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The promoting effect of organotin compounds upon peroxidation of oleic acid

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The effect of the organotin compounds R_nSnCl_{4-n} ($n = 1$–3; where R = Me, Et, *n*-Bu and Ph) upon oleic ((*Z*)-9-octadecenoic) acid oxidation by dioxygen has been studied at 25, 37, 65, and 95 °C. The promoting effect of organotins upon the formation of oleic acid hydroperoxides is temperature dependent and is at a maximum at a temperature close to the physiological one, but the impact of organotins upon oleic acid peroxidation decreases in the presence of 2,6-di-*tert*-butylphenol. The role of organic free radicals derived from the Sn—C bond cleavage in the oxidation of oleic acid is discussed. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: organotin compounds; oleic acid; peroxidation; free radicals

INTRODUCTION

Organotin compounds are exotoxicants.[1] Organotins can elicit a wide range of endocrine and nervous-system effects, depending on the nature and number of organic groups bonded to the tin atom.[2] The most pronounced toxicity is shown by triorganotin compounds, R_3SnX.[3] The mechanism of their toxicity is very complex. It includes interaction with mitochondrial membranes to cause swelling and disruption, secondary effects derived from their ability as ionophores to derange mitochondrial functions through mediation of chloride–hydroxide ion exchange across lipid membranes, and their ability to inhibit mitochondrial oxidative phosphorylation; in chloroplasts, they inhibit photosynthetic phosphorylation. It can be assumed that these compounds influence important physiological processes such as lipid peroxidation, which can lead to diverse pathologies.[4] It was observed that the rate of lipid peroxidation in biological tissues increased in the presence of some organotin compounds.[5] It is well known that R_nSnX_{4-n} compounds can interact with organic peroxides and hydroperoxides.[6–12] In these reactions, the cleavage of an Sn—C bond and the formation of alkyl radicals (R·) is observed. These highly active radicals can take part in intermediate steps of radical chain reactions, such as unsaturated hydrocarbon oxidations, and promote them. The goal of this work was to study the influence of organotin compounds on the peroxidation of oleic acid as the model compound for lipid peroxidation.

RESULTS AND DISCUSSION

The peroxidation of oleic acid ((*Z*)-9-octadecenoic acid, R′H) follows the kinetics of hydrocarbon radical chain reactions that result in formation of peroxides, peroxyl radicals, and hydroperoxides (R′OOH) as main products.[13] Acceleration of R′OOH formation has been observed at 25, 37, 65, and 95 °C in the presence of all organotins under investigation. The kinetic curves for R′OOH production in the presence of Me_nSnX_{4-n} ($n = 1$–3) at 37 °C are shown in Fig. 1. The activity of methyl derivatives of tin increases with the number of organic groups in Me_nSnX_{4-n} ($n = 1$–3) molecules, which is in accordance with their biological activity.

The kinetic parameters for R′OOH formation in the presence of R_nSnX_{4-n} compounds are presented in Table 1 (rate constants k_i and relative change of concentration A_i values) and Table 2 (k_i/k_0 and $q_i = A_i/A_0$ values). The kinetic curves for hydroperoxides formation are well described by exponential functions, and the time dependence of plotted values of $\ln(C/C_0)$ is linear, which corresponds to a pseudo-first-order reaction. The fact that k_i/k_0 is greater than unity

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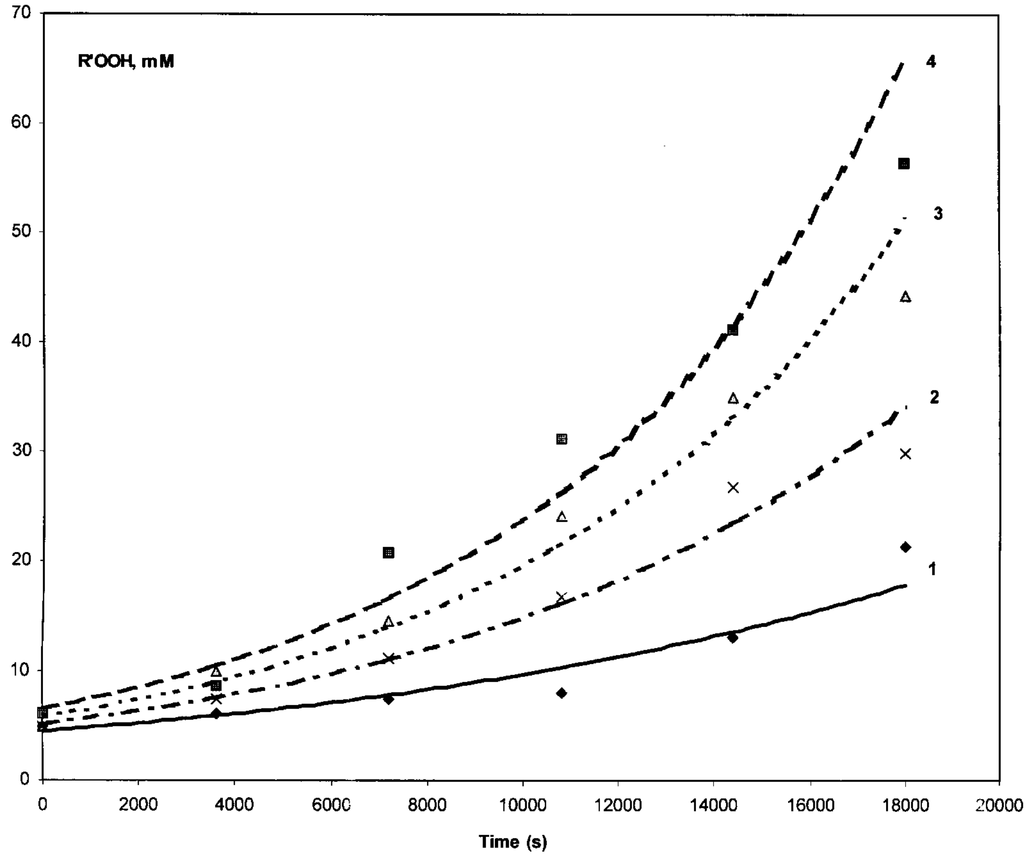

Figure 1. Curves for R′OOH formation in the presence of Me_nSnCl_{4-n} at 37 °C: (1) oleic acid without additive (——); (2) with $MeSnCl_3$ (- . - . -); (3) with Me_2SnCl_2 (. . . . .); (4) with Me_3SnCl (- - -). The additive concentration was 1 mM.

over the whole range of temperatures under investigation implies that the rate of R′OOH formation is greater than the rate of R′OOH decomposition in these conditions. For all the systems studied, k_i/k_0 and $q_i = A_i/A_0$ values have their maxima at 25–37 °C and decrease with temperature growth. This shows that the magnitudes of the organotin effects are the greatest at temperatures close to the physiological temperature. The curves for R′OOH formation in the

Table 1. R′OOH formation rate constants k_i and $A_i = (C - C_0)/C_0$ in the presence of organotin compounds at various temperatures

	25 °C		37 °C		65 °C	
Additives	$k_i \times 10^{-4}$ (s^{-1})	A_i	$k_i \times 10^{-4}$ (s^{-1})	A_i	$k_i \times 10^{-4}$ (s^{-1})	A_i
No additives	0.57	3.27	0.69	3.6	2.9	90.84
$MeSnCl_3$	0.92	3.7	1.1	5.57	2.93	111.17
Me_2SnCl_2	0.97	4.05	1.3	6.25	2.95	113.3
Me_3SnCl	1.36	7.25	1.5	10.7	3.21	115.75
$EtSnCl_3$	0.98	3.75	1.04	5.06	3.3	129.32
Et_2SnCl_2	1.1	4.5	1.3	9.04	3.26	131.95
Et_3SnCl	2.18	6.37	1.4	9.64	3.33	137.38
n-Bu_2SnCl_2	0.99	4.56	1.01	4.8	3.31	126.72
n-Bu_3SnCl	1.03	4.9	1.09	5.1	3.4	134.44
$PhSnCl_3$	0.94	4.45	1.05	6.1	3.15	117.2
Ph_2SnCl_2	0.96	4.76	1.29	6.9	3.25	124.2
Ph_3SnCl	1.17	5.45	1.33	9.5	3.42	141.6

Table 2. k_i/k_0 and $q_i = A_i/A_0$ values for R′OOH formation in the presence of organotin compounds at various temperatures

	25 °C		37 °C		65 °C	
Additives	k_i/k_0	q_i	k_i/k_0	q_i	k_i/k_0	q_i
No additives	1	1	1	1	1	1
$MeSnCl_3$	1.6	1.13	1.57	1.43	1.09	1.22
Me_2SnCl_2	1.71	1.22	1.85	1.61	1.1	1.25
Me_3SnCl	2.38	2.21	2.17	3.27	1.19	1.3
$EtSnCl_3$	1.71	1.14	1.58	2.41	1.23	1.43
Et_2SnCl_2	1.93	1.29	1.6	1.72	1.22	1.46
Et_3SnCl	2.18	1.82	1.79	2.45	1.23	1.45
n-Bu_2SnCl_2	1.74	1.4	2.01	2.62	1.23	1.4
n-Bu_3SnCl	1.8	1.49	1.47	1.45	1.26	1.55
$PhSnCl_3$	1.65	1.36	1.49	1.54	1.05	1.03
Ph_2SnCl_2	1.68	1.46	1.83	2.52	1.20	1.38
Ph_3SnCl	2.05	1.67	1.4	2.55	1.26	1.56

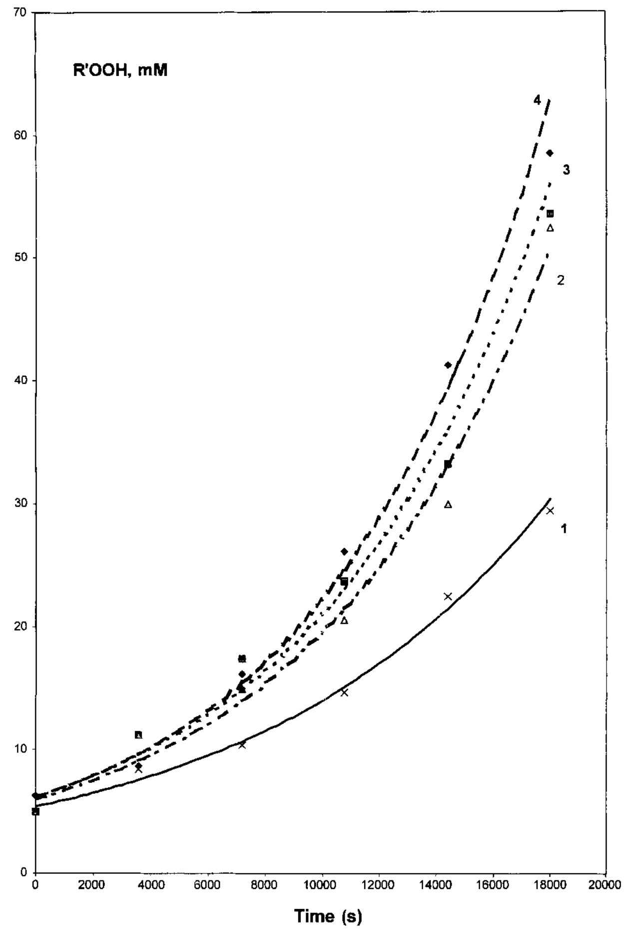

Figure 2. Curves for R′OOH formation in the presence of various R_3SnCl species at 37 °C: (1) oleic acid without additive (——); (2) with Et_3SnCl_3 (- . - . -); (3) with Ph_3SnCl (. . . . .); (4) with Me_3SnCl (- - -). The additive concentration was 1 mM.

presence of R_3SnX compounds (R = Me, Et, n-Bu, Ph) at 37 °C are shown in Fig. 2. The greatest effect on R′OOH acceleration at this temperature is observed for Me_3SnCl, the least effect is for Bu_3SnCl. This fact correlates with the literature data concerning the dependence of organotin biological activity upon the organic group.

It is well known that S_H2 bimolecular radical substitution at the tin atom can proceed quite easily. The interaction of peroxyl radicals with organotin compounds leads to the cleavage of Sn—C bonds and the formation of active alkyl radicals, R·:[14]

$$R'OO\cdot + R_nSnX_{4-n} \rightarrow R_{n-1}SnX_{4-n}(OOR') + R\cdot \qquad (1)$$

Clearly, these reactions can lead to the growth of active radical concentrations that may serve as initiators and result in acceleration of R′OOH formation.

On the other hand, the decrease of k_i/k_0 values along with temperatures above 37 °C can be explained by the relative increase of R′OOH decomposition rates in reactions of R_nSnX_{4-n} with hydroperoxides at higher temperature:

$$R'OOH + R_nSnX_{4-n} \rightarrow R_nSnX_{3-n}(OOR') + HX \qquad (2)$$

The promoting effect of R_nSnX_{4-n} upon R′OOH formation depends on temperature. The greatest effect is shown by Me_3SnCl in the temperature range 25–37 °C. At higher temperatures the k_i/k_0 values of all systems are within the range 1.1–1.26.

The relative changes of concentrations, $A_i = (C_i - C_0)/C_0$ (C_i = R′OOH concentration after 5 h of oxidation; C_0 = R′OOH concentration before oxidation), are presented in Table 1. These results correlate strongly with the kinetic data: whereas A_i increases with rise in temperatures, the q_i ($q_i = A_i/A_0$) values have their maximum in the range 25–37 °C. All the organotin compounds promote oleic acid

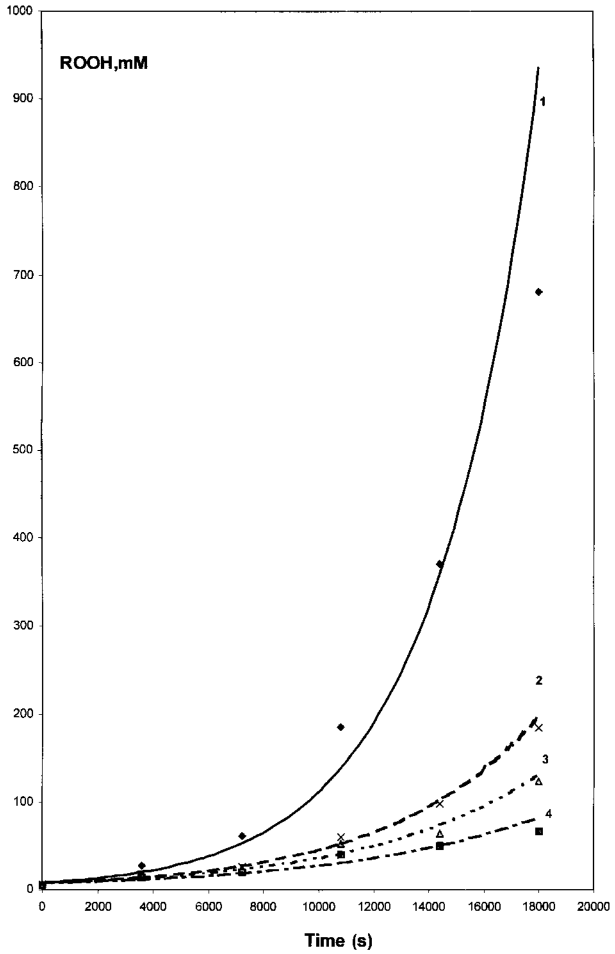

Figure 3. Kinetic curves for R′OOH formation in the presence of R_nSnX_{4-n} (R = Et) and 2,6-di-*tert*-butylphenol at 65 °C: (1) oleic acid without additive (——); (2) with Et_3SnCl (- - -); (3) with Et_2SnCl_2 (. . . . .); (4) with $EtSnCl_2$ (- . - . - .). The additive concentration was 1 mM. The ratio of Et_nSnX_{4-n} to 2,6-di-*tert*-butylphenol was 1:1.

peroxidation. This effect might be one of the causes of high organotin compound toxicities.

It is well known that sterically hindered phenols are effective synthetic antioxidants.[15] Oleic acid oxidation has also been studied in the presence, both of organotin compounds and the inhibitor of radical chain reactions, 2,6-di-*tert*-butylphenol. R′OOH formation curves in the presence of methyl derivatives of tin and inhibitor are shown in Fig. 3. The rate of R′OOH formation decreases when compared with the rate of the process without additives. The values k_i, k_i/k_0, A_i, and q_i in the presence of R_nSnX_{4-n} and 2,6-di-*tert*-butylphenol are presented in Table 3. It is interesting to note that the values of k_i/k_0 and q_i depend strongly upon both the nature and the number of R in R_nSnX_{4-n}. In the presence of 2,6-di-*tert*-butylphenol and $PhSnCl_3$ the decrease of the rate of R′OOH formation is at a

Table 3. R′OOH formation rate constants k_i, k_i/k_0, $A_i = (C - C_0)/C_0$, and $q_i = A_i/A_0$ values for oleic acid oxidation in the presence of R_nSnX_{4-n} and 2,6-di-*tert*-butylphenol at 65 °C

Additives	$k_i \times 10^{-4}$ (s^{-1})	k_i/k_0	A_i	q_i
No additives	2.7 ± 0.28	1	90.84	1
2,6-Di-*tert*-butylphenol only	1.73 ± 0.15	0.64	32.7	0.36
$MeSnCl_3$	1.81 ± 0.12	0.67	17.6	0.19
Me_2SnCl_2	1.76 ± 0.18	0.65	15.6	0.17
Me_3SnCl	2.25 ± 0.06	0.83	38.1	0.42
$EtSnCl_3$	1.39 ± 0.16	0.52	16.25	0.18
Et_2SnCl_2	1.51 ± 0.16	0.56	19	0.19
Et_3SnCl	1.84 ± 0.09	0.68	28.5	0.31
n-Bu_2SnCl_2	1.45 ± 0.07	0.53	11.4	0.13
n-Bu_3SnCl	1.61 ± 0.036	0.59	11.5	0.13
$PhSnCl_3$	1.62 ± 0.009	0.6	12.7	0.14
Ph_2SnCl_2	2.37 ± 0.2	0.88	36.5	0.37
Ph_3SnCl	2.46 ± 0.14	0.91	71.2	0.78

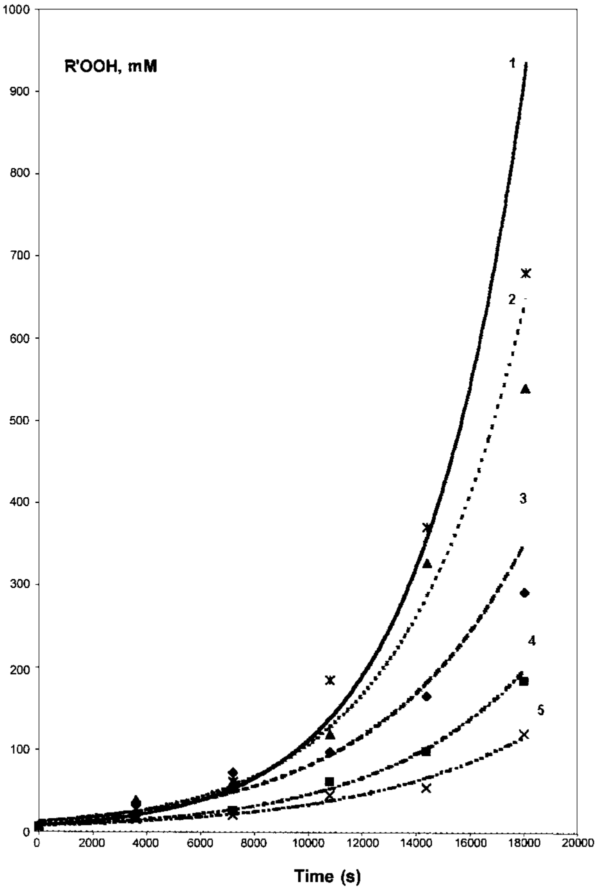

Figure 4. The dependence of R′OOH formation upon the nature of the R group in R_3SnX compounds in the presence of 2,6-di-*tert*-butylphenol at 65 °C: (1) without additive (——); (2) with Ph_3SnX (. . . . .); (3) with Me_3SnX (- - -); (4) with Et_3SnX (- . - . - .); (5) with Bu_3SnX (- . . . - . . . -). The ratio of R_3SnX to 2,6-di-*tert*-butylphenol was 1:1.

minimum, whereas in case of Ph_3SnCl as organotin additive it is at a maximum. For all the additives, the value of the inhibiting effect decreases with the growth of the R number, i.e. in accordance with their promoting activity. It can be seen that in the cases of $PhSnCl_3$, $EtSnCl_3$, Et_2SnCl_2, n-Bu_2SnCl_2, $(n\text{-}Bu)_3SnCl$, and Me_2SnCl_2 the inhibiting effects are of almost equal level with the effect of 2,6-di-*tert*-butylphenol as the only additive, but in the cases of other compounds this effect is a significantly lesser one. The dependence of oleic acid oxidation upon the nature of the organic group in the presence of R_3SnCl (R = Me, Et, n-Bu, Ph) and the inhibitor is demonstrated in Fig. 4. It can be seen that in this case the greatest effect of inhibition is observed for n-Bu_3SnCl and the least effect is for Ph_3SnCl.

EXPERIMENTAL

Oleic acid [(Z)-octadecenoic acid] (Sigma) was used as supplied. The oxidation of a constant volume of oleic acid (5 ml) was carried out in a thermostatic cell using a constant-rate air flow of 2–4 ml min at 25, 37, 65 and 95 °C in the presence of $MeSnCl_3$, Me_2SnCl_2, Me_3SnCl, $EtSnCl_3$, Et_2SnCl_2, Et_3SnCl, n-Bu_2SnCl_2, $(n\text{-}Bu)_3SnCl$, $PhSnCl_3$, Ph_2SnCl_2, Ph_3SnCl. Under these conditions the oxidation proceeded in the 'kinetic range', i.e. in such a way that the oxidation rate was independent of the air volume passing through the cell.[15] The oxidation proceeds without addition of radical chain initiators, i.e. as on auto-oxidation. At temperatures 25–37 °C before addition of R_nSnX_{4-n} the air flow had been passed through the oleic acid for 2 h. All organotin compounds used were purchased, or were synthesized and purified by normal methods, to purities of not less than 98%. The additive concentrations were 10^{-3} M in all experiments. In the case of the simultaneous presence of the organotin promoter and 2,6-di-*tert*-butylphenol the concentration ratio was 1:1. The rate of R'OOH formation was determined by the iodometric titration method.

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