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Journal of Molecular Structure (Theochem) 620 (2003) 93–106

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Viewpoint

Vitamin E models. Can the anti-oxidant and pro-oxidant dichotomy of α-tocopherol be related to ionic ring closing and radical ring opening redox reactions?

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Received 30 May 2002; accepted 14 August 2002

Abstract

The free radical scavenging mechanism, leading to a quinodal structure via an oxidative ring opening is exothermic. However, the ionic oxidative ring opening is endothermic. Consequently, the ionic reductive ring closing must be exothermic. This leads to the suggestion that Vitamin E may be recovered, unchanged, thus effectively acts as a catalyst for the following reaction

$$2HOO^{\cdot} + H_3O^{(+)} + NADH \rightarrow 2HOOH + H_2O + NAD^{(+)}, \qquad \Delta E \approx -120 \text{ kcal mol}^{-1}.$$

As Vitamin E is biologically recycled, a single α-tocopherol molecule may convert numerous $HOO^{\cdot}$ radical to H_2O_2 which is accumulated if not removed at the same rate, enzymatically, with the participation of catalase (Fe) or glutathione peroxidase, GP_x(Se). This accumulation of peroxide, which may be referred to as a 'peroxide traffic jam', may well be the reason of the pro-oxidant effect of Vitamin E.

Keywords: Vitamin E; Pro-oxidant; Anti-oxidant; Free radical oxidative ring opening; Ionic reductive ring closing; Biological recycling of Vitamin E; Vitamin E as a catalyst

1. Preamble

1.1. The nature of oxidative stress

Since chemical reactions are usually not quantitative, up to 5% of the oxygen we inhale may be converted to 'reactive oxygen species' (ROS) [1]. During normal metabolism, as food is oxidized in

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0166-1280/03/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S0166-1280(02)00604-8

the living cells, oxygen is being reduced to water. The reduction (1) is a multi-step process; the intermediate stages correspond to the ROS

$$O_2 \rightarrow O_2^{\cdot(-)} \rightarrow HO{-}O^{\cdot} \rightarrow HO{-}O:^{(-)} \rightarrow H_2O_2 \rightarrow \cdots \rightarrow HO^{\cdot} \rightarrow H_2O. \quad (1)$$

When any of these ROS escape from this sequence of reductive reactions, they may damage internal structures of the cell including DNA, RNA and various proteins, in addition to the cell membrane. Such damage also leads to degenerative diseases, as well as a weakened immune system [2].

As an educated guess, we might say that in every human being, ROS may strike and damage each single DNA molecule, perhaps as many as 10,000 times a day. To prevent the propagation of mutations, approximately 99% of the damaged DNA strands may be restored by DNA repair enzymes. The remaining 1% escapes the repair action of the enzymes, leaving approximately 100 damaged strands of DNA in the system. Lipid peroxidation may also cause great damage [3–5]. All of these damages can accumulate over time, eventually causing atherosclerosis, cancer and other degenerative diseases such as Parkinson's and Alzheimer's diseases.

The body has two types of mechanisms to eliminate ROS before they assert any damage. These include

(i) Enzymatic reductions of ROS beyond the regular process,
(ii) Scavenging of ROS by anti-oxidant compounds.

With advanced age, both of these mechanisms fight a losing battle against ROS. However, even at a younger age, the ammunition for these anti-oxidant mechanisms must come from a healthy diet, which is not always practiced or available. In such cases, the 'healthy diet' does include dietary supplement. Needless to say, it is important that young people acquire a vigilant attitude concerning their diets in order to reap the long-term benefits.

1.2. Essential nutrient components

Both of the above two mechanisms to fight ROS require special nutrients.

For mechanism (i), it may be some trace element such as magnesium, vanadium, chromium, manganese, iron, copper, zinc or selenium (Mg, V, Cr, Mn, Fe, Cu, Zn, or Se) that may be needed at the active site of some enzyme. If these trace elements are not available, mechanism (i) would not be operative. For example, the natural selenium (Se) level in the soil is highly variable. It is common knowledge that in the USA, the Eastern Coastal Plain and the Pacific Northwest have the lowest levels of Se. In these areas, the daily Se intake of the population is in the range of 60–90 μg. In contrast, in areas rich with Se, the range of daily Se intake is 60–200 μg. The average daily US intake is approximately 125 μg. Those living where the highest levels of Se exist also have the lowest levels of lung, colon, bladder, pancreas, breast and ovarian cancers. Thus, if the soil is depleted of Se, then the vegetation will not have an adequate amount of Se, and the local diet would reflect the low Se content. The recommended daily intake should be in the vicinity of 300 μg. It may well be that the diet of the whole North American continent is too low in Se. This may be responsible for North Americans having some of the highest worldwide levels of degenerative ailments such as cancer and cardiovascular diseases as well as Alzheimer's and Parkinson's diseases. Of course, an overdose of Se is dangerous, but is not expected to happen unless the daily intake reaches 1000 μg.

Selenium is at the active site of glutathione peroxidase, incorporated in the form of selenocysteine [6]. Mechanistically, selenium acts as a temporary oxygen carrier [7], consequently, by any definition, it is a catalyst as shown in Fig. 1.

Thus, while selenium is used at the active site of glutathione peroxidase (GP_x), other trace metals are also important. For example, Cu and Zn are cofactors of most superoxide dismutase (SOD). However, some SOD molecules contain manganese (Mn), iron (Fe) or even nickel (Ni). Also, while most catalase enzymes usually contain Fe in a heme, on occasion some catalase molecules will operate with the help of Mn.

For mechanism (ii), certain vitamins (like C and E) act as anti-oxidants in the battle against ROS. Vitamin C is water soluble and therefore functions in the aqueous phase, while vitamin E is fat soluble,

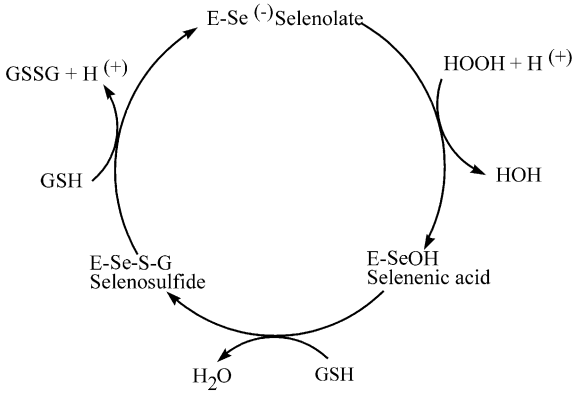


Fig. 1. A schematic mechanism of action for glutathione peroxidase (GP_x). The Se-deprotonated GP_x is denoted at the top on $E-Se^{(-)}$ selenolate. Reduced and oxidized glutathione are denoted as GSH and GSSG, respectively.

functioning in lipid bilayers and in lipoprotein micelles.

Numerous other anti-oxidants (such as lycopene, β-carotene, flavones, farnesol, allyl-methyl-disulfide, lipoic acid, coenzyme Q_{10} or ubiquinone, etc.) are also needed [8,9]. Plants produce these anti-oxidants and fruits and vegetables are expected to supply them. However, the level of these anti-oxidants in fruits and vegetables may vary not only according to the geographical location where they were produced as well as the method of production, but also vary from season to season, or with distance of transportation. Consequently, anti-oxidants may now have to be added to the food items or must be provided as a supplement in order to produce a healthy diet. If regular foodstuff was sufficiently nutritious, or if dietary supplements were included in meals, the incidence of degenerative diseases may be reduced substantially, which in turn could considerably lessen health care costs.

2. Introduction

It is generally accepted that reduction of morbidity and mortality from cardiovascular disease is associated with an increase intake of anti-oxidant vitamin E and vitamin C. This apparent cause–causality relationship has been explained on the basis of oxidative modification of low density lipoprotein (LDL). The corollary of this assumption is that the inhibition of lipid peroxidation in LDL, by vitamin E, leads to the reduction of myocardial infarction and stroke. Numerous papers testify along this line [10–12].

In the mean time, not only does vitamin E behave as a non-anti-oxidant [13] but pro-oxidant [14] effects of vitamin E have also been demonstrated. The fact that vitamin E can act as both anti-oxidant and pro-oxidant has led to the point that vitamin E has come to know as a ‘Janus molecule’ [15].

The free radical oxidation products of α-tocopherol have been analyzed by Liebler et al. [16] in 1996 showing more other extensively oxidized products than the quinoidal structure. The ionic mechanism was suggested by Roseman et al. [17] in 1999 which has led to the quinoidal structure. These mechanisms were also reviewed recently by Brigelius-Floke and Traber [18].

Under strong oxidative conditions vitamin E may undergo progressively more extensive oxidation that could lead to irreversible metabolization of the tocopherol molecule. Such a destructive oxidation [16], leading to a variety of epoxide, which may metabolize even further is shown in Fig. 2. Note that the steps at the left hand column in Fig. 2 are non-destructive as it corresponds to the formation of the quinone–hydroquinone analogue of vitamin E. Nevertheless, there exists an ionic oxidative mechanism of α-tocopherol leading to quinoidal or even to hydroquinone structure. Such a mechanism [17] is shown in Fig. 3. However, even here, some side reactions may occur. The left hand column of Fig. 3 shows the non-destructive process.

3. Scope

The present paper raises more questions than can be answered at this time, related to the dichotomy of the anti-oxidant as well as pro-oxidant nature of vitamin E.

Of course one may argue that the anti-oxidant and pro-oxidant natures of vitamin E depends on the redox

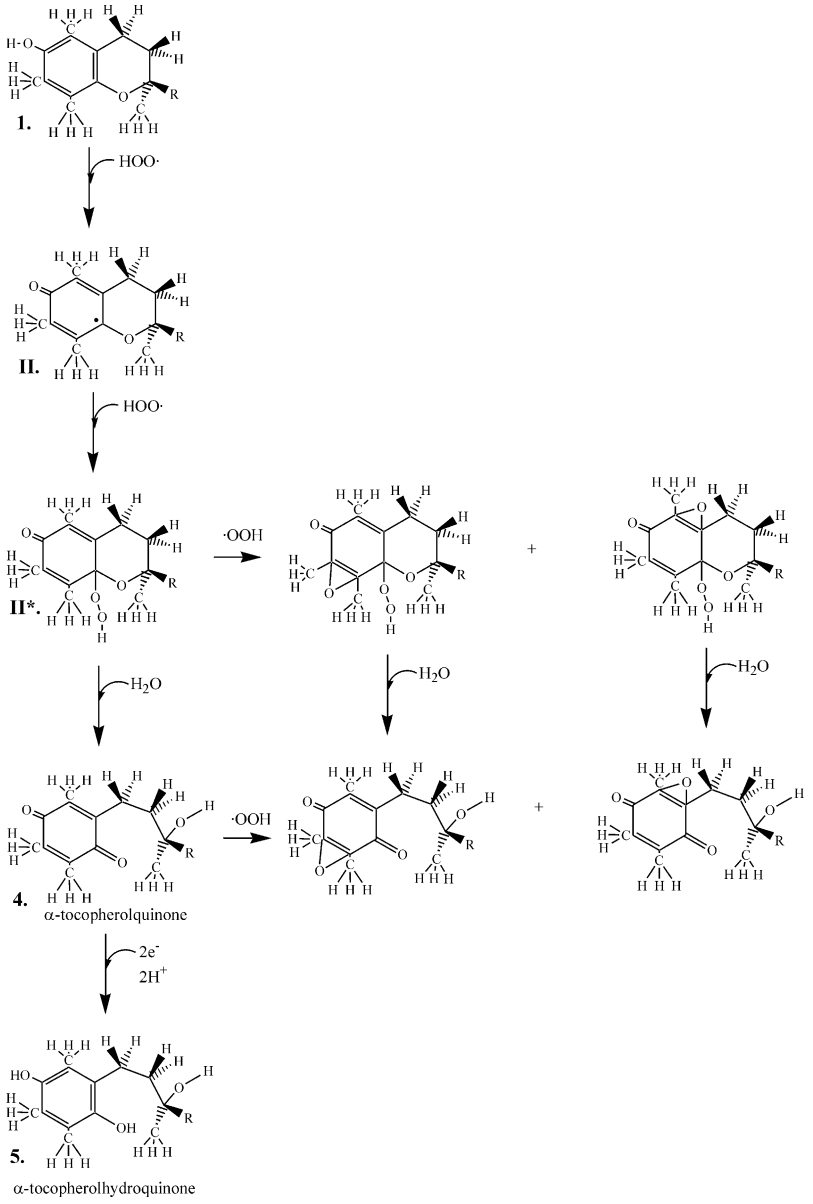


Fig. 2. A schematic mechanistic representation of non-destructive and destructive free radical oxidation of α-tocopherol by HOO·.

potential. In turn, the redox potential varies according to the Nernst equation (2)

$$E = E^0 - RT/\nu \ln\{[\text{Red}]/[\text{Ox}]\} \quad (2)$$

where ν is the number of electrons transferred and the expression [Red]/[Ox] measures the ratio of reduced and oxidized forms.

Nevertheless, it seems plausible to seek explanation at the molecular level concerning the 'traffic' which is passing through the overall reduction presented in Eq. (1). Sufficient computed results are presented to provide theoretical backing to the merit of the questions to be asked and some putative mechanistic answers suggested.

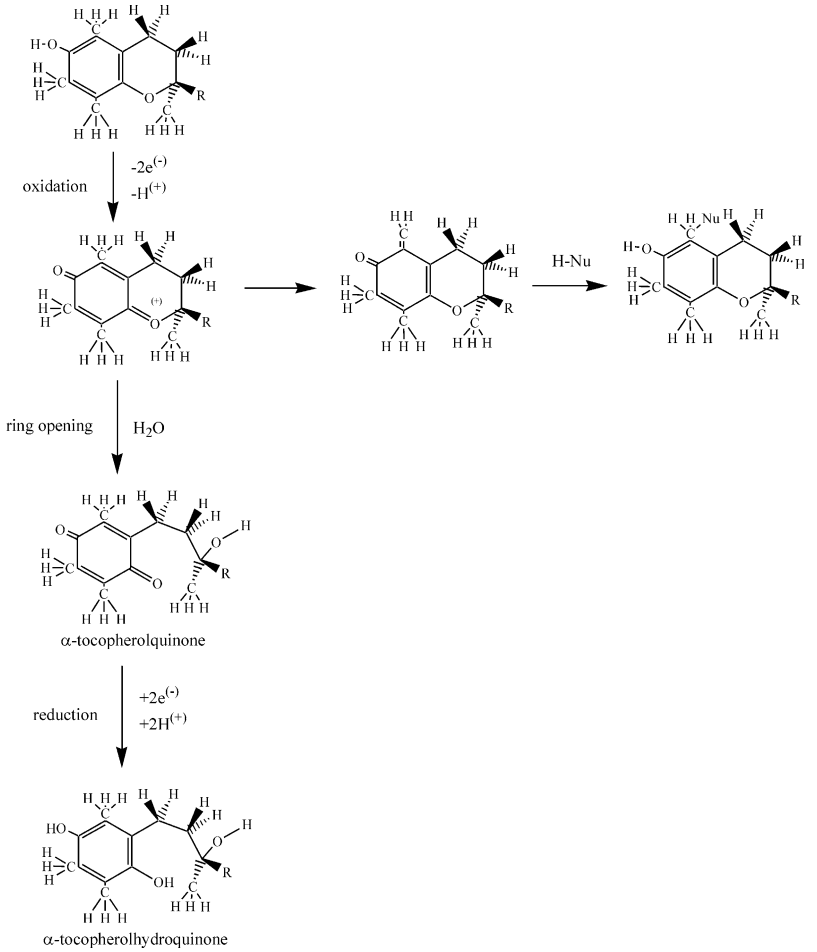


Fig. 3. A schematic mechanistic representation of non-destructive and destructive ionic oxidation of α-tocopherol.

4. Method

The definition of the relative spatial orientation as well as the numbering of the constituent atomic nuclei are shown in Fig. 3. The input files were numerically generated. No visualization tool was used for this purpose. GAUSSIAN 98 [19] calculations were carried out at the B3LYP/6-31G(d) levels of theory (Fig. 4).

For the hydride abstraction three different cations were investigated according to mild, medium and strong hydride affinity. The computed energies necessary for balanced reactions are summarized in Table 1. On the basis of the computed hydride affinities (Table 1) it seems that the $H^{(-)}$ affinity of pyridium ion is numerically close to that of $Li^{(+)}$. For this reason instead of NADH, at least on energetic grounds, Li–H may be used as a hydride donor. The computed total energies for both radical and ionic reactions are listed in Table 2.

5. Results and discussion

5.1. Molecular geometries

In the ionic mechanism, only compounds labeled **1** and **5**, have unsaturated benzenoid rings.

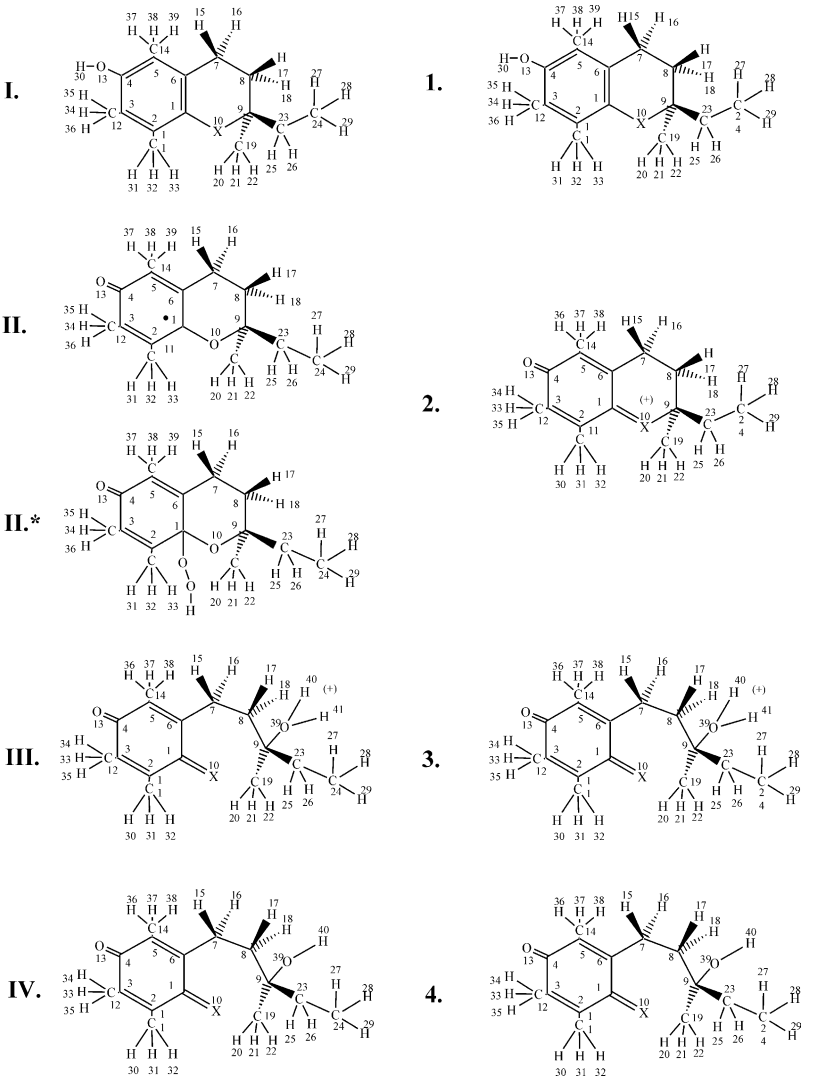


Fig. 4. Atomic numbering system of reactant, reaction intermediates and product of free radical and ionic oxidation of α-tocopherol.

Table 1
Energy components and hydride affinities for hydride abstraction as computed at the B3LYP/6-31G(d) level of theory

Cation	*E* (Hartree)	Neutral	*E* (Hartree)	Hydride affinity (kcal mol^{-1})
$Li^{(+)}$	−7.284544	LiH	−8.081922	210.570
$C_5H_6N^{(+)}$	−248.6569798	C_5H_7N	−249.455315	211.17
$CH_3^{(+)}$	−39.480388	CH_4	−40.518383	361.56

The intermediates labeled as **2** and **3** and the product molecule labeled as **4**, have quionoidal bonding. However, the quinoidal structure for **4** can clearly be seen in Fig. 5 and compared to the original vitamin E model **1**. In the free radical mechanisms reactant is labeled as I, intermediates as II and II*, while the products are specified as **III** and **IV**. Clearly **1** = **I**, **3** = **III** and **4** = **IV**.

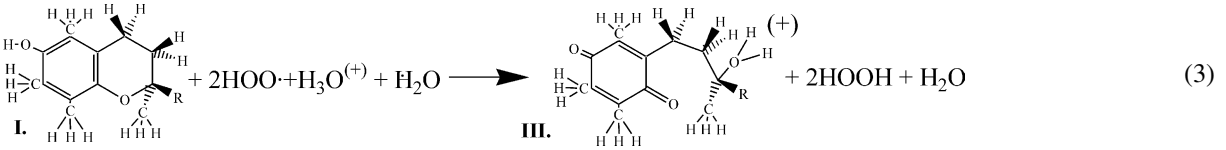
5.2. Mechanism and molecular energetics

The free radical and ionic as well as an ionic mechanism studied in the present paper are is shown in Scheme 1.

5.2.1. Radical mechanism

Fig. 6 shows the energy profile for the free radical mechanism on the basis of the data presented in Table 3. The energies of water and oxonium ions necessary for the mechanism are shown in Table 2. The thermodynamic reaction profile showing only energy minima, allows a down-hill process, in the thermodynamic sense. Consequently, the radical scavenging ability of α-tocopherol is well established on energetic grounds.

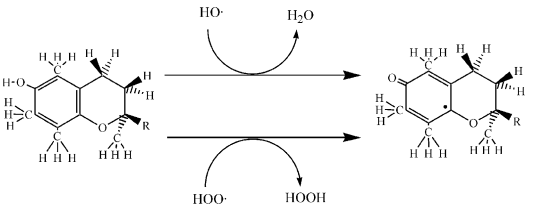
The reaction is balanced from reactant (**I**) to the first ionic product (**III**), as shown in Eq. (3)



(3)

The overall amount of energy released is − 32.49 kcal·K

While the first step, the hydrogen abstraction, may occur by either HO˙or HOO˙ attack, the energetics is expected to be considerably more exothermic, by about − 32.4 kcal·K with the HO˙ radical than with the HOO˙radical



(4)

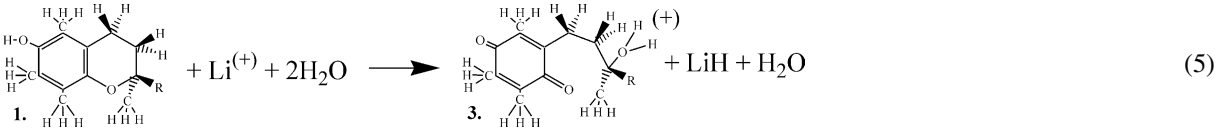
However this would only underline the validity of the conclusion reached with the use of the HOO˙ radical.

5.2.2. Ionic mechanism

The relative energies necessary to construct a thermodynamic reaction profile for the ionic reactions are summarized in Table 4. The thermodynamic reaction profile (only energy minima, without the appropriate transition states) are shown in Fig. 6 for α-tocopherol. The energies of water and oxonium ions necessary for the mechanism are shown in Table 2.

It should be emphasized that the first step involves a hydride acceptor. In biological systems it is $NAD^{(+)}$. However no full computations have been accomplished at the DFT level for the $NAD^{(+)}$/-NADH system. Protonated pyridine gives hydride affinity close to that of $Li^{(+)}$ therefore this model appears to be fairly realistic for $NAD^{(+)}$, at least on energetic grounds.

The reaction was balanced from the reactant (**1**) to the first ionic product (**3**) as shown in Eq. (5), using $Li^{(+)}$ instead of $NAD^{(+)}$



(5)

Table 2
Energy components, necessary to balance the redox reactions, computed at the B3LYP/6-31G(d) level of theory

Species	*E* (Hartree)	Species	*E* (Hartree)
$E(H^-)$	−0.461817	$E(HOO^{\cdot})$	−150.899156
$E(HO^{\cdot})$	−75.723455	$E(HOO^-)$	−151.462597
$E(H_2O)$	−76.408953	E(HOOH)	−151.532085
$E(H_3O^+)$	−76.685908	E(HOOLi)	−158.503570

The overall amount of energy released is +85.35 kcal·k.

It is clear from Fig. 7 that the steps are all endothermic. This indicated that the ionic mechanism is unlikely to occur. However, the reverse, namely the reduction back from the oxidized α-tocopherol (i.e. α-tocopherolquinone) to the original α-tocopherol would be expected to be an exothermic process (Table 5). Thus, it seems that the oxidation proceeds by the free radical mechanism while the reductive conversion, back to α-tocopherol would be expected to proceed by the ionic mechanism. This combined mechanism is shown in Fig. 8 (Table 6).

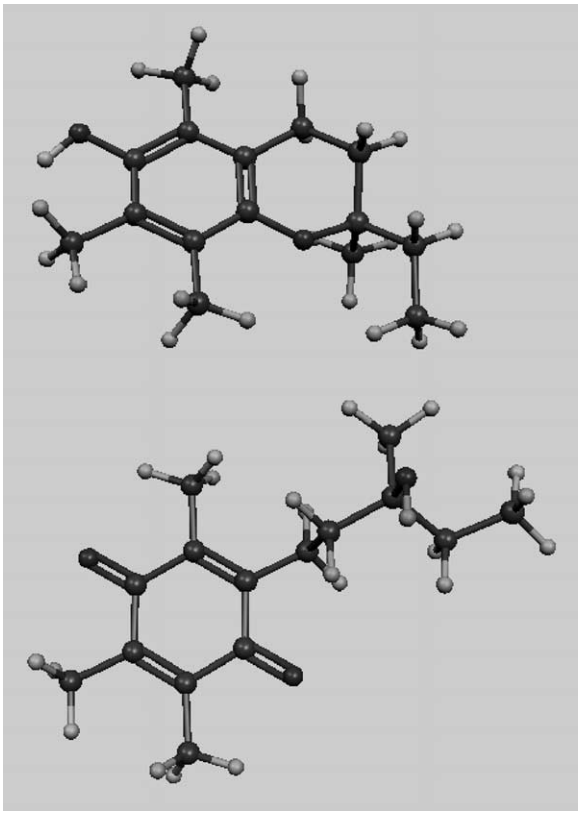


Fig. 5. Structures of α-tocopherol (top) and α-tocopherolquinone corresponding to reduced [Red] and oxidized [Ox] forms, respectively, in Eq. (2). All aromatic CC bond lengths in the top structure are in the vicinity of 1.40 Å. The single and double bond lengths in the ring of the bottom structures are in the vicinity of 1.49 and 1.35 Å, respectively.

It is believed that the coupled nature of the radical and ionic oxidation is shown, for the first time, here in Fig. 8. The energy profile for the combined mechanism is shown in Fig. 9.

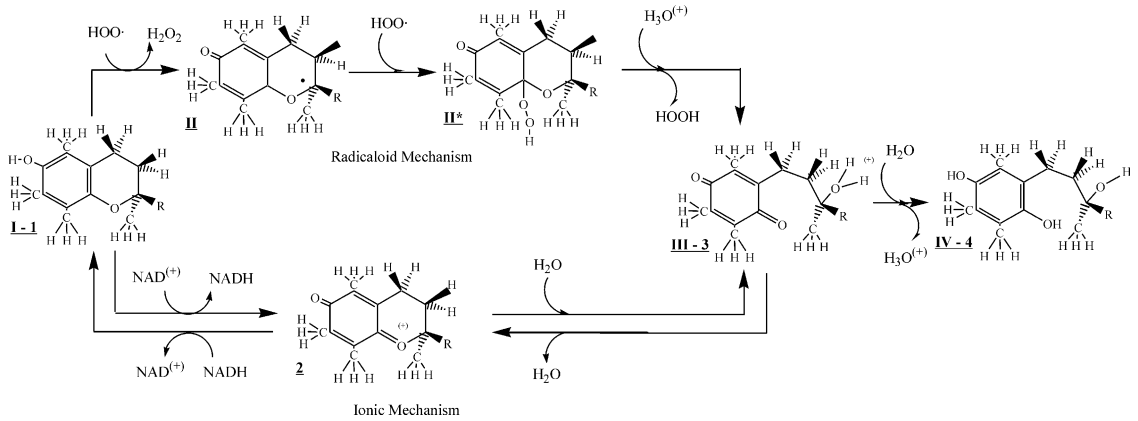
Since α-tocopherol has been used but not consumed in the coupled reaction, α-tocopherol may be regarded as a catalyst for the following overall processes

$$2HOO^{\cdot} + H_3O^{(+)} + NADH \rightarrow 2HOOH + H_2O + NAD^{(+)}, \qquad \Delta E = -120.18 \text{ kcal·k} \tag{6}$$

The essential point is, however, that α-tocopherol can only convert the peroxyradical only to hydrogen peroxide [H_2O_2] but not further. From that point onward, it is the job of the enzyme glutathione peroxidase GP_x(Se) or Catalase(Fe) to carry the process further through the full reduction to H_2O.

A schematic illustration of the overall process involving the various enzymes and non-enzymatic anti-oxidants is shown in Scheme (2).

The catalytic nature of vitamin E is shown in Fig. 10. Clearly, if vitamin E was destroyed at the end of the first step it could not produce more peroxide. Thus, under such condition its pro-oxidant nature perhaps would not ever have been ever observed. However, vitamin E is recycled, biologically, as Fig. 10 indicates and a single α-tocopherol molecule may convert numerous $HOO^{\cdot}$ radicals to H_2O_2 which is accumulated if not removed at the same rate enzymatically with the participation of Catalase(Fe) or glutathione peroxidase, GP_x(Se). This accumulation of peroxide, which may be referred to as a peroxide traffic jam, may well be the reason of the pro-oxidant effect of vitamin E.



Scheme 1.

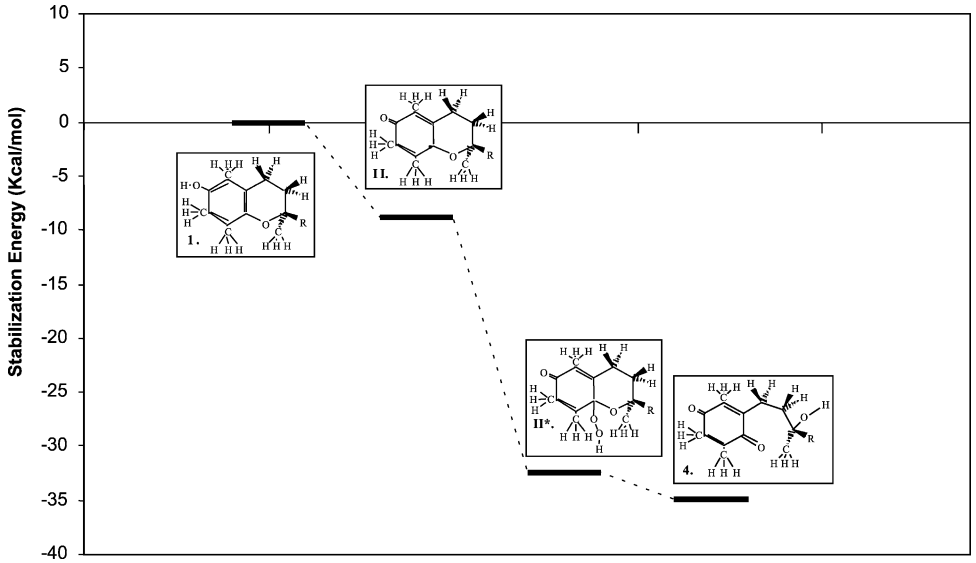


Fig. 6. Reaction profile of non-destructive free radical oxidation of α-tocopherol model by HOO˙.

Table 3
Total energy values of α-tocopherol model and its oxidized forms computed at the B3YP/6-31G(d) level of theory

Reactant, intermediates, product	*E* (Hartree)			
	Free radical route		Ionic route	
Reactant	I	−735.31212	1	−735.31212
Closed ring intermediate	II	−734.69317	2	−734.45881
Closed ring intermediate	II*	−885.63012		–
Open ring intermediate	III	−810.84221	3	−810.84221
Product	IV	−810.51082	4	−810.51082

Table 4
Total and relative energies for the free radical mechanism

Route	State	E (Hartree)	ΔE (kcal ·K)	$\Delta\Delta E$ (kcal ·K)
Neutral	$\underline{\mathbf{I}} + 2HOO^{\cdot} + H_3O^+ + H_2O$	−1190.205294	0.000	0.000
	$\underline{\mathbf{II}} + HOO^{\cdot} + HOOH + H_3O^+ + H_2O$	−1190.219272	−8.771	−8.771
	$\underline{\mathbf{II}}^* + HOOH + H_3O^+ + H_2O$	−1190.257066	−32.487	−23.716
	$\underline{\mathbf{III}} + 2HOOH + H_2O$	−1190.315332	−69.050	−36.563
	$\underline{\mathbf{IV}} + 2HOOH + H_3O^+$	−1190.260897	−34.892	34.159

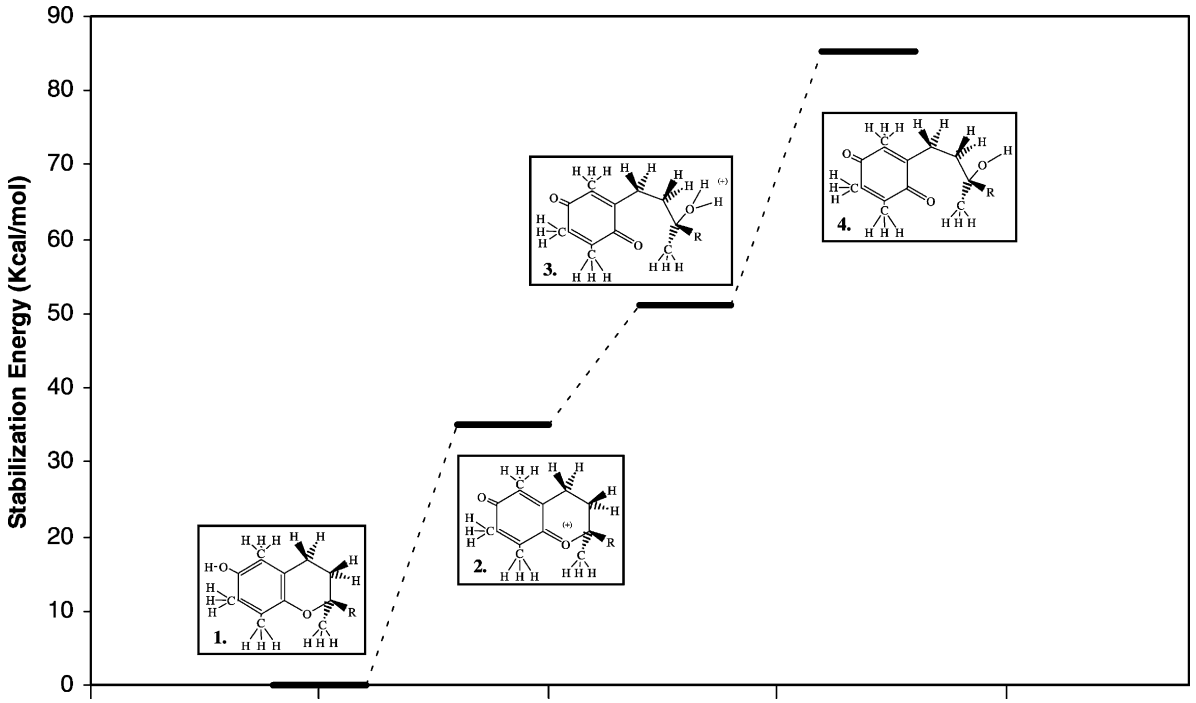


Fig. 7. Reaction profile for ionic oxidation mechanism using $Li^{(+)}$, a hydride abstractor modeling $NAD^{(+)}$.

Table 5
Total and relative energies for the ionic mechanism

Hydride abstraction initiator	State	E (Hartree)	ΔE (kcal ·K)	$\Delta\Delta E$ (kcal ·K)
Li^+	$\underline{\mathbf{1}} + Li^+ + 2H_2O$	−895.414570	0.000	0.000
	$\underline{\mathbf{2}} + LiH + 2H_2O$	−895.358638	35.098	35.098
	$\underline{\mathbf{3}} + LiH + H_2O$	−895.333085	51.133	16.035
	$\underline{\mathbf{4}} + LiH + H_3O^+$	−895.278650	85.291	34.159

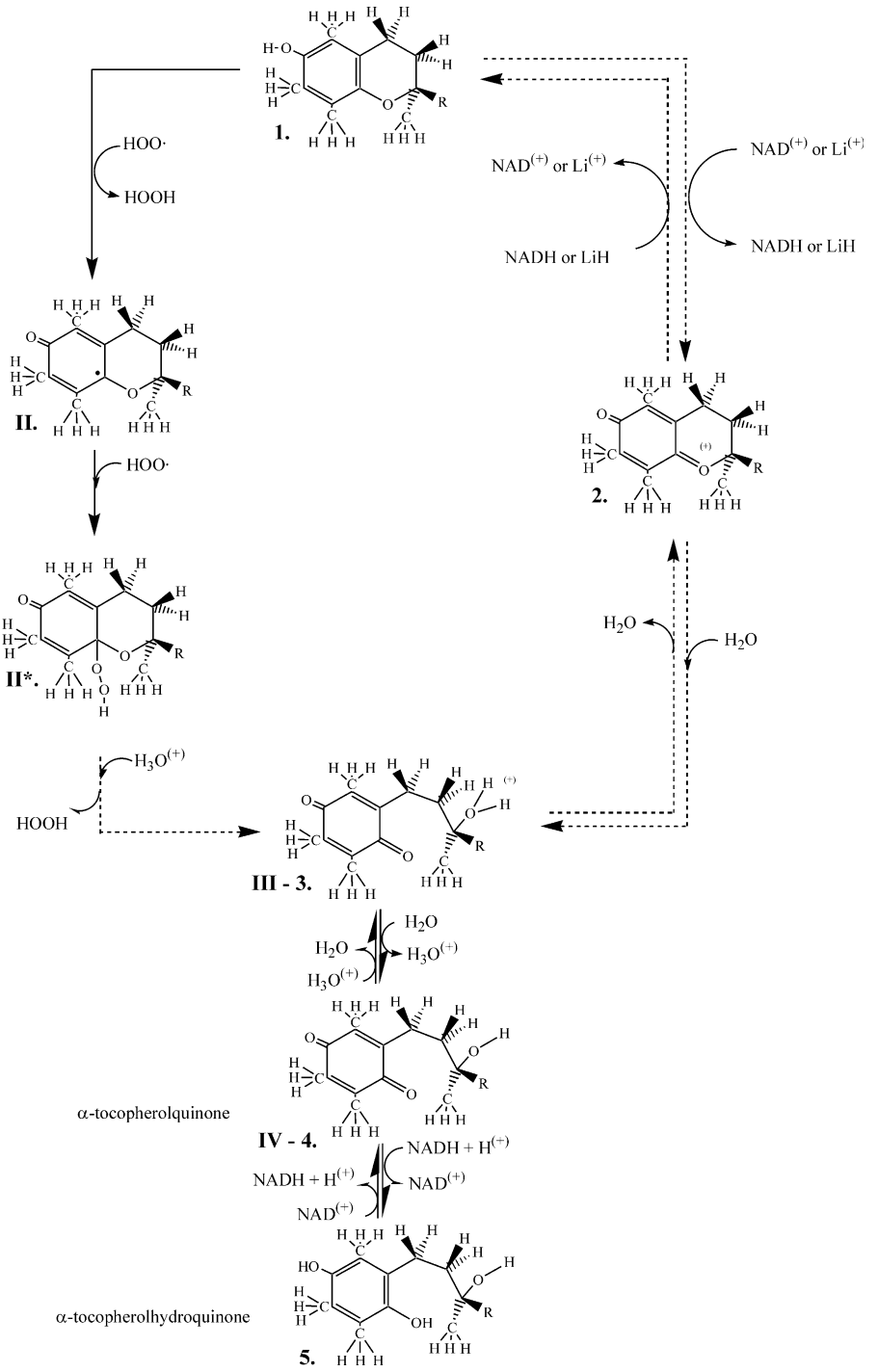


Fig. 8. The connection of a combined non-destructive free-radical and reversible ionic mechanism of oxidation of α-tocopherol quionone. Note the reversible nature of the ionic process.

Table 6
Total and relative energies for the combined mechanism of free radical oxidation and ionic reduction

Components structures	E (Hartree)	Sum of component energies (Hartree)	Relative energy ΔE (kcal·K)	Step height energy $\Delta\Delta E$ (kcal·K)
I = **1**	−735.31212	−1121.87826	0.000	0.000
2($HOO^{\cdot}$)	−301.79831			
$H_3O^{(+)}$	−76.68591			
LiH	−8.08192			
Total	−1121.87826			
II	−734.69317	−1121.89224	−8.771	−8.771
HOOH	−151.53208			
$HOO^{\cdot}$	−150.89916			
H_3O^{+}	−76.68591			
LiH	−8.08192			
Total	−1121.89224			
II*	−885.63012	−1121.93003	−32.487	−23.716
HOOH	−151.53208			
$H_3O^{(+)}$	−76.68591			
LiH	−8.08192			
Total	−1121.93003			
III$^{(+)}$ = **3**$^{(+)}$	−810.84221	−1121.98830	−69.050	−36.563
2(HOOH)	−303.06417			
LiH	−8.08192			
Total	−1121.98830			
2$^{(+)}$	−734.45881	−1122.01385	−85.085	−16.035
2(HOOH)	−303.06417			
H_2O	−76.40895			
LiH	−8.08192			
Total	−1122.01385			
1	−735.31212	−1122.06979	−120.183	−35.098
2(HOOH)	−303.06417			
H_2O	−76.40895			
$Li^{(+)}$	−7.28454			
Total	−1122.06979			

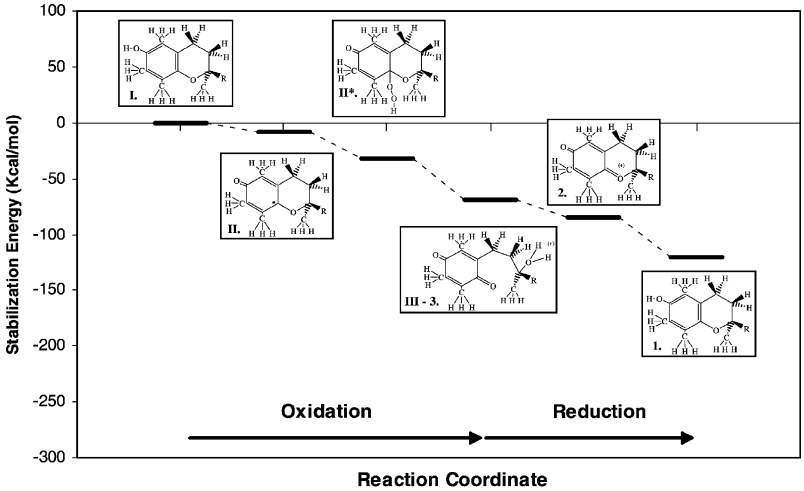
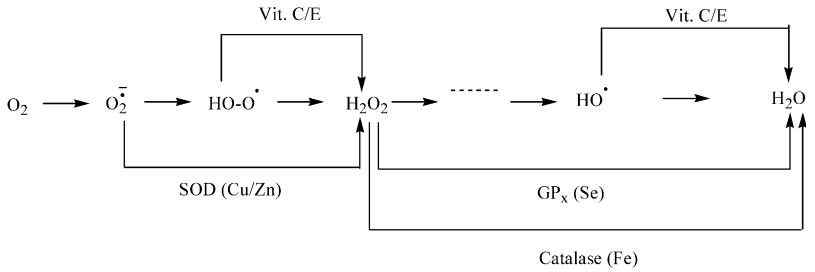


Fig. 9. Full cycle of reaction mechanism involving free radical open shell oxidation and closed shell recovery of α-tocopherol. The energy difference between initial and final states is related to the process: $2HOO^{\cdot} + Li{-}H \rightarrow HOOH + HOOLi$.



Scheme 2.

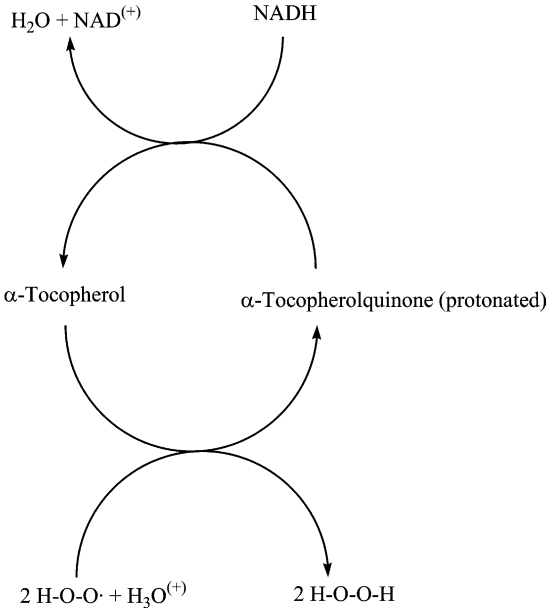


Fig. 10. Overall representation of the catalytic effect of α-tocopherol.

6. Conclusions

If vitamin E reacts with HO$^{\cdot}$ radical then the radical is converted to H_2O which represents no further problem, as it is the last station of the overall reductive process which started at O_2. However, when vitamin E reacts with HOO$^{\cdot}$ then the peroxyradical is converted to hydrogen peroxide (H_2O_2) which could cause oxidative damage.

The present investigation has shown that a substantial fraction of the oxidized vitamin E may be reduced back to active vitamin E which could, in turn, produce more hydrogen peroxide. The responsibility of removal of the hydrogen peroxide from the system bestowed upon two enzymes, the iron containing catalase (Fe) and the selenium containing glutathione peroxidase, GP_x(Se). If there is a noticeable concentration reduction of these enzymes then peroxides are accumulating, leading to a peroxide traffic-jam. This can happen for example if the Se supply is low, as discussed at the beginning of this paper. Of course, the accumulated H_2O_2, produced by vitamin E, can make a great deal of damage and consequently vitamin E may well be misjudged to be a pro-oxidant yet the phenomenon may be due to the low level of selenium.

It now appears that future clinical studies, designed to investigate the efficacy (the anti-oxidant effect) and the toxicity of the accumulated peroxide (via the pro-oxidant effect) of vitamin E should include the monitoring of other participating components of the detoxification process of ROS. Such studies should include the monitoring of the level of catalase (Fe or Mn) as well as glutathione peroxidase (Se). Nutritionists [20] and biochemists [21] have already questioned whether the imbalance of these enzymes could be a significant contributor to the damages originated from oxidative stress.

Acknowledgements

This work was supported by grants from the Global Institute of Computational Molecular and Materials Sciences and Velocet Communications Inc., Toronto, Ontario, Canada.

The authors thank Christopher N.J. Marai, Tania A. Pecora, Jacquelie M. S. Law and Michelle A. Sahai for their helpful input and discussions, as well as for the preparation of this manuscript, tables, and figures. The work of Graydon Hoare in the areas of database

management, network support, software, and distributive processsing development is also recongnized. A special thanks is extended to Andrew M. Chasse for his continuing and ongoing development of novel scripting and coding techniques, indirectly bringing about a reduction in the necessary number of CPU cycles for each computation. Advanced technical support is credited to Christopher M. Andrews and Michael R. Sahai. Last but not least, the authors wish to acknowledge Kenneth P. Chasse (Jr.) of Velocet Communications Inc. for his pioneering of great advances in all composite computer-cluster software and hardware architectures. He and the other directors of Velocet Communications Inc., specifically David C.L. Gilbert and Adam A. Heaney, are also acknowledged for providing spare CPU time for the computations needed in the preparation of this article.

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