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Theoretical Elucidation on the Antioxidant Mechanism of Curcumin: A DFT Study

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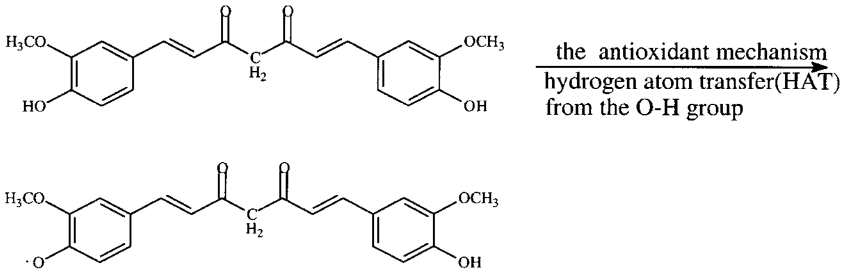
ABSTRACT



Bond dissociation enthalpies (BDEs) for the curcumin-related compounds have been calculated using density functional theory (DFT) methods. It was found that the antioxidant mechanism of curcumin was a H-atom abstraction from the phenolic group, not from the central CH$_2$ group in the heptadienone link. Curcumin, methylcurcumin, and half-curcumin had similar O–H BDEs, indicating that the two phenolic groups in curcumin were independent of each other.

Curcumin (Figure 1, A and B) is the main yellow phenolic material of turmeric and widely used as food coloring additive.[1] Numerous experimental studies have demonstrated that curcumin has various biological activities, including antioxidant activity, cancer preventive activity, and antiangiogenesis activity, etc.[2−4] Although the antioxidant mechanism of curcumin in biological and chemical systems has been extensively investigated,[5−8] there exists much controversy on this topic. Barclay et al. indicated that curcumin was a phenolic chain-breaking antioxidant and the H atom was abstracted from the phenolic group.[8] By laser flash photolysis or pulse radiolysis,[7] Jovanovic and co-workers suggested that the H-atom abstraction was mainly from the central active CH$_2$ group in the heptadienone link, and the H-abstraction from the phenolic group accounted for only $\sim$15% of the reaction. As H-atom abstraction is mainly governed by the strength of the X−H bond (X represents O

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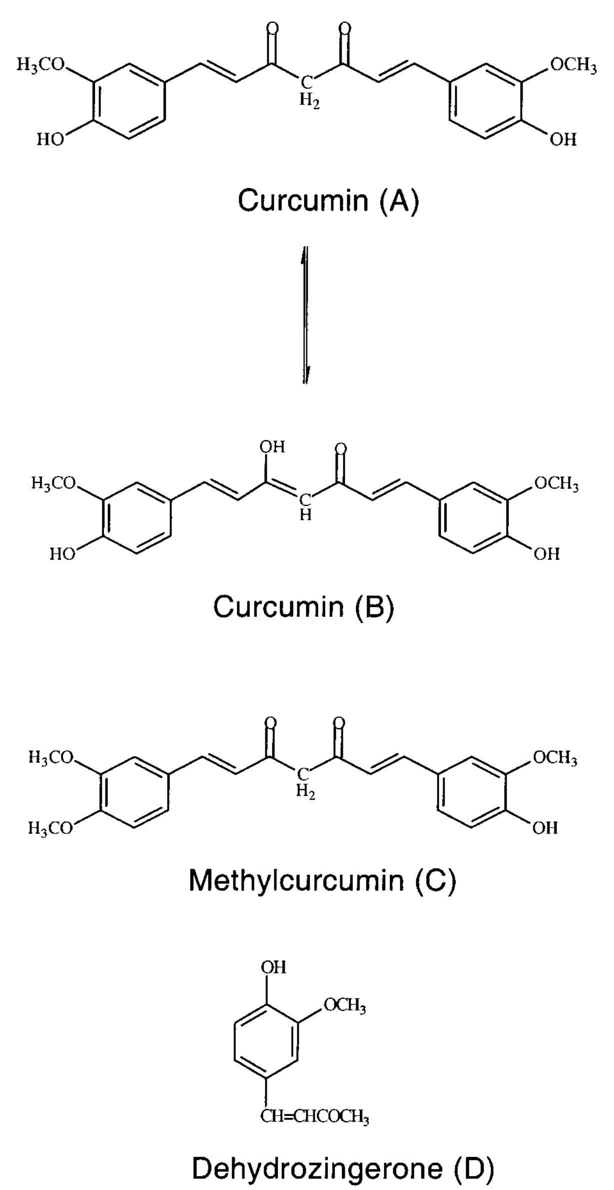

Figure 1. Structures of the curcumin-related compounds.

or C), i.e., the bond dissociation enthalpy (BDE),[9−11] X−H BDE was used as a theoretical parameter in this paper to determine the position for H-atom abstraction and to elucidate the experimental differences.

Considering the accuracy and conveniency of DFT method, B3LYP function on the basis set of 6-31G(d,p) was employed to optimize the structure of curcumin, and a combined approach ((RO) B3LYP/6-311+G (2d,2p)//AM1/AM1), which was developed recently by DiLabio et al.,[12] was used to estimate the X−H BDEs. The calculation procedures are as follows. First, molecular mechanics method MMX[13] was used to optimize the molecular structures, and then semi-empirical quantum chemical method AM1[14] was employed to perform a full geometry optimization and the determination of vibrational frequencies (a factor of 0.973 for AM1 ZPEs[12]). Finally, DFT method B3LYP[15−17] with 6-311+G (2d,2p) basis set was employed for a single point energy calculation, where open shell was treated by ROB3LYP. All quantum calculations were accomplished by program Gaussian 98.[18]

Curcumin is unique in structure, which has two isomers, β-diketone form and enol form (Figure 1, A and B). Both of the isomers were calculated with the full geometry optimization at the B3LYP/6-31G(d,p) level. From the calculated results, it can be found that the structure of β-diketone form is not completely planar and two methoxyphenol rings show a dihedral angle of −124.9°. However, each methoxyphenol ring is completely planar owing to the conjugation and the intramolecular hydrogen bond. The structure of enol form is different from that of β-diketone form. The two methoxyphenol rings in the enol form are well conjugated and coplanar. It is also interesting to note that the two forms are different in energy. The energy of enol form is 6.85 kcal/mol lower than that of β-diketone form,[19] suggesting that the enol form of curcumin predominates in solution. The present result is in good agreement with the previous study that curcumin's structure was known as diarylheptanoid initially,[20] and the ^{1}H, ^{13}C NMR spectra as well as the infrared spectra indeed indicated that curcumin-related compounds existed entirely in the enol form in solution.[8]

The calculated X−H BDEs of various curcumin-related compounds are listed in Table 1. It can be seen that the O−H BDE of the phenolic group is 5.04 kcal/mol lower than the C−H BDE of the central CH$_2$ for curcumin A, suggesting the H-atom abstraction mainly occurred in the phenolic group.

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(19) Total electronic energies of molecule A and molecule B calculated at the B3LYP/6-31G(d,p) level are −1263.6051318 hartree and −1263.6160515 hartree, respectively.

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Table 1. Bond Dissociation Enthalpies (BDEs, in kcal/mol) of Curcumin-Related Compounds

	A	B	C	D
TE_P[a]	−1263.962194	−1263.970126	−1303.264912	−652.248844
TE_R[b]	−1263.318214	−1263.328980	−1302.620593	−651.605154
TE_R[c]	−1263.308696	−1263.271247	−1302.606262	
EC_p[d]	0.407377	0.407611	0.437492	0.227074
EC_R[e]	0.391807	0.391456	0.421907	0.213679
EC_R[f]	0.390267	0.390896	0.419973	
O−H BDE	82.32	80.19	82.53	83.46
C−H BDE	87.36	116.07	90.34	
k_{inh}[g]	34×10^4			17×10^4

[a] Total electronic energies of the parent molecules. [b] Total electronic energies of the radicals derived from H-abstraction of the phenolic hydroxyl. [c] Total electronic energies of the radicals derived from H-abstraction of the central CH_2 group in the heptadienone link. [d] Enthalpy correction for the parent molecules. [e] Enthalpy correction for the radicals derived from H-abstraction of the phenolic hydroxyl. [f] Enthalpy correction for the radicals derived from H-abstraction of the central CH_2 group in the heptadienone link. [g] The absolute rate constants from ref 8.

The optimized structures have shown that the enol form of curcumin (molecule B) is more stable in solution, and the central CH_2 group does not exist in this case. However, to compare with curcumin A, we also calculated the C−H BDE of the central CH group in the heptadienone link for molecule B. The results indicate that the H-atom abstraction from the C−H bond is very difficult, because the C−H BDE (116.07 kcal/mol) is considerably high. This supports the idea that the H-atom abstraction occurs from the phenolic group. Moreover, the O−H BDE of the phenolic group for molecule B is ∼2 kcal/mol lower than that of molecule A.

If one hydroxyl group was replaced by the OCH_3 group (methylcurcumin, molecule C), the O−H BDE changed a little comparing with that of molecule A. Molecule D is a half-curcumin in the keto form, namely dehydrozingerone, whose O−H BDE is roughly the same as that of molecule A. Since the O−H BDEs of molecules A, C, and D are similar to one another, it seems the two phenolic groups in curcumin are independent of each other. Furthermore, the absolute radical-scavenging rate constant (k_{inh}) for molecule A in chlorobenzene (Table 1) is double that of half-curcumin, molecule D, consistent with the fact that the two phenolic groups are isolated in curcumin. Moreover, the C−H BDE of the central CH_2 group is ∼8 kcal/mol higher than the O−H BDE of the phenolic group for molecule C. This also demonstrates further that the donation of H atom is not from the central CH_2 group, but from the two phenolic groups.

Pulse radiolysis study in aqueous and laser flash photolysis study in the acetonitrile solution indicated that the curcumin radical was an oxygen-centered radical rather than a carbon-centered radical.[21] The calculated spin density of oxygen in phenoxyl radical derived from molecule A is 0.228177, much lower than that of carbon in carbon-centered radical derived from the same molecule, 0.769618, which indicates that the phenoxyl radical is less reactive than the carbon-centered radical. This is also supported by the fact that the energy of phenoxyl radical is ∼5 kcal/mol lower than that of carbon-centered radical (Table 1).

Now, it is clear that the O−H BDE of the phenolic group is much lower than the C−H BDE of the central CH_2 group in the heptadienone link for the curcumin-related compounds, suggesting that the antioxidant mechanism of curcumin is a H-atom abstraction from the phenolic group, not from the central CH_2 group. Moreover, curcumin, methylcurcumin, and half-curcumin have similar O−H BDEs, indicating the two phenolic groups in curcumin are independent of each other.

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