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A Computational Study of Antioxidant Potential of Diterpenoid Amides in the Extract of the Leaves of *Erythrophleum fordii*

Nghiên cứu tiềm năng chống oxi hóa của các hợp chất Diterpenoid Amides trong chiết xuất từ lá của cây Lim xanh bằng phương pháp Hóa tính toán

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Abstract

Antioxidant properties of 4 diterpenoid amide derivatives (3HDTA, 3ADTA, 3TDTA, 6HDCA) have been investigated via hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET) mechanisms using density functional theory (DFT) methods. The characterizing thermodynamic parameters such as C–H bond dissociation enthalpy (BDE), ionization energy (IE), electron affinity (EA) and proton affinity (PA) have been calculated for the gas phase at the B3LYP/6-311G(d,p) model chemistry. The results show that the antioxidant capacity follows decreasing trend: 3TDTA > 6HDCA > 3HDTA > 3ADTA. H-atoms at C nearby π-bond play an important role in the antioxidant ability of diterpenoid amides via HAT mechanism (i.e. C7). 3HDTA is considered the most antioxidant potential with the BDE (C-H) values at C7 atom is 70.52 kcal/mol. Moreover, via the SETPT mechanism 6HDCA is the most potential with IE and EA value are 9.37 eV and 0.990eV, respectively. Via SPLET mechanism, 3TDTA and 6HDCA show higher antioxidant capacity with PA value are 324.27 and 338.22 kcal/mol, singly.

*Keywords:*Erythrophleum fordii, diterpenoid amide; antioxidant; HAT; SET-PT; SPLET, DFT.

Tóm tắt

Tính chất chống oxi hóa của bốn dẫn xuất diterpenoid amide (3HDTA, 3ADTA, 3TDTA, 6HDCA) đã được khảo sát bằng lý thuyết phiếm hàm mật độ (DFT) thông qua các cơ chế chuyển nguyên tử H (HAT), chuyển đơn điện tử-chuyển proton (SET-PT) và mất proton chuyển điện tử liên tiếp (SPLET). Các thông số nhiệt động học đặc trưng như năng lượng phân ly liên kết C-H (BDE), năng lượng ion hóa (IE), ái lực điện tử (EA) và ái lực proton (PA) đã được tính toán trong pha khí ở mức lý thuyết B3LYP/6-311G(d,p). Kết quả chỉ ra rằng khả năng chống oxi hóa giảm theo chiều hướng 3TDTA > 6HDCA > 3HDTA > 3ADTA. Các nguyên tử H tại nguyên tử C gần liên kết π (i.e. C7) đóng vai trò quan trọng trong khả năng chống oxi hóa của các hợp chất diterpenoid amides theo cơ chế HAT. Hợp chất 3HDTA được xem như là chất chống oxi

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hóa tiềm năng nhất với giá trị BDE(C-H) tại nguyên tử C7 bằng 70.52 kcal/mol. Ngoài ra, theo cơ chế SETPT, hợp chất 6HDCA tỏ ra là chất chống oxi hóa tiềm năng nhất với giá trị IE và EA lần lượt bằng 9.37 và 0.990eV. Theo cơ chế SPLET, hợp chất 3TDTA và 6HDCA có khả năng chống oxi hóa cao hơn với giá trị PA lần lượtbằng 324.27 và 338.22 kcal/mol.

Từ khóa: Erythrophleum fordii, diterpenoid amide; chất chống oxi hóa; HAT; SET-PT; SPLET, DFT.

1. Introduction

Erythrophleum fordii (Leguminosae) is a large tree species that is widely distributed in China, Taiwan and Vietnam. It is a medicinal and least toxic plant. It is used as a medicine for invigoration and promotion of blood circulation[1]. Recently, Du *et al*[2] have reported phytochemical investigation from the leaves of *Erythrophleum fordii* resulted in the isolation of 13 compounds[2]. The isolation, structural elucidation and biotesting of three novel cassaine diterpenoid–diterpenoid amide dimers, seven new cassaine diterpenoid amides, erythrophlesins and 3 beta-hydroxynorery throsuamid from the leaves of E. *fordii* were performed[2]. Among them, diterpenoid amides represent as ones of the most massive components with significantly selective cytotoxic activities (IC_{50}< 10 μM) against cancer cells. Manh-Hung T.*et al* [3] reported a phytochemical investigation into the bark of *Erythrophleum fordii.* This experiment isolated and characterized four new compounds, two new cassaine diterpenoids (erythrofordin T and U) and two new cassaine diterpenoid amines (erythroformine A and B), as well as nine known compounds. The results in this *in vitro* study suggest that cassaine diterpenoid amines had potential application in the treatment of human lung. In fact, cassaine diterpene amines showed potent cytotoxic activity against all non-small cell lung cancer cell lines less than 6 μM[3]. Insight into the possible antioxidant mechanisms of these interesting compounds may allow explaining their interesting medicinal activities.

Thus, in this work, the antioxidant capacities of four selected diterpenoid amides identified in the leaves of *Erythrophleum fordii* including 3β-Hydroxydinorerythrosuamide (**3HDTA**), 3β-Acetoxydinorerythrosuamide (**3ADTA**), 3β-Tigloyloxydinorerythrosuamide (**3TDTA**) and 6α-Hydroxydinorcassamide (**6HDCA**) (Figure 1) were evaluated. Three common mechanisms, namely the hydrogen atom transfer (HAT), single electron transfer (SET) mechanisms and sequential proton loss electron transfer (SPLET) were taken into account. The characterizingthermodynamic parameters including bond dissociation enthalpy (BDE), vertical ionization energy (IE), affinity electrons (EA) and the proton affinity (PA) were calculated for the gas phase using density-functional theory (DFT) at B3LYP/6-311G(d,p) model chemistry.

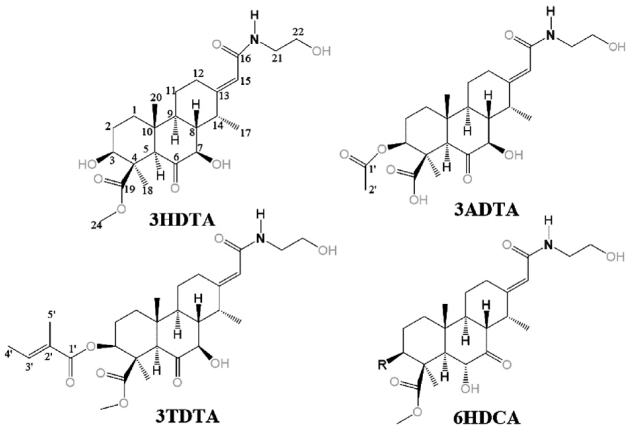

Figure 1: Chemical structures and numbering atomic sites of four studied diterpenoid amides.

2. Theoretical and Computational Methods

The geometry optimization and the vibrational frequency calculation of each compound and the related radicals, cationic and anionic radicals were calculated using B3LYP/6-311G(d,p) methods. All calculations were performed using the Gaussian 09 Revision E.01 suite of program[4].

Three common antioxidant mechanisms are represented as follows:

- Hydrogen atom transfer (HAT)

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

- Single electron transfer (SET)

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

- Sequential proton loss electron transfer (SPL-ET)

$$R\text{-}H \rightarrow R^{-} + H^{+} \qquad (PA)$$

The BDE, IE, EA and PA values were determined from total enthalpies of the individual species in the gasphase, as follows:

$$BDE(ArO\text{–}H) = H(ArO^{\bullet}) + H(H^{\bullet}) - H(ArOH)$$

$$IE = H(AH^{\bullet+}) - H(AH)$$

$$EA = H(AH^{\bullet-}) - H(AH)$$

$$PA = H(A^{-}) + H(H^{+}) - H(AH)$$

Where His the enthalpy of different species at 298.15 K and 1.0 atm. The enthalpies were estimated from the given expression: $H(T) = E_0 + ZPE + H_{trans} + H_{rot} + H_{vib} + RT$. The H_{trans}, H_{rot}, and H_{vib} are the translational, rotational, and vibrational contributions to the enthalpy, respectively. E_0 is the total energy at 0 K and ZPE is the zero-point vibrational energy.

3. Results and Discussion

3.1. Optimized structure and molecular properties

Figure 2 shows the optimized geometry of four diterpenoid amides. It can be observed in Figure 2 that molecular structures are stabilized by forming several hydrogen bonds with different oxy atoms with high electron density. For example, the length of hydrogen bonds recognizing in 3HDTA (Figure 2-A) varies from 1.86 to 1.99Å, while the hydrogen bond length changes from 1.85 to 2.04Å for 3ADTA (Figure 2-B), 1.86 to 2.04Å for 3TDTA (Figure 2-C) and 1.86 to 1.93Å for 6HDCA (Figure 2-D).

The HOMO and LUMO structures show that diterpenoid amide moiety plays as electron donating as well as accepting center of the compounds. The HOMO and LUMO of four studied compounds are present in Figure 3. It is observed that HOMO structures are found that C=C, C=O bonds and oxygen, nitrogen with high electron densities (i.e. red color parts) than the other parts of the molecule. In the cases of 3HDTA, HOMO orbital has high electron density at C13=C15, C16–N… Moreover, LUMO orbital displays at substituent of cyclohexane rings such as: C12–C13, C16–N, C17–H, C13=C15, C16–O… (Figure 3-A).

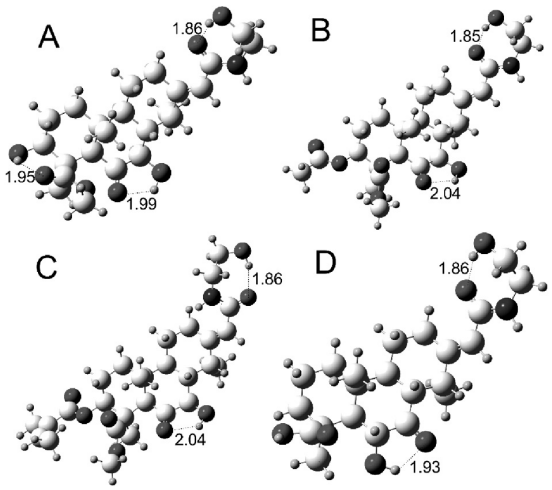

Figure 2: Optimized structures of the diterpenoid amides: (A) 3HDTA, (B) 3ADTA, (C) 3TDTA and (D) 6HDCA at the B3LYP/6-311G(d,p) level of theory.

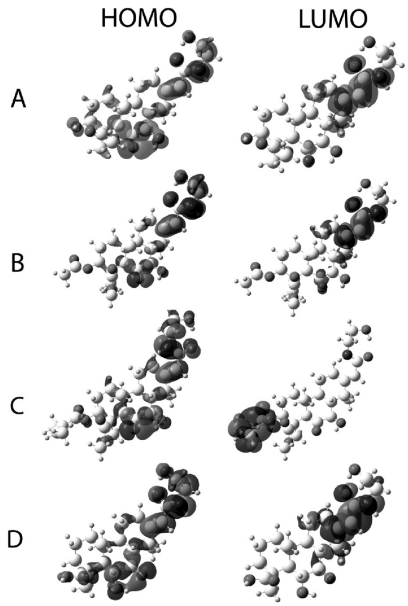

Figure 3: HOMO and LUMO distributions of four diterpenoid amides: (A) 3HDTA, (B) 3ADTA, (C) 3TDTA and (D) 6HDCA.

3.2. The antioxidant capacity of diterpenoid amides

3.2.1. The H atom transfer (HAT) mechanism

In this study, the BDEs(C-H) corresponding to the weakest C-H bond of each diterpenoid amides in the gas phase are computed at B3LYP/6-311G(d,p) level of theory (Table 1).

As a result, the highest H atom donating ability of the studied compounds follows decreasing trend: 3TDTA > 3HDTA ≈6HDCA >3ADTA. The lowest BDE(C–H) value is determined at C7–H position. The lowest BDE (C–H) of 3TDTA, 3HDTA, 6HDCA and 3ADTA are equal to 69.44, 70.52, 70.86 and 72.96 kcal/mol, respectively. The H-donating capacity at C7 is easier than the other C–H bonds because C6=O bond nearby C7 that makes this bond to dissociate easily. In comparison with BDE of phenol (89.4 kcal/mol)[5] and α-terpinene (74.4 kcal/mol)[6], these four compounds are the potential antioxidants via HAT mechanism.

3.2.2. The single electron transfer followed by proton transfer (SET-PT) mechanism

The ionization energy (IE) and electron affinity (EA) are important parameters of the antioxidants characterizing the single electron transfer (SET) mechanism. IE value is corresponding to the electron donating capacity. The electron affinity (EA) represents the amount of energy released when an electron is added to a neutral molecule in the gaseous state to form a negative ion. The lower IE value is, the easier electron transfer is, while the higher EA value is the easier electron acceptor is.

Hence, vertical IE and EA of diterpenoid amide compounds are systematically computed using the semi-empirical PM6 method. The results are reported in Table 2. IE values fluctuate from 9.37 (6HDCA) to 9.59 eV (3ADTA). In comparison with IE of phenol (8.49 eV), α-pinene (8.07 eV), limonene (8.3 eV)[7], the ones of these four diterpenoid amides are all higher. It means that the electron transfer is not favored in this case. In contrast, the four compounds have high EA values which follows the trend: 6HDCA (0.990 eV) > 3HDTA (0.979 eV) > 3ADTA (0.934 eV) > 3TDTA (0.714 eV). This illustrates that studied four diterpenoid amides may have the high antioxidant capacity via electron accepting capacity from free radicals.

Table 1: Calculated the BDE(C-H)s for diterpenoid amides in the gas phase by B3LYP/6-311G(d,p) model chemistry

Compounds	C–H bond positions	BDE(i), kcal/mol	ΔBDE*, kcal/mol	PA (kcal/mol)
3HDTA	C21–H	88.47	0.93	344.92
	C22–H	88.87	0.53	
	C14–H	78.92	10.48	
	C7–H	**70.52**	18.88	
3ADTA	C22–H	88.88	0.52	346.61
	C7–H	72.96	16.44	
3TDTA	C7–H	**69.44**	19.96	324.27
6HDCA	C22–H	89.02	0.38	338.22
	C6–H	**70.86**	18.54	
*ΔBDE = |BDE(O-H)phenol – BDE(C-H)|, (BDE(O-H)phenol = 89.4 kcal/mol[5])				

Table 2: Vertical ionization energy (IE), electron affinity (EA) calculated by PM6

Compounds	IE (eV)	EA (eV)
3HDTA	9.53	0.979
3ADTA	9.59	0.934
3TDTA	9.58	0.714
6HDCA	9.37	0.990

3.2.3. The sequential proton loss electron transfer (SPLET) mechanism

In the first step of the SPLET mechanism, diterpenoid amides donate a proton to free radicals that is characterized by proton affinity (PA) values. The easier proton donating capacity corresponds to lower PA value. The lower PA is described for higher antioxidant capacity via this mechanism. PA values of each diterpenoid amide calculated at B3LYP/6-311G(d,p) method are reported in Table 1.

As can be seen in Table 1, the calculated PA values of four compounds increase from 324.27 kcal/mol (for 3TDTA) to 346.61 kcal/mol (for 3ADTA). Thus, the antioxidant capacity follows decreasing trend: 3TDTA > 6HDCA > 3HDTA > 3ADTA corresponding to PA values of 324.27, 338.22, 344.92 and 344.92 kcal/mol, respectively. It means that 3TDTA may be the most potential antioxidant via this mechanism.

4. Conclusions

In this study, the antioxidant capacity of 4 diterpenoid amide compounds extracted from the leaves of *Erythrophleum fordii* has been studied via HAT, SET and SPLET mechanisms. Semi-empirical PM6 and B3LYP/6-311G(d,p) DFT methods were used to calculate various thermodynamic parameters including BDE, IE, EA and PA. The obtained results show that 3HDTA, 3ADTA, 3TDTA and 6HDCA represent as potential antioxidants via HAT mechanism. The easiest C–H breaking bond is usually found at the C7 atom located nearby π bonds. The SET mechanism demonstrates that 6HDCA is considered the most antioxidant potential with EA value of 0.99 eV. Via SPLET mechanism, 3TDTA and 6HDCA are high antioxidant capacity with PA value of 324.27 and338.22 kcal/mol, singly.

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