DFT STUDY OF FREE RADICAL SCAVENGING ACTIVITY OF FLAVONOID MORIN

Z. Marković, D. Milenković, Jelena Đorović, Jasmina M. Dimitrić Marković, Višnja Stepanić, B. Lučić, D. Amić

Abstract: Reaction enthalpies related to mechanisms of free radical scavenging by flavonoid morin were calculated by DFT method in gas-phase, water, DMSO and benzene. Thermodynamically favored mechanism depends on reaction medium: SPLET (sequential proton loss electron transfer) is preferred in water and DMSO, and HAT (hydrogen atom transfer) is predominant in gas-phase. In benzene these two mechanisms are competitive.

Keywords: morin, flavonoids, radical scavenging, DFT, BDE

Introduction

Morin (3,5,7,2',4'-pentahydroxyflavone) is a yellow crystalline substance of acid properties extracted from wood of old fustic (*Chlorophora tinctoria*). It is widely distributed, biologically active, flavonol which occurs in family *Moraceae* (e.g., in white mulberry (*Morus alba*) and fig (*Ficus carica*)), in almond (*Prunus dulcis*, family *Rosaceae*), in sweet chestnut (*Castanea sativa*, family *Fagaceae*) and many other herbs and fruits (Basile et al., 2000; Wijeratne et al, 2006).

Mechanisms of flavonoid free radical scavenging activity

There are at least three fundamental and widespread reaction pathways through which flavonoids (Fl-OH) and other phenolic compounds act as antioxidants activity:

$$\text{Fl–OH} + \text{RO}^{\bullet} \rightarrow \text{Fl–O}^{\bullet} + \text{ROH} \qquad (1)$$

is known to involve complex processes.

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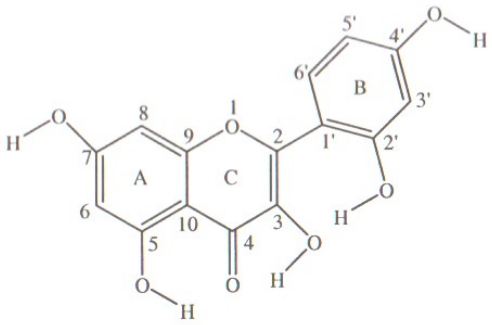

Figura 1. Hemijska struktura morina
Figure 1. Chemical structure of morin

Antioxidant Mechanisms

Preferred mechanism of antioxidant activity of a certain flavonoid can be concluded from the relative ΔBDE and ΔIP values. These values are calculated as the difference between BDE and IP values of flavonoid compound (morin in this case) and phenol as a reference compound.

From Table 1, it can be seen that the most active position susceptible to HAT mechanism is that with the most negative value of ΔBDE. SET-PT mechanism could be related to the most negative value of ΔIP as well as to the smallest value of ΔPDE. For both mechanisms in all media this is the 3-OH position. The results concerning gas-phase showed ΔIP value of −65 kJ mol^{-1} and ΔBDE value of −22 kJ mol^{-1}.

Tabela 1. ΔBDE, ΔIP i ΔPDE O-H vrednosti morinovih O-H grupa (u odnosu na fenol)
Table 1. ΔBDE, ΔIP, and ΔPDE values of morin OH groups (with regard to phenol)

	DFT		
	ΔBDE	ΔIP	ΔPDE
Gas		−65	
3-OH	−22		43
Water		−11	
3-OH	−31		−20
Benzen		−31	
3-OH	−27		4
DMSO		−7	
3-OH	−31		−24

Hydrogen atom transfer

$$Fl\text{–}OH \rightarrow Fl\text{–}O^{\bullet} + H^{\bullet} \qquad (2)$$

Single electron transfer followed by proton transfer

$$Fl\text{–}OH \rightarrow Fl\text{–}OH^{\bullet+} + e^{-} \qquad (3)$$

Second step is deprotonation of $Fl\text{–}OH^{\bullet+}$:

$$Fl\text{–}OH^{\bullet+} \rightarrow Fl\text{–}O^{\bullet} + H^{+} \qquad (4)$$

Sequential proton loss electron transfer

$$Fl\text{–}OH \rightarrow Fl\text{–}O^{-} + H^{+} \qquad (5)$$

In the second step electron transfer from $Fl\text{–}O^{-}$ takes place:

$$Fl\text{–}O^{-} \rightarrow Fl\text{–}O^{\bullet} + e^{-} \qquad (6)$$

Therefore, comparison of BDEs, IPs and PAs can indicate the most probable mechanism from the thermodynamic point of view (Rimarčik et al, 2010).

The objective of the present work is to study radical scavenging activity of morin using theoretical DFT calculation. The enthalpies of morin species, related to their free radical scavenging mechanisms in gas-phase and in polar and non-polar solvents, are calculated.

Methodology section

The conformations of different morin forms (neutral, radical, radical-cation, and anion) are fully optimized with the new local density functional method (M05-2X), recently developed by the Truhlar group (Zhao et al, 2005; Zhao et al, 2006), by using the 6-311++G (d, p) basis set as implemented in the Gaussian 09 package (Frisch et al., 2009). This new hybrid meta exchange-correlation functional is parameterized so that it includes both nonmetallic and metallic compounds.

Results and discussion

Since the behavior of the different OH groups in polyphenolic compounds is largely influenced by electronic effects of the neighboring groups and the overall geometry of the molecule, the conformation can be regarded as the first parameter of importance in analyzing the antioxidant capacity of any polyphenolic molecule, morin in this case (Figure1).

Conclusion

In this work, conformational analysis, as well as the phenolic OH bond dissociation enthalpies, proton affinities, and ionization potential, related to HAT, SPLET, and SET-PT mechanisms of flavonoid morin were studied.

The results obtained using the M05-2X/6-311++G(d,p) level of theory imply non planar structure of morin as the most stable one. This most stable form is significantly distorted from planarity in all solvents, and additionally stabilized by three IHBs, while the other rotamers are stabilized by one or two IHBs.

The present study revealed that both DFT method could be useful tools in studying energetics of free radical scavenging action of flavonoids. The results indicate that not only gas-phase calculations should be taken under consideration. This means that it is very important to perform calculations in polar and non-polar solvents to elucidate preferred mechanism of free radical scavenging action of flavonoids.

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References

Basile A., Sorbo S., Giordano S., Ricciardi L., Ferrara S., Montesano D., Castaldo Cobinachi R., Vuotto M. L., & Ferrara L. (2000). Antibacterial and allelopathic activity of extract from Castanea sativa leaves. Fitoterapia, *(*71): 110-116.

Wijeratne S.S.K., Abou-Zaid M.M., Shahidi F. (2006). Antioxidant Polyphenols in Almond and Its Coproducts. Journal Agricultural and Food Chemistry. (54): 312-318.

Rimarčik J., Lukeš V., Klein E. & Ilčin M. (2010). Study of the solvent effect on the enthalpies of homolytic and heterolitic N–H bond cleavage in *p*-phenylenediamine and tetracyano-*p*-phenylenediamine. Journal of Molecular Structure (Theochem). (952): 25-30.

Zhao Y., Schultz, N. E., & Truhlar, D. G. (2005). Exchange-correlation functional with broad accuracy for metallic and nonmetallic compounds, kinetics, and noncovalent interactions. Journal of Chemical Physics. (123): 161103.

Zhao Y., Schultz, N. E., & Truhlar, D. G. (2006). Design of density functionals by combining the method of constraint satisfaction with parametrization for thermochemistry, thermochemical kinetics, and noncovalent interactions. Journal Chemical Theory and Computation. (2): 364-382.

DFT ISTRAŽIVANJA AKTIVNOSTI FLAVONOIDA MORINA

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Izvod: Reakcione entalpije povezane sa mehanizmima aktivnosti slobodnih radikala morina su izračunate sa DFT metodom u gasu, vodi, benzenu i DMSO. Termodinamički favorizovan mehanizam zavisan je od reakcije u polarniom mediju: u polarnom rastvaraču (voda i DMSO) SPLET (sekvencijalni gubitak protona i transfer elektrona) je prioritetan mehanizam, a u nepolarnom benzenu (i gasu) HAT (transfer vodonika) mehanizam je odgovoran za aktivnost slobodnih radikala morina.

Ključne reči: morin, flavonoidi, skupljanje radikala, DFT, BDE