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Theoretical Study on the Antioxidant Activity of Curcumin

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The computational results for curcumin at the B3LYP/6-31G(d,p) level show that the enol form of curcumin is more stable than the diketo form because of an intramolecular hydrogen bond, which extends the conjugation effect in the enol chain, formed in the enol structure. *Cis*-diketone form can not be obtained, presumably due to the strong repulsion between the carbonyl dipoles aligned in parallel. According to the phenolic O—H bond dissociation enthalpy, curcumin in its most stable form can be suggested to be a relatively good antioxidant. In order to avoid overcoming H-bond interaction and to improve the antioxidant activity of curcumin, a catechol moiety was incorporated into curcumin for designing a novel antioxidant. It is found that the designed molecule is much more efficient to scavenge radical than curcumin, comparable to vitamin E. Moreover, the ionization potential of the designed molecule is similar to that of curcumin, indicating that the designed molecule can not display the prooxidant effect.

Keywords curcumin, density functional theory, O—H bond dissociation enthalpy, ionization potential, antioxidant activity

Introduction

Free radicals play important roles in causing many diseases, deteriorating foods, and degrading chemical materials. Hence in recent years, there has been growing interest in selecting efficient antioxidants with low toxicity to reduce the damage of radicals.[1-3] Furthermore, rational design strategies based on structure-activity relationship have been proposed to direct the synthesis and selection of novel antioxidants.[4,5] This might be helpful to further the study in this field and accelerate the selection of antioxidants.

Due to the deficiency of synthesized antioxidants such as high side-effect and high price, much attention has been paid to the selection and modification of natural antioxidant contained in plants, such as curcumin. Curcumin is one of the most widely used food coloring additive, which is obtained from the spice turmeric.[6] Owing to high biological activities including antioxidant activity, cancer preventive activity, and antiangiogenesis activity, *etc*.,[7-9] curcumin-related compounds are expected to be developed as drugs or antioxidants. The antioxidant mechanism of curcumin in biological and chemical systems has been extensively investigated experimentally[10-13] and theoretically,[14,15] and is believed to relate to a H-atom abstraction process from the phenolic groups.[13-15] The structure of curcumin consisting of two orthmethoxylated phenols and a β-diketone form of heptadienone link is schemed in Figure 1. We can see that it is very unfavorable for the H-abstraction reaction from the phenolic groups in curcumin owning to the existence of intramolecular hydrogen bond. In order to solve this problem, we incorporate a catechol moiety into curcumin and design a novel antioxidant. It is prudent to use a catechol moiety, in which the potentiality of catechol moiety used in rational design of antioxidants had been investigated by density functional theory (DFT) method B3LYP on the basis set of 6-31G(d,p).[16]

In this paper, three aspects have been focused on. First, the structure of curcumin is optimized at density functional level to investigate the stable form. Secondly, the O—H bond dissociation enthalpy (BDE) is used to predict antioxidant activity and explain experimental results. Finally, a new compound is rationally designed based on the structure of curcumin.

Calculation methods

Considering the accuracy and conveniency of DFT method, B3LYP function on the basis set of 6-31G(d,p) was employed to optimize the different structures of curcumin. Since the geometry of curcumin is experimentally determined in low-dielectric solution, the optimization is performed in the presence of a solvent using the Polarized Continuum (overlapping spheres) model (PCM) of Tomasi and coworkers.[17,18] The harmonic frequency calculations are performed at the same level to verify whether they are minima with all real

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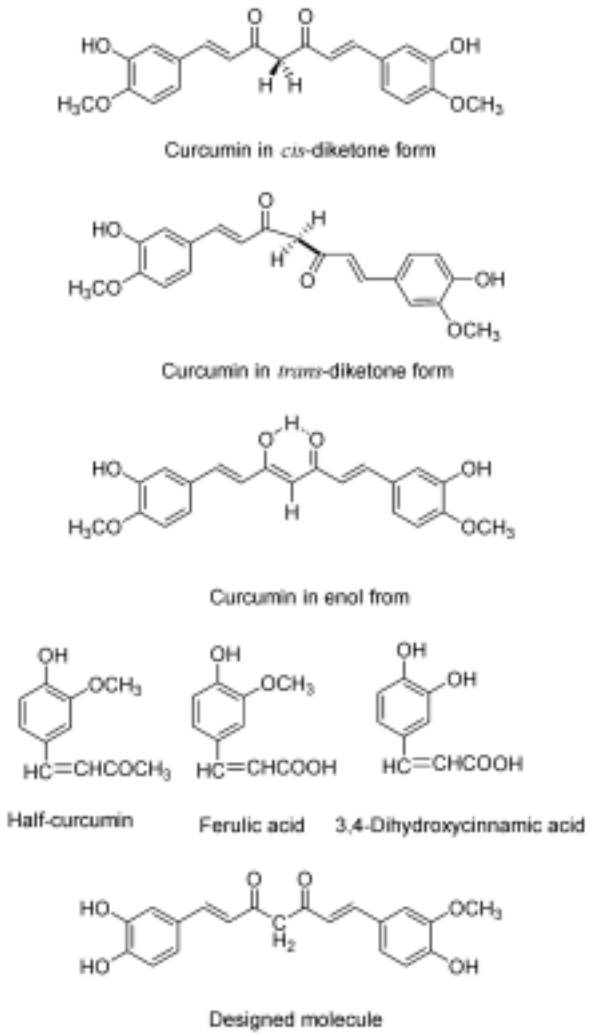

Figure 1 Structures of curcumin and relevant antioxidants.

frequencies. A combined approach (RO) B3LYP/6-311+G (2d,2p)//AM1/AM1, which was developed recently by DiLabio *et al*.,[19] can be successfully applied to estimate the O—H BDEs for phenolic antioxidants.[14,20,21] The calculation procedures are as follows. First, molecular mechanics method MMX[22] was used to optimize the molecular structures. Second, semiempirical quantum chemical method AM1[23] was employed to perform a full geometry optimization and the determination of vibrational frequencies (scaled by a factor of 0.973 for AM1 ZPEs[19]). Finally, single-point energy computations were completed at the B3LYP/6-311+G (2d,2p) level of DFT theory[24-26] for the closed-shell systems, but for open-shell ones, ROB3LYP method was used.

For the calculation of the ionization potential (IP), we used another method (B3LYP/6-31G(d)//AM1/AM1), which was shown to be capable of obtaining the IPs of polysubstituted aromatics accurately.[27,28] All quantum calculations were accomplished using program Gaussian 98.[29]

Results and discussion

Stable structure of curcumin in the presence of a solvent

Curcumin has two isomers, β-diketone form and enol form. For β-diketone form, it may exist as *cis*- or *trans*-diketone (see Figure 1). The ^{1}H and ^{13}C NMR spectra as well as the infrared spectra indicated that curcumin-related compounds existed entirely in the enol form in low-dielectric solution (*e.g.* chlorobenzene).[13] In order to investigate the structure of curcumin, three possible conformers of curcumin were optimized at the B3LYP/6-31G(d,p) level using the PCM model. The stationary points were positively identified as minima point by evaluation of the frequencies. No matter how endeavor, the *cis*-diketone structure was not found and only *trans*-diketone structure was obtained, presumably due to the strong repulsion between the carbonyl dipoles aligned in parallel. From the calculated results, we find that the energy of enol form is 6.79×4.184 kJ/mol lower than that of *trans*-diketone form,[30] similar to the calculated value in the gas,[14] suggesting that the enol form predominates the structural nature of curcumin. This result is in good agreement with the earlier study that curcumin's structure was known as diarylheptanoid at first.[31] The optimized 3D structure of curcumin in enol form is shown in Figure 2. The computed results also indicate that the enol form of curcumin is more stable than the diketone structure resulting from string internal H-bond formed in enol, which can effectively extended the conjugation along the enol chain.

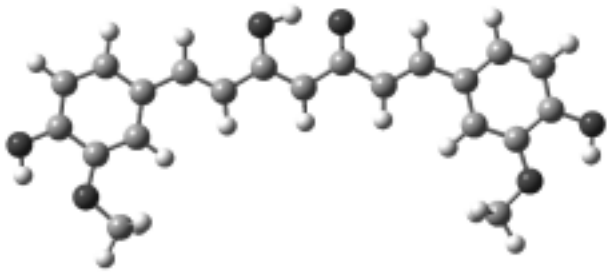

Figure 2 3D structure of curcumin in enol form.

Using BDE data to predict reactivity

From the structure of curcumin, it is not surprising that it acts as an antioxidant, and its antioxidant activity can be characterized by the O—H bond dissociation enthalpy (BDE) to certain extent.[32-34] Calculated O—H BDEs of curcumin and relevant antioxidants (Figure 1) are listed in Table 1, together with the experimental antioxidant activity.[10] The enol form of curcumin has three O—H bonds, two phenolic O—H bonds and one O—H bond in enol groups, and two phenolic O—H BDEs are similar to each other. However, the O—H bond in enol group is very strong, reflected from the considerably high O—H BDE of 104.6×4.184 kJ/mol. The phenolic O—H BDE of curcumin in *trans*-diketone form is *ca.* 2×4.184 kJ/mol higher than that of curcumin in enol

Table 1 Bond dissociation enthalpies (BDEs) of curcumin and relevant antioxidants

Antioxidant	Cucumin		Half-curcumin	Ferulic acid	3,4-Dihydroxycinnamic acid	Designed molecule
	trans-Diketone form	Enol form				
TE_P [a]	−1263.96219	−1263.97013	−652.24884	−688.18165	−648.87461	−1224.65205
TE_R [b]	−1263.31821	−1263.32898	−651.60515	−687.35063	−648.24054	−1224.02005
EC_p [c]	0.407377	0.380162	0.212844	0.190051	0.174294	0.350960
EC_R [d]	0.391807	0.364102	0.198852	0.176016	0.160338	0.337381
BDE [e]	82.32	80.23, 80.60 [f] 104.6 [g]	83.10	84.88	77.09	76.01
Activity [h]	0.371	nd [i]	nd [i]	0.666	0.281	nd [i]

[a] Total electronic energies (hartree) of the parent molecules. [b] Total electronic energies (hartree) of the radicals derived from H-abstraction of the phenolic hydroxyl. [c] Enthalpy correction (hartree) for the parent molecules. [d] Enthalpy correction (hartree) for the radicals derived from H-abstraction of the phenolic hydroxyl. [e] BDE (in 4.184 kJ/mol)$=H_r+H_h-H_p$, in which H_r is the enthalpy for radicals generated after H abstraction, H_h is the enthalpy for hydrogen atom, −0.49764 hartree, and H_p the enthalpy for the parent molecule. [f] For strong phenolic OH (right side on drawing). [g] For enol OH. [h] Relative antioxidant activity from Ref. 10. [i] Not be determined.

form, indicating that curcumin in its most stable form is a relatively good antioxidant. The O—H BDEs of curcumin and half-curcumin are similar, consistent with the two phenolic groups in curcumin independent of each other.[13] Ferulic acid and half-curcumin have similar structure, but the O—H BDE of the former is 2.56× 4.184 kJ/mol higher than that of the latter, suggesting that the antioxidant activity of the half-curcumin is higher than that of ferulic acid.

The existing structure-activity relationship[32,36] (SAR) of antioxidants to scavenge free radicals indicates that hydrogen bond formed in the antioxidants does not enhance the activity, but hydrogen bond formed in the radical produced after H-abstraction will stabilize the radical and is favorable to increase the antioxidant activity. According to SAR, we can predict that 3,4-dihydroxycinnamic acid should have higher activity than curcumin and Ferulic acid. The experimental results show that the order of the relative antioxidant activity is 3,4-dihydroxycinnamic acid > curcumin > Ferulic acid. Our calculations show that the order of the calculated O—H BDEs is 3,4-dihydroxycinnamic acid <curcumin<Ferulic acid, which is in good accordance with the experimental result. But the O—H BDE of 3,4-dihydroxycinnamic acid is much lower than that of ferulic acid, which is *ca.* 8×4.184 kJ/mol. The low O—H BDE of 3,4-dihydroxycinnamic acid ascribes to the two effect of *ortho* hydrogen of catechol, intramolecular hydrogen bond effect and the *ortho* hydroxyl electronic effect that had been investigated by DFT method on the basis set of 6-31G(d,p). [16]

Rational design of curcumin to enhance reactivity

Curcumin in its most stable form is a relatively good antioxidant with respect to peroxyl radical oxidation, although inferior to vitamin E (as α-tocopherol) which has the O—H BDE of 77×4.184 kJ/mol.[36] However, in the process of donating a phenolic H-atom for trapping free radical, curcumin need overcome intramolecular hydrogen bond, which decreases the antioxidant activity. Hence, in order to improve the antioxidant activity and avoid overcoming hydrogen bond of curcumin, we incorporate a catechol moiety into curcumin and design a novel antioxidant.

The O—H BDE for the hydroxyl group in the *para*-position relative to alkyl chain of the designed molecule is calculated to be 76.01×4.184 kJ/mol, much lower than that of curcumin, comparable to vitamin E. This suggests that the designed molecule is much more efficient to scavenge radical than curcumin. More importantly, the designed molecule-derived radical possesses second abstractable phenolic hydrogen. And the corresponding O—H BDE is calculated to be 77.40× 4.184 kJ/mol,[37] which is much lower than that of curcumin. Moreover, we can introduce a catechol moiety into another phenolic ring, the new antioxidant can donor four abstractable phenolic hydrogens to trap free radical and is much more efficient than the designed molecule. Experimental studies of the inhibitory activity against human immunodeficiency virus showed that these compounds containing catechol substructure had much higher activity than curcumin analogues.[38]

As a good antioxidant, it not only has relatively low O—H BDE, which facilitates the H-abstraction reaction between antioxidant and radical, but also has relatively high ionization potential (IP),[34,39] which decreases the electron transfer rate between antioxidant and oxygen, and thus, reduces the pro-oxidative potency of antioxidant. To obtain the information of IP for the designed molecule, we calculated the IP of this compound, and the calculated results are listed in Table 2. As seen from Table 2, the IP of the designed molecule is similar to that of curcumin, indicating that the designed molecule can not display the prooxidant effect.

Conclusion

Three possible conformers of curcumin were optimized at the B3LYP/6-31G(d,p) level using the PCM model. The calculation results show that the enol form of curcumin is more stable than the diketo form. This is due to the intramolecular hydrogen bond formed in the

Table 2 Ionization potentials (IPs) for curcumin and designed molecule

Antioxidant	Curcumin	Designed molecule
TE_P [a]	−1263.555144	−1224.248700
TE_c [b]	−1263.306226	−1223.995168
ZPE_p [c]	0.379875	0.350960
ZPE_c [d]	0.376322	0.347314
IP [e]	154.03	156.80

[a] Total electronic energies (hartree) of the parent molecules. [b] Total electronic energies (hartree) of the cation radicals derived from electron-transfer. [c] Zero point energies (hartree) of the parent molecules. [d] Zero point energies (hartree) of the cation radicals derived from electron-transfer. [e] IP (in 4.184 kJ/mol)=(TE_c + ZPE_c×0.973)−(TE_p+ZPE_p×0.973).

enol with the extended conjugation in the enol chain. *Cis*-diketo form can not be obtained, presumably due to the strong repulsion between the carbonyl dipoles aligned in parallel. According to the phenolic O—H BDE, curcumin in its most stable form can be suggested to be a relatively good antioxidant. In order to avoid overcoming H-bond interaction and to improve the antioxidant activity of curcumin, a catechol moiety was incorporated into curcumin and a novel antioxidant was designed. It is found that the designed molecule is much more efficient to scavenge radical than curcumin, comparable to vitamin E. Moreover, the IP of the designed molecule is similar to that of curcumin, indicating that the designed molecule can not display the prooxidant effect.

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