DFT Study of Substituent Effects on Antioxidant Activity of Kaempferol in the Gas Phase

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Abstract

In this work, the study of various substituted Kaempferol derivatives is presented. The bond dissociation energies (BDE) have been calculated using B3LYP level and different basis sets in gas-phase. Calculated results show that the BDE values of substituted Kaempferol range from about 77 to 100 kcal/mol, demonstrating that Kaempferol is an effective chain-breaking antioxidant that prevents lipid peroxidation. Also we can seen, Cl, OH, CN, NH, and CH groups in C3’ position and CH3, OH and NH2 groups in C5’ position and NH2 and CN groups in C6’ position destabilize the parent Kaempferol molecule and stabilize the radical; hence, it decreases the O-H BDE.

Keywords: Kaempferol; Antioxidant Activity; BDE; Free Radical

1. Introduction

Oxidation reactions are the major cause of the irreversible deterioration of biological systems and synthetic polymers. Oxidation generally corresponds to a free radical chain reaction [1]. The most important reactive radical intermediates formed during oxidation reactions are hydroxyl (HO‘), alkoxyl (RO‘) and peroxyl (ROO‘) radicals [1, 2].

Owing to the presence of at least one paired electron, free radicals will constantly seek to react with other cellular structures, altering DNA and destroying membranes through lipid per-oxidation. And there is strong evidence that free radicals could induce oxidative damage in bio-molecules and play an important role in many diseases associated with old age, notably Alzheimer's disease, Parkinson disease, cardiovascular disease and cancer. Recently, there has been growing interest in finding efficient and novel antioxidants from natural compound, such as flavonoids and phenols [3-5], to meet the requirements of pharmaceuticals, chemical and food industries.

Flavonoids are a group of plant secondary metabolites characterized by adiphenylpropane structure. They are widely distributed in the plant kingdom and are common constituents of fruits, vegetables and some beverages. Flavonoids may play a role in the decreased risk of chronic diseases associated with a diet rich in plant-derived foods. A positive relationship between the ingestion of foods containing flavonoids and a reduced risk of developing cancer and cardiovascular diseases has indeed been observed in some epidemiological studies [6-10]. In vitro and
**in vivo** investigations have shown plausible mechanisms by which flavonoids may confer cancer and cardiovascular protection [11]. Evidence also suggests that certain flavonoids may be useful in the treatment of several diseases [12-17]. Some of this evidence comes from the study of plants used in traditional medicine to treat a wide range of pathologies, which has revealed that flavonoids are common bioactive constituents of these plants.

The flavonoid Kaempferol (3, 5, 7-trihydroxy-2-(4-hydroxyphenyl)-4H-1- and in plants used in traditional medicine.

Although there are over two thousand articles in PubMed reporting the isolation and/or biological properties of this flavonoid, there is not any report summarizing or analyzing all this information.

Our aim is to provide a theoretical explanation to the relationship between the antioxidant activity of Kaempferol and the molecular structure or O-H bond dissociation energy.

![Fig1. Kaempferol structure](image1)

![Fig2. Optimized structures of Kaempferol and corresponding radicals](image2)
2. Computational Details

The geometries of the molecules and respective radicals were optimized using DFT method with B3LYP functional [18-20] and the 6–31G, 6–311G, 6–311G** basis set [18,19] in the gas-phase. The ground-state geometries of molecules were optimized at restricted B3LYP level and the geometry of the radicals were optimized at the unrestricted B3LYP open shell (half electron) level. Optimized structures and corresponding radicals are shown in Fig. 1 and Fig. 2. All calculations were performed using Gaussian 03 program package [21].

The hydroxyl bond dissociation energies of each corresponding hydroxyl group of radicals were calculated.

In the HAT mechanism, the bond dissociation enthalpy (BDE) of the phenolic O-H bond is one of the important parameters in evaluating the antioxidant action; the lower the BDE, the easier the dissociation of the phenolic O-H bond. Bond dissociation energy, BDE, is defined as:

\[
\text{BDE} = E(\text{R}^+) + E(\text{H}^+) - E(\text{R}-\text{H})
\]

3. Results And Discussion

3.1 Bond Dissociation Energy (BDE) of Kaempferol

In this study the relationship between the antioxidant activity of Kaempferol and substituted Kaempferol with the molecular structure and O-H bond dissociation energy was investigated. Calculated BDEs for Kaempferol were listed in table 1.

The hydroxyl bond dissociation energies of each corresponding hydroxyl group of Kaempferol were calculated. It can be seen that the BDE values of Kaempferol range from about 74 to 106 kcal/mol[22], demonstrating that Kaempferol is an effective chain-breaking antioxidant that prevents lipid peroxidation. Moreover, the molecules are observed to have the possibility of generating radicals at positions 3-OH, 4'-OH, 5-OH and 7-OH because of the lower values of BDE. Comparison between BDE and antioxidant activity are defined as below:

BDE values

\[
3\text{-OH} < 4\text{-OH} < 7\text{-OH} < 5\text{-OH}
\]

Antioxidant activity

\[
3\text{-OH} > 4\text{-OH} > 7\text{-OH} > 5\text{-OH}
\]

3.2 Calculation of Bond Dissociation Energy (BDE) for Substituted Kaempferol

BDE for substituted Kaempferol in different position with H, Cl, NO\textsubscript{2}, NH\textsubscript{2}, CN, CH\textsubscript{3} and OH groups were calculated. The results are listed in table 2.

<table>
<thead>
<tr>
<th>Levels and Basis Sets</th>
<th>BDE (cal/mol)</th>
<th>ΔBDE (cal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP/6-31G</td>
<td>74.21649</td>
<td>86.17037</td>
</tr>
<tr>
<td>B3LYP/6-311G</td>
<td>75.31104</td>
<td>86.68648</td>
</tr>
<tr>
<td>B3LYP/6-311G**</td>
<td>77.75302</td>
<td>88.81289</td>
</tr>
</tbody>
</table>

Table2. Calculated BDEs and ΔBDEs for Kaempferol and substituted Kaempferol in gas-phase by using B3LYP/6-311G** method

<table>
<thead>
<tr>
<th>X</th>
<th>C2'</th>
<th>ABDE (kcal/mol)</th>
<th>C4'</th>
<th>ABDE (kcal/mol)</th>
<th>C5'</th>
<th>ABDE (kcal/mol)</th>
<th>C6'</th>
<th>ABDE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>88.81289</td>
<td>0</td>
<td>88.81289</td>
<td>0</td>
<td>88.81289</td>
<td>0</td>
<td>88.81289</td>
<td>0</td>
</tr>
<tr>
<td>NO\textsubscript{2}</td>
<td>90.98750</td>
<td>2.174602</td>
<td>89.29325</td>
<td>0.48035</td>
<td>100.14900</td>
<td>11.33611</td>
<td>90.48393</td>
<td>3.42960</td>
</tr>
<tr>
<td>Cl</td>
<td>91.30125</td>
<td>2.4835</td>
<td>86.97150</td>
<td>-1.84139</td>
<td>89.92075</td>
<td>1.10785</td>
<td>90.67375</td>
<td>1.86085</td>
</tr>
<tr>
<td>CN</td>
<td>90.61100</td>
<td>1.79810</td>
<td>88.60300</td>
<td>-0.20989</td>
<td>91.17575</td>
<td>2.36285</td>
<td>81.88875</td>
<td>-6.92414</td>
</tr>
<tr>
<td>NH\textsubscript{2}</td>
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<td>1.73535</td>
<td>78.12375</td>
<td>-10.68914</td>
<td>77.81000</td>
<td>-11.00289</td>
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<td>-1.27664</td>
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<tr>
<td>CH\textsubscript{3}</td>
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<td>86.90875</td>
<td>-1.90414</td>
<td>86.21850</td>
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<td>1.98635</td>
</tr>
<tr>
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<td>79.44150</td>
<td>-9.37139</td>
<td>79.25325</td>
<td>-9.55964</td>
<td>100.7765</td>
<td>11.96361</td>
</tr>
</tbody>
</table>
Comparison of BDE values for substituted Kaempferol

C2'-CL > C2' -NO2 > C2' -OH > C2' -CN > C2' -NH2 > C2'-CH3 > C2'-H

C3'-NO2 > C3'-H > C3' -CN > C3'-CL > C3' -CH3 > C3'-OH > C3'-NH2

C5'-NO2 > C5'-CN > C5'- CL > C5'-H > C5'-CH3 > C5'-OH > C5'-NH2

C6'-OH > C6'-NO2 > C6'-CH3 > C6'-CL > C6'-H > C6'-NH2 > C6'-CN

For substituent's placed on C2' (Fig 3(A)) the O-H BDE of structure with Cl substituent was higher in comparison to BDE value of other substituent. For C3'substituted Kaempferol (Fig 3B) with CN, Cl, CH3, OH and NH2 the BDE values are lower in comparison to the Kaempferol. For C5'substituted Kaempferol (Fig 3C) with NO2, Cl and CN the BDE values are higher in comparison to the Kaempferol and For C6'substituted Kaempferol with CH3, OH and NO2 the BDE values are lower in comparison to the Kaempferol. For C6'substituted Kaempferol (Fig 3D) with OH, NO2, CH3 and Cl the BDE values are 11.96, 3.42, 1.98 and 1.86 kcal/mol higher than BDE value of Kaempferol, respectively.

Obtained results can be interpreted that Cl, NO2, OH, CN, NH2 and CH3 groups in C2' position, NO2 group in C3' position, NO2, CN and Cl groups in C5' position and OH, NO2, CH3 and Cl groups in C6' position stabilize the parent molecule and destabilize the radical; hence, it increases the O-H BDE.

Generally the donating capacity of hydrogen atom depends on charge on oxygen and hydrogen atoms. This is confirmed by the obtained results. Low BDE values are often attributed to the higher positive charge on hydrogen atom and the high antioxidant potential.

Fig3. Substituted Kaempferol on A) C2′ , B) C3′ , C) C5′,  D) C6′ (X=H, Cl,NO2 , NH2, CN, CH3 and OH)
4. Conclusions

In this article, the bond dissociation energies of O-H for various substituted Kaempferol were calculated in gas-phase. It can be seen that the BDE values of Kaempferol range from about 74 to 106 kcal/mol, demonstrating that Kaempferol is an effective chain-breaking antioxidant that prevents lipid peroxidation. For substituent’s placed Cl, OH, CN, NH₂ and CH₃ groups in C3′ position, CH₃, OH and NH₂ groups in C5′ position and NH₂ and CN groups in C6’ position destabilize the parent Kaempferol molecule and stabilize the radical; hence, it decreases the O-H BDE.

References
