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## QUANTUM-CHEMICAL CALCULATIONS IN STUDYING OF THE PROPERTIES OF 1-(CARBOXY)-1-(*N*-METHYLAMIDE)-2-(3',5'-di-*tert*-BUTYL)-4-HYDROXYPHENYL)-PROPIONATES SODIUM AND POTASSIUM IN BIOLOGICAL ENVIRONMENT

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**Abstract.** Energies of formation, enthalpies, and entropies of the conformers of 1-(carboxy)-1-(*N*-methylamide)-2-(3',5'-di-*tert*-butyl)-4-hydroxyphenyl)-propionic acid and sodium and potassium 1-(carboxy)-1-(*N*-methylamide)-2-(3',5'-di-*tert*-butyl)-4-hydroxyphenyl)-propionates are calculated by quantum-chemical methods in the PM6 approximation. A doubling of signals in the  $^1\text{H}$  NMR spectrum of the first conformer is observed, which merge into singlets when the compound is heated. Changes in the structure of the conformers and donor-acceptor complexes (solvates) occur with the preservation of the metal–ligand coordination bond. Calculations of the characteristics of 1-(carboxy)-1-(*N*-methylamide)-2-(3',5'-di-*tert*-butyl)-4-hydroxyphenyl)-propionic acid and sodium and potassium 1-(carboxy)-1-(*N*-methylamide)-2-(3',5'-di-*tert*-butyl)-4-hydroxyphenyl)-propionates in the PM6 approximation make it possible to predict structure and properties of the solvated structures. Energies of homolysis of the H–O bond  $D(\text{OH})$  are calculated, and a linear dependence of the antioxidant activity on  $D(\text{OH})$  for the structures of the studied compounds is demonstrated. The results make it possible to predict the properties of antioxidants in biological environment.

**Keywords:** quantum-chemical calculation, MOPAC 2009, conformer, binding energy, nuclear magnetic resonance and infrared spectroscopies, antioxidant, structure.

### 1. Introduction

Modern quantum-chemical software makes it possible to calculate the energy parameters and structure of chemical compounds [1-6]. The importance of computational methods is obvious, being comparable with that of XDR analysis.

In this paper, we determined the molecular parameters of two conformers of the -(carboxy)-1-(*N*-methylamide)-2-(3',5'-di-*tert*-butyl)-4-hydroxyphenyl)propionic acid molecule (**1**) based on two minima in the potential energy surface of the structure calculated in the PM6 approximation and the splitting of the  $^1\text{H}$  NMR signals from the aromatic cycle metaprotons and from the protons of the *tert*-butyl groups. The minima in the energies of formation of sodium (**2**) and potassium (**3**)-1-(carboxy)-1-(*N*-methylamide)-2-(3',5'-di-*tert*-butyl)-4-hydroxyphenyl)-propionates correspond to the structures in which the metal cation forms coordination bonds. The energy of homolysis of the HO bond  $D(\text{OH})$  of the phenolic hydroxyl group was demonstrated to be dependent on the structure of the molecules and hydrate and donor-acceptor complexes. An enhancement in the antioxidant properties of the lipid fraction collected from the liver of mice after injection of these compounds was revealed and correlation between the constant of antioxidant activity (AOA) and the energy of homolysis of the H–O bond  $D(\text{OH})$  of the structures of the antioxidants was established.

### 2. Experimental

The parameters of the structures of the compounds obtained were calculated in the PM6 approximation (MOPAC2009, Version 8.288W [6]). The  $^1\text{H}$  NMR spectra were recorded on Bruker WM-400 (400 MHz) instrument relative to the signals from the residual proton of a deuterated solvent (acetone- $d_6$  or DMSO- $d_6$ ). IR spectra were recorded on a PERKIN-ELMER 1725-X spectrometer in the solid phase (crystals) in the diffuse reflection mode. The antioxidant activity was determined by the method of inhibition of methyl oleate oxidation at

310 K in the presence of the lipid fraction of the liver of strain C3HA mice that were administered an injection of the drug (100 mg/kg) 1 h before slaughter. The concentrations of peroxides in the lipid fraction of methyl oleate were determined by the method described in [7]. Conformer **2** was prepared as described in [8]. The  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ );  $\delta$  ppm: 1.26 (s, 18H, *t*Bu); 1.79 (s, 3H, COCH<sub>3</sub>); 3.37 (s, 2H, CH<sub>2</sub>); 3.40–3.48 (br s, HOH) 1; 6.42–6.46 (br s, 1H, OH); 6.79 (s, H, Ar); 7.20–7.27 (br s, 1H, NH). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3643 (OH); 3550–3100 (br, HOH); 3321 (NHCOCH<sub>3</sub>); 2957 (CH); 1550–1615 (br, HNCO, COO<sup>-</sup>, C=C).

**Crystal hydrate 2·12H<sub>2</sub>O.** A solution of 4.2 g (~0.01 mol) of **2** in 50 ml of water was placed into a vessel and kept there at room temperature under conditions of slow crystallization for 3–4 days until crystals were formed. The crystals were isolated to obtain 4.1 g (~66 %) of compound **2·12H<sub>2</sub>O**. The  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ );  $\delta$  ppm: 1.26 (s, 18H, *t*Bu); 1.79 (s, 3H, COCH<sub>3</sub>); 3.37 (s, 2H, CH<sub>2</sub>); 3.40–3.48 (br s, HOH); 6.42–6.46 (br s, 1H, OH); 6.79 (s, H, Ar); 7.20–7.27 (br s, 1H, NH). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3643 (OH); 3550–3100 (br, HOH); 3321 (NHCOCH<sub>3</sub>); 2957 (CH); 1550–1615 (br, HNCO, COO<sup>-</sup>, C=C). Determined: 37.11 % C, 8.48 % H, 2.16 % N, 3.36 % Na; C<sub>20</sub>H<sub>52</sub>NO<sub>18</sub>Na. Calculated: 38.89 % C, 8.48 % H, 2.28 % N, 3.72 % Na.

When heated to 378–388 K, **2·12H<sub>2</sub>O** yields **2·2H<sub>2</sub>O**. The  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ );  $\delta$  ppm: 1.26 (s, 18H, *t*Bu); 1.79 (s, 3H, COCH<sub>3</sub>); 3.37 (s, 2H, CH<sub>2</sub>); 3.40–3.48 (br s, HOH); 6.42–6.46 (br s, 1H, OH); 6.79 (s, H, Ar); 7.20–7.27 (br s, 1H, NH). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3643 (OH); 3550–3100 (br, HOH); 3321 (NHCOCH<sub>3</sub>); 2957 (CH); 1550–1615 (br, HNCO, COO<sup>-</sup>, C=C). Determined: 55.13 % C, 7.65 % H, 3.16 % N, 5.44 % Na; C<sub>20</sub>H<sub>32</sub>NO<sub>8</sub>Na. Calculated: 54.91 % C, 7.32 % H, 3.20 % N, 5.26 % Na.

Conformer **3** was prepared by analogy with **2**; its constants turned out to be close to the published data [8]. The  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ );  $\delta$  ppm: 1.27 (s, 18H, *t*Bu); 1.80 (s, 3H, COCH<sub>3</sub>); 2.48 (s, 2H, CH<sub>2</sub>); 3.41–3.46 (br s, HOH); 6.42–6.47 (br s, 1H, OH); 6.79 (s, H, Ar); 7.22–7.26 (br s, 1H, NH). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3644 (OH); 3550–3100 (br, HOH); 3323 (NHCOCH<sub>3</sub>); 1550–1620 (br, HNCO, COO<sup>-</sup>, C=C). Conformer **1.** A 5-ml portion of a 10 % HCl solution was added to 100 ml of aqueous solution of **2·12H<sub>2</sub>O** (6.2 g = ~0.01 mol); the precipitate was isolated, dried at 298–303 K, and recrystallized from a 9:1 toluene-ethanol mixture (yield, 92–96 %;  $T_m$  = 468–471 K). The  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ );  $\delta$  ppm: 1.326 (s, 9H, *t*Bu); 1.341 (s, 12H, *t*Bu); 1.87 (s, 3H, COCH<sub>3</sub>); 3.22 (s, 2H, CH<sub>2</sub>); 6.737, 6.758 (s, s (2:1) 2H, Ar); 7.69–7.27 (br s, 1H, NH). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3637 (OH); 3338 (NHCOCH<sub>3</sub>); 2954, 2913, 2872 (CH); 1716 (COOH); 1623 (HNCOCH<sub>3</sub>);

1536 (C=C), 1214, 1155, 1121. Determined: 63.24 % C, 7.95 % H, 3.86 % N; C<sub>20</sub>H<sub>29</sub>NO<sub>6</sub>. Calculated: 63.31 % C, 7.70 % H, 3.69 % N. According to [8],  $T_m$  = 471–473 K.

**Potassium-3-(3',5'-di-*tert*-butyl-4'-hydroxyphenyl)-propionate (4).** A mixture of 29.4 g (~0.1 mol) of methyl ester of 3-(3',5'-bis-*tert*-butyl-4'-hydroxyphenyl)-propionic acid with 5.6 g (0.1 mol) KOH, 25 ml of water, and 200 ml of dioxane were boiled for 3 h. Then, the reaction mixture was cooled, and the precipitate was isolated and recrystallized from aqueous ethanol (8:2); as a result, 24.4 g (~74 %) of compound **4** was obtained (temperature of melting accompanied by decomposition was  $T_m$  = 493–498 K). The  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ );  $\delta$  ppm: 1.26 (s, 18H, *t*Bu); 2.62 (t, 2H, CH<sub>2</sub>CH<sub>2</sub>CO); 2.89 (t, 2H, CH<sub>2</sub>CO); 6.46 (s, 1H, OH); 6.79 (s, H, Ar). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3649 (OH); 3324 (HOH); 2952 (CH); 1669 (COO); 1547 (C–C); 1416 (C–O–).

**Sodium-3-(3',5'-di-*tert*-butyl-4'-hydroxyphenyl)-propionate (5).** A mixture of 29.4 g (~0.1 mol) of methyl ester of 3-(3',5'-bis-*tert*-butyl-4'-hydroxyphenyl)-propionic acid with 4.0 g (0.1 mol) NaOH, 20 ml of water, and 180 ml of dioxane. The yield was 22.7 g (~74 %); the temperature of melting accompanied by decomposition was  $T_m$  = 498–503 K. The  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ );  $\delta$  ppm: 1.25 (s, 18H, *t*Bu); 2.61 (t, 2H, CH<sub>2</sub>CH<sub>2</sub>C); 2.90 (t, 2H, CH<sub>2</sub>CO); 6.45 (s, 1H, OH); 6.80 (s, H, Ar). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3642 (OH); 3326 (HOH); 2958 (CH); 1671 (COO); 1547 (C–C); 1416 (C–O–).

**3-(3',5'-Di-*tert*-butyl-4'-hydroxyphenyl)-propionic acid (6).** A 10 ml portion of 10 % HCl was added to 3.3 g (~0.01 mol) of compound **4** dissolved in 100 g of water. Then, the precipitate was isolated, dried at 298–303 K, and recrystallized from a toluene-ethanol mixture (9:1); the yield was 2.4 g, (~83 %) of compound **6** ( $T_m$  444–445 K; (according to [9],  $T_m$  = 444–445 K). The  $^1\text{H}$  NMR spectrum (CDCl<sub>3</sub>- $d_6$ );  $\delta$  ppm: 1.44 (s, 18H, *t*Bu); 2.62 (t, 2H, CH<sub>2</sub>CH<sub>2</sub>CO,  $J$  = 7.8 Hz); 2.89 (t, 2H, CH<sub>2</sub>CO,  $J$  = 7.8 Hz); 5.10 (s, 1H, OH); 6.99 (s, H, Ar). IR spectrum;  $\nu$ ,  $\text{cm}^{-1}$ : 3643 (OH); 2957 (CH); 1720 (C–O).

### 3. Results and Discussion

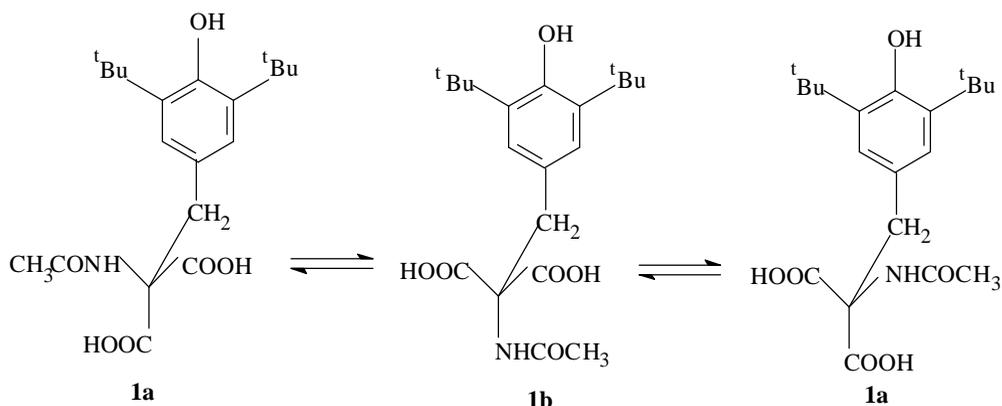
Synthesis of biologically active compounds is associated with the development of low-toxicity and water soluble substances. Antioxidants from the class of sterically hindered phenols and derivatives of malonic acid are promising, since the combination of these two components in a single structure makes it possible to obtain the expected results, whereas the current level of computational methods makes it possible to predict the properties of compounds based on quantum-chemical calculations. The objects of the study were compounds **1–3**, in which one of the carbon atoms forms bonds with

different substituents. In the molecule of **1**, one of the carbon atoms is bonded to three functional substituents, a circumstance that allows studying conformational transitions with the account of their thermodynamic functions. The conclusion that the conformers are formed is based on an analysis of  $^1\text{H}$  NMR spectra and quantum-chemical calculations, which are indicative of the existence of two minima in the energies of formation of the structures of conformers **1a** and **1b** (Scheme 1).

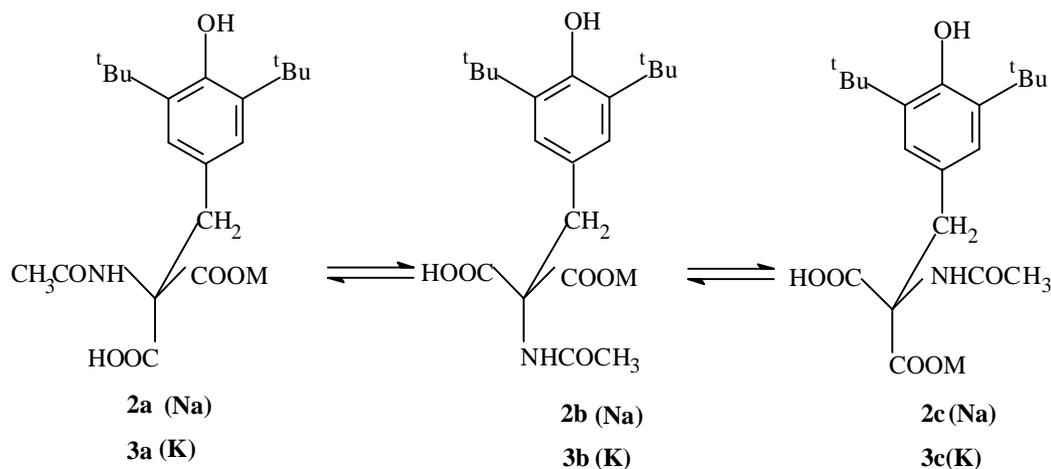
The  $^1\text{H}$  NMR spectrum of **1** exhibited two signals from the protons of the *tert*-butyl groups and the metaprotons of the aromatic ring, with the ratio of intensities of  $\sim 1:2$ . Upon heating, the doublet signals from the metaprotons merge into singlets, a feature typical of fast (in the NMR time scale) reversible processes. The energies of formation of structures **1a** and **1b** were found to be  $-1198.93$  and  $-1195.59$  kJ/mol, respectively. The value of  $\Delta H_f^\circ(\mathbf{1a-1b}) = 3.34$  kJ/mol corresponds to the energy of reversible isomerization of the two conformers. For the equilibrium between the structures **1a** and **1b**, the changes in the enthalpy ( $H^\circ$ ), entropy ( $S^\circ$ ), and Gibbs

energy ( $G^\circ$ ) were calculated to be  $\Delta H^\circ = +341.17$  J/mol,  $\Delta S^\circ = 8.64$  J/(mol K),  $\Delta G^\circ = -2233.55$  J/mol. According to the Boltzmann equation, the thermodynamic equilibrium constant is  $K \approx 2.5$ . Compounds **2** and **3** have three structures (Scheme 2).

The energies of formation of structures **2a** and **2b** of molecule **2** were found to be  $-1507.29$  and  $-1499.10$  kJ/mol. The difference between the energies of **2b** and **2a** was calculated to be  $+8.33$  kJ/mol. The energies of formation of structures **3a** and **3b** of molecule **3** were  $-1461.96$  and  $-1439.75$  kJ/mol, respectively. The difference in the energies of formation of **2a** and **2c** was estimated to be  $> 800$  kJ/mol. For the equilibrium between the structures **2a** and **2b**,  $\Delta H^\circ = -1046.58$  J/mol and  $\Delta S^\circ = -8.93$  J/(mol K) ( $\Delta G^\circ = 1614.56$  J/mol,  $K \approx 0.5$ ). For the similar structures of compound **3**,  $\Delta H^\circ = +59.73$  J/mol and  $\Delta S^\circ = -0.21$  J/mol ( $\Delta G^\circ = -2.85$  J/mol,  $K = 1.0$ ). Compounds **2** and **3** form crystal hydrates (for example, structures **2a** $\cdot 2\text{H}_2\text{O}$ , **2b** $\cdot 2\text{H}_2\text{O}$ , **3a** $\cdot 2\text{H}_2\text{O}$ , and **3b** $\cdot 2\text{H}_2\text{O}$ , (see Table 1).



Scheme 1



Scheme 2

In structures **2** and **3**, the metal atoms are located over the six-membered cycle and form coordination bonds with the oxygen atom of the carboxy group and the oxygen atom of the amide group (**2a**) or the oxygen atoms of the two carboxy groups (**2b**).

Fig. 1 indicates the numbering of the atoms in structures **1a** and **3b** whereas Table 2 presents the results of calculations of the bonds between the atoms and the respective bond angles. The structures of the compounds are consistent with the IR spectra, which exhibit no characteristic frequencies of the C=O bond of the carboxy group, but a broad band near  $1600\text{ cm}^{-1}$ .

The specificity of the structures of compounds **2** and **3** as compared to the structure and properties of **4** is obvious (Fig. 2).

Compounds **2** and **3** are water-soluble, which makes them promising for biological research. The results of quantum-chemical calculations for reversible solvation were analyzed and summarized in [1, 10]. The solvation of compounds **2** and **3** is depicted in Scheme 3, which is drawn based on the energies of formation and enthalpies and entropies of the initial and intermediate structures (Table 3).

Structures **2 or 3** correspond to hydrates **2d** and **3d**. The constants for the equilibrium between the initial

structures **2 or 3**, crystal hydrates **2d** and **3d**, and anion **1c** were calculated by the Boltzmann equation proceeding from the reversibility of the solvolysis reactions and the calculated values of the activity and entropy of the respective structures in the PM6 approximation. The quantum-chemical calculations suggest that the structures of compounds whose potassium or sodium atoms participate in the formation of coordination bonds may be predominant in aqueous solution. The experimental and calculation results are indicative of the neutral properties of the solution in passing from structure **2 or 3** ( $\text{pK}_a \sim 7.1$ ) to anion **1c** ( $\text{pK}_a \sim 6.9$ ). In the process of crystallization of compound **2**, the saturated aqueous solution yields a crystal hydrate with 12 water molecules **2x12H<sub>2</sub>O**; this fact additionally supports the possibility of formation of solvates of compounds **2** and **3** in aqueous solution. The solvation of compounds **4** and **5** is presented in Scheme 4.

The formation of acid **6** is a consequence of hydrolysis of salts **4** or **5**, aqueous solutions of which are characterized by  $\text{pK}_a \sim 8.1$ .

Under the solvation conditions, equilibrium is established between compounds **4** or **5**, anion **1d**, and acid **6** (Table 4).

Table 1

Energies of formation ( $-H_f^\circ$ ) of compounds 1-3, enthalpies ( $H^\circ$ ) and entropies ( $S^\circ$ ) at 298 K

Structure	$-H_f^\circ$ , kJ/mol	$H^\circ$ , kJ/mol	$\Delta H^\circ$ , J/mol	$S^\circ$ , J/mol	$DS^\circ$ , J/mol
<b>1a</b>	1198.9	83.6		835.6	
<b>1b</b>	1195.6	83.9	+0.4	844.2	+8.6
<b>2a</b>	1507.3	86.2		835.3	
<b>2b</b>	1499.1	85.1	-1046.6	826.4	-8.9
<b>3a</b>	1462.0	85.8		832.1	
<b>3b</b>	1439.8	86.1	+59.7	831.9	-0.2
<b>2a</b> ·2H <sub>2</sub> O	2008.6	103.2		963.5	
<b>2b</b> ·2H <sub>2</sub> O	2022.7	103.7	+453.2	975.1	+11.5
<b>3a</b> ·2H <sub>2</sub> O	1982.1	100.9		941.9	
<b>3b</b> ·2H <sub>2</sub> O	1971.8	103.0	+2096.5	964.6	+22.6

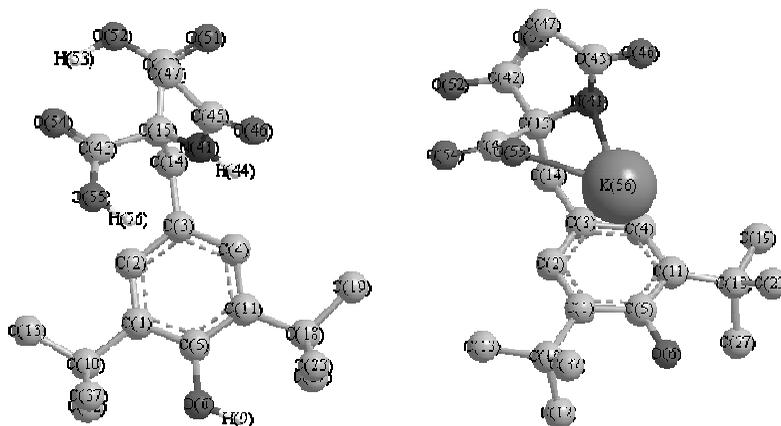


Fig. 1. Structures of **1a** and **3a** according to MOPAC files in the PM6 approximation and presentation in ChemBio3d-program

Table 2

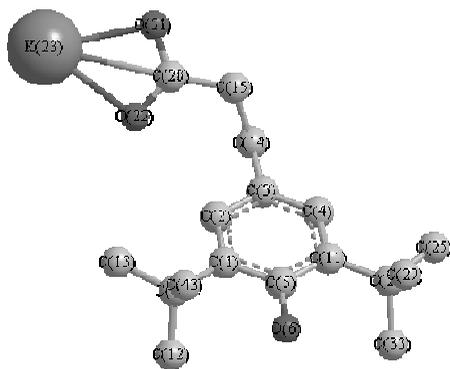
**Bond length and valence angles  
in the structures of molecules 1–3**

Molecule	Bond-Bond	Length, d/Å	Bond angle	$\omega/\text{grad}$
<b>1a</b>	O(6) – H(56)	5.075	C(5) – O(6) – H(56)	35.5
<b>1a</b>	O(6) – H(44)	5.664	C(5) – O(6) – H(44)	24.5
<b>1a</b>	O(6) – O(55)	5.757	C(1) – C(10) – C(3)	17.7
<b>1a</b>	O(6) – O(46)	7.409		
<b>2a</b>	O(6) – Na(56)	3.787	C(1) – C(10) – C(3)	18.0
<b>2a</b>	O(6) – O(55)	5.585	C(5) – O(6) – Na(56)	42.8
<b>2a</b>	O(6) – O(46)	6.359	C(5) – O(6) – H(44)	26.87
<b>2a</b>	O(55) – Na(56)	2.282		
<b>2a</b>	O(46) – Na(56)	2.885		
<b>2a</b>	C(3) – Na(56)	2.747		
<b>2a</b>	C(5) – Na(56)	2.929		
<b>3a</b>	O(6) – K(56)	4.130	C(1) – C(10) – C(3)	18.3
<b>3a</b>	O(6) – O(55)	5.936	C(5) – O(6) – K(56)	44.9
<b>3a</b>	O(6) – O(46)	6.998	C(5) – O(6) – H(44)	23.5
<b>3a</b>	O(55) – K(56)	2.626		
<b>3a</b>	O(46) – K(56)	3.158		
<b>3a</b>	C(3) – K(56)	3.105		
<b>3a</b>	C(5) – K(56)	3.299		

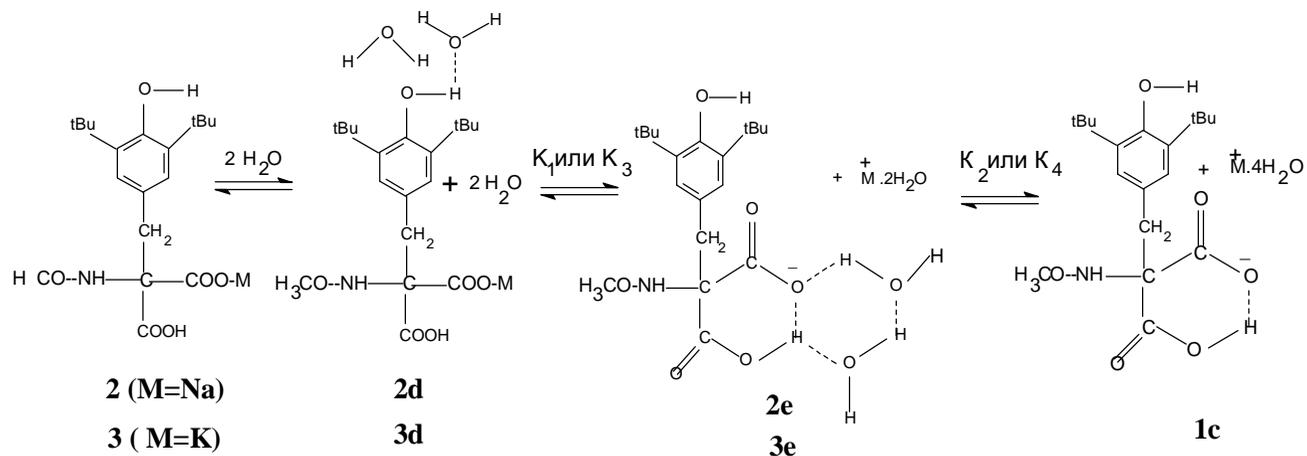
Table 3

**Structures of compounds 2 and 3  
and their Gibbs energies under conditions of solvation at 298 K**

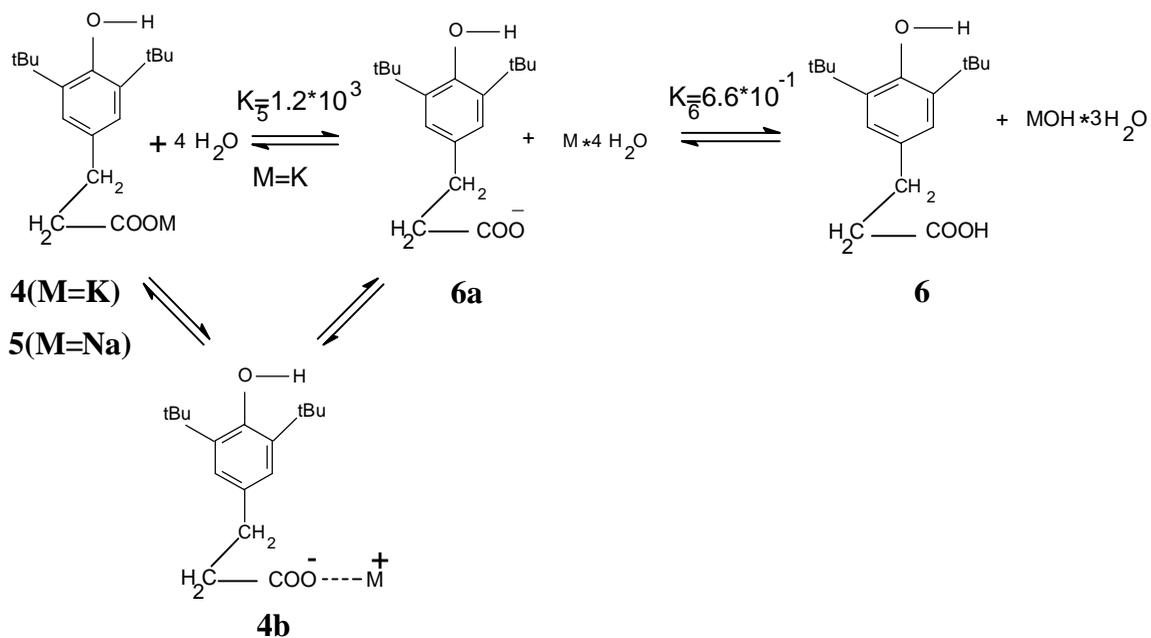
Structure	$H^{\circ}$ , J/mol	$\Delta H^{\circ}$ , J/mol	$S^{\circ}$ , J/mol	$\Delta S^{\circ}$ , J/mol	$\Delta G^{\circ}$ , J/mol
<b>2d</b>	100943.2		941.9		
2H <sub>2</sub> O	15306.2		359.1		
<b>2d</b> +2 H <sub>2</sub> O	116249.4		1301.1		
<b>2e</b> ·2H <sub>2</sub> O	98506.2		940.7		
K·2H <sub>2</sub> O	23964.2		356.4		
<b>2e</b> ·2H <sub>2</sub> O + K·2H <sub>2</sub> O	122470.5	+6221.1	1297.0	-4.0	+7425.0
$K_1=5 \cdot 10^{-2}$					
<b>2e</b> ·2H <sub>2</sub> O + K·2H <sub>2</sub> O	122470.5	+211.9	1297.0		
<b>2e</b> + K·4H <sub>2</sub> O	122682.4		1327.9	+30.9	-9005.2
$K_2=3.8 \cdot 10^1$					
<b>1d</b>	103208.4		963.5		
2H <sub>2</sub> O	15306.2		359.2		
<b>1d</b> + 2H <sub>2</sub> O	118514.6		1322.7		
<b>1e</b> ·2H <sub>2</sub> O	98506.2		940.7		
Na·2H <sub>2</sub> O	23564.7		349.5		
<b>1e</b> ·2H <sub>2</sub> O + Na·2H <sub>2</sub> O	122070.9	+3556.4	1290.1	-32.5	+13253.3
$K_3=4.7 \cdot 10^{-3}$					
<b>1e</b> + Na·4H <sub>2</sub> O	122924.89	+853.9	1353.2	+63.1	-17938.0
$K_4=1.4 \cdot 10^3$					



**Fig. 2.** Structure of **4** according to a MOPAC file in the PM6 approximation and presentation in Chembio3d-program



*Scheme 3*



*Scheme 4*

Table 4

## Structures of compounds 4–6 and their Gibbs energies under conditions of solvation at 298 K

Structure	$H^{\circ}$ , J/mol	$\Delta H^{\circ}$ , J/mol	$S^{\circ}$ , J/mol	$\Delta S^{\circ}$ , J/mol	$\Delta G^{\circ}$ , J/mol
<b>4</b>	68371.9		737.3		
4H <sub>2</sub> O	29535.7		387.0		
<b>4</b> + 4H <sub>2</sub> O	97907.6		1124.3		
<b>6a</b>	63549.1		692.3		
K·4H <sub>2</sub> O	40635.5		512.1		
<b>6a</b> + K·4H <sub>2</sub> O	104184.6	+6277.0	1204.5	+80.2	-17607.7
$K_5 = 1.2 \cdot 10^3$					
<b>6</b>	64119.5		692.6		
KOH·3H <sub>2</sub> O	31126.5		436.6		
<b>6</b> + KOH·3H <sub>2</sub> O	82791.3	-21393.3	1129.3	-75.2	+1016.3
$K_6 = 6.6 \cdot 10^{-1}$					
<b>5</b>	68628.1		739.3		
4H <sub>2</sub> O	29535.7		387.0		
<b>5</b> + 4H <sub>2</sub> O	98163.8		1126.3		
<b>6a</b>	63549.1		692.3		
Na·4H <sub>2</sub> O	40877.9		537.4		
<b>6a</b> + Na·4H <sub>2</sub> O	104427.0	+6263.2	1229.7	+103.4	-30822.1
$K = 2.6 \cdot 10^5$					
<b>6</b>	64119.5		692.6		
NaOH·3H <sub>2</sub> O	33044.8		438.7		
<b>6</b> + NaOH·3H <sub>2</sub> O	97164.3	-7262.7	1131.4	-98.3	+22039.6
$K = 1.3 \cdot 10^{-4}$					

Table 5

Energies of formation ( $-H_f^{\circ}$ ) and energies of homolysis  $D_{(OH)}$  of the O–H bond in the structures of compounds 1–6, crystal hydrates, anions, and solvates

Compound (structure)	$-H_f^{\circ}$ (AlkArOH), kJ/mol	$-H_f^{\circ}$ (AlkArO <sup>•</sup> ), kJ/mol	$D_{(OH)}$ , kJ/mol
<b>1a</b>	1198.9	1093.2	323.8
<b>1b</b>	1195.6	1091.0	321.8
<b>1c</b>	1484.9	1402.0	300.9
<b>3a</b>	1507.3	1427.3	297.9
<b>3b</b>	1499.1	1413.2	303.8
<b>3a</b> ·2H <sub>2</sub> O	2008.7	1925.9	300.7
<b>3b</b> ·2H <sub>2</sub> O	2022.7	1920.0	320.8
<b>3a</b> ·12H <sub>2</sub> O	4631.9	4551.4	298.7
<b>2a</b>	1462.0	1372.1	307.9
<b>2b</b>	1439.8	1352.9	304.9
<b>2a</b> ·2H <sub>2</sub> O	1982.1	1872.8	328.4
<b>2b</b> ·2H <sub>2</sub> O	1971.8	1855.7	334.1
<b>2a</b> ·12H <sub>2</sub> O	4586.3	4499.1	310.6
<b>4</b>	852.8	762.7	308.0
<b>5</b>	843.9	752.3	309.5
<b>4b</b>	179.8	69.4	328.5
<b>6a</b>	843.2	767.5	293.7
<b>6</b>	709.8	584.9	342.9

Based on the results of calculations in the PM6 approximation, we determined the enthalpies and entropies of structures **4** or **5**, **1d**, and **6** of the corresponding compounds. Under hydrolysis conditions, equilibrium is established. According to these data, compounds **4** and **5** in the case of aqueous solution should exist predominantly in the form of structures **1d** and **4b** (separated ion pair). However, the results of determination of the antioxidant activity of compound **4** suggest that in biological media the **4b** contact pair dominates. The bond dissociation energy  $D_{(OH)}$  was calculated based on the minimum energies of formation of structures of molecules **1–6** and their phenoxy radicals (AlkArO<sup>•</sup>, Table 5):

$$D_{(OH)} = -H^{\circ}f(\text{AlkArO}^{\bullet}) + H^{\circ}f(\text{H}) - H^{\circ}f(\text{AlkArOH}),$$

where  $-H^{\circ}f(\text{AlkArO}^{\bullet})$  is the energies of formation of the phenoxy radical,  $-H^{\circ}f(\text{AlkArOH})$  is the energy of phenol formation and the energies of formation of the hydrogen atom (+217.986 kJ/mol).

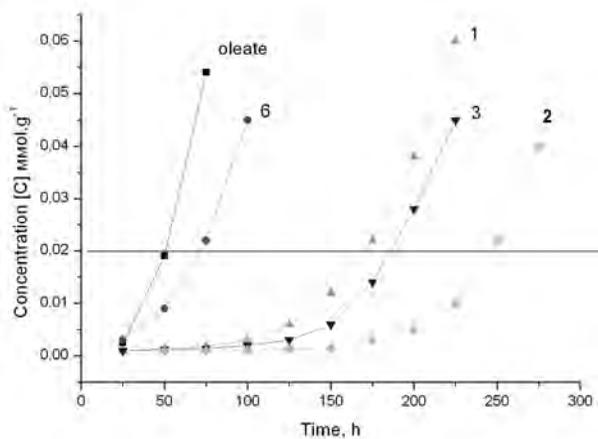
In Table 5 the enthalpy of formation of the phenoxy radical is the energy of formation of phenol and the enthalpy of formation of the hydrogen atom (+218.0 kJ/mol).

The data in Table 5 are indicative of the dependence of  $D_{(OH)}$  on the structure (**2a** or **2b**) of compounds **2** and **3** and their crystal hydrates. The molecules of the hydrates form hydrogen bonds with the hydrogen atom of the hydroxyl group of the phenol

fragment, which leads to an increase in the energy of the H–O bond homolysis.

The nature of the metal atom (sodium or potassium) also affects the value of  $D_{(\text{OH})}$ , which manifests itself in the rotamer structures and dihydrates.

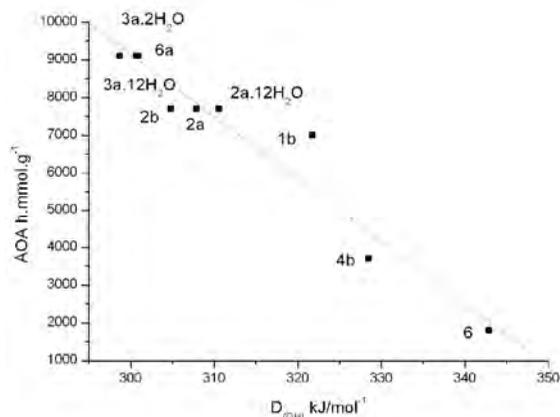
The antioxidant properties of these compounds were determined by oxidizing methyl oleate in the presence of the lipid fraction (extract) collected from the liver of “C<sub>3</sub>HA” strain mice that were administered an injection of the drug 1 h before slaughter. The advantage of this method is associated with the ability to test both fat- and water-soluble compounds under suitable conditions. Fig. 3 shows the kinetic curves of peroxide accumulation during oxidation of methyl oleate in the presence of lipids extracts of compounds **1–6**. The AOA value was calculated as the ratio of the difference between the induction periods in the curves corresponding to the oxidation of methyl oleate with ( $\tau_1$ ) and without ( $\tau_0$ ) lipid extract to the concentration of added extract ( $(C):\text{AOA} = (\tau_1 - \tau_0)C^{-1} \cdot \text{h} \cdot \text{mmol}^{-1} \cdot \text{g}$  (Fig. 3), according to the method described in [11].



**Fig. 3.** The kinetic curves of peroxide accumulation during oxidation of methyl oleate in the presence of lipids extracts of compounds **1-3** and **6**

The induction period was defined as the time it took to reach a concentration of peroxides of  $0.02 \text{ mmol} \cdot \text{g}^{-1}$ . The reaction of peroxide radicals with the inhibitor is reversible, with the equilibrium constant  $K$  being dependent on according to the Boltzmann equation. The value of  $D_{(\text{OH})}$  for the methyl oleate hydroperoxide molecule was calculated to be  $320.57 \text{ kJ/mol}$ . The values of  $D_{(\text{OH})}$  for the studied structures are listed in Table 5. According to these data, for the anions (structures **1c** and **6a**) and sodium malonate **2** ( $\text{struc} \Delta E_f^\circ \exp(-\Delta E_f^\circ \times kT)$ , tures **2a** $\times 2\text{H}_2\text{O}$ , **2b** $\times 2\text{H}_2\text{O}$ ), the values of  $D_{(\text{OH})}$  are low ( $297\text{--}310 \text{ kJ/mol}$ ). Consequently, we believe that these structures determine the efficiency of the compounds obtained in aqueous and biological media. The correlation

between the experimental data on the AOA and the calculated values of  $D_{(\text{OH})}$  are displayed in Fig. 4.



**Fig. 4.** Dependence of AOA of the conformers of the crystal hydrates of compounds **1-6** and the anions of the energy of homolysis of the OH bond  $D_{(\text{OH})}$  ( $r = 0.9783$ )

Comparison of the experimental and calculation results suggests that there is a linear correlation (with  $r^2 = 0.9774$ ) between the AOA and  $D_{(\text{OH})}$  for a number of structures of the studied compounds, which can be present in biological media and determine their antioxidant properties. Such structures comprise **2a** $\times 2\text{H}_2\text{O}$  and **3a** $\times 12\text{H}_2\text{O}$  solvates, anion **6a**, contact ion pair **4b**, and (hydroxyalkyl)propionic acid **6**.

## 4. Conclusions

Calculations of the parameters of molecules **1-3** in the PM6 approximation make it possible to determine the energies of transition and thermodynamic constants of equilibrium between the two conformers. Based on the calculated parameters of solvation and data on *in vitro* determination of the efficiency of the antioxidants under study using mouse live lipid extracts, a correlation between the AOA constants and the energy of homolysis of the O–H bond in antioxidant structures that can exist in biological media was established.

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**КВАНТОВО-ХІМІЧНІ РОЗРАХУНКИ ПРИ ДОСЛІДЖЕННІ ВЛАСТИВОСТЕЙ 1-(КАРБОКСИ)-1-(N-МЕТИЛАМІД)-2-(3',5'-ДИ-ТРЕТ.-БУТИЛ-4'-ГІДРОКСИФЕНІЛ)-ПРОПІОНАТІВ НАТРІЮ І КАЛІЮ У БІОЛОГІЧНОМУ СЕРЕДОВИЩІ**

*Анотація.* За допомогою квантово-хімічних розрахунків у наближенні РМ6 розраховані енергії утворення, ентальпії та ентропії конформерів 1-(карбокси)-1-(N-метиламід)-2-(3',5'-ди-трет.-бутил-4'-гідроксифеніл)-пропіонової кислоти та

1-(карбокси)-1-(N-метиламід)-2-(3',5'-ди-трет.-бутил-4'-гідроксифеніл)-пропіонатів натрію і калію. Знайдено подвоєння сигналів в  $^1\text{H}$  ЯМР спектрі першого конформера, які при нагріванні зливаються в синглети. Зміна структури конформерів і донорно-акцепторних комплексів (сольватів) відбувається із збереженням координаційного зв'язку металу з лігандом. Розрахунок в наближенні РМ6 структур 1-(карбокси)-1-(N-метиламід)-2-(3',5'-ди-трет.-бутил-4'-гідроксифеніл)-пропіонової кислоти та 1-(карбокси)-1-(N-метиламід)-2-(3',5'-ди-трет.-бутил-4'-гідроксифеніл)-пропіонатів лужних металів дає можливість прогнозувати будову і властивості сольватованих структур. Розраховано енергії гомолізу зв'язку Н-О ( $D_{\text{OH}}$ ) та встановлено лінійну залежність антиокиснювальної активності від  $D_{\text{OH}}$  структур досліджуваних сполук. Результати досліджень дають можливість прогнозувати властивості антиоксидантів у біологічному середовищі.

*Ключові слова:* квантово-хімічний розрахунок, морас2009, конформер, енергія зв'язку, ЯМР та ІЧ-спектроскопія, антиоксидант, структура.