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EFFECTS OF SUBSTITUENTS ON C–H BOND DISSOCIATION ENTHALPIES OF *ENT*-KAURANE DITERPENOIDS: A DFT STUDY

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ABSTRACT

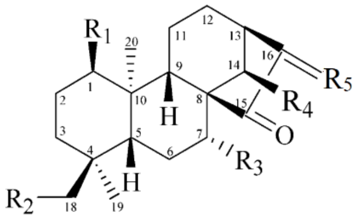
C–H bond dissociation enthalpies (BDEs) of seven *ent*-kaurane diterpenoids extracted from *Croton tonkinensis* Gagnep. have been investigated by using density functional theory (DFT) method. The calculations were performed at the M05-2X/6-31+G(d) level of theory. Additionally, insight into the effects of different substituents including $–NH_2$, –OH, $–NO_2$, –SH, –CN, –Cl, $–CONH_2$, $–CH-(CH_3)_2$, $–NHCOCH_3$, $–OCOCH_3$ and $–C_2H_5$ on BDE have also been provided. The results showed that the BDE value of *ent*-16(S)-18-acetoxy-7β-hydroxykaur-15-one compound is the lowest, being 83.5 kcal/mol. Among substituents binding at C16 position of this molecule, $–NH_2$ has the most remarkable influence on the BDE (C–H) value. Indeed, the BDE of C16–H significantly decreases from 83.5 to 68.4 kcal/mol when replacing $–CH_3$ group by $–NH_2$ one at the C16 position. The obtained results may provide more information for organic synthesis of *ent*-kaurane based – novel antioxidant compounds.

Keywords: DFT, BDE, *ent*-kaurane diterpenoids, substituent, antioxidant.

1. INTRODUCTION

The genus *Croton* L. (Euphorbiaceae) comprises of about 800 species which were primarily found in tropical areas among which 31 species are distributed in Vietnam [1]. *Croton tonkinensis* Gagnep., locally known as “Kho sam Bac Bo” or “Kho sam cho la” is a small indigenous plant in Northern Viet Nam. Its leaves have been used to treat burns (boils), abscesses, impetigo, abdominal pain, dyspepsia, gastric and duodenal ulcers [2], stomachache as well as to cure malaria paradise, urticarial, leprosy, psoriasis and genital organ prolapse [1-4]. Phytochemical investigations on C. *tonkinensis* have shown the presence of benzoic acid, sterols, long-chain alkyl alcohols, flavonoid glucosides [5] and *ent*-kaurane diterpenoids [6-13]. Recently, several studies revealed that the presence of *ent*-kaurane diterpenoids was correlated to toxicity [11] anti-inflammatory and cancel chemo-preventive activities [9, 16], which prompted us to continuously investigate the antioxidant potential of these phytochemical constituents.

In this study, the C–H bond dissociation enthalpies (BDEs) of seven *ent*-kaurane diterpenoids extracted from *Croton tonkinensis* Gagnep including: *ent*-18-acetoxy-7β-hydroxykaur-16-en-15-one (**1**) [15, 16], *ent*-1α-acetoxy-7β,14α-dihydroxykaur-16-en-15-one (**2**) [7, 9], *ent*-16(S)-18-acetoxy-7β-hydroxykaur-15-one (**3**) [10, 16], *ent*-7β,14α-dihydroxykaur-16-en-15-one (**4**) [9,17], *ent*-18α-acetoxy-7α,14β-dihydroxykaur-16-en-15-one (**5**) [9], *ent*-1α,14α-diacetoxy-7β-hydroxykaur-16-en-15-one (**6**) [10], *ent*-1α,7β-diacetoxy-14α-hydroxykaur-16-en-15-one (**7**) [10] compounds (Figure 1) are systematically calculated at M05-2X/6-31+G(d) level of theory in order to evaluated the antioxidant potential via hydrogen atom transfer (HAT) mechanism. In addition, the effects of different substituents such as $–NH_2$, –OH, $–NO_2$, –SH, –CN, –Cl, $–CONH_2$, $–CH\text{-}(CH_3)_2$, $–NHCOCH_3$, $–OCOCH_3$ and $–C_2H_5$ on BDE values will be investigated in the attempt to ameliorate their antioxidant activity.



Compound	R_1	R_2	R_3	R_4	R_5
1	H	OAc	OH	H	$=CH_2$
2	OAc	H	OH	OH	$=CH_2$
3	H	OAc	H	OH	$-CH_3$
4	H	H	OH	OH	$=CH_2$
5	H	OAc	OH	OH	$=CH_2$
6	OAc	H	OH	OAc	$=CH_2$
7	OAc	H	OAc	OH	$=CH_2$

Figure 1. Chemical structures of seven *ent*-kaurane diterpenoids.

2. COMPUTATIONAL METHOD

All calculations were performed using the Gaussian 09, revision E.01 program package [19]. The geometry optimization and vibrational frequency calculation were conducted at the M05-2X/6-31+G(d) level of theory. Hydrogen atom transfer (HAT), an important antioxidant mechanism, is considered in our study [19, 20].

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

BDE value was calculated in the gas phase as follows [21, 22]:

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

where H is the total enthalpy of the studied species at 298.15 K, 1 atm and is usually estimated from the expression:

$$H(T) = E_0 + ZPE + H_{trans} + H_{rot} + H_{vib} + RT.$$

in which H_{trans}, H_{rot}, 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. The enthalpy value for the hydrogen atom in the gas phase is calculated at the same level of theory.

3. RESULTS AND DICUSSION

3.1. Optimized structure of seven *ent*-kaurane diterpenoids

Figure 2 shows the views of geometrical structures of seven *ent*-kaurane diterpenoids optimized at the M05-2X/6-31+G(d) level of theory in the gas phase.

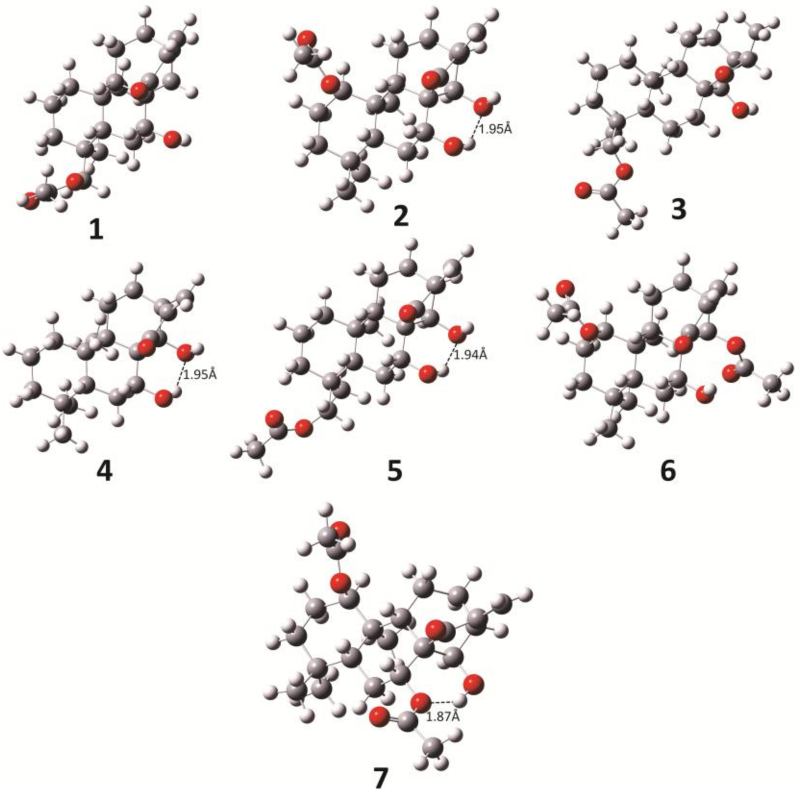


Figure 2. Chemical structures of seven *ent*-kaurane diterpenoids optimized at the M05-2X/6-31+G(d) level of theory.

It can be seen that all the molecules are characterized by three cyclohexane rings fused together. The structures of some molecules such as compounds **2**, **4**, **5** and **7** are stabilized by forming intra-molecular hydrogen bonding between O atoms with high electron density and neighboring H-atom. The lengths of hydrogen bond recognized in compounds **2**, **4** and **5** forming between C7–OH…OH–C14 vary about from 1.94–1.95 Å, whereas the hydrogen bond length of C14–OH…O–Ac at C7 position in compound **7** is approximately 1.87 Å.

3.2. C–H bond dissociation enthalpies (BDEs) of seven *ent*- kaurane diterpenoids

BDE is a key parameter to evaluate the activity of an antioxidant via hydrogen atom transfer mechanism (HAT). The lowest BDE is defined for the relevant position of C–H/O–H where the easiest hydrogen atom donating can take place.

The BDE value of all possible C–H/O–H bonds were firstly calculated by PM6 semi-empirical method to determine which bond is the weakest. The BDEs of evaluated bonds were then being calculated at the higher M05-2X/6-31+G(d) level of theory. The M05-2X method gives the closest results to the experimental values compared to other DFT methods (*i.e.* calculated at M05-2X/6-311+G(d,p) and experimental BDEs for quercetin are 87.6 and 87.2 kcal/mol, respectively) [19]. The results obtained for the studied compounds are displayed in Table 1.

Table 1. BDE(C–H) values of seven *ent*-kaurane diterpenoids calculated at the M05-2X/6-31+G(d) level of theory in the gas phase.

Compound	**C–H bond position**	**BDE(i), kcal/mol**	**ΔBDE*, kcal/mol**
1	C5–H	89.9	0.5
2	C9–H	90.8	1.4
3	C16–H	**83.8**	–5.5
4	C5–H	90.3	0.9
5	C5–H	89.8	0.4
6	C7–H	88.0	–1.4
7	C14–H	90.3	0.9

ΔBDE = BDE(C–H) - BDE(O–H)$_{phenol}$, BDE(O–H)$_{phenol}$ = 89.4 kcal/mol [23]

It is observed that the BDE(C–H) values vary from 83.8 to 90.9 kcal/mol. The easiest H-donating ability at C16 of compound **3** with BDE(C–H) of 83.8 kcal/mol can be explained by the reason that the electron-withdrawing inductive effect (–I) of C17=O group induces an electron-releasing phenomenon from the carbon atom, and consequently increases the polarization of the C16–H bond. The H-atom donating capacity of the analyzed compounds follows decreasing trend: compound **3** > compound **6** > compound **5** ≈ compound **1** > compound **4** ≈ compound **2**.

In comparison with BDE(O–H) of phenol (89.4 kcal/mol) [23] and α-terpinene (74.4 kcal/mol) [24], almost the BDE (C–H) values of these compounds are higher, except the one of compound **3**. It means that these seven studied *ent*-kaurane diterpenoids do not show considerable antioxidant activity via HAT mechanism. A computational-design study is needed in order to improve their activity. This can be achieved by adding various substituents on the structure of parent molecules.

3.3. The effect of various substituents on BDE (C–H)

Compound **3** which has the lowest BDE(C–H) value among studied compounds, was chosen for the calculation of substituent effects. Methyl group located at C16-position is replaced by various substituents including $–NH_2$, –OH, $–NO_2$, –SH, –CN, –Cl, $–CONH_2$, $–CH-(CH_3)_2$, $–NHCOCH_3$, $–OCOCH_3$ and $–C_2H_5$. These selected groups represent for different electron-withdrawing (–I) and donating (+I) effects. The BDE(C16–H) of all modified structures were calculated at the M052X/6-31G level of theory and displayed in Table 2.

Table 2. Influences of substituents on BDE(C16–H) values (kcal/mol) calculated at the M052X/6-31G level of theory.

Substituents	**BDE(C16–H)**	**ΔBDE***
$-CH_3$	83.5	–5.9
-H	98.5	9.1
-OH	77.4	–12.0
-Cl	88.6	–0.8
-CN	83.4	–6.0
$-NH_2$	**68.4**	**–21.0**
$–NHCOCH_3$	76.4	–13.0
$–OCOCH_3$	87.0	–2.4
$–C_2H_5$	84.1	–5.3
$–CONH_2$	84.0	–5.4
$–CH-(CH_3)_2$	83.7	–5.7
$–NO_2$	89.1	–0.3
–SH	81.2	–8.2

ΔBDE = BDE(C–H) – $BDE(O–H)_{phenol}$, $BDE(O–H)_{phenol}$ = 89.4 kcal/mol [23]

As can be seen in Table 2, the calculated BDE(C16–H) value significantly varies when changing substituent groups at C16 position. Moreover, the substituents exhibiting high electron densities with the presence of lone pair of electrons such as $–NH_2$, $–NHCOCH_3$, $–OCOCH_3$, –SH, –OH influence more strongly on BDE than others.

Particularly, the BDE value noticeably decreases from 83.5 to 68.4 kcal/mol when $–CH_3$ is replaced by $–NH_2$ group. Thus, $–NH_2$ has the most influence on the BDE(C–H) value among substituents binding at C16 position of this molecule.

In addition, it is worth to note that the modification of compound **3** by –OH, $–NH_2$ and $–NHCOCH_3$ groups may improve the antioxidant capacity via HAT mechanism of the molecule. In comparison with BDE(O-H) of phenol (89.4 kcal/mol) [23] BDE(C–H) values of modified molecules with –OH, $–NH_2$ and $–NHCOCH_3$ are much lower, showing ΔBDE of –12.0, –21.0 and –13.0 kcal/mol, respectively.

4. CONCLUSIONS

In this study, the BDE thermochemical parameter characterizing for HAT antioxidant mechanism of seven *ent*-kaurane diterpenoids extracted from *Croton tonkinensis* Gagnep. has been calculated using density functional theory (DFT) method. The obtained results reveal that BDEs calculated at M05-2X/6-31+G(d) vary from 83.8 to 90.9 kcal/mol. These studied compounds do not represent as potential antioxidants via HAT mechanism.

Additionally, insight into the effect of different substituents on BDE(C16–H) has been provided by replacing $–CH_3$ group at C16 position of compound **3** by $–NH_2$, –OH, $–NO_2$, –SH, –CN, –Cl, $–CONH_2$, $–CH\text{-}(CH_3)_2$, $–NHCOCH_3$, $–OCOCH_3$ and $–C_2H_5$ groups. The results showed that $–NH_2$ group has the most remarkable effect to BDE(C16–H) and the antioxidant capacity via HAT mechanism significantly increases in the cases of –OH, $–NH_2$ and $–NHCOCH_3$ substituents. This finding may provide more information for organic synthesis of *ent*-kaurane based – novel antioxidant compounds.

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