

ANTIOXIDANT POTENTIAL OF FIVE COMPOUNDS FROM THE MARINE FUNGUS *ASPERGILLUS FLOCCULOSUS* BY DFT METHOD: HAT AND SET MECHANISM

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Received: 25 July 2018; Accepted for publication: 15 November 2018

Abstract. Antioxidant potential of five compounds, ochraceopone F (1), aspertetranone D (2), cycloechinulin (3), wasabidienone E (4) and mactanamide (5) in the extracts from marine fungus *Aspergillus flocculosus* in Nha Trang was investigated by computational chemistry methods. All calculations were performed at the theoretical level M05-2X/6-31+G(d) in the gas phase. The physicochemical parameters including bond dissociation enthalpy (BDE), ionization potential (IP), electron affinity (EA) which characterize HAT (Hydrogen atom transfer) and SET (Single electronic transfer) antioxidant mechanisms were calculated.

As a result, the H-atom donating ability of the studied compounds increases in the descending order of BDE value (1) > (2) > (3) > (4) ≈ (5). Wherein the compounds (4) and (5) represent as the most potential antioxidant with the lowest BDE in the gas phase being 73.2 and 74.8 kcal/mol. Moreover, the electronic donating ability of the compounds increases as function of the descending order of IE value (2) > (1) > (5) > (3) > (4). And the electron accepting ability decreases in descending EA value (4) > (3) > (2) > (5) > (1). Compound (4) (wasabidienone E) has the smallest IE value of 6.50 eV and has the highest EA value of 2.26 eV.

Keywords: *Aspergillus flocculosus*, antioxidant, DFT, HAT, SET.

Classification numbers: 1.1, 1.2.1, 1.5.4

1. INTRODUCTION

Several marine secondary metabolites possess large diversities in structure as well as interesting biological activities [1]. Sponges and fungi, two of marine natural products potentially

developed in drug designs, have attracted several attentions in the recent time [2]. It is reported that sponges may provide a large part of secondary metabolites playing roles as chemical protective agents for associated microorganisms [3].

In our previous experimental study, we collected *Aspergillus flocculosus* which is a species of marine fungus lived at Nha Trang bay in Viet Nam [4]. In this marine product, we identified five compounds present in its extract, by using HPLC technique, including ochraceopone F (1), aspertetranone D (2), cycloechinulin (3), wasabidienone E (4), and mactanamide (5) [4] (Fig. 1).

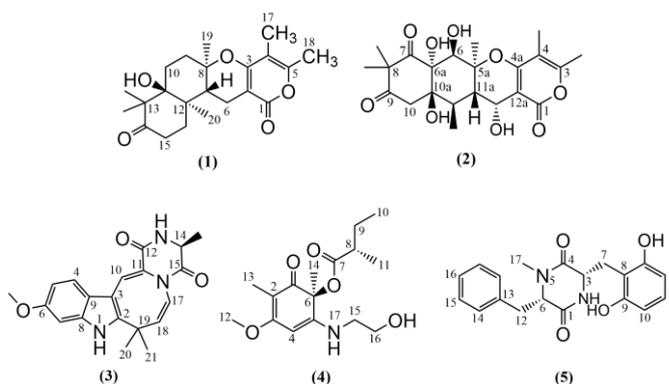


Figure 1. Chemical structure and numbering sites of studied compounds, ochraceopone F (1), aspertetranone D (2), cycloechinulin (3), wasabidienone E (4) and mactanamide (5)

The above five compounds have shown various biological activities throughout different studies in the literature. For example, Shin *et al* demonstrated the bioactivities of all these isolated compounds from *Aspergillus flocculosus* on the basis of cell viability assay and osteoclastogenesis one [4]. As a result, compound (5) presents interesting inhibitive effect against osteoclastogenesis and this may tend to therapeutic drugs application.

Although the literature review shows various biological activities of these compounds, to the best of our knowledges, their antioxidant potential has not been evaluated by both experimental and theoretical approaches yet. Thus, the goal of study is to predict the free radical scavenging activity of five compounds *via* two widely accepted mechanisms: hydrogen atom transfer (HAT) mechanism and single electron transfer (SET). The intrinsic parameters of the studied compounds including bond dissociation enthalpies (BDE), ionization potential (IP) and electron affinity (EA) were calculated by density functional theory (DFT) approach at the M05-2X/6-31+G(d) level of theory in the gas phase.

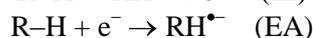
2. COMPUTATIONAL METHODS

Gaussian 09 Rev.E.01 program package was used for all calculations [5]. The geometries and vibrational frequencies were investigated at the M05-2X/6-31+G(d) model chemistries in the gas phase. The HAT and SET mechanisms, which are the most widely accepted antioxidant actions, were evaluated [6,7].

+ Hydrogen atom transfer (HAT):



+ Single electron transfer (SET):



Three intrinsic properties including BDE, adiabatic IE and EA which characterize for the above mechanisms were calculated in the gas phase as follows [8,9].

$$\text{BDE}(\text{R-H}) = H(\text{R}^\bullet) + H(\text{H}^\bullet) - H(\text{R-H})$$

$$\text{IE} = H(\text{RH}^{\bullet+}) + H(\text{e}^-) - H(\text{R-H})$$

$$\text{EA} = H(\text{RH}^{\bullet-}) + H(\text{e}^-) - H(\text{R-H})$$

where H is the sum of electronic and thermal enthalpies of the studied species at 298.15K and 1 atm which can be found from the output data files.

3. RESULTS AND DISCUSSION

3.1. Structural, electronic properties and orbital distributions

Figure 2 shows the optimized structures, HOMO, LUMO distribution and electrostatic potential (ESP) maps calculated at the M05-2X/6-31+G(d) level of theory for ochraceopone F (A), aspertetranone D (B), cycloechinulin (C), wasabidienone E (D) and mactanamide (E).

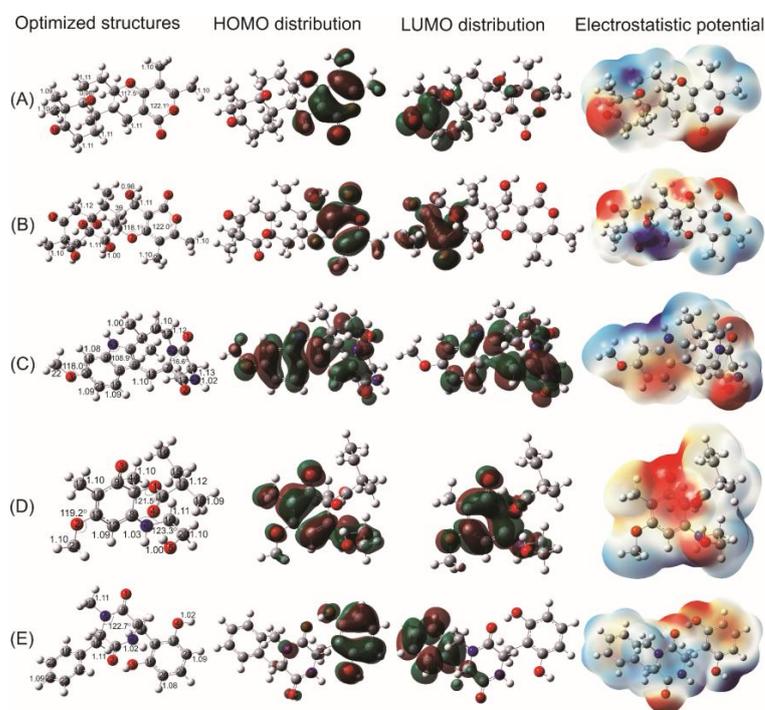


Figure 2. Geometries, HOMO, LUMO and ESP maps performed at the M05-2X/6-31+G(d) level of theory for ochraceopone F (A), aspertetranone D (B), cycloechinulin (C), wasabidienone E (D) and mactanamide (E).

The structures of the studied compounds are characterized by several double bonds located along rings to form a conjugated system that produces an electron-withdrawing effect. The highest occupied molecular orbitals (HOMOs) and the lowest occupied ones (LUMOs) of the five studied compounds are also presented in Figure 2. We can see that both frontier orbitals are distributed at the rings and the C=O groups. For that reason, the electron transfer reactions may occur at the rings. Finally, Figure 2 also displays electrostatic potential (ESP) maps of five

compounds. In principal, the electrostatic potential levels are represented by different ranges of colors: the red color as the most negative electrostatic potential while the blue one as the most positive potential. As can be seen in Figure 2, the most negative electrostatic potential regions are located at oxygen atom positions, while the positive electrostatic potential areas contain the C atoms, N-atom of rings.

3.2. Evaluation of antioxidant potential

3.2.1. Hydrogen atom transfer (HAT) mechanism

Bond dissociation enthalpy (BDE) values is calculated in detail at the M05-2X/6-31+G(d) model chemistries in the gas phase. The obtained results are shown in Table 1.

Table 1. BDE, IP and EA values of five studied compounds calculated at the M05-2X/6-31+G(d) model chemistries in the gas phase.

Bond positions	BDE (kcal/mol)	IP (eV)	EA (eV)
Ochraceopone F (1)		7.72	-0.01
C6-H	83.4		
C17-H	87.9		
C7-H	95.0		
Aspertetranone D (2)		8.10	0.48
C6-H	91.9		
C12-H	80.2		
Cycloechinulin (3)		6.63	0.60
C14-H	80.0		
N1-H	75.3		
Wasabidienone E (4)		6.50	2.26
C8-H	85.9		
C15-H	85.7		
C13-H	84.1		
C16-H	90.6		
N17-H	73.2		
Mactanamide (5)		7.65	0.09
C6-H	81.4		
C3-H	74.8		
C7-H	86.9		
C17-H	93.6		

The Table 1 showed that, for compound (1), at position C6-H, the hydrogen atom donating capacity is the highest with the lowest BDE in the gas phase being 83.4 kcal/mol. Similarly, for compounds (2), (3), (4), (5) are sequence at position C12-H, N1-H, N17-H, C3-H with BDE values in turn 80.2, 75.3, 73.2 and 74.8 kcal/mol. Besides, the H-atom donating ability of the studied compounds increases in the descending order of BDE value (1) > (2) > (3) > (4) ≈ (5). Wherein the compounds (4) and (5) represent as the most potential antioxidant with the lowest

BDE in the gas phase being 73.2 and 74.8 kcal/mol. In comparison with the BDEs values of other well-known antioxidants such as phenol (87.2 kcal/mol) [10], α -terpinene (74.4 kcal/mol) [11], wasabidienone E, mactanamide, cycloechinulin may be considered as potential antioxidant.

3.2.2. Single electron transfer (SET) mechanism

Single electron transfer consists in an important mechanism of antioxidant [9,10]. In a modern concept, a good antioxidant *via* SET mechanism is not only a good electron donor, characterized by ionization potential (IP), but also a good electron acceptor from free radical, represented by electron affinity (EA) property. The lower the IE value is, the easier electron donation is, while the higher the EA is, the easier electron acceptance is.

The M05-2X/6-31+G(d) model chemistry was used to calculate IP and EA values in the gas phase. The electronic donating ability of the compounds increases as function of the descending order of IP value (2) > (1) > (5) > (3) > (4). And the electron accepting ability decreases in descending EA value (4) > (3) > (2) > (5) > (1). Compound (4) has the smallest IP value of 6.50 eV and has the highest EA value of 2.26 eV. By comparing with the IP of phenol, i.e. 8.49 ± 0.02 eV [12] and other well-known antioxidant such as falcarinol, α -vetivone with IP being 8.35, 8.06 eV [11], respectively, these values are considerably low.

4. CONCLUSIONS

The antioxidant potential of five compounds including ochraceopone F (1), aspertetranone D (2), cycloechinulin (3), wasabidienone E (4) and mactanamide (5) was investigated by computational chemistry methods *via* HAT and SET mechanisms. Density functional theory (DFT) M05-2X/6-31+G(d) in the gas phase was employed to compute the characterizing thermochemical parameters including BDE, IE, EA. It is showed that wasabidienone E (4) can be a very promising antioxidant activity *via* the HAT mechanism. The lowest bond dissociation enthalpy being 73.2 kcal/mol is found at N17-H position. Furthermore, wasabidienone E (4) is the most active antioxidant via its electron transfer mechanism.

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