SYNERGISM OF SULFUR-CONTAINING PHENOL (SO-4) WITH MEXIDOL, α-TOCOPHEROL, AND PHOSPHOLIPIDS

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The antioxidant activity of mexidol (a 3-hydroxypyridine derivative) and sulfur-containing sterically hindered phenol (SO-4) was studied in an initiated oxidation model system in comparison α-tocopherol and dibunol. A linear dependence of the oxidation inhibition effect on the concentration of both substances is established. The antioxidants are capable of destroying hydroperoxides and inhibiting their accumulation. The joint inhibiting action of SO-4 in combination with mexidol, α-tocopherol and phospholipids was observed for the first time.

In recent years, the task of stabilizing food products, cosmetic oils, and fatty bases of pharmaceutical preparations is frequently solved using synergetic compositions, which include either several oxidation inhibitors mutually enhancing the effect of each other or a combination of an antioxidant with a synergetic agent. Such agents (e.g., some phospholipids) usually do not produce any significant inhibition effect by themselves, but substantially increase the activity of the main antioxidant. The assortment of nontoxic antioxodants has been recently significantly expanded to include, in particular, mexidol and emoxypine. Despite the wide use of these drugs in clinics, where they have shown good therapeutic properties, the mechanism of their antioxidant action is still incompletely clear [1 – 3]. Another interesting group of antioxidants are sulfur-containing phenols, which are capable to effectively inhibit oxidation via several different mechanisms [4 – 6].

It was established that a sulfur-containing sterically hindered phenol, bis-[3-(3,5-di-*tert*-butyl-4]-hydroxyphenyl)-propyl]disulfide (SO-4) synthesized at the Institute of Organic Chemistry (Novosibirsk), exhibits no significant local and general toxicity and does not influence embryogenesis and progeny development, which makes possible the use of this antioxidant in medicine [7].

This paper presents the results of investigations into the antiradical (AR) activity and antioxidant (AO) properties of SO-4 and mexidol (a 3-hydroxypyridine derivative) in comparison to some well-known inhibitors. Based on these data, prospects for the combined use of antioxidants belonging to various classes as additional means of nonspecific therapy and as agents stabilizing model and natural unsaturated lipids with respect to oxidation are assessed.

MATERIALS AND METHODS OF INVESTIGATION

The AR activity was studied using a chemiluminescence technique in a model system of the initiated oxidation of ethylbenzene [8]. The AO properties (degree of oxidation inhibition) were tested using methyl oleate (MO) as a model substrate, in which the oxidation process was initiated at 60°C at a rate of $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1} by thermal decomposition of AIBN present in a concentration of 3×10^{-3} M. The oxidation rate was monitored by measuring the oxygen uptake kinetics with the aid of a Warburg pressure gauge [9]. The inhibition effect was evaluated in terms of the AO activity that was quantitatively measured as $A_{AO} = (\tau_i - \tau_s)/\tau_s$, where τ_i and τ_s are the induction periods of substrate oxidation in the presence of a given inhibitor and without it, respectively. The AO effect was compared to that determined for a reference inhibitor in terms of the ratio τ_i/τ_{ref}, where τ_{ref} is the induction periods of substrate oxidation in the presence of this reference agent. The oxidation process was studied by monitoring the kinetics of hydroperoxide accumulation by means of inverse iodometric technique in the course of MO autooxidaiton at 60°C in chlorobenzene.

The reference inhibitors were α-tocopherol (α-TP) and dibunol. All antioxidants were used in comparable concen-

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trations. The joint inhibiting effect of a mixture was characterized by the absolute difference $\Delta\tau$ of the induction periods of MO oxidation in the presence of the given composition (τ_Σ) and the sum of individual induction periods $\Sigma\tau_i$ (additive action) ($\Delta\tau = \tau_\Sigma - \Sigma\tau_i$). Alternatively, the relative synergetic effect was expressed by the ratio $(\Delta\tau/\Sigma\tau_i) \times 100\%$.

The experiments were performed with α-TP (6-hydroxy-2,5,7,8-tetramethyl-2-phytylchromane) and dibunol (1-hydroxy-2,6-di-*tert*-butyl-4-methylbenzene) from Serva (Germany). The oxidation substrate was MO obtained from the Institute of Organic Chemistry (Novosibirsk), which was purified by double vacuum distillation at 105°C in argon flow. The purity of phospholipids (egg yolk phosphatidylcholine) was checked by TLC. Mexidol was synthesized at the Emanuel Institute of Biochemical Physics (Moscow). SO-4 was obtained from the Institute of Organic Chemistry (Novosibirsk). The purity of all antioxidants was checked by UV and IR spectroscopy and HPLC. The HPLC measurements were performed on a Milikhrom A-02 system equipped with a spectrophotometric detector (double-beam UV spectrophotometer; flow cell volume, 1.2 μl) and a Nucleosil 100 – 5 column. Elution was performed in a gradient mode using water, methanol, and acetonitrile at a flow rate of 100 μl/min. The purity (main substance content) of all antioxidants was no less than 99.9%.

RESULTS AND DISCUSSION

Table 1 gives the formulas and chemical structures of antioxidants studied. Mexidol is 3-hydroxy-6-methyl-2-ethylpyridine succinate, and a specific feature of the SO-4 structure is a disulfide moiety, which is mirror-spaced from the aromatic system by a three-unit hydrocarbon chain.

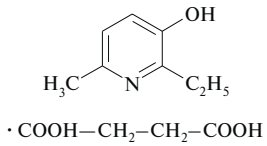
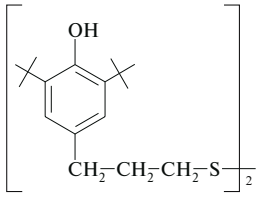
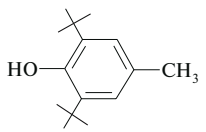
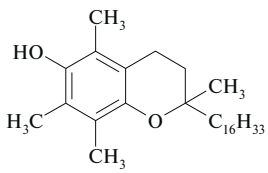
The rate constant k_7 of the elementary AO reaction with peroxy radicals and the inhibition factor f (showing the number of free radicals interacting with one inhibitor molecule) were determined using the CL technique for reaction VII according to the commonly accepted scheme:

$$(\mathrm{InH} + \mathrm{RO_2^\bullet} \xrightarrow{k_7} \mathrm{In^\bullet} + \mathrm{ROOH}), \qquad \text{(VII)}$$

where InH and $\mathrm{In^\bullet}$ are the inhibitor and its radical, respectively.

The characteristics of mexidol, SO-4, α-TP, and dibunol were determined under the same conditions. It was found that the compounds studied exhibited high AR activity. In particular, SO-4 and dibunol had comparable reaction rate constants of $k_7 = 1.3 \times 10^4$ and $1.4 \times 10^4\ \mathrm{M^{-1}\ sec^{-1}}$, respectively. For mexidol, this constant was $k_7 = 2.8 \times 10^4\ \mathrm{M^{-1}\ sec^{-1}}$, in agreement with published data [10]. The value for α-TP ($k_7 = 3.6 \times 10^6\ \mathrm{M^{-1}\ sec^{-1}}$) was about 250 times greater compared to the reaction rate constants of SO-4 and

TABLE 1. Structures and Kinetic Characteristics of Antioxidants

Compound	Name	Structure	$k_7 \times 10^{-4}$, $\mathrm{M^{-1}\ sec^{-1}}$	f	τ_i, min ($C_{AO} = 2 \times 10^{-4}$ M)*	$A_{AO} = (\tau_i - \tau_s)/\tau_s$
I	Mexidol (3-hydroxy-6-methyl-2-ethylpyridine succinate)		2.80	2.0	110	3.2
II	SO-4 (bis-[3-(3,5-di-*tert*-3-butyl-4′-hydroxyphenyl)propyl]disulfide		1.30	3.8	240	8.2
III	Dibunol (2,6-di-*tert*-bityl-4-methylphenol)		1.40	2.0	190	6.3
IV	α-Tocopherol (6-hydroxy-2,5,7,8-tetramethyl-2-phytylchroman)		360.00	2.0	160	5.2

* Other conditions as indicated in the legend to Fig. 1; all differences are reliable for $p \le 0.05$.

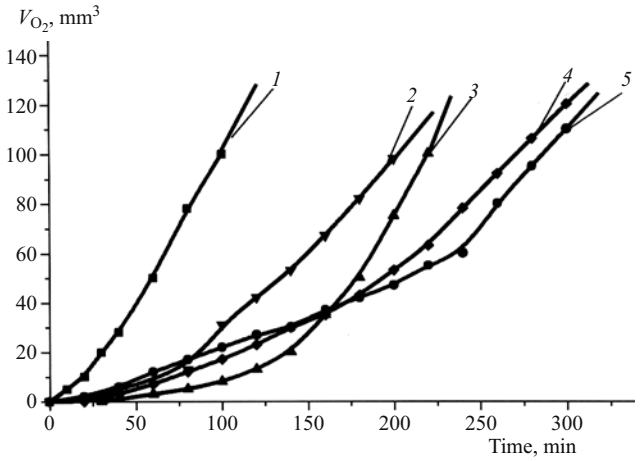


Fig. 1. Oxygen uptake kinetics by MO in chlorobenzene (*1*) in the absence of inhibitors and (*2 – 4*) in the presence of mexidol, α-TP, and dibunol, respectively (C_{AO} = const = 1×10^{-4} M, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, T = 60°C).

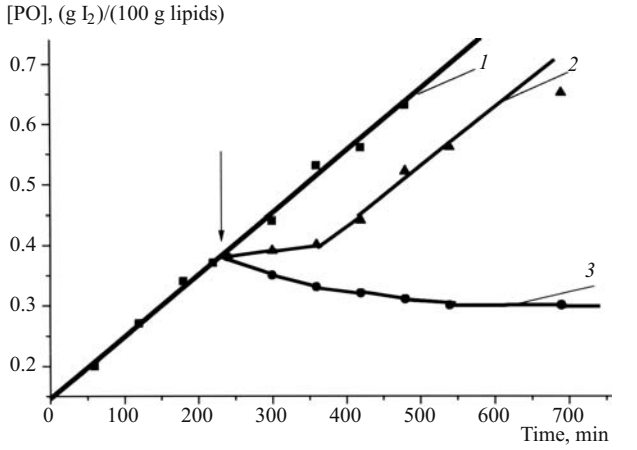


Fig. 2. Hydroperoxide accumulation and decomposition kinetics during MO autooxidation at T = 60°C (*1*) in the absence antioxidants and (*2*, *3*) in the presence of mexidol and SO-4, respectively, in the same concentration C_{AO} = const = 2×10^{-4} M. The arrow indicates the moment of antioxidant introduction.

dibunol. The stoichiometric coefficient f for SO-4 is close to 4 (f = 3.8), while that for mexidol, dibunol, and α-TP is f = 2 (Table 1). Thus, about four peroxide radicals are, on the average, lost on each SO-4 molecule, which is explained by the presence of two independent reaction centers in its structure.

All antioxidants increased the induction period of oxidation for the model substrate. Figure 1 shows the kinetics of MO oxidation (in terms of the oxygen uptake) without inhibitors and in the presence of various AO agents at the same concentration. As can be seen, the presence of inhibitors significantly decreases the slope of kinetic curves as compared to the control profile. An important specific feature of the AO effect of SO-4 and mexidol is a significant reduction in the maximum initial oxidation rate as compared to that in the control test. Indeed, at an antioxidant concentration of $C_{AO} = 1 \times 10^{-3}$ M, the oxidation rate decreases by a factor of 1.3 in the presence of SO-4 and by a factor of 8.3 in the presence of mexidol. No such effect is observed for α-TP and dibunol.

It can be suggested that SO-4 and 3-hydroxypyridine are capable of destroying hydroperoxides. In order to check for this hypothesis, we have studied the kinetics of hydroperoxide accumulation during MO autooxidation before and after antioxidant introduction. At a certain moment, an antioxidant in a concentration of 2×10^{-4} M was introduced into the system with a substrate oxidized to a sufficiently large extent corresponding to a peroxide level of [PO] = 0.38 (g I_2)/(100 g lipids). It was established (Fig. 2) that SO-4 and mexidol decompose 44.4 and 19.7% of hydroperoxides. Thus, owing to their hybrid structure, the antioxidants act via two mechanisms: (i) elimination of peroxy radicals and (ii) molecular destruction of hydroperoxides.

In recent years, it was established that a direct proportionality between the oxidation induction period and concentration for some natural antioxidants is valid only in the region of small concentrations, while an increase in the concentration may be accompanied by a decrease in the efficiency of inhibition [9, 11 – 14]. In this context it was also important to study the possible dependence of the induction period on the antioxidant content in the substrate. The AO effect was studied in a broad range of concentrations and it was found that, for dibunol, SO-4, and mexidol, the induction period increases in direct proportion to their concentration in the model system, whereas for α-TP this dependence has an extremal character with a maximum (Fig. 3), in agreement with published data [9]. Under the experimental conditions studied, the maximum in τ was observed at an α-TP concentration of 2.5×10^{-4} M. The AO activity of mexidol was comparable with that of α-TP. In equal concentrations, SO-4 ensured a longer period of induction (inhibition) than did dibunol and α-TP. Thus, the displacement of disulfide moiety away from the benzene ring and the absence of π – ρ conjugation increases the AO effect. Probably, various parts of the SO-4 molecule operate according to different mechanisms.

Synthetic antioxidants are now widely used for the stabilization of systems containing natural oxidation inhibitors such at α-TP. Therefore, the next stage of this investigation was devoted to elucidating the mechanism of the joint AO action of SO-4 and α-TP and determining their optimum concentration providing for the maximum synergetic inhibition effect. For this purpose, the AO efficiency of binary of SO-4 – α-TP mixtures was compared to the predicted additive effect produced by the independently acting components.

The synergetic effect was studied as a function of the concentration of each component. The optimum interval of SO-4 concentrations in this system was within $(1.5 – 2.0) \times 10^{-4}$ M. In this case, SO-4 produces the maximum

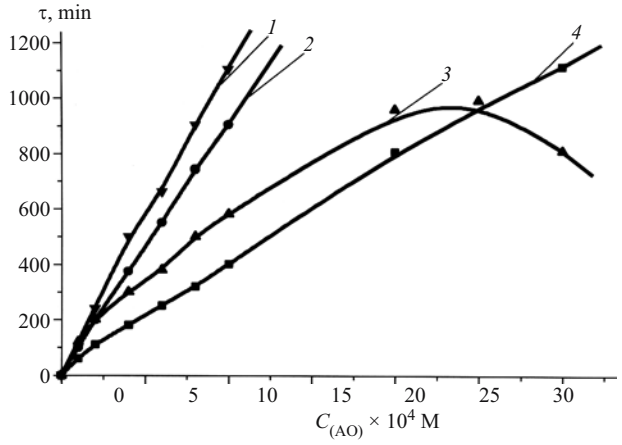


Fig. 3. Plots of the oxidation induction period τ versus antioxidant content C for (*1*) SO-4, (*2*) dibunol, (*3*) α-TP, and (*4*) mexidol ($W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, $T = 60°C$).

synergetic effect (65 – 68%) with respect to α-TP. This effect increases with the α-TP content in the mixture (Fig. 4*a*, Table 2).

The possible mechanism of synergetic action in this binary antioxidant mixture is as follows. α-TP has a high value of the reaction rate constant k_7 (Ph 1OH), while the AR activity of the spatially hindered phenol SO-4 (Ph 2OH) is significantly lower. The oxidation of α-TP is accompanied by the formation of active tocopheroxy radicals [15 – 17], while the oxidation of spatially hindered phenols proceeds with the formation of inactive phenoxy species [18 – 20]. In the initial oxidation stages, the more active inhibitor is predominantly consumed and the active tocopheroxy radicals induce rapid hydrogen exchange with the spatially hindered phenol via the reaction

$$Ph_1O^{\bullet} + Ph_2OH \leftrightarrow Ph_1OH + Ph_2O^{\bullet}.$$

The reduced form of the active antioxidant can also terminate oxidation chains via the reaction

$$Ph_1OH + RO_2 \rightarrow ROOH + Ph_1O^{\bullet}.$$

where $Ph_2O^{\bullet}$ phenoxy radicals are low active and virtually do not participate in the subsequent chain process.

Then, the joint action of SO-4 – mexidol combinations was studied for the first time. The optimum interval of SO-4 concentrations in this system was within $(1 – 5) \times 10^{-4}$ M (Fig. 4*b*), while the content of mexidol can be varied within a broader range of $(2 – 20) \times 10^{-4}$ M (Table 3). In this case, SO-4 and mexidol produces the maximum synergetic effect (50%) as compared to their separate action. The obtained results show that spatially hindered phenols can form highly effective synergetic mixtures with hydroxypyridine derivatives.

The mechanism of this synergism is probably as follows. Mexidol has a relatively higher value of the reaction rate constant k_7 (Ph 3OH) as compared to that of the spatially hindered phenol SO-4 (Ph 2OH), the AR activity of which is about half of that for mexidol. The oxidation of mexidol is accompanied by the formation of rather active radicals, while the oxidation of spatially hindered phenols proceeds with the formation of inactive phenoxy species [20]. In the initial oxidation stages, the more active inhibitor (mexidol) is predominantly consumed and the active species induce rapid hydrogen exchange with the spatially hindered phenol via a reaction, the equilibrium of which is strongly shifted toward the right-hand part:

TABLE 2. Synergetic AO Effect of α-TP and SO-4 Mixtures with Various Concentrations of Components (MO Substrate, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, $T = 60°C$)

Test No.	$C_{AO} \times 10^{-4}$, M	τ_i, min (individual)	τ_Σ, min (mixture)	τ_i, min	Δτ, min	$(\Delta\tau/\Sigma\tau_i) \times 100$ %
			C_{SO-4} = const = 1×10^{-4} M, τ_i = 130 min			
1	0.25	60	230	190	40	17.4
2	2.50	160	510	290	220	76
3	5.00	350	970	480	490	102
4	7.50	450	1200	580	620	107
5	10.00	600	1210	730	480	66
6	15.00	800	980	930	50	5.4
			$C_{\alpha\text{-TP}}$ = const = 2.5×10^{-4} M, τ_i = 160 min			
1	0.10	75	280	235	45	19
2	1.00	130	510	290	220	76
3	2.00	240	710	400	310	78
4	4.00	500	870	660	210	32
5	6.00	760	710	920	210	– 23
6	8.00	900	690	1060	370	– 35

Note: all differences are reliable for $p \le 0.05$.

$$Ph_3O^{\bullet} + Ph_2OH \leftrightarrow Ph_3OH + Ph_2O^{\bullet}.$$

which corresponds to regeneration of the active form of mexidol. As was demonstrated above, the synergetic effect in mexidol mixtures with the spatially hindered phenol SO-4 increases due to the ability of these antioxidants to decompose hydroperoxides without the formation of free radicals (thus, excluding the additional pathway of antioxidant consumption in the reaction with alkoxy radicals. The inhibition efficiency corresponding to the maximum joint action of mixtures can be reached using mexidol alone at concentrations 2.5 times as large as that in the synergetic mixture.

Finally, the synergetic effect of SO-4 was studied in mixtures with phospholipids (PLs), in comparison to the properties of reference drugs (dibunol and α-TP), which were reported to exhibit synergism with PLs [9]. The joint action of antioxidants with PLs was compared to the AO effect of individual components. As is known, PLs do not inhibit oxidation, but can play the role of synergetic agents in mixtures with antioxidants.

Table 4 presets the kinetic characteristics of oxygen uptake during MO oxidation in the presence of antioxidants and their mixtures with PLs. A comparative analysis of the oxidation induction periods shows that PL – antioxidant mixtures are more effective than the corresponding individual antioxidants, which is manifested by an increase in τ and a decrease in the maximum oxidation rate ($W^{-1}_{O_2max}$). As can be seen

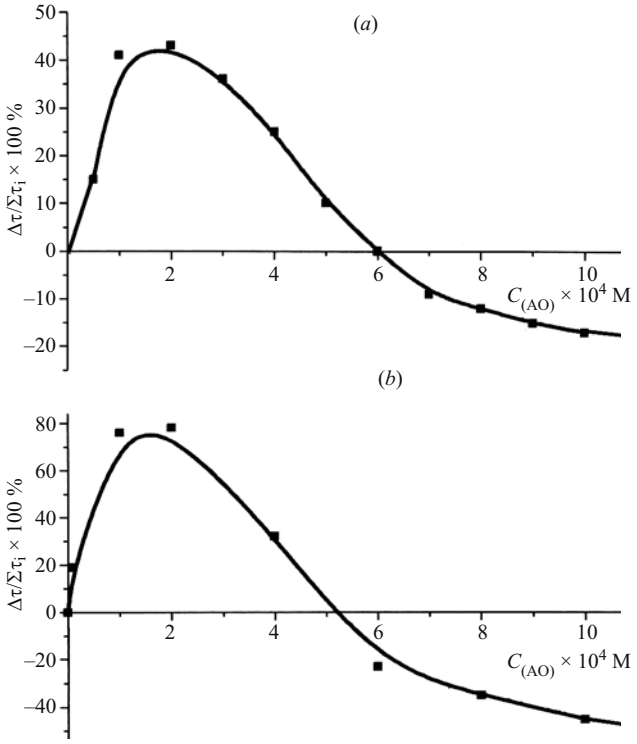


Fig. 4. Dependence of the synergetic effect on the SO-4 concentration in (*a*) α-TP – SO-4 mixtures ($C_{α–TP}$ = const = 2.5×10^{-4} M, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, $T = 60°C$) and (*b*) mexidol – SO-4 mixtures ($C_{mexidol}$ = const = 1×10^{-4} M, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, $T = 60°C$).

TABLE 3. Synergetic AO Effect of Mexidol and SO-4 Mixtures with Various Concentrations of Components (MO Substrate, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, $T = 60°C$)

Test No.	$C_{AO} \times 10^{-4}$, M	τ_i, min (individual)	τ_Σ, min (mixture)	$\Sigma\tau_i$, min	$\Delta\tau$, min	$(\Delta\tau/\Sigma\tau_i) \times 100\%$
		C(SO-4) = const = 1×10^{-4} M, τ_i = 130 min				
1	1.0	60	190	270	80	42.1
2	2.0	110	240	360	120	50.0
3	5.0	220	350	540	190	54.3
4	7.0	280	410	680	270	65.9
5	8.0	320	450	710	260	57.8
6	10.0	400	530	840	310	58.5
7	16.0	650	780	1230	450	57.7
8	20.0	800	930	1460	530	57.0
9	25.0	950	1080	1680	600	55.6
10	30.0	1100	1230	1910	680	55.3
11	35.0	1300	1430	2210	780	54.6
		$C_{mexidol}$ = const = 1×10^{-4} M, τ_i = 60 min				
1	0.5	80	140	160	20	14.2
2	1.0	130	190	270	80	42.1
3	2.0	240	300	430	130	43.3
4	4.0	500	560	740	180	24.3
5	5.0	580	640	720	80	11.1
6	7.0	800	860	790	– 70	– 8.9
7	10.0	1100	1160	980	– 180	– 18.4

Note: all differences are reliable for $p \le 0.05$.

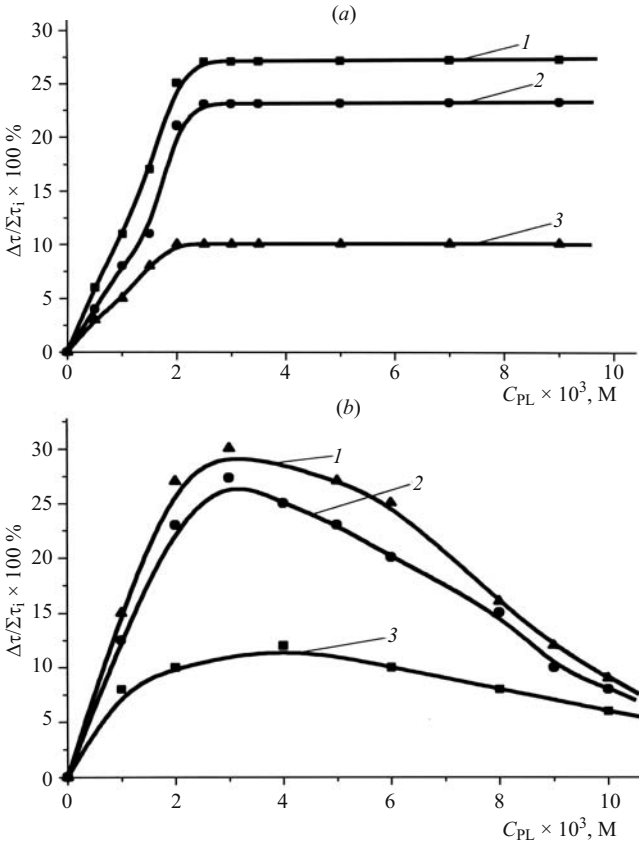


Fig. 5. Dependence of the synergetic effect in various antioxidant – PL systems (*a*) on the PL concentration in mixtures with (*1*) α-TP, (*2*) SO-4, and (*3*) dibunol (C_{AO} = const = 2×10^{-4} M, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, T = 60°C) and (*b*) on the (*1*) α-TP, (*2*) SO-4, and (*3*) dibunol concentration at C_{PL} = const = 5×10^{-3} M, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, T = 60°C).

from these data, the PL – antioxidant mixtures obey a relation indicative of a synergism in the system studied: $\tau_i < \tau_\Sigma$, where τ_i and τ_Σ are the induction periods in the presence of antioxidant alone and in the mixture with PLs, respectively, and

$$W_{O^2}^{-1} > W_{O_2\Sigma}^{-1},$$

where $W_{O^2}^{-1}$ and $W_{O_2\Sigma}^{-1}$ are the rates of MO oxidation in the presence of antioxidant alone and in the mixture with PLs, respectively.

Figure 5a shows the dependence of the synergetic effect on the PL content in the mixtures with various antioxidants. As can be seen, all curves exhibit generally the same character: (i) in the region of PL concentrations within $C_{PL} = (0 – 3) \times 10^{-3}$ M, the synergetic effect increases in direct proportion to the PL content in the mixture; (ii) the region of $C_{PL} = (3 – 5) \times 10^{-3}$ M corresponds to attaining a plateau; (iii) subsequent increase in C_{PL} is accompanied by a gradual decrease in the synergetic effect. It can be suggested that the system of nonenzymatic protection of lipids from oxidation involves both antioxidants and synergetic agents such as PLs.

Figure 5b shows plots of the synergetic effect versus antioxidant content in compositions with PLs. The synergetic effect of PLs on the AO activity decreases in the sequence α-TP > SO-4 > dibunol, which implies that, for the same synergetic agent (PL), the effect depends on the chemical structure of a particular inhibitor. The synergetic effect is maximum for the spatially hindered phenols and minimum for the spatially substituted antioxidants.

The mechanism of synergism in the mixtures of α-TP with PLs was considered in [9], where direct experiments showed that polyunsaturated fatty acids (entering into a PL composition) favor the recovery of an active phenolic form of α-TP. This leads to a decrease in the α-TP participation in the side reaction X (according to the commonly accepted scheme) that otherwise results in additional initiation of the oxidation process. In addition, aminoalcohols (such as ethanolamine, choline, etc.) entering into the composition of PLs can destruct hydroperoxides via nonradical pathways, thus excluding another channel of α-TP consumption in the reactions with hydroxy and alkoxy radicals generated during hemolytic decomposition of peroxides.

Thus, synergetic antioxidant compositions have good prospects for wide use as a means of increasing the useful properties and storage time of biologically active lipids, food products, cosmetics, and medicinal preparations.

ACKNOWLEDGMENTS

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TABLE 4. Kinetic Characteristics of Oxygen Uptake during MO Oxidation in the presence Antioxidants and Their Mixtures with PL ($C_{AO} = 2 \times 10^{-4}$ M, $C_{PL} = 5 \times 10^{-4}$ M, $W_{in} = 4.2 \times 10^{-8}$ M^{-1} sec^{-1}, T = 60°C).

Antioxidant	τ_i, min (individual)	τ_Σ, min (mixture)	$W_{max}^{-1} \times 10^{-7}$, M/sec (individual)	$W_{max}^{-1} \times 10^{-7}$, M/sec (mixture)	Δτ, min	$(\Delta\tau/\Sigma\tau_i) \times 100$ %
α-TP	160	200	6.50	6.00	40	25.0
SO-4	240	300	12.10	4.35	60	20.9
Dibunol	190	210	6.30	5.80	20	9.5

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