



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

Mohammad Momen Heravi^{a,*}, Yalda Sabahi^a and Touran Ardalan^b

^aDepartment of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran

^bYoung Researchers and Elite Club, Mashhad Branch, Islamic Azad University, Mashhad, Iran

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 see, 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.

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[•]), alkoxy (RO[•]) and peroxy (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 a diphenylpropane 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

*Corresponding Author

E-mail address: drmh@mshdiau.ac.ir

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.

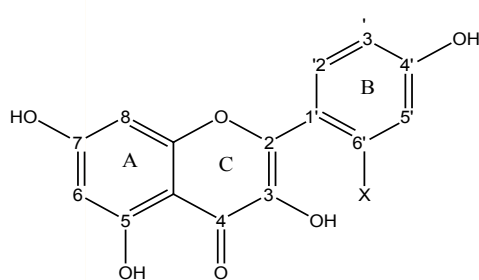


Fig1. Kaempferol structure

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.

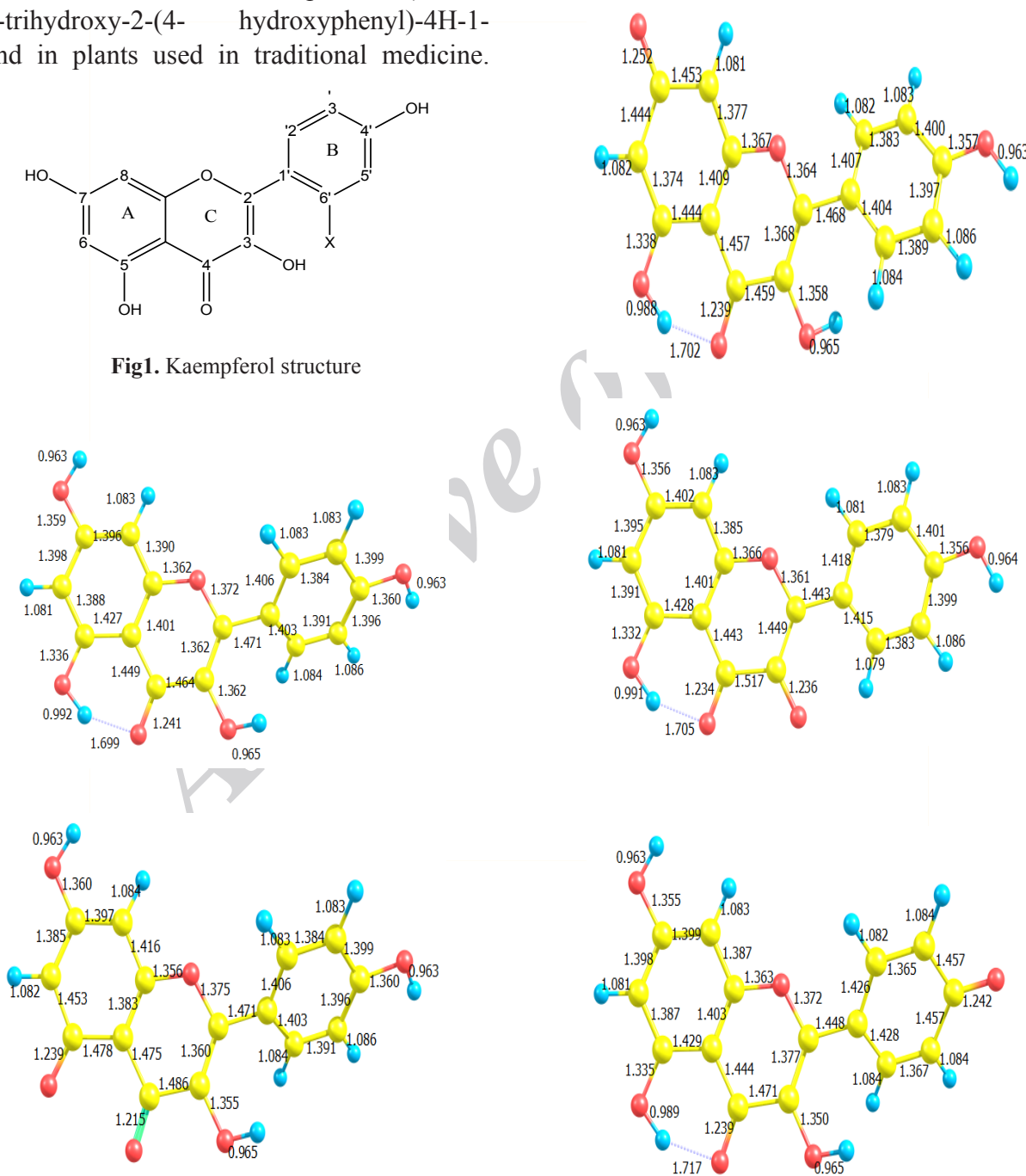


Fig2. Optimized structures of Kaempferol and corresponding radicals (yellow balls: Carbon atom, Blue balls: Hydrogen atom and red balls: Oxygen atom)

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:

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

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 BEDs 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



Antioxidant activity



3. 2 Calculation of Bond Dissociation Energy (Bde) for Substituted Kaempferol
BDE for substituted Kaempferol in different position with H, Cl, NO₂, NH₂, CN, CH₃ and OH groups were calculated. The results are listed in table 2.

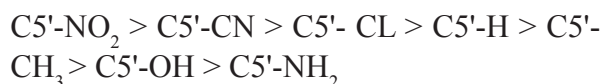
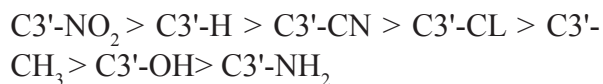
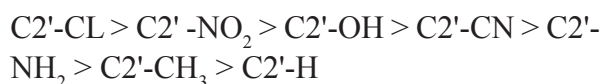
Table1. Calculated BDEs for Kaempferol in gas-phase

Levels and Basis Sets	BDE (kcal/mol)			
	3-OH	4'-OH	5-OH	7-OH
B3LYP/6-31G	74.21649	86.17037	105.06715	90.48393
B3LYP/6-311G	75.31104	86.68648	105.30140	90.851583
B3LYP/6-311G**	77.75302	88.81289	106.16296	93.78966

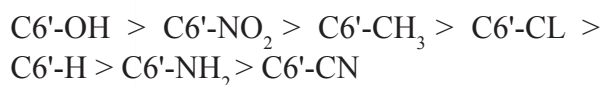
Table2. Calculated BDEs and ΔBDEs for Kaempferol and substituted Kaempferol in gas-phase by using B3LYP/6-311G** method

X	C2'		C3'		C5'		C6'	
	BDE (kcal/mol)	ΔBDE (kcal/mol)	BDE (kcal/mol)	ΔBDE (kcal/mol)	BDE (kcal/mol)	ΔBDE (kcal/mol)	BDE (kcal/mol)	ΔBDE (kcal/mol)
H	88.81289	0	88.81289	0	88.81289	0	88.81289	0
NO ₂	90.98750	2.174602	89.29325	0.48035	100.14900	11.33611	92.24250	3.42960
Cl	91.30125	2.48835	86.97150	-1.84139	89.92075	1.10785	90.67375	1.86085
CN	90.61100	1.79810	88.60300	-0.20989	91.17575	2.36285	81.88875	-6.92414
NH ₂	90.54825	1.73535	78.12375	-10.68914	77.81000	-11.00289	87.53625	-1.27664
CH ₃	90.36000	1.54710	86.90875	-1.90414	86.21850	-2.59439	90.79925	1.98635
OH	90.79925	1.98635	79.44150	-9.37139	79.25325	-9.55964	100.7765	11.96361

Comparison of BDE values for substituted Kaempferol



:



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 C5'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.

The O-H BDE of structure with NH₂ and CN substituent in C6' position were lower 1.27664 and 6.92414 kcal/mol in comparison to 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.

However, 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.

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.

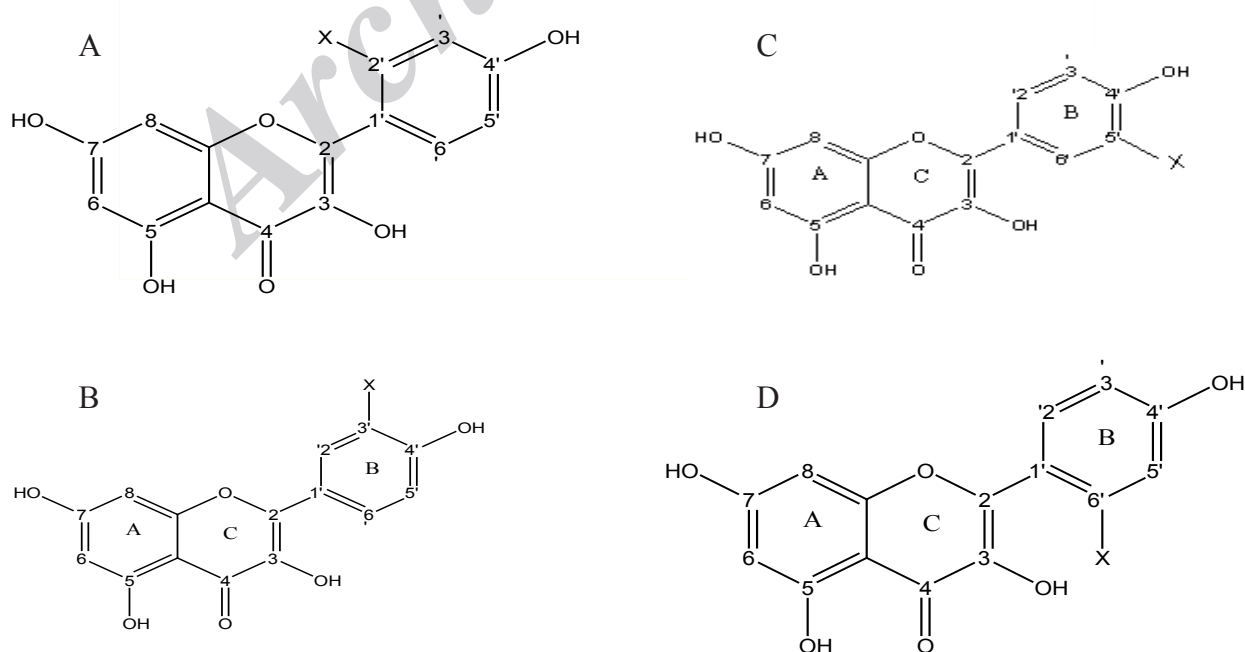


Fig3. Substituted Kaempferol on A) C2' , B) C3' , C) C5' , D) C6' (X=H, Cl,NO₂ , NH₂, CN, CH₃ and OH)

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

- [1] F. Gugumus. Oxidation inhibition in organic materials, Vol. 1. CRC Press, Boca Raton. 1990.
- [2] Q. Zhu, XM. Zhang, AJ. Fry, Polym. Degrad. Stab. 57 (1997) 43.
- [3] M. Meyer, Int. J. Quantum Chem. 76 (2000) 724.
- [4] J. Wright, E. R. Johnson, G. A. DiLabio, J. Am. Chem. Soc. 123 (2001), 1173.
- [5] V. B. Luzhkov, Chem. Phys. 314 (2005) 211.
- [6] M. G. Hertog, E. J. Feskens, P. C. Hollman, M. B. Katan, D. Kromhout, Lancet, 342 (1993) 1011.
- [7] M. L. Neuhouser, Nutr. Cancer. 50 (2004) 7.
- [8] L. Le Marchand, Biomed. Pharmacother, 56 (2002) 301.
- [9] D. Maron, Curr. Atheroscler. Rep. 6 (2004) 73.
- [10] R. Garcia-Closas, C. A. Gonzalez, A. Agudo, E. Riboli, Cancer Causes Control. 10 (1999) 71.
- [11] E. Middleton, C. Kandaswami, T. Theoharides, Pharmacol. Rev. 52 (2000), 673.
- [12] H. K. Wang, Expert. Opin. Investig. Drugs. 9 (2000) 2103.
- [13] M. Lopez-Lazaro, Curr. Med. Chem. Anticancer Agents. 2 (2002) 691.
- [14] Y. Li, H. Fang, W. Xu, Mini Rev. Med. Chem. 7 (2007) 663.
- [15] M. Lopez-Lazaro, Mini Rev. Med. Chem. 9 (2009) 31.
- [16] W. Ren, Z. Qiao, H. Wang, L. Zhu, L. Zhang, Med. Res. Rev. 23(2003) 519.
- [17] H. P. Hoensch, W. Kirch, Int. J. Gastrointest. Cancer. 35 (2005) 187.
- [18] A. D. Becke, J. Chem. Phys. 98 (1993) 5648.
- [19] A. D. Becke, Phys. Rev. A. 38 (1988) 3098.
- [20] C. Lee, W. Yang, R. Parr, Phys. Rev. B. 37 (1988) 785.
- [21] Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA, Jr., Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada V, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain M-C, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2003) GAUSSIAN 03, Revision A.1, Gaussian, Inc., Pittsburgh.
- [22] M. Leopoldini, T. Marino, N. Russo, M. Toscano, J. Phys. Chem B. 108 (2004) 4922.