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PEROXIDES-XI

Correlation between the Structure and Inhibiting Activity of Phenosan Derivatives

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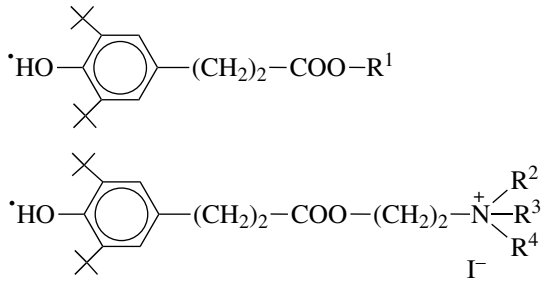
Abstract—Sterically hindered phenolic antioxidants (AOs) of the IKhFAN family are characterized as inhibitors of initiated oxidation of methyl oleate in homogeneous chlorobenzene solutions and in aqueous emulsions in the presence of dodecyl sulfate. The IKhFANs inhibit oxidation by scavenging peroxo radicals and by decomposing hydroperoxides to yield molecular products. The effect of an IKhFAN is governed by its chemical structure and by oxidation conditions. The IKhFANs slow down methyl oleate oxidation in lipid solution more effectively than comparable concentrations of α-tocopherol, dibunol, phenosan K, or phenosan ester. The most effective is IKhFAN-10, in which the R^3 radical is the shortest (CH_3). The inhibiting effect of the AOs weakens markedly with increasing chain length of R^3. The specific features of the observed oxidation kinetics are explained by the formation of microheterogeneous systems involving AOs. In these systems, the phenolic OH groups are directed to the micelle center and, as a consequence, can hardly react with $RO_2^{\bullet}$ radicals. In the IKhFAN group in which R^3 ranges from C_8H_{17} to $C_{16}H_{33}$, the induction period grows in proportion to the number of carbon atoms. In an aqueous emulsion, the overall inhibiting effects of structurally different IKhFANs are similar and weaker than effects in homogeneous solution.

A promising approach to the problem of developing effective antioxidants (AOs) is synthesis of "hybrid" molecules containing different groups capable of exerting either independent or synergistic effects on substrate oxidation in the lipid or aqueous phase. Researchers of the Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, have synthesized a number of sterically hindered AOs based on phenosan (β-3,5-di-*tert*-butyl-4-hydroxyphenylpropionic acid). The molecules of these compounds contain an ethanolamine residue substituted at the quarternary nitrogen atom by one or several alkyl radicals varying in the number of carbon atoms from 1 to 16 (Scheme 1). These inhibitors are known as IKhFANs. It was earlier demonstrated that they do not produce any general or local toxic effect, do not affect embryogenesis or the development of descendants, show antiacetylcholinesterase activity [1], and control cell growth in plants [2].

Consideration of the chemical structures of phenosan derivatives (Scheme 1) suggests that some of them (e.g., phenosan and its methyl ester) are lipophilic and form homogeneous solutions with lipids, while those containing a polar moiety (quarternary nitrogen atom) can spontaneously form micelles in which the phenolic hydroxyls are hidden inside a microreactor, owing to the orientation of the polar and nonpolar groups. The purpose of this work is to study the inhibiting effect of phenosan derivatives on lipid oxidation in homogeneous and micellar solutions, elucidate the mechanism of inhibition, and establish a correlation between the structure and activity of the inhibitors. The antioxidant activity of the IKhFANs is compared with that of dibunol and α-tocopherol, well-known AOs.

EXPERIMENTAL

The antiradical activity of the AOs was evaluated by chemiluminescence measurements in the initiated oxidation of ethylbenzene [3]. Oxidation kinetics were studied by measuring oxygen uptake in a Warburg-type manometric device for the oxidation of methyl oleate (MO), a model substrate, in chlorobenzene (inert solvent) and in aqueous emulsion in the presence of dodecyl sulfate as a surfactant (the ratio of the aqueous phase to the lipid phase was 1:1). The process was initiated by decomposing azobisisobutyronitrile at 60°C. The initiation rate in



Scheme 1.

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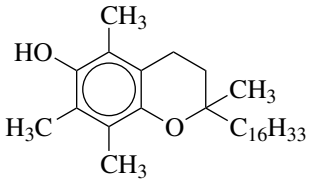
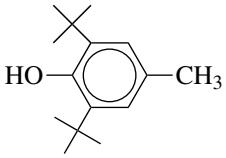
Table 1. Properties of AOs

No.	Name	Substituents				$k_7 \times 10^4$, l mol^{-1} s^{-1}	τ*, min	$AA = \frac{\tau_i - \tau_{st}}{\tau_{st}}$
		R^1	R^2	R^3	R^4			
1	Phenosan K	K^+	–	–	–	2.20	920	35.4
2	Methyl ester of phenosan	$-CH_3$	–	–	–	2.30	1050	40.4
3	IKhFAN-9	–	$-CH_3$	–	$-CH_3$	0.79	1025	39.4
4	IKhFAN-10	–	$-CH_3$	$-CH_3$	$-CH_3$	0.59	1125	43.3
5	IKhFAN-10-C-8	–	$-CH_3$	$-C_8H_{17}$	$-CH_3$	1.06	350	13.5
6	IKhFAN-10-C-10	–	$-CH_3$	$-C_{10}H_{21}$	$-CH_3$	0.98	500	19.2
7	IKhFAN-10-C-12	–	$-CH_3$	$-C_{12}H_{25}$	$-CH_3$	0.97	425	16.3
8	IKhFAN-10-C-16	–	$-CH_3$	$-C_{16}H_{33}$	$-CH_3$	0.94	1075	41.5
9	α-Tocoferol					360.00	600	23.1
10	Dibunol					1.40	950	36.5

* [AO] = 1×10^{-3} mol/l.

our experiments was 4.2×10^{-8} mol l^{-1} s^{-1}. The inhibitors were characterized in terms of their antioxidant activity (AA), defined as $AA = (\tau_i - \tau_{st})/\tau_{st}$, where τ_s and τ_i are the induction periods in substrate oxidation in the absence and presence of an AO, respectively. Hydroperoxide accumulation kinetics in MO autooxidation in chlorobenzene at 60°C was studied by back iodometric titration.

Micelle formation was studied by refractometry [4] and the Rebinder method [5].

The following AOs were tested: α-tocopherol (6-hydroxy-2,5,7,8-tetramethyl-2-phytylchroman; Serva, Germany), dibunol (1-hydroxy-2,6-di-*tert*-butyl-4-methylbenzene; Serva, Germany), IKhFAN-9 (*N*,*N*-dimethylaminoethyl β'-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate) as succinate, IKhFAN-10 (*N*,*N*,*N*-trimethylaminoethyl β'-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate) as iodide, IKhFAN-10-C-8 (*N*,*N*-dimethyl-*N*-octylaminoethyl β'-(3,5-di-*tert*-butyl-4-hydroxyphenylpropionate) as bromide, IKhFAN-10-C-10 (*N*,*N*-dimethyl-*N*-decylaminoethyl β'-(3,5-di-*tert*-butyl-4-hydroxyphenylpropionate) as bromide, IKhFAN-10-C-12 (*N*,*N*-dimethyl-*N*-dodecylaminoethyl β'-(3,5-di-*tert*-butyl-4-hydroxyphenylpropionate) as bromide, and IKhFAN-10-C-16 (*N*,*N*-dimethyl-*N*-hexadecylaminoethyl β'-(3,5-di-*tert*-butyl-4-hydroxyphenylpropionate) as bromide.

The IKhFANs were synthesized at the Emanuel Institute of Biochemical Physics. Phenosan K (potassium 3,5-di-*tert*-butyl-4-hydroxyphenylpropionate) and methyl phenosan ester (methyl 3,5-di-*tert*-butyl-4-hydroxyphenylpropionate) were synthesized at the Vorozhtsov Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences. The phenosan derivatives were synthesized by the transesterification of commercial methyl phenosan ester into dimethylaminoethyl ester followed by the quarternization of the nitrogen atom [6]. The purity of the resulting AOs was checked by high-performance liquid chromatography on a Milikhrom A-02 chromatograph fitted with a Nucleosil 100-5 column and a double-beam UV spectrophotometric detector. Chromatograms were obtained in the gradient elution mode using water, methanol, and acetonitrile as eluents. The flow rate was 100 μl/min, and the cell volume was 1.2 μl. The concentration of the desired AO was always no less than 99.9%.

RESULTS AND DISCUSSION

We estimated, by luminescence measurements, the rate constants of the AO–peroxo radical reactions, which are conventionally written as

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

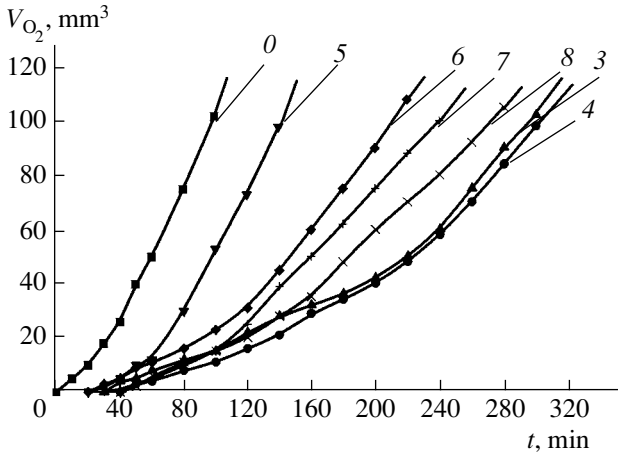


Fig. 1. Oxygen uptake kinetics in the initiated oxidation of MO at a fixed AO concentration of [AO] = 2×10^{-4} mol/l. Curve *0* represents the control experiment ([AO] = 0). The numbers given to the other curves are AO numbers in Table 1. MO : chlorobenzene = 1 : 1; $w_i = 4.2 \times 10^{-8}$ l mol^{-1} s^{-1}; T = 60°C.

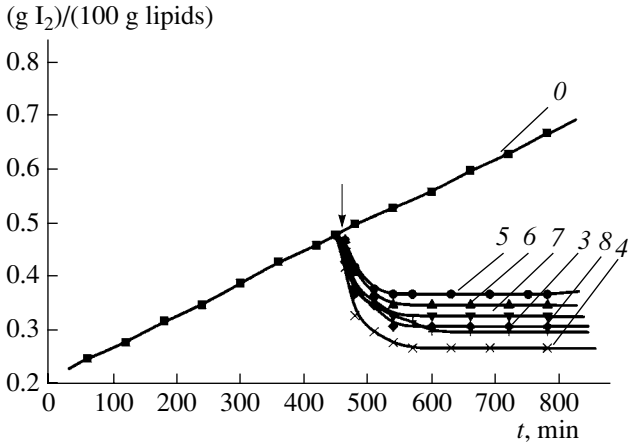


Fig. 2. Hydroperoxide accumulation kinetics in the autooxidation of MO at a fixed AO concentration. The curves are numbered as in Fig. 1. The arrow marks the time point at which an AO is introduced into the reaction mixture. T = 60°C.

Varying oxidation conditions, we determined the inhibition factor f, which is the number of reacted free radicals per inhibitor molecule. The antiradical activity k_7 of IKhFANs was compared with those of dibunol and α-tocopherol. The k_7 values for phenosan K and its methyl ester are similar (Table 1) and are comparable with the rate constant of reaction (VII) for dibunol (1.40×10^4 l mol^{-1} s^{-1}). The antiradical activities of IKhFAN-9 and IKhFAN-10 are lower by a factor of 1.5 to 2 (Table 1). The fact that the k_7 values of these IKhFANs are lower than that of dibunol is explained by the effect of the acceptor substituents, which are known to reduce the antiradical activity of AOs [7]. The IKhFANs are markedly inferior to α-tocopherol ($k_7 = 3.6 \times 10^6$ l mol^{-1} s^{-1}) in reacting with $RO_2^{\bullet}$. Their inhibition factor, like those of most AOs, is close or equal to 2. Thus, the AOs examined act through scavenging $RO_2^{\bullet}$ radicals, which are responsible for oxidation. On the average, each inhibitor molecule scavenges two free radicals.

One can see that the AO molecules have either a substituted amino group or a quarternary ammonium base fragment. These classes of compounds can break down hydroperoxides (ROOH) [8]. Kinetically, the nonradical decomposition of ROOH shows itself as a decrease in the initial and maximum substrate oxidation rates (w_{in} and w_{max}, respectively). In view of this, we analyzed the behavior of these kinetic parameters in a series of experiments at a fixed concentration of the IKhFANs (Fig. 1). Introducing an IKhFAN into the oxidation system not only extends the induction period over that of the control experiment but also reduces w_{in} and w_{max} (Table 2). Note that w_{in} and w_{max} are most affected by IKhFAN-9, IKhFAN-10, and IKhFAN-10-C-16 (Table 2). It is likely that the capacity for decomposing hydroperoxides is a specific feature of the AOs in question. To confirm this hypothesis, we carried out a direct study of the kinetics of accumulation of hydroperoxides after adding an IKhFAN to partially oxidized MO (Fig. 2). The hydroperoxide concentration decreased markedly over the first hour after an AO was added and then remained low throughout the observation period (8 h). In the control experiment, the peroxides accumulated continuously. The most potent hydroperoxide decomposers are IKhFAN-9, IKhFAN-10, and IKhFAN-10-C-16 (Table 3). The results of two independent experiments suggest that the AOs take part in breaking down primary oxidation products. Hydroperoxide decomposition is likely to yield molecular products, as follows from the fact that no secondary initiation of oxidation takes place.

Thus, the AOs considered are capable of effectively terminating oxidation chains by reacting with peroxo radicals. Furthermore, they prevent secondary initiation through decomposing the peroxides by a nonradical mechanism.

Mechanistic studies are necessary to understand the overall inhibiting effect of new AOs with various structures. We compared the effects of IKhFANs with the effects of dibunol and α-tocopherol. Oxygen uptake curves for solutions containing comparable amounts of IKhFANs are plotted in Fig. 1. All the compounds in question slow down MO oxidation (Table 1). The AOs can be divided into two groups according to the way the induction period varies with AO concentration in the oxidation system (Fig. 3). For phenosan K, its methyl ester, dibunol, IKhFAN-9, and IKhFAN-10, the concentration dependence is linear (Fig. 3a). Note that the inhibiting effect of these IKhFANs is greater than that of α-tocopherol by a factor of about 2, and greater than that of dibunol, phenosan K, or its methyl ether by 30% (Fig. 3a, Table 1). The longest induction periods

Table 2. Kinetic data for methyl oleate oxidation in the presence of AOs

C [AO] $\times 10^{-4}$, mol/l	τ_{ind}, min	$w_{in} \times 10^{-7}$, mol l^{-1} s^{-1}	$w_{max} \times 10^{-7}$, mol l^{-1} s^{-1}	$\frac{w_{max}MO}{w_{max}AO}$	f_{eff}	
					f(CL)	f(MO)
Methyl oleate						
0	26	1.90	8.00	1.0	–	–
IKhFAN-9						
1	100	1.77	7.20	1.1	1.9	2.6
2	200	1.24	4.93	1.6		2.6
4	410	0.93	4.40	1.8		2.6
6	600	0.74	3.45	2.3		2.6
8	820	0.44	3.41	2.4		2.6
10	1025	0.21	3.35	2.4		2.6
IKhFAN-10						
1	110	1.06	5.95	1.3	2.0	2.8
2	210	0.74	4.52	1.8		2.8
4	450	0.62	3.92	2.1		2.8
6	670	0.54	3.31	2.4		2.8
8	900	0.37	3.27	2.4		2.8
10	1125	0.31	3.18	2.5		2.8
IKhFAN-10-C-8						
1	50	1.86	7.67	1.0	2.2	0.6
2	60	1.49	7.08	1.1		0.6
4	80	0.92	5.06	1.6		0.5
6	100	0.73	4.15	1.9		0.6
8	225	0.57	3.72	2.2		0.7
10	350	0.29	3.47	2.3		0.9
IKhFAN-10-C-10						
1	50	1.24	5.58	1.4	2.6	1.3
2	90	1.06	4.43	1.8		1.0
4	100	0.93	4.13	2.0		1.0
6	180	0.28	4.00	2.0		0.8
8	325	0.21	3.72	2.2		1.0
10	440	0.20	3.31	2.4		1.1
IKhFAN-10-C-12						
1	60	1.65	6.98	1.1	2.4	1.3
2	100	1.49	4.65	1.7		1.3
4	190	0.74	4.20	1.9		1.2
6	260	0.72	4.10	2.0		1.1
8	400	0.62	3.55	2.3		1.3
10	540	0.60	3.35	2.4		1.4
IKhFAN-10-C-16						
1	75	1.06	4.22	1.9	2.8	1.9
2	130	0.93	4.09	2.0		1.6
4	200	0.90	3.65	2.2		1.8
6	475	0.47	3.57	2.2		2.0
8	750	0.37	3.44	2.3		2.4
10	1075	0.35	3.19	2.5		2.7

Note: $w_i = 4.2 \times 10^{-8}$ l mol^{-1} s^{-1}; $T = 60°C$. f(CL) is the inhibition factor derived from chemiluminescence measurements for ethylbenzene. f(MO) is the inhibition factor derived from MO oxidation kinetics.

Table 3. Kinetic data characterizing peroxide decomposition in MO autooxidation in the presence of IKhFANs

No.	System	Autooxidation		ROOH decomposed in 7 h, %
		$w_{accum} \times 10^{-4}$; $(g\ I_2)/(100\ g\ lipids)\ s^{-1}$	$w_{decomp} \times 10^{-4}$, $(g\ I_2)/(100\ g\ lipids)\ s^{-1}$	
1	MO (control)	5.90	–	–
2	MO + IKhFAN-10	–	5.60	54.7
3	MO + IKhFAN-9	–	4.80	48.4
4	MO + IKhFAN-10-C-8	–	4.2	41.0
5	MO + IKhFAN-10-C-10	–	4.5	44.1
6	MO + IKhFAN-10-C-12	–	4.8	46.8
7	MO + IKhFAN-10- C-16	–	5.1	50.1

Note: $[AO] = 2 \times 10^{-4}$ mol/l; $T = 60°C$.

throughout the concentration range examined were observed for IKhFAN-10.

For the other group of inhibitors, the induction period change versus concentration curves are S-shaped (Fig. 3b). This group is made up by AOs whose molecules have an ethanolamine residue substituted, at the N atom, with alkyl radicals differing in the number of carbon atoms (see Scheme 1). The S-shaped curves for these AOs fall into three portions (Fig. 3b). Initially, the induction period grows linearly with increasing concentration for all AOs. Next comes a rather narrow region where the induction period is invariable. Starting at some threshold concentration, the overall inhibiting effect continues increasing in proportion to the AO concentration.

Obviously, this difference in inhibiting properties arises from structural differences. It is important to establish a correlation between the threshold AO concentration (kink position) and the chain length of the alkyl substituent (R^3). We demonstrate in Fig. 4 that the threshold concentration decreases as the chain of R^3 is lengthened. This correlation suggests that macromolecules can form in solution at some AO concentrations,

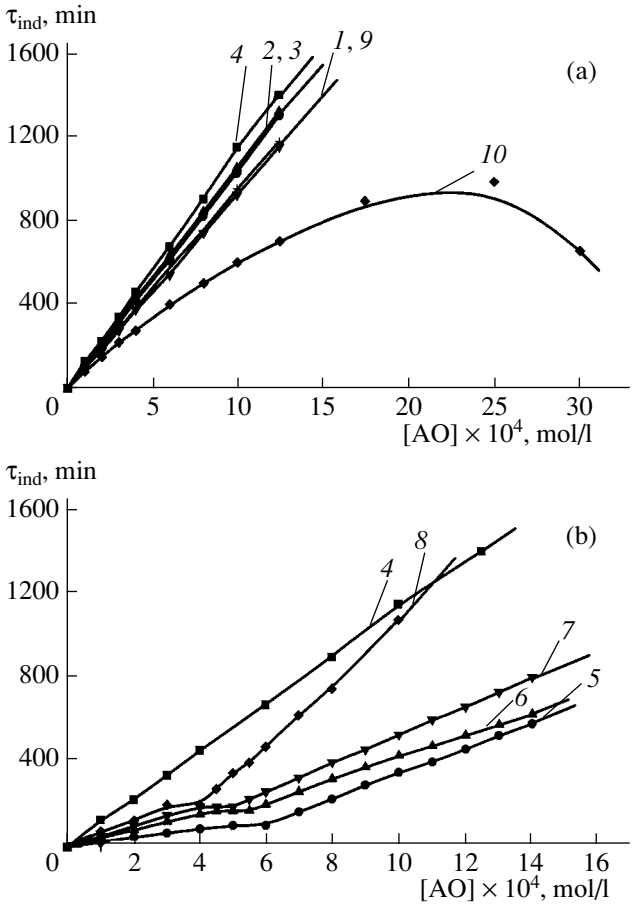


Fig. 3. Change in the induction period as a function of AO concentration: (*1*–*8*) AOs 1–8 in Table 1, (*9*) dibunol, and (*10*) α-tocopherol. For oxidation conditions, see the caption to Fig. 1.

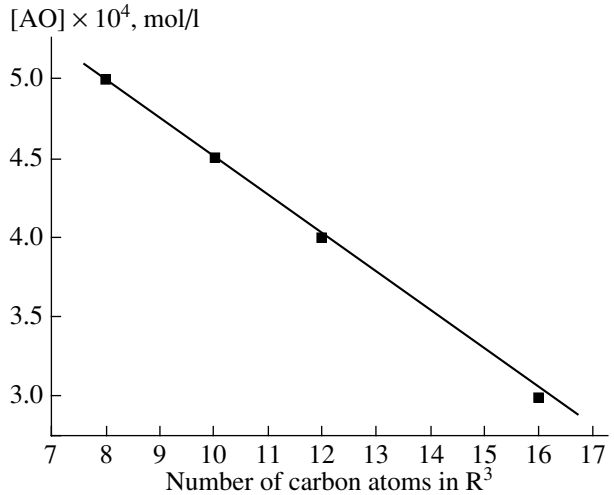


Fig. 4. Critical concentration as a function of the chain length of the R^3 radical.

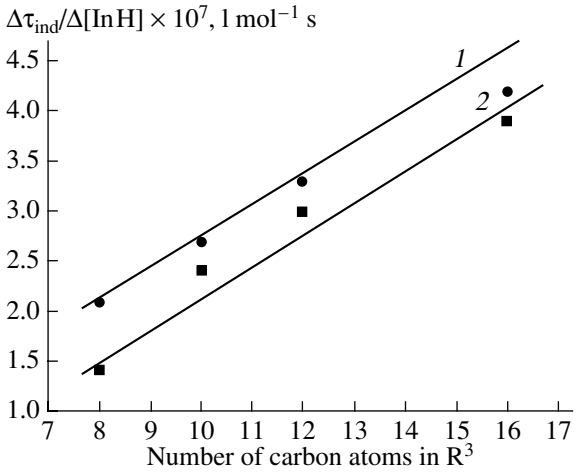


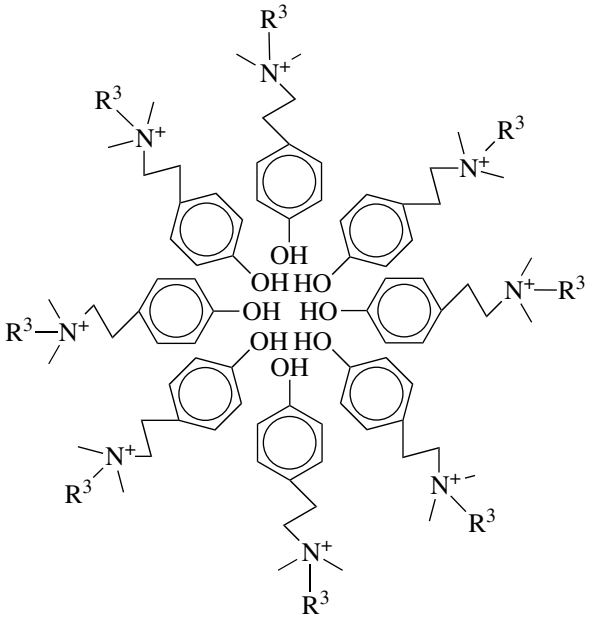
Fig. 5. $\Delta\tau_{ind}/\Delta[InH]$ as a function of the chain length of the R^3 radical for the (*1*) third and (*2*) first portions of the τ_{ind} versus [AO] curves.

since critical micelle concentration is known to decrease with increasing chain length of the hydrocarbon radical in the polar molecule [9].

It is noteworthy that the slopes of the first and third portions of the induction period versus AO concentration curves are different, depending on the chain length of the R^3 substituent. The slope of a curve was characterized by an incremental ratio of the induction period to AO concentration, $\Delta\tau_{ind}/\Delta[InH]$. Evidently, there is a direct correlation between $\Delta\tau_{ind}/\Delta[InH]$ and the chain length of the R^3 radical (Fig. 5). Using this correlation, the $\tau_{ind} = f[InH]/w_i$ equation, and the initiation rate determined experimentally by the inhibitor method ($w_i = 4.2 \times 10^{-8}$ mol l^{-1} s^{-1}), we were able to estimate, for a varied AO concentration, the effective value of f (f_{eff}), which is the number of free radicals lost per inhibitor molecule.

It was demonstrated by chemiluminescence measurements that, in the oxidation process in ethylbenzene, f_{eff} for AOs that have no substituents at the nitrogen atom is close or equal to 2 (Table 2). For the other group of inhibitors (IKHFAN-9 and IKHFAN-10, which have a long-chain substituent), $f_{eff} > 2$ and there is a correlation between f_{eff} and the chain length of the R^3 radical (Table 2).

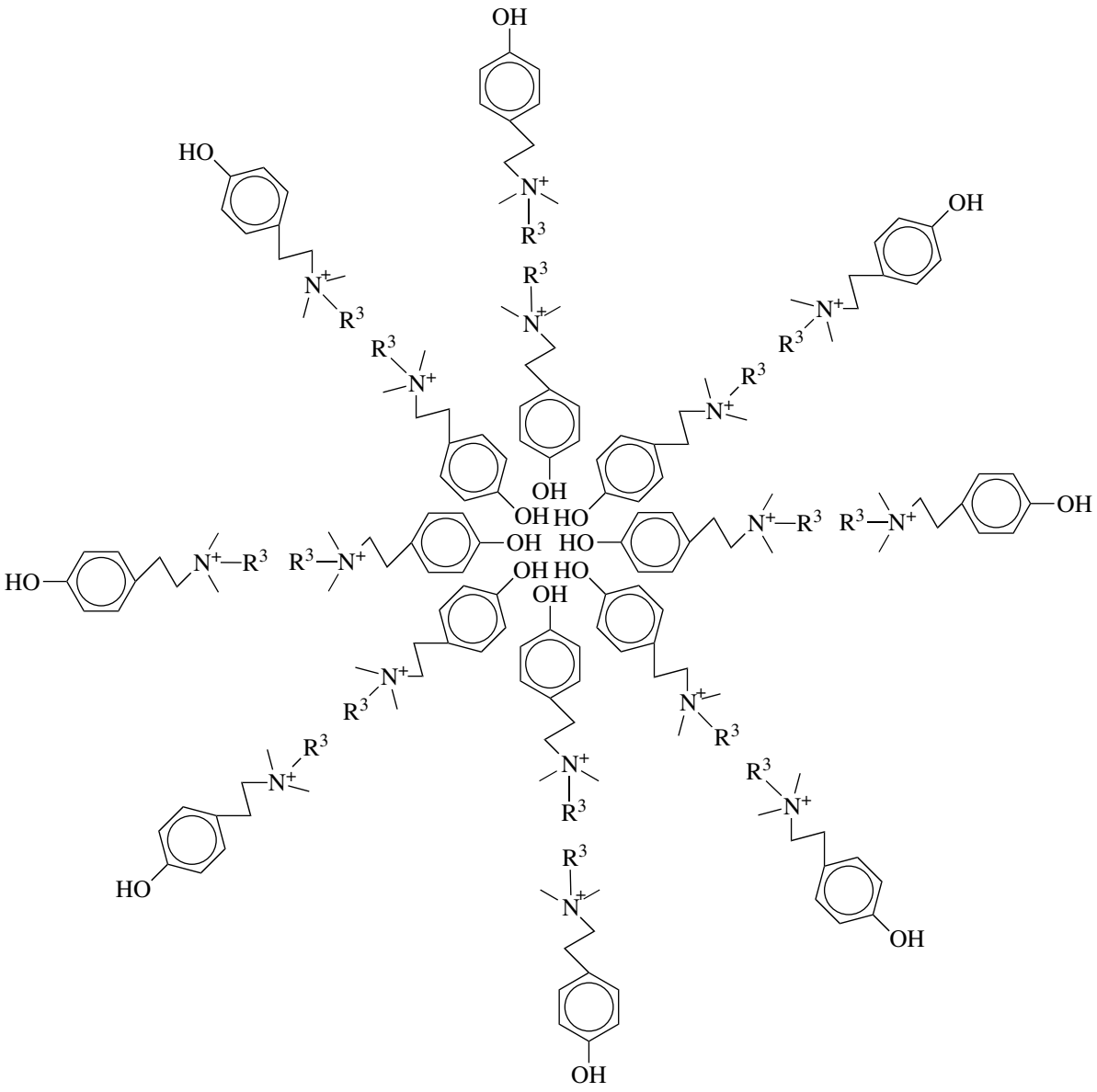
For MO, another kind of substrate, f_{eff} calculated from inhibition data is higher for the AOs unsubstituted at the nitrogen atom and is much lower for the AOs that have a long-chain alkyl substituent R^3 (Table 2). This finding is evidence of micelle formation. As the chain length of R^3 grows, f_{eff} increases, in accordance with the data obtained by luminescence measurements (Table 2). For IKhFAN-10-C-16, in which the R^3 substituent is the longest, consisting of 16 carbon atoms, f_{eff} increases with increasing AO concentration.



Scheme 2.

The above findings can be explained in terms of the formation of microheterogeneous systems. At comparatively low AO concentrations, the AOs with a long-chain R^3 substituent form micelles in which the phenolic OH group is hidden inside a microreactor (Scheme 2). The AO molecules in these micelles cannot react with $RO_2^{\cdot}$ radicals, and f_{eff} is relatively low as a result. The threshold concentration, which takes a particular value for each AO, marks the completeness of a monolayer. Further raising the inhibitor concentration causes self-assembly of a two-layer structure in which some of the phenolic OH groups are hidden inside the micelle and the other face is the outer surface of the microheterogeneous system (Scheme 3). Obviously, the ease of formation of a two-layer structure depends on the length of the hydrocarbon radical at the quaternized nitrogen atom. The data listed in Table 2 demonstrate that f_{eff} grows with increasing chain length of the R^3 substituent. It can be assumed that the radius and, accordingly, the surface area of a liposome increase with increasing chain length of R^3 (Scheme 3). As this takes place, the micelle holds progressively more AO. The long hydrocarbon radicals orient the AO molecules so that the phenolic OH groups are located on the outer surface of the micelle and can readily react with peroxo radicals (Scheme 3).

To verify the hypothesis of AO structuring in oxidation systems, we studied the AO concentration dependence of refractive index. We found that, at some threshold AO concentrations, the optical properties of the solutions change sharply and the refractive index versus concentration curve shows a kink due to micelle formation. Using the Rebinder method [5], we esti-



Scheme 3.

mated the critical micelle concentrations, which appeared to be nearly equal to the threshold concentrations. Thus, the results of independent experiments confirm the hypothesis of the formation of microheterogeneous systems in lipid solutions. The supramolecular structure of micelles is known to depend on the nature and concentration of the compound having both nonpolar and polar moieties (amphipathic or amphihic compound) [8].

Therefore, the inhibition of lipid oxidation is governed by not only the antiradical activity of the AO (k_7) and the decomposability of ROOH, but also by the formation of lipid-containing microheterogeneous systems. In the case of monolayer micelles, the phenolic OH groups of the AO molecules are presented to the center of the microreactor and do not react with peroxo radicals responsible for oxidation. As a consequence, the overall effectiveness of substituted AOs is much lower than that of their unsubstituted analogues (Table 2). In two-layer structures, some of the active groups of AO molecules having a long-chain substituent (R^3 radical containing 12 through 16 carbon atoms) are presented to the liposome center and the others are presented to the liposome surface, increasing the overall inhibiting effect.

Considering the above results, we found it necessary to study the kinetics of lipid oxidation in aqueous emulsion in the presence of dodecyl sulfate at a water : chlorobenzene ratio of 1 : 1. Figure 6 plots the induction period as a function of AO concentration for oxidation

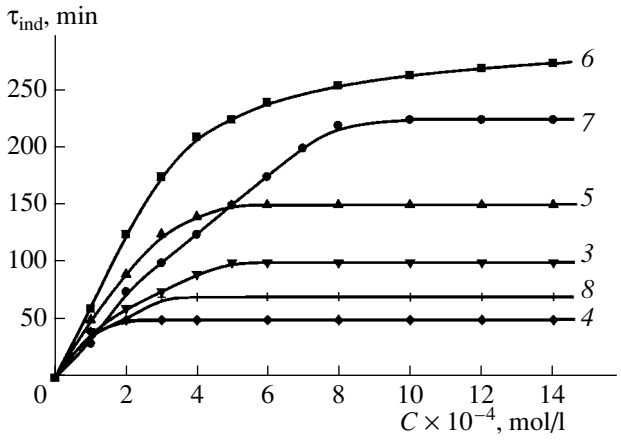


Fig. 6. Change in the induction period as a function of AO concentration for the initiated oxidation of MO in aqueous emulsion. The numbers given to the curves are AO numbers in Table 1. For oxidation conditions, see the caption to Fig. 1.

in aqueous emulsion. All the curves are similar, irrespective of AO structure: in the concentration range $(2.0–4.5) \times 10^{-4}$ mol/l, they flatten out, and further raising the AO concentration does not extend τ_{ind}. The maximum value of τ_{ind} decreases with increasing chain length of the R^3 radical. Note that the curves in Fig. 5 have the same shape as the first and second portions of the curves in Fig. 3b. This fact is likely to be explained by the formation of the same type of microheterogeneous system, specifically, microreactors in which the kernel is formed by phenolic OH groups and the outer shell is formed by R^3-substituted ammonium groups. In this case, dodecyl sulfate stabilizes (solubilizes) the system by reacting with the hydrophilic moieties of the inhibitor molecules [9].

Thus, the results presented here demonstrate that the AO effect of IKhFANs depends on their molecular structure and oxidation conditions. IKhFAN-9 and IKhFAN-10 (in which R^3 contains 0 and 1 carbon atom, respectively) in homogeneous and heterogeneous solutions are more active than well-known synthetic and natural AOs such as dibunol and α-tocopherol. Their analogues with long-chain substituents at the quaternized nitrogen atom exert a weaker overall inhibiting effect because of the formation of microheterogeneous systems. However, their effect strengthens with increasing chain length of the R^3 radical.

Two-layer structures formed by IKhFANs with R^3 substituents as long as the higher fatty acids in phospholipids (which contain 18–22 carbon atoms) are expected to be comparable in size with biomembranes. Therefore, they are expected to be strongly held by cell membranes and to stabilize nonenzymatic oxidation processes on their inner (cytoplasmic) and outer sides.

Owing to their relatively low toxicity and high effectiveness, the IKhFANs are considered to be candidate AOs for stabilizing the oxidation of pulps and emulsions of various edible and bioactive lipids.

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