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# 6-Amino-5-hydroxy-2,3-dimethylpyrimidin-4(3*H*)-one as an efficient inhibitor of free radical oxidation

**Stanislav A. Grabovskiy,* Yulia S. Grabovskaya, Arcadiy V. Antipin and Natalia N. Kabal'nova**

*Ufa Institute of Chemistry, Russian Academy of Sciences, 450054 Ufa, Russian Federation.*
*E-mail: stas_g@anrb.ru*

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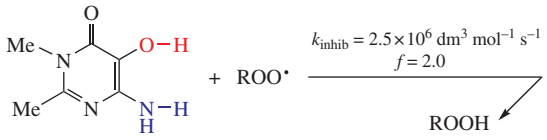
**6-Amino-5-hydroxy-2,3-dimethylpyrimidin-4(3*H*)-one inhibits initiated styrene oxidation with the same efficiency as vitamin E compounds. Calculations at M05/MG3S level of theory for the abstraction of a hydrogen atom by a peroxyl radical indicate an early transition state, which closely resembles a pre-reaction hydrogen bond-containing complex responsible for the high rate constant.**

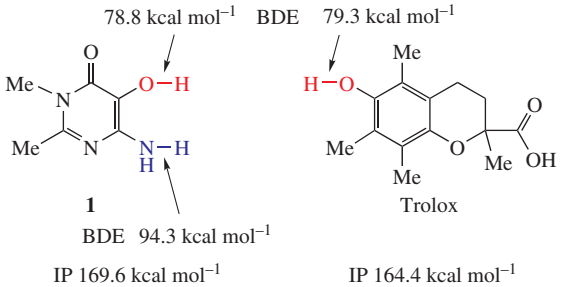



Inhibitors of free radical processes are extensively used in the chemical and food industries as well as in medicine and other areas. The majority of the inhibitors includes synthetic and natural phenols. The development of criteria for toxicity, stability and efficiency of the inhibitors requires a constant search for new substances of this class.[1]

In recent investigations of the antioxidant activity for 5-hydroxy- and 5-aminouracil derivatives, it has been found that these compounds inhibit free radical oxidation.[2–4] The 5-hydroxy derivatives are characterized by inhibition rate constants $k_{inhib}$ of (2.3–6.1)×10$^4$ dm$^3$ mol$^{-1}$ s$^{-1}$ and stoichiometric factor *f* of 1.0–2.0, whereas the 5-aminouracil derivatives have higher rate constants for their reactions with peroxyl radical, namely up to 10$^5$ dm$^3$ mol$^{-1}$ s$^{-1}$, and lower *f* values in the range of 0.08–0.70.[5] These characteristics are close to the values for undissociated forms of ascorbic acid derivatives, namely $k_{inhib}$ = 8.4×10$^4$ dm$^3$ mol$^{-1}$ s$^{-1}$ and *f* ≈ 1, and at the same time lower than the rate constants for the corresponding anions, *i.e.* 5.0×10$^7$ dm$^3$ mol$^{-1}$ s$^{-1}$.[6]

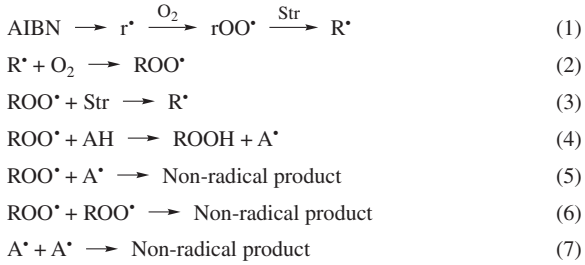
According to the current understanding,[1] the efficiency of a free radical inhibitor can be preliminarily estimated from the data on the ionization potential (IP) and the strength of the X–H bond attacked by a radical, where X is a heteroatom. It is discussed that the weaker an X–H bond, the higher the rate constant of reactions with peroxyl radicals, this assumption being useful for a preliminary analysis only.[1] For more reliable estimation, it is necessary to take into account the IP value, since compounds with low IP can be oxidized immediately by air oxygen.[1,6]

In this work, we used experimental and quantum-chemical methods to investigate the antioxidant properties of a non-aromatic inhibitor 6-amino-5-hydroxy-2,3-dimethylpyrimidin-4(3*H*)-one **1**. Our calculations of the bond dissociation energy (BDE) and IP at M06-2X/MG3S level of theory indicate that the efficiency of compound **1** as an inhibitor should be comparable to Trolox as an analogue of α-tocopherol. We have chosen Trolox for the calculation, since for α-tocopherol it is more time-consuming. α-Tocopherol was used further in our kinetic experiments as a reference inhibitor.




The antioxidative properties of compound **1**, namely the reactivity toward peroxyl radicals, were investigated using the classical method of initiated styrene oxidation in chlorobenzene at 37 °C.[7,8] Oxygen uptake was monitored by changing the pressure using a gas-absorption apparatus according to the known procedure.[2,5] Compound **1** was synthesized as described.[9]

In general, the oxidation of styrene (Str) initiated by AIBN and inhibited by compound **1** (AH), can be represented by the following set of reactions.[1,7,8]




The rate of oxygen consumption without an inhibitor (Figure 1, curve *1*) was defined by the styrene concentration of 8.13 mol dm$^{-3}$ and the initiation rate $v_i$ of 0.49×10$^{-8}$ mol dm$^{-3}$ s$^{-1}$ at 310 K. The addition of compound **1** as an inhibitor led to a decrease in the chain length and in the rate of oxygen uptake (Figure 1, curves *2* and *3*), thus resulting in the appearance of an induction effect. Calculation of kinetic parameters was performed using the known equations.[8]

The presence of inhibitor **1** at concentrations of 10–100 μmol dm$^{-3}$ led to a decrease in the oxygen consumption rate. At the same time, the 6-amino-2,3-dimethylpyrimidin-4(3*H*)-one analogue, which had no hydroxy group at 5-position of the pyrimidine ring, did not affect the rate of styrene oxidation. For compound **1**, the induction effect increased with elevation of its concentration

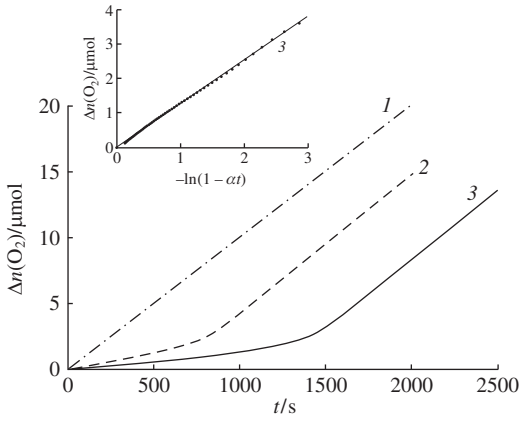



**Figure 1** Kinetic curves of oxygen consumption for the oxidation of styrene in chlorobenzene: (*1*) without an inhibitor, and in the presence of compound **1** at (*2*) $C_0 = 1.98 \times 10^{-6}$ mol dm$^{-3}$ and (*3*) $C_0 = 3.96 \times 10^{-6}$ mol dm$^{-3}$. Inset: the linear dependence $\Delta n(O_2)$ *vs.* $\ln(1 - \alpha t)$ in the induction period for curves (*3*), where $\alpha = v_i f^{-1}[\mathbf{1}]^{-1}$.

(Figure 1). After the end of the induction period, the oxygen consumption rate in the system reached the rate of styrene oxidation in the absence of the inhibitor, *i.e.*, the products of inhibitor conversion did not affect the styrene oxidation. This is confirmed by the linear dependence of $\Delta n(O_2)$ *vs.* $\ln(1 - \alpha t)$, where $\alpha = v_i f^{-1}[\mathbf{1}]^{-1}$ (Figure 1, inset), which is typical of processes with the same key reactions.[10] Based on the kinetic curves obtained and taking into account the initiation rate with α-tocopherol as a reference inhibitor, the rate constant for the reaction of compound **1** with peroxyl radicals formed from styrene was calculated to be $(2.5–0.7) \times 10^6$ dm$^3$ mol$^{-1}$ s$^{-1}$, while the stoichiometric factor was 2.0 – 0.1. Thus, the efficiency of compound **1** as an inhibitor of free radical oxidation matches that of vitamin E compounds in nonpolar organic solvents, their rate constants being $3.2 \times 10^6$, $1.3 \times 10^6$, $1.4 \times 10^6$, and $4.4 \times 10^5$ dm$^3$ mol$^{-1}$ s$^{-1}$ for α-, β-, γ- and δ-tocopherol, respectively,[7] and like most phenolic antioxidants, tocopherols are also known to trap two peroxyl radicals.[11–13]

In addition to the experiment, we carried out a theoretical investigation of the reactivity of compound **1** toward peroxyl radicals by calculation of the reaction barrier height for the hydrogen atom abstraction. In general, for the systems with a considerable contribution of different electronic configurations, like compound **1** with its conjugated double bonds near the reaction center, it is important to choose an adequate method of quantum-chemical calculations.[14,15] It was found[16] that the hydrogen atom abstraction from phenol by methylperoxyl radical could be modeled by DFT calculation using M05 density functional with MG3S basis set, and the quality of results was comparable to the calculations using the Møller–Plesset multiconfiguration perturbation theory (MRMP2), with good agreement with the experimental data[5] for hydrogen atom abstraction from 5-hydroxy- and 5-aminouracil derivatives. Therefore, in this work we used the proposed M05/MG3S method to calculate the reaction barrier height for the hydrogen atom abstraction from compound **1** by *tert*-butylperoxyl radical.

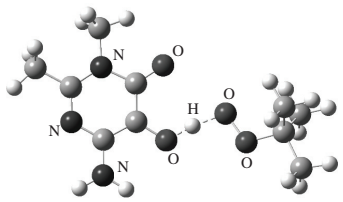



**Figure 2** Geometry of the transition state in the hydrogen atom abstraction from compound **1** by Bu$^t$OO$^\bullet$ radical, calculated at SMD(styrene)–M05/MG3S level of theory.

**Table 1** Key geometric parameters in the abstraction of an H-atom from compound **1** by Bu$^t$OO$^\bullet$ radical, obtained at the SMD(styrene)–M05/MG3S level of theory.

| Medium | $r_{H–O}$/Å | $r_{OO–H}$/Å | $r_{OO}$/Å | $\phi$/deg | $\Delta H^0$/kcal mol$^{-1}$ |
|---|---|---|---|---|---|
| Gas phase | 1.137 | 1.260 | 1.338 | 0.1 | 7.00 |
| Styrene | 1.108 | 1.306 | 1.338 | 8.9 | 7.08 |

The calculations were performed for the gas phase, as well as with consideration of the effect of styrene as a solvent according to the solvation model based on density (SMD) approximation, with full geometry optimization of the starting complex of *tert*-butylperoxyl radical with compound **1** and the transition state. The results for the transition state are presented in Figure 2 and Table 1.

The geometry demonstrated in Figure 2 differs from those obtained for N-methylated derivatives of 5-hydroxyuracil[5] and for phenol[16] at the same level of theory. The angle $\phi$ between the H-atom being abstracted and the pyrimidine ring plane, namely the C(6)–C(5)–O–H dihedral angle, is insignificant (see Table 1) even if the solvent effect is taken into consideration, unlike, *e.g.*, for 1,3,6-trimethyl-5-hydroxyuracil[5] and 2,6-di-*tert*-butyl-4-methylphenol calculated in this work, where it is 67.5° and 93.3°, respectively, in the corresponding transition states. It has been shown[5] that *ca.* 2 kcal mol$^{-1}$ energy can be consumed for the change of this angle in the transition state. For compound **1** the length of the O–H bond being attacked changes by 0.141 Å in the transition state with respect to the starting molecule. This value is close to the parameters for 1,3,6-trimethyl-5-hydroxyuracil and 2,6-di-*tert*-butyl-4-methylphenol, *viz.*, 0.115 and 0.139 Å, respectively. In this case, owing to less strength of the O–H bond in comparison with the previously studied pyrimidin-4-(3*H*)-one derivatives, an early transition state closely resembles a pre-reaction complex between the radical and the inhibitor, in which the hydrogen bond between the H atom being abstracted and the 4-keto group is not broken. The energy barriers in the gas phase and in the solvent, within the model of nonspecific solvent effect, are nearly equal (see Table 1). Apparently, the elevation of the barrier due to the increase in the $\phi$ angle in the solvent medium is compensated by shortening the O–H bond being broken. As expected, the $\Delta H^0$ value itself is smaller than those obtained previously for pyrimidin-4(3*H*)-one derivatives,[5] which agrees well with the rate constant for the reaction of compound **1** with styrene peroxyl radical.

Thus, it has been found that 6-amino-5-hydroxy-2,3-dimethylpyrimidin-4(3*H*)-one **1** is an efficient inhibitor of free radical oxidation, and that its parameters are similar to those of vitamin E compounds. According to calculations using M05/MG3S method, the hydrogen atom abstraction by a peroxyl radical from compound **1** is characterized by an early transition state, while the energy barrier of this reaction is lower than that for other pyrimidin-4(3*H*)-one derivatives.

This study was carried out within the framework of the State target no. AAAA-A17-117011910035-5. The calculations were performed using the cluster supercomputer at the Ufa Institute of Chemistry, Russian Academy of Sciences (UIC RAS). The authors are grateful to the center of collective use 'Chemistry' of the UIC RAS for providing UV-VIS and NMR spectroscopic studies.

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