

THERMOCHEMICAL PARAMETERS OF ERGOTHIONEINE: A DFT STUDY USING M06, WB97XD AND TPSSTPSS METHODS

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ABSTRACT

Antioxidant properties of ergothioneine (ESH) have been investigated via hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET) mechanisms. Three new DFT methods including M06, WB97XD and TPSSTPSS at the 6-311++G(2df,2p) basis set were used to compute the thermochemical parameters of ESH in the gas phase. Based on these methods, bond dissociation enthalpy (BDE), ionization energy (IE), proton dissociation enthalpy (PDE), proton affinity (PA) and electron transfer enthalpy (ETE) were calculated. The results were also compared with the values obtained by B3LYP method. The calculated results show that ergothioneine plays a role as a potential antioxidant via HAT mechanism.

Keywords: ergothioneine, antioxidant, HAT, SET-PT, SPLET, BDE, IE, PA, ETE.

1. INTRODUCTION

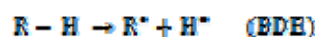
Antioxidants have played an important role in protection against oxidative stress present in food as well as human (health) biology. Particularly, natural and safer antioxidants have received great interest for food, pharmacological and medicinal applications [1]. Ergothioneine (ESH) (2-mercaptohistidine trimethylbetaine) based on histidine, one of classes of intracellular thiols, is also a typical natural antioxidant. ESH is found in most plant and animal tissues such as sea urchin eggs and has many beneficial roles in human health [2, 3], especially its role as an effective scavenger for reactive oxidative species [3]. ESH has also been used to reduce the toxicity of N-acetyl-cysteine to neuronal cells and protects cells against peroxy nitrite-dependent DNA damage [4]. Theoretical DFT studies evaluate the structure of these thiols and the thermodynamics of their reaction with alkyl thiols, HO[•] and H₂O₂ [5].

In this study, we aim to find out on detail the antioxidant capacity of ergothioneine (ESH) via three different antioxidant mechanisms including hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET)) by using density functional theory (DFT)-based computational method. Three new DFT methods namely M06, WB97XD and TPSSTPSS were employed to calculate various thermodynamic parameters including BDE, IE, PDE, PA and ETE. The obtained results were also compared with the computed B3LYP ones at the same basis sets.

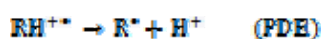
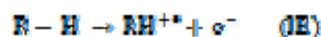
2. THEORETICAL AND COMPUTATIONAL METHODS

The geometry optimization and the vibrational frequency calculation of each compound and the corresponding radical, cationic radical and anion were primarily performed at the B3LYP/6-311G(d,p) level of theory [6]. Their single point electronic energies were then calculated at the 6-311++G(2df,2p) level of theory using four DFT methods namely B3LYP, M06, WB97XD and TPSSTPSS. Generally, three common mechanisms of antioxidant action have been proposed and widely accepted as follows [7, 8]:

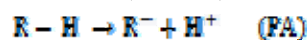
- Hydrogen atom transfer (HAT)



- Single electron transfer followed by proton transfer (SET-PT)



- Sequential proton loss electron transfer (SPLET)



The reaction enthalpies of an antioxidant in gas phase at 298.15 K and 1 atm are calculated as follows:

$$\text{BDE} = H(\text{R}^\bullet) + H(\text{H}^\bullet) - H(\text{R-H}) \quad (1)$$

$$\text{IE} = H(\text{RH}^{\bullet+}) + H(\text{e}^-) - H(\text{R-H}) \quad (2)$$

$$\text{PDE} = H(\text{R}^\bullet) + H(\text{H}^+) - H(\text{RH}^{\bullet+}) \quad (3)$$

$$\text{PA} = H(\text{R}^-) + H(\text{H}^+) - H(\text{R-H}) \quad (4)$$

$$\text{ETE} = H(\text{R}^\bullet) + H(\text{e}^-) - H(\text{R}^-) \quad (5)$$

where H is the total enthalpy of the studied species at the temperature of 298.15 K and usually estimated from the expression below:

$$H = E_0 + \text{ZPE} + H_{\text{trans}} + H_{\text{rot}} + H_{\text{vib}} + RT.$$

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. The enthalpies of H-atom (H^\bullet), proton (H^+), and electron (e^-) are taken from literature [8]. Vibrational frequencies obtained at the B3LYP/6-311G(d,p) level of theory were scaled by a factor of 0.9669 [9]. The semi-empirical PM6 method was employed to calculate the IEs. In this work, all calculations were performed using the Gaussian 09 software [10].

3. RESULTS AND DISCUSSION

3.1. Stable conformation of ESH

Three conformations of ESHs denoted as ESH_A, ESH_B and ESH_C are shown in Figure 1. In comparison with the x-ray diffraction (XRD) data [5], the B3LYP/6-311G(d,p) geometrical parameters of ESH_A slightly deviate from the experimental values. For example, the calculated and experimental data of the C=S bonds are 1.678 Å and 1.690 Å, respectively. The calculated C2-N1 and C2-N3 bonds are 1.375 Å and 1.367 Å which are little larger than the experimental ones with amount of 0.025 Å and 0.017 Å [4]. The C4=C5 bond of 1.357 Å is quite close to the XRD data (1.350 Å) [5]. Based on this analysis, the B3LYP/6-311G(d,p) method can be considered as the good method to provide the suitable structures for the next calculations.

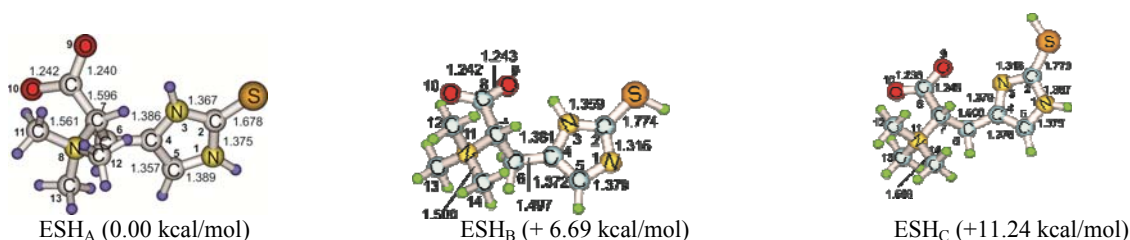


Figure 1. Optimized structures of ergothioneine A, B and C.

The relative energies in comparison with ESH_A were also indicated under each image. The energy of ESH_A is lower than ESH_B and ESH_C of 6.69 kcal/mol and 11.24 kcal/mol, respectively. It is clear that ESH_A consists of a long p- π conjugation chain and known as the most stable structure. Our interest is therefore set on the study of antioxidant properties of ESH_A.

3.2. Hydrogen atom transfer (HAT) antioxidant mechanism

As already mentioned above, HAT mechanism is characterized by BDE (X-H) values, a key parameter to evaluate the activity of an antioxidant, that are related to the abilities of donating hydrogen atom and forming radical form. The BDEs of N1-H, N3-H and C5-H bonds of imidazole ring (see Figure 1 for definition of atom numbering) were calculated by various methods and present in Figure 2.

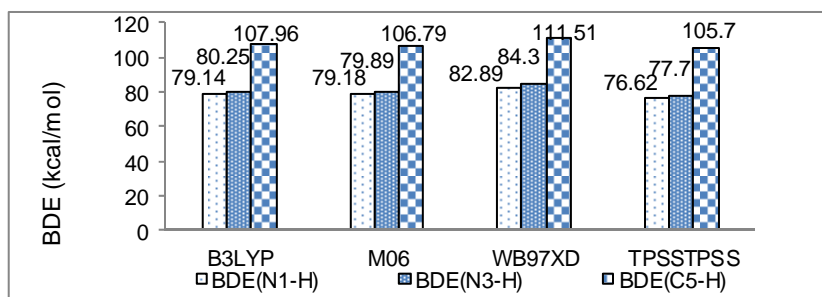


Figure 2. BDEs (kcal/mol) of different X-H bonds of ergothioneine.

As can be seen in Figure 2, the BDEs obtained by all methods follows the order: BDE(N1-H) < BDE(N3-H) < BDE(C5-H). For example, the BDEs obtained by M06 method

for these bonds are 79.18, 79.89 and 106.96 kcal/mol, respectively. The values calculated by TPSSTPSS are 76.62, 77.70 and 105.72, respectively.

By comparison, the results obtained by various methods, one observed no significant difference between them. In fact, the deviations of BDEs (N1-H) calculated by M06, WB97XD and TPSSTPSS 0.04, 3.75 and -2.52 kcal/mol compared to B3LYP method, respectively.

3.3. Single electron transfer followed by-proton transfer (SET-PT) antioxidant mechanism

Ionization energy (IE) and proton dissociation enthalpy (PDE) consist in important parameters characterizing single electron transfer followed by proton transfer (SET-PT) mechanism for antioxidant activity of an organic compound. Therefore, in this section we also evaluated systematically the IE and PDE of ESH using various methods.

Table 1. Ionization energies (IEs) of ergothioneine calculated by different DFT and PM6 methods and IE deviation of DFT results compared to that calculated by PM6.

Methods	IE (kcal/mol)	IE _{DFT} - IE _{PM6} (kcal/mol)
B3LYP	147.22	-15.28
M06	148.65	-13.85
WB97XD	147.57	-14.93
TPSSTPSS	144.69	-17.81
PM6	162.50	0.00

PM6 method has been known as an appropriate method used to calculate IEs [7, 8]. The obtained results generally approach the available experimental values. This is confirmed by the calculation of IE of 1H-imidazole (C₃H₄N₂) and 2-methyl-1H-imidazole (C₄H₆N₂). The calculated IEs for these compounds are 8.86 eV and 8.4 eV, respectively. These results are in good agreement with the experimental values of 8.81 eV for 1H-imidazole [11] and 8.5eV for 2-methyl-1H-imidazole [11]. The calculated IEs by various methods of ergothioneine and its deviations compared to that obtained by PM6 are reported in Table 1.

The second step of SET-PT mechanism is characterized by proton dissociation enthalpy (PDE) that displays thermodynamically preferred C-H group for deprotonation of formed radical cation. The calculated PDE(C-H), PDE(N3-H) and PDE(N1-H) of the radical cation species formed in the first step of the SET-PT mechanism are reported in Figure 3.

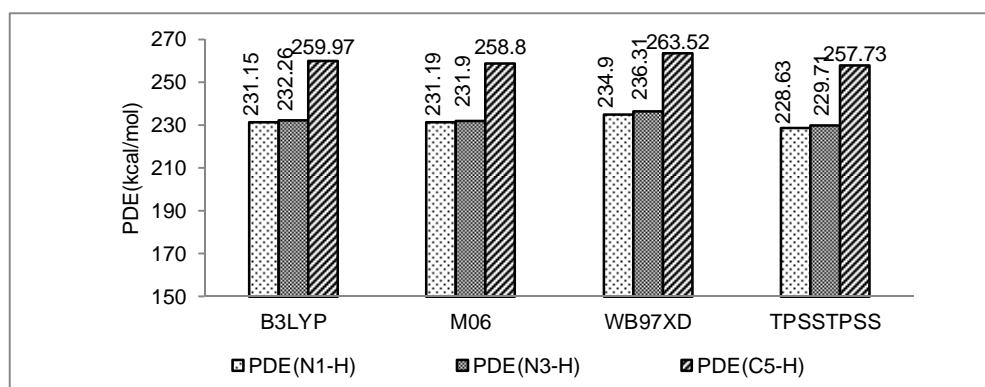


Figure 3. PDEs (kcal/mol) of ergothioneine radical cations calculated by different DFT methods.

It is observed that the obtained PDEs are arranged in the following order: PDE(N1-H) < PDE(N3-H) < PDE(C5-H). For example, PDE(N1-H), PDE(N3-H) and PDE(C5-H) calculated at M06/6-311++G(2df,2p) are 231.19, 231.90 and 263.52 kcal/mol, respectively. TPSSTPSS method gives the lowest PDEs for these bonds of being 228.63, 229.71 and 257.73 kcal/mol, respectively while the largest results obtained by WB97XD are of 234.90, 236.31 and 263.52 kcal/mol, respectively. In conclusion, the results obtained by various methods follow the same tendency. The deviations generally lie in the 0-3 kcal/mol range (as shown in Figure 3). For example, the deviation of PDEs(C-H) computed by M06, WB97XD and TPSSTPSS -1.17, 3.55 and -2.24 kcal/mol compared to B3LYP method, respectively.

3.4. Sequential proton loss electron transfer (SPLET) mechanism

Sequential proton loss electron transfer (SPLET) mechanism is characterized by proton affinity (PA) and electron transfer enthalpy (ETE). These values were calculated by various DFT methods at 6-311++G(2df,2p) basis set and given in Table 2.

Table 2. PAs and ETes of ergothioneine at N3 position obtained by DFT/ 6-311++G(2df,2p).

Methods	PA (kcal/mol)	ETE (kcal/mol)
B3LYP	333.64	61.12
M06	333.29	63.11
WB97XD	334.18	64.63
TPSSTPSS	334.06	58.15

The lower PA is generally described for higher antioxidant capacity via SPLET mechanism. The results obtained by B3LYP/6-311G(d,p) show that the PAs increase in the order: PA(at N3) < PA(at N1) < PA(at C) with the corresponding values of 337.23, 339.83 and 363.75 kcal/mol, respectively. Therefore, the calculations of PA and ETE of ESH at higher 6-311++G(2df,2p) level of theory were performed for the N3 position which showed the lowest PA. Table 2 displays the PAs and ETes calculated by various DFT-based methods. Regarding ETE results, one observed larger deviations (lying in the 1-3 kcal/mol range) among used methods. The lowest ETE is 58.15 kcal/mol resulted from TPSSTPSS method whereas WB97XD one showed the highest values of 64.63 kcal/mol. PA and ETE calculated by B3LYP at N3 position are 333.64 and 61.12 kcal/mol, respectively. In comparison to the corresponding IEs of the neutral form (IE= 147.22 kcal/mol), the ETE is significantly lower. This indicates that single electron transfer process from an anionic form is more favorable than that of neutral one.

4. CONCLUSIONS

In this work, the antioxidant action of ergothioneine was studied via HAT, SET-PT and SPLET mechanisms from the thermodynamic point of view. Four DFT methods including B3LYP, M06, WB97XD and TPSSTPSS were used to calculate various thermodynamic parameters of (BDE, IE, PDE, PA and ETE).

The thermodynamic parameters calculated at B3LYP/6-311++G(2df,2p) and M06/6-311++G(2df,2p) are consistent together. The lowest bond dissociation enthalpy was found at the N1-H bond, whose BDEs is estimated about 79.14 and 79.18 kcal/mol, respectively. The predicted PDE, PA and ETE using both considered methods at the basis set of 6-311++G(2df,2p) are 231.15 and 231.19 kcal/mol, 333.64 and 333.29 kcal/mol, 61.12 and 63.11

kcal/mol, respectively. The IE value obtained at the PM6 method is much higher than that computed by other DFT ones and can be estimated about 162.50 kcal/mol or 7.05 eV.

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TÓM TẮT

CÁC THÔNG SỐ NHIỆT ĐỘNG HỌC CỦA ERGOTHIONEINE: NGHIÊN CỨU BẰNG CÁCH SỬ DỤNG CÁC HÀM MẬT ĐỘ M06, WB97XD VÀ TPSSTPSS

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Tính chất chống oxy hóa của ergothioneine (ESH) được nghiên cứu thông qua ba cơ chế: chuyển nguyên tử hydro (HAT), chuyển điện tử - chuyển proton (SET-PT) và chuyển proton-mất điện tử (SPLET). Ba phương pháp hàm mật độ (DFT) gồm M06, WB97XD và TPSSTPSS tại bộ hàm cơ sở 6-311++G(2df,2p) được sử dụng để tính toán các thông số nhiệt động học trong pha khí. Dựa trên các phương pháp này đã tính toán năng lượng phân li liên kết (BDE), năng lượng ion hóa (IE), năng lượng phân li proton (PDE), ái lực proton (PA) và năng lượng chuyển điện tử (ETE). Kết quả cũng được so sánh với các giá trị tính toán tại phương pháp B3LYP. Kết quả cho thấy ESH đóng vai trò là một chất chống oxy hóa tiềm năng thông qua cơ chế HAT.

Từ khóa: ergothioneine, chống oxy hóa, HAT, SET-PT, SPLET, BDE, IE, PA, ETE.