ANALYSIS OF FREE RADICAL SCAVENGING ACTIVITY OF MORIN 2'- O⁻ PHENOXIDE ANION

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Abstract: Reaction enthalpies related to mechanisms of free radical scavenging activity of morin phenoxide anion 2'-O^- (dominant species at physiological pH of 7.4) were calculated by DFT method in gas-phase, water, benzene and DMSO. Thermodynamically favoured mechanism depends on the polarity of reaction media: in polar solvents (water and DMSO) the SPLET (sequential proton loss electron transfer) mechanism is preferred, and in non-polar benzene (and in gas-phase) the HAT (hydrogen atom transfer) mechanism is responsible for the free radical scavenging activity of morin phenoxide anion.

Keywords: morin phenoxide anion, radical scavenging, hydrogen atom transfer, sequential proton loss electron transfer, bond dissociation enthalpy

Introduction

Morin (3,5,7,2',4'-pentahydroxyflavone) belongs to the flavonoid group of polyphenolic compounds found ubiquitously in plant kingdom. It can be found in wood of old fustic, in osage orange, white mulberry, fig, almond and sweet chestnut, and many other herbs and fruits used as herbal medicines (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 morin phenoxide anion ($Ar(OH)O^-$) act as antioxidants activity:

$$Ar(OH)O^- + RO^\bullet \rightarrow Ar(O^\bullet)O^- + ROH \qquad (1)$$

is known to involve complex processes.

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Hydrogen atom transfer

$$Ar(OH)O^- \rightarrow Ar(O^\bullet)O^- + H^\bullet \qquad (2)$$

Single electron transfer followed by proton transfer

$$Ar(OH)O^- \rightarrow Ar(OH^{\bullet+})O^- + e^- \qquad (3)$$

Second step is deprotonation of $(Ar(OH^{\bullet+})O^-)$:

$$Ar(OH^{\bullet+})O^-) \rightarrow Ar(O^\bullet)O^-) + H^+ \qquad (4)$$

Sequential proton loss electron transfer

$$Ar(OH)O^- \rightarrow Ar(O^-)O^- + H^+ \qquad (5)$$

In the second step electron transfer from $Ar(O^-)O^-$ takes place:

$$Ar(O^-)O^- \rightarrow Ar(O^\bullet)O^- + e^- \qquad (6)$$

Reaction enthalpies of the individual steps of three free radical scavenging mechanisms (HAT, SET-PT and SPLET) may offer insight which mechanism is thermodynamically preferred. 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 mechanisms of radical scavenging activity of morin phenoxide anion using DFT method. In our previous article we performed DFT calculations of reaction enthalpies related to the free radical scavenging mechanisms of morin molecule in various media (Markovic et al., 2012). In this paper we extend DFT calculations to phenoxide anion of morin.

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. The vibrational frequencies are obtained from diagonalization of the corresponding M05-2X Hessian matrices. The nature of the stationary points is determined by analyzing the number of imaginary frequencies: 0 for minimum and 1 for transition state. Relative enthalpies were calculated at 298 K.

Results and discussion

The behavior of the different OH groups in morin 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 morin phenoxide anion (Figure1).

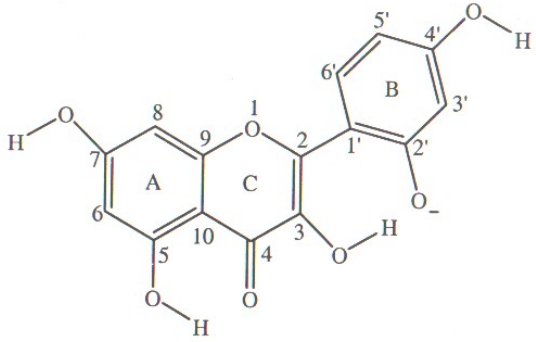

Figura 1. Hemijska struktura morin 2'-O⁻ fenoksidnog anjona
Figure 1. Chemical structure of morin 2'-O⁻ phenoxide anion

As can be seen from Table 1, gas-phase preferred mechanism of action is HAT, because BDE values of OH groups of 2'-O⁻ phenoxide anion are lower than corresponding IP and PA values. In water, IP is slightly lower than the BDE values, but PA of OH groups are significantly lower than corresponding BDEs and IP. This indicates that SPLET mechanism thermodynamically represents the most probable reaction pathway in water. In polar aprotic solvent DMSO, SPLET is also preferred mechanism. In non-polar benzene, entering HAT is more probable than SPLET. In all media, SET-PT mechanism is not the preferred one: in gas-phase and benzene BDEs have lower values (HAT is preferred), and in polar water and DMSO most probable mechanism is SPLET (PAs are much lower than IP).

DFT reaction enthalpies related to the three mechanisms of antiradical activity of 2'-O⁻ phenoxide anion in gas and water are presented in Table 1.

Tabela 1 . Antiradikalska aktivnost 2`-O⁻ fenoksidnog anjona u različitim rastvaračima

Table 1. Antiradical activity of 2'-O⁻ phenoxide anion in different media

	HAT	SET-PT		SPLET	
	BDE	IP	PDE	PA	ETE
gas					
3-OH	397	324	1395	1769	-50
5-OH	398		1395	1715	5
7-OH	324		1321	1617	28
4'-OH	310		1307	1662	-30
water					
3-OH	365	261	104	164	201
5-OH	361		100	127	234
7-OH	341		80	101	240
4'-OH	332		71	118	214
dmso					
3-OH	389	388	119	213	294
5-OH	404		134	166	356
7-OH	344		74	110	352
4'-OH	333		62	136	395
benzene					
3-OH	397	399	413	632	180
5-OH	397		413	577	234
7-OH	338		354	500	253
4'-OH	325		341	541	199

Conclusion

On the basis of performed DFT calculations it appears that first deprotonation of morin molecule results in 2'-O⁻ phenoxide anion. This anion is dominant species at physiological pH of 7.4. Reaction enthalpies related to HAT, SET-PT and SPLET mechanisms of free radical inactivation by 2'-O⁻ phenoxide anion were calculated by DFT method. Entering SPLET mechanism represents thermodynamically preferred reaction pathway in water (and in polar aprotic DMSO), where PAs of OH groups are considerably lower than corresponding BDEs. In non-polar solvent benzene (and in gas-phase) HAT is the most probable pathway.

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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.

Markovic Z., Milenkovic D., Đorovic J., Dimitric-Markovic J.M., Stepanic V., Lucic B., Amic D. (2012). Analysis of free radical scavenging activity of morin 2'- O^- phenoxide anion. Journal Agricultural and Food Chemistry.

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

Frisch, M. J., Trucks, G. W., Schlegel, H. B., et al. (2009). Gaussian 09, revision A.1-SMP.Wallingford, CT: Gaussian, Inc.

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.

ANALIZA AKTIVNOSTI RADIKLA MORIN 2'-O^- FENOKSIDNOG ANJONA

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Izvod: Reakcione entalpije povezane sa mehanizmima aktivnosti slobodnih radikala morin fenoksidnog anjona 2'-O^- (dominantne vrste na fiziološkom pH=7.4) 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 gasovitoj fazi HAT (transfer vodonika) mehanizam je odgovoran za dobru sposbnost skupljanja slobodnih radikala morin fenoksidnog anjona 2'-O^-.

Ključne reči: morin fenoksidni anjon, sakupljanje radikala, transfer atoma vodonika, sekvencijalni gubitak protona i transfer elektrona, entalpija disocijacije veze.