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Antioxidant Activity of Uracil Derivatives

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Abstract—The antiradical properties of a number of uracil derivatives are studied in initiated 1,4-dioxane oxidation as a model reaction. The antioxidant activity of the uracil derivatives as inhibitors is estimated. The antiradical activity of the compounds is quantitatively characterized in terms of the effective rate constant of inhibition, fk_{In}.

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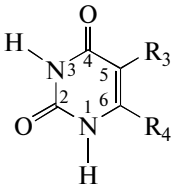
Some pyrimidine derivatives, such as 6-methyluracil, 5-fluorouracil, and 5-hydroxy-6-methyluracil, are medicines with a rather wide range of action. For example, 6-methyluracil is known as an antiulcerous drug and is also used in the treatment of hepatitis and pancreatitis [1, 2]. These and many other drugs are antioxidants (AOs), which is another indication of their biological activity. In addition, it is known that the pharmacological effect of many drugs often correlates with their antioxidant activity [3–7]. Therefore, determination of the quantitative characteristics of potential drugs as antioxidants is of importance.

In the present work, the kinetic laws of the inhibition effect of a number of uracils were studied and the effective inhibition rate constants of initiated 1,4-dioxane oxidation as a model reaction were measured.

The compounds with the following general formula were used as antioxidants:



where $R_3 = OH$, $R_4 = CH_3$ (**I**); $R_3 = Br$, $R_4 = CH_3$ (**II**); $R_3 = NH_2$, $R_4 = CH_3$ (**III**); $R_3 = NO_2$, $R_4 = CH_3$ (**IV**); $R_3 = N$-methylpiperidine, $R_4 = CH_3$ (**V**) and $R_3 = N$-methylmorpholine, $R_4 = CH_3$ (**VI**).

EXPERIMENTAL

The antiradical properties of the uracil derivatives were studied for the initiated radical chain oxidation of 1,4-dioxane as a model reaction under kinetic control at 348 K. Azobisisobutyronitrile (AIBN) was used as the initiator of the oxidation process. The quantitative characteristic of antiradical activity was the effective inhibition constant fk_{In}, where f is the inhibitor capacity equal to the number of radical intermediates that decay on one inhibitor molecule in the chain termination events and k_{In} is the rate constant for oxidation chain termination on the inhibitor [8]. The values of fk_{In} were determined by estimating the influence of uracil on the oxidation rate of a model substrate. The measurements were carried out using the multipurpose manometric differential setup described in detail in [9].

Uracil and its derivatives absorb UV light. For this reason, the stoichiometric inhibition coefficient was measured (for 5-hydroxy-6-methyluracil as an example) by spectrophotometry on a Shimadzu UV-2401PC spectrophotometer. The inhibitor disappearance kinetics was studied under 1,4-dioxane oxidation conditions at a wavelength of 279 nm, at which uracil showed the highest absorbance.

The initiation rate was calculated using the equation $V_i = k_i[\text{AIBN}]$, where k_i is the initiation rate constant. It was assumed in the calculation of the initiation rate that $k_i = 2ek_d$, where k_d is the rate constant for AIBN decomposition, and e is the probability of radical escape to the bulk. Reference data on AIBN decomposition in cyclohexanol [10–12] were used in the calculation of the AIBN decomposition rate,

$$\log k_d = 17.70 - 35/(4.575T \times 10^{-3}), \quad e = 0.5.$$

1,4-Dioxane was purified using a standard procedure [13]. AIBN was twice recrystallized from freshly distilled ethanol and dried in vacuo.

RESULTS AND DISCUSSION

The antiradical activity of six uracil derivatives (**I**–**VI**) was studied for initiated 1,4-dioxane oxidation as the model reaction. Under standard experimental conditions, the initiated oxidation of 1,4-dioxane is

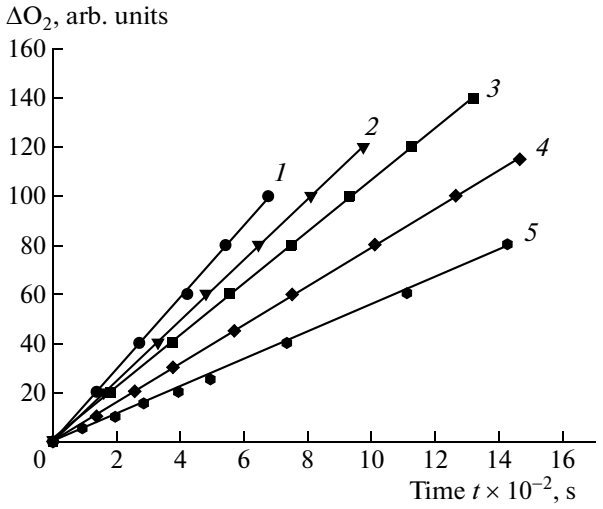


Fig. 1. Typical oxygen uptake kinetics in 1,4-dioxane oxidation in the presence of 5-amino-6-methyluracil (**III**) at concentrations of (*1*) 0, (*2*) 0.5×10^{-4}, (*3*) 0.75×10^{-4}, (*4*) 1.25×10^{-4}, and (*5*) 1.75×10^{-4} mol/l; $V_i = 1 \times 10^{-7}$ mol l^{-1} s^{-1}, 348 K.

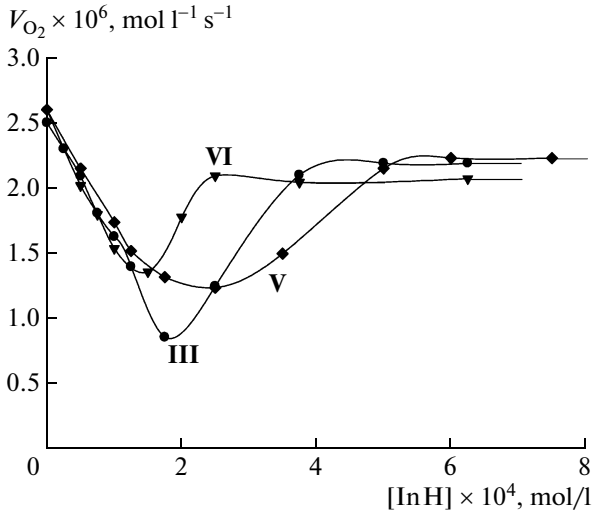


Fig. 2. Initial oxygen uptake rate in 1,4-dioxane oxidation versus the concentration of compounds **III**, **V**, and **VI**; $V_i = 1 \times 10^{-7}$ mol l^{-1} s^{-1}, 348 K.

kinetically controlled and proceeds via a radical chain mechanism with quadratic chain termination (VI). It includes a number of elementary steps[1] common for most organic compounds [8, 11, 14]:

$$I \rightarrow 2r^{\bullet}, \quad r^{\bullet} + RH \rightarrow rH + R^{\bullet}, \qquad \text{(i)}$$

$$R^{\bullet} + O_2 \rightarrow RO_2^{\bullet}, \qquad \text{(I)}$$

$$RO_2^{\bullet} + RH \rightarrow ROOH + R^{\bullet}, \qquad \text{(II)}$$

$$ROOH \rightarrow RO^{\bullet} + HO^{\bullet}, \qquad \text{(III)}$$

$$RO_2^{\bullet} + RO_2^{\bullet} \rightarrow Pr_2. \qquad \text{(VI)}$$

In the presence of an inhibitor, the chain termination on the $RO_2^{\bullet}$ radical takes place via the reactions

$$RO_2^{\bullet} + InH \rightarrow ROOH + In^{\bullet}, \qquad \text{(VII)}$$

$$RO_2^{\bullet} + In^{\bullet} \rightarrow Pr, \qquad \text{(VIII)}$$

$$In^{\bullet} + RH \rightarrow InH + R^{\bullet}. \qquad \text{(X)}$$

Here, I is the initiator; RH is the oxidation substrate; InH is the inhibitor; Pr is the molecular product; $R^{\bullet}$ and $RO_2^{\bullet}$ are alkyl and peroxyl radicals of 1,4-dioxane, respectively; and $R^{\bullet} = C_4H_7O_2$.

The introduction of an uracil derivative into the model system decreases the rate of 1,4-dioxane oxidation via chain termination on molecules of these substances (reactions (VII) and (VIII)) [9, 14]. The typical oxygen uptake kinetics in the absence and in the presence of compound **III** as an example are shown in Fig. 1. It was established earlier [15] that a hydrogen atom is detached from the weaker, N1–N bond of uracil to form a nitrogen-centered radical, which then interacts with the peroxyl radical of 1,4-dioxane via reaction (VIII).

The initial oxygen uptake rates under the inhibition conditions were derived from the kinetic curves. The initial 1,4-dioxane oxidation rates and the chain lengths at different concentrations of some uracils are listed in Table 1.

The dependence of the initial rate of initiated 1,4-dioxane oxidation on the concentration of any uracil is complicated. These data for compounds **III**, **V**, and **VI** are plotted in Fig. 2. It can be seen that the initial rate of 1,4-dioxane oxidation first decreases as the inhibitor concentration is increased to a certain value, indicating that the compounds considered exert an inhibition effect and that reaction (VII) takes place. As [InH] is further raised (above the extremum value), the initial rate of 1,4-dioxane oxidation, which probably indicates the inversion of the properties of the inhibitor and the occurrence of competing reaction (X): at uracil concentrations higher than 0.2 mmol/l, the rate of reaction (X) exceeds that of reaction (VII); i.e., chain transfer to the inhibitor occurs [11]. At inhibitor concentrations higher than 0.4 mmol/l, the initial rate of 1,4-dioxane oxidation becomes constant and close to the rate of uninhibited oxidation.

The 1,4-dioxane oxidation rate in the presence of an inhibitor is described by Eq. (1), which is valid for low inhibitor concentrations at which the chain mech-

[1] The elementary step numbering used here is traditional for oxidation mechanisms.

Table 1. Dependences of the initial 1,4-dioxane oxidation rate (V_0), chain length (ν), and inhibition efficiency (F) on the uracil concentration ($V_i = 1 \times 10^{-7}$ mol l^{-1} s^{-1}, 348 K)

Parameter	Uracil	[InH] × 10^4, mol/l							
		0.0	0.25	0.5	0.75	1.0	1.25	1.5	2.5
$V_0 \times 10^6$, mol l^{-1} s^{-1}	**I**	2.15	1.62	1.47	–	1.33	–	–	1.11
	II	2.5	2.2	2.08	1.9	–	1.78	–	–
	V	2.6	–	2.15	–	1.8	1.52	–	1.24
	VI	2.6	–	2.02	1.8	1.54	–	1.36	–
ν	**I**	22	16	15	–	13	–	–	11
	II	25	22	21	19	–	18	–	–
	V	26	–	22	–	18	15	–	12
	VI	26	–	20	18	15	–	14	–
F	**II**	0	0.17	0.36	0.55	–	0.72	–	–
	III	0	0.10	0.36	0.66	0.82	1.01	–	–
	IV	0	0.17	0.29	–	0.46	–	0.63	–
	VI	0	–	0.51	0.75	1.10	–	1.54	–

anism of oxidation persists [8, 16]. In our experiments, this requirement is fulfilled (Table 1).

$$F = \frac{V_0^0}{V_0} - \frac{V_0}{V_0^0} = fk_{\text{In}}[\text{AO}]/\sqrt{2k_6V_\text{i}}, \qquad (1)$$

where V_0^0 and V_0 are the initial oxygen uptake rates in 1,4-dioxane oxidation in the absence and in the presence of an inhibitor, respectively; [AO] is the concentration of the added antioxidant; and k_{In} and $2k_6$ are the rate constants of oxidation chain termination on the inhibitor and quadratic chain termination on the peroxyl radicals of the substrate, respectively [11, 14].

For the compounds examined, this relationship is satisfactorily valid in the $[\text{InH}] \le [\text{InH}]_{\min}$ concentration range (correlation coefficient of $R = 0.98$–0.99). The plots shown in 3 plots visualize this relationship for some of the compounds. The effective inhibition rate constants found at $2k_6 = 6.73 \times 10^7$ l mol^{-1} s^{-1} [11] and $V_\text{i} = 1 \times 10^{-7}$ mol l^{-1} s^{-1} are given in Table 2. An analysis of data from other works [15, 17, 18] indicates that the reactivities of the uracil derivatives toward structurally different radicals are similar. The uracils should be classified as inhibitors of medium reactivity, like ionol (Table 2).

For compounds **I**–**IV**, the dependence of the effective inhibition rate constant on the uracil structure is satisfactorily described by the Taft equation [19]:

$$\log k_{\text{In}} = \log k_0 + \rho\sigma^* \ (R = 0.99).$$

From the plot shown in Fig. 4, obtained by least-squares fitting, we derived $\rho = -(7.05 \pm 1.2) \times 10^{-2}$ and $\log k_0 = (4.38 \pm 0.1)$. The negative value of ρ indicates that the antioxidant power of uracil increases on passing from electron-withdrawing to electron-donating substituents.

The dependence of the disappearance rate of the inhibitor 5-hydroxy-6-methyluracil on its concentration was studied to determine the stoichiometric inhi-

Table 2. Effective rate constants for the reaction of the peroxyl radical of 1,4-dioxane with various uracils ($V_i = 1 \times 10^{-7}$ mol l^{-1} s^{-1}, 348 K)

Compound	$fk_{\text{In}} \times 10^{-3}$, l mol^{-1} s^{-1}
I	17.0 ± 2.0
II	14.6 ± 1.6
III	21.0 ± 2.0
IV	12.0 ± 1.3
V	19.0 ± 2.0
VI	27.0 ± 3.0
Ionol*	10.0 ± 1.2
6-Aminouracil**	18.0 ± 3.0
5-Bromouracil**	13.0 ± 2.0
5-Fluorouracil**	12.0 ± 2.0
5-Nitro-6-methyluracil**	5.0 ± 0.5
6-Methyluracil**	8.0 ± 1.2
Uracil**	30.3 ± 4.1

*Data rom [18].

**Data from [15, 17]. $V_i = 4 \times 10^{-7}$ mol l^{-1} s^{-1}, 348 K, isopropyl alcohol as an oxidation substrate.

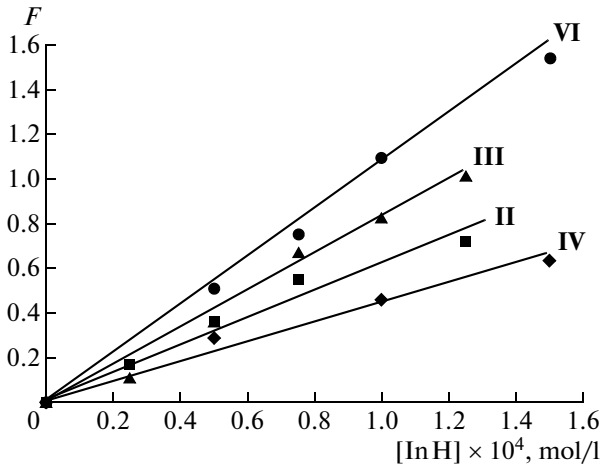


Fig. 3. Inhibition efficiency F versus the concentration of **II**, **III**, **IV**, and **VI**; $V_i = 1 \times 10^{-7}$ mol l^{-1} s^{-1}, 348 K.

bition coefficient. By monitoring the variation of the concentrations of compound **I**, we found that the initial rate of 5-hydroxy-6-methyluracil disappearance increases linearly in the concentration range from 1.7×10^{-5} to 8.3×10^{-5} mol/l (Fig. 5). This indicates that the reaction is first-order with respect to the inhibitor concentration. It was shown previously that the initiated oxidation of 1,4-dioxane at $T = 348$ K and $V_i = 1 \times 10^{-7}$ mol l^{-1} s^{-1} proceeds via a chain mechanism (Table 1) in which chain termination is mainly due to reaction (VI). In this case, the inhibitor disappearance rate is given by the first-order differential equation

$$V = -\frac{d[InH]}{dt} = \frac{k_{In}}{\sqrt{2k_6}}[InH]\sqrt{V_i}. \quad (2)$$

It follows from Eq. (2) that

$$\tan\alpha = \frac{k_{In}}{\sqrt{2k_6}}\sqrt{V_i},$$

where k_{In} is the rate constant for the reaction of peroxyl radicals with 5-hydroxy-6-methyluracil. The inhibition rate constant was calculated from the dependence of the initial disappearance rate of compound **I** on its initial concentration in the range from 1.7×10^{-5} to 8.3×10^{-5} mol/l. The initial disappearance rate was $k_{In} = (8.6 \pm 0.5) \times 10^3$ l mol^{-1} s^{-1}. The constant k_{In} should be treated as an effective quantity because the N–H bond of uracil forms a hydrogen bond with an oxygen atom of 1,4-dioxane.

It was found earlier (Table 2) that $fk_{In} = 17.0 \times 10^3$ l mol^{-1} s^{-1}. Therefore, the stoichiometric inhibition coefficient is $f = 2$. It can be assumed that $f = 2$ for the structurally similar compounds **II**–**VI** as well.

CONCLUSIONS

The antiradical properties of the following uracil derivatives were studied in initiated 1,4-dioxane oxidation: 5-hydroxy-6-methyluracil (**I**), 5-bromo-6-methyluracil (**II**), 5-amino-6-methyluracil (**III**), 5-nitro-6-methyluracil (**IV**), 5-(*N*-methylpiperidine)-6-methyluracil (**V**), and 5-(*N*-methylmorpholine)-6-methyluracil (**VI**).

At 348 K, the effective rate constants of the inhibition of 1,4-dioxane oxidation by compounds **I**, **II**, **III**, **IV**, **V**, and **VI** ($fk_{In} \times 10^{-3}$) are 17.0 ± 2.0, 14.5 ± 1.6, 21.0 ± 2.0, 12.0 ± 1.3, 19.0 ± 2.0, and 27.0 ± 3.0 l mol^{-1} s^{-1}, respectively.

The stoichiometric inhibition coefficient f is 2 for all of the compounds.

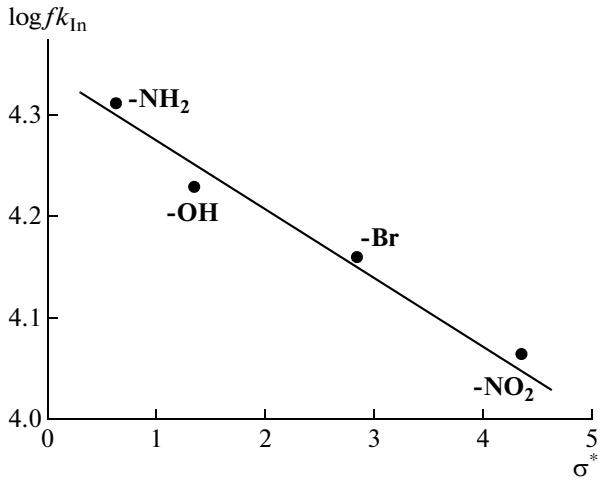


Fig. 4. Logarithm of the effective inhibition rate versus the Taft induction constant.

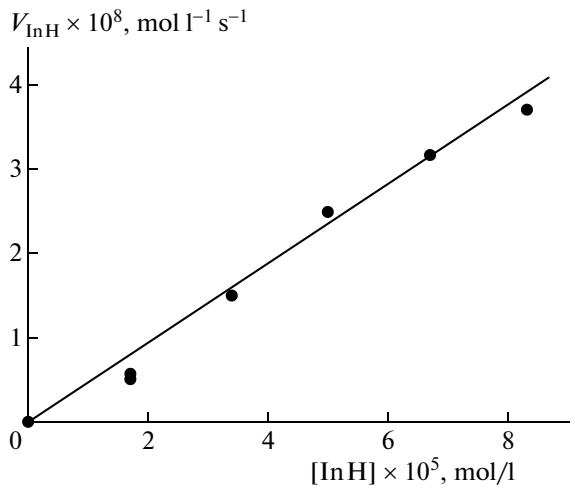


Fig. 5. Initial rate of the disappearance of compound **I** versus its initial concentration in 1,4-dioxane oxidation; $V_i = 1 \times 10^{-7}$ mol l^{-1} s^{-1}, 348 K.

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