Phosphorus-containing derivatives of 2,6-di(*tert*-butyl)phenol: the antioxidant activity and properties of the corresponding phenoxyl radicals

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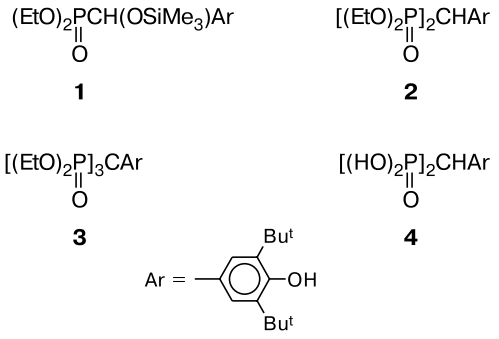
The properties of phenoxyl radicals generated by the oxidation of mono-, di-, and triphosphorus derivatives of 2,6-di(*tert*-butyl)-4-methylphenol (ionol) were studied by ESR. These compounds exist as conformers that are interconvertible with a temperature-dependent rate. Numerical processing of the ESR spectra gave the thermodynamic and activation parameters that characterize the interconversion of the conformers. The antioxidant activities of the compounds were studied in a model oxidation of oleic acid and with biological objects. These phenols efficiently inhibited radical oxidation reactions.

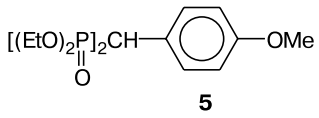
Key words: 2,6-di(*tert*-butyl)phenols, phosphonates, antioxidant activity, phenoxyl radicals, ESR.

Derivatives of 2,6-di(*tert*-butyl)-4-methylphenol (ionol) are efficient antioxidants.[1] They are biologically active compounds capable of inhibiting lipid peroxidation and lowering the oxidative stress of the organism. In recent years, we have proposed a convenient route to a number of ionol derivatives with one, two, or three phosphorus-containing groups, starting from easily accessible 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde and trimethylsilyl esters of phosphorus(III) acids.[2—4] Here we studied the antioxidant properties of phosphorus-containing ionol derivatives **1**—**4**.



A comparative analysis of the antioxidant activity was performed against reference compound **5** containing no 2,6-di(*tert*-butyl)phenol fragment.

The antioxidant activities of 2,6-di(*tert*-butyl)phenols are determined by the stability of the corresponding



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phenoxyl radicals.[1] We generated phenoxyl radicals from compounds **1**—**4** and studied their properties by ESR.

Experimental

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance 400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ for compounds **2** and **3**, DMSO-d_6 for **1**, and D_2O for **4** with Me_4Si (^1H, ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P) as standards. All reactions were carried out in anhydrous solvents under dry argon. ESR spectra were recorded on a Bruker ER 200 D-SRC instrument fitted with an ER 4105 DR double resonator (~9.5 GHz) and an ER 4111 VT thermocontroller and on a Bruker EMX-8/2.7 instrument. Diphenylpicrylhydrazyl (DPPH, $g = 2.0037$) was used as a standard in the determination of the g-factor. Spectra were simulated with the WinEPR SimFonia v 1.25 program (Bruker).

Compounds **1**—**5** were prepared according to our procedure[3,4] by reactions of trimethylsilyl esters of phosphorus(III) acids with 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde and 3,5-di(*tert*-butyl)-4-hydroxybenzoyl chloride. The physicochemical constants of compounds **2**—**4** (see Ref. 3) and **5** (see Ref. 4) were identical with the literature data.

***O,O*-Diethyl [3,5-di(*tert*-butyl)-4-hydroxyphenyl(trimethylsilyloxy)methyl]phosphonate (1)** was obtained from diethyl

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trimethylsilyl phosphite (6.2 g) and 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde (3.1 g). The yield was 92%, m.p. 102 °C. ^{31}P (^1H) NMR ($CDCl_3$), δ: 20.49. ^1H NMR ($CDCl_3$), δ: 0.02 (s, 9 H, Me_3Si); 1.10—1.20 (m, 6 H, $C\underline{H}_3CH_2O$); 1.38 (s, 18 H, Bu^t); 3.70—4.00 (m, 4 H, CH_2O); 4.97 (d, 1 H, C(1)H, $^2J_{P,H}$ = 12 Hz); 6.93 (s, 1 H, OH); 7.19 (s, 2 H, C_6H_2). ^{13}C NMR ($CDCl_3$), δ: 0.42 (s, Me_3Si), 16.62 (d, $\underline{C}H_3CH_2O$, $^3J_{P,C}$ = 6 Hz); 16.77 (d, $\underline{C}H_3CH_2O$, $^3J_{P,C}$ = 5 Hz); 30.82 (s, $\underline{Me}_3C$); 34.96 (s, $Me_3\underline{C}$); 62.24 (d, CH_2O, $^2J_{P,C}$ = 8 Hz); 62.67 (d, CH_2O, $^2J_{P,C}$ = 7 Hz); 71.74 (d, C(1), $^1J_{P,C}$ = 170 Hz); 124.21, 128.45, 138.94, 153.91 (all s, C_6H_2).

Phosphorus-containing phenols were oxidized to the corresponding radicals with PbO_2 in toluene (compounds **1**—**3**) and with 3,6-di(*tert*-butyl)-1,2-benzoquinone in THF and exposure to radiation (**4**). A KGM-24-150 lamp with a focusing unit was used as a light source for the photoreaction; the light was passed through a ZhS-16 light filter to isolate a radiation with λ ≥ 500 nm.

Antioxidant activity was studied in a model oxidation of oleic acid (99% purity, Sigma) and with biological objects (liver homogenates of *Wistar* rats provided by the Department of Biology of the M. V. Lomonosov Moscow State University). The oxidation of oleic acid was studied on a temperature-controlled setup at 50, 65, and 90 °C. Air was bubbled through an oxidation cell at a constant rate of 2—4 mL min^{-1}. Under these conditions, the oxidation was kinetically controlled (*i.e.*, its rate did not depend on the volume of the oxygen supplied).[5] Accumulation of intermediate oxidation products from oleic acid RH (hydroperoxides ROOH) and oxidation products from liver homogenates as a stable complex with thiobarbituric acid (TBARS) was monitored by iodometric titration and spectrophotometry, respectively.[6]

Liver homogenates were prepared as follows.[7] A weighed sample of the tissue (0.5 g) was ground with 1.2% KCl (19.5 mL), the homogenate (2 mL) was mixed with $2.6 \cdot 10^{-3}$ *M* ascorbic acid (0.1 mL) and $4 \cdot 10^{-5}$ *M* Mohr salt (0.1 mL) and 40% trichloroacetic acid (TCA, 1 mL) were added. The solution was heated on a water bath at 65 °C for 10 min and centrifuged at 3000 rpm for 10 min. A portion (2 mL) of the centrifuged solution was withdrawn and heated with 0.8% thiobarbituric acid (1 mL) on a boiling bath for 10 min. The upper phase was sampled and its optical density (*A*) was measured at λ = 532 nm versus a blank solution: KCl (2 mL) + TCA (1 mL) + TBA (1 mL).

Results and Discussion

ESR study of the properties of phenoxyl radicals generated from compounds 1—4

Earlier,[8] the properties of radicals generated in the one-electron oxidation of the phosphorus-containing 2,6-di(*tert*-butyl)phenol derivative $RCH[PO(OPr^i)_2]_2$ have been studied at different temperatures. We employed ESR to investigate the properties of paramagnetic species generated in the oxidation of phosphonates **1**—**4**. Phenols **1**—**3** were oxidized with PbO_2 in toluene. The ESR spectra of all three aroxyl radicals **1**$^\bullet$—**3**$^\bullet$ are strongly temperature-dependent. Temperature-induced changes in the ESR spectrum of phenoxyl **1**$^\bullet$ indicate the presence in

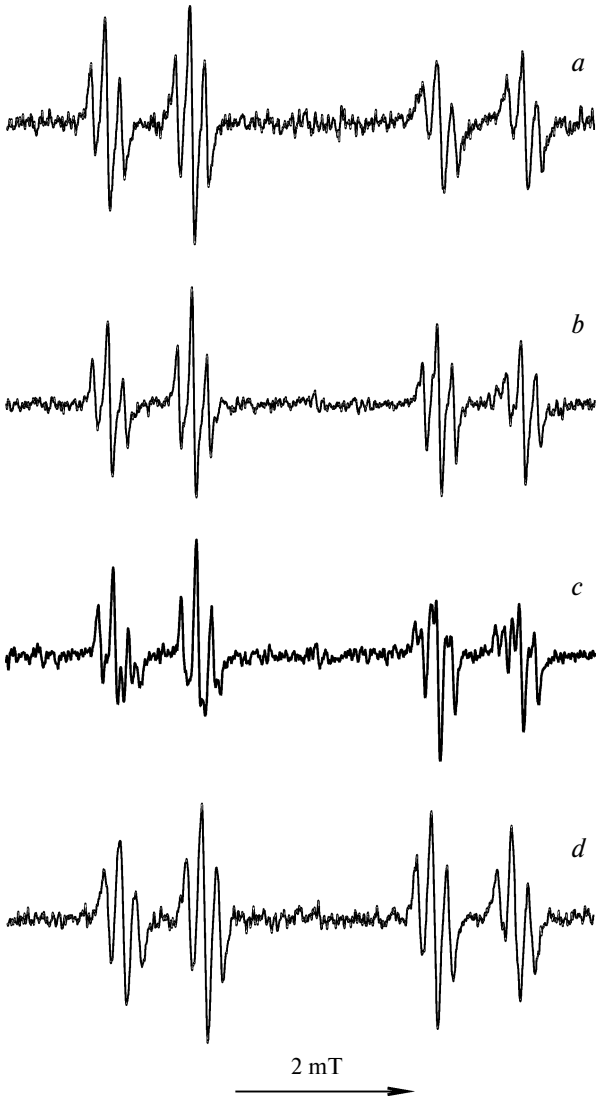


Fig. 1. Temperature dependence of the ESR spectra of radical **1**$^\bullet$, *T*/K: 210 (*a*), 240 (*b*), 280 (*c*), and 300 (*d*).

solution of two paramagnetic species in equilibrium. In the 190—300 K range, the ESR spectrum of radical **1**$^\bullet$ is a superposition of two signals, either being a doublet (1 : 1) of doublets (1 : 1) of triplets (1 : 2 : 1) (Fig. 1). Such a hyperfine structure (HFS) can be due to a coupling of the unpaired electron with the magnetic phosphorus nucleus (^{31}P, I = 1/2, 100%), one methine proton, and two equivalent *meta*-protons (^1H, I = 1/2, 100%). The parameters of the ESR spectra of phenoxyl **1**$^\bullet$ and the other radicals studied are given in Table 1. The relative intensities of the signals for two paramagnetic forms of radical **1**$^\bullet$ varied very strongly with the temperature so that the ESR spectra recorded at 210 and 300 K contain virtually one signal of the two. From the temperature dependence of the ESR spectra it follows that the resulting radical exists in solution as two conformers **1A**$^\bullet$ and **1B**$^\bullet$ that have different energies and are interconvertible upon a temperature

Table 1. HFC constants and *g* factors of the radicals generated in the oxidation of compounds **1**—**4**

Radical	T_1		T_2	
	a/mT	*g*	*a*/mT	*g*
1•	200 K		300 K	
	a(P) = 3.97	2.0057	*a*(P) = 3.69	2.0055
	a(1 H) = 1.0		*a*(1 H) = 0.97	
	a(2 H) = 0.17		*a*(H) = 0.18	
2•	190 K		300 K	
	a(1 P_1) = 3.13	2.0043	*a*(2 P) = 2.68	2.0046
	a(1 P_2) = 2.1		*a*(3 H) = 0.18	
	a(3 H) = 0.18			
3•	190 K		320 K	
	a(1 P_1) = 3.15	2.0054	*a*(1 P) = 5.19	2.0054
	a(2 P_2) = 0.93		*a*(2 H) = 0.18	
	a(2 H) = 0.18			
4•	220 K		290 K	
	a(1 P_1) = 2.88	2.0049	*a*(1 P_1) = 2.82	2.0049
	a(1 P_2) = 2.67		*a*(1 P_2) = 2.7	
	a(2 H) = 0.16		*a*(2 H) = 0.16	
	a(1 H) = 0.14		*a*(1 H) = 0.14	

change. The close values of the parameters of the isotropic ESR spectra (see Table 1) suggest close geometries of these conformers.

The temperature dependence of the ESR spectra of radicals **2**• and **3**• is manifested by unequal broadening of the components. The ESR spectrum of phenoxyl **2**• in toluene at 190 K is a doublet (1 : 1) of doublets (1 : 1) of quartets (1 : 3 : 3 : 1) due to a hyperfine coupling (HFC) of the unpaired electron with two nonequivalent magnetic ^{31}P nuclei and three equivalent protons (two *meta*-protons and one methine proton) (see Table 1). An increase in the temperature results in alternating broadening of the spectral components with $\Sigma m_{IP} = 0$ (Fig. 2). At 250 K, these components coalesce, being broadened virtually to zero. With a further increase in the temperature, the components with $\Sigma m_{IP} = 0$ become more intense to produce at 300 K an ESR spectrum as a triplet (1 : 2 : 1) (with the partially broadened central component) of quartets (1 : 3 : 3 : 1). Such a shape of the spectrum is due to an HFC of the unpaired electron with two equivalent magnetic ^{31}P nuclei and three equivalent protons.

The most stable phenoxyl **3**• is generated in the oxidation of phenol **3**, which is evident from a blue color (characteristic of aroxyls) of its solution in toluene. The temperature dependence of the ESR spectrum of this radical was studied in the 190—340 K range. At 190 K, its spectrum may be interpreted as a doublet (1 : 1) of triplets (1 : 2 : 1) of triplets (1 : 2 : 1), which arises from an HFC of the unpaired electron with three magnetic ^{31}P nuclei, two of which are equivalent and have a lower HFC constant than the third one (see Table 1), and two equivalent *meta*-protons (Fig. 3). With an increase in the temperature, the lines with $\Sigma m_{IP} = \pm 1/2$ in the ESR spectrum of radical **3**• broadened, which indicated the presence of its energy-degenerate interconvertible conformers in solution. In contrast to aroxyl **2**•, the interconversion rate of the conformers does not reach the rapid exchange even at 340 K.

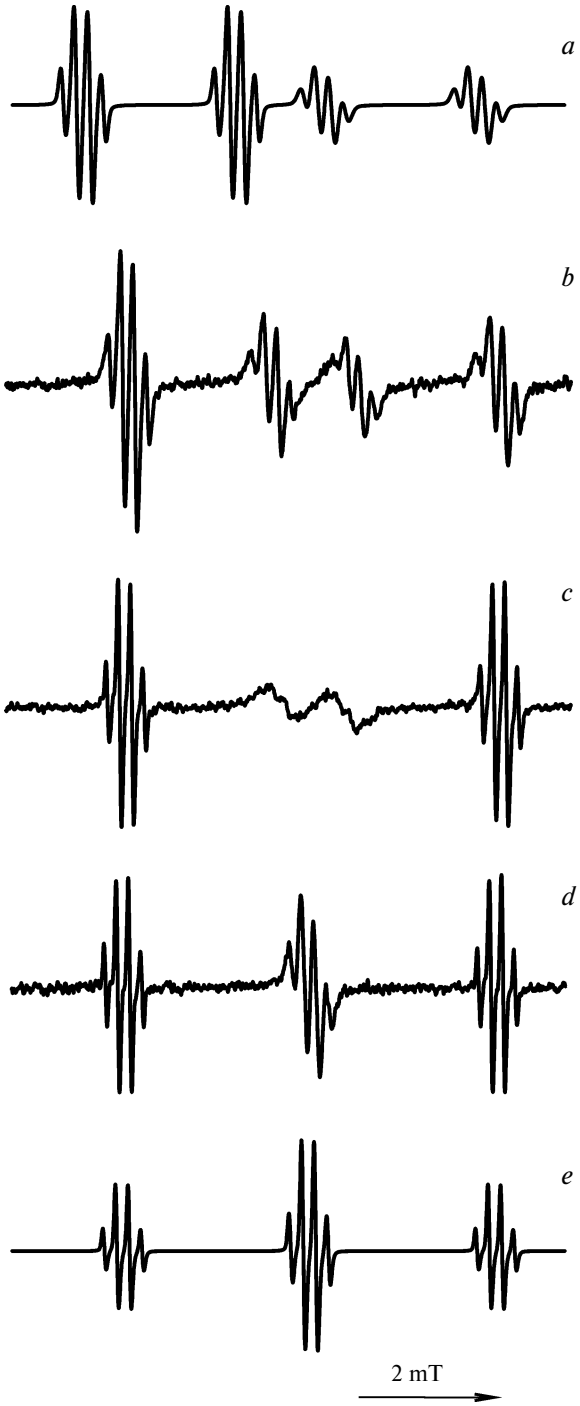


Fig. 2. Temperature dependence of the ESR spectra of radical **2**•: simulated spectra for **2A**• at 200 (*a*) and 300 K (*e*) and experimental spectra (*b*—*d*) at 200 (*b*), 240 (*c*), and 300 K (*d*).

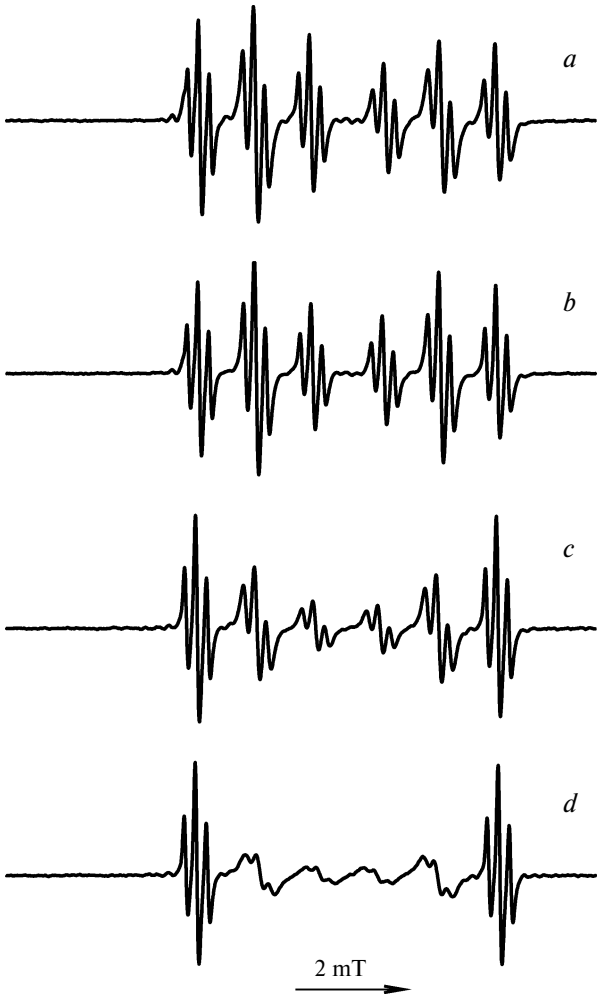


Fig. 3. Temperature dependence of the ESR spectra of radical **3**, *T*/K: 200 (*a*), 220 (*b*), 250 (*c*), and 270 K (*d*).

In contrast to phenols **1**—**3**, aroxyl **4**• generated in the oxidation of phenol **4** is unstable, which precluded recording of its ESR spectrum under the identical conditions (PbO_2, toluene, 280 K). That is the reason why we generated the phenoxyl radical by dehydrogenating phenols with photoexcited 3,6-di(*tert*-butyl)-1,2-benzoquinone.[9] The ESR spectrum of the resulting radical **4**• at 220 K is a doublet (1 : 1) of doublets (1 : 1) of doublets (1 : 1) of triplets (1 : 2 : 1) due to an HFC with two nonequivalent magnetic ^{31}P nuclei, the methine proton, and two equivalent *meta*-protons (see Table 1). A temperature dependence of the ESR spectrum of this radical was not studied because of its low stability.

The geometries of radicals **1**•—**3**• can be inferred from an analysis of the HFS parameters of their ESR spectra. It is known that in π-radicals, the HFC constant with respect to the proton bound to the α-C atom depends on the dihedral angle θ between the plane passing through the C—H bond and the plane passing through the axis of the *p*-orbital occupied by the unpaired electron (equation (1)).[10] A similar dependence is true for HFC with other magnetic nuclei (^{19}F and ^{31}P).

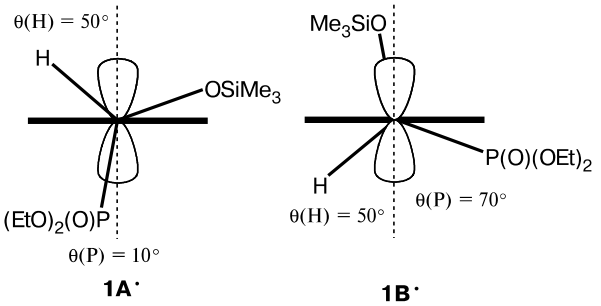


Fig. 4. Two conformers of radical **1**•.

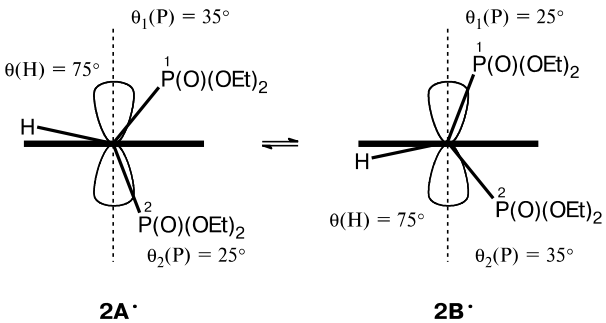
$$A_\theta(H) = A_0(H) \cdot (\cos\theta)^2, \quad (1)$$

where θ is the dihedral angle for the C—H bond; $A_\theta(H)$ is the HFC constant with respect to this proton; $A_0(H)$ is the HFC constant with respect to the proton with θ = 0°.

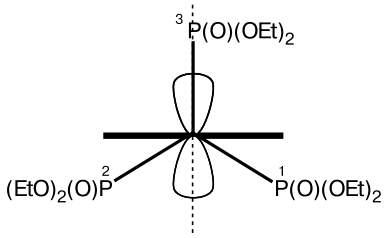
Taking $A_0(H)$ to be 2.2 mT, we obtain by Eq. (1) θ(H) ≈ 50° for radical **1**• and $\theta_1(H) \approx 75°$ and $\theta_2(H) \approx 105°$ for radical **2**•. Under the assumption of a near-tetrahedral geometry of the C atom in the *para*-substituents of radicals **1**• and **2**•, one can calculate the dihedral angles for the phosphonate groups in these aroxyl radicals. For two possible conformers of radical **1**• (Fig. 4), these angles are $\theta_1(P) \approx 10°$ (**1A**•) and $\theta_2(P) \approx 70°$ (**1B**•). The high experimental value of the HFC constant $A_\theta(^{31}P)$ = 3.69 mT in this aroxyl corresponds only to conformer **1A**•.

In radical **2**•, the calculated θ(P) values are ~25° and 35°, which correspond to two possible conformers **2A**• and **2B**• (Scheme 1). They have identical geometry, differing only in relative arrangement of the phosphonate groups: $\theta_1(P) > \theta_2(P)$ in conformer **2A**• and $\theta_1(P) < \theta_2(P)$ in conformer **2B**•.

Scheme 1



Using the expression like (1), θ(P) ≈ 10°, and $A_\theta(^{31}P)$ = 3.69 mT for radical **1**•, we obtain $A_0(^{31}P)$ = 3.8 mT. The HFC constants $A_1(^{31}P)$ = 3.1 mT and $A_2(^{31}P)$ = 2.5 mT calculated for this $A_0(^{31}P)$ value, $\theta_1(P) \approx 25°$, and



3•

Fig. 5. Conformation of radical **3**•.

$\theta_2(P) \approx 35°$ agree well with the experimental constants (see Table 1).

For aroxyl **3**•, a similar calculation of the dihedral angles gave $\theta_1(P) = \theta_2(P) \approx 60°$ and $\theta_3(P) \approx 22°$. Its apparent conformation is shown in Fig. 5.

As noted above, the conformers of phenoxyl **2**• are structurally identical. Because of this, they are degenerate in energy and an exchange between them gives rise to the experimentally observed temperature dependence of the ESR spectrum of radical **2**•. Using ESR data for this radical in the range of "rapid" exchange of phosphonate groups, we estimated the activation parameters of the conformational equilibrium.

Broadening of the components with $\Sigma m_I = 0$ in the ESR spectrum, which is due to rapid exchange of two magnetic nuclei with $I = 1/2$, is governed by the known formula:[11]

$$\Delta\Gamma = \gamma_e\tau(\delta H)^2/4, \qquad (2)$$

where $\Delta\Gamma$ is the line broadening, γ_e is the electron magnetogyric ratio, δH is the distance between the lines of separate conformers in the ESR spectrum, and τ is the reduced lifetime calculated by the formula

$$\tau = \tau_I\tau_{II}/(\tau_I + \tau_{II}),$$

where τ_I and τ_{II} are the lifetimes of the corresponding conformers. The lifetimes of the conformers are related to the probabilities P of their formation and their concentrations by the expression

$$\tau_I/\tau_{II} = P_I/P_{II} = C_I/C_{II},$$

where C_I and C_{II} are the concentrations of the corresponding conformers. In this case, it is obvious that $P_I = P_{II}$. With known temperature dependences of the lifetimes of both conformers, one can estimate the enthalpy and entropy of activation of their interconversion by employing the following formula:

$$1/\tau = kT/h^*\exp(\Delta S^{\#}/R)\exp(-\Delta H^{\#}/RT) \qquad (3)$$

where τ is the lifetime of a separate isomer, k is the Boltzmann constant, h^* is the Planck constant, R is the universal gas constant, T is the absolute temperature, and $\Delta H^{\#}$ and $\Delta S^{\#}$ are the activation parameters. In this case, the activation parameters are $\Delta H^{\#} \cong 14.1\pm0.8$ kJ mol^{-1} and $\Delta S^{\#} \cong -102.3\pm2$ J mol^{-1} K^{-1}.

It is unclear why aroxyl **1**• exists as two conformers. Apparently, this is due to a specific nonvalence interaction between the phosphonate and trimethylsilyloxy substituents. Nevertheless, an analysis of the temperature dependence of the ESR spectra of this aroxyl makes it possible to estimate the thermodynamic parameters characterizing the equilibrium between their conformers.

For this purpose, we simulated ESR spectra of conformers **1A**• and **1B**•. The ESR spectra at intermediate temperatures were obtained by superposition of the simulated spectra; the HFC constants for the phosphorus atoms and the mole fractions of the conformers P_A and $P_B = 1 - P_A$ were varied in such a way as to attain the best fit to the experimental spectra. The P_A/P_B ratio for the resultant spectrum determines the equilibrium constant of the interconversion of the conformers. Using the known formula

$$\ln K = -\Delta G/(RT) = -\Delta H/(RT) + -\Delta S/R, \qquad (4)$$

where K is the equilibrium constant, ΔG is the Gibbs energy change of the interconversion of the stereoisomers, and the ΔH and ΔS are the changes in the enthalpy and entropy, respectively. The thermodynamic parameters of the interconversion are $\Delta H = -26$ kJ mol^{-1} and $\Delta S = -91$ J mol^{-1} K^{-1}. However, these parameters should be regarded only as estimates. The ratio of the magnitudes and signs of the equilibrium entropy and enthalpy is such that one conformer is virtually completely converted into the other in the 200—300 K range.

Study of the antioxidant activities of phosphorus-containing 2,6-di(tert-butyl)phenols

The antioxidant activities of compounds **1**—**5** were studied in a model oxidation of oleic ((*Z*)-octadec-9-enoic) acid and with biological objects: liver homogenates of *Wistar* rats. We found that compounds **1**—**4** in the oxidation of oleic acid (RH substrate) at 50—90 °C exhibit a pronounced inhibitive effect on the formation of primary oxidation products, namely, hydroperoxides ROOH. Phenols **1**—**4** were superior to the standard antioxidant ionol, compounds **1**, **2**, and **4** being the best inhibitors (Fig. 6). The data from the model experiment were compared with those obtained in the oxidation of the liver homogenates of *Wistar* rats. For comparison, we studied the oxidation of liver homogenates in the presence of compound **5** containing no 2,6-di(*tert*-butyl)phenol fragment. Data on TBARS accumulation from liver homogenates in the presence of phenol **4**, compound **5**, and ionol over 4 h are shown in Fig. 7. It can be seen that phosphonate-containing 2,6-di(*tert*-butyl)phenol noticeably inhibits the accumulation of TBARS. Compound **5**

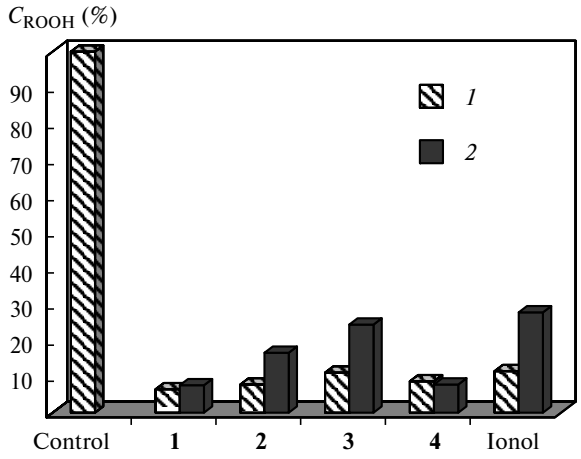


Fig. 6. Antioxidant activities of phenols **1**—**4** in the accumulation of hydroperoxides ROOH during the oxidation of oleic acid at 50 (*1*) and 65 °C (*2*). The oxidation duration is 4 h; the concentrations of the additives are 10^{-3} mol L^{-1}. The ROOH content in the oxidation of oleic acid without additives (blank experiment) was taken as 100%.

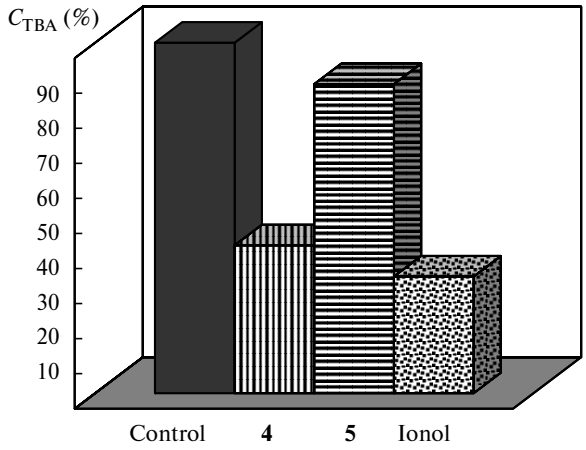
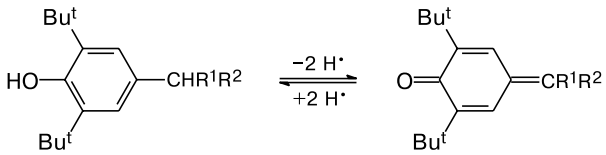


Fig. 7 Antioxidant activities of compounds **4** and **5** and ionol in the accumulation of TBA-dependent oxidation products of liver homogenates of *Wistar* rats at 65 °C (the level of TBA-dependent products in the blank experiment was taken as 100%). The concentrations of the additives are 10^{-3} mol L^{-1}; the oxidation duration is 4 h.

does not act as an antioxidant, providing nearly the same concentration of TBA-dependent oxidation products as in the blank test. Phenols **1** and **2** are better antioxidants than phenols **3** and **4**. Phenol **1** and ionol have comparable inhibitive effects, being inferior to phenol **2**. Interestingly, the inhibitive effect of a 1 : 1 mixture of these phenols and ionol is appreciably higher than the effects of these compounds used separately in the same concentration. Apparently, a synergism takes place in this case.[12]

A comparison of the antioxidant effects and stabilities of the phenoxyls generated in the oxidation of compounds **1**—**4** revealed no direct correlation between these parameters. For instance, the phenoxyls become more stable in the order: $\mathbf{4}^{\bullet} < \mathbf{1}^{\bullet} \approx \mathbf{2}^{\bullet} < \mathbf{3}^{\bullet}$, while their antioxidant activity increases in the order: $\mathbf{3}^{\bullet} < \mathbf{2}^{\bullet} \approx \mathbf{4}^{\bullet} < \mathbf{1}^{\bullet}$. This dependence can be explained by the possible formation of the quinonoid structure for phenols **1**, **2**, and **4** [13] (Scheme 2).

Scheme 2



In this case, the poorly reactive radical of the inhibitor, which is involved in chain termination during the oxidation of a substrate, can be generated both with participation of the phenolic OH group and by abstraction of the benzyl H atom, which will enhance its inhibitive effect. For compound **3**, the formation of a quinonoid structure is impossible so its antioxidant activity is substantially lower.

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