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SUBSTITUENT EFFECTS ON THE ANTIOXIDANT ACTIVITY OF MONOSUBSTITUTED 3,3'-DIINDOLYLMETHANE: A DFT STUDY

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Abstract: 3,3'-diindolylmethane (DIM) is an indole compound with proven health benefits and thus potential preventive medicine and therapeutic applications. Herein, the origins of the substituent effects on the antioxidant activity of monosubstituted 3,3'-diindolylmethanes (DIMs) were studied *in silico* by calculating their thermochemical properties using the (RO)B3LYP/6–311++G(2df,2p)//B3LYP/6–31G(d) method. It was found that the compounds 2-NHMe-DIM, 2-OH-DIM and 2–MeO-DIM have the lowest BDE(N1–H) values (78.4–78.9 kcal.mol^{-1}), while that for the C8–H bond is observed in the 2-HO-DIM compound (67.0 kcal.mol^{-1}). The presence of substitutes can decrease the ionization energies of the DIMs, however the effects of substitutes on the proton affinity were not clearly observed. The investigation on the HOO$^{\bullet}$ radical scavenging following the hydrogen atom transfer mechanism indicated that the compound 2-NHMe-DIM has the highest rate constant with k = 9.72×10^9 L.mol^{-1}.s^{-1}. Thus, it is suggested that the 2-NHMe-DIM is a powerful antioxidant.

Key words: antioxidants; indole; Brassica; bond dissociation energies; substituent effects; 3,3'-diindolylmethane; glucosinolates.

1. Introduction

Antioxidants play an important role in reducing the effect of oxidants in the environment as well as within the human body [1, 3]. Among synthetic and natural antioxidants, DIM and its derivatives stand out for their high antioxidant efficiency [4, 6]. 3,3'-Diindolylmethane (DIM) (Figure 1) formed by the hydrolysis of indole glucosinolates in the human body under enzyme conditions, has potentially useful biological activity including the activity of enzyme systems in drug metabolism the anti-cancer properties with low toxicity,

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and the antioxidant activity [4, 5, 7-10]. The experimental studies showed that DIM and its derivatives have potential radical scavenging activities and some of their derivatives exhibit greater antioxidant activity than vitamin E (i.e., *α*-tocopherol) in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) model expressed by IC$_{50}$ values [5]. The theoretical studies also indicated that the indole family has potential antioxidant properties [6, 11]. Previous studies also showed that the hydrogen atom transfer (HAT) mechanism plays an important role in the antioxidant activity in lipophilic environments (biological environments) [12, 13]. Thus, the bond dissociation energy (BDE) of the X–H (X = C, N) is a key descriptor of the antioxidant activity of antioxidants including DIMs. However, most of the studies only focused on evaluation of antioxidant properties of the indole-3-carbinols [4, 5, 11], while DIM which is more stable intermediates of the hydrolysis of glucobrassicin, has not been studied with regard to its antioxidant activity yet. Thus the investigation of substituent effects on the antioxidant activity of DIM derivatives following three typical mechanisms (HAT, the single electron transfer followed by proton transfer (SETPT), the sequential

proton loss electron transfer (SPLET) [13,14]) by calculating the thermal properties (i.e. BDEs, IEs and PAs) is necessary to evaluate the antioxidant activity of their family compounds. Hence, the purpose of this study is to investigate the influence of various substituents in the indole ring on the thermochemical properties of the X–H (X = N, C) bonds of the monosubstituted DIMs and evaluate the antioxidant activity of these compounds.
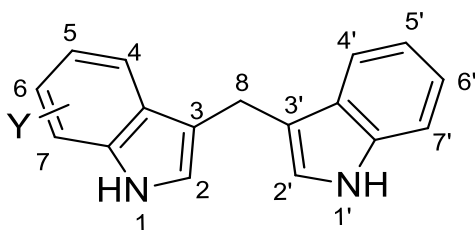
Y = CF₃, Cl, CN, F, Me, NMe₂, NH₂, NHMe, OH, OMe, Ph

Figure 1. *3,3'-diindolylmethane (DIM) and derivatives*

2. Computational methods

The thermochemical properties of the compounds were obtained following well established methodologies[15,16] by using the Gaussian 09 suite of programs [17]. All of the compounds and related radicals, cationic radicals, and anions were optimized, and their vibrational frequencies were determined at the B3LYP/6−31G(d) level of theory. The single point electronic energies were then calculated by the (RO)B3LYP/6−311++G(2df,2p) method [13,18]. The lowest electronic energy conformer that contains possible intermolecular hydrogen bonds was used for further analysis [16, 19, 20]. The antioxidant mechanisms were analyzed following previously described methodology [13, 14, 16]. The reaction enthalpies of the individual steps of the radical scavenging mechanism in gas phase (at 298.15 K and 1 atm) were calculated according to the literature [14, 21, 22].

The enthalpy value for the hydrogen atom in the gas phase was calculated at the same level of the studied compounds. The calculated enthalpies of the proton (H⁺) and electron (e⁻) were taken from the literature [14, 23-25]. Vibrational frequencies obtained at the

B3LYP/6-31G(d) level of theory were scaled by a factor of 0.9594 [26, 27].

3. Results and discussions

3.1. Bond dissociation energies and the hydrogen atom transfer (HAT) mechanism

3.1.1. Evaluation

Previous studies have shown that the BDE value is a key parameter to evaluate the activity of an antioxidant following the HAT [13, 14, 28]. Thus, the BDEs of all possible X–H (X = C, O, N) bonds breaking in the DIM compound were calculated and presented in the Figure 2. It was shown that the BDE of (C8–H) is significantly lower than that of the N1–H bond by 8.1 kcal.mol⁻¹. To fully evaluate the effects of substituents on the antioxidant activity of DIM derivatives, therefore, in this work we focus on both the C8–H, N1–H and N1'–H bonds.
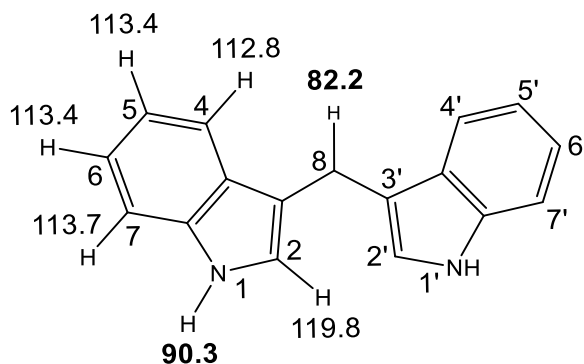

Figure 2. *The calculated BDEs(X–H) (X = N, C) of DIM*

3.1.2. BDE(X–H) (X = N, C) of monosubstituted 3,3'-diindolylmethane and the effect of substituents

The introduction of the substituents with different nature into an aromatic ring gives compounds with unique properties. To fully evaluate the effects of the substituents on the BDEs(X–H) (X = N, C) in all positions, the BDEs(X–H) (X = N, C) for these substituted DIMs were calculated in a gas phase and the results were given in Table 1. It is generally observed that the effects of substituents on BDE values of C−8 and N1−H bonds are more significant than those of N1'−H. Thus, the BDE values were obtained in the range of 67.0−84.8 kcal.mol⁻¹ and 78.4−94.0 kcal.mol⁻¹ for the C8−H and N1−H bonds, respectively. However,

the rule of the substituent effect is not clear in all positions. In the 2 and N positions, the effect of substituents on the change of BDE(X–H) values is significant, while that is minor for other positions. For example, the presence of Cl and OH at N and 2 positions reduces the BDE(N–H) to −12.3 and −15.2 kcal.mol^{-1}, respectively, compared with the parent DIM, whereas the BDE(C8–H) values are considerably low in

the presence of OH, NHMe and MeO groups by approximately 11 kcal.mol^{-1}. Thus, the lowest BDE(C8–H) is observed at the 2-HO-DIM with 67.0 kcal.mol^{-1}, whilst that of BDE(N–H) is found at the 2-NHMe-DIM, 2-OH-DIM and 2−MeO-DIM in the range of 78.4–78.9 kcal.mol^{-1}. On the basis of these calculated values, these compounds are the most potential antioxidants following the HAT mechanism.

Table 1. *The calculated ΔBDEs (compared with DIM) in gas phase of monosubstituted DIMs*

Y	Substitution position																
	2			4			5			6			7			N	
	C8	N1	N1'	C8	N1	N1'	C8	N1	N1'	C8	N1	N1'	C8	N1	N1'	C8	N1
CF$_3$	-4.2	0.0	0.5	-3.4	0.9	-0.5	0.4	1.4	1.0	-2.0	0.2	-1.3	0.0	3.5	0.4	-1.0	-0.8
Cl	-1.6	-3.0	0.3	2.6	-1.1	0.2	0.3	0.6	0.7	-1.5	-1.5	-1.0	0.1	2.3	0.3	-12.3	-1.1
CN	-3.5	1.4	0.9	2.1	0.9	1.5	0.4	1.6	1.4	-1.3	0.2	-0.5	0.0	3.7	0.7	-1.4	-0.4
F	-1.2	-6.0	0.5	1.9	-0.7	0.4	0.2	0.4	0.5	-1.5	-2.0	-1.2	0.1	1.2	0.3	-7.4	-0.8
Me	-2.0	-1.4	-0.1	0.8	-1.1	-0.9	-0.1	-0.3	-0.11	-1.6	-2.3	-1.5	0.0	-0.6	-0.1	-1.8	-1.5
NMe$_2$	-2.0	-8.7	-0.2	0.5	-2.8	-1.4	-0.3	-4.1	-0.3	-1.8	-7.6	-1.7	0.1	-5.2	-0.2	-1.7	-1.4
NH$_2$	-3.4	-8.8	-0.3	-0.6	-8.0	-0.4	-0.4	-2.2	-0.4	-1.9	-6.3	-1.8	0.2	-6.8	-0.1	-1.8	-1.4
NHMe	-3.3	-11.2	-0.1	1.9	-4.1	1.5	-0.4	-2.7	-0.6	-2.0	-7.8	-1.8	0.1	-7.8	-0.2	-1.8	-1.4
OH	-15.2	-11.1	0.0	2.1	-2.3	-0.2	0.2	-1.0	0.2	-2.2	-4.3	-2.0	0.0	1.2	-0.1	-1.7	-1.3
OMe	-1.0	-11.6	0.0	1.7	-2.4	-0.9	0.1	-1.7	0.1	-1.9	-4.4	-1.6	0.0	-1.0	-0.2	-1.8	-1.3
Ph	-4.0	-0.6	-0.1	-3.6	-0.7	0.4	-0.1	-0.1	0.1	-1.5	-2.1	-1.3	-3.6	-3.3	-3.7	-1.8	-1.4
DIM: BDE(N–H) = 90.3 kcal.mol^{-1}, BDE(C8–H) = 82.2 kcal.mol^{-1}																	

Table 2. *The calculated vertical ΔIEs (kcal.mol^{-1}) (compared with phenol) in gas phase of monosubstituted DIMs*

Y	Substitution position					
	2	4	5	6	7	N
CF$_3$	-28.6	-31.8	-28.6	-28.1	-28.6	-27.0
Cl	-32.3	-35.1	-31.6	-32.1	-31.8	-30.7
CN	-26.3	-31.1	-26.5	25.8	-26.5	-23.8
F	-32.3	-35.3	-31.8	-32.1	-32.1	-27.0
Me	-36.9	-37.4	-36.0	-36.7	-36.2	-37.4
NMe$_2$	-39.4	-43.1	-45.9	-49.6	-40.1	-37.4
NH$_2$	-39.2	-43.4	-42.0	-43.4	-39.2	-35.7
NHMe	-42.9	-46.6	-44.7	-47.3	-39.0	-36.7
OH	-35.5	-40.6	-37.4	-37.6	-37.6	-34.1
OMe	-36.4	-42.0	-39.7	-40.4	-39.0	-35.5
Ph	-38.5	-38.5	-37.1	-38.5	-41.1	-38.3
IE $_{vertical}$ (DIM) = 162.8 kcal.mol^{-1}; IE $_{vertical}$ (phenol) = 196.9 kcal.mol^{-1}						

3.2. Ionization energies and the sequential electron transfer proton transfer mechanism

The SETPT mechanism is characterized by the ionization energy (IE) and the proton dissociation energy. The first step (the sequential electron transfer) plays a key role in the antioxidant activity following the

SETPT mechanism [13, 29]. Thus, the vertical ΔIE values of the monosubstituted DIMs, which are compared with those of phenol, were calculated using the same model in gas phase and shown in the Table 2. As can be seen from the Table 2, the presence of the substitutes reduced the IEs of the studied compounds by

about 23.8–49.6 kcal.mol^{-1}. In which, the greatest reduction of IEs is related to the electron donating group (EDG) such as NMe$_2$, NHMe, NH$_2$, OH, MeO and Ph by around 36 kcal.mol^{-1} (Table 2). Generally, a compound is considered to follow the SET mechanism when the absolute value of ΔIE (relative to phenol) is higher than 36 kcal/mol [13, 30]. Hence, this implies that a sequential electron transfer mechanism is responsible for these DIMs with strong EDG substituents including NMe$_2$, NHMe, NH$_2$, OH, MeO and Ph, while a HAT mechanism is favored for the remaining monosubstituted DIMs.

3.3. Proton affinities and the sequential proton loss electron transfer mechanism

The potential for the SPLET mechanism was also assessed; SPLET is defined by the proton affinity (PA) and the electron transfer enthalpies [31, 32]. The proton loss process is the first step of the SPLET mechanism and governs the SPLET mechanism [32]. To further exploit this point, the ΔPAs of studied compounds compared with the DIM (DIM: PA(N1–H) = 347.2 kcal.mol^{-1}, PA(C8–H) = 371.1 kcal.mol^{-1}) were calculated in gas phase and shown in the Table 3.

Table 3. The calculated ΔPAs in gas phase of monosubstituted DIMs

Y	Substitution position																
	2			4			5			6			7			N	
	C8	N1	N1'	C8	N1	N1'	C8	N1	N1'	C8	N1	N1'	C8	N1	N1'	C8	N1
CF$_3$	-4.1	-8.4	-0.3	13.1	-7.1	-3.7	5.2	-6.4	0.4	4.7	-6.6	-0.9	4.8	-3.7	-1.0	1.2	-1.5
Cl	4.8	-7.2	1.5	12.4	-6.1	-1.2	7.9	-2.9	1.4	7.0	-2.9	0.5	7.1	-1.0	0.6	-62.5	-0.3
CN	-10.2	-11.8	-2.2	0.9	-9.7	-1.6	-2.4	-10.1	-0.8	1.8	-10.2	-2.5	1.7	-6.9	-2.5	-7.2	-4.0
F	6.8	-8.1	1.8	12.2	-1.7	-0.3	5.1	-0.7	1.8	8.3	-0.7	1.1	8.3	-0.3	1.1	-9.8	-2.0
Me	10.1	2.9	2.9	11.5	2.6	1.8	11.6	3.3	2.9	11.5	3.5	3.1	11.3	2.8	3.1	10.4	3.0
NMe$_2$	9.2	-1.2	3.8	11.8	-0.3	0.5	24.5	2.9	3.3	12.2	4.0	1.2	25.0	2.3	3.2	9.7	2.6
NH$_2$	14.2	-0.8	1.7	0.9	1.3	-1.5	12.5	4.8	3.5	12.7	5.5	4.0	11.3	0.3	3.5	-3.3	2.3
NHMe	12.9	-0.5	6.3	6.8	4.8	-1.3	13.0	6.0	3.6	12.9	5.7	4.2	11.6	2.1	11.4	8.0	2.5
OH	-43.4	-7.6	-1.5	15.3	2.2	1.4	12.3	2.7	3.9	10.2	2.4	2.0	11.6	5.0	3.2	1.4	1.9
OMe	10.7	-5.8	3.4	15.2	3.3	4.8	12.3	3.2	4.0	11.1	3.6	2.8	13.5	3.6	5.8	-17.6	1.4
Ph	-4.5	-1.3	2.1	13.7	0.2	1.2	7.6	1.4	-1.5	8.4	-1.4	1.7	5.1	-4.2	-1.7	3.9	1.3
DIM: PA(N1–H) = 347.2 kcal.mol^{-1}, PA(C8–H) = 371.1 kcal.mol^{-1}																	

It is clear from the Table 3 that the effects of substitutes on the PAs are not clearly observed for each position. While the presence of the strong EWGs (CF$_3$, CN, F, Cl) seemed to reduce the PA values, EDGs (Me, NMe$_2$, NH$_2$ NHMe) rose those values. Considering the same substitute, the effect of the substitutes on the PA(C8–H)s is more significant than that for the PA(N–H)s. The lowest PA(C8–H) is observed at the Cl-N-DIM with 308.6 kcal.mol^{-1}, while that for the PA(N–H) is found at 2-CN-DIM with 335.4 kcal.mol^{-1}. Thus Cl-N-DIM has the lowest PA value in all the studied compounds. Among the calculated PA values, the Cl-N-DIM derivative has the highest antioxidant activity.

3.4. HAT mechanism reaction of HOO* radical with the selected studied compounds

3.4.1. Potential energy surface (PES)

The free energy change of the first step calculated for each mechanism in a reaction of the selective compounds with HOO$^•$ radicals in vacuum indicated that the reactions following the sequential proton and sequential electron transfer mechanisms are not spontaneous in either of the studied environments; only the HAT pathway yielded exothermic and spontaneous reactions. Hence the SETPT and SPLET mechanisms are generally not favored for the HOO$^•$ radical scavenging activity of any of the studied DIMs in the gas phase. On the basis of the calculated data, the HAT mechanism appears to be the main radical scavenging pathway for the monosubstituted DIMs in the non-polar environments, thus the study on the PES was only focused in this mechanism.

In this study, the reactions of compounds DIM, 2-NHMe-DIM, 2-OH-DIM and 2−MeO-DIM with a HOO• radical were studied to glean further insights into the antioxidant capacity of the DIMs. The B3LYP/6-31G(d) method was used to calculate the energies of the reactants (R), the transition states (TS), the intermediates (Int) and the products (P). The PESs are displayed in Figure 3 and all optimized TS structures are shown in Figure 3.

Examination of the structures of the TSs reveals that the H···OOH and X···H (X = C8, N1) distances are in the range of 1.226−1.366 Å and 1.156−1.329 Å, respectively.

The X···H···O (X = C8, N1) angles are in the range of 166.2−177.4° (Figure 4). It is clear from Figure 2 that the energies of the studied TSs are in the range of −4.6 to 8.1 kcal.mol^{-1}. The compound 2-NHMe-DIM-N-H-OOH is expected to have the highest antioxidant activity because of the lowest energy of its transition state (−4.7 kcal.mol^{-1}), which is in a good agreement with the conclusions of the analysis presented above.
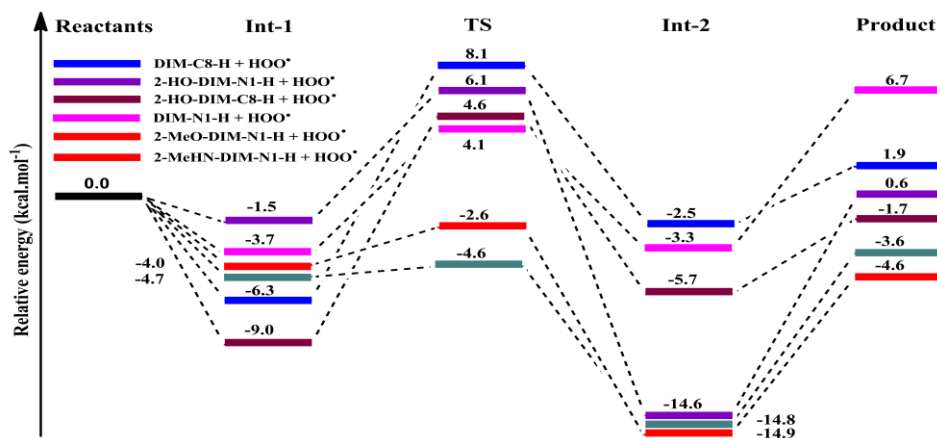
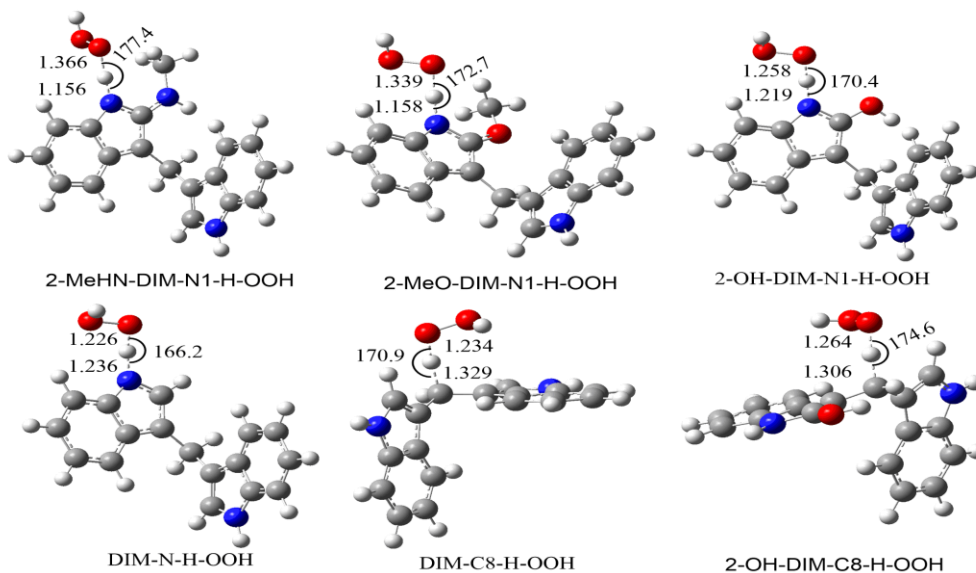

Figure 3. PES of reaction between the selected compounds and HOO•

Figure 4. Optimized geometries of transition states according to HAT mechanism between the selective compounds and HOO• radical in gas phase

3.4.2. Kinetic study

For further insights into the HOO$^\bullet$ radical scavenging activity of the selective compounds, calculations of the kinetics of the reactions were also performed. The Gibbs free energy of activation ($\Delta G^{\neq}$) and rate constants (k) were calculated at the B3LYP/6-31G(d) level at 298.15 K and presented in Table 4.

Table 4*. The calculated $\Delta G^{\neq}$ and k at the B3LYP/6-31G(d) level of theory at 298.15 K in the gas phase*

Reaction	$\Delta G^{\neq}$	k_{eck}
DIM-N-H-OOH	12.3	1.93×10^5
DIM-C8-H-OOH	16.6	1.37×10^2
2-OH-DIM-C8-H-OOH	13.8	1.25×10^4
2-OH-DIM-N-H-OOH	9.5	3.74×10^8
2-MeO-DIM-N-H-OOH	6.5	3.80×10^8
2-NHMe-DIM-N-H-OOH	4.0	8.72×10^9

As can be seen from the Table 4, the rate constants are in the range of 1.25×10^4–8.72×10^9 L.mol^{-1}.s^{-1}. It is also worth noting that the DIM-N-H+ HOO$^\bullet$ reaction has a lower energy barrier and proceeds faster than the DIM-C8-H+ HOO$^\bullet$ reaction ($\Delta G^{\neq}$ = 12.6 kcal.mol^{-1}, k = 1.93×10^5 L.mol^{-1}.s^{-1} compared to $\Delta G^{\neq}$ = 16.6 kcal.mol^{-1}, $k = 1.37\times10^2$ L.mol^{-1}.s^{-1} for the DIM-C8-H+ HOO$^\bullet$ reaction) despite the lower BDE value of DIM-C8-H compared with the DIM-N-H. This deference needs further investigation. It was found that compounds 2-NHMe-DIM and 2-MeO-DIM have the highest rate constants for N1−H bond with $k = 9.72\times10^9$ and 3.80×10^8 L.mol^{-1}.s^{-1}, respectively. These reactions are faster than the HOO$^\bullet$ radical scavenging of Trolox or ascorbic acid (k_{Trolox} = 5.30×10^5 L.mol^{-1}.s^{-1}, k_{Asc} = 2.65×10^5 L.mol^{-1}.s^{-1})[31,33]. This again suggests that compounds 2-NHMe-DIM and 2-MeO-DIM are promising antioxidants.

4. Conclusions

The effects of substituents on the thermochemical properties and the antioxidant activity of DIM derivatives have been investigated using the (RO)B3LYP/6−311++G(2df,2p)//B3LYP/6−31G(d) method. It was found that the lowest BDE(C8−H) is observed at the 2-HO-DIM with 67.0 kcal.mol^{-1}, whereas that for BDE(N−H) is found at the 2-NHMe-DIM, 2-OH-DIM and 2−MeO-DIM in the range of 78.4–78.9 kcal.mol^{-1}. The effects of substitutes on the proton affinity are not clearly observed, while a presence of substitutes can reduce the ionization energies of DIMs. The investigation of the HOO$^\bullet$ radical scavenging following the HAT mechanism indicated that the compound 2-NHMe-DIM has the highest rate constant with k = 9.72×10^9 L.mol^{-1}.s^{-1}. Thus the 2-NHMe-DIM compound is a promising antioxidant.

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NGHIÊN CỨU DFT VỀ ẢNH HƯỞNG CỦA NHÓM THẾ LÊN HOẠT TÍNH CHỐNG OXY HÓA CỦA DẪN XUẤT THẾ MỘT LẦN TỪ 3,3'-DIINDOLYLMETHANE

Tóm tắt: 3,3'-diindolylmethane (DIM) là một hợp chất indole với các lợi ích sức khỏe đã được chứng minh, có tiềm năng trong y học dự phòng và các ứng dụng điều trị. Ở đây, cơ sở ảnh hưởng của nhóm thế lên hoạt tính chống oxi hóa của các dẫn xuất 3,3'-diindolylmethane thế một lần (DIMs) đã được nghiên cứu bằng tính toán các tính chất nhiệt động hóa học của DIMs sử dụng lý thuyết DFT tại mức lý thuyết (RO)B3LYP/6−311++G(2df,2p)//B3LYP/6−31G(d). Kết quả đã cho thấy các hợp chất 2-NHMe-DIM, 2-OH-DIM and 2-MeO-DIM có giá trị BDE(N1-H) thấp nhất (78.4−78.9 kcal.mol^{-1}), trong khi BDE thấp nhất tại liên kết C8-H của hợp chất 2-HO-DIM (67.0 kcal.mol^{-1}). Sự hiện diện của nhóm thế có thể làm giảm năng lượng ion hóa của DIMs, tuy nhiên các ảnh hưởng của nhóm thế lên ái lực proton không được quan sát rõ ràng. Khảo sát khả năng bắt gốc tự do HOO• theo cơ chế chuyển nguyên tử hdro cho thấy hợp chất 2-NHMe-DIM có hằng số tốc độ lớn nhất với k = 9.72×10^9 L.mol^{-1}.s^{-1}. Do đó, chúng tôi đề xuất 2-NHMe-DIM là hợp chất có hoạt tính chống oxi hóa cao nhất của DIMs.

Từ khóa: Antioxidants; indole; Brassica; bond dissociation energies; substituent effects; 3,3'-diindolylmethane; glucosinolates.