to characterize all their conformations as minima or saddle points and to evaluate the zero-point energy (ZPE) corrections which we have included in the relative energy and IP values.

Natural bond orbital (NBO) analysis implemented in the Gaussian 03 package [9] was used to evaluate bond order in all systems and to explore the delocalization and conjugation.

Solvent effects were computed in the framework of self-consistent reaction field polarizable continuum model (SCRF-PCM) [10–12] implemented in the Gaussian 03 code [4], using the UAHF [13] set of solvation radii to build the cavity for the solute in the gas phase equilibrium geometry. Single-point estimation of the solvation energy was considered adequate to describe the behavior of the studied systems in water that, except for the species **7**, they are characterized by a remarkable conformational rigidity. However, in order to further verify our approximation, in the case of species **7**, we performed a geometry optimization in solvent and the results demonstrated that, also for this critical situation, structure and conformation are very similar in gas phase and in water (see supporting information). In particular, the largest deviation in the bond lengths which concerns the O-H distances is of 0.02 Å . C–O–H valence angles are mainly affected by medium and the largest discrepancy, which in this case is of 1.9°. Finally, the torsional angles vary few degrees except for that of C_2–C–C–O (see Scheme 1) that differs 16.0° with respect to the corresponding parameter in the gas phase.

Gas phase BDE was calculated at 298 K as $-\Delta H$ for the reaction:

$$\text{ArOH} \Rightarrow \text{ArO}^{\bullet} + \text{H}^{\bullet},$$

where ArO$^{\bullet}$ is the most stable radical species deriving from the global minimum of each neutral antioxidant.

Adiabatic IP was obtained as difference between the ArOH and ArOH$^{+\bullet}$ SCF energies. BDE and IP values in water were given in terms of total free solvation energy variation (ΔG).

3 Results and discussion

For the sake of clarity we have chosen to discuss the BDE and IP trends after a detailed presentation of the conformational properties and the relative stabilities of radicals for each system.

3.1 Structural and conformational features

The hydroquinone derivative **1** (see Scheme 1) named acremonin A [1] differs from compound **2** only by a methyl substituent on O_5 and presents two hydroxyl groups in the positions 2 and 5 of the six-membered ring.

Starting from the gas phase absolute minimum of compound **1**, upon H abstraction from hydroxyl groups, two radicals (2-OH and 5-OH) were obtained. The optimization procedure followed by vibrational analysis indicated that both radicals are minima with the 5-OH species being most stable at 0.89 kcal/mol (see Table 1) with respect to the 2-OH one.

Radicalization gave rise to a CO double bond formation in both cases as confirmed by bond order value (1.510). The unpaired electron appeared to be delocalized over the whole ring because of the high possibility of conjugation, but the

Table 1 B3LYP/6-311++G** relative energies for radical species deriving from parent molecules **1**,**3**,**4**,**6**,**7**. All values are in kcal/mol

Compound	ΔE_{gas}
1	
Radical 2-OH	0.89
Radical 5-OH	0.00
3	
Radical **3**AI	0.00
Radical **3**AII	3.67
Radical **3**BI	1.64
Radical **3**BII	5.39
4	
Radical **4**CI	0.21
Radical **4**CII	1.22
Radical **4**DI	0.00
Radical **4**DII	0.10
6	
Radical 3-OH	22.20
Radical 6-OH	0.00
7	
Radical 1-OH	0.00
Radical 4-OH	2.07

spin density distribution suggested a greater probability of finding it over the entire aromatic ring (see 1 of Fig. 1). In fact, the localization of the odd electron on the site from which the H atom was initially removed preserves the system aromaticity allowing the corresponding resonance form to be stabilized with respect to the others. From the compound **2** only a radical was formed. For this radical several resonance structures are possible. They are stabilized by the presence of the electron-withdrawing group in para position with respect to the hydroxyl. Also, in this case and for the same reason as in the acremonin **1**, the unpaired electron was mainly localized on the oxygen from which the H atom was removed although the spin distribution indicated the possibility of finding it on the whole ring (see 2 of Fig. 1).

The radical cations deriving from acremonin **1** and **2** were found structurally similar to the neutral molecules except for the elongation of some C–C bond of the six-membered ring and for the shortening of C_2–O and C_5–O bond lengths. As is evident in Fig. 2, the spin distribution in both cases (1 and 2) evidences a pronounced peak involving the oxygen atom of the O–H group linked to the C_2 carbon and a series of other small peaks on the remaining atoms of the phenyl system. This is a clear indication that electron deficiency is located at first in the oxygen atom of C_2–OH moiety and then distributed in the benzene ring because of delocalization effect.

The systematic names of stereoisomers **3** and **4** are (3R*, 4S*)-3,4-dihydroxy-7-methyl-3,4-dihydro-1(2H)-naphthalenone and (3S*,4S*)-3,4-dihydroxy-7-methyl-3,4-dihydro-1 (2H)-naphthalenone, respectively.

Depending on the mutual position of the hydrogen atoms of hydroxyl groups, two stable minima for each stereoisomer can be obtained (**3**A, **3**B, **4**C and **4**D of Fig. 3). The B3LYP/6-311++G** optimization indicates a global minimum for the system **3** in which a hydrogen bond of 2.240 Å between the C_4–OH donor group and OH–C_3 acceptor (see **3**A of Fig. 3 and Scheme 1) is present. Changing the role of donor and acceptor groups, a new relative minimum (see **3**B of Fig. 3), located at 1.21 kcal/mol above **3**A was reached. Because these minima can be obtained mutually by a simple rotation of the OH groups with a small expense of energy, it is probable that the two species coexist. As regards system **4**, the global minimum (**4**D of Fig. 3) appears to be more stable at 1 kcal/mol with respect to the relative one (**4**C of Fig. 3). As in the case of the stereoisomer **3**, the two minima are obtainable one from the other suggesting the contemporary presence of the two forms.

Due to the probable coexistence of two minima of comparable energy for both neutral molecules **3** and **4**, all the possible radical species originated by them were taken into account. The optimization of the four species deriving from system **3** gave as preferred forms in which the hydrogen bond is retained and clearly shortened (**3**AI and **3**BI of Fig. 4). In particular, the radical **3**AI was found more stable at 1.64 kcal/mol with respect to the **3**BI (see Table 1). **3**AII and **3**BII (see Fig. 4) were located at 3.67 and 5.39 kcal/mol above the **3**AI global minimum (see Table 1).

Computations have shown the radical species deriving from the conformers C and D of the compound **4** (see **4**CI, **4**CII, **4**DI and **4**DII of Fig. 4) to be practically isoenergetic because no particular stabilizing effect for some of these radicals is conjecturable. The global minimum **4**DI was found only 1.22 kcal/mol below the less stable isomer **4**CII.

Spin distribution on all radical species deriving from compounds **3** and **4** showed only a peak lying always on the oxygen atom from which H atom was removed (see 3 and 4 of Fig. 1). The absence of double bonds on the B ring (see Scheme 1), and hence of conjugation, confines the odd electron to a narrow zone of the molecule without the possibility to communicate with the A ring.

Radical cations of **3** and **4** stereoisomers do not present significant geometrical modifications with respect to the parent neutral molecules. Spin distribution analysis (see 3 and 4 of Fig. 2) indicated that in both cases the electron is removed from the π system of phenyl ring with a further involvement of the oxygen linked to C_1 atom of B ring.

2-(3-dihydroxy-3-methylbutyl) benzene-1–4 diol (**7** of Scheme 1) is known to be the precursor for type **5** (2-(1-hydroxy-1-methyl)2,3-dihydrobenzofuran-5-ol) and **6** (2,2-dimethylchroman-3,6 diol) compounds. All of these systems possess an aromatic moiety, possibly of polyketide origin, substituted by a hemiterpene unit [1]. The antioxidant activity of these species depends on the number and the location of the hydroxyl groups.

The presence of the phenolic (or diphenolic) ring assures that as a free radical is generated at the phenolic oxygen, it is stabilized by delocalization over the aromatic ring. On the contrary, the radicalization of an alcoholic –OH group, especially if belonging to a saturated side chain, gives rise to species having very high energies.

For the reasons discussed before, a single radical can be obtained for the system **5**. For this last species we have

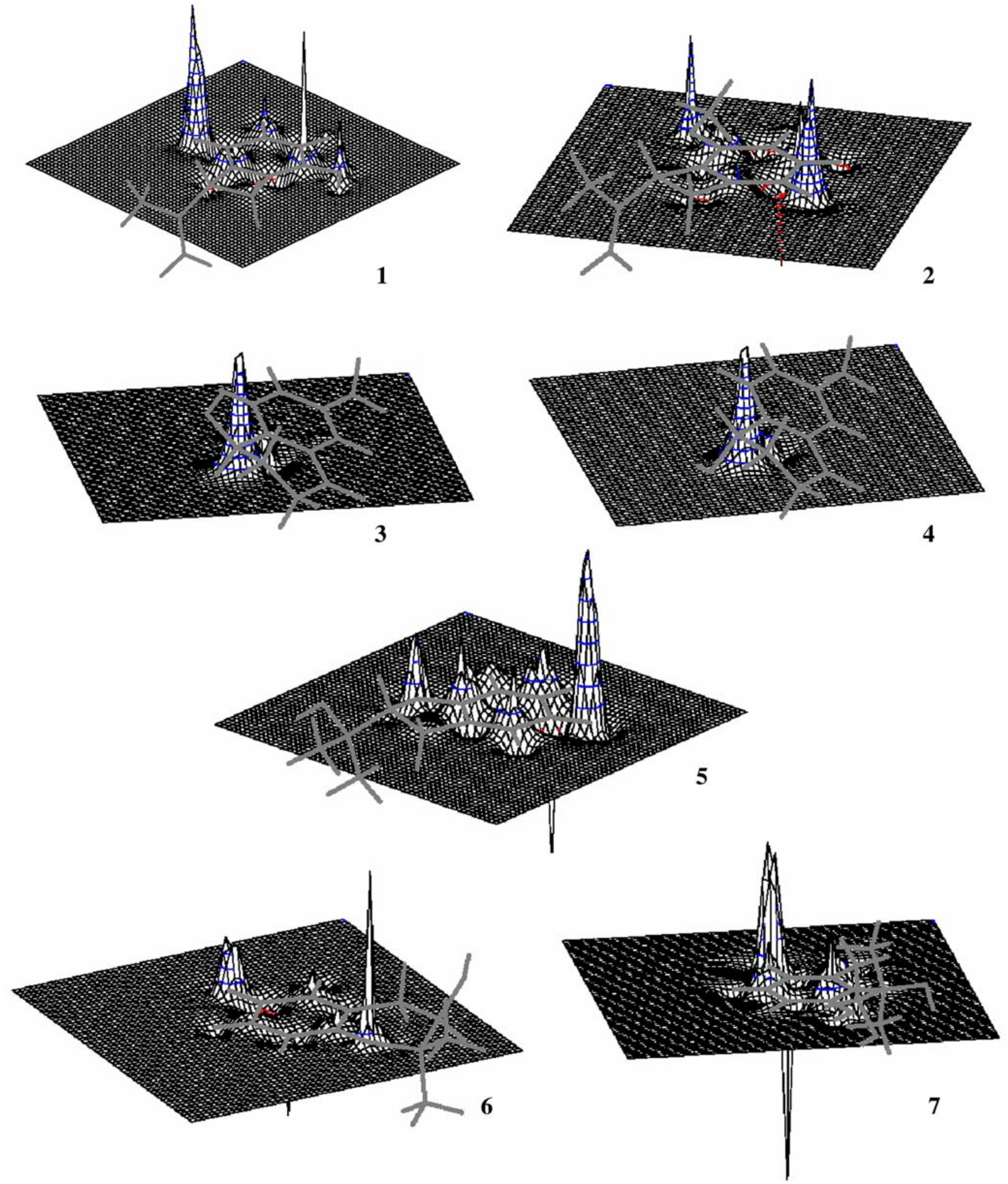


Fig. 1 Spin density distribution in the most stable radicals corresponding to **1–7** compounds, respectively

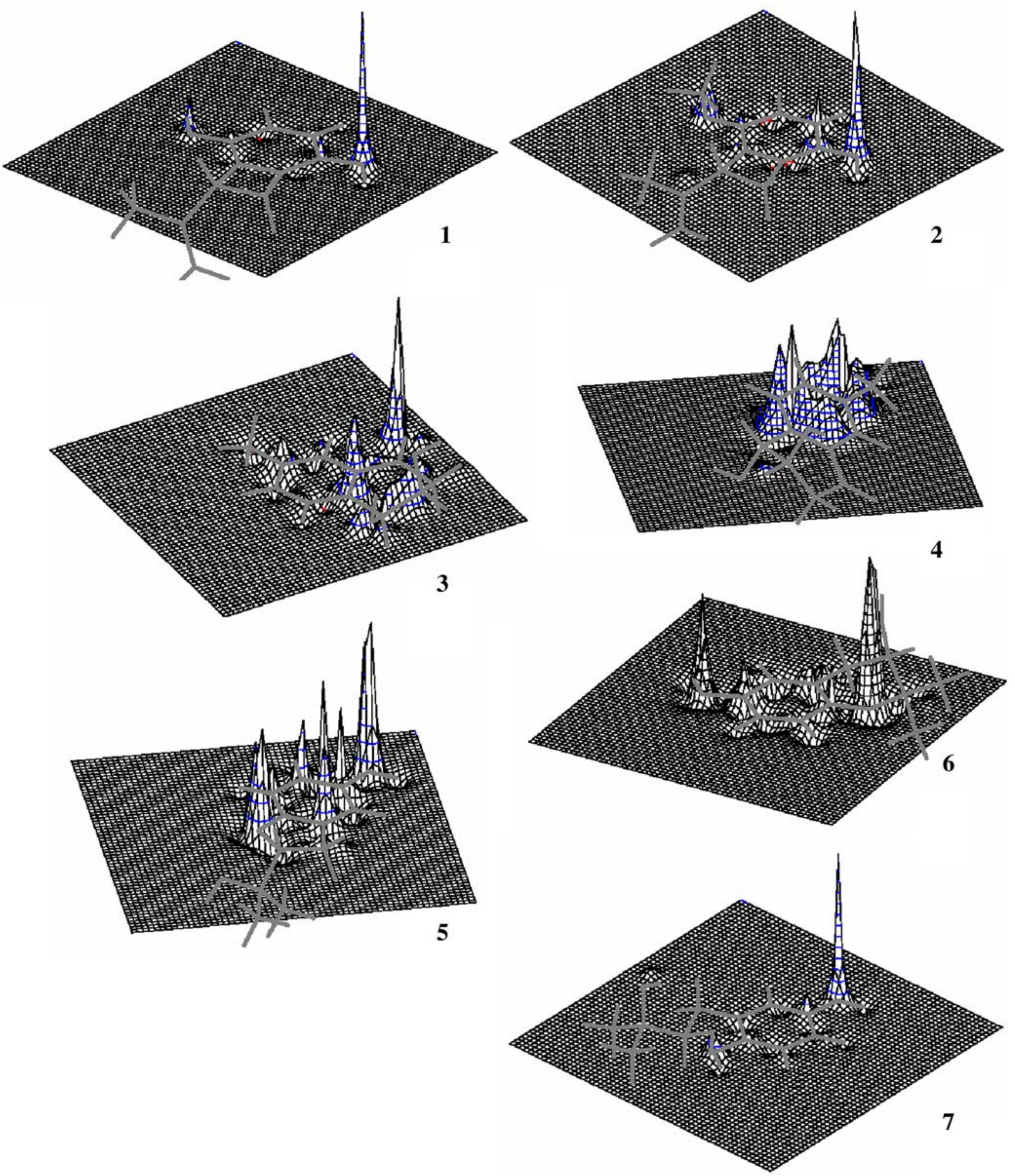


Fig. 2 Spin density distribution in the radical cations of **1–7** compounds

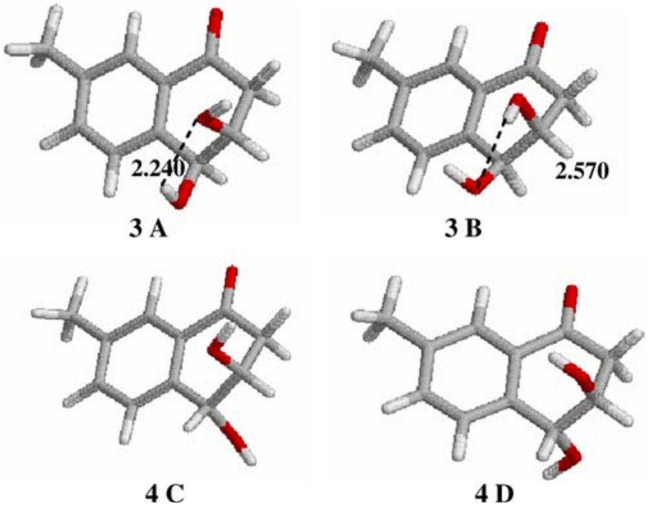


Fig. 3 B3LYP/6-311++G** equilibrium structures of **3** and **4** most stable conformers

Table 2 B3LYP/6-311++G** Bond dissociation enthalpy (BDE) and ionization potential (IP) values in gas phase and in water for systems 1-7. All values are in kcal/mol

Systems	BDE_{gas}	BDE_{water}	IP_{gas}	IP_{water}
1	77.99	85.05	172.23	117.87
2	78.00	85.00	167.46	123.07
3	99.90	112.47	196.00	144.48
4	100.75	116.65	196.27	143.12
5	77.99	84.21	165.10	115.42
6	76.69	84.97	163.57	113.96
7	76.33	85.08	172.20	121.33

found the common geometrical aspect of those molecules in which, upon abstraction of an H atom from a phenolic –OH group, a quinone like moiety is formed. Even if delocalization exclusively involves the ring A, the conjugation effect explains the presence of a peak of electronic spin density also on the oxygen atom belonging to the five-membered ring B (see 5 of Fig. 1). However, in the most probable resonance form, the highest spin density was found on the original radicalization site. This is again due to the possibility of keeping the aromaticity of the phenyl system.

Radical cation showed the same features of the neutral system (see 5 of Fig. 2) with a spin density distribution involving a branch of molecule starting from the hydroxyl group on ring A until the oxygen atom of the ring B.

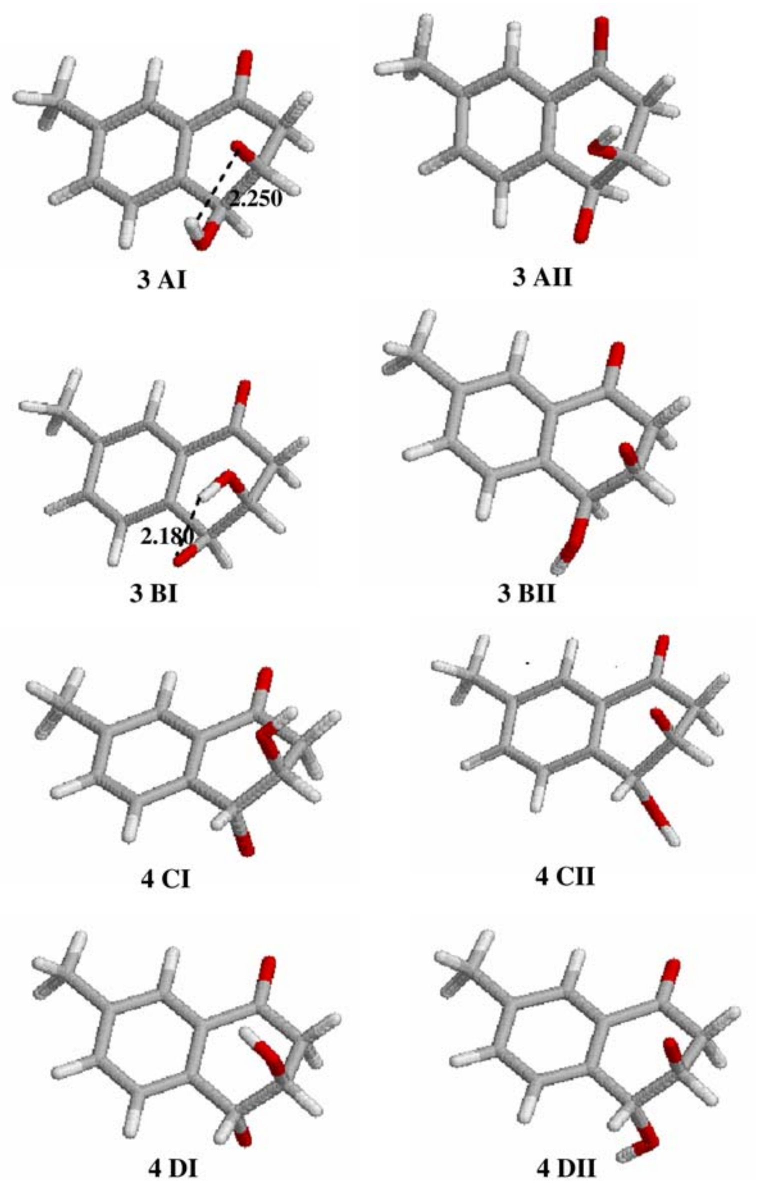
The compound **6** is particularly interesting because it has a structure similar to that of the 6-hydroxy-2,2,5,7,8-pentamethylchroman, HPMC α-tocopherol model [14] that is a potent antioxidant. Two –OH groups of phenolic and alcoholic nature are present on rings A and B, respectively. Because of the considerable conjugation and delocalization effects, the 6-OH was found to be the most stable radical lying at -22.20 kcal/mol (see Table 1) below the 3-OH one. The large energy difference between the 6-OH and 3-OH radicals demonstrates again that alcoholic –OHs cannot participate in the antioxidant activity. The spin distribution of 6-OH radical (see 6 of Fig. 1) underlined the possibility of delocalization on the ring A and furan oxygen thanks to the presence of the C–C double bonds and hence of the conjugation. For the 3-OH radical we found as expected an isolated big peak on the alcoholic oxygen.

In the radical cation a very similar spin distribution as in the case of 6-OH radical was proposed (see 6 of Fig. 2).

The compound **7** contains two phenolic –OH groups in the six-membered ring and two alcoholic groups in the side chain. Because of the flexibility of this side chain, the number of conformational minima is large. In fact, the energy difference between the global and the less stable relative minimum was of only 1.3 kcal/mol. In the equilibrium geometry, hydrogen atoms belonging to the hydroxyl phenolic groups, are arranged on a plane with a torsional angle of 180°. The –OH group closer to the substituent presents the hydrogen atom faced in such a way as to alleviate the possible steric hindrance (H–O-4-3 torsional angle of 180°).

Since, as demonstrated before, no antioxidant ability can be generally ascribed to the alcoholic –OH groups, we have radicalized the global minimum only at –OH phenolic level.

Radicalization of the 4-OH group generated a radical species (see Table 1) less stable at about 2.07 kcal/mol with respect to radical 1-OH. This difference was mainly attributed to the presence of the substituent in ortho position with



3 AI 3 AII

3 BI 3 BII

4 CI 4 CII

4 DI 4 DII

Fig. 4 B3LYP/6-311++G** equilibrium structures of **3** and **4** most stable radicals

respect to 1-OH group. In fact, upon radicalization of the 1-OH hydroxyl, two resonance structures are generated whose electronic deficiency on carbons can be immediately supplied by 4-OH and $–CH_2–CHOH–C(CH_3)_2OH$ electron-drawing groups directly linked to these atoms.

The spin density for the most stable radical of the compound **7** (see 7 of Fig. 1) indicated that the unpaired electron is delocalized over the entire aromatic ring. However, the most pronounced peak was found located on the original radicalization site.

The subtraction of an electron to the neutral system **7** generated a radical cation for which the spin distribution showed clearly only the phenyl ring A π system involvement (see 7 of Fig. 2).

4 BDE and IP evaluation

As mentioned before, BDE and IP are two important factors for determining the efficiency of an antioxidant.

In the present paper, the computed BDE values, reported in Table 2, are referred to the most stable radical species deriving from the global minimum of each antioxidant compound.

Calculations were performed in gas phase and in solvent because the antioxidants generally work in physiological liquids. On the other hand, the complete characterization of these molecules requires that their electronic and geometrical features be firstly determined in the absence of any complicated effect of the solvent.

The most active systems able to act through the H-atom transfer mechanism both in gas phase and in solution are those with the smallest BDE. Instead, low IP values indicate, the best candidates for the electron transfer mechanism.

The stability of the radicals associated with that of antioxidant parent molecules affects both the BDE and IP values. As demonstrated before and in some previous works [14–16], the stabilization of radical species and hence the antioxidant activity depends mainly on the number of hydroxyl phenolic groups in the molecule and is strengthened by conjugation and delocalization effects.

On the basis of these general assumptions, we could hypothesize the best performance for the systems **1** and **7**.

In fact, a look at the Table 2 shows that these two compounds together with the species **2**, **5** and **6** have the lowest BDEs both in gas phase and in solvent. The two-hydroxyl functionality on the phenolic ring explains why the molecules **1** and **7** show these low values of BDE. In the other systems characterized by a single –OH phenolic group, the presence of the oxygen atoms in the ring B offers a further possibility to delocalize the odd electrons (**5** and **6**). Instead, the stability of the compound **2** mono phenolic radical is due to the $-CH_3$ electron-drawing group in para position with respect to hydroxyl. The BDE values of the systems **3** and **4** demonstrate that the alcoholic –OH groups in the saturated cycle B are not easily radicalized because the systems formed after the O–H bond breaking cannot be stabilized either by delocalization or conjugation effects.

The trend of BDEs in water was different from that obtained in the gas phase. The absolute values of this quantity for the compounds **1**, **2**, **5**, **6** and **7** were found however, very similar to each other in aqueous solution as well as in vacuum, but very different from those relative to the remaining systems **3** and **4**. The different positions of the antioxidants in the sequence of BDE values obtained in the two media seem to be an effect of their more or less pronounced polarity. In fact, the analysis of the gas phase dipole moments (μ) of the five most active antioxidants reported hereafter, 0.538 (**1**), 1.061 (**2**), 3.962 (**5**), 3.939 (**6**) and 5.366 (**7**) D, shows that the BDE order found in water overlaps that of the μ values except for the system **7** that we have found at the end of the series. It is worth remembering that this last compound, unlike all others, is very flexible and that the rapid conformational changes occurring not only in gas phase but also in solution, could bring down the dipole moment with a consequent new placement of the compound in the BDE trend. In any case, we would underline that the energy differences at issue here are so small that the position in the BDE series is quite irrelevant.

On the basis of the IPs we have obtained a trend of reactivity different from that proposed by BDE values (see Table 2).

The molecules **3** and **4** seem to be the less active systems also in the framework of an electron transfer mechanism in both gas and solvent phases. The same arguments used previously for rationalizing BDE values can be reintroduced now to explain this finding.

The compounds **1** and **7**, favored in the case of an H atom transfer, are the less efficient as antioxidants in an electron transfer mechanism. This fact is related to a minor number of resonance structures able to stabilize the radical cations with respect to the compounds **5** and **6**, in which also the oxygen atom of ring B can support the electron deficiency, and to the compound **2**, in which it is possible to compensate the positive charge because of the presence of the methyl.

The IP trend is again different when we go from gas to condensed phase and in both cases the differences between the absolute values of IPs are much more marked than those between BDEs. This last fact allows us to focus attention essentially on the **6**, **5**, **2** and **1** systems. The activity trends in vacuum and in solvent, limited to these four compounds, showed a single inversion that concerns the antioxidants **1** and **2**. Since the ionization process in solution is much more complicated for a simple extraction of one electron, we think that it is inappropriate to try an explanation of this inversion on the basis of theoretical computations. On the other hand, the general indication in the two sets of calculations is essentially the same.

No experimental data is available in literature for all these molecules. No comparison between our computed and experimental values is therefore possible. In some previous B3LYP theoretical study devoted to the determination of BDE of free radicals with antioxidant properties, authors [17,18] debate for a long time about the reliability of this computational tool. The general opinion is that B3LYP generally underestimates BDE values even at the limit of large basis sets. However, these conclusions spring from the comparison with the various experimental counterparts that unfortunately often give conflicting information. Confirming of this fact as relating to the BDE of phenol (that is normally the reference compound), many experimental sources suggest values that go from 91.6 ± 0.3 [19] to 88.2 ± 0.5 [20] to 87.3 ± 1.0 [21] to 84.0 ± 1.0 kcal/mol [22]. Thus, the B3LYP/6-311++G** value of 82.9 kcal/mol [14] could be affected by an error more (8.7 kcal/mol) or less (1.1 kcal/mol) pronounced dependently on the experimental reference.

Our previous works on this subject [14–16] demonstrated that, if nothing else, the theoretical tool used gives reliable results when relative BDE values are considered. Here, nevertheless, we have considered it interesting to report absolute BDE values because of their systematic absence in literature. On the other hand, taking as reference the phenol, the switch over to relative quantities is rapid.

Conclusions

B3LYP/6-311++G** density functional approach was used to study in gas phase and in aqueous solution some antioxidant compounds extracted from fungi living in association with marine algae.

The study, performed on seven molecules and all their possible radicals, was addressed to the determination of geometrical and energetic features in order to identify the factors influencing the values of the BDE and the adiabatic IP that in turn determine if an H-atom or an electron transfer mechanism is adopted to carry out the biological activity.

On the basis of the results obtained we draw the following conclusions:

- The most efficient hydrogen donors systems are characterized by the ortho of phenolic functionality. In principle, this fact assures a number of radical species often very close in energy to that fully participates in to the antioxidant activity. These radicals are strongly stabilized by several resonance structures that allow the odd electron to be delocalized over the whole molecule.
- The delocalization and conjugation effects rather than the presence of two –OH phenolic groups, favor, instead, the lowering of IP values thus affecting the capacity of antioxidants to donate a single electron.
- The behavior of these compounds do not change significantly when we go from gas to condensed phase. In fact, despite the possible discrepancies inside the single activity sequences in the two media, the general indication is practically the same.

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