UDC 541:544.165 DOI: 10.18698/1812-3368-2019-3-96-104

NEW QUANTUM CHEMICAL METHOD FOR ASSESSING THE RELATIVE ACTIVITY OF ANTIOXIDANTS

T.A. Yarkova[1] tat772003@list.ru
A.M. Gyulmaliev[2] gyulmaliev@ips.ac.ru

[1] **K.G. Razumovsky Moscow State University of Technologies and Management (the First Cossack University), Moscow, Russian Federation**
[2] **A.V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, Moscow, Russian Federation**

Abstract

A new method for evaluating the antioxidant activity of organic compounds based on quantum chemical calculations of their electronic structure using the *DFT B3LYP/6-31G (d, p)* method has been proposed. The geometric parameters of antioxidant molecules were optimized and the reactivity indices were determined from the energy values of the highest occupied and the lowest unoccupied molecular orbitals: absolute electronegativity; electronic chemical potential; absolute "chemical hardness". The found indicators allow us to quantify the antioxidant activity by building their dependence on the energy of the lower vacant molecular orbitals. The correlation of the obtained parameters with the standard, such as trolox, allows determining the relative antioxidant activity of the test substance

Keywords

Antioxidant activity, quantum chemical method, chemical stability, molecular orbitals, trolox

Received 20.09.2018

Introduction. The formation of free radicals, which in many cases are very reactive particles, accompanies a significant number of chemical and biochemical processes occurring both in living organisms and in products produced by humans, for example, in food, cosmetics, medicines. In particular, the free radical mechanism is characteristic of oxidation processes occurring in air. Therefore, antioxidants (AO) are used to control the chemical composition and impart stability in oxidation processes with active forms of oxygen. The mechanism of action of the most common AO is a chemical interaction with an active free radical to form chemically stable particles. From this position, an AO should have the structure of a reducing agent with a significant system of conjugated bonds for the successful delocalization of a free electron. Thus, the sources of formation of

active radicals and the ways of their balanced inhibition play an important role in many sectors of the national economy, which, in particular, in the chemistry of drugs led to the creation of a new scientific direction — *QSAR (Quantitative Structure – Activity Relationship).* The basis of this trend is a mathematical apparatus that allows for correlations between the features of the chemical structure of compounds and their antioxidant activity [1, 2].

Methods. Here is the list of the experimental methods for the determination of anti-radical activity: spectrometric; electrochemical; chromatographic, etc. [3]. Conventionally, these methods can be divided into two types: 1) methods based on changing a certain indicator of a substance before and after interacting with an AO; 2) methods of comparison with the standard, the antioxidant capacity of which is taken as a unit [4–6]. As noted in [2]: "Methods for the study of total antioxidant activity (AOA) differ in the type of oxidation source, oxidizable compound, and method for measuring the oxidized compound. These methods provide a wide range of results that cannot be used separately, and the results should be interpreted with caution".

Currently, AOA is most often evaluated by correlating with trolox — a synthetic water-soluble analog of vitamin E. Trolox according to its chemical structure is 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-carboxylic acid, and the AOA is quantitatively evaluated in Trolox equivalents of *TEAS*. For this photometric method after inhibition is measured by the optical density at 450 nm. Specific absorption is determined by the formula

$$\text{Inhibition}\left(\text{A}\%\right)=\frac{100\left(D_0-D_1\right)}{D_0},$$

where D_0 is the absorption of the control; D_1 is absorption in the presence of an antioxidant sample. The method is standardized on an individual compound, which was used as tolox [3, 5].

Note that the methods for determining the AOA, along with the undoubted advantages, are very time consuming and require the use of special equipment [7], expensive reagents and experience in carrying out the determination. Consequently, the search for a new method for determining the AOA, which makes it possible to simplify and narrow down the experimental part of the work, has undoubted practical value.

The objective is to create a new method for assessing the relative activity of antioxidants according to the results of quantum chemical calculations of their electronic structure.

All calculations were performed using the *DFT B3LYP/6-31G (d, p)* method using the *GAMESS v.7.1* program with full energy optimization and calculation

of the frequencies of normal vibrations [8]. The geometric parameters of the molecule, the distribution of electron density and energy characteristics were calculated by the formulas

$$E_0 = E_{\text{elec}} + ZPE; \;\; E = E_0 + E_{\text{vib}} + E_{\text{rot}} + E_{\text{transt}};$$

$$H = E + RT; \;\; G = H - TS,$$

where E_{elec} is the electron energy of the molecule; ZPE is zero-point energy; E_{vib} is the vibrational energy of a molecule at temperature T = 298 K; E_{rot} is rotational energy, E_{transt} is translational energy; H is enthalpy; R is gas constant; G is the Gibbs free energy; S is entropy.

For the evaluation of AOA, the structures of generally accepted antioxidants were used (Table 1). The results of calculations of the values of the characteristics of these molecules are also given in Table 1: thermal energy E_T; heat capacity with a constant volume of C_V, the energy of the highest occupied and the lowest unoccupied molecular orbitals of the E_{HOMO} and E_{LUMO}.

The energy characteristics of molecules (Table 1) can be used to quantify their relative antioxidant activity. The proposed method for assessing the relative activity of AO is based on the determination of reactivity indices [9, 10]. Thus, the energy of the highest occupied (E_{HOMO}) and the energy of the lowest unoccupied (E_{LUMO}) molecular orbitals (HOMO, LUMO) play an important role in the chemical stability of the molecule, since HOMO has the ability to release an electron, and LUMO, acting as an acceptor, receives it. According to Kupmans theorem, the ionization potential I and electron affinity A depend on the energy of molecular orbitals as follows:

$$I = -E_{\text{HOMO}}; \;\; A = -E_{\text{LUMO}}.$$

The width of the band gap ΔE indicates the resistance of the molecule to excitation and can be determined from the difference of the energies of molecular orbitals: $\Delta E = E_{\text{HOMO}} - E_{\text{LUMO}}$. Absolute electronegativity χ is the ability of a molecule to attract electron density q:

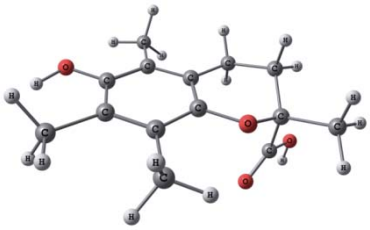
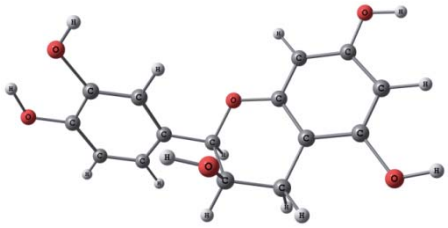
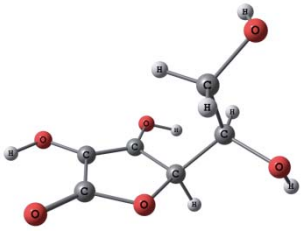
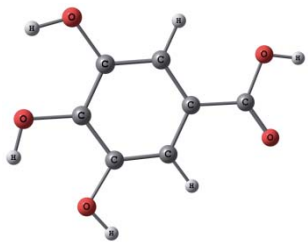
$$\chi = -\frac{1}{2}\,(E_{\text{HOMO}} + E_{\text{LUMO}}).$$

The electronic chemical potential μ is defined as the change in electron energy with a change in the total number of electrons N, it is equal in absolute value to absolute electronegativity, but with the opposite sign: $\mu = -\chi$. Absolute "chemical rigidity" η is the resistance of a molecule to chemical attack

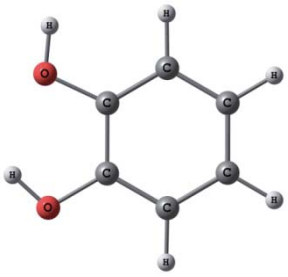
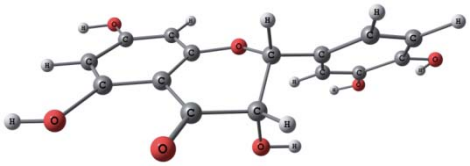
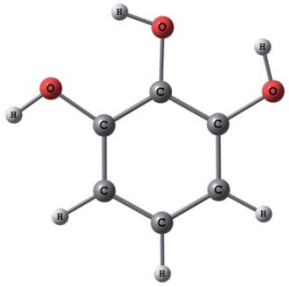
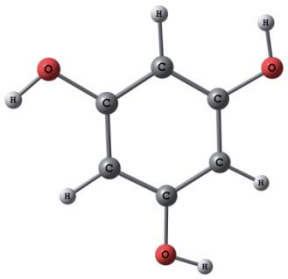
$$\eta = \frac{1}{2}\,\left(E_{\text{LUMO}} - E_{\text{HOMO}}\right).$$

Table 1

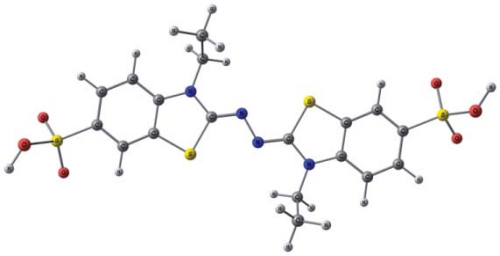
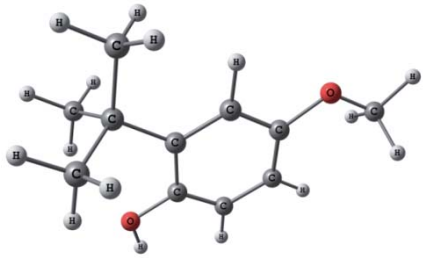
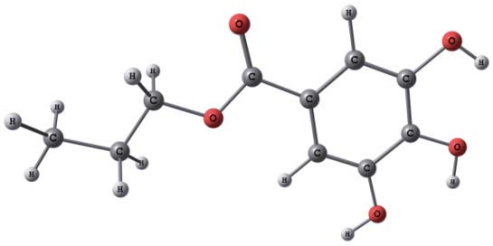
The results of the calculation of the electronic structure of antioxidants*

Title / Optimized Structure	Energy characteristics
Trolox 	E_0= −844.981153 au E = −844.962551 au H = −844.961606 au G= −845.027536 au E_{elec}= −845.2801385 au E_T = 199.289 kcal / mol C_V = 70.183 cal / (mol · K) S = 138.760 cal / (mol · K) E_{HOMO} = −0.18631 au E_{LUMO} = 0.00177 au
Catechin 	E_0 = −1031.101454 au E = −1031.083054 au H = −1031.082110 au G = −1031.147698 au E_{elec} = −1031.3728704 au E = 181.863 kcal / mol C_V = 73.380 cal / (mol · K) S = 138.043 cal / (mol · K) E_{HOMO} = −0.2042 au E_{LUMO} = −0.00256 au
Ascorbic acid 	E_0 = −684.610745 au E = −2959.374556 au H = −684.597415 au G = −684.649448 au E_{elec} = −684.7598689 au E_T =101.349 kcal / mol C_V = 44.429 cal / (mol · K) S = 109.512 cal / (mol · K) E_{HOMO}= −0.23286 au E_{LUMO}= −0.03400 au
Gallic acid 	E_0 = −646.370995 au E = −646.360180 au H = −646.359236 au G = −646.407192 au E_{elec} = −646.4993657 au E_T = 87.340 kcal / mol C_V = 41.373 cal / (mol · K) S = 100.933 cal / (mol · K) E_{HOMO} = −0.21996 au E_{LUMO} = −0.03879 au

Continuation of Table 1

Title / Optimized Structure	Energy characteristics
Pyrocatechin 	E_0 = −382.590308 au E = −382.583538 au H = −382.582594 au G = −382.620841 au E_{elec} =−382.6992862 au E_T = 72.633 kcal / mol C_V = 26.577 cal / (mol · K) S = 80.499 cal / (mol · K) E_{HOMO} = −0.20685 au E_{LUMO} = 0.00750 au
Quercetin 	E_0 = −1105.125933 au E = −1105.106879 au H = −1105.105935 au G = −1105.173338 au E_{elec} = −1105.3784155 au E_T = 170.392 kcal / mol C_V = 74.972 cal / (mol · K) S = 141.861 cal / (mol · K) E_{HOMO} = −0.21425 au E_{LUMO} = −0.04207 au
Floroglucin 	E_0 = −457.807118 au E = −457.799049 au H = −457.798105 au G = −457.839164 au E_{elec} =−457.9202367 au E_T = 76.046 kcal / mol C_V = 31.405 cal / (mol · K) S = 86.417 cal / (mol · K) E_{HOMO} = −0.20566 au E_{LUMO} = 0.01843 au
Pyrogallol 	E_0 = −457.807150 au E = −457.799308 au H = −457.798364 au G = −457.839009 au E_{elec} = −457.9204064 au E_T = 75.990 kcal / mol C_V = 31.250 cal / (mol · K) S = 85.545 cal / (mol · K) E_{HOMO} = −0.21468 au E_{LUMO} = 0.02172 au

End of Table 1

Title / Optimized Structure	Energy characteristics
2, 2-azobis (2,3.-dihydro-3-ethylbenzo-thiazole-6-sulfonic acid) ABTS 	E_0 = −2959.406201 au E = −2959.374556 au H = −2959.373611 au G = −2959.474658 au E_{elec} = −2959.7656731 au E_T = 245.430 kcal / mol C_V = 116.395 cal / (mol · K)) S = 212.670 cal / (mol · K)) E_{HOMO} = −0.19704 au E_{LUMO} = −0.05365 au
3-tertbutyl-4-hydroxyanisole 	E_0 = −579.015116 au E = −579.001617 au H = −579.000673 au G = −579.053734 au E_{elec} = −579.2652984 au E_T = 165.463 kcal / mol C_V = 53.004 cal / (mol · K) S =111.677 cal / (mol · K) E_{HOMO} = −0.19488 au E_{LUMO} = 0.00344 au
Propyl gallate 	E_0 = −764.228911 au E = −764.213604 au H = −764.212660 au G = −764.272038 au E_{elec} = −764.4418847 au E_T = 143.248 kcal / mol C_V = 56.416 cal / (mol · K) S = 124.973 cal / (mol · K) E_{HOMO} = −0.21655 au E_{LUMO} = −0.03325 au

*1 au = 27.211 eV = 627.5095 kcal / mol.

"Chemical mildness", or the tendency to chemical effects, $S = (1/2)\eta$, the index of electrophilicity $\omega = \mu^2 / (2\eta)$. The calculated values of the reactivity indexes of the considered antioxidants are given in Table 2.

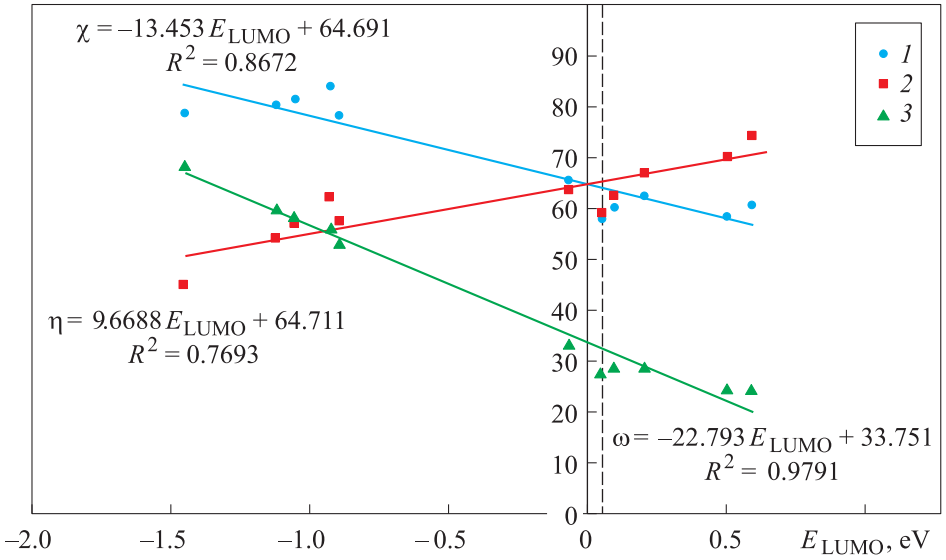
The functions of the reactivity indexes of antioxidants (χ, η, ω) HOMO energies, built on the basis of the data given in Table 2 are shown in the Figure. The dependences obtained are described by linear equations with good correlation coefficients. The curve of the dependence of the electrophilicity of molecules ω on the energy of E_{HOMO} has an inverse relationship. Indeed, the more negative the energy of an E_{HOMO}, the stronger this molecule will hold an electron acquired from the side that is, it will exhibit electron-withdrawing properties. If the energy of the E_{HOMO} increases, then with the electron recoil, the molecule is excited, this corresponds to the transition of the electron from the HOMO to its LUMO. Moreover, if E_{HOMO} is of great importance, then the electron will easily leave the molecule, therefore, this molecule will be an electron donor. The same simple interpretations have lines corresponding to χ and η.

Table 2

Antioxidant Reactivity Indices

Antioxidant	E_{HOMO}, eV	E_{LUMO}, eV	χ, kcal / mol	η, kcal / mol	ω, kcal / mol
Trolox	−5.07	0.05	57.9	59.01	28.41
Catechin	−5.56	−0.07	64.87	63.27	33.26
Gallic acid	−5.99	−1.06	81.18	56.84	57.97
Ascorbic acid	−6.34	−0.93	83.73	62.39	56.18
Pyrocatechin	−5.63	0.20	62.54	67.25	29.08
Quercetin	−5.83	−1.13	80.42	54.02	59.86
Floroglucin	−5.84	0.59	60.54	74.17	24.71
Pyrogallol	−5.60	0.50	58.74	70.31	24.54
ABTS	−5.36	−1.46	78.66	44.99	68.76
3-tertbutyl-4-hydroxyanisole	−5.30	0.09	60.07	62.22	28.99
Propyl gallate	−5.89	−0.90	78.38	57.51	53.41

It is possible to reduce the essence of the proposed method to the following: the reference antioxidant is determined, in this case, trolox. According to the results of quantum chemical calculations of the E_{HOMO} value, the reference molecule is placed on the figure (dashed line in the figure). The vertical dashed line that crosses the dependency lines divides the considered antioxidants into "strong" and "weak" relative to the reference antioxidant, i.e., compounds whose reactivity indices lie to the left of the standard, exhibit weaker antioxidant properties than trolox. The difference in the indices can serve as a criterion for quantifying the relative activity of the AO.



Dependencies of reactivity indices of various antioxidants on the energy of the lowest unoccupied molecular orbital in comparison with the standard (trolox):

1 is electronegativity χ; *2* is absolute chemical hardness η; *3* is electrophilicity ω

Conclusion. As a result of quantum-chemical calculations of the indexes of the reactivity of organic molecules, dependences that allow us to compare the antioxidant properties of these compounds with a standard without a laboratory experiment were obtained. The proposed method can be used to predict the possibility of using a substance as an antioxidant and a relative quantitative evaluation of antioxidant properties.

REFERENCES

[1] Zefirov N.S., Palyulin V.A. Fragmental approach in QSPR. *J. Chem. Inf. Comput. Sci.*, 2002, vol. 42, no. 5, pp. 1112–1122. DOI: 10.1021/ci020010e

[2] Lazareva N.V. O kolichestvennoy svyazi mezhdu strukturoy organicheskikh soedineniy i ikh biologicheskoy aktivnost'yu [About quantitative relationship between the structure of organic compounds and their biological activity.]. *Istoriya khimii: oblast' nauki i uchebnaya distsiplina* [History of Chemistry: Field of Science and Academic Discipline]. Moscow, MSU Publ., 2001, pp. 60–81 (in Russ.).

[3] Khasanov V.V., Ryzhova G.L., Mal'tseva E.V. Methods of the antioxidant investigations. *Khimiya rastitel'nogo syr'ya* [Chemistry of Plant Raw Material], 2004, no. 3, pp. 63–75 (in Russ.).

[4] Perevozkina M.G. Testirovanie antioksidantnoy aktivnosti polifunktsional'nykh soedineniy kineticheskimi metodami [Testing antioxidant activity of polyfunctional compounds by kinetic methods]. Novosibirsk, SibAK Publ., 2014.

[5] Masek A., Chrzescijanska E., Latos M., et al. Antioxidant and antiradical properties of green tea extract compounds. *Int. J. Electrochem. Sci.*, 2017, no. 12, pp. 6600–6610.

[6] Il'yasov I.R., Beloborodov V.L., Tyukavkina N.A. The induction period of formation of ABTS'+ as a characteristic of the antiradical activity of some natural antioxidants. *Farmatsiya* [Pharmacy], 2008, no. 8, pp. 14–17 (in Russ.).

[7] Alekseev A.V., Proskurnina E.V., Vladimirov Yu.A. Determination of antioxidants by sensitized chemiluminescence using 2,2'-azo-bis(2-amidinopropane). *Moscow Univ. Chem. Bull.*, 2012, vol. 67, iss. 3, pp. 127–132.
DOI: https://doi.org/10.3103/S0027131412030029

[8] Granovsky A.A. Introduction to the Firefly.
Available at: http://classic.chem.msu.su/gran/gamess/index.html (accessed: 15.08.2018).

[9] Shubin L. Dynamic behavior of chemical reactivity indices in density functional theory: a Bohn — Oppenheimer quantum molecular dynamics study. *J. Chem. Sci.*, 2005, vol. 117, iss. 5, pp. 477–483. DOI: https://doi.org/10.1007/BF02708352

[10] Pearson R.G. Absolute electronegativity and hardness correlated with molecular orbital theory. *PNAS*, 1986, vol. 83, no. 22, pp. 8440–8441.
DOI: https://doi.org/10.1073/pnas.83.22.8440

Yarkova T.A. — Cand. Sc. (Chem.), Assoc. Professor, Department of Chemistry, Physics and Mathematics, K.G. Razumovsky Moscow State University of Technologies and Management (the First Cossack University) (Zemlyanoy val ul. 73, Moscow, 109004 Russian Federation).

Gyulmaliev A.M. — Dr. Sc. (Chem.), Professor, Chief Researcher, A.V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences (Leninskiy prospekt 29, Moscow, 119991 Russian Federation).

Please cite this article as:

Yarkova T.A., Gyulmaliev A.M. New quantum chemical method for assessing the relative activity of antioxidants. *Herald of the Bauman Moscow State Technical University, Series Natural Sciences*, 2019, no. 3, pp. 96–104. DOI: 10.18698/1812-3368-2019-3-96-104

Издательство МГТУ им. Н.Э. Баумана
105005, Москва, 2-я Бауманская ул., д. 5, стр. 1
press@bmstu.ru
http://baumanpress.ru

Подписано в печать 06.06.2019
Формат 70 × 108/16
Усл.-печ. л. 9,0
Отпечатано в типографии МГТУ им. Н.Э. Баумана
105005, Москва, 2-я Бауманская ул., д. 5, стр. 1
baumanprint@gmail.com