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Oxidation of Phenylphosphonites with Aqueous Hydrogen Peroxide

A. T. Teleshev[a], E. N. Mishina[a], D. A. Ganin[a], V. Yu. Mishina[a], I. V. Abrashina[a], E. E. Nifant'ev[a], A. S. Kononihin[b,c], I. A. Popov[b,c], and E. N. Nikolaev[b,c]

[a] *Moscow Pedagogical State University, Department of Chemistry, Nesvizhskii per. 3, Moscow, 119021 Russia*
e-mail: teleshevat@rambler.ru

[b] *Institute of Energy Problems of Chemical Physics, Russian Academy of Sciences, Moscow, Russia*

[c] *Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, Moscow, Russia*

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Abstract—An effective route to the oxidation of organic derivatives of trivalent phosphorus with an aqueous solution of hydrogen peroxide was considered. Phenylphosphonites, including those having a hydrolytically unstable phosphorus–nitrogen bond were involved into the oxidation. The identification of oxidation products, the phenylphosphonates, was carried out using the method of ion cyclotron resonance mass spectrometry with Fourier transform combined with electrospray ionization, and by ^{31}P and ^{1}H NMR spectroscopy. The influence of an effective antioxidant of natural origin, quercetin, on the oxidation was demonstrated.

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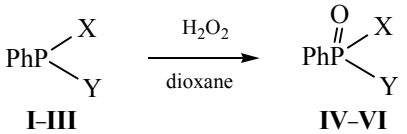
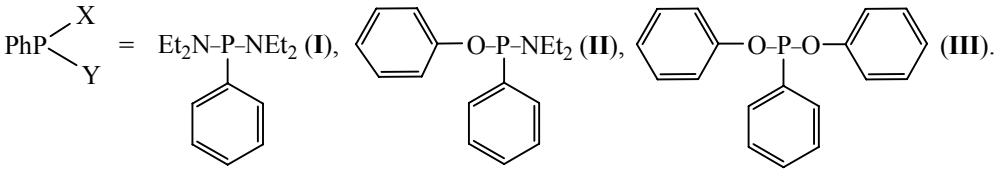
The hydroxy radical is extremely reactive and can oxidize almost all low molecular weight organic compounds [1–3]. A well-known source of the hydroxy radicals is hydrogen peroxide which is capable of effective oxidation of organic compounds including trivalent phosphorus derivatives [4]. The use of hydrogen peroxide for the selective oxidation of the organic compounds of phosphorus(III) is of practical interest, because organophosphorus substances containing pentavalent phosphorus are used in common practice. The use of free hydrogen peroxide, in contrast to the bound one, for example, hyperol [5], does not affect the purity of the oxidation products. However, it should be noted that in preparative practice of organophosphorus chemistry aqueous solution of hydrogen peroxide is commonly used, which not always leads to successful results since the majority of phosphorus(III) organic compounds are insoluble in water and some are readily hydrolyzed [6, 7].

In this paper we discuss the possibilities and conditions for oxidation using an aqueous solution of hydrogen peroxide of a class of phosphorus(III) organic compounds, phosphonites **I–III**, including those containing hydrolytically unstable phosphorus–nitrogen bond (**I, II**), (Scheme 1).

Scheme 1.



I–III **IV–VI**



For the identification of the oxidation products, we suggested to use, along with NMR spectroscopy, the method of mass spectrometry of ion cyclotron resonance with Fourier transform (FTICR-MS) in combination with electrospray ionization. The implementation of the FTICR-MS method for the analysis of organophosphorus compounds is less known than NMR spectroscopy. However, as shown, for example, in [8], the FTICR-MS method can be used effectively for the identification of both individual organophosphorus compounds and in complex mixtures. The main advantages of this method are the ultra-high resolution and accuracy of the mass measurement [9, 10]. On the basis of modern FTICR mass spectrometer with an accuracy in mass measuring of 1 ppm it is possible to identify exactly the empirical formula of a low molecular weight (≤500 Da) phosphorus-containing compound [11].

Preparative oxidation of compounds 1–3 was carried out using 36% aqueous solution of hydrogen peroxide dissolved in dioxane at 8–12°C [12]. According to the ^{31}P NMR spectra, the oxidation of 1.1 mmol of a phosphonite **I–III** in these conditions was completed in 1–2.5 h. The oxidation of diester **III** proceeds faster than that of compounds containing a phosphorus–nitrogen bond.

The reaction products **IV–VI** were identified after separation by the accurate measurement of their masses with the FTICR-MS using electrospray for the ionization of the sample. Additional structural information about the phosphonates **IV–VI** was obtained from ^{31}P and ^{1}H NMR spectroscopy.

In the ICR mass spectrum of compound [$Et_2NP(O)\cdot(Ph)NEt_2$] **IV** of the molecular weight 268.3 there is a series of peaks corresponding to the solvated, protonated, and sodium-containing mono-, di-, and trimolecular cations (Fig. 1 and table).

In the ICR mass spectrum of the product $PhOP(O)\cdot(Ph)NEt_2$ **V** (molecular weight 289.3) there are peaks that characterize the protonated and cationized (sodium) forms of monomer and dimer of compound

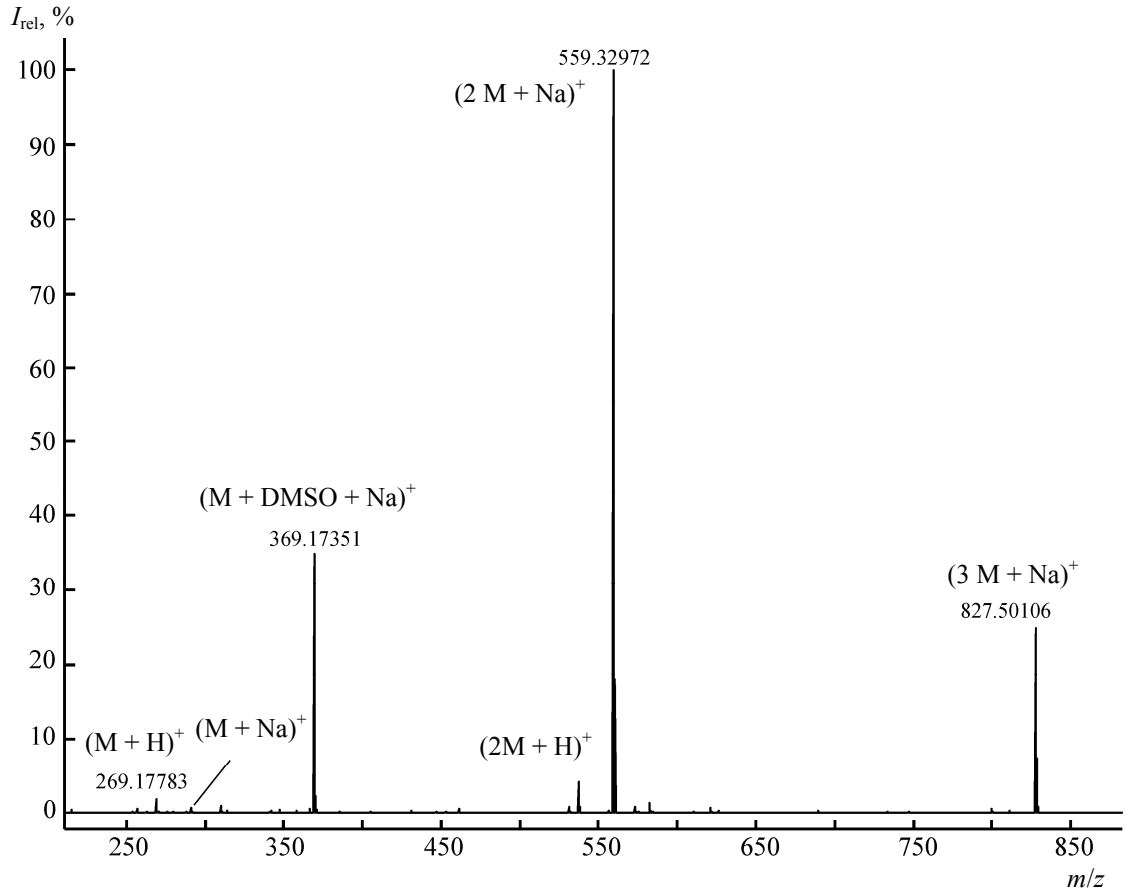


Fig. 1. ICR mass spectrum of compound **IV.**

Ions characterizing the ICR mass spectra of oxidized products **IV–VI**

Compound	Ion	*m*/*z*	Calculated mass, Da	Error, ppm
IV	$Et_2NP(O)(Ph)NEt_2+H^+$	269.17783	269.17773	0.38
	$Et_2NP(O)(Ph)NEt_2+Na^+$	291.15979	291.15967	0.42
	$Et_2NP(O)(Ph)NEt_2+DMSO+Na^+$	369.17351	369.17361	–0.27
	$2Et_2NP(O)(Ph)NEt_2+H^+$	37.34854	537.34818	0.69
	$2Et_2NP(O)(Ph)NEt_2+Na^+$	559.32972	559.33013	–0.72
	$3Et_2NP(O)(Ph)NEt_2+Na^+$	827.50106	827.50058	0.58
V	$PhOP(O)(Ph)NEt_2+H^+$	290.13046	290.13044	0.06
	$PhOP(O)(Ph)NEt_2+Na^+$	312.11252	312.11239	0.42
	$PhOP(O)(Ph)NEt_2+ДМСО+H^+$	368.14447	368.14438	0.24
	$PhOP(O)(Ph)NEt_2+DMSO+Na^+$	390.12628	390.12633	–0.11
	$2PhOP(O)(Ph)NEt_2+H^+$	79.25385	580.25361	0.40
	$2PhOP(O)(Ph)NEt_2+Na^+$	601.23566	601.23556	0.17
VI	$PhOP(O)(Ph)OPh+Na^+$	333.06573	333.06510	1.89
	$PhOP(O)(Ph)OPh+DMSO+Na^+$	411.07867	411.07904	–0.89
	$PhOP(O)(Ph)OPh+2DMSO+Na^+$	489.09277	489.09298	–0.42
	$2PhOP(O)(Ph)OPh+Na^+$	643.14020	643.14099	–1.23
	$3PhOP(O)(Ph)OPh+Na^+$	953.21619	953.21687	–0.71

V, and the corresponding solvated ions of the mono-product (Fig. 2, table). The presence in the spectrum of an unidentified peak with *m*/*z* 363.2 should be noted that corresponds to the ion, which at the fragmentation gives the signal of the starting material **V**.

Molecular mass of [PhOP(O)(Ph)OPh] **VI** is 310.3. In the ICR mass spectrum of this compound in contrast to the spectra of **IV** and **V**, there are only two distinct groups of signals corresponding to the solvated and sodium-containing mono- and bimolecular cations and there is no series of the ions of a protonated form (Fig. 3, table).

The selectivity of the phenylphosphonites oxidation was monitored involving NMR spectroscopy on the ^{31}P nuclei. We found that under the used conditions the aqueous solution of hydrogen peroxide oxidizes phenylphosphonites selectively, without affecting the hydrolytically unstable phosphorus–nitrogen bond. Figure 4a shows the ^{31}P NMR spectrum of the dioxane solution of phenylphosphonous tetraethyldiamide **III** and aqueous hydrogen peroxide after 1.5 h keeping the reaction mixture. The spectrum contains the signal of only one reaction product, the phenylphosphonate **IV**.

To determine the characteristics of oxidation of phenylphosphonites with hydrogen peroxide, and especially those of the compounds containing a hydrolytically unstable phosphorus–nitrogen bond, we used quercetin, a well-known antioxidant of natural origin [13]. The studies with this compound were performed in the tube of the ^{31}P NMR spectrometer, containing dioxane solution of 36% aqueous hydrogen peroxide. Nature of the effect of quercetin on the process confirms the radical chain mechanism of oxidation of the phosphorus(III) organic compounds by hydrogen peroxide [4]. Thus, we found that the rate of oxidation of hydrolytically stable triphenylphosphine is reduced by about half with the introduction of an antioxidant in the reaction mixture, taken in equimolar amounts relative to the organophosphorus compound. In contrast, the oxidation of the phenylphosphonous amide in the presence of quercetin has a pronounced feature. Compared with the control experiment (Fig. 5, curve *1*), quercetin actually slows down the process of the phosphonite **I** oxidation at the initial stage of the reaction (Fig. 5, section AB of the curve *2*). However, then occurs a more intense conversion of phenylphosphonite (Fig. 5, section BC, curve *2*).

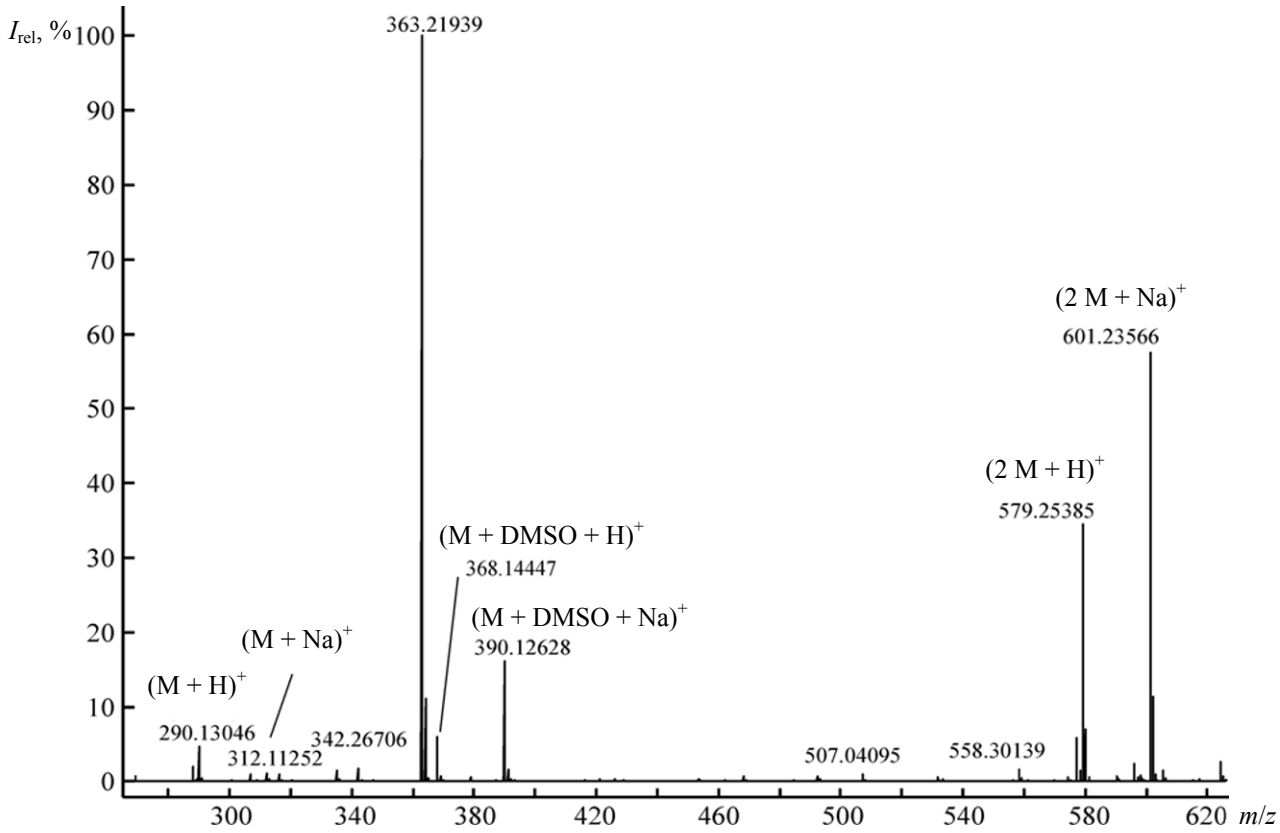


Fig. 2. ICR mass spectrum of compound **V.**

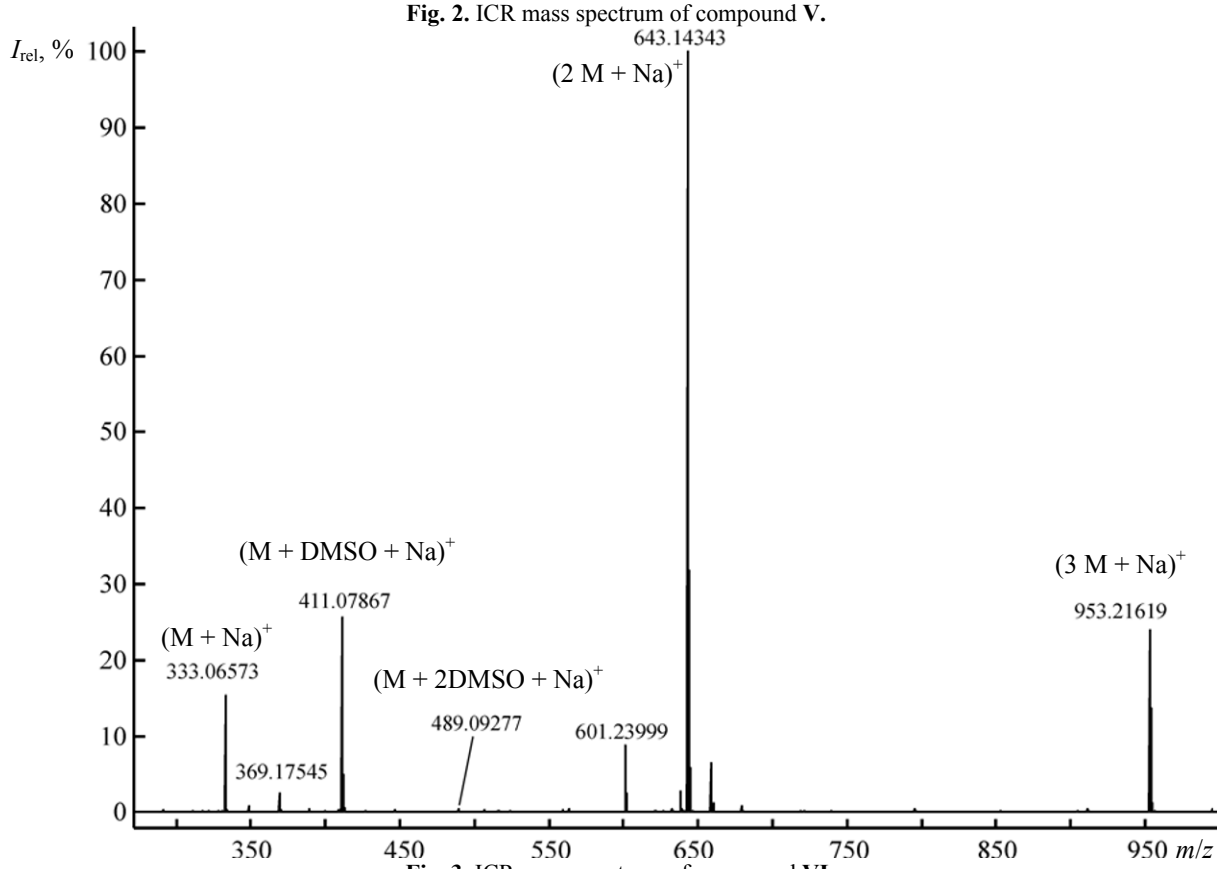


Fig. 3. ICR mass spectrum of compound **VI.**

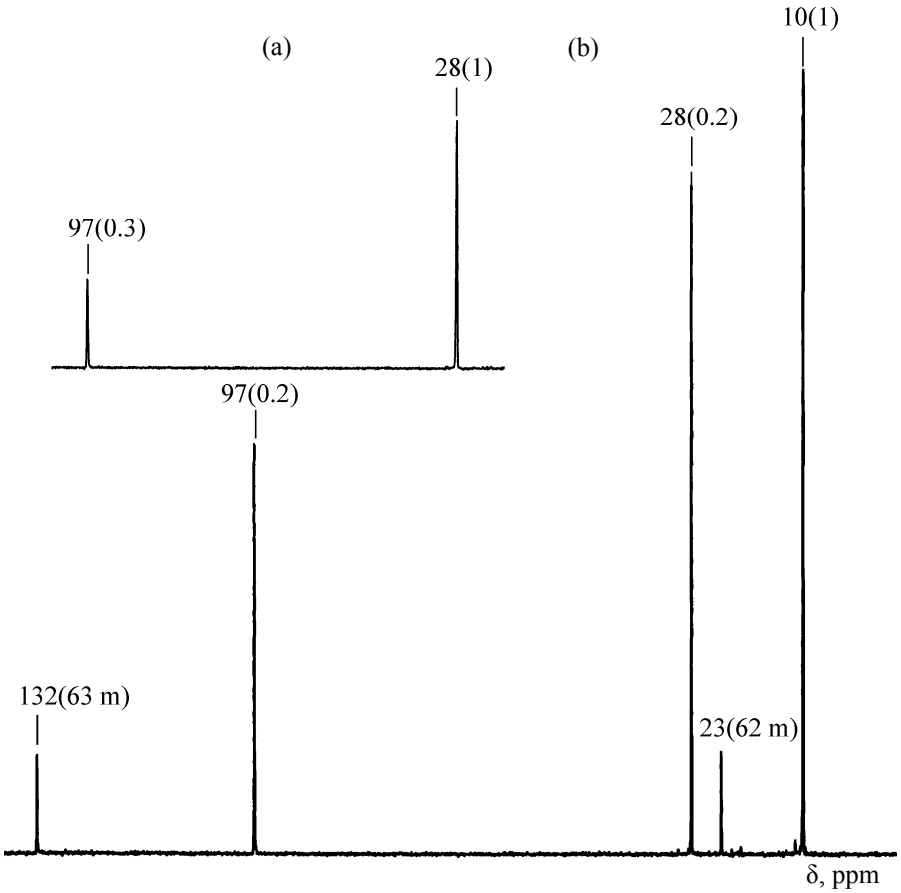


Fig. 4. ^{31}P NMR spectra of the reaction mixtures: (a) phosphonite–hydrogen peroxide and (b) phosphonite–hydrogen peroxide–quercetin.

We assume that the quercetin in the initial stage of the reaction quenches the phosphonite **I** oxidation due to the formation of quercetinyl radicals (Scheme 2).

The quercetinyl radicals are resonace stabilized structures and are unable to continue the chain of free radical reactions [14]. Note that to date the actual

Scheme 2.

$$H_2O_2 \longrightarrow 2HO^{\bullet}$$

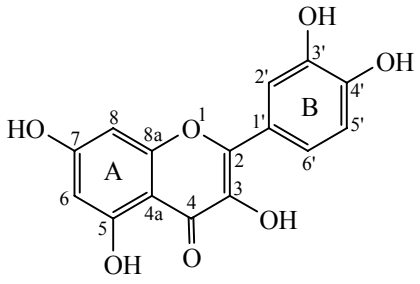
$$HO^{\bullet} + {:}PPh(NEt_2)_2 \longrightarrow HO\dot{P}Ph(NEt_2)_2$$

$$HO\dot{P}Ph(NEt_2)_2 + H_2O_2 \longrightarrow (HO)_2PPh(NEt_2)_2 + HO^{\bullet}$$

$$(HO)_2PPh(NEt_2)_2 \longrightarrow OPPh(NEt_2)_2 + H_2O$$

$$[Qu](OH)_5 + OH^{\bullet} \longrightarrow [Qu](OH)_4O^{\bullet} + H_2O$$

$[Qu](OH)_5$ =



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source of radical species among the hydroxy groups of quercetin molecule has not been established. There is an evidence of the greatest contribution to the antiradical activity of flavonoid of hydroxy groups of the catehol group of ring B, but simultaneously a significant effect on the antiradical activity of quercetin hydroxy group in C^3 position is noted [14, 15].

The intensification of conversion of phenylphosphonite **I** (Fig. 5, section BC in the curve *2*) is probably due to blocking the phosphorylation of the quercetin hydroxy groups responsible for the generation of radical species and subsequent unimpeded oxidation of phosphorus(III)-containing quercetin into the corresponding oxide (Scheme 3).

Scheme 3.

$$[Qu\}(OH)_{5-n} + PPh(NEt_2)_2 \longrightarrow \{[Qu\}(OH)_4OPPh(NEt_2)_{2-n}\} + nHNEt_2$$

$$\{[Qu\}(OH)_4OPPh(NEt_2)_{2-n}\} + H_2O_2 \longrightarrow \{[Qu\}(OH)_4OP(O)Ph(NEt_2)_{2-n}\} + H_2O$$

$n = 1, 2.$

Comparative spectral characteristics of the reaction mixtures phosphonite–hydrogen peroxide (Fig. 4a) and phosphonite–hydrogen peroxide–quercetin (Fig. 4b) indicate just this course of the process. The ^{31}P NMR spectrum of the reaction mixture phosphonite–hydrogen peroxide–quercetin after 1.5-h of keeping contains the signals of initial phosphonite **I**, phosphonate **IV**, the product of quercetin phosphorylation, and its oxidized forms at 97, 28, 132, 23, and 10 ppm, respectively.

Thus, the possibility of selective oxidation of the phosphorus(III) organic compounds, including those containing hydrolytically unstable phosphorus–nitrogen bond, with an aqueous solution of hydrogen peroxide was demonstrated. To identify the oxidation products we suggest to apply the FTICR method of mass spectrometry in combination with electrospray ionization. The effect of quercetin on the oxidation of phosphorus(III) organic compounds with hydrogen peroxide is shown to be consistent with the concept of the radical chain mechanism of the process. It is established that the specific effect of quercetin on the system of phenylphosphonous amide–hydrogen peroxide is due to the blocking phosphorylation of quercetin. The last note should be taken into account at the functionalization of antioxidants of natural origin.

EXPERIMENTAL

The ^1H and ^{31}P NMR spectra were recorded on a JNM-ECX400 spectrometer (Jeol) with internal tetramethylsilane as well as relatively to the residual proton signals of the solvent ($CDCl_3$, 7.27 ppm), or with external 85% phosphoric acid. The mass spectra were obtained on the ICR hybrid mass spectrometer Finnigan LTQ FT (Thermo Electron, Bremen, Germany), which consists of a linear quadrupole ion trap and the FT-ICR mass spectrometer with a 7 T superconducting solenoid. The exact mass values of the objects were measured on the FT-ICR mass spectrometer in positive mode with an error of ~2 ppm. External calibration was carried out using a standard mixture for mass spectrometer setup and calibration (caffeine, MRFA, Ultramark). The electrospray initial parameters are as follows: capillary voltage 3 kV, the feed rate of the solvent in the capillary 1.5 ml min^{-1}. The test samples were prepared as solutions in DMSO.

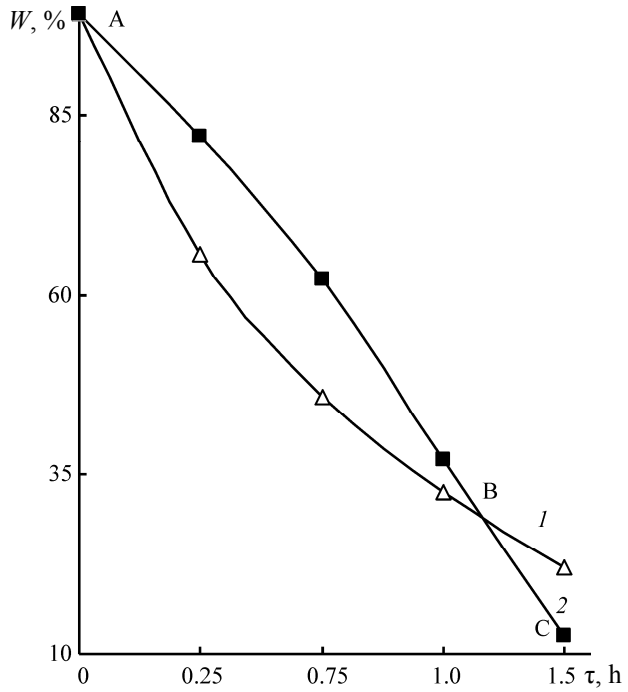

Fig. 5. Dependence of the oxidation rate of phosphonite **I** on the introduction of quercetin.

Phenylphosphonous tetraethyldiamide I was synthesized by reacting dichlorophenylphosphine with excess diethylamine [10]. The product is clear, colorless mobile liquid, bp 137°C (4 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 t (12H, CH_3, $^3J_{HH}$ 7.25 Hz), 3.11 m (8H, CH_2 $^3J_{PH}$ 9.87 Hz), 7.25 m (1H, $CH_{arom.}$, $^3J_{HH}$ 6.63 Hz), 7.36 m (2H, $CH_{arom.}$, $^3J_{HH}$ 1.82 Hz), 7.46 m (2H, $CH_{arom.}$, $^3J_{PH}$ 4.75 Hz). ^{31}P NMR spectrum (hexane), δ 97 ppm.

Phenyl diethylamidophosphonite II was prepared by reacting equimolar amounts of phenol and compound **I** (method *a*) [16], as well as by aminolysis of diphenyl phenylphosphonite **III** (method *b*) [12]. The product is a clear, slightly yellowish, mobile liquid. The ^{31}P NMR spectrum (dioxane), δ_P 131 ppm.

Diphenyl phenylphosphonite III. To 2.05 g (8 mmol) of phenylphosphonous tetraethyldiamide **I** was gradually added 1.52 g (16 mmol) of phenol. The mixture was stirred for 30 min in an argon atmosphere, then heated to 110°C until complete homogenization. With the continuous stirring, the reaction mixture was left under these conditions for 2 h. Then the reaction vessel was connected to a vacuum line and the reaction mixture was kept successively: (a) 2 h at 110°C and 2 h at 170°C (15 mm Hg), (b) 2 h at 110°C and 4 h at 140°C (1 mm Hg). The reaction product is a clear, colorless mobile liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.19 m (6H, $CH_{arom.}$), 7.32 m (4H, $CH_{arom.}$), 7.54 m (2H, $CH_{arom.}$) 7.64 m (1H, $CH_{arom.}$), 7.98 m (2H, $CH_{arom.}$, $^3J_{PH}$ 14 Hz, $^3J_{HH}$ 8 Hz). ^{31}P NMR spectrum (dioxane), δ_P 158 ppm.

Phenylphosphonic tetraethyldiamide IV. To 0.28 g (1.1 mmol) of phenylphosphonous tetraethyldiamide **1** dissolved in 5 ml of dioxane at cooling to 8–12°C while stirring was added dropwise 1.1 mmol of 36% solution of H_2O_2. The reaction mixture was kept for 2.5 h. The reaction product was isolated by column chromatography on silica gel eluting with dioxane (R_f 0.8). After removing the solvent in a film evaporator the residue was kept in a vacuum (1 mmHg) at 50°C for 4 h. Yield 96%. The reaction product is a transparent yellow viscous liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.96 t (12H, CH_3, $^3J_{HH}$ 6,94 Hz), 3.01 m (8H, CH_2, $^3J_{PH}$ 10.23 Hz), 7.37 m (3H, $CH_{arom.}$), 7.70 m (2H, $CH_{arom.}$). ^{31}P NMR spectrum (dioxane), δ_P 28 ppm.

Phenyl diethylamidophenylphosphonite V was prepared from phenyl diethylamidophenylphosphinite **II** along the procedure of the synthesis of compound **IV**. The duration of the mixture exposure was 1.5 h. The product was isolated by column chromatography on silica gel eluting with dioxane (R_f = 0,8). After distilling off the solvent, the residue was kept in a vacuum (1 mm Hg) at 50°C for 4 h. Yield 97%. The reaction product is a transparent yellow viscous liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 t (6H, CH_3, $^3J_{HH}$ 7.12 Hz), 3.12 m (4H, CH_2, $^3J_{PH}$ 11.33 Hz), 6.78 m (1H, $CH_{arom.}$), 6.84 m (2H, $CH_{arom.}$, $^3J_{HH}$ 8.04 Hz), 7.11 m (2H, $CH_{arom.}$), 7.45 m (3H, $CH_{arom.}$), 7.85 d.d (2H, $CH_{arom.}$, $^3J_{PH}$ 12.79 Hz). ^{31}P NMR spectrum (dioxane), δ_P 23 ppm.

Diphenyl phenylphosphonate VI was prepared from diphenyl phenylphosphonite **III** along the method of preparing compound **IV**. The exposure duration was 1 h. After distillation of the solvent, the residue was kept in a vacuum (1 mm Hg) at 50°C for 4 h. Yield 98.7%. The reaction product is a transparent yellow viscous liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.16 m (6H, $CH_{arom.}$), 7.29 m (4H, $CH_{arom.}$, $^3J_{HH}$ 8 Hz), 7.51 m (2H, $CH_{arom.}$), 7.61 m (1H, $CH_{arom.}$, $^3J_{HH}$ 7.31 Hz), 7.97 d.d (2H, $CH_{arom.}$, ^3J PH 13,52 Hz, $^3J_{HH}$ 8 Hz). ^{31}P NMR spectrum (dioxane), δ_P 11 ppm.

General procedure of the oxidation of phenylphosphonites with hydrogen peroxide in the presence of quercetin. The tube of NMR spectrometer was filled with the solution of phenylphosphonite (0.22 mmol) in dioxane (0.6 ml). Then to the solution was added an equimolar amount of quercetin and 36% aqueous solution of hydrogen peroxide in 30% deficit. The ^{31}P NMR spectra were recorded at the initial moment of the reaction and after 15, 45, 60, and 90 min. Parallel to this experiment, with the same intervals were recorded spectra of the phenylphosphonite dioxane solution of the same concentration with 36% aqueous hydrogen peroxide solution taken in 30% deficit, without quercetin.

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