Kinetic characteristics of the reaction of resveratrol with peroxyl radicals and natural thiols in aqueous medium

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The method of competing reactions was used to determine the rate constants of the reaction of resveratrol (RVT) with peroxyl radicals formed on decomposition of the azoinitiator AAPH in aqueous solutions at 37 °C. The polymethine dye **A** (3,3′-di-γ-sulfopropyl-9-metylthiacarbocyanine-betaine pyridinium salt) was used as a competing acceptor of radicals. It was found that resveratrol can be involved in the reaction with natural thiols, glutathione (GSH) and cysteine (CSH), in aqueous solutions at 37 °C. The reaction of RVT with thiols (thiol—ene reaction) follows a chain mechanism and accelerates in the presence of H_2O_2. The results obtained can be useful for understanding the physiological role of thiols in oxidation processes.

Key words: resveratrol, thiol—ene reaction, glutathione, cysteine, antioxidants, kinetics.

trans-Resveratrol (RVT, 3,5,4′-trihydroxystilbene) is known as phytoalexin, which is present in grapes and red wines in relatively large amounts. A high content of resveratrol in red wine (0.1—15 mg L^{-1}) is believed to be related to the so-called "French paradox", an unusually low level of cardiovascular and oncological diseases observed in some regions of France with a high-calorie diet, which includes a large amount of fats and a regular consumption of red wine.[1—4] It is known that resveratrol prevents the development of atherosclerosis,[5—9] has anti-inflammatory,[10] neuroprotective, cardioprotective, and antitumor activity.[11,12] The protective effect of resveratrol is associated with the antioxidant properties of phenolic compounds. It was found that RVT inhibits lipid peroxidation in blood cells treated with peroxynitrite[13] and in cell membranes;[14,15] inhibits oxidation of lipoproteins.[16—19]

The data on the reactivity of RVT in the reactions with active oxygen species (peroxyl and hydroxyl radicals, radical anion O_2^{-}) are very contradictory. Thus, in the works[20,21] RVT is called a strong lipophilic antioxidant comparable in activity with α-tocopherol;[22] in the work[14] the authors present the evidence that RVT is considerably weaker than both α-tocopherol and trolox in of the oxidation of liposomes of phosphatidylcholine initiated by various oxidants; while in the work[23] the authors suppose that RVT and α-tocopherol form a synergistic mixture, in which RVT reduces the tocopheroxyl radical. At the same time, it is RVT that is regarded to be responsible for the "antioxidant power" of red wine, although it is not its main phenolic component.[24]

The studies of the antiradical activity of *trans*- and *cis*-isomers of RVT and some other hydroxyl-substituted stilbenes in the homogeneous solutions in oxidizing styrene[25,26] showed that these phenolic compounds are medium strength inhibitors terminating the oxidation chains: the reaction rate constant of RVT with the peroxyl radical did not exceed $1.5 \cdot 10^5$ mol^{-1} L s^{-1} (at 30 °C).[26] In aqueous media, the antiradical activity of RVT has been studied mainly with respect to hydroxyl radicals formed under γ-radiolysis conditions[27—30] generated by the Fenton reaction,[31] as well as by laser flash photolysis.[32]

In the present work, we study the kinetics of the reaction of RVT with hydrogen peroxide and peroxyl radicals formed upon decomposition of 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AAPH) in aqueous solutions. Since, unlike most phenolic antioxidants, RVT contains an unsaturated bond conjugated with two phenolic fragments, it can exist in *trans*- and *cis*-form

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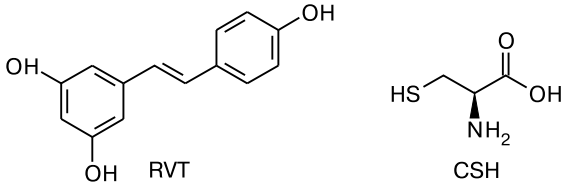
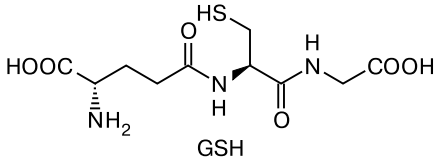
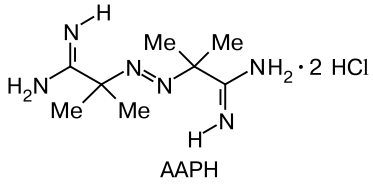
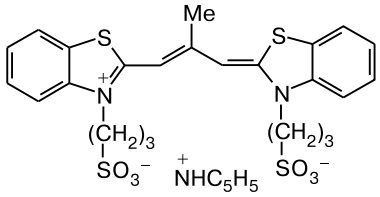
and actively react with thiyl radicals.[33—35] This was the reason that we paid special attention to the study of the reaction of resveratrol with natural thiols, cysteine (CSH) and glutathione (GSH), which, similarly to resveratrol, are bioantioxidants. The antioxidant functions of thiols are manifested in the reaction with hydroxyl radicals, reduction of hydrogen peroxide, hydroperoxides, and disulfide bonds —S—S—, prevention of oxidation of proteins.[36—39] In the work,[40] the rate constants of the reaction of CSH and GSH with peroxyl radicals were determined by the method of competing reactions using a polymethine dye and it was found that thiyl radicals are formed in low yield during reduction of hydrogen peroxide with thiols. In the present work, this procedure was used for determining the kinetic characteristics of the reaction of resveratrol with peroxyl radicals and studying the reaction between resveratrol and thiols CSH and GSH (thiol—ene reaction). It should be noted that in recent years the number of works (especially in the field of medical chemistry) on the reactions of unsaturated substrates with thiols as a method for the synthesis of heterochain compounds has increased dramatically. However, the thiol-ene reactions of natural thiols remain practically uninvestigated.









Dye **A**

Experimental

trans-Resveratrol (RVT, ABCR GmbH), glutathione (GSH), and cysteine (CSH) (Sigma-Aldrich), hydrogen peroxide (Usol´-khimprom) were used without preliminary purification. The azoinitiator AAPH (2,2´-azobis(2-methylpropionamidine) dihydrochloride, Fluka) was used for generation of peroxyl radicals. The anionic polymethine dye **A**, (3,3´-di-γ-sulfopropyl-9-metylthiacarbocyanine-betaine pyridinium salt, Gosniikhimfotoproekt)[41] was used as the spectrokinetic probe.

Bidistilled water was used for preparation of base solutions of the dye, H_2O_2, CSH, GSH and as a reaction medium. Base solutions of resveratrol were prepared in ethanol (Medkhimprom). The reactions were carried out in aqueous medium with the addition of base solutions of reagents (1—10 μL). The concentration of resveratrol and the polymethine dye was registered spectrophotometrically: RVT has a characteristic absorption band at 304—308 nm ($\varepsilon = 0.3 \cdot 10^5$ L mol^{-1} cm^{-1}), the dye **A** absorbs at 543 nm ($\varepsilon = 0.77 \cdot 10^5$ L mol^{-1} cm^{-1}).[40,41] The concentration of H_2O_2 in the base solution was controlled by the iodometric method.

All the reactions were carried out at a physiological temperature of 37 °C in a glass thermostated cell and/or directly in thermostated quartz cells of Ultraspec 1100 Pro (l = 1 cm) and Shimadzu 3101 spectrophotometers (the "New Materials and Technologies" Multi-Access Center of the N. M. Emanuel Institute of Biochemical Physics of the Russian Academy of Sciences). The experimental error in determination of kinetic characteristics of the reaction of resveratrol with thiols did not exceed 10%.

Results and Discussion

Figure 1, *a* shows the change in the absorption spectra of RVT during reaction with peroxyl radicals formed upon decomposition of AAPH (the spectra were recorded every 1 min) and practically parallel kinetic curves of its consumption at different initial concentrations (see Fig. 1, *b*). According to the theory,[22,42,43] the independence of the rate of the phenol consumption (a free radical scavenger) from the initial concentration indicates that in this concentration range all the radicals generated by the initiator are accepted by the phenol. The rate of the phenol consumption is

$$-\mathrm{d[PhOH]}/\mathrm{d}t = W_\mathrm{i}/f,$$

where $W_\mathrm{i} = k_\mathrm{i}$ [AAPH] is the rate of generation of radicals upon initiator decomposition, f is the stoichiometric coefficient indicating how much $RO_2^\bullet$ in total reacts with one molecule of PhOH. In aqueous solutions, the rate constant value for the decomposition of AAPH into radicals at 37 °C is equal to $k_\mathrm{i} = 1 \cdot 10^{-6}$ s^{-1}.[44,45] In Fig. 1, *b*, it is seen that at a concentration [RVT] > $0.7 \cdot 10^{-5}$ mol L^{-1} and $W_\mathrm{i} = 1.8 \cdot 10^{-8}$ mol L^{-1} s^{-1} resveratrol is consumed at a practically constant rate of $0.9 \cdot 10^{-8}$ mol L^{-1} s^{-1}, which is 0.5 W_i. This means that under the experimental conditions, the stoichiometric coefficient for RVT is equal to 2.

The rate constant of the reaction of resveratrol with peroxyl radicals was determined by the method of competing reactions tested in the work[40] for evaluation of the antiradical activity of natural thiols. A water-soluble poly-

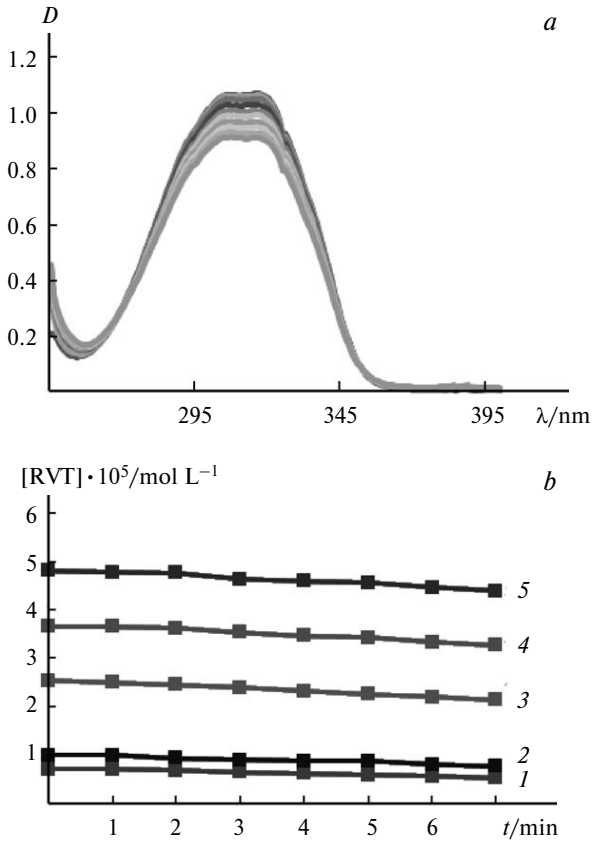


Fig. 1. (*a*) Consumption of RVT ($3.66 \cdot 10^{-5}$ mol L^{-1}) at the reaction with radicals formed upon decomposition of AAPH (18 mmol L^{-1}) in aqueous medium at 37 °C (the spectra were recorded every 1 min). (*b*) Kinetic curves of consumption of RVT in the reaction with radicals, [AAPH] = 18 mmol L^{-1}; [RVT]$\cdot 10^5$ mol L^{-1}: 0.7 (*1*), 0.99 (*2*), 2.72 (*3*), 3.66 (*4*), and 4.82 (*5*).

methine dye **A** with known spectral characteristics[40,41] and rate constant of the reaction with peroxyl radicals $RO_2^{\bullet}$ initiated by AAPH in aqueous medium served as a spectrokinetic probe (a base comparison acceptor). At 37 °C, $k_A = 5.4 \cdot 10^4$ L mol^{-1} s^{-1}, the stoichiometric coefficient $f = 1$. At close concentrations of resveratrol and dye in the presence of AAPH, consumption of both components is observed (Fig. 2). At a constant rate of radical initiation, the rate of the dye consumption decreases upon addition of RVT, *i.e.*, the latter acts as a competing acceptor of radicals.

The kinetic scheme describing the generation of the radicals (1), their reaction with two acceptors PhOH (2) and **A** (3), and quadratic termination in recombination and/or disproportionation reactions (4—6) looks as follows:

$$\text{AAPH} \rightarrow RO_2^{\bullet} \text{ (initiation, } W_i = k_i\,[\text{AAPH}]) \qquad (1)$$

$$RO_2^{\bullet} + \text{PhOH} \rightarrow \text{PhO}^{\bullet} + \text{ROOH} \quad (k_{\text{PhOH}}, \text{ reaction with resveratrol}) \qquad (2)$$

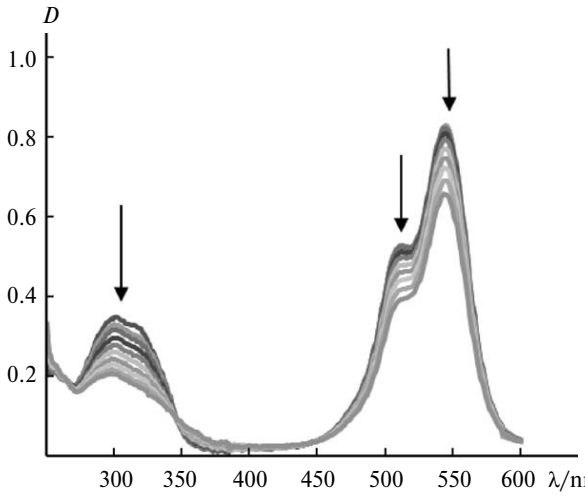


Fig. 2. The over-time changes in the absorption spectra of an aqueous solution containing $1.1 \cdot 10^{-5}$ mol L^{-1} of dye **A**, $1.1 \cdot 10^{-5}$ mol L^{-1} of RVT, and $18 \cdot 10^{-3}$ mol L^{-1} of AAPH at 37 °C (the spectra were recorded every 1 min).

$$RO_2^{\bullet} + A \rightarrow A^{\bullet} \ (k_A) \quad (W_A \text{ is the rate of consumption of A}) \qquad (3)$$

$$RO_2^{\bullet} + \text{PhO}^{\bullet} \rightarrow \text{Products} \quad \text{(recombination/disproportionation)} \qquad (4)$$

$$A^{\bullet} + A^{\bullet} \rightarrow \text{Products} \qquad (5)$$

$$A^{\bullet} + \text{PhO}^{\bullet} \rightarrow \text{Products.} \qquad (6)$$

Since at the rate of radical initiation $W_i \leq 3 \cdot 10^{-8}$ mol L^{-1} s^{-1} and the concentrations [**A**] and [PhOH] $> 5 \cdot 10^{-6}$ mol L^{-1} the dye and RVT intercept all the radicals, the disproportionation reaction of radicals $RO_2^{\bullet}$ was excluded. It is obvious that reactions (4) and (5) proceed at high rates and provide for resveratrol a stoichiometric coefficient $f = 2$ and for dye **A** $f = 1$.[40,41] In reaction (6), the alkyl radical $\mathbf{A}^{\bullet}$ reacts with phenoxyl radical, therefore the rate constant of this reaction can be high enough to compete with reaction (4).

If $W(6) >> W(4)$, we can assume that $W_i = W_{\text{PhOH}} + W_{\mathbf{A}}$. In this case, the concentration of the peroxyl radicals is $[RO_2^{\bullet}] = W_i/\{k_{\mathbf{A}}[\mathbf{A}] + k_{ef}\,[\text{PhOH}]\}$ and $k_{ef} = k_{\text{PhOH}}$. If $W(6) << W(4)$, than $k_{ef} = 2\,k_{\text{PhOH}}$.

The rate of the dye consumption with the addition of PhOH is expressed by the equation

$$W_{\mathbf{A}} = k_{\mathbf{A}}\,[\mathbf{A}]\,[RO_2^{\bullet}] = (k_{\mathbf{A}}\,[\mathbf{A}]\,W_i)/\{k_{\mathbf{A}}[\mathbf{A}] + k_{ef}\,[\text{PhOH}]\}. \qquad (7)$$

To analyze the experimental data, it is convenient to transform Eq. (7) to the form

$$1/W_{\mathbf{A}} = (1 + (k_{ef}/k_{\mathbf{A}}) \cdot ([\text{PhOH}]/[\mathbf{A}]))/W_i. \qquad (8)$$

Table 1. The rates of consumption of dye **A** and RVT in the reaction with radicals formed upon decomposition of AAPH

Entry	$[PhOH] \cdot 10^5$/mol L^{-1}	$W_{PhOH} \cdot 10^8$/mol L^{-1} s^{-1}	$[\mathbf{A}] \cdot 10^5$/mol L^{-1}	$W_{\mathbf{A}} \cdot 10^8$/mol L^{-1} s^{-1}	[PhOH] : [**A**]
1	0	0	1.07	1.5	—
2	0.6	0.77	0.94	1.06	0.64
3	0.65	1.06	0.63	0.54	1.04
4	0.9	1.37	0.44	0.33	2.04
5	0.91	0.91	1.03	0.59	0.89
6	1.15	1.3	0.3	0.14	4.43
7	1.9	1.32	0.82	0.22	2.3

Equation (8) was used in the work[40] for analysis of experimental data and determination of the rate constants of the reaction of peroxyl radicals with thiols.

Table 1 shows the experimentally measured rates of consumption of dye **A** and RVT for different concentration ratios [PhOH] : [**A**]. From Fig. 3, it is seen that the dependence of the rate of dye **A** consumption on the concentrations of both reagents is linearized in the coordinates of Eq. (8). The segment equal to $1/W_i$ is cut off on the ordinate axis, while the value $k_{ef} = 11.7 \cdot 10^4$ mol^{-1} L s^{-1} can be calculated from the slope of the line $tg\varphi = k_{ef}/(k_{\mathbf{A}} \cdot W_i)$.

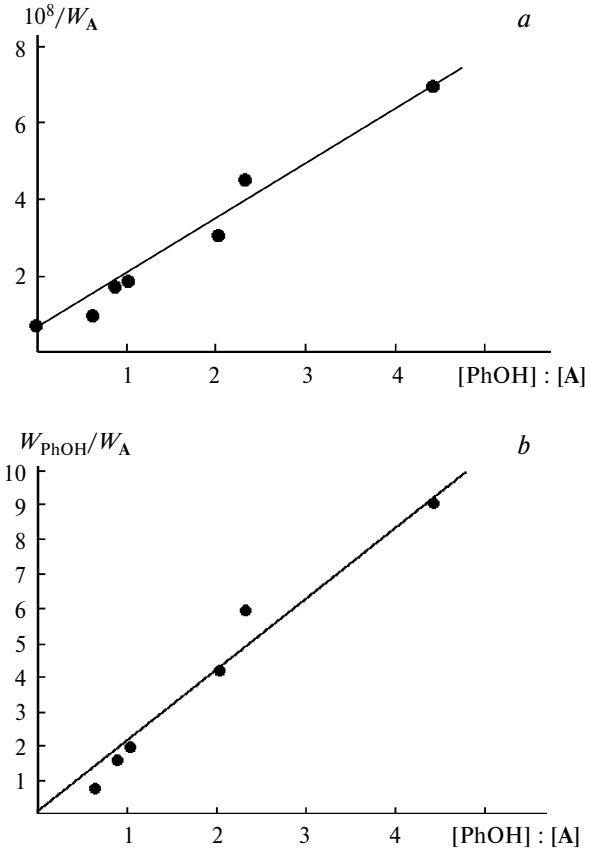


Fig. 3. (*a*) The dependence of the rate of dye **A** consumption ($W_{\mathbf{A}}$) on the ratio of concentrations of RVT and **A** ([PhOH] : [**A**]) in the coordinates of Eq. (8). (*b*) The dependence of the ratio of rates of consumption of RVT and the dye ($W_{PhOH}/W_{\mathbf{A}}$) on the ratio of their concentrations ([PhOH] : [**A**]) in the coordinates of Eq. (9).

Since the absorption spectra of resveratrol and the dye practically do not overlap (see Fig. 2), the rates of the resveratrol consumption were measured simultaneously with the measurements of the dye consumption rate. From the analysis of equations (1)—(6), it follows that the ratio of rates is proportional to the ratio of their concentrations:

$$W_{PhOH}/W_{\mathbf{A}} = (k_{PhOH}\,[PhOH])/(k_{\mathbf{A}}\,[\mathbf{A}]). \qquad (9)$$

Figure 3, *b* shows that the experimental data are linearized in the coordinates of Eq. (9). Taking into account the slope of the resulting straight line ($tg\varphi = k_{PhOH}/k_{\mathbf{A}} = 1.96$), the value $k_{PhOH} = tg\varphi \cdot k_{\mathbf{A}} = 10.6 \cdot 10^4$ mol^{-1} L s^{-1} was calculated. The k_{ef} and k_{PhOH} values are similar within a 10% error. This means that peroxyl radicals are consumed mainly in parallel reactions with the dye and resveratrol. It is noteworthy that the rate constant of the reaction of resveratrol with peroxyl radicals in aqueous solution equal to $(1.1 \pm 0.1) \cdot 10^5$ mol^{-1} L s^{-1} is close to the values obtained in oxidizing styrene[25,26] and characterizes RVT as a medium strength inhibitor.

The hydroxy group at position 4′ of resveratrol is predominantly involved in the reactions with peroxyl radicals.[25,26,29] More active and less selective hydroxyl radicals (HO$^{\bullet}$), along with the hydrogen atom abstraction from the phenolic hydroxyls, adds to the double bond, which results in the formation of resveratrol desintegration products, *p*-hydroxybenzaldehyde and 3,4-dihydroxybenzoic aldehyde and acid.[27,28] It is also known that thiyl radicals readily undergo addition to the double bonds.[33,34] These reactions lie in the basis of the reactions of thiols with unsaturated compounds, which are called *click*-chemistry thiol—ene reactions,[46—50] mainly used for the synthesis of linear and branched heterochain polymers. It was noted that terminal double bonds are more active in the addition of thiols, therefore, compounds with one or more terminal unsaturated bonds were used as the ene monomer component for the synthesis of polymers. In the works,[51,52] we observed the reaction of mercaptoethanol and glutathione with β-carotene, the

molecule of which contain 11 conjugated unsaturated bonds. It was noted that the rate of its consumption with the addition of glutathione without hydroperoxide additives is relatively low. Since the resveratrol molecule contains a double bond, though not terminal but activated by the conjugation with the phenol rings, it was of interest to investigate its reactions with GSH and more active[40] CSH.

Figure 4, *a* shows the kinetic curves of the resveratrol consumption in the reaction with these thiols. It can be seen that the reaction of RVT with CSH proceeds much faster than with GSH. The kinetic curve with CSH is S-shaped, which indicates a complex auto-accelerated character of the process. The maximum reaction rate, determined by the slope of the tangent at the inflection point (W_{max}), has a complex dependence on the initial concentrations of CSH and RVT. From the slope of these dependences in logarithmic coordinates (Fig. 4, *b*), it follows that the kinetic equation for W_{max} has the form

$$W_{max} = a[RVT][CSH]^{0.7},$$

where the parameter $a = 0.003$ (mol L^{-1})$^{-0.7}$ s^{-1}.

Resveratrol reacts with glutathione much slower (see Fig. 4, *a*, curve *2*), but the reaction is accelerated by the addition of hydrogen peroxide. In the work,[40] it was shown that radicals are formed in low yield in the reaction of GSH with H_2O_2 and a specific rate of the radical formation in this reaction was determined

$$\varpi = W_i/\{[H_2O_2][GSH]\} = 0.07 \cdot 10^{-3} \text{ mol}^{-1} \text{ L s}^{-1}.$$

Figure 5 (curve *1*) shows the dependence of the initial rate of resveratrol consumption on the rate of radical initiation with the additives of glutathione with H_2O_2 ($W_i = \varpi[H_2O_2][GSH]$).

It is seen that the dependence is nonlinear, but becomes a straight line in logarithmic coordinates (see Fig. 5, curve *2*). From Fig. 5 it follows that: 1) the rate of RVT consumption is an order of magnitude higher than W_i; 2) the order of the reaction in W_i determined from the slope of curve *2* is equal to 0.7 ($W_{RVT} \sim (W_i)^{0.7}$). These data is an evidence in favor of the chain mechanism of RVT consumption (the chain length $\nu = |d[RVT]/dt|/W_i \sim$ ~ 10—100). In the absence of oxygen, the mechanism of the thiol—ene process in an excess of glutathione can be represented by the following reactions (Scheme 1).

According to Scheme 1, the rate of RVT consumption $W_{RVT} \sim (W_i)^{0.5}$. Under aerobic conditions, the RVT*• radicals can add O_2, while the resulting peroxyl radicals can be involved in the chain termination. Apparently, the proportionality $W_{RVT} \sim (W_i)^{0.7}$ observed in the experiment can be explained by this circumstance, since all the reactions were conducted in air. It is possible that the autocatalytic unfolding of the reaction of RVT with cysteine (see Fig. 4), which is much more active than glu-

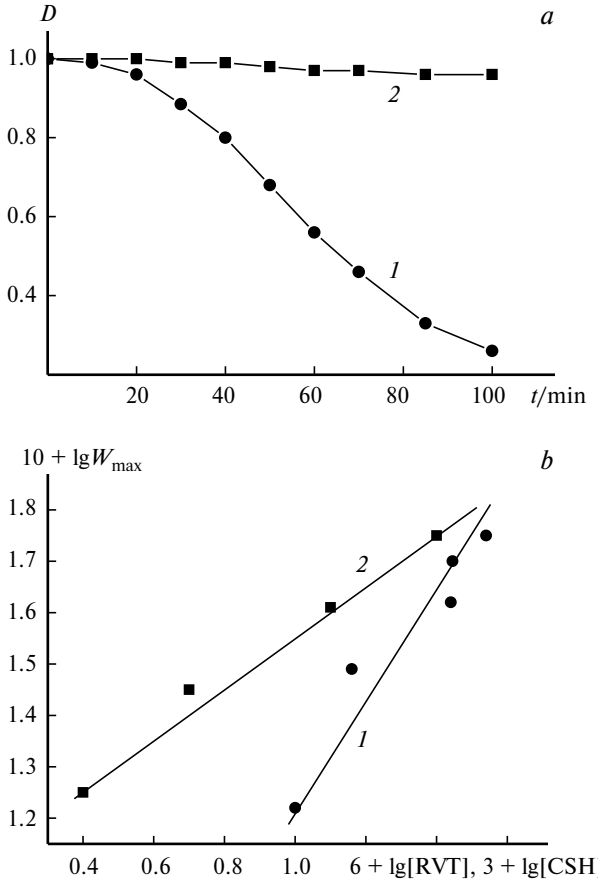


Fig. 4. (*a*) Kinetic curves of the consumption of RVT in the reaction with 25 mmol L^{-1} of cysteine (*1*) and glutathione (*2*). (*b*) The dependence of the maximum rate of RVT consumption (W_{max}) on the concentrations of CSH (*1*) at [RVT] = = 0.032 mmol L^{-1} and on the concentrations of RVT (*2*) at [CSH] = 25 mmol L^{-1}, 37 °C, an aqueous solution.

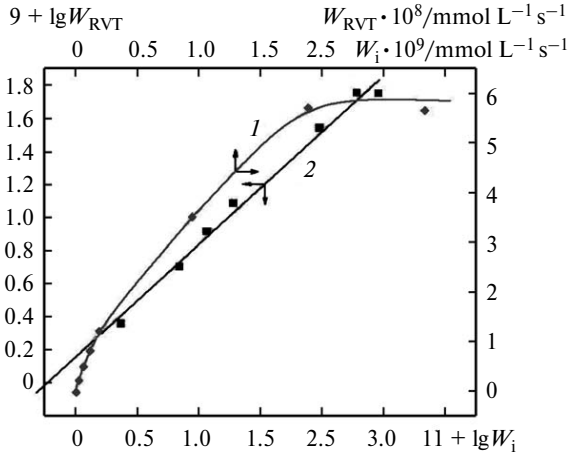
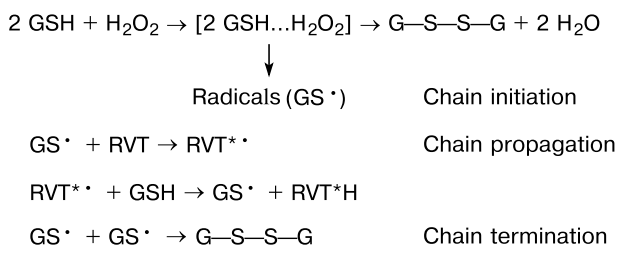


Fig. 5. The dependence of the rate of RVT consumption (W_{RVT}) on the initiation rate (W_i) in normal (*1*) and logarithmic (*2*) coordinates; an aqueous medium, 37 °C. [RVT] = $2 \cdot 10^{-5}$ mol L^{-1}, [GSH] = 5 mmol L^{-1}, [H_2O_2] = 0.22—27 mmol L^{-1}.

Scheme 1



RVT*• is an alkyl radical resulting from the addition of the thiyl radical to the double bond of resveratrol.

tathione in the reactions with oxygen and radicals, is also caused by the effect of oxygen, which generates radicals and then hydrogen peroxide in the reactions:

$$CSH + O_2 \rightarrow CS^{\bullet} + HO_2^{\bullet}$$

$$HO_2^{\bullet} + HO_2^{\bullet} \rightarrow H_2O_2 + O_2$$

The formation of H_2O_2 increases the rate of initiation in the system RVT—CSH and, consequently, the rate of resveratrol consumption. The studies of the thiol—ene reactions under anaerobic conditions, as well as the influence of oxygen and medium on the rate and mechanism of these important for bioantioxidants reactions, is the subject of our future research.

In conclusion, we found that resveratrol reacts with peroxyl radicals in aqueous media. The reaction rate constant was determined ($(1.1\pm0.1)\cdot10^5$ mol^{-1} L s^{-1}), which is similar to the values obtained in oxidizing styrene[25,26] and characterizes RVT as a medium strength inhibitor. It was established for the first time that resveratrol actively reacts with cysteine in aqueous solutions. The reaction with glutathione is slower and accelerates with the addition of hydrogen peroxide. The thiol-ene reaction with resveratrol follows a chain mechanism with a chain length of several dozen. These results may be important for understanding the physiological role of thiols in the overall oxidation process.

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