

ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ  
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ  
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ  
АРМЕНИЯ

Հայաստանի քիմիական հանդես 60, №1, 2007 Химический журнал Армении

ОБЩАЯ И ФИЗИЧЕСКАЯ ХИМИЯ

УДК 541.124.7:518.5

NUMERICAL SIMULATION OF METHYL LINOLEATE PEROXIDATION INHIBITED BY  $\alpha$ -  
TOCOPHEROL

L. A TAVADYAN, A. A. KHACHOYAN, G. A. MARTOYAN and A. KAMAL-ELDIN

A.B. Nalbandyan Institute of Chemical Physics  
of National Academy of Sciences of Armenia., Yerevan

Dept. of Food Science, Swedish Univ. of Agric. Sci. Uppsala, Sweden

Submitted 10 XII 2006

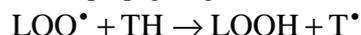
A kinetic model of methyl linoleate peroxidation inhibited by  $\alpha$ -tocopherol was constructed. Good accord was obtained with experimental data at 40°C. Model was numerically analyzed by the value method based on Hamiltonian systematization of kinetic equations. The extremal complex behavior of reaction induction period in relation to  $\alpha$ -tocopherol initial concentration is related to the increase in the ratios of [tocopheroxyl radical]/[peroxyl radical] and the {tocopherol mediated peroxidation rate}/{rate of termination by combination of tocopheroxyl and peroxyl radicals}. The prooxidant influence of autoinitiation reaction with  $\alpha$ -tocopherol and hydroperoxide are important too.

Fig. 4, table 1, references 26.

**Introduction**

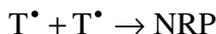
$\alpha$ -Tocopherol (Fig.1) is recognized as the most important antioxidant with respect to protection against oxidative damage of polyunsaturated fatty acids in foods and biological systems [1–4].

The mechanism of the antioxidant action of  $\alpha$ -tocopherol relies on scavenging of chain-carrying lipid peroxy radicals ( $\text{LOO}^\bullet$ ) that would otherwise cause oxidative damage in biological membranes and other lipid-containing structures.  $\alpha$ -Tocopherol (TH) acts as a chain-breaking antioxidant by donating its phenolic hydrogen to the chain-propagating  $\text{LOO}^\bullet$  radical yielding a hydroperoxide and a less reactive  $\alpha$ -tocopheroxyl radical ( $\text{T}^\bullet$ )



$\text{T}^\bullet$  reacts with another  $\text{LOO}^\bullet$  or  $\text{T}^\bullet$  forming non-radical products (NRP)





The complex dependence of the induction period and lipid peroxidation rate during the induction period on the initial concentration of  $\alpha$ -tocopherol is connected with prooxidative effects.

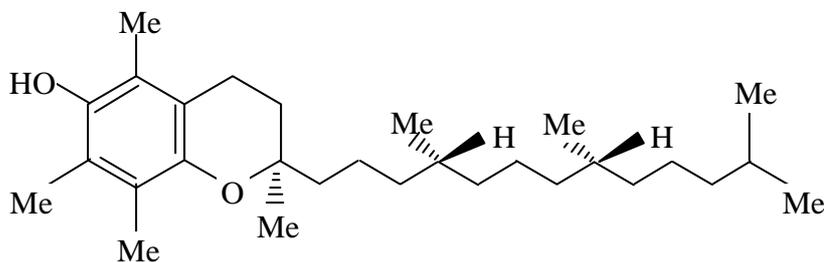


Fig.1. Structure of  $\alpha$ -tocopherol (5,7,8-trimethyl tocol) (TH).

This complexity leads to the observed inconsistency in the reported relative activities of the different tocopherols in various in vitro experiments [3–7]. The aims of this paper are: first — construct the model with great predictive ability and second — numerically analyzed it to describe extremal complex effect of induction period dependence of  $\alpha$ -tocopherol.

### Kinetic Model and Methods

The value method [8] was used for numerical modeling and analysis of methyl linoleate peroxidation reaction in the presence of  $\alpha$ -tocopherol. The experiment was a study on the inhibition of methyl linoleate oxidation by  $\alpha$ -tocopherol (12–68 mM) in the presence of initial methyl linoleate hydroperoxides at 40°C [3].

The mechanism of chain-breaking antioxidant activity of  $\alpha$ -tocopherol in lipid peroxidation reactions is thoroughly studied [1–7]. It allowed constructing a kinetic model of peroxidation reaction of the model lipid, methyl linoleate, inhibited by  $\alpha$ -tocopherol (Table). When constructing the kinetic model, particular interest was paid to the existing data on the elementary reactions and on the autooxidation routes of  $\alpha$ -tocopherol in the reaction products [3, 4].

Besides the traditional reactions usually describing the chain process of methyl linoleate peroxidation, reactions of hydroperoxyl radical and hydrogen peroxide formation and their further reactions are included in the kinetic model. Similarly, together with the reactions describing the chain-breaking antioxidant activity of  $\alpha$ -tocopherol, reactions responsible for the prooxidant properties of  $\alpha$ -tocopherol (i.e. chain propagation reaction with the participation of  $\alpha$ -tocopheroxyl radicals, steps of autoinitiating chain-branching via the reactions of TH with peroxide compounds and the decomposition of quinolide peroxides being formed) are included in the kinetic scheme. The possibilities of chain termination reactions with the participation of various free radicals are also taken into consideration (table).

The rate constants of the reactions are calculated for the temperatures at 40°C using Arrhenius equation based on handbooks and other literature [9–24].

The kinetic significance of the individual reaction is determined by value magnitude  $G_j(t)$ , which is a response relation to the reaction target parameter at instant of time on the small disturbance of the step rate at the initial instant of time to

$$G_j(t) = \frac{\partial f_0[r_1(t), \dots, r_n(t)]}{\partial r_j} \Big|_{r_j = r_j(t_0)}, \quad j = 1, 2, \dots, n \quad (1)$$

where  $r_j(t)$  is the rate of j step

The value contribution of an individual step takes also into consideration the magnitude of the reaction's rate:

$$h_j(t) = G_j(t)r_j(t) \quad (2)$$

The value magnitudes of the individual steps of the reaction mechanism are determined by Hamiltonian systematization of kinetic equations. The calculation was made by VALKIN computing software [8]. In the given computing software, the systems of differential equations were integrated using of calculation subprogram ROW-4A [25].

*Table*

**The kinetic model of peroxidation reaction of the model lipid, methyl linoleate, inhibited by  $\alpha$ -tocopherol at 40°C**

N	The Chain Reaction's Steps	Rate Constants	Reference
1	$LH + O_2 \rightarrow L^\bullet + HOO^\bullet$	$2.24 \times 10^{-10}$	[9, 15]
2	$L^\bullet + O_2 \rightarrow LOO^\bullet$	$8.75 \times 10^8$	[11]
3	$LOO^\bullet + LH \rightarrow L^\bullet + LOOH$	76.3	[14, 21]
4	$LO^\bullet + LH \rightarrow LOH + L^\bullet$	$1.26 \times 10^7$	[11, 16]
5	$HOO^\bullet + LH \rightarrow L^\bullet + H_2O_2$	228	[12]
6	$HOO^\bullet + LOOH \rightarrow LOO^\bullet + H_2O_2$	$6.71 \times 10^2$	[11]
7	$LO^\bullet + LOOH \rightarrow LOH + LOO^\bullet$	$3.79 \times 10^8$	[11]
8	$LOO^\bullet + H_2O_2 \rightarrow LOOH + HOO^\bullet$	$1.14 \times 10^2$	[18]
9	$LOO^\bullet \rightarrow L(-H) + HOO^\bullet$	$5.49 \times 10^{-2}$	[21]
10	$LOO^\bullet + LOO^\bullet \rightarrow L(-H)O + LOH + O_2$	$2.01 \times 10^7$	[14, 21]
11	$LOOH \rightarrow LO^\bullet + \bullet OH$	$1.23 \times 10^{-8}$	[22]
12	$LOOH \rightarrow L(-H)O + H_2O$	$3.69 \times 10^{-8}$	[26]
13	$TH + LO^\bullet \rightarrow T^\bullet + LOH$	$10^9$	*

14	$\text{TH} + \text{LOO}^\bullet \rightarrow \text{T}^\bullet + \text{LOOH}$	$1.85 \times 10^6$	[11]
15	$\text{TH} + \text{HOO}^\bullet \rightarrow \text{T}^\bullet + \text{H}_2\text{O}_2$	$5.55 \times 10^6$	[12]
16	$\text{T}^\bullet + \text{LH} \rightarrow \text{TH} + \text{L}^\bullet$	$3.97 \times 10^{-2}$	[19]
17	$\text{T}^\bullet + \text{LOOH} \rightarrow \text{TH} + \text{LOO}^\bullet$	10.6	[11]
18	$\text{T}^\bullet + \text{H}_2\text{O}_2 \rightarrow \text{TH} + \text{HOO}^\bullet$	10.6	**
19	$\text{T}^\bullet + \text{O}_2 \rightarrow \text{TMQ} + \text{HOO}^\bullet$	$1.16 \times 10^{-2}$	[13]
20	$\text{T}^\bullet + \text{T}^\bullet \rightarrow \text{TH} + \text{TMQ}$	$1.28 \times 10^3$	[10]
21	$\text{T}^\bullet + \text{HOO}^\bullet \rightarrow \text{TH} + \text{O}_2$	$0.75 \times 10^8$	[20]
22	$\text{L}^\bullet + \text{TMQ} \rightarrow \text{NRP}$	$9.30 \times 10^5$	[10]
23	$\text{LOO}^\bullet + \text{TMQ} \rightarrow \text{NRP}$	$8.35 \times 10^2$	[24]
24	$\text{LOOH} + \text{TH} \rightarrow \text{LO}^\bullet + \text{T}^\bullet + \text{H}_2\text{O}$	$6.60 \times 10^{-6}$	[10, 11]
25	$\text{HOOH} + \text{TH} \rightarrow \text{T}^\bullet + \text{}^\bullet\text{OH} + \text{H}_2\text{O}$	$6.60 \times 10^{-6}$	*
26	$\text{}^\bullet\text{OH} + \text{LH} \rightarrow \text{L}^\bullet + \text{H}_2\text{O}$	$10^{10}$	***
27	$\text{T}^\bullet + \text{LOO}^\bullet \rightarrow \text{o-T-OOL}$	$1.23 \times 10^8$	[20]
28	$\text{T}^\bullet + \text{LOO}^\bullet \rightarrow \text{p-T-OOL}$	$0.27 \times 10^8$	[20]
29	$\text{o-T-OOL} \rightarrow \text{LO}^\bullet + \text{o-TE}^\bullet$	$5.54 \times 10^{-8}$	[20]
30	$\text{o-TE}^\bullet + \text{LOO}^\bullet \rightarrow \text{o-TE-OOL}$	$1.50 \times 10^8$	[20]
31	$\text{o-TE-OOL} \rightarrow \text{o-TE-O}^\bullet + \text{LO}^\bullet$	$6.34 \times 10^{-10}$	[20]
32	$\text{o-TE-O}^\bullet + \text{LH} \rightarrow \text{o-TEQ} + \text{L}^\bullet$	$1.26 \times 10^7$	****
33	$\text{o-TE-O}^\bullet + \text{TH} \rightarrow \text{o-TEQ} + \text{T}^\bullet$	$10^9$	****
34	$\text{p-T-OOL} \rightarrow \text{LO}^\bullet + \text{TQ-O}^\bullet$	$6.34 \times 10^{-10}$	[20]
35	$\text{T}^\bullet + \text{HOO}^\bullet \rightarrow \text{o-T-OOH}$	$2.70 \times 10^8$	[20]
36	$\text{T}^\bullet + \text{HOO}^\bullet \rightarrow \text{p-T-OOH}$	$0.60 \times 10^8$	[20]

<sup>1</sup>The values of rate constants of the reaction are given in the units of M, s.

<sup>2</sup>Some of reaction steps haven't show because of their too low rates' constants and low significance for reaction mechanism.

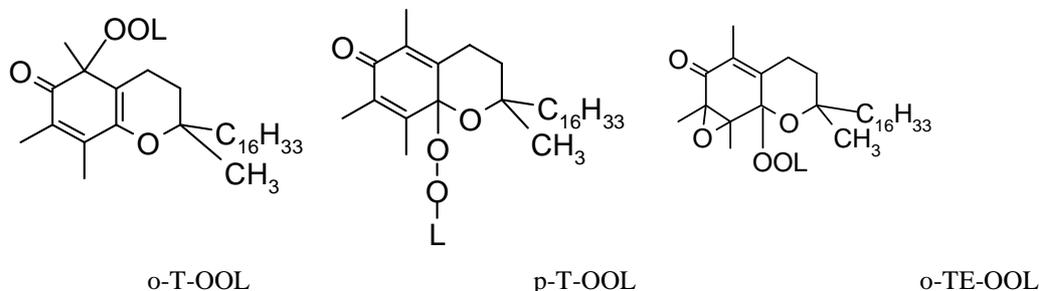
\*The rate constant of this reaction is accepted as close to the rate constant of diffusion-controlled reaction with participation of polyatomic molecules.

\*\*The rate constant is accepted as equal to the similar step 17.

\*\*\* The rate constant of this reaction is accepted as close to the rate constant of diffusion-controlled reaction with participation of small molecules

\*\*\*\*It's commonly assumed that this step's rate constant is equal to the rate constant of hydrogen atom abstraction from the molecules of methyl linoleate and  $\alpha$ -tocopherol by alkoxy radicals.

\*TMQ — tocopherol methylenquinone.



## Results and Discussions

### *Numerical description of the experimental kinetic data*

One of the main criteria of the correctness of a constructed reaction kinetic model is its ability to adequately describe experimental results. The experimental data used in the work describes the kinetics of methyl linoleate peroxidation at 40°C under a wide range of initial concentrations of the reaction species,  $\alpha$ -tocopherol and hydroperoxide [3].

As is shown in fig. (2,3) the calculated data obtained according to the kinetic model (table) describes, with good precision, the experimental data. It can also be observed from data shown in fig. (3) that the kinetic model precisely describes the complex character of the dependence of the induction period on the initial concentrations of  $\alpha$ -tocopherol.

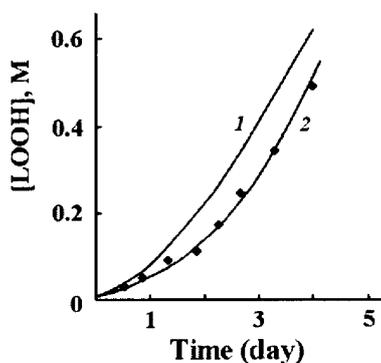


Fig. 2. Kinetic curves of hydroperoxide accumulation during the peroxidation of methyl linoleate at 40°C. Initial concentrations  $[LH]_0 = 3$  M,  $[LOOH]_0 = 10^{-2}$  M. 1 – calculation, 2 – experiment [3].

The kinetic model of the peroxidation reaction of methyl linoleate inhibited by  $\alpha$ -tocopherol was analyzed by the numerical value method in order to reveal the roles; i.e. kinetic significances of individual steps and chemical species of the reaction. The dynamics of value contributions change of most essential steps of the kinetic model of methyl linoleate peroxidation inhibited by  $\alpha$ -tocopherol are presented in fig. 4. The value analysis allowed revealing the following peculiarities of the course of the reaction.

The participation of  $\alpha$ -tocopherol, shown by the reactions (13)-(36), is subdivided into two reaction categories: (I) steps for which the value contributions were positive (set the right of the central axis in fig. 4) were responsible for the antioxidant properties of  $\alpha$ -tocopherol, and (II) steps the value contributions of which were negative and (set to the left of the central axis in fig. 4) were responsible for the prooxidant properties of  $\alpha$ -tocopherol.

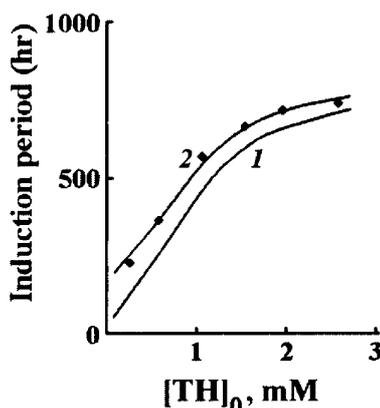


Fig. 3. Dependence of the induction period of the peroxidation reaction of methyl linoleate on the initial concentration of  $\alpha$ -tocopherol  $[TH]_0$  at 40°C. Initial concentrations  $[LH]_0 = 3$  M,  $[LOOH]_0 = 2 \times 10^{-2}$  M. Induction period is measured as TH 99.99% consumption. 1 – calculation, 2 – experiment [3].

The reactions of  $\alpha$ -tocopherol with peroxy radicals (step 14), of  $\alpha$ -tocopheroxy radicals with the peroxy radicals (steps 27, 28), of  $\alpha$ -tocopheroxy radicals with each other (step 20), and of peroxy radicals with tocopherylmethylenquinone (step 23) were revealed to play the most essential role in the manifestation of antioxidant properties of  $\alpha$ -tocopherol.

The chain transfer steps, (16) and (17), i.e. the abstraction reaction of hydrogen atom by  $\alpha$ -tocopheroxy radical from the molecules of methyl linoleate and hydroperoxide, have the most essential prooxidant activity. It should be mentioned that the total rate of these steps is commensurable in magnitude with the rate of the chain propagation step (3) with the participation of peroxy radicals as lipid peroxidation reaction in the presence of  $\alpha$ -tocopherol proceeds in tocopherol mediated peroxidation (TMP) regime [1, 3, 4]. The inhibiting activity of  $\alpha$ -tocopherol is conditioned by the essentially high concentration in the reaction medium of tocopheroxy radical compared with that of lipoperoxy (on average by three orders of magnitude). This increases the possibility of the cross reactions of chain termination with the participation of  $T^\bullet$ .

An essential contribution in the manifestation of the prooxidant properties of  $\alpha$ -tocopherol is made by the reactions of free radicals as the result of homolytic decomposition of quinolide peroxides (o-TOOL, p-TOOL, o-TE-OOL) in the steps 29, 31 and 34. Moreover, their contribution at high  $[TH]_0$  is commensurable with the contribution of the autoinitiation, chain-branching steps, as a result of homolytic decomposition of hydroperoxide.

The value analysis allowed revealing one of the main reasons for the complex, non-linear dependence of the length of the induction period ( $\tau$ ) and that of reaction rate on the initial concentrations of  $\alpha$ -tocopherol, presented in fig. 3. Value contribution of the of the autoinitiation reaction involving the molecules of  $\alpha$ -

tocopherol and hydroperoxide (step 23) essentially increases with increasing  $[TH]_0$ , eventually increasing the essentially of the contribution of reaction (11) of the homolytic decomposing of hydroperoxide. This allows the conclusion that reaction (24) essentially influences the type of dependence of  $\tau$  and the reaction rates of lipid peroxidation on the initial concentration of  $\alpha$ -tocopherol.

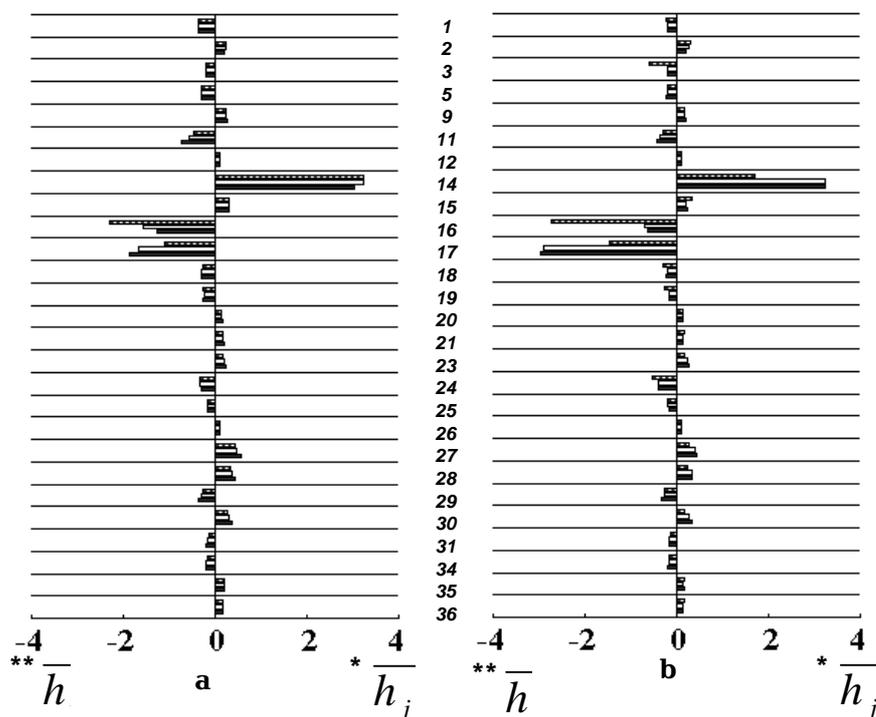


Fig. 4. The dynamics of the relative value contributions of the individual steps of the peroxidation reaction of methyl linoleate inhibited by  $\alpha$ -tocopherol at its' various initial concentrations. a -  $[TH]_0 = 3 \times 10^{-4}$  M, b -  $[TH]_0 = 3 \times 10^{-3}$  M. Is shown steps with

$$|\overline{h_j}| > 10^{-6}. \quad {}^* \overline{h_j} = -(\lg |\overline{h_j}|)^{-1} \text{ and } \quad {}^{**} \overline{h_j} = (\lg |\overline{h_j}|)^{-1}, \quad \text{where } \quad \overline{h_j} = h_j \left( \sum_{j=1}^{36} h_j^2 \right)^{-1/2}.$$

-10% , -50% , -90% [TH] consumption.

It appears that non-linear and in some cases extreme dependence of  $\tau$  on  $[TH]_0$  [2, 5, 6] is the result of the manifestation of prooxidant properties of  $\alpha$ -tocopherol at the expense of simultaneous autoinitiation reaction course with the participation of the molecules of TH and LOOH and the TMP reactions (16) and (17). The changes of rates' constants significances of steps (16), (17) and (24) 3,4 time are greatly affect of induction period dependence of initial concentration of  $\alpha$ -tocopherol, and that's means too of a great value of these steps.

In summary, the kinetic model presented in table adequately describes the experimental results including simultaneous manifestation of the anti- and pro- oxidant properties of  $\alpha$ -tocopherol in the process of lipid peroxidation.

**α-ՏՈԿՈՖԵՐՈԼՈՎ ԱՐԳԵԼԱԿՎԱԾ ՄԵԹԻԼԼԻՆՈԼԵԱՏԻ ՊԵՐՕՔՍԻԴԱՅՄԱՆ ՌԵԱԿՑԻԱՅԻ ԹՎԱՅԻՆ ՄՈԴԵԼԱՎՈՐՈՒՄ**

**Լ. Ա. ԹԱՎԱԴՅԱՆ, Ա. Ա. ԽԱՉՈՅԱՆ, Գ. Ա. ՄԱՐՏՈՅԱՆ և Ա. ՔԱՄԱԼ-ԷԼԴԻՆ**

Կառուցված է α-տոկոֆերոլով արգելակված մեթիլլինոլեատի պերօքսիդացման ռեակցիայի կինետիկական մոդել: Մոդելը ադեկվատ նկարագրում է 40°C ստացված փորձնական արդյունքները: Ինդուկցիոն ժամանակահատվածի բարդ, ոչգծային կախվածությունը α-տոկոֆերոլի սկզբնական կոնցենտրացիայից բացատրված է [տոկոֆերօքսիլ ռադիկալ]/[պերօքսիլ ռադիկալ] կոնցենտրացիաների և համապատասխանաբար {տոկոֆերոլի խթանմամբ պերօքսիդացման արագություն}/{տոկոֆերօքսիլ և պերօքսիլ ռադիկալների ռեկոմբինացիայի արագություն} հարաբերությունների աճով, ինչպես նաև α-տոկոֆերոլի հիդրոպերօքսիդի մոլեկուլների մասնակցությամբ ընթացող ինքնահարուցման ռեակցիայով:

**ЧИСЛЕННОЕ МОДЕЛИРОВАНИЕ РЕАКЦИИ ПЕРЕКИСНОГО ОКИСЛЕНИЯ  
МЕТИЛЛИНОЛЕАТА, ИНГИБИРОВАННОЙ  
α-ТОКОФЕРОЛОМ**

**Լ. Ա. ԿԱՎԱԴՅԱՆ, Ա. Ա. ԽԱՉՈՅԱՆ, Գ. Ա. ՄԱՐՏՈՅԱՆ և Ա. ԿԱՄԱԼ-ՋԼԻՆ**

Построена кинетическая модель реакции перекисного окисления метиллинолеата, ингибированной α-токоферолом. Модель адекватно описывает экспериментальные кинетические данные, полученные при 40°C. Нелинейная, сложная зависимость периода индукции реакции от начальной концентрации α-токоферола объяснена увеличением соотношения концентраций [токофероксильный радикал]/[пероксильный радикал] и соответственно ростом соотношения скоростей {скорость перекисного окисления с участием α-токоферола}/{скорость рекомбинации токофероксильных и пероксильных радикалов}, так же, как и прооксидантным влиянием реакции автоинициирования с участием молекул α-токоферола и гидропероксида.

**REFERENCES**

- [1] Bowry V.W., Ingold K.U. // Acc. Chem. Res., 1999, v.32, p.27.
- [2] Burlakova E.B., Karshakov S.A., Khrapova N.G. //Biol. Membran, 1998, v.15, p.137.
- [3] Kamal-Eldin A., Makinen M., Lampi A., Hopia, A. // Eur. Food Res. Technol., 2002, v.214, p.52.
- [4] Kamal-Eldin A., Appelqvist L. //Lipids, 1996, v.31, p.671.
- [5] Mukai K., Noborio S., Nagaoka S.I. // Int. J. Chem. Kinet. 2005, v.37, p.605.
- [6] Naumov V.V., Vasilev R.F. //Kinetika i kataliz, 2003, v.44, p.111.
- [7] Yanishlieva N.V., Marinova E.M. // Fat Sci. Technol. 1992, v.94, p.374.
- [8] Tavadyan L.A., Martoyan G.A. Analysis of kinetic models of chemical reaction systems. Value Approach. Yerevan, Gitutium, 2005, p.247.
- [9] Benson S.W. Thermochemical kinetics. New York, John Willey Sons, 1968, p. 312.
- [10] Denisov E.T., Azatyan V.V. Chain reactions inhibition. London, Taylor & Francis, 2000, p. 326.
- [11] Denisov E.T., Denisova T.G. Handbook of antioxidants: bond dissociation energies, rate constants, activation energies and enthalpies of reactions. CRC Press, Boca Ration, 2<sup>nd</sup> ed. New York, 2000, p. 430.

- [12] Denisov E.T., Denisova T.G., Pokidova T.S. Handbook of free radical initiators. New York, John Wiley & Sons, 2002, p.268.
- [13] Doba T., Burton G.W., Ingold K.U., Matsuo M. // J. Chem. Soc. Chem. Commun., 1984. p. 461.
- [14] Howard J.A., Ingold K.U. // Can. J. Chem., 1967, v.45, p.793.
- [15] Korchek S., Chenier J.H.B., Howard J.A., Ingold K.U. // Can. J. Chem., 1972, v.50, p.2285.
- [16] Landolt-Bornstein. Numerical data and functional relationships in science and technology. New Series, group II. Vol 13e. Springer-Verlag, Berlin, 1984, p. 5.
- [17] Maillard B., Ingold K.U. Scaiano J.C. // J. Am. Chem Soc. 1983, v.105, p.5095.
- [18] Mardoyan V.A., Tavadyan L.A., Nalbandyan A.B. // Chem. J. of Arm., 1985, v.38, p.473.
- [19] Remorova A.A., Roginsky V.A. // Kinetika i kataliz, 1991, v.32, p.808.
- [20] Roginsky V.A. Phenolic antioxidants. Moscow, Nauka, 1988, p.245.
- [21] Roginsky V.A., Barsukova T. // Chem. Phys. Lipids., 2001, v.111, p.87.
- [22] Roginsky V.A., Utkin I.V. // Kinetika i kataliz, 1991, v.4, p.814.
- [23] Tavadyan L.A. // Chim. Phis., 1986, v.5, p.63.
- [24] Zolotova N.B., Galieva F.A., Tokareva M.B., Denisov E.T. // Kinetika i kataliz, 1979, v.20, p.48.
- [25] Gotwald B.A., Wanner G.A. // Simulation, 1982, v.37, p 169.
- [26] Matienko L.I., Goldina L.A., Skibida I.P., Majzus Z.K. // Izv. AN. SSSR, ser. chim. 2, 1975, p.287.