

KAZIMIERZ MILER
DANUTA CHOMIAK

AN ATTEMPT AT CORRELATING ANTIOXIDATIVE ACTIVITY OF PHENOLIC COMPOUNDS AND ENERGY OF THEIR ARYL-HYDROXYL BONDS

Meat and Fat Research Institute, Warsaw

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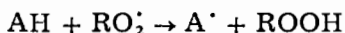
The forecasting formula for the calculation of antioxidative activity of phenolic compounds has been proposed. The curvilinear dependence between energy of bond C-O (aryl-hydroxyl) and activity of both: mono- and poly-hydroxyphenols has been established.

An immense literature on antioxidative activity of phenolic compounds [3, 6, 10, 15, 16] points to a causal relationship between structure and efficacy of these antioxidants. In most cases the authors do not go beyond verbal descriptions of their investigations. Only two sources were found to report on this relationship by means of functional descriptions [1, 5]. One of these two attempts [1], was correlating the antioxidative activity of hydroquinones with their red-ox potential. In the second study [5], the activity was correlated with the magnitude of frequency shifts of the O-H stretching vibrations. This attempt was criticized [17] since it led to results contrary to expectations.

The drawback of correlating the antioxidative activity with the red-ox potential is the limited scope of its applicability (the hydroquinone series). Consequently, there is still a need to determine the relationship between antioxidative activity of phenols and their structure. The present study provides a proposed formulation of this relationship whereby only informations concerning the structure of the phenolic compounds, and tabulated values of dipol moments introduced by the respective substituents are required. The proposed formulation of the relationship was verified by comparing the calculated antioxidate activities with the respective data determined experimentally, published elsewhere [6].

I. FORMULATION OF THE PROBLEM

The inhibition reaction, commonly presented as:



may take place when its summary energetic effect is positive. The less energy is required to produce the radical $\text{A} \cdot$ the easier it is for the reaction of inhibition to occur. Formation of the radical involves the cleavage of a hydrogen atom at this A-H bond which — taking in account all mesomeric effects — is at the highest excitation level. Two types of A-H bonds appear in phenolic antioxidants: O-H and C-H. In this case the latter is primarily involved not only because of its lower bonding energy (99 kcal/mol versus 111 kcal/mol of the O-H bond) [11], but also due to the fact that in radical reactions the substituent, depending on its type, is introduced to a phenol molecule always in "orto", "para" or "meta" positions in relation to the OH group but never in place of the OH group hydrogen.

Due to delocalization of electrons in the phenol ring the excitation state in this molecule is easily transferred to any place in the ring, although it is not quite clear what factors influence the probability of locating it in a particular position. It is probable that excitation of a C-H starts at an entirely different site of the ring and then, owing to mesomeric effects, is translocated into this particular bond. Considering the well-known fact that such a strong antioxidant as BHT, for example, has in its "orto" and "para" positions not $\text{C}_{\text{ar}}\text{-H}$ but $\text{C}_{\text{ar}}\text{-C}$ bond, whose energy is ca 126 kcal/mol (Cf. Table 4), it can be assumed that excitation of the C-H bond is initiated at some other site of the antioxidant molecule.

Many authors [6, 15] stress the indispensability of the hydroxyl group for production antioxidative effects. This prompts a surmise that the excitation occurs at the aryl-hydroxyl bond because of the lower energy of the C-O bond as compared with that of the O-H bond (Cf. Table 4). It seems, therefore, that the activity of a given phenolic antioxidant may be correlated with the energy of its aryl-hydroxyl bond. It can be anticipated that the antioxidative activity will increase with diminishing of this energy, however after reaching a maximal value a further energy drop causes a lowering of the antioxidative activity — for reasons reported by Bolland and ten Have [1] and discussed by Uri [17].

Hence, not anticipating a particular functional formulation at this moment we may, however, postulate that it must be a curvilinear dependence, exhibiting a maximum.

According to existing opinions [8], bond energy is a function of bond length, which in turn depends on the π -electron order of the bond. Since the bond order conceived in this way depends on the magnitude of charge

shift between atoms forming this bond — and that is linked with a dipole moment — it seems possible to estimate this shift and the bond energy from the value of the dipole moment.

II. ESTIMATING THE ARYL-HYDROXYL BOND ENERGY

Energy of a given bond can be calculated from its length by means of the familiar Morse formula. However, when the type of bond is changed also the parameters of this formula must be changed which leads to considerable computational problems.

Basing upon the data collected in Table 1, the following relationship was found to be applicable to the main types of bonds present in a phenolic antioxidant:

$$E = E_0 e^{-ad^3} \quad (1)$$

d — bond length.

Table 1. Bond energy as a function of bond length

No.	Bond	Type	Length (Å)	Bond energy kcal/mol
1	C—C	C—C	1.543	81.5 } (14)
		C=C	1.353	
		C≡C	1.208	
2	C—C	C—C	1.541	83 } (11)
		C=C	1.337	
		C≡C	1.204	
3	C—H	sp ³	1.094	103 } (14)
		sp ²	1.079	
		sp	1.057	
4	C—O		10.11 (13b)	99 (11)
		C—O	1.43	84 } (11)
		C=O	1.23	

Figures in brackets stand for bibliography references

Values of the parameters of the equation as well as comparison of the calculated and experimentally obtained data are given in Table 2. Basing on the above and using data for bond lengths collected in Table 3, the bond energies for an unsubstituted phenol molecule were calculated. The results are presented in Table 4.

As mentioned above, the bond lengths depend on their π -electron order. The following formula given by Jenkins [9], here quoted after Staab [14], was used:

$$\frac{1}{d^2} = a + bp \quad (2)$$

p — bond order.

Table 2. Parameters of equation (1); comparison of the calculated and the empirical values of energy

No.	Bond	Parameter	Value of bond energy	
			empirical	calculated
1	C—C	$E_0 = 454.16 \text{ kcal/mol}$ $a = 0.46628 \text{ \AA}^{-3}$	81.9	81.9
			145.0	143.1
			198.0	199.6
2	C—C	$E_0 = 422.97 \text{ kcal/mol}$ $a = 0.44451 \text{ \AA}^{-3}$	83.0	83.2
			147.0	146.2
			194.0	194.7
3	C—H	$E_0 = 524.90 \text{ kcal/mol}$ $a = 1.25242 \text{ \AA}^{-3}$	99.0	98.7
			103.0	101.8
			106.0	108.8
4	C—O	$E_0 = 583.78 \text{ kcal}$ $a = 0.66299 \text{ \AA}^{-3}$	121.0	119.6
			84.0	84.0
			170.0	170.0

Table 3. Bond lengths in a phenol molecule (13b)

Bond	d (Å)
O—H	0.958
O—Ar	1.360
C—C ar	1.395
H—C ar	1.084

Table 4. Bond energy in a phenol molecule

Bond	E (kcal/mole)
O—H	111.0
O—Ar	110.1
C—C ar	126.5 128.1*)
H—C ar	106.5

*) Depending on source. See Tables 1 and 2

Using the data given in Table 5, parameters of this dependence were calculated for the C—O bond. The results are quoted in the same Table. The π -electron orders of bonds result from asymmetry of charges caused by asymmetry of orbitals. For example, the free pairs of electron in oxygen, traditionally recorded as electrons $2s^2$, include an admixture of orbital p, hence they occupy hybridized orbital [4]. This asymmetry of orbitals induces the asymmetry of charge and the occurrence of dipole moments.

Table 5. Correlation between order and length of C—O bonds

Order (p)	d (Å)	Parameter of equation (2)
1.000	1.43	$a = 0.3229$
1.256	1.36	$b = 0.1697$
2.000	1.23	$r = 0.9988$

Gołębiewski [8], following Chirgwin and Coulson [2] as well as Gladney [7], defines the π -electron order of bond as follows:

$$\pi_{ij} = \frac{1}{2} \sum_{k=1}^n (q_{ik} S_{jk} + q_{jk} S_{ik}) \quad (3)$$

S — values of the overlapping integrals

q — weight factors (shares).

In the above formula the right-hand sum is a measure of charge asymmetry. Marking it as Q_w and taking into account the presence of the δ -bond we can present the π -electron bond order for C-O as:

$$P_{C-O} = 1 + \frac{Q_w}{2} \quad (4)$$

Due to the delocalization of π -electrons in the phenol ring deformations of their orbitals originating from the presence of substituents are easily transferred affecting the overall Q_w value. According to Platt [12], this effect can be calculated basing on vector addition rules and taking in account the rule on alternating charges in electron density.

The following is obtained accordingly:

$$Q_w = \sum_{k=1}^6 (-1)^{i-1} \cdot Q_{si} \cdot \cos \Theta_i \quad (5)$$

i — successive carbon number in the phenol ring counted clockwise (the OH group is at carbon No. 1)

Q_{si} — distortion of the "p" orbital caused by substituent at the i-th carbon atom in the ring.

Q_i — angle between the C_1-C_4 axis in the phenol ring and the projection on the ring plane of the vector of the dipol moment induced by the substituent at the i-th carbon atom.

The distortion in symmetry of the π -electron orbitals induced by a substituent is proportional to the dipol moment linked to this substituent. Basing on the definition of the dipol moment and taking in account the angle at which its vector pierces the ring plane in its centre one can calculate the Q_s value, which is proportional to the asymmetry of the "p" orbital in the $C_{ar}-C_{al}$ bond. Values of dipole moment, induced in the phenol molecule by various substituents, excerpted from available sources [13], as well as the corresponding Q_s values calculated according to the above described outlines, are collected in Table 6.

The angle Θ is determined by means of the formula:

$$\Theta_i = (i-1) \cdot 60 + \varphi_i \quad (6)$$

φ_i — deviation from multiplicity of the 60° angle resulting from differences of radii in first atoms of substituents at vicinal carbon atoms in the ring.

With the use of simple trigonometry the values of angle φ_1 for particular atom configurations at vicinal carbons in the rings were calculated. The results are given in Table 7.

In most phenolic antioxidants substituents appear at carbon 2 or carbon 2 and 6 which leads to certain changes in values of the Θ_1 angle resulting from interaction between the substituents. Assuming that the interacting charges are proportional to Q_s , it is possible to calculate these deviations using the equation for Coulomb forces and taking into account the tridimensionality of the interaction space. Values of the deviations (τ) were calculated for the most frequently occurring substituents on carbon 2 and 6. The figures are in Table 8.

Table 6. Dipole moments and Q_s values contributed into a phenol molecule by various substituents

Substituent	μ (D)	Q_{si} (jES)
—OH	1.61	0.489
—OCH ₃	1.16	0.279
—CH ₃	0.35	0.106
—CH ₂ CH ₃	0.35	0.078
—CH ₂ CH ₂ CH ₃	0.65	0.113
—CH(CH ₃) ₂	0.65	0.179
—C(CH ₃) ₃	0.45	0.126
—CH=CH ₂ CH ₃ (trans)	0.71	0.127
—CH=CH ₂ CH ₃ (cis)	-0.71	-0.130
—CH ₂ CH=CH ₂	0.50	0.087
—CH=CH ₂	0.37	0.082
—C=O	-2.96	-0.801
 CH ₃		

Considering the above, formula (6) gets a more general form:

$$\Theta_1 = (i-1) \cdot 60 + \varphi_1 + \tau_1 \quad (7)$$

Interactions between substituents modify somewhat the values of the dipole moment projection onto the ring plane, consequently affecting the Q_s values. The altered Q_s figures related to the above mentioned cases are presented in Table 8 (the Q'_s column). Formulas (5) and (7) or (5) and (6) as well as the appropriate values of Q_{si} or Q'_{si} and φ_1 or possibly τ_1 from Tables 6, 7 and 8 can be used to obtain Q_w value for any phenolic antioxidant. Introducing the value Q_w into equation (4) we get the π -electron order of the aryl-hydroxyl bond. Applying, in turn, this value to equation (2) and taking in account the parameters from Table 5, the length of the bond can be calculated. Equation (1) and the parameters in Line 4, table 3 provide data on energy of the aryl-hydroxyl bond in a molecule of a given phenolic antioxidant.

Table 7. Values of φ angle for particular arrangements of atoms attached to vicinal ring carbons

The first atom of substituent at carbon No.			φ_i (deg)
i-1	i	i+1	
O	O	O	0.00
O	O	C	-2.05
O	O	H	3.15
O	C	C	-2.05
O	C	H	3.21
O	H	H	3.15
O	H	C	-2.10
O	C	O	0.00
O	H	O	0.00
C	C	C	0.00
C	C	O	2.05
C	C	H	5.25
C	O	O	2.05
C	O	H	5.20
C	H	H	5.25
C	H	O	2.10
C	O	C	0.00
C	H	C	0.00
H	H	H	0.00
H	H	C	-5.25
H	H	O	-3.15
H	C	C	-5.25
H	C	O	-3.21
H	O	O	-3.15
H	O	C	-5.20
H	C	H	0.00
H	O	H	0.00

III. CORRELATION OF ANTIOXIDATIVE ACTIVITY WITH ENERGY OF THE ARYL-HYDROXYL BOND

Due to the reasons mentioned in Part I a curvilinear dependence between the antioxidative activity and the energy of aryl-hydroxyl bond is anticipated. It follows from the presented arguments that this dependence should have a maximum and also should provide the values of calculated activity $A \geq 0$. This is insufficient information to define the accurate functional form of the dependence. They may however be sufficient to obtain an approximation of the real dependence by determining, as far as possible, an accurate empirical relationship.

Table 8. Values of τ angle for ortho-monosubstituted and orthobisubstituted phenols

Compounds	Site of substitution "i"	Substituent	τ_i (deg)	Q'_i (jES)
2-methylphenol	1	—OH	-12.29	0.500
	2	—CH ₃	0.00	0.106
6-methylphenol	1	—OH	12.29	0.500
	6	—CH ₃	0.00	0.106
2-methoxyphenol	1	—OH	-12.29	0.500
	2	—OCH ₃	20.95	0.299
6-methoxyphenol	1	—OH	12.29	0.500
	6	—OCH ₃	-20.95	0.299
2-hydroxyphenol	1	—OH	-12.29	0.500
	2	—OH	12.29	0.500
6-hydroxyphenol	1	—OH	12.29	0.500
	6	—OH	-12.29	0.500
syringol	1	—OH	0.00	0.489
	2	—OCH ₃	20.54	0.298
	6	—OCH ₃	-20.54	0.298
Pirogallol	1	—OH	0.00	0.489
	2	—OH	13.92	0.504
	6	—OH	-13.92	0.504

In the course of searching for an empirical function that could relatively well approximate the unknown real dependence, the following four functions were tested as to their applicability:

$$1. A = a + bE + cE^2 + dE^3 \quad (8)$$

$$2. A = aE^b \cdot e^{-cE} \quad (9)$$

$$3. A = A_m \cdot \exp[-a^2(E - E_m)^2] \quad (10)$$

$$4. A = A_m \cdot \exp[-a^2(\ln E - \ln E_m)^2] \quad (11)$$

A — antioxidative activity

E — the aryl-hydroxyl bond energy

The material used in testing the above equations consisted of data on activity of 21 phenolic compounds retrieved from literature [6] and tabulated in Table 9. The energy of aryl-hydroxyl bond for these compounds was calculated according to the method given in Part II. The results are also provided in Table 9. Parameters of the equations 8 to 11 were determined by means of the least squares method. The parameters were used to compute respective values of the activity. It turned out that equation (9) was completely useless in describing the sought dependence on account of the fact that values calculated with it were drastically different from the experimental data.

The best convergency with the experimental data was obtained with equation (10). Consequently, this correlation was analyzed as to its effectiveness by examining the significance of the correlation coefficient for

Table 9. Anti-oxidative activity of phenols.

Column 1 — activity determined experimentally, after (6),

2 — activity determined from formula (12),

3 — activity determined from formula (12a) or (12b)

Compound	Q _w (JES)	E _{c-o}	1	2	3
2-tertbutylphenol	0.420	104.00	0.26	0.15	0.17
2,4,6-trimethylphenol	0.287	98.08	1.19	1.38	1.36
BHA	0.141	91.81	1.25	1.95	0.95
2,6-dimethoxyphenol (syringol)	0.423	103.95	0.33	0.15	0.18
4-methylsyringol	0.317	99.37	0.53	1.00	1.05
4-propylsyringol	0.310	99.07	0.70	1.08	1.13
BHT	0.269	97.31	2.35	1.61	1.50
2,4,6-tritertbutylphenol	0.249	96.44	2.35	1.85	1.59
2-methyl, 6-tertbutylphenol	0.384	102.26	1.00	0.35	0.40
4-methyl, 6-tertbutylphenol	0.314	99.24	0.84	1.03	1.09
2,4-ditertbutyl, 6-methylphenol	0.258	96.83	0.90	1.75	1.56
phenol	0.489	106.90	0.01	0.03	0.03
3-methylphenol(m-crezol)	0.542	109.09	0.00	0.01	0.004
3-isopropylphenol	0.579	110.69	0.00	0.001	0.001
2,4-ditertbutylphenol	0.294	98.38	0.66	1.29	1.29
2-izopropyl, 6-tertbutylphenol	0.352	100.98	1.30	0.61	0.68
pyrocatechol	0.356	101.06	1.00	0.57	0.98
hydroquinone	0.00	85.79	0.78	0.39	0.50
4-tertbutylpirocatechol	0.230	95.63	1.57	2.02	1.63
tolu-hydroquinone	0.060	88.34	0.94	0.97	0.88
2,5-tertbutylhydroquinone	0.000	85.79	0.31	0.39	0.50

the linear form of this equation. The result was quite satisfactory and for this reason the correlation we were looking for could be presented in the form of the following empirical dependence:

$$A = 2.19 \exp [0.0263(E - 93.90)^2] \quad (12)$$

It should be said that the linear form of it has a very high correlation coefficient: $r = -0.96105$ which corresponds to statistical significance at the level of $P < 0.001$.

Considering that Table 9 includes both mono- and polyhydroxide phenols, it seems useful to present a detailed form of equation [10] separately for each group of these compounds. Thus we have

a) for mono-hydroxyphenols

$$A = 1.618 \exp [-0.03328(E - 95.788)^2] \quad (12a)$$

The correlation coefficient of the linear form of this equation is $r = -0.9620$ which relates to a level of significance $P < 0.001$.

b) for poly-hydroxyphenols

$$A = 1.64 \exp [-0.01395(E - 95.01)^2] \quad (12b)$$

The correlation coefficient for the linear form of this equation is $r = -0.83510$, which relates to a level of significance $0.10 > P > 0.05$. This somewhat lower statistical significance for polyhydroxide phenols probably results from limited data in the group ($n = 5$).

The values of antioxidative activity of the compounds listed in Table 9 were calculated with the use of equations (12), (12a) and (12b). The results were put into the same table next to data obtained experimentally in order to illustrate the convergence of the figures.

Summing up, it seems possible to apply equations (12) and (12b) to estimate antioxidative activity of phenolic compounds in those circumstances where for technical reasons or lack of time the experimental determinations are not possible.

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Authors address: 02-532 Warszawa, Rakowiecka 36

K. Miler, D. Chomiak

PRÓBA SKORELOWANIA AKTYWNOŚCI PRZECIWIUTLENIAJĄCEJ ZWIĄZKÓW
FENOLOWYCH Z ENERGIAŁ WIAZANIA ARYL-HYDROKSYL

Instytut Przemysłu Mięsnego i Tłuszczowego, Warszawa

Streszczenie

W wyniku analizy informacji literaturowych, dotyczących związku pomiędzy budową chemiczną podstawowych fenoli, a ich aktywnością przeciwutleniającą, przedstawiono w pracy propozycję skorelowania tej aktywności z energią wiązania aryl-hydroksyl. Zaproponowano także sposób wyliczania tej energii na podstawie wielkości momentów dipolowych wnoszonych przez poszczególne podstawniki. Przydatność proponowanych zależności funkcyjnych testowano na przykładzie dwudziestu jeden związków fenolowych, uzyskując wysoką zgodność wyników obliczonych z doświadczalnymi. W pracy zamieszczono tabele, zawierające elementy niezbędne do wyliczenia energii wiązania aryl-hydroksyl, jak też szczegółowe postaci równań korelacyjnych do wyliczenia wielkości aktywności przeciwutleniających.