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Expanding the antioxidant activity into higher temperatures – fullerene C_{60} conjugated with α-tocopherol analogue as a hybrid antioxidant in saturated lipid systems

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Oxidative stability of two fatty acids: stearic acid (STA) as a model of saturated lipid and linolenic acid (LNA) as model of polyunsaturated lipid containing C_{60} derivative with covalently bonded hydroxychromanyl moiety as analogue of α-tocopherol (F-1) was monitored by differential scanning calorimetry. The overall Arrhenius kinetic parameters (activation energy E_a, pre-exponential factor Z, and rate constants k) of non-isothermal oxidative decomposition indicate that in saturated hydrocarbons the hybrid C_{60}+hydroxychromane derivative is effective antioxidant acting at temperatures above 120°C, expressed as 9 kJ/mol increase of E_a and values of k twice smaller than for oxidation of non-inhibited pure STA. However, experiments with LNA oxidized at temperatures above 80°C indicated that the hybrid derivative did not improve the oxidative stability of polyunsaturated lipids at higher temperatures (E_a, Z and k's are almost the same as for oxidation of pure LNA). We suggest that C_{60} is able to inhibit STA autoxidation due to formation of thermally stable adducts with alkoxyl radicals whereas autoxidation LNA is mediated by peroxyl radicals that are not effectively scavenged by C_{60}.

Keywords: Fullerene, Tocopherol, Antioxidant, Lipids, Hydrocarbon oxidation, Oxidation kinetics

INTRODUCTION

Peroxidation (autoxidation) of lipids and hydrocarbons (LH) is a chain process mediated by alkyl and alkylperoxyl radicals ($L^\bullet$ and $LOO^\bullet$, respectively) where after the initiation, i.e., generation of primary radical species, a series of consecutive additions of molecular oxygen (reaction 1, with k_{p1}~10^9 M^1s^{-1}) and abstraction of hydrogen (reaction 2, with k_{p2} ~10-100 $M^{-1}s^{-1}$) form the kinetic propagation chain [1]:

$$L^\bullet + O_2 \xrightarrow{k_{p1}} LOO^\bullet \quad (1)$$

$$LOO^\bullet + LH \xrightarrow{k_{p2}} LOOH + L^\bullet \quad (2)$$

For low partial pressures of oxygen not all radicals react with molecular O_2, moreover, at higher temperatures the products of propagation chain like hydroperoxides (LOOH) might undergo subsequent thermal or metal-induced decomposition, therefore, the autoxidation can be mediated by species other than alkylperoxyls. For example, when the process occurs at higher temperatures (in lubricants) or with limited access to oxygen (polymers) the propagation can be facilitated with alkyl and alkoxyl radicals [2, 3].

Application of chain-breaking antioxidants is one of the possible ways of protection of food, polymers and other hydrocarbons, as well as biomolecules being the components of living organisms. The role of chain-breaking antioxidants is to stop any of the propagation processes, mainly by reducing the propagating radicals ($Y^\bullet$= $LOO^\bullet$ or $LO^\bullet$) to relatively stable radicals or non-radical products, schematically shown as reactions 3 and 4, or by formation of non-reactive adducts (reaction 5).

$$Y^\bullet + Aox\text{-}H \rightarrow Y\text{-}H + Aox^\bullet \quad (3)$$

$$Y^\bullet + Aox^\bullet \rightarrow Y\text{-}Aox \quad (4)$$

$$Y^\bullet + antioxidant \rightarrow (Y\text{-}antioxidant)^\bullet \quad (5)$$

The rates of scavenging (reactions 3-5) depend on the nature of the antioxidant including its structure, bond strengths, stereoelectronic effects, ionisation potential, localisation and other factors. Some kinds of molecules exhibit antioxidant action under specific conditions. For example, Burton and Ingold demonstrated that β-carotene and other carotenoids (hydrocarbons with conjugated double C=C bonds) are active chain-breaking antioxidants (reaction 5) in the systems with partial oxygen pressure below 15 kPa and carotenoids lost their activity at higher oxygen pressure [4].

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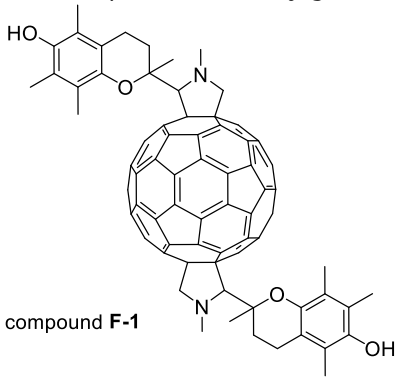
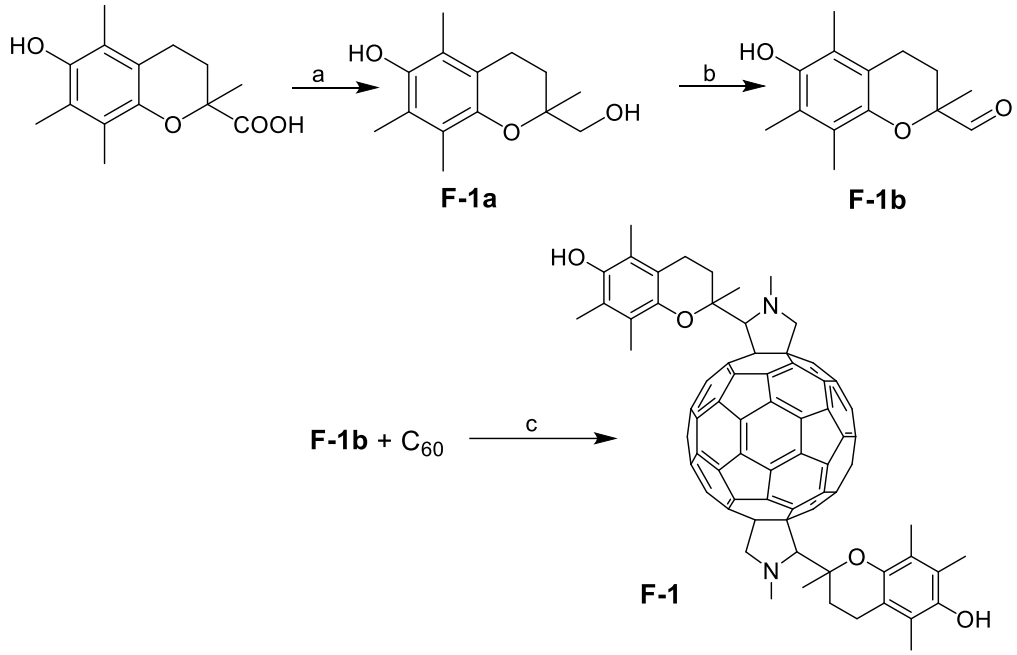
Fullerenes have been the subject of many studies, including the antiradical activity of C_{60} molecule, named the radical sponge, because of its ability to form adducts with unusually high number of benzyl, methyl and other alkyl radicals with a single C_{60} molecule [5-9]. Reactions of C_{60} with those radicals are fast and lead to the formation of stable radicals, with electrons delocalized over the whole sphere of fullerene. When passing from artificial radicals to the ones naturally occurring during autoxidation, the antiradical properties of C_{60} are not as evident - the review devoted to antioxidant properties of fullerene brings several examples of water soluble derivatives of C_{60} able to diminish the level of Reactive Oxygen Species in biologically relevant systems [10], but pristine C_{60} is claimed to be not a good chain-breaking antioxidant in a model system with styrene autoxidation [11], perhaps because the reaction with alkylperoxyl radicals is too slow to be competitive to reaction 2. On the other hand, fullerene conjugated with derivatives of phenolic antioxidant (like 2,6-di-*tert*-4-methylphenol, BHT) behaved as typical chain- breaking antioxidants. [11] Taking into account the results reported by various research teams and basing on our previous results indicating that pristine fullerene is an effective inhibitor of saturated hydrocarbon oxidation carried out at higher temperatures [12-14], we proposed a series of new hybrid antioxidants with phenolic moiety responsible for reaction with peroxyl radicals and C_{60} sphere responsible for scavenging of radical species generated at higher temperatures in oxygen-poor systems. In this work we are testing the antioxidant activity of C_{60} with a covalently bonded derivative of tocopherol, namely 6-hydroxy-2,5,7,8-tetramethylchromanyl group. Presumably, such hybrid antioxidant might connect the advantages of β-carotene (ability to scavenge radicals in the process of addition to a conjugated system of double bonds) with the advantages of α-tocopherol (low bond dissociation enthalpy facilitating the H atom transfer from phenolic O-H bond to a radical). We synthesized a derivative of C_{60} with covalently bonded chromanol moieties attached to the carbon sphere *via* N-methylpyrrolidine rings, compound **F-1**:



compound **F-1**

EXPERIMENTAL

Stearic acid, STA, (99%, Sigma-Aldrich) and linolenic acid, LNA, (POCH, 99%) were stored at 0°C in darkness. Fullerene C_{60} was of 99+% purity (MER Corporation, Tucson). 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox™), N-methylglycine (Sarcosine™), lithium aluminium hydride, ethyl acetate, hexane, manganese dioxide, dioxane, toluene, THF were purchased from Sigma-Aldrich. Toluene and THF were dried and distilled before use, other solvents were analytical grade reagents and were used as received. ^{1}H and ^{13}C NMR spectra were recorded using Varian 200 MHz instruments. Fourier transform infrared (FT-IR) spectra were obtained using Shimadzu FTIR-8400S spectrometer in the 4000-400 cm^{-1} range. Thermogravimetry was performed using TA Q50 instrument at a heating rate of 20 K/min in nitrogen (platinum vessels were used). Oxidation process of STA and LNA was monitored by differential scanning calorimetry (Du Pont 910 apparatus with Du Pont 9900 thermal analyzer and normal pressure, recently refurbished cell was used). Temperature and cell constant were calibrated with ultrapure indium standard. TA Instruments software (General V4.01) was used for collecting the data and for determination of temperatures from DSC curves. The oxidations were performed under oxygen flow of 6 dm^3/h. Samples (3.0-3.5 mg) were heated from 50 to 250°C in an open aluminium pan with a linear heating rate β (2.5; 5.0; 7.5; 10.0; 12.5; 15.0; 17.5; 20.0 K/min). As a reference material an empty aluminium pan was used. Temperatures of extrapolated start of oxidation, T_e, were determined from the plots of heat flow *versus* temperature dependence for each β. Multistep synthesis routes for derivative **F-1** are depicted in Scheme 1 and described in the next subsection, together with identification of final products by NMR and IR.



Scheme 1. Synthesis of fullerene derivative F-1.

Synthesis of F-1

Step a. Compound **F-1**a was obtained using the synthetic procedure reported by Huang *et al.* [15]. To a stirred solution of 0.78 g of $LiAlH_4$ (20 mmol) in dry THF (10 mL) at 0°C 300 mg (1.2 mmol) of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid in 18 mL of dry THF was added dropwise. The solution was stirred at room temperature under nitrogen for another 6 h, and 4 mL of 0.25 M NaOH was added to stop the reaction. The mixture was stirred at room temperature for 0.5 h, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ethyl acetate : hexane, 1:2 v/v) to afford 2-(hydroxymethyl)-2,5,7,8-tetramethylchroman-6-ol (**F-1a**) in 75% yield. Analysis: FT-IR (KBr disc 300 mg + 1 mg **F-1b**) [cm^{-1}]: 3550 (O-H), 2950 (str, C-H); 1250 (str, C-O). ^{13}C NMR (200 MHz, acetone-d_6) δ (ppm): 146.7, 146.2, 123.9, 120.8, 118.3, 113.9, 82.4, 76.5, 75.0, 68.9, 29.2, 22.0, 21.3, 13.0, 12.1, 11.3.

Step b. Compound **F-1b** was obtained using the synthetic procedure reported by Reynaud *et al.* [16]. The compound **F-1a** (100 mg, 0.42 mmol) was dissolved in ethyl acetate (6 mL), and after addition of MnO_2 (1.2 g, 12 mmol) the heterogeneous mixture was vigorously stirred for 1 h. Then the mixture was filtered through celite, dried over Na_2SO_4, and concentrated. The residue was purified by filtration through a silica gel column (hexane : ethyl acetate, 3:7, v/v) to give 6-hydroxy-2,5,7,8-tetramethylchromane-2-carbaldehyde (**F-1c**) in 80% yield. Analysis: FT-IR (KBr disc 300 mg+1 mg **F-1c**) [cm^{-1}] 3504 (O-H), 2950 (str C-H); 1680-1720 (str C=O).

Step c. The final fullerene derivative was obtained using the Prato method, described in our previous paper. [13] A mixture of C_{60} (70 mg, 0.14 mmol), sarcosine (43 mg, 0.69 mmol, 5 eq.), **F-1c** (25 mg, 0.14 mmol, 1 eq.) and 60 mL of dry toluene was stirred in reflux for 24 h in a 100-mL flask. The reaction mixture was cooled down and the solvent was removed under reduced pressure. The residue was purified by column chromatography (dioxane : toluene, 1:9, v/v) to give 35 mg prod*uct **F-1** as a brown solid (29% yield based on converted C_{60}). Analysis: ^1H NMR (200 MHz, $CDCl_3$, TMS) δ (ppm): 5,13 (s, 1H), 4.15-3.63 (s, 2H), 4.12-3.59 (s, 2H), 2.66 (s, 1H), 3,42-2,32 (s, 2H), 1.88-1.77 (s, 9H), 1.40 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 147.56; 134.66; 128.78; 128.56; 126.94; 81.01; 77.83; 76.56; 74.76; 35.91; 29.88; 22.78; 22.25; 13.01; 11.77; 10.51 The weight loss was 47% in the temperature range 250-600°C, which corresponds to two groups attached to the fullerene molecule.

RESULTS AND DISCUSSION

In our previous papers we reported the kinetic parameters of oxidation of several lipid and hydrocarbon matrices like saturated [17] and unsaturated [18] fatty acids and their esters, oils [19, 20], polyethylene [21]. Recently, we compared the antioxidant behaviour of four C_{60} adducts with

simple monohydroxyphenols [13] and we demonstrated that for high temperature oxidation of saturated hydrocarbons the conjugates of C_{60} with simple phenols are more active antioxidants than the building blocks (pristine C_{60} and phenols) used separately. In our present work we extended our search onto conjugates with analogue of α-tocopherol due to reasons explained in the Introduction section.

Differential scanning calorimetry is a very useful tool for monitoring the rate of oxidation of non-volatile materials like hydrocarbons and lipids. Typical DSC traces for non-isothermal oxidation of STA containing 2 mM of **F-1** are presented in Figure 1 with the way of determination of temperature of extrapolated start of oxidation, T_e, as a cross-section of tangents of baseline and thermal peak of oxidation.

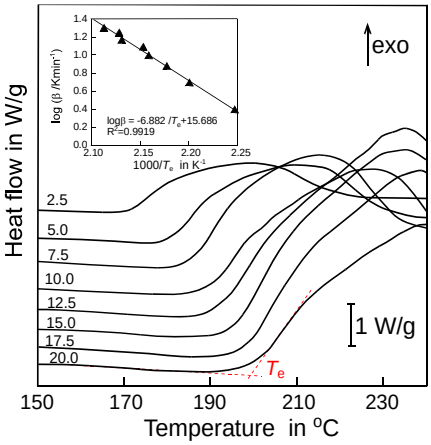


Figure 1. DSC curves of non-isothermal oxidative decomposition of STA containing **F-1** (C = 2.0 mM) recorded for linear heating rates β from 2.5 to 20.0 K/min, as indicated over each curve. Curves were shifted vertically for clarity of presentation. *Inset*: Plot of logβ versus 1000/T_e for oxidation of STA containing 2.0 mM **F-1**.

Within one series, each curve was recorded for a different linear heating rate (β) and one can observe that at higher β a higher T_e was determined (see Fig. 1). The values T_e recorded for the whole series of β's are listed in Table 1 (the presented values T_e are the mean of at least three measurements). For the same β value, the comparison of temperatures of start of oxidation of pure stearic acid with the T_e values measured for STA containing **F-1** clearly demonstrates the inhibiting effect of **F-1**, that always causes a prolongation (5-7°C) of the lag phase, defined here as extended range of temperatures without detectable thermal effect of spontaneous oxidation. Such shift of T_e to higher temperatures can be interpreted as antioxidant effect of the additive. Thus, non-isothermal oxidation monitored by DSC is an alternative method to other accelerated tests like Oxidative Stability Index or Rancimat Test [18-20].

Due to the simplicity of measurement and short time of each sample analysis, non-isothermal oxidation mode has an advantage over accelerated tests, because the changes of T_e recorded for several different β can be used for calculation of the overall kinetic parameters, activation energy (E_a) and pre-exponential factor Z for oxidation processes by the Ozawa-Flynn-Wall's method [12, 17, 19, 21], from the linear dependence:

$$\log \beta = a \times T_e^{-1} + b \qquad (6)$$

where the slope $a = -0.456\ E_a / R$ and intersection $b = -2.315 + \log(ZE_a / R)$, and R is the gas constant (8.314 [J mol^{-1}K^{-1}]).

Table 1 also contains the kinetic parameters measured and calculated for oxidation of pure STA (E_a = 116 ± 8 kJ/mol and Z = 1.34 × 10^{13} s^{-1}) being in reasonable agreement with the activation energy of isothermal oxidation of saturated fatty

Table 1. Temperatures of start of oxidation (T_e) obtained for different heating rates (β), statistical parameters of straight line equation $\log\beta = a/T_e + b$, and overall kinetic parameters E_a - activation energy, Z - pre-exponential factor, k - rate constants obtained for oxidation of pure STA and STA containing 2 mM derivative **F-1**. The errors of E_a were calculated from the standard error σ of the slope a calculated with confidence level 90% ($\sigma_{90\%}$).

STEARIC ACID (STA)			*STA with 2 mM **F-1***		
β [K/min]	T_e [K]	Statistical and kinetic parameters	β [K/min]	T_e [K]	Statistical and kinetic parameters
2.5	437	a = -6.36	2.5	444	a = -6.8819
5.0	447	b = 14.95	5.0	454	b = 15.8680
7.5	452	R^2 = 0.9982	7.5	457	R^2 = 0.9919
10.0	456	E_a = 116 ± 8 kJ/mol	10.0	463	E_a = 125 ± 9 kJ/mol
12.5	458	$Z = 1.34 \times 10^{13}$ min^{-1}	12.5	464	$Z = 1.01 \times 10^{14}$ min^{-1}
15.0	461	$k_{50°C} = 2.50 \times 10^{-6}$ min^{-1}	15.0	468	$k_{50°C} = 5.66 \times 10^{-7}$ min^{-1}
17.5	465	$k_{100°C} = 8.07 \times 10^{-4}$ min^{-1}	17.5	470	$k_{100°C} = 2.93 \times 10^{-4}$ min^{-1}
20.0	466	$k_{150°C} = 6.66 \times 10^{-2}$ min^{-1}	20.0	473	$k_{150°C} = 3.45 \times 10^{-2}$ min^{-1}
		$k_{200°C} = 2.16 \times 10^{0}$ min^{-1}			$k_{200°C} = 1.49 \times 10^{0}$ min^{-1}
		$k_{250°C} = 3.61 \times 10^{1}$ min^{-1}			$k_{250°C} = 3.12 \times 10^{1}$ min^{-1}

acids [17]. The comparison of activation parameters for oxidation of pure STA and STA with 2 mM **F-1** suggests ca. 9 kJ/mol increase of the overall activation barrier, but taking into account our former experience, the reaction rates are more reliable and trustful parameters than the E_a. This is because the so called accelerated tests of the oxidation of lipids and hydrocarbons are carried out at temperatures above 100°C, that is, at temperatures very close or even higher than the isokinetic temperature, T_{iso}, the temperature at which two different processes have the same rate constants. Above T_{iso} the process with higher E_a proceeds faster than the process characterized by lower E_a [14, 19], as a consequence of cross-section of exponential functions describing the Arrhenius rate constant:

$$k = Z \exp(-E_a/RT) \qquad (7)$$

originating from different sets of E_a and Z. This phenomenon is a source of a series of counterintuitive observations, for example, the inversion of oxidative stabilities or inversion of antioxidant effect into pro-oxidant effect when the results from lower temperatures are compared with the results of experiments performed at higher temperatures. Perhaps, this is also a possible explanation why α-tocopherol and its simple analogues are not good antioxidants in lipid systems oxidized at temperatures above 110°C as in OSI, Rancimat, or Oxipress test [22, 23]. In our system the values of k calculated from eqns. 7 for STA and STA containing **F-1** are also listed in Table 1 for temperatures 50-250°C. Indeed, we can observe that addition of **F-1** improves the oxidative stability of STA at temperatures below 200°C (at 250°C the values of k are close for both systems).

We also performed a series of experiments with LNA, chosen as a completely different model of polyunsaturated fatty acid to be oxidized, in the presence of **F-1** (see Fig. 2).

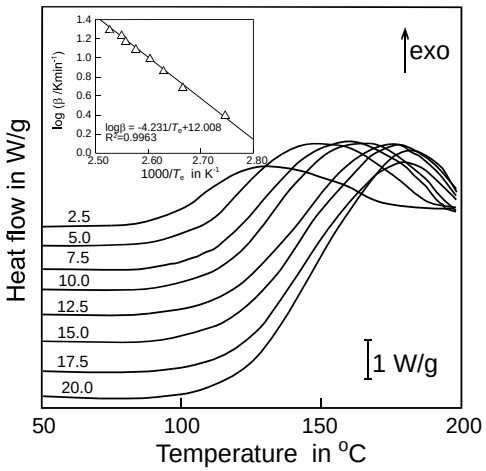


Figure 2. DSC curves of non-isothermal oxidative decomposition of LNA containing **F-1** (C = 2.0 mM) recorded for linear heating rates β from 2.5 to 20.0 K/min, as indicated over each curve. Curves were shifted vertically for clarity of presentation. Inset: Plot of logβ *versus* 1000/T_e for oxidation of LNA containing 2.0 mM **F-1**.

LNA reacts with oxygen ca. 170 times faster than STA and due to this reason LNA is often used for studies of antioxidant activity of phenolic antioxidants by the DSC method, with T_e values by about 100°C lower than for oxidation of STA. The results are presented in Table 2, where the data are compared with oxidation parameters for LNA without the additive (results taken from ref. [13]).

The kinetic data presented in Table 2, E_a, Z and k's are similar, that is, the addition of **F-1** to LNA did not cause any inhibiting effect This observation is in disagreement with the inhibiting effect of **F-1** in STA, but is a good example of the important role of the lipid/hydrocarbon matrix taken as model system for testing the antioxidant

Table 2. Results (T_e, statistical parameters of equation 1, E_a, Z, and k) obtained for oxidation of pure LNA and LNA containing **F-1** (C = 2 mM). Symbols are the same as explained in the heading to Table 1.

LINOLENIC ACID (LNA)			*LNA with 2 mM **F-1***		
β [K/min]	T_e [K]	Statistical and kinetic parameters	β [K/min]	T_e [K]	Statistical and kinetic parameters
2.5	366	a = -4.3015	2.5	364	a = -4.2231
5.0	375	b = 12.1509	5.0	375	b = 12.0076
7.5	383	R^2 = 0.9879	7.5	380	R^2 = 0.9963
10.0	385	E_a = 78 ± 6 kJ/mol	10.0	384	E_a = 77 ± 3 kJ/mol
12.5	391	$Z = 3.10 \times 10^{10}$ min^{-1}	12.5	388	$Z = 2.27 \times 10^{10}$ min^{-1}
15.0	392	$k_{50°C} = 6.81 \times 10^{-3}$ min^{-1}	15.0	391	$k_{50°C} = 8.04 \times 10^{-3}$ min^{-1}
17.5	393	$k_{100°C} = 3.38 \times 10^{-1}$ min^{-1}	17.5	392	$k_{100°C} = 3.74 \times 10^{-1}$ min^{-1}
20.0	396	$k_{150°C} = 6.68 \times 10^{0}$ min^{-1}	20.0	395	$k_{150°C} = 7.04 \times 10^{0}$ min^{-1}
		$k_{200°C} = 7.02 \times 10^{1}$ min^{-1}			$k_{200°C} = 7.11 \times 10^{1}$ min^{-1}
		$k_{250°C} = 4.70 \times 10^{2}$ min^{-1}			$k_{250°C} = 4.62 \times 10^{2}$ min^{-1}

activity of any compound. One of the possible explanations is that a clear inhibiting effect (lag phase) can be observed for sufficiently active chain-breaking antioxidants, when the rate constant of inhibition (reactions 3-5, depending on the mechanism) is by three orders of magnitude greater that the rate constant of propagation. Thus, the same molecule can act as antioxidant in the saturated hydrocarbons, where k_p = 0.00034 $M^{-1}s^{-1}$ (hexadecane at 30°C [24]) but it will be not active in LNA (k_p = 48 $M^{-1}s^{-1}$ at 37ºC [25]). This hypothesis would be valid for C_{60} conjugated with simple phenols and can, to some extent, explain the better activity of the C_{60} component in derivative **F-1**. Lack of clear inhibiting effect in the LNA matrix indicates almost complete deactivation of the tocopherol-like component (hydroxychromanyl part) in **F-1** at higher temperatures. This rather disappointing observation can be justified in another way, with the assumption taken that in polyunsaturated fatty acids the autoxidation is mediated by alkylperoxyl radicals. In this case the hydroxychromanyl site reacts with the radicals but at 90-120ºC the process of breaking the chain is not effective since the "tocopheroxyl" radical is still able to abstract H atom from a bis-allyl position of polyunsaturated LNA. Similar mechanism has been proposed by Liebler *et al.* [26] at lower temperatures (30ºC) in homogeneous solutions and also by Stocker *et al.* [27] and Ingold *et al.* [28] for LDL oxidation in the presence of α-tocopherol and was named tocopherol mediated peroxidation (TMP). Taking into account that the tocopheroxyl radical formed in reaction 3 is not reduced immediately (for example, in reaction 4) it is very plausible that at 90-120ºC this radical will attack the weakest C-H bond in LNA and reinitiate a new chain of propagation. Such mechanism of reinitiation is also probable in STA at temperatures much higher than for oxidation of LNA, however, as mentioned above, k_p for saturated hydrocarbons is by four orders of magnitude lower than k_p for LNA, moreover, autoxidation of saturated hydrocarbons at high temperatures with limited access to molecular oxygen proceeds with participation of radical species other than alkylperoxyls. As it was observed by other researchers and described in the Introduction, under such conditions C_{60} is able to efficiently scavenge alkyl and alkoxyl radicals, thus preventing the system against reinitiation or branching the kinetic chain of oxidation.

Concluding, we designed and prepared a C_{60} derivative with covalently bonded analogue of α-tocopherol (hydroxychromanyl moiety) and tested its antioxidant activity in two model lipid matrices: saturated (stearic acid) and polyunsaturated (linolenic acid) during the non-isothermal oxidation monitored by differential scanning calorimetry. The obtained kinetic parameters of oxidation (activation energy, pre-exponential factor and rate constants calculated for the overall oxidation process) indicate a clear antioxidant effect of the derivative in the saturated system but no antioxidant effect was detected during oxidation of linolenic acid. The presented results show the important role of the hydrocarbon used as model lipid for assessment of the antioxidant activity at higher temperatures in the range 90-180ºC, typical for accelerated tests of oxidative stability.

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РАЗШИРЯВАНЕ НА АНТИОКСИДАНТНАТА АКТИВНОСТ ПРИ ВИСОКИ ТЕМПЕРАТУРИ – ФУЛЕРЕН C_{60} СПРЕГНАТ С α-ТОКОФЕРОЛОВ АНАЛОГ КАТО ХИБРИДЕН АНТИОКСИДАНТ В НАСИТЕНИ ЛИПИДНИ СИСТЕМИ

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(Резюме)

Оксидативната стабилност на две мастни киселини - стеаринова киселина (STA) като модел на наситен липид и линоленова киселина (LNA) като модел на полиненаситен липид, съдържащ C_{60} производно с ковалентно свързана хидроксихроманилова част като аналог на α-токоферол (F-1) е проследена чрез диференциална сканираща калориметрия. Общите Арениусови кинетични параметри (активираща енергия E_a, пре-експоненциален фактор Z и скоростни константи k) на неизотермното оксидативно разлагане показват, че в наситени въглеводороди хибридното C_{60}+хидроксихроманово производно е ефективен антиоксидант, действащ при температури над 120°C, изразено като 9 kJ/mol нарастване на E_a и стойности на k два пъти по-малки отколкото при окисление на неинхибирана чиста STA. Опитите с LNA, окислена при температури над 80°C показват обаче, че това хибридно производно не подобрява оксидативната стабилност на полиненаситени липиди при високи температури (E_a, Z и k's са почти същите, както при окисление на чиста LNA). Ние предполагаме, че C_{60} може да инхибира автоокислението на STA поради образуване на термично стабилни адукти с алкоксилни радикали, докато в автоокислението на LNA участват пероксилни радикали, които не са ефективно уловени от C_{60}.