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Antiradical Activity of 2-Substituted 4-(1,3-Thiazol-4-yl)-1,2-dihydroxybenzenes

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Abstract—Antiradical activity of 2-substituted 4-(1,3-thiazol-4-yl)-1,2-dihydroxybenzenes in the reaction with 1,1-diphenyl-2-picrylhydrazyl stable radical has been studied. Kinetic parameters of the process have been determined. Energy of homolytic dissosiation of the O–H bond of the studied compounds has been computed by DFT simulation in the 6-31G(p,d) basis set. The calculated bond energies correlate with the experimental rate constants.

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Thiazole derivatives are known for anti-inflammatory and antitumor action [1]; some of them, for example, thiamine [2] and aminothiazoles [3] also exhibit antioxidant activity. We have demonstrated that thiazole derivatives containing 1,2-dihydroxybenzene fragment inhibit Twin-80 oxidation and are efficient phenol-type antioxidants, trapping peroxyl and alkoxyl radicals that are formed in the course of organic compounds oxidation [4].

$$PhOH + ROO^{\bullet}(RO^{\bullet}) \rightarrow PhO^{\bullet} + ROOH(ROH).$$

Various test systems are applied for preliminary estimation of antiradical activity; such tests include interaction of the studied compounds with stable or *in situ* generated radicals [5]. We have chosen as model the reaction of stable colored radical 1,1-diphenyl-2-picrylhydrazyl (DPPH$^{\bullet}$) with potential antiradical reagents: derivatives of 4-(1,3-thiazol-4-yl)-1,2-dihydroxybenzene and their structural analogs.

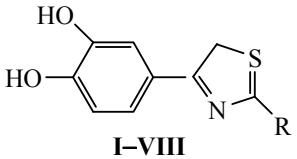
Ab initio simulations are also often used to estimate the antioxidant activity; in particular, the calculation of the energy of the O–H bond homolytic dissosiation (BDE), for it is one of the important parameters of phenol-type antioxidants governing their inhibitor properties [6].

In this work the results of measurements of kinetic parameters of reactions between 2-substituted 4-(1,3-thiazol-4-yl)-1,2-dihydroxybenzenes, their structural analogs, and DPPH$^{\bullet}$ radical were compared with the BDE values calculated by quantum-chemical methods; the antiradical activity of the tested compounds was quantified.

In ethanol medium at 298 K the reaction between pyrocathehol and DPPH$^{\bullet}$ occurred within several seconds; the rate constant under these conditions was 960 L mol^{-1} s^{-1} [7]. The rate constants of the studied thiazolyldihydroxybenzenes are apparently even larger for they react with DPPH$^{\bullet}$ even faster than pyrocatechol. The reaction slowed down in the presence of small amount of acid. To get reliable kinetic data by spectrophotometry 0.1 mmol/L of HCl was enough [8]. Further increase of HCl concentration did not lead to significant decrease in the reaction rate; therefore, in this work the interaction of derivatives **I–VIII** with DPPH$^{\bullet}$ was studied at c(HCl) = 0.1 mmol/L.

As a result of the reaction of thiazole, pyrocatechol, and 4-methylpyrocatechol with DPPH$^{\bullet}$ the initially colored solution suffered discolorization (Fig. 1). Condi-tions being the same, 2,4-diphenylthiazole did not react with the radical; thus, the antiradical activity of the thiazolyldihydroxybenzene derivatives was due to the OH groups of pyrocatechol fragment. The primary interaction products were likely of quinoid

nature; that was proved by no interaction between DPPH$^{\bullet}$ and resorcinol (in the latter case quinone formation was impeded).



I–VIII

R = Me (**I**), C_6H_4OH-4 (**II**), $C_6H_3(OMe)_2$-3,4 (**III**), indol-3-yl (**IV**), Ph (**V**), HNC_6H_4Cl-4 (**VI**), HNC_6H_4Cl-3 (**VII**), $HNC_6H_3(CH_3)_2$-3,4 (**VIII**).

The interaction of dihydroxybenzenes with DPPH$^{\bullet}$ can be described by reactions (1)–(3) [7, 9].

$$DPPH^{\bullet} + HOPhOH \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} DPPH\text{-}H + HOPhO^{\bullet}, \quad (1)$$

$$DPPH^{\bullet} + HOPhO^{\bullet} \xrightarrow{k_2} DPPH\text{–}H + OPhO, \quad (2)$$

$$2HOPhO^{\bullet} \xrightarrow{k_3} HOPhOH + OPhO. \quad (3)$$

At equimolar reagents ratio, the kinetic curves could be linearized in the second-order reaction coordinates (Fig. 1). The obtained reaction rate orders with respect to the substrate were close to 1 for the majority of the studied compounds (see table); therefore, the rate order with respect to DPPH$^{\bullet}$ was also 1. The tabulated second-order rate constants were calculated from the linear $k_{eff} = f(c_0)$ plots (Fig. 2).

Thus, under the experimental conditions reaction (1) was the rate-limiting step, and the derived overall rate constants (k) could characterize antiradical activity of the studied compounds.

All studied derivatives **I**–**VIII** were more reactive towards DPPH$^{\bullet}$ than similar compounds without the thiazole ring (see table). Thus, thiazole derivatives were more efficient antiradical agents than pyrocatechol or 4-methylpyrocatechol.

Additional experiments allowed determination of the stoichiometric inhibition coefficient (f), number of DPPH$^{\bullet}$ radicals reacting with a single antioxidant molecule. Such experiments consisted in addition of varied amounts of the substrate to excess of DPPH$^{\bullet}$. In the cases of pyrocatechol, 4-methylpyrocatechol, and the majority of the thiazolyldihydroxybenzenes (except for **VI**–**VIII**), the f values (see table) were close to 2, being consistent with the presence of two hydroxy groups, hydrogen donors, in their molecules.

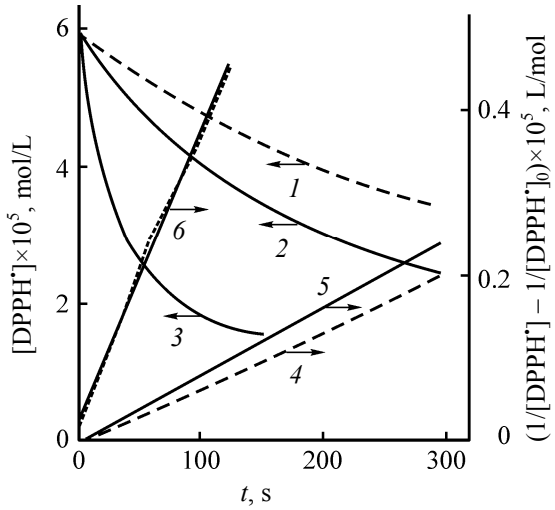
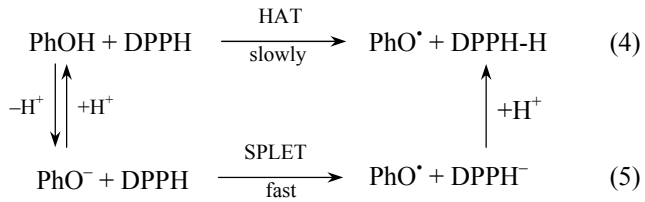


Fig. 1. Kinetic curves of DPPH$^{\bullet}$ consumption (c_0 = 60 μmol/L) (*1*–*3*) and their linearizations in the second-order reaction coordinates (*4*–*6*): reaction with 4-methylpyrocatechol (*1*, *4*), **V** (*2*, *5*), and **VIII** (*3*, *6*).

Kinetics of phenol-type antioxidants interaction with DPPH$^{\bullet}$ may be described by alternative mechanisms (4), (5) [8–10].



(4)

(5)

Kinetic and calculated parameters of antiradical activity

Compound	f	$n(S)$	k, L mol^{-1} s^{-1}	BDE, kJ/mol
I	2.5±0.4	0.8±0.2	56±18	324.05
II	1.8±0.3	0.8±0.3	55±16	323.80
III	2.1±0.2	0.8±0.2	54±10	323.47
IV	2.4±0.3	0.8±0.2	86±13	322.71
V	2.6±0.1	1.0±0.4	67±9	325.39
VI	1.4±0.3	0.8±0.3	109±23	322.46
VII	1.3±0.1	0.4±0.2	107±30	322.63
VIII	1.5±0.3	0.5±0.2	160±40	321.79
Pyrocatechol	2.0±0.6	1.0±0.2	5±1	334.26
4-Methylpyrocatechol	2.1±0.6	0.8±0.1	18±5	328.03

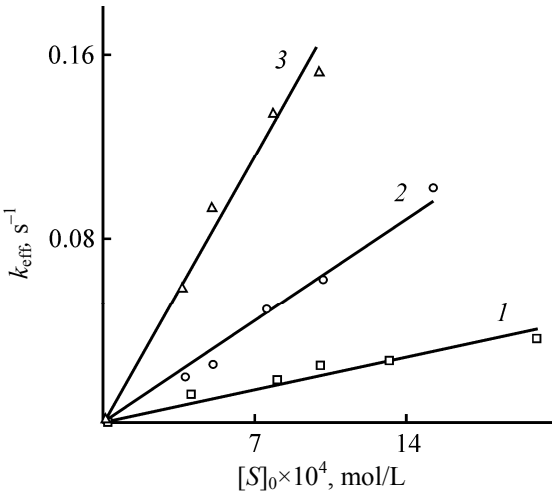


Fig. 2. Effective rate constant of the reaction with DPPH$^{\bullet}$ as a function of the initial concentration of 4-methylpyrocatechol (*1*), **V** (*2*), and **VIII** (*3*).

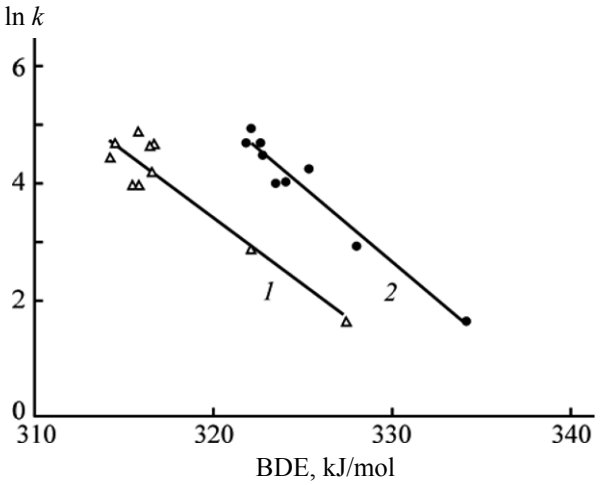


Fig. 3. Logarithm of rate constant of substituted 4-(1,3-thiazol-4-yl)-1,2-dihydroxybenzenes and similar compounds in reaction with DPPH$^{\bullet}$ as a function of the energy of the O–H bond homolytic dissosiation. (*1*) at BDE calculated with B3LYP/6-31G(p,d) (vacuum); (*2*) at BDE calculated with PCM//B3LYP/6-31G(p,d) (in the solvent).

The first pathway (4), direct transfer of a hydrogen from the antioxidant molecule (HAT, hydrogen atom transfer), is typical of the reactions in organic aprotic solvents. The second pathway (5), transfer of an electron from phenolate ion to DPPH$^{\bullet}$ (SPLET, sequential proton-less electron transfer) is more common in the cases of solvents having donor-acceptor properties. Therefore, reacting via the SPLET pathway could likely account for the high reactivity of the studied compounds towards DPPH$^{\bullet}$ in pure ethanol. The introduction of the strong acid decreased the phenolate form concentration, thus decelerating the reaction due to the change in its mechanism [7, 10]. Hence, under the kinetic experiment conditions, the reaction of DPPH$^{\bullet}$ with the studied compounds is likely to occur via the HAT mechanism.

If the HAT mechanism was operative, the kinetic parameters should be correlated with the BDE value of the O–H bond. We determined the BDE values by quantum-chemical simulation. The energy of homolytic dissosiation was computed for the O–H bond in *para*-position with respect to the thiazole group (preliminary studies showed higher stability of such radicals). The DFT methods were found to be more reliable in determination of the relative bond dissociation energy rather than the absolute values of these energies [11]; such methods were previously tested on a wide range of phenol antioxidants [12]. Relative BDE values were determined as free energy of the isodesmic reaction (6) [13].

$$XPhOH + PhO^{\bullet} \rightarrow XPhO^{\bullet} + PhOH. \quad (6)$$

Absolute energy of the homolytic O–H bond dissosiation was found by addition of the relative BDE values to BDE of phenol (371.5 kJ/mol [14]).

As expected, the increase in the bond dissosiation energy resulted in slowing down the studied reaction (Fig. 3). The correlation coefficient between ln k and BDE [the latter was computed by B3LYP/6-31G(p,d) method for the vacuum] was 0.88.

In order to account for the solvent effect, we used the PCM method and the B3LYP exchange-correlation functional. Even indirect accounting for the solvent effect in the frame of implicit solvent model significantly improved the correlation between the experimental and the simulated data (Fig. 3, curve *2*, R^2 = 0.95).

To conclude, the studied derivatives of 4-(1,3-thiazol-4-yl)-1,2-dihydroxybenzene **I–VIII** showed high antiradical activity. Their reaction with DPPH$^{\bullet}$ under the kinetic experiment conditions occurred via direct hydrogen transfer. The experimental rate constants of the reaction with DPPH$^{\bullet}$ were strongly correlated with the theoretically computed energies of the homolytic O–H bond dissosiation.

EXPERIMENTAL

Visible range absorption spectra were measured on a the high-speed Specord S300 UV-VIS spectrometer (Germany) equipped with temperature-controlled cell and magnetic stirrer; $\varepsilon_{DPPH^\bullet}$ (1.10±0.03) × 10^4 L mol^{-1} cm^{-1}.

Thiazoles **I–V** were prepared as described in [15], compounds **VI–VIII** were synthesized similarly. 1,1-Diphenyl-2-picrylhydrazyl (Aldrich) was used as received. Dimethylsulfoxide DMSO (Lubny-Farm) was purified by distillation under reduced pressure. Pyrocatechol and resorcinol were purified by sublimation; reactive grade 4-methylpyrocatechol was obtained by multiple recrystallizations from toluene. All solutions were prepared just before the experiments.

Kinetics of phenol antioxidants interaction with DPPH$^\bullet$. The reactions were carried out in ethanol in the presence of 0.1 mmol/L of HCl, at 298 K. Prior to the experiment, DPPH$^\bullet$ solution was incubated at 298 K during 15 min; then, an aliquot of the substrate (in ethanol or DMSO) was added. Absorption at 517 nm was traced in time.

Under conditions of the pseudo first-order reaction, the substrate concentration was at least 10 times higher than $[DPPH^\bullet]_0$. In order to eliminate the effect of the absorbing product, the pseudo first-order rate constant was determined using the Guggenheim method [9]. The reaction rate order with respect to the substrate was determined using the Van't-Hoff method.

The linearized kinetic curves were processed using the least-squares method; the values of f, k, and $n(S)$ were presented in the $x \pm \Delta x$ form (x being the calculated parameter, Δx being the confidence interval).

Determination of stoichiometric inhibition coefficient. An aliquot of the tested compound was added to DPPH$^\bullet$ solution (75 μmol/L), and the solution absorbance at 517 nm was measured after 30 min. The substrates concentration ranged between 7.5 and 50 μmol/L.

Determination of energy of the homolytic O–H bond dissosiation. Simulations were performed using GAMESS-US software package (R1 version of 1.10.2010) applying the 6-31G(p,d) basis set [16] and the B3LYP exchange-correlation functional [17]. The solvent was accounted for by the polarizable continuum model [18]. BDE values of the O–H bond of the antioxidants were calculated similar to [11].

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