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Effects of α-tocopherol and related compounds on reactions involving various organic radicals

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Abstract—Effects of α-tocopherol, PMC, and a number of the respective sulfur-containing analogues on reactions involving various organic radicals were studied. The test compounds were found to interact with alkyl radicals more effectively than with peroxyl radicals. The presence of a sulfur atom in structures of the respective analogues did not produce significant effects on reactivity. Derivatives of 5-hydroxy-1,3-benzoxathiol-2-one and 6-hydroxy-1,4-benzoxathiin-2(3*H*)-one displayed a high reactivity toward α-hydroxyalkyl radicals.

Non-fermentative free-radical processes are known to play an important role in functioning of the organism in its normal and pathological states. Activation of these processes may cause a number of diseases, including such common ones as those of cardiovascular and oncological nature.[1] An important role in regulation of free-radical oxidative processes is featured by vitamin E and, in particular, α-tocopherol. Its antioxidant properties are due to its high efficiency in the reduction reactions of oxygen-centered radicals. A number of studies have been performed with the aim of conferring new valuable properties to α-tocopherol. The studies by Ingold and co-workers[2,3] on elucidation of physico-organic fundamentals of α-tocopherol's mode of action and synthesis of its more effective analogues deserve particular attention in this respect. Wright and co-workers[4] have synthesized hydroxylated vitamin E derivatives, which proved to be more efficient antioxidants. With a view to preparing more hydrophilic vitamin E analogues, the widely known agents Trolox (6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid),[2,5] PMC (2,2,5,7,8-pentamethylchroman-6-ol),[2] as well as TMOH (2-(hydroxymethyl)-2,5,7,8-tetramethylchroman-6-ol)[2] and its glycosylated derivative (tocopherol monoglucoside, TMG)[6] have been synthesized.

In our studies, the concept of important role of free-radical fragmentation reactions in biosystem damage is developed.[7–10] These reactions involve carbon-centered α-hydroxyl-containing radicals. Realization of these reactions leads not only to destruction of biologically important compounds, but also to formation of signaling molecules responsible for cell proliferation and apoptosis.[11] Further, we have shown[12,13] that α-tocopherol and a number of its analogues, as well as some other vitamins, are capable of changing the direction of free-radical processes involving carbon-centered radicals.

The purpose of this work was synthesis of α-tocopherol analogues, which, while having antioxidant properties, could also effectively influence the free-radical processes involving carbon-centered radicals. Therefore, a series of sulfur-containing derivatives of α-tocopherol have been synthesized, the structures of which, together with those of other compounds used in this study, are shown in Figure 1.

α-TcOH and PMC were from Aldrich. Compounds **I**, **II**, and **IV**–**VII** were prepared according to procedures described in the literature.[14,15] Compounds **III** and **VIII** were prepared by methylation of compounds **I** and **III**, respectively, according to a known procedure.[16] Purity of the synthesized compounds (at least 99%) was controlled by TLC and GLC, and the respective structures were confirmed by NMR and MS spectrometry.[17]

For the substances studied, enthalpies of homolytic O–H bond dissociation (BDE) were calculated using the PC GAMESS version[18] of the GAMESS (US) QC package.[19] Geometries and frequencies of normal

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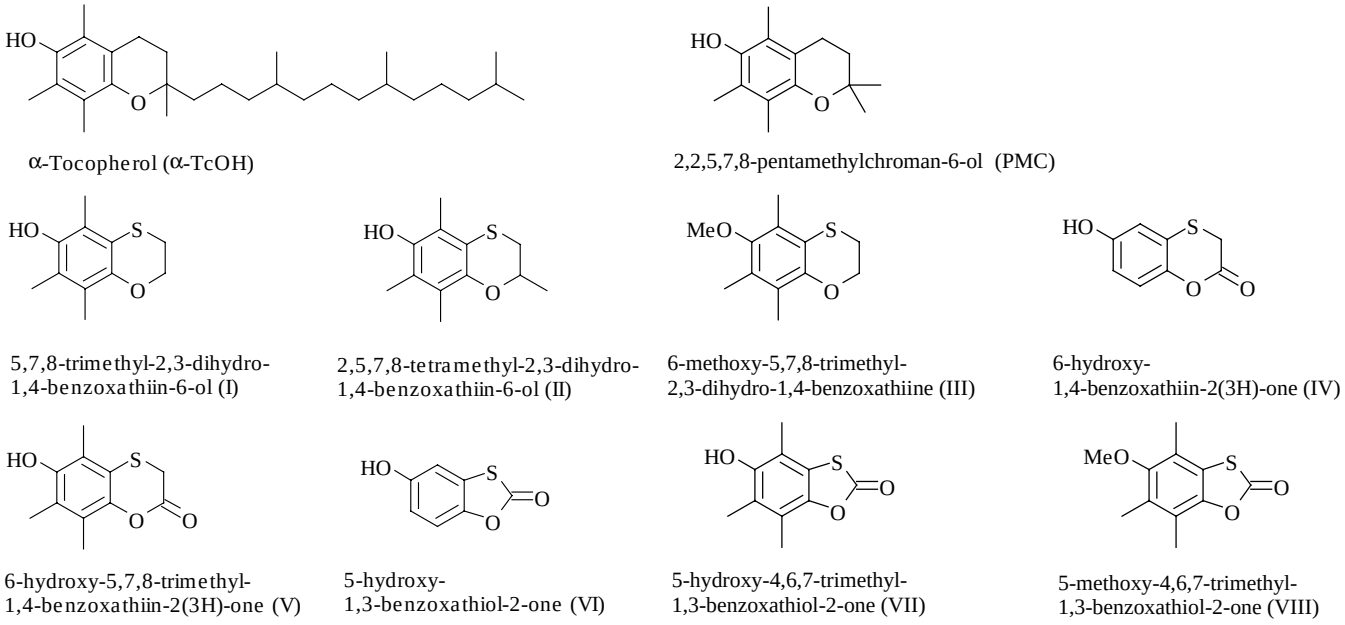


Figure 1. Structures of the compounds studied.

vibrations for molecules of the compounds and the respective radicals were calculated according to the DFT theory using the (RO)B3LYP/6-31G(d) method. For optimized geometries, the total energies were calculated using the (RO)B3LYP/6-311++G(2d, 2p) method. The BDE calculation procedure is described in detail in the literature.[20]

Reactivity of the compounds under study toward peroxyl ($ROO^{\bullet}$), alkyl ($R^{\bullet}$), and α-hydroxyl-containing radicals ($CH_3{}^{\bullet}CHOH$) was evaluated according to their effects on product formation in the course of radiolysis of ethanol and hexane in aerated and deaerated solutions. The procedures of solution preparation, irradiation, and final product analysis are described elsewhere.[13]

On radiolysis of deaerated hexane, formation of hexenes and dodecanes as the main products is known to proceed according to the following scheme:[21,22]

$$C_6H_{14} \xrightarrow{\gamma} \dot{C}_6H_{13} \xrightarrow{\dot{C}_6H_{13}} C_6H_{12} + C_6H_{14} \quad (1)$$

$$\dot{C}_6H_{13} \xrightarrow{\dot{C}_6H_{13}} C_{12}H_{26} \quad (2)$$

The formation of dodecanes on radiolysis, unlike that of hexenes, occurs due to reaction (2) only. Therefore, it is more correct to evaluate reactivity of the compounds under study according to their effects on the total yield of dodecanes, $\sum G(C_{12}H_{26})$, formed on recombination of C2 and C3 radicals of hexane (see Table 1).

Radiolysis of hexane under aerated conditions leads to formation of the corresponding hexanols and hexanones as the main products. Here, the following processes take place:[21–23]

$$C_6H_{14} \xrightarrow{\gamma} \dot{C}_6H_{13} \xrightarrow{O_2} C_6H_{13}O\dot{O} \xrightarrow{+H} C_6H_{13}OOH \longrightarrow \text{hexanol-2, hexanol-3, hexanone-2, hexanone-3} \quad (3)$$

The data showing the effects of α-tocopherol and its analogues on total yields of hexanones $\sum G(\text{One})$ and hexanols $\sum G(\text{Ol})$, as well as on the sum of the above-named yields $\sum G(\text{Ox})$, are presented in Table 1.

The experimental data presented in Table 1 show that all of the compounds studied are characterized by a rather low antioxidant activity while inhibiting hexane oxida-

Table 1. Effects of the compounds under study (1 mM) on total yields of hexanones $\sum(\text{One})$, hexanols $\sum(\text{Ol})$, the sum of yields of oxygenated products $\sum(\text{Ox})$, and total yield of dodecanes $\sum(C_{12}H_{26})$

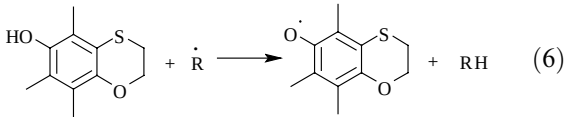
Additive	G (molecule/100 eV)				BDE (kcal/mol)
	$\sum(\text{One})$	$\sum(\text{Ol})$	$\sum(\text{Ox})$	$\sum(C_{12}H_{26})$	
—	0.99 ± 0.04	0.54 ± 0.02	1.53 ± 0.06	0.44 ± 0.03	—
α-TcOH	0.74 ± 0.03	0.36 ± 0.02	1.10 ± 0.05	0.06 ± 0.01	75.7
PMC	0.77 ± 0.02	0.32 ± 0.02	1.09 ± 0.04	0.06 ± 0.01	75.7
I	0.71 ± 0.02	0.33 ± 0.02	1.04 ± 0.04	0.07 ± 0.01	77.2
II	0.76 ± 0.02	0.34 ± 0.01	1.10 ± 0.03	0.07 ± 0.01	77.0
III	0.96 ± 0.03	0.52 ± 0.02	1.48 ± 0.05	0.43 ± 0.03	—
V	0.81 ± 0.02	0.37 ± 0.01	1.17 ± 0.03	0.22 ± 0.03	80.6
VII	0.75 ± 0.02	0.35 ± 0.02	1.10 ± 0.04	0.15 ± 0.01	80.4
VIII	0.92 ± 0.04	0.51 ± 0.02	1.43 ± 0.06	0.31 ± 0.03	—

tion. Thus, the sum of oxygenated product yields, $\sum G(\mathrm{Ox})$, was brought down by approximately 30% by all of the compounds under study. Compounds (**III**) and (**VIII**) manifested no antioxidant activity due to the absence of hydroxyl groups in their molecular structures. Introduction of sulfur atoms in the structures of α-tocopherol analogues (**I**–**III**, **V**, **VII**, and **VIII**) does not alter their antioxidant properties (see Table 1). This is evidence of inability of the arylsulfides to decompose hydroperoxides according to reactions (4) and (5), which is characteristic of alkylsulfides:[24]

$$\mathrm{ROOH} + \mathrm{R^1{-}S{-}R^2} \rightarrow \mathrm{ROH} + \mathrm{R^1{-}SO{-}R^2} \qquad (4)$$

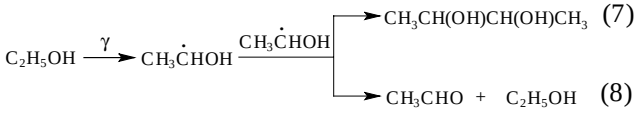
$$\mathrm{ROOH} + \mathrm{R^1{-}SO{-}R^2} \rightarrow \mathrm{ROH} + \mathrm{R^1{-}SO_2{-}R^2} \qquad (5)$$

On radiolysis of deaerated hexane, addition of the test compounds produced more pronounced effects. Thus, all of the compounds, except the methylated derivatives, effectively lowered dodecane formation yields, and the efficiency of their interaction with $^{\cdot}C_6H_{13}$ species increased with decreasing BDE values (see Table 1) for O–H bonds of the test compounds. This fact points to reaction (6) as the main way of interaction of alkyl radicals and the compounds being studied. The lack of hydroxyl groups in compounds (**III**, **VIII**) deprives them of the ability to react according to (6), therefore they do not alter the dodecane yields $\sum G(\mathrm{C_{12}H_{26}})$ on radiolysis of hexane (see Table 1).



(6)

Reactivity of compounds (**I**–**VIII**) toward α-hydroxyl-containing radicals was assessed according to the effects of the former on product yields in radiolysis of ethanol. It has been reliably established[25] that the $CH_3{}^{\cdot}CHOH$ species formed on γ-irradiation of ethanol give 2,3-butanediol and acetaldehyde:



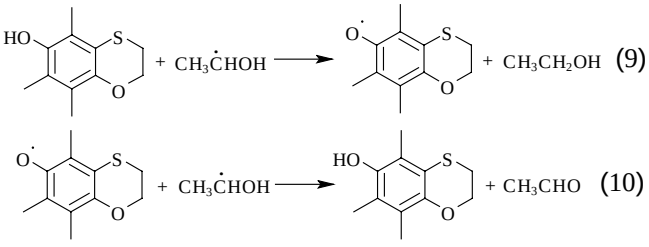
Reaction (7) is the only way by which 2,3-butanediol can be formed, whereas CH_3CHO can result from other processes as well. Therefore, the 2,3-butanediol yield may serve as an index of the test compound reactivity toward the $CH_3{}^{\cdot}CHOH$ species. The yield values for acetaldehyde (AA) and 2,3-butanediol (BD) formed in the presence of the test additives, as well as calculated BDE values, are shown in Table 2.

In the course of radiolysis of deaerated ethanol in the presence of additives (except for compound **III**), the direction of free-radical processes involving α-hydroxyethyl radicals changes in such a way that the yield of acetaldehyde increases at the expense of decreased yield of 2,3-butanediol (recombination product of $CH_3{}^{\cdot}CHOH$ radicals). This points to the ability of the named compounds to oxidize the α-hydroxyethyl radicals formed on radiolysis.

Table 2. Effects of the compounds under study (1 mM) on yields of acetaldehyde (AA) and 2,3-butanediol (BD) formed in radiolysis of deaerated ethanol

Additive	*G* (molecule/100 eV)		BDE (kcal/mol)
	AA	BD	
—	1.61 ± 0.17	1.38 ± 0.04	—
α-TcOH	2.73 ± 0.14	0.21 ± 0.02	75.7
PMC	2.72 ± 0.19	0.22 ± 0.02	75.7
I	2.73 ± 0.13	0.33 ± 0.01	77.2
II	2.74 ± 0.18	0.32 ± 0.02	77.0
III	1.62 ± 0.10	1.32 ± 0.03	—
IV	2.93 ± 0.18	0.08 ± 0.01	85.9
V	3.10 ± 0.16	0.09 ± 0.01	80.6
VI	2.92 ± 0.17	0.09 ± 0.01	85.7
VII	3.13 ± 0.12	0.08 ± 0.01	80.4
VIII	3.02 ± 0.17	0.08 ± 0.01	—

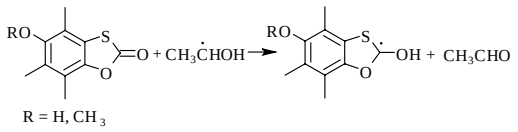
The decrease in yields of 2,3-butanediol and increase in yields of acetaldehyde observed on radiolysis of ethanol solutions of α-TcOH, PMC, or compounds **I** and **II**, are due to oxidation (10) of α-hydroxyethyl radicals by phenoxyl radicals formed from the additives. It is noteworthy that the efficiency of reaction (9) correlates well with BDE values for the named compounds.



In the course of reduction of α-hydroxyethyl radicals by reaction (9) in solutions containing additives with lower BDE values, more phenoxyl radicals are formed, which then oxidize α-hydroxyethyl radicals to acetaldehyde by reaction (10) while regenerating molecules of the additives. This mechanism is also evidenced by the fact that α-TcOH, PMC, as well as compounds **I** and **II**, are characterized by very low yields of decomposition in ethanol, not exceeding 0.2 molecule/100 eV.

Compound **III**, obtained by methylation of the OH group in compound **I**, does not alter the product yields in radiolysis of ethanol because it cannot react according to (9) and (10). As evidenced by the data presented in Table 2, compounds **IV**–**VIII**, containing carbonyl groups, are more efficient oxidizers of $CH_3{}^{\cdot}CHOH$ radicals. The presence of carbonyl group in structures of the named compounds leads to a more substantial decrease in yields of 2,3-butanediol with simultaneous increase of acetaldehyde yields. It is noteworthy that compound **VIII**, which has no OH groups, retains the ability to oxidize $CH_3{}^{\cdot}CHOH$ radicals, unlike compound **III**. This

points to the presence of a carbonyl group in the abovementioned compounds as a factor increasing significantly the ability to oxidize α-hydroxyethyl radicals by reaction (11):



(11)

The ability of carbonyl-containing compounds to oxidize various radicals formed from alcohols has been shown earlier.[26]

On confronting the data obtained in radiolysis studies of hexane and ethanol, the following conclusion can be made: analogues of α-tocopherol, in particular compounds of types **IV**–**VIII**, are unique agents regulating free-radical reactions of various types. Thus, the presence of a hydroxyl group in the structure imparts to such agent the ability to reduce organic radicals to the initial molecules. The presence of a carbonyl group makes an agent capable of oxidizing alcohol radicals. As a rule, substances having such properties can block fragmentation reactions of α-hydroxyl-containing radicals occurring in biologically important molecules. Taking into account the convenience of preparative methods for compounds of type (**IV**–**VII**), as well as the presence of pharmacological activity,[27] they may be of interest as potential radioprotectors, medicinal drug products, and industrial antioxidants.

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17. Compound **I**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.40–4.26 (m, CH_2, OH), 3.20–3.00 (m, CH_2), 2.15 (s, $3CH_3$), MS (*m*/*z*, I%) 210 (M^+, 89), 195 (M−CH_3, 5), 182 (M−CO, 6), 154 (100), mp 104 °C. Compound **II**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.30–4.00 (m, CH), 3.05 (s, OH), 2.95 (d, J = 1.7 Hz, CH_2), 2.15 (s, $3CH_3$), 1.47 (d, J = 6.2, CH_3), MS (*m*/*z*, I%) 224 (M^+, 60), 195 (27), 183 (17), 154 (100), mp 88 °C. Compound **III**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.39–4.29 (m, CH_2), 3.63 (s, CH_3O), 3.19–3.05 (m, CH_2), 2.14 (s, $3CH_3$), MS (*m*/*z*, I%) 224 (M^+, 100), 209 (M−CH_3, 79), mp 49 °C. Compound **IV**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.00–6.60 (m, 3H), 3.45 (s, CH_2), MS (*m*/*z*, I%) 182 (M^+, 54), 154 (M−CO, 75), 153 (100), mp 170 °C. Compound **V**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.60 (br, OH), 3.40 (s, CH_2), 2.30–2.10 (m, $3CH_3$), MS (*m*/*z*, I%) 224 (M^+, 75), 209 (M−CH_3, 1.7), 196 (M−CO, 100), mp 199 °C. Compound **VI**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.25 (s, OH), 7.20–6.60 (m, 3H), MS (*m*/*z*, I%) 168 (M^+, 100), 140 (M−CO, 29), 112 (M−2CO, 91), mp 174 °C. Compound **VII**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.70 (br, OH), 2.40–2.10 (m, $3CH_3$), MS (*m*/*z*, I%) 210 (M^+, 78), 182 (M−CO, 13), 154 (M−2CO, 100), mp 159 °C. Compound **VIII**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 3.67 (s, CH_3O), 2.30–2.15 (m, $3CH_3$), MS (*m*/*z*, I%) (M^+, 100), mp 83 °C.
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