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*Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on Her Jubilee*

# Effect of Organotin Compounds and Their Complexes with Phosphatidylcholine on Peroxide Oxidation of Lipid Structural Fragments

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**Abstract**—Oxidation of a lipid structural fragment, oleic acid, in the presence of a series of organotin compounds and their complexes with phosphatidylcholine was studied at 25, 37, 65, and 95°C. At a nearly physiological temperature, acceleration of hydroperoxide accumulation in the presence of these complexes was observed. At 65°C, addition of organotin derivatives leads to increase in the initial rate of hydroperoxide accumulation, but the kinetic curves acquire an *S*-like character as the reaction progresses. These data indicate that the rate of decomposition of hydroperoxides exceeds the rate of their accumulation. In the presence of 2,6-di-*tet*-butylphenol as antioxidant, the promoting effect of organotin compounds disappears. A possible reaction mechanism and the role of radical species arising from dissociation of the C–Sn bond are discussed.

Organotin derivatives $R_nSnX_{4-n}$ are widely used as stabilizers for polymeric materials, antifouling coatings, catalysts, and biocides. Organotin compounds are ecotoxicants whose action depends on their structure [1]. The mechanism of toxic effect of organotin compounds is fairly complicated, and it cannot be regarded as thoroughly studied. It is assumed that these compounds are capable of reacting with cell membranes, finally leading to their decay, accelerating ion exchange processes, and inhibiting oxidative and photochemical phosphorylation [2–4]. Among $R_nSnX_{4-n}$ compounds, the most toxic are $R_3SnX$. Biological activity of organotin compounds is generally interpreted in terms of their ability to bind to cysteine and hystidine moieties of proteins [2, 3]. On the other hand, one cannot rule out the possibility for organotin compounds to be involved in other biological processes occurring in cells, specifically in peroxide oxidation of lipids. The latter process is very important from the viewpoint of physiology, and it follows a radical chain mechanism [4–5]. Acceleration of peroxide oxidation of lipids in cells leads to accumulation of hydroperoxides, decay of cell membranes, and various pathologies in living bodies.

Insofar as organotin compounds exhibit electron-acceptor properties, it was presumed that their toxicity originates from interaction with electron-donor groups in biomolecules. Reactions of organotin compounds with phosphorus-containing biomolecules, such as phospholipids, ATP, nucleic acids, etc., were shown to inhibit the synthesis of phospholipids and their intracellular transport, which may be responsible for the antiproliferative activity of organotin derivatives [6, 7]. It must also be taken into account that organotin compounds can react with phosphorus-containing fragments of biomolecules in cell membranes to form complexes with dative Sn–O–P bonds [8, 9]. In this case, the mechanism of peroxide oxidation of lipids may change.

The goal of the present work was to study peroxide oxidation of oleic [(*Z*)-octadecenoic] acid in the presence of complexes derived from $R_nSnCl_{4-n}$ and phosphatidylcholine [$^{-}OP(O)(OH)OCH_2CH_2\overset{+}{N}(Me)_3$, PChol] which is a short-chain analog of phospholipids, as well as to compare the effects of the complexes $(R_3SnCl)_2 \cdot PChol$ (R = Me, Ph), $R_2SnCl_2 \cdot PChol$ (R = Me, Bu), and $RSnCl_3 \cdot PChol$ (R = Me, Ph) with that produced by the organotin compounds themselves.

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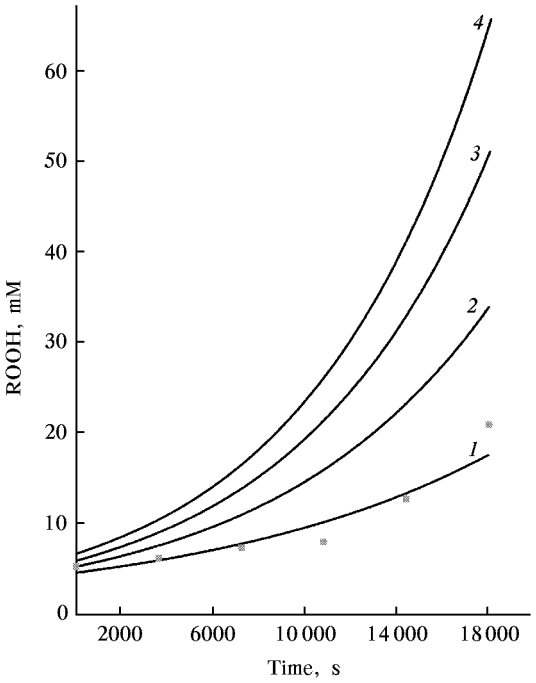


**Fig. 1.** Kinetic curves for accumulation of hydroperoxides R′OOH in the oxidation of oleic acid in the presence of organotin compounds (1 mM) at 37°C: (*1*) no organotin compound added, (*2*) $MeSnCl_3$, (*3*) $Me_2SnCl_2$, (*4*) $Me_3SnCl$.

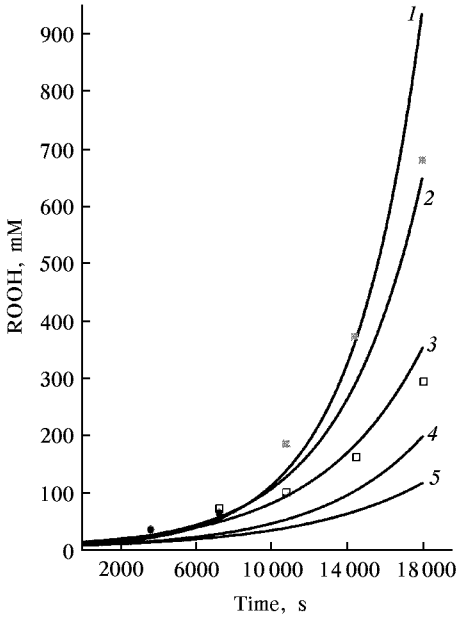


**Fig. 2.** Kinetic curves for accumulation of hydroperoxides R′OOH in the presence of 2,6-di-*tert*-butylphenol and organotin compounds $R_3SnCl$ at 65°C: (*1*) no organotin compound added, (*2*) $Ph_3SnCl$, (*3*) $Me_3SnCl$, (*4*) $Et_3SnCl$, (*5*) $Bu_3SnCl$. Concentration of 2,6-di-*tert*-butylphenol and organotin additive 1 mM.

The oxidation of oleic acid as R′H hydrocarbon follows a radical chain mechanism and leads to formation of peroxides and hydroperoxides R′OOH as intermediate products which are capable of decomposing to give alcohols and carbonyl compounds [10]. In the presence of $R_nSnCl_{4-n}$ (R = Me, Ph, $n$ = 1–3; R = Bu, $n$ = 2, 3), the formation of R′OOH is accelerated at 25, 37, 65, and 95°C. The rate constant increases in parallel with the number of organic groups in the organotin molecule, which is consistent with variation of biological activity of these compounds (Fig. 1). The kinetic curves for accumulation of hydroperoxides in the presence of organotin compounds are well described by exponential equations, and the corresponding semilog plots are linear, in keeping with the first-order kinetics. Therefore, we can calculate relative parameters characterizing kinetic relations of the process [$k_i/k_0$ and $q_i = A_i/A_0$, where $k_0$ is the pseudofirst-order rate constant for oleic acid oxidation in the absence of organotin compound, and $k_i$ is the same in the presence of it; $A_i = (c_i - c_0)/c_0$; $c_i$ is the concentration of peroxides 5 h after the reaction onset, $c_0$ is the initial hydroperoxide concentration in experiments without addition of organotin compounds; and $A_0$ is an analogous quantity for experiments with no organotin compound added]. For the compounds under study, $k_i/k_0 > 1$ and $q_i = A_i/A_0 > 1$ throughout the examined temperature range (25–95°C); the above quantities reach their maximal values at 37°C, i.e., at a temperature close to physiological. The strongest promoting effect was observed at that tamperature for $Me_3SnCl$, and the weakest, for $Bu_2SnCl_2$. It is well known that $S_N2$ substitution reactions at a tin atom occur very readily [11, 12]. The observed acceleration of oleic acid oxidation in the presence of $R_nSnCl_{4-n}$ may be explained on the assumption that these compounds react with peroxyl radicals, leading to rupture of the C–Sn bond and formation of C-centered alkyl radicals:

$$R'OO^{\cdot} + R_nSnCl_{4-n} \longrightarrow R_{n-1}SnCl_{4-n}(OOR') + R^{\cdot}$$

Sterically hindered phenols are known to act as antioxidants which effectively inhibit radical processes, including liquid-phase radical chain oxidation of hydrocarbons [13, 14]. We examined oxidation of oleic acid in the presence of $R_nSnCl_{4-n}$ and 2,6-di-*tert*-butylphenol simultaneously. In all cases, the oxidation of oleic acid was inhibited, and the magnitude of the inhibitory effect depended on the nature and number of organic groups in organotin compounds. The effect weakened as the number of organic groups in the organotin molecule increased. In the presence of $PhSnCl_3$, $EtSnCl_3$, $Et_2SnCl_2$, $Bu_2SnCl_2$,

$Bu_3SnCl$, and $Me_2SnCl_2$, the effect was almost the same as in the presence of 2,6-di-*tert*-butylphenol; for the other organotin compounds, the effect was considearbly weaker. In the series of $R_3SnCl$ derivatives, the greatest inhibitory effect of 2,6-di-*tert*-butylphenol was observed for $Bu_3SnCl$, and the smallest, for $Ph_3SnCl$ (Fig. 2).

Complexes of organotin compounds with phosphatidylcholine accelerate accumulation of hydroperoxides at 37°C (Fig. 3). The complexes $(R_3SnCl)_2 \cdot$ PChol (R = Me, Ph), $(R_2SnCl_2)_2 \cdot$PChol (R = Me, Bu), and $RSnCl_2$–PChol (R = Me, Ph) act as prooxidants, and their promoting effect is comparable with that observed for the corresponding organotin compounds $R_nSnCl_{4-n}$. At higher temperature (65°C), in the initial period (during ~3 h), the oxidation of oleic acid is appreciably accelerated. However, later on, the rate of hydroperoxide accumulation in the presence of organotin compounds sharply decreases, and the kinetic curves acquire an *S*-like shape (Fig. 4). This indicates that, after a certain time, the rate of hydroperoxide decomposition in the presence of complexes becomes equal to the rate of their formation.

The kinetic curves for accumulation of R′OOH at 37°C in the presence of the complexes well fit exponential equations, and the corresponding log plots are linear (correlation coefficient 0.93–0.98). Table contains the rate constants $k_i$ and ratios $k_i/k_0$, which were calculated assuming first order of the reaction (when oleic acid is present in excess). Analysis of the kinetic data and the quantities $A_i = (c_i - c_0)/c_0$ and $q_i = A_i/A_0$ shows that all the complexes under study accelerate the oxidation process and that their promoting effect increases as the number of organic groups in the complex increases. The strongest acceleration is observed for the complex $(Ph_3SnCl)_2 \cdot$PChol, and the weakest, for $PhSnCl_3 \cdot$PChol. At 65°C, the kinetic curves are *S*-shaped, and they are approximated with a sufficient accuracy by third-degree polynomials. For quantitative analysis, we selected initial parts of the above dependences, corresponding to the first ~3 h of the oxidation process. They are also described by $e^{at}$ functions. The values of $k_i$, $k_i/k_0$, and $q_i = A_i/A_0$ (see table) characterize the ratio of initial rates of oleic acid oxidation at 65°C in the presence of the complexes $R_nSnCl_{4-n} \cdot$PChol and in the absence of them. It is seen that in the initial period the complexes act as prooxidants, and their effect is comparable with the effect of the corresponding organotin compounds. Thus the complexes with phosphatidylcholine are systems with a variable effect. In the initial period, they promote oxidation of oleic acid, while at higher conversion they inhibit the process. These results do not contradict the assumption that binding of toxic organotin compounds to phospholipids does not prevent them from promoting peroxide oxidation of lipids; radical species formed by dissociation of the C–Sn bond could be responsible for that effect.

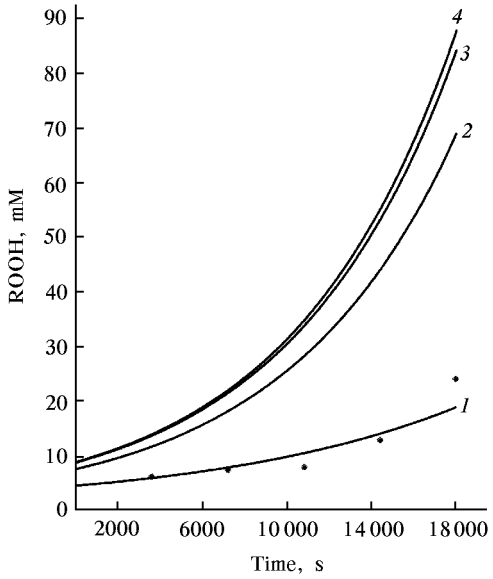


**Fig. 3.** Kinetic curves for accumulation of hydroperoxides in the oxidation of oleic acid at 37°C (*1*) in the absence of additives and in the presence of (*2*) $MeSnCl_3 \cdot$PChol, (*3*) $Me_2SnCl_2 \cdot$PChol, and (*4*) $(Me_3SnCl)_2 \cdot$PChol. Concentration of $MeSnCl_3 \cdot$PChol and $Me_2SnCl_2 \cdot$PChol 1 mM; concentration of $(Me_3SnCl)_2 \cdot$PChol 0.5 mM.

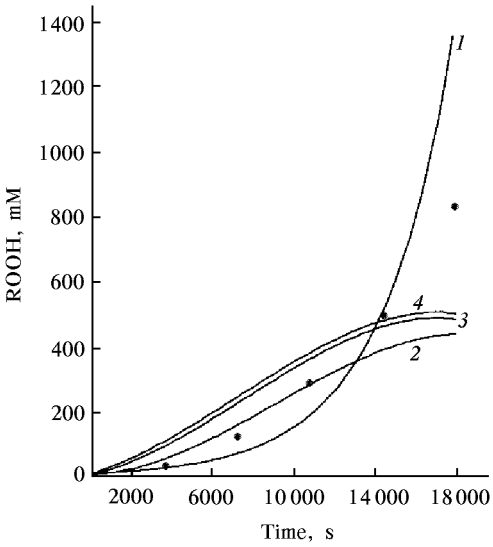


**Fig. 4.** Kinetic curves for accumulation of hydroperoxides in the oxidation of oleic acid at 65°C (*1*) in the absence of additives and in the presence of (*2*) $PhSnCl_3 \cdot$PChol, (*3*) $Ph_2SnCl_2 \cdot$PChol, (*4*) $(Ph_3SnCl)_2 \cdot$PChol. Concentration of $PhSnCl_3 \cdot$PChol and $Ph_2SnCl_2 \cdot$PChol 1 mM; concentration of $(Ph_3SnCl)_2 \cdot$PChol 0.5 mM.

Kinetic parameters of oleic acid oxidation in the presence of phosphatidylcholine complexes with organotin compounds $R_nSnCl_{4-n} \cdot PChol$ at 37 and 65°C

| Additive | 37°C | | 65°C | |
|---|---|---|---|---|
| | $k_i/k_0$ | $q_i$ | $k_i/k_0$ | $q_i$ |
| No additive | 1 | 1 | 1 | 1 |
| $MeSnCl_3 \cdot PChol$ | 2.11 | 2.06 | 1.41 | 1.23 |
| $Me_2SnCl_2 \cdot PChol$ | 2.15 | 2.64 | 1.51 | 1.31 |
| $(Me_3SnCl)_2 \cdot PChol$ | 2.14 | 2.61 | 1.63 | 1.39 |
| $Bu_2SnCl_2$ | 2.16 | 2.9 | 1.59 | 1.19 |
| $(Bu_3SnCl)_2 \cdot PChol$ | 2.21 | 2.85 | 1.66 | 1.54 |
| $PhSnCl_3 \cdot PChol$ | 2.12 | 2.09 | 1.44 | 1.24 |
| $Ph_2SnCl_2 \cdot PChol$ | 2.25 | 2.33 | 1.59 | 1.22 |
| $(Ph_3SnCl)_2 \cdot PChol$ | 2.31 | 2.45 | 1.85 | 1.49 |

## EXPERIMENTAL

The oxidation of oleic acid was studied in the temperature range from 25 to 95°C using a setup maintained at constant temperature with continuous supply of air at a flow rate of 2–4 ml/min. The reaction occurred in the kinetic region, i.e., the rate of oxidation did not depend on the volume of supplied oxygen [15]. The reaction was carried out as autooxidation with no initiators; therefore, at 25–37°C, before addition of $R_nSnCl_{4-n}$ and $R_nSnCl_{4-n} \cdot PChol$, air was preliminarily bubbled through oleic acid over a period of 2 h. Oleic acid of pure grade (a mixture of *cis* and *trans* isomers) was used. The concentration of hydroperoxides was determined by standard procedure (titration with a 0.01 N solution of sodium thiosulfate [16]). The coefficients of approximation of kinetic curves were 0.93–0.993. All organotin compounds were synthesized and purified by known methods; their purity was no less than 98%. Phosphatidylcholine was synthesized from the corresponding calcium salt (Sigma), following the procedure reported in [17]; Amberlite CG-50 resin was used for $Ca^{2+}$ exchange. The complexes $RSnCl_3 \cdot PChol$, $R_2SnCl_2 \cdot PChol$, and $(R_3SnCl)_2 \cdot PChol$ (R = Me, Ph, $n$ = 1–3; Bu, $n$ = 2–3) were synthesized as described in [18]. In all experiments the concentration of $R_nSnCl_{4-n}$ and $RSnCl_3 \cdot PChol$ and $R_2SnCl_2 \cdot PChol$ was $1 \times 10^{-3}$ M. The concentration of $(R_3SnCl)_2 \cdot PChol$ was $0.5 \times 10^{-3}$ M. The concentration ratio of 2,6-di-*tert*-butylphenol and $R_nSnCl_{4-n}$ was 1 : 1.

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