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Kinetic and ab Initio Study of the Prooxidant Effect of Vitamin E. Hydrogen Abstraction from Fatty Acid Esters and Egg Yolk Lecithin

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Abstract: A kinetic and ab initio study of the prooxidant effect of vitamin E derivatives has been carried out. Rates of hydrogen abstraction from various fatty acid esters and egg yolk lecithin by tocopheroxyl radicals have been determined spectrophotometrically. The second-order rate constant for the hydrogen abstraction dramatically increases as the number of π-electron systems activating the hydrogen (C=C double bonds) increases from zero to two. The rate constants per an active hydrogen for the various fatty acid esters that contain hydrogens activated by two π-electron systems are similar to one another. In order to interpret the observed features of the rate constants, ab initio calculations of models for the fatty acid esters have been carried out. From the calculation results, it is shown that the observed features of the rate constant can be explained in terms of the pseudo-π-conjugation between the C=C double bond and the active hydrogen–carbon bond. The bulkier the substituent groups at the 5- and 7-positions of the tocopheroxyl radical, the smaller the rate constant of the hydrogen abstraction. This substitution effect is likely due to the steric hindrance by the substituent groups at the 5- and 7-positions. The pseudo-first-order rate constant of egg yolk lecithin is much smaller than that expected from those for the fatty acid moieties contained in the lecithin.

Introduction

It is well-known that vitamin E (α-, β-, γ-, and δ-tocopherols) inhibits the autoxidation of organic molecules in the liquid phase, and the mechanism has been studied extensively by numerous investigators.[1,2] Furthermore, vitamin E is present in cellular membranes and edible oils and acts as an antioxidant by protecting polyunsaturated lipids or fatty acids from peroxidation.

The antioxidant properties of tocopherols (TocH) have been ascribed to hydrogen abstraction from the OH group in the tocopherols by a peroxyl radical (LOO$^\bullet$). The hydrogen abstraction produces a tocopheroxyl radical (Toc$^\bullet$), which combines with another peroxy radical (reactions 1 and 2).[3,4]

$$\mathrm{LOO^\bullet + TocH \xrightarrow{k_1} LOOH + Toc^\bullet} \tag{1}$$

$$\mathrm{LOO^\bullet + Toc^\bullet \rightarrow nonradical\ products} \tag{2}$$

Several investigators showed that α-tocopherol in high concentration acts as a prooxidant during the autoxidation of polyunsaturated fatty acids (LH).[5-7] This prooxidant effect of α-tocopherol leads to an increase of hydroperoxides with a conjugated diene structure. Loury et al.[5] and Terao et al.[6] proposed that tocopheroxyl radicals participate in this prooxidant effect through reactions 3 and 4 where reaction 3 is a hydrogen abstraction from

$$\mathrm{Toc^\bullet + LH \xrightarrow{k_3} TocH + L^\bullet} \tag{3}$$

$$\mathrm{Toc^\bullet + LOOH \xrightarrow{k_{-1}} TocH + LOO^\bullet} \tag{4}$$

the polyunsaturated fatty acids and a chain-transfer reaction. Reaction 4 is a reversal of reaction 1. These reactions are very important in order to understand fully the antioxidant and prooxidant properties of vitamin E. However, so far the kinetics of these reactions have not been studied. Thus, we have recently determined the rate constant k_{-1} for reactions of alkyl hydroperoxides with a tocopheroxyl radical.[8] The rates k_{-1} are about 7 orders of magnitude lower than k_1 for reaction 1 of α-tocopherol with a peroxy radical.[3,9]

In the present work, we have determined the second-order rate constant k_3 for reactions of various fatty acid esters with tocopheroxy radicals. The rate k_3 has been compared with k_{-1} for reaction 4. Quantitative theoretical considerations of the rate constants for such reactions have not been studied as far as we know. In order to interpret observed features of the rate constants quantitatively, it is desirable to perform nonempirical molecular orbital calculations at a reliable level of theory. Accordingly, we have carried out ab initio calculations of models for the fatty acid esters. Calculation results are consistent with the experimental results. The effect of substituent groups at the 5- and 7-positions of tocopheroxyl radical has also been studied. It is worthwhile to know how the rates of the reactions with vitamin E radical change on going from the fatty acid esters to a biochemical system. We have thus measured the rate constant for the reaction of egg yolk lecithin with a tocopheroxyl radical. In Figure 1 we give the structures of the molecules studied in this work. A preliminary report of this work was given recently.[10]

Experimental Section

Sample Preparation. Ethyl stearate (stearic acid ethyl ester (**1**)), ethyl oleate (oleic acid ethyl ester (**2**)), ethyl linoleate (linoleic acid ethyl ester (**3**)), methyl linoleate, ethyl linolenate (linolenic acid ethyl ester (**4**)), ethyl arachidonate (arachidonic acid ethyl ester (**5**)), and *cis*-4,7,10,13,16,19-docosahexaenoic acid ethyl ester (**6**) (>99%, respectively) were obtained from the Sigma Chemical Co. and were used without further purification.

As reported previously,[8] vitamin E radicals (α-, β-, γ-, and δ-tocopheroxyl radicals) are not stable, and thus stable 5,7-diethyltocopheroxyl radical (**7**), 5,7-diisopropyltocopheroxyl radical (**8**), 7-*tert*-bu-

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[†] Ehime University.
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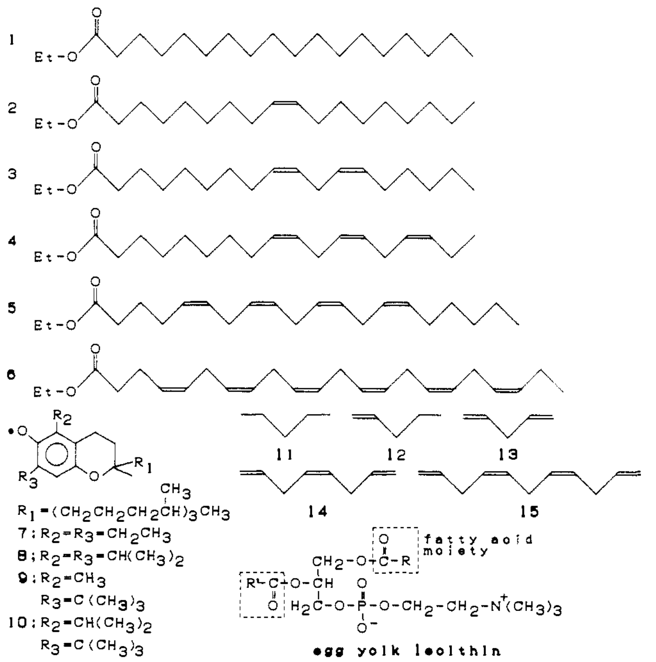

Figure 1. Structures of molecules studied in this work.

tyl-5-methyltocopheroxyl radical (**9**), and 7-*tert*-butyl-5-isopropyltocopheroxyl radical (**10**) are used for the present work. Preparation of 5,7-diethyltocopherol, 5,7-diisopropyltocopherol, and 7-*tert*-butyl-5-methyltocopherol was reported in a previous paper.[11] 7-*tert*-Butyl-5-isopropyltocopherol was synthesized by condensation of isophytol with 7-*tert*-butyl-5-isopropylhydroquinone, according to a procedure similar to that used by Nilsson et al.[12] The tocopheroxyl radicals with substituent groups at the 5- and 7-positions **7**–**10** were prepared by the PbO_2 oxidation of the corresponding tocopherol in benzene under a nitrogen atmosphere.

In order to estimate ratios of hydroperoxides in the unsaturated fatty acid esters, we measured the absorption at 234 nm due to the hydroperoxides.[13] The ratios of the hydroperoxides in the samples were estimated to be lower than 0.3%.

Egg yolk lecithin was isolated by the Bligh–Dyer method.[14] Analyses of fatty acid moieties contained in the lecithin were made by gas chromatography on the methylated derivatives of free fatty acids obtained from the hydrolysis of the lecithin. The analytical values obtained are as follows: Palmitic acid, 34.7%; palmitoleic acid, 1.6%; stearic acid, 9.8%; oleic acid, 27.5%; linoleic acid, 16.5%; arachidonic acid, 3.8%; and *cis*-4,7,10,13,16,19-docosahexaenoic acid, 6.1%. The average molecular weight of the lecithin was estimated to be 774.14. By thin-layer chromatography, the amount of hydroperoxides in the sample was found to be negligible.

Measurements of Rate Constants. The setup and the experimental procedures for the measurements of the rate constants were described in detail elsewhere.[8,10] Briefly, the kinetic data were obtained with a Jasco UVIDEC-660 spectrophotometer by mixing equal volumes of benzene solutions of **1**–**6** or egg yolk lecithin and **7**–**10** under a nitrogen atmosphere. All the measurements were performed at 25.0 ± 0.5 °C.

The pseudo-first-order rate constant for reaction 3 (k_{obsd}) was determined by following a decrease in absorbance of **7**–**10** (for example, at 417 nm in **8**[15]). The rate constant k_{obsd} is given by eq 5 where k_0 denotes

$$k_{obsd} = k_0 + k_3[LH] \quad (5)$$

the rate constant for natural decay of **7**–**10**, k_3 stands for the second-order rate constant for reactions of **1**–**6** or egg yolk lecithin (LH) with **7**–**10**, and [LH] refers to the molar concentration of LH. These rate parameters were obtained by plotting k_{obsd} against [LH].

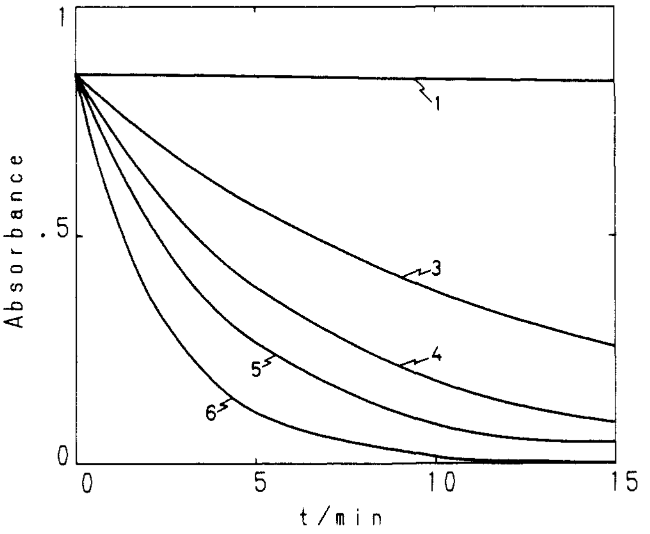

Figure 2. Decay of **8** for a reaction with **1** and **3**–**6** observed at 417 nm in benzene at 25.0 °C. $[Toc^\bullet]_{t=0}$ and $[LH]_{t=0}$ are about 0.17 and 75.0 mM, respectively.

Table I. Rate Constants for Reaction of Fatty Acid Ethyl Esters (**1**–**6**) with Tocopheroxyl Radical (**8**) in Benzene at 25 °C

	k_3 (M^{-1} s^{-1})[a]	k_{abstr}/H (M^{-1} s^{-1})
ethyl stearate (**1**)	$\ll 10^{-5}$	
ethyl oleate (**2**)	1.04×10^{-5}	2.60×10^{-6}
ethyl linoleate (**3**)	1.82×10^{-2}	9.10×10^{-3}
ethyl linolenate (**4**)	3.84×10^{-2}	9.60×10^{-3}
ethyl arachidonate (**5**)	4.83×10^{-2}	8.05×10^{-3}
cis-4,7,10,13,16,19-docosahexaenoic acid ethyl ester (**6**)	9.05×10^{-2}	9.05×10^{-3}

[a] Experimental errors <±5%.

Reaction between Fatty Acid Esters and Tocopheroxyl Radical

Experimental Results. The time dependence of the decrease in absorbance at 417 nm observed when ~0.34 mM benzene solution of **8** is mixed with 150 mM benzene solution of **1** and **3**–**6** (1:1 in volume, final concentration of fatty acid ester is 75.0 mM) is shown in Figure 2. The rate constants for reactions 3 (k_3) of the fatty acid esters with **8** are given in Table I. Since **1**, which does not contain allylic hydrogen atoms, did not react with **8**, we estimated that k_3 of **1** must be $\ll 10^{-5}$ M^{-1} s^{-1}. As shown in Table I, k_3 increases as the number of C=C double bonds in the fatty acid esters increases (**1** < **2** < **3** < **4** < **5** < **6**). Accordingly, the allylic hydrogen abstraction is considered to play a major role in the high reactivity of the unsaturated fatty acid ester in reaction 3. The allylic hydrogen is activated by the π-electron system (C=C double bond).

The k_3 value of **2** is about 3 orders of magnitude lower than that of **3**. Ethyl oleate (**2**) has four hydrogen atoms activated by a single π-electron system. On the other hand, **3** has two hydrogen atoms activated by two π-electron systems. Consequently, the two hydrogen atoms activated by two π-electron systems will contribute to the high reactivity of **3**. In fact, as listed in Table I, **3**–**6** containing hydrogen atoms activated by two π-electron systems show similar reactivity. These fatty acid esters **3**–**6** have 2, 4, 6, and 10 hydrogen atoms activated by two π-electron systems, respectively. The rate constants per an active hydrogen (k_{abstr}/H) of **3**–**6** given in Table I are similar to one another.

In conclusion, the second-order rate constant for the hydrogen abstraction of the fatty acid esters (k_3) dramatically increases as the number of π-electron systems activating the hydrogen (C=C double bonds) increases from zero to two. The rate constants per an active hydrogen k_{abstr}/H for the various fatty acid esters that contain hydrogens activated by two π-electron systems are similar to one another.

Calculation Results. In order to interpret the observed features of the rate constants, ab initio self-consistent field (SCF) calcu-

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Table II. Dissociation Energy (*D*) and Length (*r*) of C_m–H_a Bond, Overlap Population (*S*) between C_m and H_a, and Gross Orbital Population (*P*) in the 1s Orbital of H_a for Optimized Geometries of **11–15**

	D(au)^a	r (Å)	S	P
pentane (**11**)	0.180	1.088	0.383	0.952
1-pentene (**12**)	0.166	1.089	0.382	0.940
1,4-pentadiene (**13**)	0.149	1.091	0.378	0.930
1,*cis*-4,7-octatriene (**14**)^b	0.147	1.092	0.378	0.932
1,*cis*-4,*cis*-7,10-undecatetraene (**15**)^b	0.145	1.092	0.377	0.933

^{a} The restricted Hartree–Fock (RHF) and the unrestricted Hartree–Fock (UHF) schemes were adopted for closed-shell molecules and radicals, respectively. *D* was calculated as the change in total molecular energy in the C–H dissociation of the optimized closed-shell molecule into a hydrogen atom and the nonoptimized radical. Accordingly, *D* thus obtained may be larger than the experimental value. ^{b} In **14** and **15**, there are two and three kinds of unequivalent C_m–H_a bonds at the 3- and 6-positions and at the 3-, 6-, and 9-positions, respectively. In **14** and **15**, these C_m–H_a bonds are close in *D*, *r*, *S*, and *P* to one another.

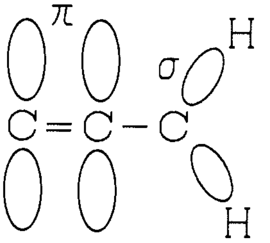

Figure 3. Schematic sketch of σ-orbital lying along C_m–H_a bond and π-orbital projecting perpendicular to the C=C bond.

lations of models for the fatty acid esters have been carried out with the GAUSSIAN82 program.[16] The basis set used in the present calculations is STO-3G. Full geometry optimization was performed by the energy gradient method. Pentane (**11**), 1-pentene (**12**), 1,4-pentadiene (**13**), 1,*cis*-4,7-octatriene (**14**), and 1,*cis*-4,*cis*-7,10-undecatetraene (**15**) can be regarded as the models for **1–5**, respectively. The properties concerning the C–H bond that dissociates (C_m–H_a bond) in the optimized geometries of **11–15** are summarized in Table II.

The C_m–H_a dissociation energy (*D*) decreases and the C_m–H_a bond length (*r*) increases in **11–13** as the number of C=C double bonds increases, and those are nearly constant in **13–15**. From these calculation results, the rate constant of the H_a abstraction is expected to be as follows: **11** < **12** < **13** ~ **14** ~ **15** (that is, **1** < **2** < **3** ~ **4** ~ **5**). These calculation results are consistent with the experimental results of k_{abstr}/H.

The observed features of the rate constant of the H_a abstraction can be explained in terms of the pseudo-π-conjugation between C=C double bond and the C_m–H_a bond. As shown in Figure 3, the σ-orbital lying along the C_m–H_a bond has the component parallel to the π-orbital projecting perpendicular to the C=C bond in **2–6**. Accordingly, it is considered that the σ-orbital is conjugated with the π-orbital in **2–6** and that the σ-electrons are drawn to the π-orbital. Since the C_m–H_a bonds in **2** and **3** are conjugated with one and two C=C double bonds, respectively, the σ electrons in **3** are drawn to a larger extent than that in **2**. As a result, the electron density around the C_m–H_a bond, that is, the overlap population between C_m and H_a (*S*) and the gross orbital population in the 1s orbital of H_a (*P*), is expected to be as follows: **1** > **2** > **3** ~ **4** ~ **5** ~ **6**. In fact, the calculated results of *S* and *P* decrease in **11–13** as the number of C=C double bonds increases and are nearly constant in **13–15** (Table II). It is thus considered that the strength of C_m–H_a bond is as follows: **1** > **2** > **3** ~ **4** ~ **5** ~ **6**. This explanation is consistent with the experimental results. Therefore, the pseudo-π-conjugation between the C_m–H_a and C=C bonds indeed play an important role in C_m–H_a bonding.

Table III. Rate Constants for Reaction of Methyl Linoleate with Tocopheroxyl Radicals (**7–10**) in Benzene at 25 °C

	k_3 (M^{-1} s^{-1})^a
5,7-diethyltocopheroxyl radical (**7**)	4.97×10^{-2}
5,7-diisopropyltocopheroxyl radical (**8**)	1.86×10^{-2}
7-*tert*-butyl-5-methyltocopheroxyl radical (**9**)	1.61×10^{-2}
7-*tert*-butyl-5-isopropyltocopheroxyl radical (**10**)	1.10×10^{-3}

^{a} Experimental errors <±5%.

Table IV. Rate Constants for Reaction of Egg Yolk Lecithin with Tocopheroxyl Radical (**8**) in Benzene at 25 °C

[Lec] (M)	k_{obsd} (s^{-1})^a	k_{expd} (s^{-1})
9.68×10^{-3}	8.09×10^{-5}	2.01×10^{-4}
1.94×10^{-2}	1.50×10^{-4}	4.01×10^{-4}
2.90×10^{-2}	2.19×10^{-4}	6.00×10^{-4}
3.87×10^{-2}	2.84×10^{-4}	8.02×10^{-4}

^{a} Experimental errors <±5%.

Effect of Substituent in Tocopheroxyl Radical

The second-order rate constants for the hydrogen abstraction (k_3) from methyl linoleate by **7–10** in benzene are given in Table III. The k_3 value for the reaction of methyl linoleate with **8** is much the same as that of ethyl linoleate (**3**) with **8**. The bulkier the substituent groups at the 5- and 7-positions of tocopheroxyl radical, the smaller the k_3 value. This substitution effect is likely due to the steric hindrance by the substituent groups. The bulky substituent groups at the 5- and 7-positions of the tocopheroxyl radicals may inhibit the hydrogen abstraction by interfering with access of methyl linoleate to the active site at the 6-position. The steric hindrance plays an important role in the reactions.

Reaction between Egg Yolk Lecithin and Tocopheroxyl Radical

Reaction between a Mixture of Fatty Acid Esters and Tocopheroxyl Radical. Egg yolk lecithin contains two fatty acid moieties. It is interesting to examine whether or not the rate constant of the hydrogen abstraction of egg yolk lecithin is the same as that expected from those of the fatty acid moieties contained in the lecithin. At first, we studied the reaction of mixtures of fatty acid esters in order to ensure that the reaction rate constant of the mixture could be estimated from those of the fatty acid esters contained in the mixture.

The pseudo-first-order rate constant expected for the mixture (k_{expd}) can be estimated in the following ways

$$k_{expd} = \sum k_{LH}[LH] \qquad (6)$$

where k_{LH} refers to the second-order rate constant of a fatty acid ester LH. For example, for the mixture of 6.68×10^{-2} M **1**, 4.37×10^{-2} M **2**, 2.38×10^{-2} M **3**, 5.73×10^{-3} M **5**, and 8.86×10^{-3} M **6**, k_{expd} and k_{obsd} were estimated to be 1.51×10^{-3} and 1.53×10^{-3} s^{-1}, respectively. From such results, it was shown that k_{obsd} is indeed in accord with k_{expd} on the basis of eq 6.

Reaction between Egg Yolk Lecithin and Tocopheroxyl Radical. The rate constants of the hydrogen abstraction from egg yolk lecithin by **8** (k_{obsd}) are given in Table IV. The second-order rate constant (k_3) was found to be 7.02×10^{-3} M^{-1} s^{-1}. The expected value of the pseudo-first-order rate constant of lecithin (k_{expd}) is given by

$$k_{expd} = 2[\mathrm{Lec}]\sum k_{LH}x_{LH} \qquad (7)$$

where [Lec] and x_{LH} stand for the molar concentration of the lecithin and the mole fraction of a fatty acid contained in the lecithin, respectively. Since egg yolk lecithin contains two fatty acid moieties, 2[Lec] is equal to the sum of the molar concentrations of the fatty acids contained in the lecithin. We assumed that the second-order rate constant of a fatty acid moiety (k_{LH}) is the same as that of the corresponding ethyl ester given in Table I. The expected values (k_{expd}) thus obtained are listed in Table IV. The observed values (k_{obsd}) are 35–40% of the corresponding

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k_{expd}. There is, as yet, no unambiguous explanation for this contradiction, but possible ones are suggested in the following. In the first place, the formation of reverse micelles in the benzene solution should be noted. Lecithins are prone to aggregate into reverse micelles in nonprotic solvents.[17,18] The formation of the reverse micelles might prevent **8** from reacting with the fatty acid moiety. It will be necessary to make some measurements in an inert polar solvent (e.g., *tert*-butyl alcohol) where reverse micelles do not form from lecithins. Another possibility of resolving the above contradiction is that the steric hindrance between the two fatty acid moieties contained in the lecithin may affect the kinetics. Since the two moieties are quite close to each other in lecithin,[19] **8** may not easily access the active site of these moieties.

Discussion

As described in a previous section, the second-order rate constant for the hydrogen abstraction of the fatty acid esters (k_3) dramatically increases as the number of π-electron systems activating the hydrogen (C=C double bonds) increases from zero to two. This result is in agreement with that obtained for reactions between hydrocarbons and peroxy radicals by Howard and Ingold.[20] Tocopheroxyl radicals produced in cellular membranes and edible oils are likely to react with polyunsaturated lipids or fatty acids by abstracting hydrogen atoms activated mainly by two π-electron systems.

As mentioned above, the observed features of the rate constant can be explained in terms of the pseudo-π-conjugation between the C=C double bond and the active hydrogen–carbon bond. The presence of a long or efficient π-conjugated system near the active hydrogen atom in fatty acid esters may lead to an increase in reactivity. On the contrary, if the two C=C double bonds (π-electron systems) are nearly perpendicular to each other, the π-conjugation near the active site is not efficient and the reactivity may decrease.

We have recently succeeded in measuring k_{-1} for reactions of alkyl hydroperoxides with **8**,[8] i.e., the reversal of reaction 1. In benzene solution at 25 °C, k_1 $(1.34\text{–}3.65) \times 10^{-1}$ M^{-1} s^{-1}. In the present work, we have measured k_3 for the reactions of **1**–**6** with **8** and of the methyl linoleate with **7**–**10**. The values of k_{-1} are only about 1 order of magnitude larger than those of k_3. These results suggest that reactions 3 and 4 may relate to the prooxidant effect of α-tocopherol in high concentration. Therefore, if polyunsaturated lipids coexist with hydroperoxides in membranes or edible oils, the rate of disappearance of tocopheroxyl radical will be represented by the equation

$$-d[\mathrm{Toc}^\bullet]/dt = k_3[\mathrm{LH}][\mathrm{Toc}^\bullet] + k_{-1}[\mathrm{LOOH}][\mathrm{Toc}^\bullet] \quad (8)$$

where [Toc•] and [LOOH] denote the molar concentrations of the tocopheroxyl radicals and the hydroperoxides, respectively.

The above-mentioned radical-decay reactions (eqs 3 and 4) may occur competitively with reaction 2 or with radical dimer formation (reaction 9)[21] Neither reaction 2 nor reaction 9 participates in

$$\mathrm{Toc}^\bullet + \mathrm{Toc}^\bullet \xrightarrow{k_7} \text{nonradical products} \quad (9)$$

the prooxidant effect of α-tocopherol. On the contrary, reaction 2 contributes to the antioxidant effect of α-tocopherol.

In the initial stage of lipid degradation, the concentration of hydroperoxides will be much lower than that of polyunsaturated fatty acids, and thus the second term in eq 8 is negligible. Consequently, the prooxidant effect of α-tocopherol will be induced by the hydrogen abstraction (reaction 3) between tocopheroxyl radical and polyunsaturated fatty acids. On the other hand, if the autoxidation proceeds, lipid hydroperoxides increase and reaction 4 will play an important role in the prooxidant effect of α-tocopherol. These facts suggest that not only reaction 3 but also reaction 4 participates in the prooxidant effect of α-tocopherol.

Conclusion

A kinetic and ab initio study of the prooxidant effect of vitamin E derivatives has been carried out. The rates of the H_a abstraction from **1**–**6** and egg yolk lecithin by **7**–**10** have been determined spectrophotometrically. The second-order rate constant k_3 dramatically increases as the number of π-electron systems activating the hydrogen (C=C double bonds) increases from zero to two. The rates k_{abstr}/H for the various fatty acid esters that contain hydrogens activated by two π-electron systems are similar to one another. In order to interpret the observed features of k_3 and k_{abstr}/H, ab initio calculations of models for **1**–**5** have been carried out. From the calculation results, it is shown that the observed features of k_3 and k_{abstr}/H can be explained in terms of the pseudo-π-conjugation between the C=C double bond and the C_m–H_a bond. The bulkier the substituent groups at the 5- and 7-positions of tocopheroxyl radical, the smaller k_3. This substitution effect is likely due to the steric hindrance by the substituent groups at the 5- and 7-positions. The pseudo-first-order rate constant k_{obsd} of egg yolk lecithin is much smaller than the corresponding k_{expd}.

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Supplementary Material Available: Optimized geometries of **11**–**15** (Figure 4) (2 pages). Ordering information is given on any current masthead page.

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