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Antioxidant Activity of 2-Methyl-1,3-benzoxazol-6-ol

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Abstract—Antioxidant effect of 2-methyl-1,3-benzoxazol-6-ol in radical chain oxidation of organic compounds with molecular oxygen was studied. Antiradical activity in the reaction with stable diphenylpicrylhydrazyl radical was examined by photocolorimetry. The kinetic parameters of the reaction of 2-methyl-1,3-benzoxazol-6-ol with peroxy radicals of different natures were determined by volumetric and chemiluminescence methods. A relation was found between the antioxidant activity and electronic structure parameters calculated by quantum-chemical methods. Factors responsible for differences in chemiluminescence in the oxidation of organic substances with different polarities in the presence of the title compound were analyzed.

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Inhibition of radical chain oxidation of organic substances and materials based thereon via addition of antioxidant is a quite significant problem from both practical and theoretical viewpoints [1]. Phenol derivatives occupy an important place among inhibitors of oxidation of organic compounds. Sterically hindered monohydric phenols have been studied most thoroughly, and they belong to a group of laboratory and industrial antioxidants. In the recent time, increased interest is attracted by unhindered phenols which constitute the base of natural antioxidants. The most promising but poorly studied as antioxidants are heterocyclic phenols; they are interesting due to their pronounced physiological activity and broad synthetic potential [2].

The present study was aimed at elucidating specificity of the antioxidant effect of 2-methyl-1,3-benzoxazol-6-ol (**I**) in liquid-phase oxidation of ethylbenzene, isopropylbenzene, and methyl ethyl ketone. The activity of compound **I** in the reaction with stable colored 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical was examined by photocolorimetry. Compound **I** was found to react with DPPH in nonpolar organic solvents, benzene and hexane. Regardless of the solvent nature, the reaction was of first order with respect to the substrate and DPPH, and the reaction rate is given by the equation $W = k[\mathrm{DPPH}][\mathbf{I}]$. The rate constants calculated using the above equation were 5.6 ± 0.2 and 1.80 ± 0.07 $\mathrm{l\,mol^{-1}\,s^{-1}}$ in hexane and benzene, respectively. The antiradical activity of compound **I** turned out to be somewhat higher than that of standard antioxidant Ionol [peroxy radical acceptor; $k = 1.50\pm0.06$ and 0.27 ± 0.01 $\mathrm{l\,mol^{-1}\,s^{-1}}$ in hexane and benzene, respectively]. In going from hexane to benzene the reaction rate constant decreases, presumably due to the known ability of DPPH to form π-complexes with aromatic hydrocarbons. Insofar as 2-methyl-1,3-benzoxazole having no hydroxy group does not react with DPPH, we can state with certainty that the reaction center in the 2-methyl-1,3-benzoxazol-6-ol (**I**) molecule is the hydroxy group.

The reactivity of 2-methyl-1,3-benzoxazol-6-ol (**I**) toward radicals determines its antioxidant properties in the radical-initiated oxidation of ethylbenzene. Addition of compound **I** to the reaction mixture in the oxidation of ethylbenzene inhibits the process. The kinetic curves for oxygen absorption in the presence of **I** (Fig. 1) clearly displayed an induction period (τ) whose duration is directly proportional to the concentration of compound **I**; this indicates oxidation chain termination as a result of reaction with peroxy radicals derived from ethylbenzene.

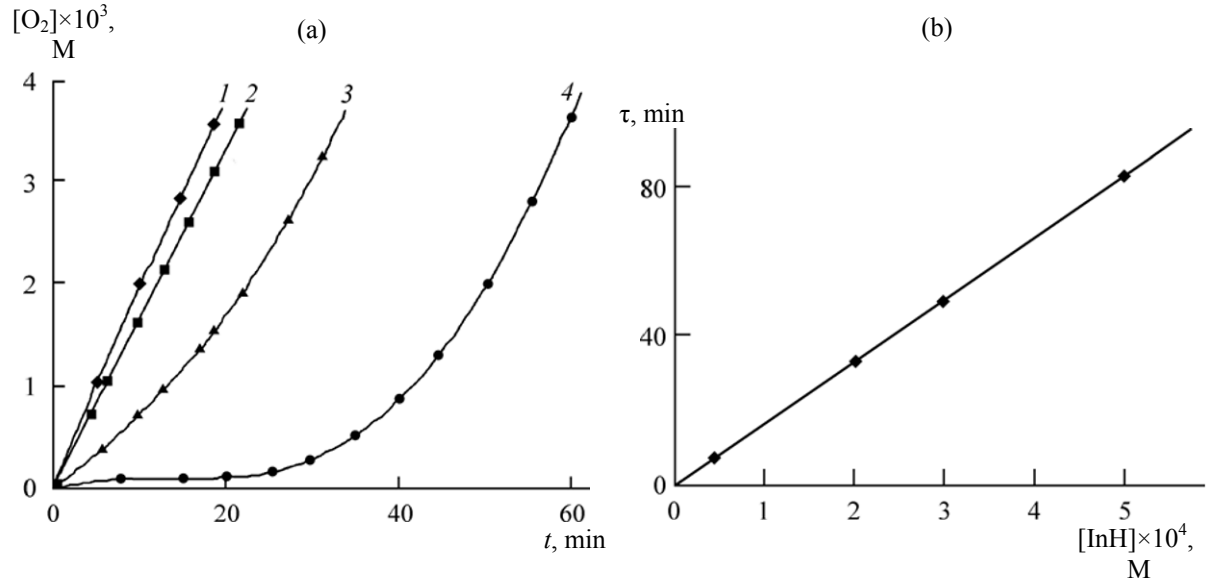


Fig. 1. (a) Kinetic curves for oxygen absorption in the radical-initiated oxidation of ethylbenzene (*1*) in the absence of inhibitor and (*2–4*) in the presence of 2-methyl-1,3-benzoxazol-6-ol (**I**); [InH] × 10^4, M: (*2*) 0.1, (*3*) 0.5, (*4*) 2.0; (b) dependence of the induction period on the concentration of 2-methyl-1,3-benzoxazol-6-ol (**I**); $W_i = 2 \times 10^{-7}$ mol l^{-1} s^{-1}, 343 K.

2-Methyl-1,3-benzoxazol-6-ol (**I**) also showed antioxidant activity in high-temperature autooxidation of ethylbenzene (Fig. 2); however, in this case the inhibition efficiency was lower than in the presence of Ionol; this may be related to unproductive consumption of compound **I**.

A direct proof for the fact that 2-methyl-1,3-benzoxazol-6-ol (**I**) does react with peroxy radicals derived from ethylbenzene was obtained by the chemiluminescence method. Chemiluminescence (I_0) appears due to recombination of peroxy radicals during oxidation of organic substances.

$$RO_2^{\cdot} + RO_2^{\cdot} \xrightarrow{k_6} [ROOOOR] \longrightarrow R{=}O^* \longrightarrow R{=}O + h\nu. \quad (1)$$

Addition of compound **I** to the reaction mixture in the oxidation of ethylbenzene leads to sharp reduction in the chemiluminescence intensity, i.e., inhibitor **I** reacts with substrate peroxy radicals. This effect becomes stronger as the inhibitor concentration increases (Fig. 3). The kinetic parameters for the reaction of hydroxybenzoxazole **I** with peroxy radicals were calculated using Eq. (2) [3] and were compared with the corresponding values obtained by volumetric analysis (Table 1).

$$\left[\frac{\partial(I/I_0)}{\partial t}\right]_{max} = 0.22 \frac{k_7}{\sqrt{k_6}} \sqrt{W_i}. \quad (2)$$

The rate constants determined by different methods differed from each other. The chemiluminescence data should be considered to be more accurate, for the corresponding procedure is less complicated by possible side processes with participation of antioxidant. The obtained data indicate that the reaction center in molecule **I** in the reaction with peroxy radicals, as with DPPH, is the hydroxy group in the benzene ring.

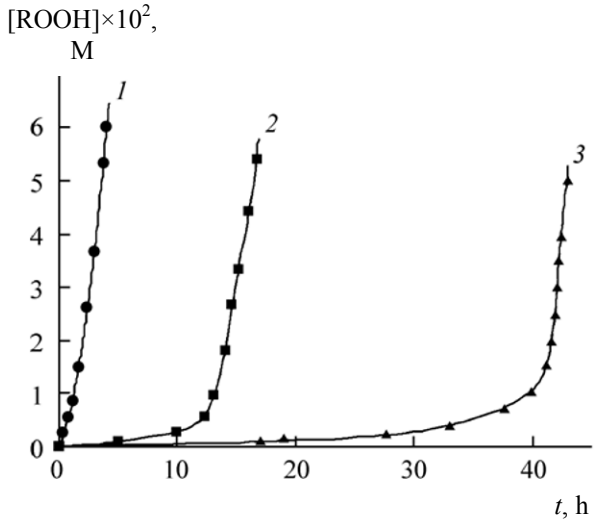


Fig. 2. Kinetic curves for accumulation of hydroperoxide in the oxidation of ethylbenzene (*1*) in the absence of inhibitor and in the presence of (*2*) 2-methyl-1,3-benzoxazol-6-ol (**I**) and (*3*) Ionol; [InH] = 1.25×10^{-4} M, 393 K.

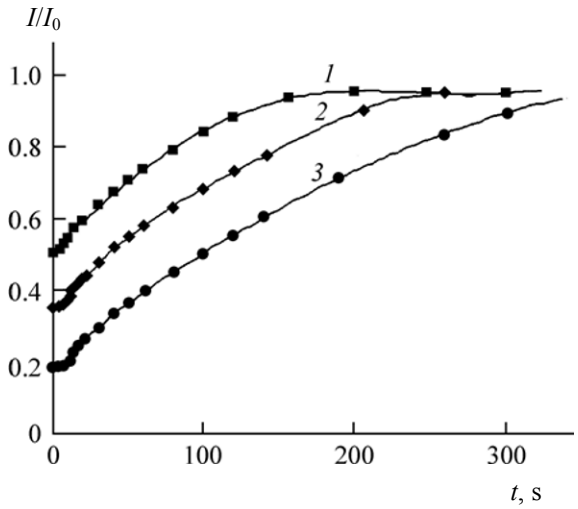
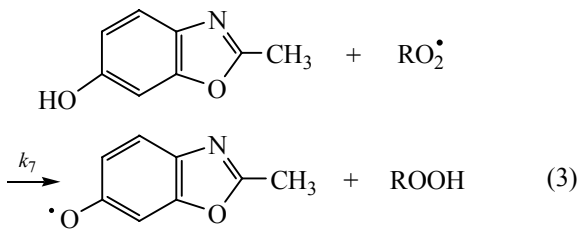


Fig. 3. Variation of the relative chemiluminescence intensity in the initiated oxidation of ethylbenzene in the presence of 2-methyl-1,3-benzoxazol-6-ol (**I**); $c_{\mathbf{I}}$, M: (*1*) 1×10^{-5}, (*2*) 2×10^{-5}, (*3*) 3×10^{-5}; $W_i = 5.4 \times 10^{-7}$ mol l^{-1} s^{-1}, 343 K.



(3)

On the basis of the k_7 values for 2-methyl-1,3-benzoxazol-6-ol at different temperatures (333–353 K) we calculated the Arrhenius activation parameters and obtained the general equation for the rate constant:

$$k_7 = (9.6 \pm 0.5) \times 10^8 \exp - [(27400 \pm 800)/RT]\ \text{l mol}^{-1}\ \text{s}^{-1}.$$

The resulting values were consistent with those typical of phenol type inhibitors, which confirms the proposed mechanism of antioxidant action of compound **I**.

Table 1. Parameters[a] of antioxidant effect of 2-methyl-1,3-benzoxazol-6-ol (**I**), Ionol, and phenol in the radical-initiated oxidation of ethylbenzene; $W_i = 5.4 \times 10^{-7}$ mol l^{-1} s^{-1}, temperature 343 K

Compound	Stoichiometric inhibition coefficient	$k_7 \times 10^{-4}$, l mol^{-1} s^{-1}
2-Methyl-1,3-benzoxazol-6-ol	2.0 (2.1)	3.40±0.03 (6.50±0.07)
Ionol	2.0 (2.0)	5.0±0.4 (5.00±0.25)
Phenol	0.3 (0.3)	0.60±0.02 (0.60±0.01)

[a] According to volumetric data. The data obtained by the chemiluminescence method are given in parentheses.

We also examined antioxidant properties of compound **I** toward different peroxy radicals and determined specificity of chemiluminescence in different substrates. The kinetic curves for chemiuminescence in the oxidation of both ethylbenzene and isopropylbenzene in the presence of 2-methyl-1,3-benzoxazol-6-ol (**I**) conform to a classical shape (Figs. 3, 4a). The oxidation of methyl ethyl ketone in the presence of compound **I** was characterized by deviation from the classical pattern: the chemiluminescence intensity increased in the initial part of the induction period (Fig. 4b). These findings may be rationalized assuming that the process is accompanied by one more reaction involving compound **I** or the corresponding radical, which also gives rise to chemiluminescence. Most probably, such reaction is combination of peroxy radicals derived from methyl ethyl ketone and radicals derived from the inhibitor.

$$RO_2^{\cdot} + PhO^{\cdot} \xrightarrow{k_8} \text{Reaction products.} \qquad (4)$$

To identify the source of additional chemiluminescence in the oxidation of methyl ethyl ketone in the presence of 2-methyl-1,3-benzoxazol-6-ol (**I**) as inhibitor, we examined the effects of different factors: nature of the emission activator, nature and concentration of initiator, and the presence of oxygen. No increase in chemiluminescence intensity was observed in the absence of initiator or oxygen, and the chemiluminescence intensity did not depend on the nature of initiator. Increase in the initiator concentration was accompanied by rise in chemiluminescence intensity. The above data suggest that a new chemiluminescence emitter appears with participation of peroxy radicals.

The dependence shown in Fig. 5 supports the assumption that reaction (4) is responsible for additional chemiluminescence in the examined system. At an inhibitor concentration exceeding 7.5×10^{-5} M the ΔI value approaches a constant value (Fig. 5, curve *1*); this means that at an antioxidant concentration higher than a certain value decay of all peroxy radicals follows reaction (3), so that chemiluminescence may result only from reaction (4). At a lower antioxidant concentration both recombination of peroxy radicals [reaction (1)] and reaction (4) contribute to the overall chemiluminescence. In this case, proceeding from the kinetic scheme of inhibited oxidation and stationary state, we arrived at:

$$(d[RO_2^{\cdot}])/dt = W_i - k_6[RO_2^{\cdot}]^2 - k_7[RO_2^{\cdot}][PhOH] - k_8[RO_2^{\cdot}][PhO^{\cdot}] = 0;$$

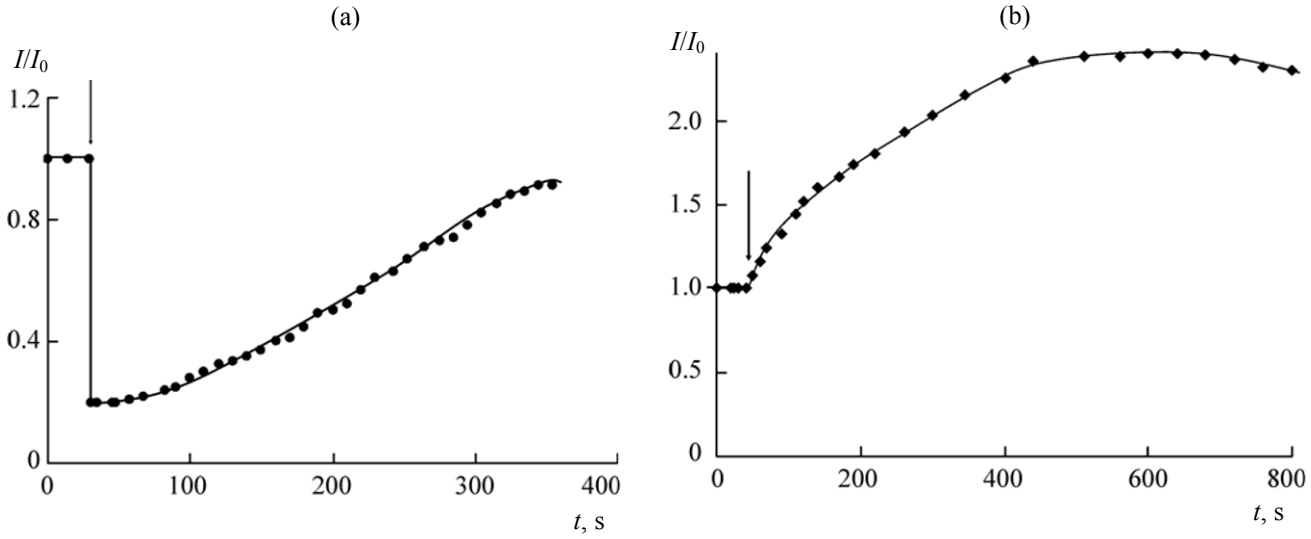


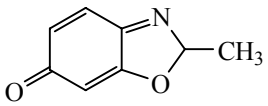
Fig. 4. Variation of the relative chemiluminescence intensity in the AIBN-initiated oxidation of (a) isopropylbenzene and (b) methyl ethyl ketone in the presence of 3×10^{-5} mol l^{-1} of 2-methyl-1,3-benzoxazol-6-ol (**I**); $W_i = 5.4\times10^{-7}$ mol l^{-1} s^{-1}, 333 K, [DBA] = 3×10^{-4}

$$(d[PhO^-])/dt = k_7[RO_2^-][PhOH] - k_8[RO_2^-][PhO^\bullet] = 0.$$

Taking into account that $I = \eta_6 k_6[RO_2^\bullet]^2 + \eta_8 k_8[RO_2^\bullet][PhO^\bullet]$, the relative chemiluminescence intensity in the oxidation of hydrocarbons is given by Eq. (5):

$$\Delta I = \frac{\eta_8 - 2\eta_6}{2} W_i - \frac{k_6}{2(\eta_8 - 2\eta_6)k_7^2} \frac{\Delta I^2}{[InH]^2}. \qquad (5)$$

Here, $\Delta I = I - I_0$; I and I_0 are, respectively, the chemiluminescence intensities in the presence and in the absence of inhibitor; η_6 and η_8 are the chemiluminescence quantum yields of reactions (1) and (4), respectively; k_6 and k_7 are the rate constants of reactions (1) and (3), respectively; and W_i is the rate of formation of free radicals. Insofar as the experimental data fit a linear relation in the coordinates $\Delta I = f(\Delta I^2/[InH]^2)$ (Fig. 5, plot *2*), the proposed mechanism of chemiluminescence in the oxidation of methyl ethyl ketone in the presence of 2-methyl-1,3-benzoxazol-6-ol seems to be valid. Thus a new emitter is formed as a result of reaction (4). Most probably, such an emitter is iminoquinone **II** with the following structure.



II

This compound is formed in the singlet excited state. It is involved in hydrogen bonding with polar methyl ethyl ketone molecules present in the system and is thus converted into the excited triplet state [4], and the excitation energy is transferred to the activator.

$$RO_2^\bullet + PhO^\bullet \rightarrow P_s^* \xrightarrow{\text{Polar molecule}} P_t^* \rightarrow P + A^* \rightarrow A + h\nu.$$

In the oxidation of ethylbenzene and isopropylbenzene, iminoquinone **II** molecule in the excited singlet state is deactivated very rapidly; therefore, no chemiluminescence is observed in the induction period.

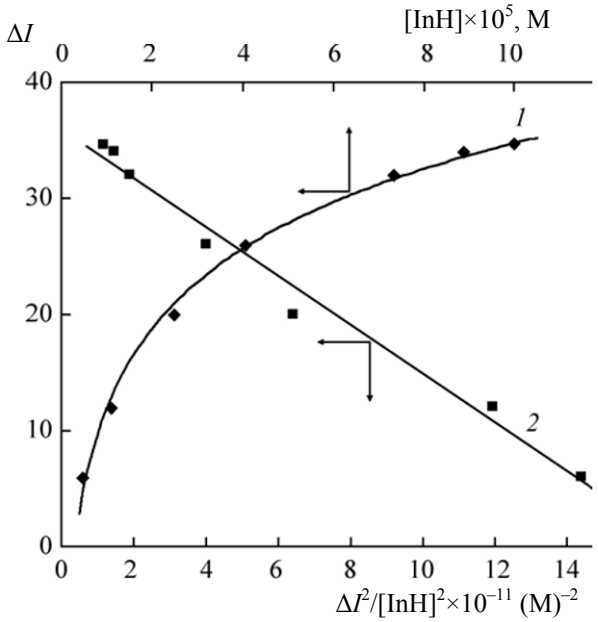


Fig. 5. Plots of ΔI vs. (*1*) concentration of 2-methyl-1,3-benzoxazol-6-ol (**I**) and (*2*) $\Delta I^2/[InH]^2$ for the oxidation of methyl ethyl ketone; $W_i = 5.4\times10^{-7}$ mol l^{-1} s^{-1}, 333 K.

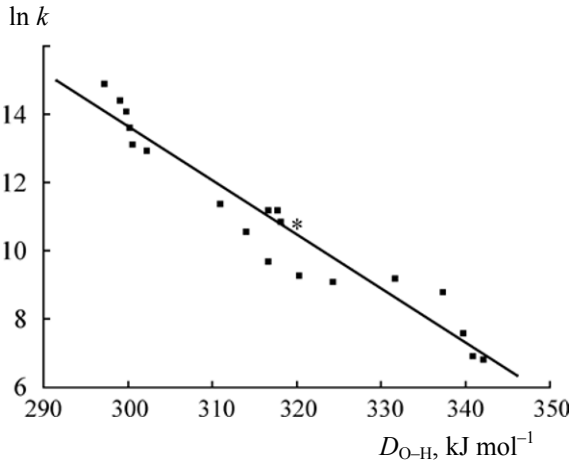


Fig. 6. Correlation between lnk_7 and O–H bond energy ($D_{O–H}$) in molecules of sterically unhindered phenols; the point corresponding to 2-methyl-1,3-benzoxazol-6-ol (**I**) is marked with an asterisk.

Table 2 contains the rate constants for the reactions of 2-methyl-1,3-benzoxazol-6-ol with different peroxy radicals, which were determined using classical equation (2) and Eq. (5). It is seen that k_7 decreases by more than an order of magnitude in going from ethylbenzene to isopropylbenzene. This may be attributed to the higher reactivity of *sec*-alkylperoxy radicals as compared to *tert*-alkylperoxy radicals.

Comparison of the kinetic parameters for the oxidation of ethylbenzene and methyl ethyl ketone shows that antioxidant **I** in nonpolar medium is slightly more efficient than in polar medium (Table 2). This may be related to the formation of hydrogen bonds between antioxidant and methyl ethyl ketone molecules.

We also tried to rationalize high reactivity of the examined antioxidant toward peroxy radicals $RO_2^{\cdot}$ in terms of the restricted and unrestricted Hartree–Fock approximations. Using AM1 semiempirical method we determined one of the most important electronic structure parameters of molecule **I** and phenol molecule, the energy of the O–H bond ($D_{O–H}$). The OH bond in 2-methyl-1,3-benzoxazol-6-ol turned out to be much weaker than in phenol ($D_{O–H}$ 321.67 and 363.83 kJ mol^{-1}, respectively); just this factor is most likely to be responsible for the higher reactivity of compound **I** compared to phenol. The O–H bond in molecule **I** is weakened due to donor effect of the five-membered heterocycle fused to the benzene ring.

Table 2. Rate constants for reactions of 2-methyl-1,3-benzoxazol-6-ol with peroxy radicals derived from different substrates, $W_i = 5.4 \times 10^{-7}$ mol l^{-1} s^{-1}, [DBA] = 3×10^{-4} M

Substrate	Temperature, K	k_7, l mol^{-1} s^{-1}
Ethylbenzene	343	$(6.50 \pm 0.07) \times 10^4$
Ethylbenzene	333	$(4.8 \pm 0.2) \times 10^4$
Isopropylbenzene	343	$(4.4 \pm 0.2) \times 10^3$
Methyl ethyl ketone	333	$(1.70 \pm 0.09) \times 10^4$

The calculated O–H bond energies were verified by plotting a correlation between ln k_7 and $D_{O–H}$ values known for sterically unhindered phenols [5]. The correlation included the kinetic data for phenols studied experimentally by other authors [6]. As follows from Fig. 6, the point for 2-methyl-1,3-benzoxazol-6-ol fits that correlation, indicating applicability of the latter for a wide series of phenolic compounds, including heterocyclic ones.

To conclude, 2-methyl-1,3-benzoxazol-6-ol (**I**) is an effective inhibitor of oxidation of organic compounds. Its antioxidant effect involves termination of radical chains via reaction with peroxy radicals derived from substrate, and it follows general relations intrinsic to inhibitory effect sterically unhindered phenols. Specificity of chemiluminescence in the oxidation of organic compounds with different polarities in the presence of 2-methyl-1,3-benzoxazol-6-ol (**I**) was determined.

EXPERIMENTAL

Compounds necessary for our study were synthesized and identified at the Chemistry of Biologically Active Substances Department, Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine.

The reaction kinetics were studied by volumetric (following oxygen absorption, chemiluminescence (following luminescence intensity; FEU-38 multiplier), photocolorimetric (KFK-3 photometer), and iodometric methods (autooxidation). Azobis(isobutyronitrile) (AIBN) was used as radical initiator. The rate of initiation W_i was calculated with account taken of the thermal decomposition constant of AIBN [1]. Dibromoanthracene was used s activator in chemiluminescence studies. The reagents used were purified according to known procedures [5, 7].

The antioxidant activity of inhibitors (InH) was quantitatively characterized by induction period τ,

stoichiometric inhibition coefficient, and rate constant k_7 for its reaction with peroxy radicals $RO_2^{\cdot}$ derived from the substrate.

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