# STUDY OF FREE RADICALS SCAVENGING ACTIVITY OF ERODIOL USING DFT

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**Abstract**: Density functional theory calculations were performed to evaluate the antioxidant activity of erodiol. The conformational behavior of both the isolated and the aqueous solvation species (simulated with the SMD solvation model) were analyzed at the M05-2X/6-311+G (d, p) level. The most stable tautomer of erodiol forms displayed three IHBs. The expected antioxidant activity of erodiol was justified from ionization potential (IPs) and homolytic O-H bond dissociation enthalpies (BDEs) values, which were obtained by the UM052X optimization level of the corresponding radical species. Heterolytic O-H bond cleavages (proton dissociation enthalpies, PDEs) were also computed. Calculated IP, BDE, and PA values suggested that one-step H atom transfer, rather than SPLET or SET-PT, would be the most favored mechanism for explaining the antioxidant activity of erodiol in gas phase and nonpolar solvents. In aqueous solution SPLET and SET-PT mechanisms were competitive.

**Keywords**: erodiol, depside, radical scavenging, DFT, BDE

## Introduction

Depsides are phenolic compounds predominantly found in lichens, but have also been isolated from higher plants (Ono et al., 2002; Zgorka &Gowniak, 2001; Hillenbrand et al., 2004). Some depsides have been reported to have activity against mycobacteria, Gram-positive bacteria, insects, and nematodes (Lv et al., 2009). Additionally, depsides exhibit antioxidant, antiproliferative, analgesic, antibiotic, antipyretic, anticancer, anti-HIV, antiviral and anti-inflammatory properties (Lv et al., 2009; Reynertson et al., 2006). Numerous researchers investigated the antioxidant activity of pure depsides and depside-containing plant extracts and found that these compounds constitute a part of the plant defense mechanism against oxidative stress.

## Methodology section

Density functional theory calculations were carried out with the GAUSSIAN 09 package of programs (Frisch et al., 1998). The minimum were fully optimized by M05-2X method. The 6-311+G(d,p) basis set is used, as a quite large basis set for a molecular system of such size and as a unique and enough-tested set of basic functions for H-atom transfer reactions. The choice of this basis set is also motivated by the fact that it gives reliable bond dissociation enthalpy BDE estimation in the gas phase (enthalpy difference, calculated at 298 K, for the reaction ArOH → ArO• + H•) and better description of electronic interaction far from the nucleus (i.e. electron delocalization), due to the joint use of polarization functions (d, p) and diffuse functions (+).

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## Results and discussion

In the most stable structure of erodiol, labeled 1 in Fig. 1, there are three internal hydrogen bonds (IHB) that all produce a stabilizing effect, especially the bond between the 4-OH and the C2-O carbonyl group as well as between the 11-OH and the C9-O carbonyl group. Conformations that lack these bonds (the other rotamers: 1a, 1b and 1c in Fig. 1) are less stable with respect to the absolute minimum by 21.55, 17.36, 20.08 kJ $mol^{-1}$ respectively. On the basis of these values, it is clear that the hydrogen bonds between OH a carbonyl groups have the strongest stabilizing effect, which agrees with the fact that these hydrogen bonds are shorter than hydrogen bond between 4-OH and 5-OH.

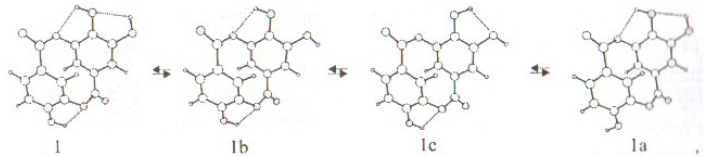


*Fig. 1. Najstabilnija konformacija erodiola 1. 1a, 1b, i 1c su manje stabilni rotameri*
Fig. 1. The most stable conformation of erodiol 1. 1a, 1b, and 1c are less stable rotamers

## Antioxidant Mechanisms

Preferred mechanism of antioxidant activity of a certain depside in this case erodiol can be concluded from the relative ΔBDE and ΔIP values. These values are calculated as the difference between BDE and IP values of erodiol and phenol as a reference compound. The BDE, IP, and PDE values computed for phenol, at the M05-2X/6-311+G(d,p) level in gas and water were presented in Table 1. According to (Wright J. S. et al., 2001), for $\Delta IP \leq -150$ kJ $mol^{-1}$ and for ΔBDE around −42 kJ $mol^{-1}$ HAT is considered as dominant mechanism, whereas for $\Delta IP > -188$ kJ $mol^{-1}$ predominant mechanism is SET-PT.

*Tabela 3. DFT izračunati parametri aktivnosti slobodnih radikala erodiola(u kJ/mol)*
Table 3. DFT calculated parameters of free radical scavenging activity of erodiol (in kJ/mol)

| | gas-phase | | | | | water | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HAT | SET-PT | | SPLET | | HAT | SET-PT | | SPLET | |
| | BDE | IP | PDE | PA | ETE | BDE | IP | PDE | PA | ETE |
| | | 742 | | | | | 292 | | | |
| 4-OH | 352 | | 932 | 1330 | 345 | 342 | | 50 | 80 | 262 |
| 5-OH | 367 | | 946 | 1371 | 318 | 346 | | 54 | 101 | 245 |
| 11-OH | 469 | | 1049 | 1358 | 433 | 369 | | 77 | 93 | 277 |

## 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 depside erodiol were studied.

The results obtained using the M05-2X/6-311+G(d,p) level of theory imply structure of erodiol as the most stable one. This most stable form is additionally stabilized by three IHBs, while the other rotamers are stabilized by one or two IHBs. The 4-OH group is the most favoured site for homolytic and heterolytic O–H breaking, in both solvents.

Based on the obtained results, DFT method predicts that the HAT mechanism is dominant in the gas phase. The SPLET and SET-PT mechanisms represent thermodynamically preferred reaction pathways in water, where IP and PAs of OH groups are considerably lower than corresponding BDEs.

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*Tabela 1. DFT izračunati parametri aktivnosti slobodnih radikala fenola (u kJ/mol)*
Table 1. DFT calculated parameters of free radical scavenging activity of phenol (in kJ/mol)

| Solvent | BDE | IP | PDE |
|---|---|---|---|
| gas-phase | 359 | 822 | 859 |
| Water | 356 | 362 | –6 |

*Tabela 2. ΔBDE, ΔIP, i ΔPDE vrednosti OH grupa erodiola (sa osvrtom na fenol)*[a]
Table 2. ΔBDE, ΔIP, and ΔPDE values of erodiol OH groups (with regard to phenol)[a]

| | Gas | | | Water | | |
|---|---|---|---|---|---|---|
| | ΔBDE | ΔIP | ΔPDE | ΔBDE | ΔIP | ΔPDE |
| | | -80 | | | -81 | |
| 4-OH | -7 | | 73 | -14 | | 56 |
| 5-OH | 8 | | 87 | -10 | | 60 |
| 11-OH | 110 | | 190 | 13 | | 83 |

[a]Sve teoretske vrednosti u poređenju sa fenolim izračunate istom metodom
[a]All theoretical values refer to phenol calculated with the same method

From Table 2., 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 both media this is the 4-OH position. The results concerning gas-phase showed ΔIP value of –80 kJ $mol^{-1}$ and ΔBDE value of –7 kJ $mol^{-1}$. According to Wright conditions (Wright et al., 2001) the SPLET and SET-PT mechanisms, which have been quoted by several authors (Foti et al., 2004; Musialik & Litwinienko, 2005; Litwinienko & Ingold, 2007; Rimarčik et al., 2010), could be discarded as possible for erodiol in all solvents under investigation (Table 3.) because the HAT mechanism seems to be the only practical or the preferred one in both media.

On the basis of inspection of data from Table 3., it is clear that the HAT mechanism is dominant in gas phase, because BDE values of OH groups are significantly lower than corresponding IP and PA values. On the basis of obtained values for BDE, PA and PDE, it is clear that 4-OH group should be more reactive OH group of erodiol. In water PAs of OH groups of erodiol are significantly lower than corresponding BDE values. This indicates that SPLET mechanism thermodynamically represents the most probable reaction pathway in polar solvent.

Since, IP has a lower value then BDE in water, and slightly higher values than the second step of SPLET mechanism (ETE), it means that both mechanisms occur simultaneously, in the aqueous phase.

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