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Theoretical exploration on free radical scavenging mechanism of curcumin analogues in water solvent

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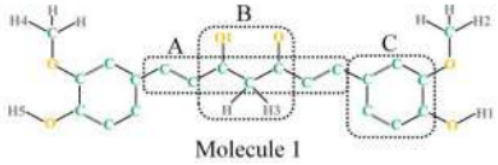
Abstract. One way to improve curcumin's possibility in preventing lipid peroxidation is through modification of carbon linker, β-diketone group and aromatic rings. However, there remains a need to explore the role of carbon linker on the free radical scavenging mechanisms of curcumin. This study uses density functional theory to explore two descriptors of free radical scavenging mechanisms, which are bond dissociation enthalpy (BDE) and adiabatic ionization potential (AIP) of curcumin and its analogues. Five analogues with different amount of carbon atoms in the linker in the presence / absence of β-diketone group are chosen. Our result shows that decreasing the amount of carbon atom from 7 to 5 atoms in the linker decreases the BDE at β-diketone group of the curcumin analogue. Moreover, increasing the amount of carbon atoms in the linker decreases the AIP of the analogues.

1. Introduction

Research attention on curcumin is increasing due to its antioxidant activities that offer extensive applications in the health-related fields. Curcumin ($C_{21}H_{20}O_6$) is a yellow compound isolated from the rhizome of Curcuma longa. In physiological conditions, curcumin exists in keto and enol tautomers [1,2]. Research about curcumin has been carried to understand antioxidant activity of curcumin which include its free radicals scavenging activity [3] and lipid peroxidation reduction [4]. This activity enables curcumin for application in treating diseases such as Alzheimer's disease, β-Thalassemia, kidney injury, skin disorders, and non-alcoholic fatty liver disease [5–9].

In performing its antioxidant activity, curcumin scavenges free radicals through different scavenging mechanisms. The mechanisms are hydrogen atom transfer (HAT), single electron transfer followed by proton transfer (SETPT), and sequential proton loss electron transfer (SPLET). The mechanisms occur depending on the environment in which curcumin exists and the radicals that react toward curcumin. For example, experiment by Jovanovic showed that in pH 3 to 7 where curcumin keto dominates, HAT mechanism rules the scavenging activity. Meanwhile, in pH above 8 where curcumin enol dominates, SET mechanism governs the activity [10]. Furthermore, theoretical calculation by Galano



Molecule	Part A	Part B
2	7 C atoms	H3 atom is attached to O1 atom
3	5 C atoms	Same as Molecule 2
4	9 C atoms	Same as Molecule 2
5	5 C atoms	Monocarbonyl
6	7 C atoms	Same as Molecule 5
7	9 C atoms	Same as Molecule 5

Scheme 1. Structure of curcumin and its modified structures. Part **A**, **B**, and **C** denote carbon linker, β-diketone group and aromatic ring.

et al. displayed that HAT and SPLET mechanisms are dominant when curcumin reacts with methoxyl radical ($\bullet OCH_3$) and trichloromethylperoxyl radical ($\bullet O_2CC_{l3}$) respectively [3].

Curcumin modification is an attempt to improve the free radical scavenging activity. Geometry of curcumin contains carbon linker, β-diketone group and two aromatic rings (Scheme 1). Previous studies have reported that the modification of β-diketone group affects the scavenging mechanism. Mary et al. modified curcumin by forming a metal complex between β-diketone group and certain metal ion and found that the complex enhances HAT and SET mechanism [11]. Li et al. reported that modified curcumin with shorter carbon linker but without β-diketone group is able to scavenge 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical through the SET mechanism experimentally [12]. Considering the role of the β-diketone group and the carbon linker, further exploration of the linker effect, in the presence and absence of the group, on scavenging mechanisms is necessary.

This paper explores the role of carbon linker on the free radical scavenging mechanism of curcumin by utilizing density functional theory (DFT) calculation to calculate two thermochemical parameters of curcumin analogues. The parameters are bond dissociation enthalpy (BDE) and adiabatic ionization potential (AIP). BDE is measured as the energy releases when an X-H bond of the curcumin is breaking prior to hydrogen transfer, while AIP is measured as the energy required to remove an electron from the curcumin prior to electron transfer. Both BDE and AIP are descriptors for HAT and SET mechanisms respectively.

2. Computational Detail

This research is conducted to explore hydrogen atom transfer and electron transfer, as modelled by (1) and (2), in two stages. First is performing DFT calculation to obtain the geometry of all molecules at ground state. The molecules involved are neutral, radical, and radical ion. The neutral molecules consist of two curcumin tautomers: keto (Molecule 1, with 7 carbon atoms in the linker) and enol (Molecule 2, also with seven carbon atom in the linker), two analogues with 5 and 9 carbon atoms in the linker with β-diketone group (Molecule 3 and 4) and three analogues with 5, 7 and 9 carbon atoms in the linker without β-diketone group (Molecule 5, 6 and 7), as illustrated in scheme 1. The radicals are constructed through hydrogen abstraction at certain X-Hn site (n = 1, 2, 3, 4, and 5) of the neutral molecules. Meanwhile, the radical ions are constructed by applying +1 charge to the neutral molecules. To obtain the geometry of the molecules at ground state, geometry optimization coupled with frequency calculation are performed using M06-2X/6-311++G(d,p) for the neutral molecules and UM06-2X/6-311++G(d,p) for the radical and the radical ion. This step will produce electronic energy and thermal correction to enthalpy of each molecules. Water solvent is included to the calculation by using polarized continuum model (PCM) calculation. All calculation is performed at 298.15 K and 1 atm using Gaussian 09 software [13].

Second is calculating BDE and AIP based on the result of the DFT calculation. The BDE and AIP are calculated according to these models and are presented in (3) and (4) respectively.

Table 1. Bond dissociation enthalpy of the seven molecules in water solvent.

Molecule	Abstraction Site	BDE (kcal/mol) Calc.	Ref.[a]	Ref.[b]
1	O-H1	84.3	78.3&78.5	82.3
	C-H2	97.9		
	C-H3	88.7	92.7	87.4
2	O-H1	84.0	77.5	80.2
	C-H2	96.2		
	O-H3	106.8		
	C-H4	97.8		
	O-H5	83.6	76.0	
3	O-H1	84.0		
	C-H2	97.7		
	O-H3	89.6		
	C-H4	98.2		
	O-H5	84.3		

Molecule	Abstraction Site	BDE (Calc., kcal/mol)
4	O-H1	83.0
	C-H2	97.6
	O-H3	104.6
	C-H4	97.7
	O-H5	83.2
5	O-H1	84.1
	C-H2	97.8
6	O-H1	83.3
	C-H2	97.7
7	O-H1	82.8
	C-H2	96.1

[a] Computed using B3LYP/6-311+G(2d,2p)//AM1 calculations. [14]
[b] Computed using (RO) B3LYP/6-311+G (2d,2p)//AM1/AM1 calculations. [15]

For this calculation, enthalpy of hydrogen (H(H·)) in water solvent is taken from the value used by szelag et al. [16].

$$AXH \rightarrow AX\cdot + H\cdot \quad (1)$$

$$AXH \rightarrow AXH^{\cdot +} + e^{-} \quad (2)$$

$$BDE = H(AX\cdot) + H(H\cdot) - H(AXH) \quad (3)$$

$$AIP = H(AXH^{\cdot +}) - H(AXH) \quad (4)$$

Where AXH, AX· and H· represents the 7 molecules, the radical form of the 7 molecules, and a hydrogen atom, respectively.

3. Results and Discussion

3.1. Bond dissociation enthalpy of curcumin analogues

Table 1 lists the chosen abstraction site and the results of the calculated BDE at each abstraction site. Molecule 1, 5, 6 and 7 have symmetrical shape, thus only O-H1 and C-H2 attached to one aromatic ring are chosen as the abstraction sites. C-H3 site in Molecule 1 is chosen as an extra abstraction site since it has been proposed by Jovanovic et al. as curcumin's possible abstraction site [9]. Molecule 2, 3 and 4 are not symmetrical, hence there are five abstraction sites chosen. Our results show that in molecule 1, BDE of O-H1 < C-H3 < C-H2. In Molecule 2, BDE of O-H1 ≈ O-H5 < C-H2 < C-H4 < O-H3. Comparing the BDEs in Molecule 1 and 2, it is concluded that O-H sites in aromatic ring always have the lowest BDEs and their values are similar. This is in agreement with the result reported by Barzegar et al. and Sun et al. [14,15].

Changing the amount of carbon atoms in the linker does not affect the BDE at aromatic ring but it does at the β-diketone group. Molecule 3, 2 and 4 that have 5, 7 and 9 carbon atoms in the linker respectively in the presence of the β-diketone group, show similar BDE values at O-H and C-H sites of aromatic ring. Molecule 5, 6, and 7 that have 5, 7 and 9 carbon atoms in the linker respectively in

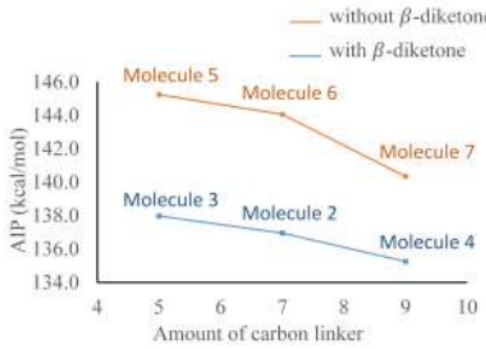


Figure 1. Plot of the AIP of the seven molecules.

Table 2. The HOMO energy of the seven molecules.

Molecule	E_{HOMO} (eV)
1	-7.36
2	-7.05
3	-7.33
4	-7.11
5	-7.21
6	-7.08
7	-6.92

the absence of the β-diketone group also show similar BDE values at sites in aromatic ring. Regardless of the amount of carbon linker and the presence / absence of β-diketone group, the BDE at O-H site in aromatic ring remains the lowest among all abstraction sites. Different result is observed at O-H3 sites of β-diketone group in Molecule 2, 3 and 4. Molecule 3 that has 5 carbon atoms in the linker has 17.2 kcal/mol lower BDE value than Molecule 2 that has 7 carbon atoms in the linker. Meanwhile Molecule 4 that has 9 carbon atoms in the linker has only 2.2 kcal/mol lower BDE value than Molecule 2.

This results suggest two important things. First, since low BDE relates to an easy HAT, the seven molecules probably can transfer a hydrogen atom from O-H site at aromatic ring easily. Thus, it is possible for curcumin and its analogues to participate in scavenging free radicals through HAT mechanism. Furthermore, the C-H3 site in Molecule 1 also has to be considered as a possible hydrogen atom transfer site, which has been supported by Jovanovic et al. [9]. Second, changing amount of carbon atom in the linker in the presence of β-diketone group is important since the linker has shown to affect the BDE at the β-diketone group.

3.2. Adiabatic ionization potential of curcumin analogues

Figure 1 plots the calculated AIP of two groups of curcumin analogues, with and without β-diketone group. The figure shows that increasing the amount of carbon atoms from 5 to 7 to 9 reduces the AIP values in both groups with an average of 3.8 kcal/mol. Overall, molecules with β-diketone group has lower AIP values. The molecules with lower AIP values can facilitate SET, the first step of SETPT mechanism, easier [16]. Thus, our result implies that increasing of the amount of carbon linker in the presence of β-diketone group improves the possibility of the molecules to scavenge free radicals through SETPT mechanism.

Table 2 lists the results of highest occupied molecular orbital (HOMO) energy of the seven molecules. Generally, increasing the amount of carbon linker increases the HOMO energy, which could be an indication of an easy electron transfer [17]. Thus, the HOMO results confirm the AIP trend analyzed above.

4. Conclusion

This study uses two descriptors, BDE and AIP, to explore the role of carbon linker on the free radical scavenging mechanisms of curcumin. Decreasing the amount of carbon atom in the linker lowers the BDE value at β-diketone group by 17.2 kcal/mol. This implies that shorter carbon linker probably can increase the possibility of curcumin to scavenge free radical through HAT mechanism at β-diketone group. On the other hand, increasing the amount of carbon atom in the linker reduces the AIP value by 3.8 kcal/mol on average. This implies that longer carbon linker probably can increase the possibility of curcumin to involve in SETPT mechanism.

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