

SOME PARTICULARITIES OF THE REACTION BETWEEN ANTIOXIDANT PHENOLIC ACIDS AND THE FREE RADICAL ABTS^{•+}: A COMPARATIVE DFT STUDY FOR THE GAS PHASE AND ETHANOL

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Abstract. The detailed mechanism of the interaction of the radical cation ABTS^{•+} with a number of food acids (gallic, ferulic, caffeic, vanillic, cinnamic, syringic, *p*-coumaric) is revealed by means of the DFT calculations. It is shown that the interaction between the neutral molecules of the studied food acids and ABTS^{•+} does not lead to any charge transfer from these molecules onto ABTS^{•+}. The almost complete conversion of the ABTS radical cation into its diamagnetic derivative occurs due to the interaction of one of the sulphonic groups of ABTS^{•+} with the acid anions through the formation of the corresponding intermolecular hydrogen bond. The clear-cut correlation between the bond lengths SO^{••}H and the experimental values of the antioxidant activity of the food acids under study was found. DFT calculations taking into account the solvent (ethanol), allow one to reveal the second clear-cut correlation between the studied activity and the values of the charge transfer from the anions of the studied food acids to ABTS^{•+}.

Keywords: antioxidant activity, radical cation ABTS^{•+}, food acid, charge transfer complex, DFT calculation.

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Introduction

Many natural chemical compounds are effective antioxidants. One can meet these compounds in many plants and other natural products [1]. In their turn, these antioxidant compounds can be divided into two classes: enzymatic and non-enzymatic antioxidants. An important group of non-enzymatic antioxidants is formed by different carboxylic food acids. First of all, it includes derivatives of hydroxycinnamic and hydroxybenzoic acids. Derivatives of these acids include such well-known compounds as gallic, caffeic, ferulic, vanillic, and other acids. These acids are able to efficiently convert free radicals into their corresponding diamagnetic derivatives (see, for example, the review [1]).

As a rule, the antioxidant properties of phenolic acids are due to the acidity of their reaction medium. So, chlorogenic, caffeic, and other acids are good antioxidants at pH values between 7 and 8 [2]. Within these pH values many phenolic food acids are being transformed into the phenolated forms of their anions. The reaction ability (and, therefore, the antioxidant activity) of these anionic forms is higher than that of the corresponding neutral acids molecules. It is due to the higher energy values of their valence electrons. Further, the above anions are being transformed into the corresponding radicals which

dimerize [3]. In theoretical works, using DFT calculations, it has been shown that in an aqueous or ethanol media, selected natural phenolic acids demonstrate the sequential proton loss electron transfer (SPLET) mechanism of their antioxidant action (in their reactions with the stable DPPH[•] radical) [4,5]. However, most often, in any concrete case (even if the data about interacting antioxidants and free radicals, and solvent nature are known) there is no knowledge about the detailed mechanisms of their interactions, or about the possible types of these mechanisms including SPLET, hydrogen atom transfer (HAT), single electron transfer (SET) [6,7]. Usually, it concerns the comparison of the influences of the number and the mutual positions of hydroxyl groups connected with benzene rings of phenolic antioxidants on their relative antioxidant activity [6], and also about the possible changes of the nature of the antioxidant mechanism which accompanies the solvent nature changes. However, the precise details of the intermolecular interactions describing the concrete stages of the studied reactions (for example, the redistributions of spin densities, charges, *etc.*, which accompany the studied reactions) are usually not considered. Most often, only some rank correlations between certain calculated parameters of antioxidant molecules and their antioxidant activity are being revealed [7]

with the corresponding conclusions that the studied antioxidant activity of phenolic acids and related substances must be based on taking into account molecular particularities for each of the studied compounds. Here it is also to be noted that the data regarding the details of the possible mechanism of antioxidant action of phenolic compounds scavenging the stable cation-radical $ABTS^{+\bullet}$ are practically absent in the known literature sources. Obviously, the given situation is mainly connected with different experimental difficulties which accompany the ABTS assay [8,9].

Thus, bearing in mind all the above reasons, the aim of the present work consists in the attempt to reveal (using DFT calculations) the detailed mechanism describing the interaction of the food acids with the radical cation $ABTS^{+\bullet}$.

Computational details

All the electronic and geometry characteristics of the molecules of the studied food acids and their complexes with $ABTS^{+\bullet}$ have been calculated by means of the DFT method using the Becke's three-parameter nonlocal-exchange functional [10] with the corresponding correlation functional proposed by Lee, C., Yang, W. and Parr, R.G. (B3LYP) in [11]. The full geometry optimization of the investigated compounds was carried out with the 6-31G* basis sets [12] which include polarization functions for all the atoms in the systems under consideration. All the studied molecular systems possessing unpaired electrons have been calculated by means of the unrestricted B3LYP method (UB3LYP). The calculations were performed by using of the GAUSSIAN09 program package [13]. The effect of the solvent (ethanol) on the electronic distribution in the studied molecular systems was taken into account using the IEFPCM model. This model is present as a standard option in the GAUSSIAN09 program package.

Results and discussion

In order to reveal the particularities of the interaction between the food acids and the radical-cation $ABTS^{+\bullet}$ it is necessary to define the structure of this radical. First of all, it should be taken into account that the cation-radical of the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) is being formed by the redox reaction between the diammonium salt of this acid and potassium persulphate [14,15]. That's why our calculations were started with the neutral diammonium salt of ABTS, which is shown in Figure 1(a). The end point of its geometry optimization is shown in Figure 1(b). One can easily see that two protons belonging firstly to the corresponding NH_4^+ cations have passed from these cations to the anion $ABTS^{2-}$. Thus, the end system is formed by the neutral molecule of ABTS and the two ammonia molecules. Further, after oxidation of neutral molecule of ABTS by potassium persulphate, it transforms into the cation-radical $ABTS^{+\bullet}$. In order to verify that the above protons also enter the structure of the cation-radical we have optimized the system $(NH_3)_2 ABTS^{+\bullet}$. Calculations show that these two protons remain in the structure of the cation-radical $ABTS^{+\bullet}$ and do not go back to the molecules of NH_3 .

The O-H bond lengths are equal to 1.04 Å and 1.08 Å for the neutral molecule of ABTS and for its cation-radical, respectively. Thus, in all the following calculations we have used the structure of the cation-radical $ABTS^{+\bullet}$ shown in Figure 1(b) (without the two molecules of NH_3).

The single occupied molecular orbital (MO) of the cation-radical $ABTS^{+\bullet}$ is shown in Figure 2. One can see that, firstly, this MO is a MO of π -type and, secondly, it covers all the atoms of the planar part of $ABTS^{+\bullet}$. Thus, any atom belonging to the planar system of $ABTS^{+\bullet}$ can interact with an antioxidant molecule. This fact essentially complicates the identification of specific atoms of $ABTS^{+\bullet}$ that could interact with an antioxidant molecule.

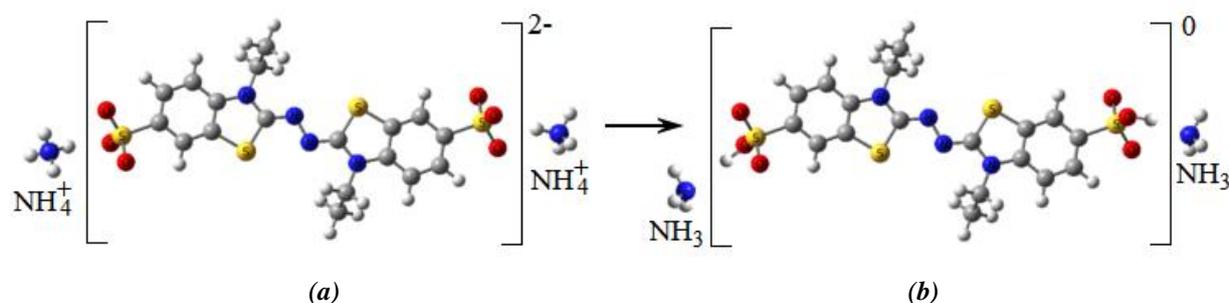


Figure 1. Formation of the cation-radical $ABTS^{+\bullet}$ from the diammonium salt of ABTS; the initial diammonium salt of ABTS: the neutral system $[(NH_4^+)_2ABTS^{2-}]$ (a); the end optimized system: neutral molecule of ABTS and two ammonia molecules (b).

It is clear that the above definition requires the corresponding theoretical investigation of different types of mutual disposition of $\text{ABTS}^{+\cdot}$ and an antioxidant molecule. It is to be noted here that in the present work we consider the such experimentally well-known food antioxidant acids as gallic, caffeic, ferulic, vanillic, and other acids which transform $\text{ABTS}^{+\cdot}$ in its diamagnetic derivative [16]. Since the results obtained are similar for all the above acids, for the sake of simplicity, we will consider the possible mechanism of their interaction with the radical $\text{ABTS}^{+\cdot}$ using gallic acid as an example.

Figure 3 show the two different types of the interaction between $\text{ABTS}^{+\cdot}$ and a neutral molecule of gallic acid. The interaction of the first type (Figure 3(a)) describes the case when the molecule of gallic acid is over the plane part of $\text{ABTS}^{+\cdot}$. The interaction of the second type (Figure 3(b)) involves one of the sulphonic groups of $\text{ABTS}^{+\cdot}$. One can see that in both these cases there is no any electronic density transferred from the molecule of gallic acid onto $\text{ABTS}^{+\cdot}$. The MOs corresponding the unpaired electron of $\text{ABTS}^{+\cdot}$ remain localized on the atoms of its planar part as it was in the case of the free $\text{ABTS}^{+\cdot}$ radical (Figure 2).

Since the above study of the interaction of the $\text{ABTS}^{+\cdot}$ radical cation with neutral molecules of the food acids did not reveal the appearance of a chemical bond between them (no bonding molecular orbitals responsible for charge transfer were formed), we have undertaken a study of the interaction of the $\text{ABTS}^{+\cdot}$ with the anions of these acids. Figure 4 show the MO which describes the distribution of the electronic density of the unpaired electron for the system: $\text{ABTS}^{+\cdot}$ in the presence of the gallic anion.

One can see that in the first case (Figure 4(a)), when the anion of the acid is situated over the plane atomic system of $\text{ABTS}^{+\cdot}$, there is a clear-cut transfer of the electronic density from this anion onto $\text{ABTS}^{+\cdot}$. However, this transfer is not complete: some part of the electronic density of the unpaired electron remains on $\text{ABTS}^{+\cdot}$. The calculations have shown that the residual charge on the gallic anion equals to $-0.507 \bar{e}$; accordingly, the structural fragment of $\text{ABTS}^{+\cdot}$ has the residual charge $+0.507 \bar{e}$.

The second possibility of the interaction between $\text{ABTS}^{+\cdot}$ and the anion of gallic acid is being realized by means of the formation of the intermolecular hydrogen bond connecting the OH group of the SO_3H group of $\text{ABTS}^{+\cdot}$ with one of the oxygen atoms of the carboxyl group of the anion (Figure 4(b)). Obviously, that in this case, the charge transfer that occurs from the anion to

$\text{ABTS}^{+\cdot}$ is almost complete.

Figure 4(b) shows that the unpaired spin electron density of the system [$\text{ABTS}^{+\cdot}$ and gallic anion] which, prior to the interaction, was localized wholly on the radical $\text{ABTS}^{+\cdot}$ (Figure 2), after interaction is localized on the anionic structural fragment of the complex. The residual charge of the gallic anion in this case equals to $-0.120 \bar{e}$ (accordingly, the structural fragment of $\text{ABTS}^{+\cdot}$ has the charge $+0.120 \bar{e}$). In other words, the interaction of the radical cation $\text{ABTS}^{+\cdot}$ and the gallic anion results in the neutral ABTS molecule and the radical derivative of gallic acid.

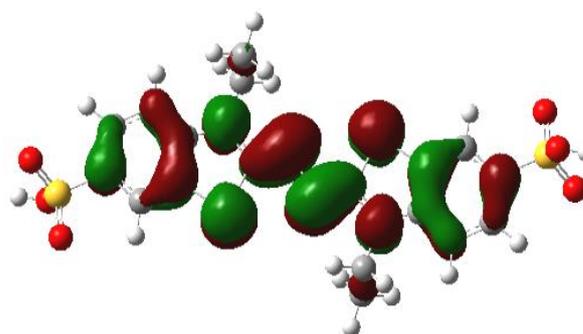


Figure 2. The spatial distribution of the electron density of the unpaired electron in $\text{ABTS}^{+\cdot}$.

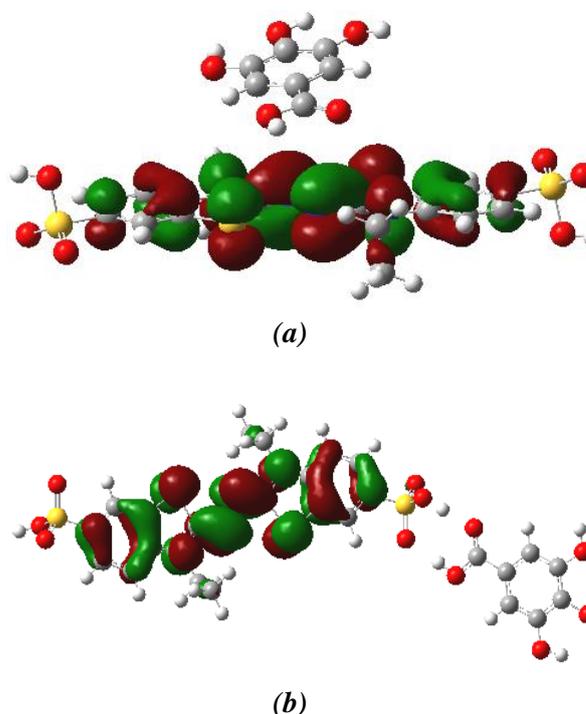


Figure 3. The electron density distribution in the system $\text{ABTS}^{+\cdot}$ and gallic acid for two different types of the interaction between $\text{ABTS}^{+\cdot}$ and a neutral molecule of gallic acid: the molecule of the acid is over the plane of $\text{ABTS}^{+\cdot}$ (a); the molecule of the acid is connected with one of the sulphonic groups of $\text{ABTS}^{+\cdot}$ (b).

For the system shown in Figure 4(b), the calculated by the DFT UB3LYP method values of spin densities also confirm the charge transfer from the gallic anion to the ABTS^{•+}. If in the case of the free ABTS^{•+} radical (Figure 3) the summarized value of the spin density on its four nitrogen atoms and its two sulphur ones (belonging to the heterocycles) equals to 0.873, for the given system (Figure 3) the value of the summarized spin density on the above-mentioned six heteroatoms is only 0.218. At the same time, for this system the summarized spin density on its structural fragment formed from the former gallic anion is equal to 0.782.

Molecular orbital aspects connected with charge transfer from the gallic anion to ABTS^{•+} can be understood based on the analysis of the occupied MOs of the active valence zone of the [ABTS^{•+} and gallic anion] complex. It was found that the bonding double-occupied HOMO-1 of the entire complex (Figure 5) which is formed due to the interaction between one of the HOMO electrons of the gallic anion with the unpaired electron of the ABTS^{•+} radical cation (*via* the oxygen atom of the corresponding sulphonic group of ABTS^{•+}), just provides the transfer of electron density from the anion to the ABTS^{•+} radical.

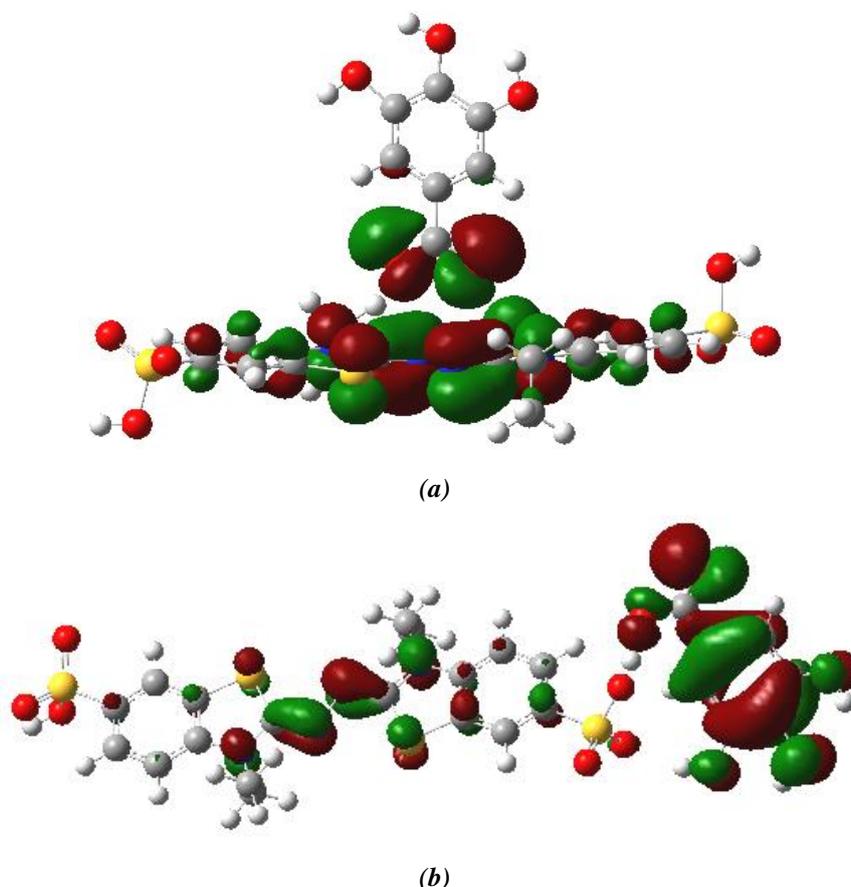


Figure 4. The electron density distribution in the system [ABTS^{•+} and gallic anion] for two different types of the interaction between ABTS^{•+} and the gallic anion: the anion is over the plane of ABTS^{•+} (a); the anion is connected with one of the sulphonic groups of ABTS^{•+} (b).

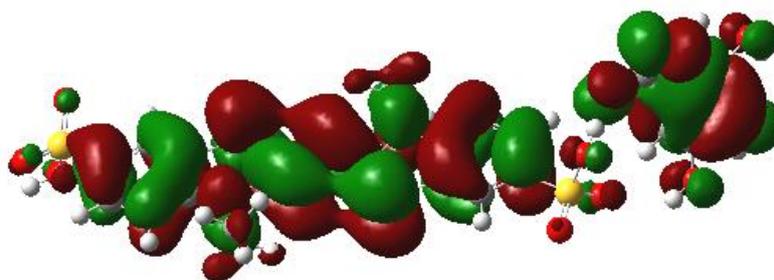


Figure 5. The HOMO-1 of the complex [ABTS^{•+} and gallic anion] formed by the one electron transfer from the double-occupied HOMO of the gallic anion to the single-occupied HOMO of ABTS^{•+}.

The same molecular orbital nature of the formed complexes [ABTS^{•+} and an anion of an acid] by means of one-electron charge transfer occurring between the HOMOs of the studied anions and the HOMO of ABTS^{•+} (and the corresponding creation of the common HOMO-1 molecular orbitals of the given complexes) were found for all of the studied food acids. As in the above-considered case of gallic acid, all these complexes contain the intramolecular hydrogen bonds between their anionic fragments and one of the sulphonic groups of ABTS^{•+}. In this connection it seems very important to reveal a possible correlation which could take place between the properties of the formed hydrogen bonds and the experimental values of the antioxidant activity of the studied food acids in their interactions with ABTS^{•+}. Such a correlation was revealed using multiple regression analysis. Table 1 contains the experimental values of IC_{50} for a number of food acids (IC_{50} is the concentrations of the food acids which lead to 50% disappearance of the colour of the standard ABTS^{•+} solution) side by side with the defined by our DFT calculations values R_{O-H} of the distances H...O of the above-mentioned intermolecular hydrogen bonds within the systems [ABTS^{•+} and anion]. Here the hydrogen atom H belongs to the sulphonic group of ABTS^{•+} and the oxygen atom O is one of the carboxyl oxygen atoms of the anion.

Comparing the values IC_{50} and R_{O-H} from Table 1 one can conclude that there is a clear-cut correlation between these two sets of data. It is easy to see that the most active acids (para-coumaric, gallic and ferulic) are being characterized by the highest values of R_{O-H} . In general, higher values of R_{O-H} correspond to the higher values of the antioxidant activity of the acids (the lower values of IC_{50}). As the anions in the systems [ABTS^{•+} and anion] are in fact converted into neutral radical derivatives of the anions of the studied acids, so the increase in the

quantity R_{O-H} means the higher ability of the system [ABTS^{•+} and anion] to decay. This decay leads to the formation of the colourless diamagnetic molecule of ABTS and the corresponding newly formed (from the considered anion) radical. Subsequently, these radicals, whose charges are almost zero, can easily dimerize.

Table 1

Experimental values of IC_{50} [16] and calculated distances R_{O-H} for the studied food acids.

Phenolic Acid	IC_{50} (mmol/mL)	R_{O-H} (Å)
<i>p</i> -Coumaric	8.21	1.667
Gallic	8.85	1.664
Ferulic	9.47	1.633
Syringic	13.97	1.595
Caffeic	18.04	1.593
Vanillic	132.10	1.589
Cinnamic	342.46	1.579

It should also be noted that the R_{O-H} value describes not only the strength of the hydrogen bond, but also the spatial distance between the two parts of the charge transfer complexes under study, namely, between the radical ABTS^{•+} and the corresponding structural fragments of the food acids' anions.

Obviously, the values of the indicated spatial distances in these complexes may depend on the redistribution of the electron density arising after charge transfer from the studied anions to the radical ABTS^{•+}. Thus, it was assumed that the quantities IC_{50} can also correlate with the residual charges on the structural fragments of the above complexes (which, previously belonged to the corresponding anions) as well as with the values of the transferred electron density. These DFT calculated values of the given charges are presented in the third column of Table 2. It can be seen that there is no correlation between these values and the corresponding values of IC_{50} .

Table 2

Residual charges on former anions' fragments and charge transfers from the anions of the studied food acids to ABTS^{•+} in the gas phase and in ethanol.

Phenolic Acid	IC_{50} (mmol/mL)	Residual charge/Charge transfer (\bar{e})	
		In the gas phase	In ethanol
<i>p</i> -Coumaric	8.21	0.020/0.980	0.047/1.047
Gallic	8.85	0.023/0.977	0.038/1.038
Ferulic	9.47	0.022/0.978	-0.073/0.927
Syringic	13.97	0.017/0.983	-0.078/0.922
Caffeic	18.04	0.021/0.979	-0.103/0.897
Vanillic	132.10	0.020/0.980	-0.113/0.887
Cinnamic	342.46	0.017/0.983	-0.128/0.872

However, since the charge distribution in the studied complexes can also be influenced by the used solvent [5] all DFT calculations were performed once again taking into account the solvent: ethanol [16]. The recalculated in this way values of the residual charges and the corresponding charge transfers from the anions to ABTS^{•+} are given in the fourth column of Table 2. One can see that now there is the clear-cut correlation between these calculated electronic parameters and the IC_{50} values. At the same time, no correlation was found between the IC_{50} values and the energy parameters describing the formation of the studied charge transfer complexes from their constituent parts.

Thus, basing on the above DFT computational results, one can conclude that the mechanism of the interaction of the studied food acids with ABTS^{•+} can be called ‘quasi-SPLET’. Here the prefix ‘quasi’ was used as the primary transfer of protons takes place from the neutral molecules of these acids to molecules of the solvents (ethanol and water; see [16]). Further, the newly formed anions of the acids give back their electrons to the ABTS^{•+} radicals. Earlier (see our work [17]) a similar situation was also found for the reaction of dihydroxyfumaric acid with the stable radical DPPH[•].

The results of the present work are in good agreement with the data of the previous theoretical work devoted to the study of the antioxidant activity of thiaflavans based on their reaction with the ABTS^{•+} radical-cation [18]. According to the previously reported data, the DFT B3LYP calculations performed in polar media demonstrates that for the given reaction the SPLET mechanism is more preferable [18]. Moreover, for thiaflavan radicals, which are formed in the process of this reaction, distribution of their spin atomic density (and, therefore, their atomic charges) changes significantly when passing from calculations in the gas phase to calculations taking into account the solvents (water or benzene). These results of the work [18] also agree with the data presented in Table 2 of the present study.

Conclusions

Basing on the DFT calculations one can draw the following conclusions. The interaction between the neutral molecules of the studied food acids and the cation-radical ABTS^{•+} does not lead to any charge transfer from these molecules onto ABTS^{•+}. However, in the case when the anions of these acids interact with one of the two sulphonic groups of ABTS^{•+} (forming the corresponding hydrogen bonds), there is practically complete electronic charge transfer from these anions onto

ABTS^{•+}. Basing on the defined geometry parameters of the above hydrogen bonds (the bond length O...H) it was revealed the clear-cut correlation between these lengths and the experimental values of the antioxidant activity of the food acids under study. The DFT calculations, by taking into account the solvent (ethanol), revealed the second clear-cut correlation between the studied activity and the summarized residual charges on the structural fragments arisen from the anions of the studied food acids after the formation of their charge transfer complexes with ABTS^{•+}, as well as with the values of the transferred electron density. The found correlations can serve as the tools for the evaluation of antioxidant activity (in the ABTS^{•+} assay) of new food acids which differ from the studied ones.

It was clarified that namely the one-electron transfer occurring from the HOMOs of the anions of the studied food acids to the HOMO of ABTS^{•+} (accompanied by the formation of the bonded double occupied HOMO-1 molecular orbitals of the formed complexes) is responsible for the formation of the studied complexes between the above anions and ABTS^{•+}.

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