

116. Theoretical Parameters to Characterize Antioxidants

Part 1

The Case of Vitamin E and Analogs

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The objectives of this work were *a*) to evaluate parameters obtained by quantum-mechanical calculations as predictors of antioxidant activities, and *b*) to obtain information on the molecular mechanism(s) underlying the antioxidant effects of vitamin E and analogs. To this effect, we selected a large series of tocopherol analogs for which some experimental antioxidant activities were available in the literature (*i.e.*, peak of oxidation potential, E_p , and rate constant of the reaction with a free radical $\log k_s$). AM1 Semi-empirical calculations were performed, the results of which were validated by *ab initio* calculations on a subset of compounds. The quantum chemical descriptors considered here (HOMO, ΔH_{ox} and ΔH_{abs}) were fairly well correlated with the experimental antioxidant activities (E_p and k_s). Moreover, these theoretical parameters were intercorrelated, suggesting that vitamin E analogs may act by a dual mechanism of single-electron transfer (SET) and direct H-atom abstraction.

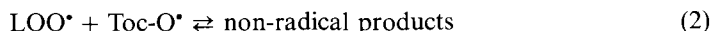
1. Introduction¹⁾ – Antioxidants are of great interest in biological and industrial processes. In biological systems, they protect vital cell components from oxidative stress (*e.g.*, lipids, proteins, and nucleic acids), whereas in industrial applications they are broadly used to prevent degradation caused by autoxidation.

As a consequence of increased radical production in many pathologies such as inflammation, neurodegeneration, and tumors, a growing interest in chain-breaking antioxidants exists since a number of years. The best known chain-breaking phenolic compounds are the vitamins E, namely α -, β -, γ -, and δ -tocopherol. These tocopherols protect lipids from peroxidation by scavenging free radicals such as peroxy (LOO^\bullet), alkoxy (LO^\bullet), and hydroxyl (HO^\bullet) radicals [1]. For comparable reasons, vitamins E find applications in drug, cosmetics, food and polymer technology [2].

The antioxidant properties of tocopherols are ascribed to the oxidation of the phenolic OH group by an oxyl radical, the first step being globally a H-atom transfer (*Reaction 1*) [1]. Since the tocopheroxyl radical produced is resonance-stabilized, it will not

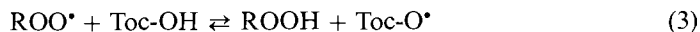
¹⁾ *Abbreviations and Symbols.* 3-21G: Split-valence basis set; AM1: Austin model 1; ArO[•]: 2,6-di(*tert*-butyl)-4-(4'-methoxyphenyl)phenoxy radical; ΔH_{abs} : relative bond-dissociation energy; ΔH_{ox} : relative adiabatic-oxidation potential; E_p : peak oxidation potential; HO[•]: hydroxyl radical; HOMO: highest occupied MO; k_s : second-order rate constant; LO[•]: alkoxy radical; LOO[•]: peroxy radical; LUMO: lowest-unoccupied MO; MO: molecular orbital; SET: single-electron transfer; RHF: restricted *Hartree-Fock*; ROHF: restricted open-shell *Hartree-Fock*; ROO[•]: poly(peroxystyryl)peroxy radical; Toc-OH: tocopherol; UHF: unrestricted *Hartree-Fock*.

continue the propagation step of the chain reaction, but will eventually combine with another oxyl radical to yield non-radical products (*Reaction 2*) [3].



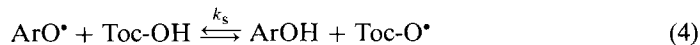
In other words, the antioxidant activity of tocopherols is attributed to their ability to scavenge free radicals. However, the mechanistic details of the reaction remain to be fully elucidated, since there is the possibility of direct H-atom transfer, single-electron transfer (SET), or a combination thereof [4].

Thus, *Burton et al.* interpreted the high antioxidant activity of α -tocopherol and its analogs in terms of stereoelectronic effects stabilizing their aryloxyl radical. To investigate the factors influencing the antioxidant efficacy of these tocopherols, rate constants of H-atom transfer were measured in the presence of the poly(peroxystyryl)peroxyl radical (ROO^\bullet) (*Reaction 3*) [1].



The existence of a substantial kinetic D isotope effect in *Reaction 3* led *Burton et al.* to conclude that tocopherols exert their antioxidant activity *via* a simple H-atom transfer [1].

Mukai and coworkers measured the second-order rate constant (k_s) for the reaction of several tocopherol derivatives with a substituted phenoxyl radical (2,6-di(*tert*-butyl)-4-(4'-methoxyphenyl)phenoxyl, ArO^\bullet) [5] [6] (*Reaction 4*):



In addition, they determined the oxidation potential (E_p) of the same compounds by cyclic voltammetry in MeCN [7–9]. From the linear correlations observed between E_p , $\log k_s$, activation energies (E_{act}) for *Reaction 4*, and vertical ionization potentials, *Mukai et al.* proposed that a SET from the tocopherols to the oxyl radicals plays a determining role in *Reaction 1*. This hypothesis was further substantiated by the fact that increasing the electron-donating capacity of the heterocyclic systems resulted in increased free-radical scavenging activity [7].

To explain the large D kinetic isotope effect in k_s , *Mukai* and coworkers postulated a proton tunneling effect which would occur below the transition state and allow the proton to cut the corner on the potential energy surface avoiding the formation of the SET species [5]. Given the dependence of tunneling on the mass of the transferred atom, a substantial D kinetic isotope effect on k_s is indeed justified in *Reaction 4* if proton tunneling occurs.

Because of the ambiguities on the detailed reaction mechanisms of free-radical scavengers and, particularly, vitamin E, it was felt that theoretical investigations could bring some clarification. Indeed, computational chemistry can be a valuable technique to elucidate reaction mechanisms and select new medicinal compounds in rational drug design. In this work, simple theoretical parameters were calculated by quantum-mechanical methods and correlated with experimental parameters, the objective being twofold,

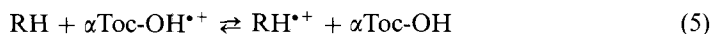
namely *a*) to propose theoretical parameters of relevance in the design of new antioxidants, and *b*) to shed light on reaction mechanisms of chain-breaking antioxidants.

2. Theoretical Parameters. – Facility of electron transfer and the stability of the radical formed by H-atom abstraction are the two characteristics considered essential for a good antioxidant activity of tocopherol analogs [6]. Hence, some simple theoretical parameters were calculated here to quantitatively express these characteristics, namely the vertical ionization potential, the relative adiabatic ionization potential (ΔH_{ox}), and the relative O–H bond dissociation enthalpy (ΔH_{abs}).

In agreement with *Koopmans'* theorem [10] and according to molecular orbital theory, the vertical ionization potential can be approximated by the energy of the HOMO (highest-occupied molecular orbital) and the electron affinity by the orbital energy of the LUMO (lowest-unoccupied molecular orbital). Indeed, this theorem states that the energy necessary to remove an electron from an orbital *i* (I_i) is equal to minus the energy of the *i* orbital ($I_i = -\varepsilon_i$). For a many-electron molecule, *Koopmans'* theorem is an approximation since it assumes that the remaining electrons do not re-organize, and that bond lengths and angles do not change after the loss of an electron.

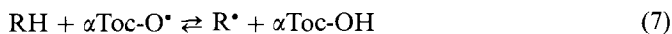
An isodesmic reaction is defined as a process in which the number of formal bonds of each type remains constant. To minimize the errors due to approximations in the calculations and to allow a direct comparison of results, two theoretical parameters based on the isodesmic *Reactions 5* and *7* were used here, namely the relative adiabatic ionization potential (ΔH_{ox}) and the relative bond dissociation energy (ΔH_{abs}).

The parameter ΔH_{ox} defined in *Eqn. 6* is related to the isodesmic *Reaction 5*. It describes the capacity of a compound RH to donate an electron and is directly related to the adiabatic ionization potential. The latter, which is calculated as the difference between the heats of formation of the optimized radical cation and the corresponding neutral species, is an index of the facility of SET from the antioxidant molecule to the free radical.



$$\begin{aligned} \Delta H_{\text{ox}} = \Delta H_f(\alpha\text{Toc-OH}) + \Delta H_f(\text{RH}^{\bullet+}) \\ - \Delta H_f(\alpha\text{Toc-OH}^{\bullet+}) - \Delta H_f(\text{RH}) \end{aligned} \quad (6)$$

The relative bond dissociation energy, ΔH_{abs} , defined by *Eqn. 8* is related to the isodesmic *Reaction 7*. It describes the capacity of a compound RH (relative to α -tocopherol) to donate a H-atom, and provides a quantitative estimate of the stability of the neutral radical species R^{\bullet} . The more stable the radical, the lower ΔH_{abs} .



$$\begin{aligned} \Delta H_{\text{abs}} = \Delta H_f(\alpha\text{Toc-OH}) + \Delta H_f(\text{R}^{\bullet}) \\ \Delta H_f(\alpha\text{Toc-O}^{\bullet}) - \Delta H_f(\text{RH}) \end{aligned} \quad (8)$$

3. Methods. – *Ab initio* calculations using Gaussian 94 [11] were carried out at the restricted *Hartree-Fock* RHF/3-21G level for closed-shell species, and at the unrestricted *Hartree-Fock* UHF/3-21G level for open-shell species. Furthermore, a single-point-re-

stricted open-shell *Hartree-Fock* ROHF/3-21G calculation was performed on all radicals because of the different degrees of spin contamination. A large degree of spin contamination leads to too negative total energies which do not reflect a real improvement of the calculations, but are the result of an artifact of the calculation method [12].

Semi-empirical calculations were performed using the AM1 Hamiltonian as implemented in MOPAC 5.0 [13]. Closed-shell species were optimized using the RHF approximation, while the open-shell species were calculated using the UHF approximation followed by a single-point ROHF calculation to avoid spin contamination.

Each molecule was fully optimized at a semi-empirical level using first MOPAC 5.0 [13], and then SPARTAN 4.0 [14] in difficult cases with unexpected geometries. MO Calculations were performed on a *Silicon Graphics Indy R4400 PC* 175-MHz workstation.

The experimental data (rate constants k_s of *Reaction 4* and peak oxidation potentials E_p) were obtained from the literature [7–9]. The choice of these experimental parameters was determined by the relative simplicity of the tests and by the reliability of the results which were conducted rigorously by the same group under identical conditions.

4. Results and Discussion. – 4.1. *Validation of the Semi-empirical Approach Using a Small Set of Compounds.* In a first series of calculations, we investigated a restricted set of nine model compounds, **1'–9'**, where the two 2-Me groups were replaced by two H-atoms to facilitate calculations. Full geometry optimization of the compounds, their radical cations, and neutral radicals were performed at a semi-empirical level using the AM1 Hamiltonian (*Table 1*) and at an *ab initio* level using the 3-21G basis set (*Table 2*).

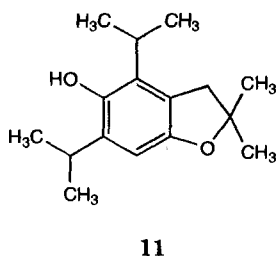
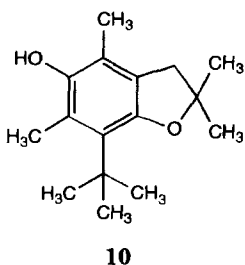
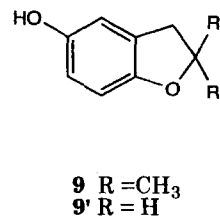
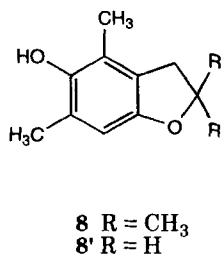
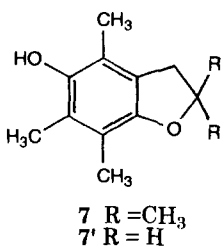
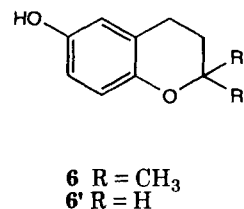
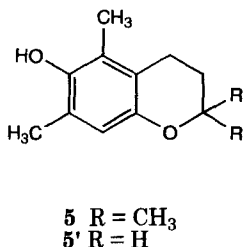
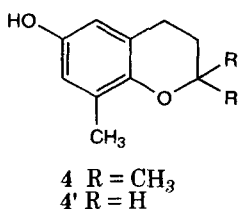
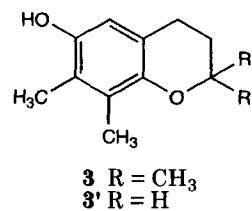
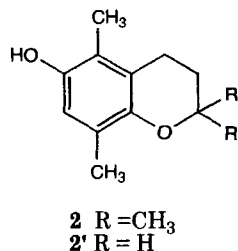
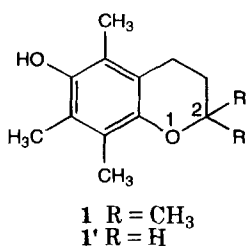
The two quantum-mechanical levels gave similar results. Thus, the correlation between ΔH_{ox} calculated at the two levels (*Tables 3* and *4*) is satisfactory (*Eqn. 9* and *Fig. 1*). Also, ΔH_{abs} values calculated by the two methods (*Tables 3* and *4*) are in good agreement (*Eqn. 10* and *Fig. 2*), with the only exception of the δ -tocopherol analog **4'** which, at the *ab initio* level, presents a high value of ΔH_{abs} . Furthermore, final geometries optimized by both methods do not differ significantly; we simply observed that the five-membered heterocyclic rings are somewhat more planar when optimized at the AM1 level than at the *ab initio* level.

$$\Delta H_{\text{ox}}^{\text{AM1}} = 0.72 (\pm 0.04) \Delta H_{\text{ox}}^{3-21\text{G}} + 0.53 (\pm 0.18) \\ n = 9; r^2 = 0.98; S = 0.36; F = 390 \quad (9)$$

$$\Delta H_{\text{abs}}^{\text{AM1}} = 0.72 (\pm 0.06) \Delta H_{\text{abs}}^{3-21\text{G}} + 0.04 (\pm 0.10) \\ n = 8; r^2 = 0.96; S = 0.21; F = 150 \quad (10)$$

The comparison between AM1 semi-empirical and 3-21G *ab initio* calculations thus shows that the former method gives quite reliable results in these applications, while consuming far less computer time.

4.2. *Study of a Large Series of Tocopherol Analogs.* 4.2.1. *Relations between Theoretical Parameters.* A large series of 25 compounds, all structurally related to vitamin E (**1–21**), were investigated by means of computational chemistry at a semi-empirical level. To reduce the dimension of the problem and to focus only on the molecular motifs of interest, the phytol chain was replaced by a Me group in all vitamin E analogs investigat-



ed. The compounds were divided into five classes based on their structural characteristics, *i.e.*, 1) six-membered tocopherol analogs (**1–6**), 2) five-membered tocopherol analogs (**7–11**), 3) 4*H*-1,2-benzodioxin-6-ol derivatives (**12a–16b**), 4) vitamin K₁ and ubiquinol analogs (**17–20**), 5) TMMP (2,3,5,6-tetramethyl-4-methoxyphenol, **21**).

The heats of formation of all compounds in their neutral, radical cation, and radical forms are grouped in *Table 5*. *Table 6* presents the theoretical parameters to be related with experimental parameters expressing antioxidant activities reported in the literature.

In this series of tocopherol derivatives, the vertical ionization potential (approximated by the energy of the HOMO) and the relative adiabatic ionization potential ΔH_{ox} (obtained from the isodesmic *Reaction 5*) are well correlated as shown by *Eqn. 11* and in

Table 1. *Heats of Formation of Tocopherols (in kcal/mol) Obtained at the Semi-empirical Level^{a)}*

	$\Delta H_{NE}^{b)}$	$\Delta H_{RC}^{UHF^{c)}$	$\Delta H_{RC}^{RHF^{d)}$	$\Delta H_{RN}^{UHF^{e)}$	$\Delta H_{RN}^{RHF^{f)}$
2'	-80.72	94.03	97.51	-58.50	-48.27
1'	-86.07	87.07	90.53	-65.33	-54.78
3'	-80.46	95.06	98.38	-58.12	-47.76
4'	-74.80	102.21	105.41	-51.10	-40.98
5'	-81.05	94.35	97.62	-59.51	-49.40
6'	-68.14	111.48	114.53	-44.26	-34.46
7'	-74.68	100.10	103.56	-53.76	-43.66
8'	-68.84	108.41	111.70	-47.48	-37.76
9'	-55.32	126.44	129.50	-31.79	-22.30

^{a)} AM1-Optimized geometries.

^{b)} Heat of formation of the neutral species.

^{c)} Heat of formation of the radical cation species using the UHF approximation.

^{d)} Heat of formation of the radical cation species using the RHF approximation.

^{e)} Heat of formation of the radical species using the UHF approximation.

^{f)} Heat of formation of the radical species using the RHF approximation.

Table 2. *Total Energies in Hartrees^{a)} Obtained by the ab initio 3-21G Method*

	$E_{NE}^{b)}$	$E_{RC}^{UHF^{c)}$	$E_{RC}^{ROHF^{d)}$	$E_{RN}^{UHF^{e)}$	$E_{RN}^{ROHF^{f)}$
1'	-610.06419	-609.84101	-609.83208	-609.48897	-609.46018
2'	-571.24549	-571.01981	-571.01087	-570.66739	-570.63849
3'	-571.24411	-571.01687	-571.00834	-570.66622	-570.63706
4'	-532.42457	-532.19391	-532.18590	-531.84457	-531.81070
5'	-571.24400	-571.01693	-571.00812	-570.66798	-570.63990
6'	-493.60114	-493.36495	-493.35609	-493.02099	-492.99257
7'	-571.23815	-571.01289	-571.00403	-570.66290	-570.63472
8'	-532.41665	-532.18714	-532.17844	-531.84062	-531.81299
9'	-454.77190	-454.53157	-454.52263	-454.19200	-454.16373

^{a)} 1 Hartree = 627.5095 kcal/mol.

^{b)} Total energy of the neutral species.

^{c)} Total energy of the radical cation species using the UHF approximation.

^{d)} Total energy of the radical cation species using the ROHF approximation.

^{e)} Total energy of the radical species using the UHF approximation.

^{f)} Total energy of the radical species using the ROHF approximation.

Table 3. *Theoretical Parameters Calculated by the Semi-empirical AM1 Method*

	$\Delta H_{ox}^{RHF^{a)}$	$\Delta H_{abs}^{RHF^{b)}$	HOMO ^{c)}		$\Delta H_{ox}^{RHF^{a)}$	$\Delta H_{abs}^{RHF^{b)}$	HOMO ^{c)}
1'	0.00	0.00	-8.39	6'	6.07	2.39	-8.57
2'	1.63	1.16	-8.40	7'	1.64	-0.27	-8.35
3'	2.24	1.41	-8.43	8'	3.94	-0.21	-8.44
4'	3.61	2.53	-8.48	9'	8.22	1.73	-8.57
5'	2.07	0.36	-8.43				

^{a)} Enthalpy of the isodesmic Reaction 5 in kcal/mol.

^{b)} Enthalpy of the isodesmic Reaction 7 in kcal/mol.

^{c)} Energy of the HOMO in eV.

Table 4. Theoretical Parameters Calculated by the ab initio 3-21G Method

	$\Delta H_{\text{ox}}^{\text{RHF}^{\text{a}}}$	$\Delta H_{\text{abs}}^{\text{RHF}^{\text{b}}}$	HOMO ^{c)}		$\Delta H_{\text{ox}}^{\text{RHF}^{\text{a}}}$	$\Delta H_{\text{abs}}^{\text{RHF}^{\text{b}}}$	HOMO ^{c)}
1'	0.00	0.00	-7.99	6'	8.12	2.86	-7.92
2'	1.57	1.88	-7.71	7'	1.26	-0.37	-7.99
3'	2.29	1.91	-7.75	8'	3.82	-0.22	-8.05
4'	4.11	6.18	-7.81	9'	10.77	2.61	-7.95
5'	2.36	0.05	-8.04				

a) Enthalpy of the isodesmic Reaction 5 in kcal/mol.

b) Enthalpy of the isodesmic Reaction 7 in kcal/mol.

c) Energy of the HOMO in eV.

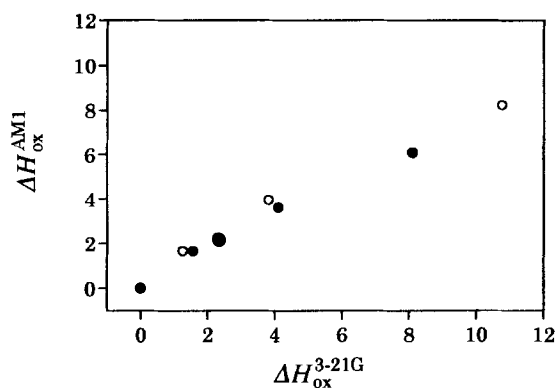


Fig. 1. Correlation (Eqn. 9) between semi-empirical derived ($\Delta H_{\text{ox}}^{\text{AM1}}$) and ab-initio-derived relative ionization potentials ($\Delta H_{\text{ox}}^{3-21\text{G}}$). (●): Compounds 1'–6'; (○): compounds 7'–9'.

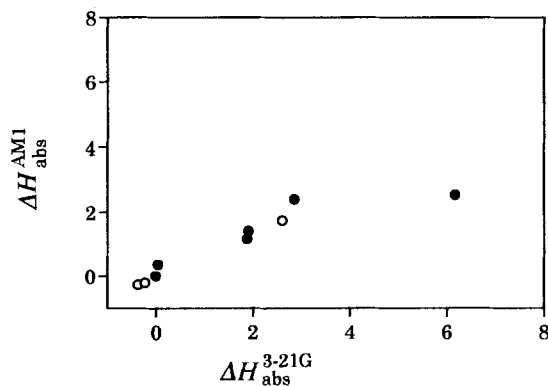
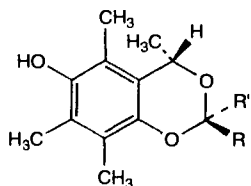
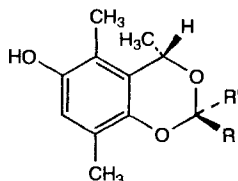
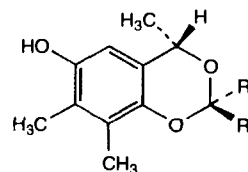
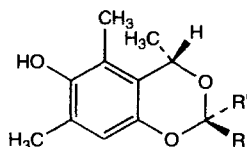
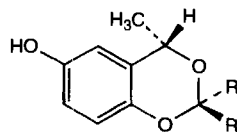
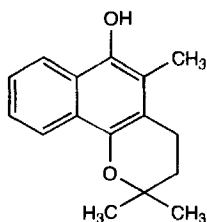
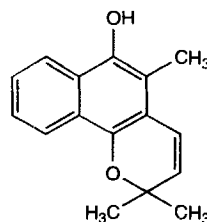
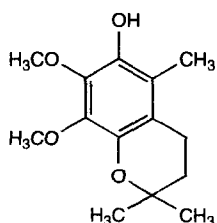
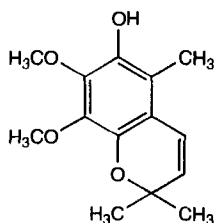
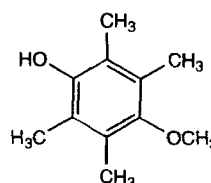


Fig. 2. Correlation (Eqn. 10) between semi-empirical derived ($\Delta H_{\text{abs}}^{\text{AM1}}$) and ab initio-derived relative bond dissociation enthalpy ($\Delta H_{\text{abs}}^{3-21\text{G}}$). (●): Compounds 1'–6'; (○): compounds 7'–9'.

Fig. 3, probably due to the limited flexibility of the compounds and to the good capacity of AM1 to evaluate the HOMO energy [15].

$$\text{HOMO} = -4.61 \cdot 10^{-2} (\pm 2.4 \cdot 10^{-3}) \cdot \Delta H_{\text{ox}} - 8.28 (\pm 0.01) \quad (11)$$

$$n = 25; r^2 = 0.94; S = 4.8 \cdot 10^{-2}; F = 360$$

**12a** R=CH₃ R'=H**12b** R'=CH₃ R=H**13a** R=CH₃ R'=H**13b** R'=CH₃ R=H**14a** R=CH₃ R'=H**15a** R=CH₃ R'=H**15b** R'=CH₃ R=H**16a** R=CH₃ R'=H**16b** R'=CH₃ R=H**17****18****19****20****21**

A correlation between the theoretical parameters ΔH_{ox} and ΔH_{abs} (representing the enthalpy of the SET and H-atom transfer reaction, respectively) was observed (Fig. 4; $r^2 = 0.67$). As shown in Fig. 4, the stereoelectronic factors that facilitate SET in this set of compounds also facilitate their H-atom abstraction. Factors stabilizing radical cations are generally independent from those stabilizing neutral radicals except for some specific classes of compounds such as vitamin E analogs and 1-aryl-1,4-dihyronicotins [16]. This result is in agreement with the good correlation existing between the values of the

Table 5. Calculated^{a)} Heats of Formation (in kcal/mol) for Vitamin E Analogs

	$\Delta H_{NE}^{b)}$	$\Delta H_{RC}^{UHF^c)}$	$\Delta H_{RC}^{RHF^d)}$	$\Delta H_{RN}^{UHF^e)}$	$\Delta H_{RN}^{RHF^f)}$
1	-91.54	78.86	82.48	-71.02	-60.65
2	-86.22	85.78	89.34	-64.22	-54.10
3	-85.74	86.55	89.98	-63.77	-53.54
4	-80.31	93.77	97.10	-56.86	-46.91
5	-86.60	85.98	89.42	-65.25	-55.29
6	-73.70	102.83	106.05	-50.07	-40.43
7	-82.46	89.67	93.23	-61.88	-51.88
8	-76.19	97.62	101.21	-55.22	-45.61
9	-62.71	115.48	118.75	-39.61	-30.23
10	-86.34	84.38	88.02	-65.93	-55.87
11	-92.59	79.73	82.94	-72.38	-62.69
12a	-125.40	50.20	53.77	-104.21	-93.67
12b	-125.08	50.21	53.78	-103.86	-93.34
13a	-119.82	57.17	60.71	-97.20	-86.93
13b	-119.49	57.22	60.78	-96.84	-86.59
14a	-120.70	57.16	60.41	-98.16	-87.81
15a	-120.10	57.63	60.93	-98.13	-88.02
15b	-119.75	57.94	61.29	-97.77	-87.66
16a	-108.28	73.60	76.65	-84.04	-74.26
16b	-107.87	73.58	76.67	-83.63	-73.87
17	-58.95	105.01	109.27	-44.65	-32.73
18	-30.68	133.09	138.78	-17.26	-3.66
19	-150.96	20.54	24.36	-128.18	-117.57
20	-122.62	48.22	65.69	-100.73	-88.50
21	-83.12	95.62	99.11	-60.88	-49.37

a) AM1 Semi-empirical method

b) Heat of formation of the neutral species.

c) Heat of formation of the radical cation species using the UHF approximation.

d) Heat of formation of the radical cation species using the RHF approximation.

e) Heat of formation of the radical species using the UHF approximation.

f) Heat of formation of the radical species using the RHF approximation.

second-order rate constant of *Reaction 4* ($\log k_s$, indicating the facility of H-atom transfer), and the values of the peak oxidation potential (E_p , indicating the facility of SET), as reported by *Mukai et al.* [7–9].

4.2.2. *Relations between Theoretical Parameters and Experimental Oxidation Potential.* A significant correlation between experimental E_p values [7–9] and ΔH_{ox} has also been observed (*Eqn. 12* and *Fig. 5*). This result indicates that the stability of radical cations is an essential characteristic to achieve low oxidation potentials.

$$E_p = 27.44 (\pm 2.40) \cdot \Delta H_{ox} + 857 (\pm 13) \quad (12)$$

$$n = 24; r^2 = 0.86; S = 47; F = 131$$

Cyclic voltammetry of compound **1** (a model of α -tocopherol) indicated that its first oxidation step is a one-electron process yielding a relatively stable radical cation [17]. This radical cation was then deprotonated to the α -tocopheroxyl radical in neutral and basic media, or it could be further oxidized to the two-electron oxidation product. The

Table 6. Theoretical^{a)} and Experimental Parameters Describing the Antioxidant Activities of Vitamin E Analogs

	$\Delta H_{\text{ox}}^{\text{RHF}^{\text{b}}}$	$\Delta H_{\text{abs}}^{\text{RHF}^{\text{c}}}$	HOMO ^{d)}	LUMO ^{e)}	$E_p^{\text{f)}$	$\log k_s^{\text{g)}$
1	0.00	0.00	-8.33	0.33	860	3.71
2	1.54	1.23	-8.33	0.35	920	3.35
3	1.70	1.31	-8.35	0.32	930	3.38
4	3.39	2.51	-8.41	0.35	990	3.00
5	2.00	0.42	-8.36	0.33	890	3.38
6	5.73	2.38	-8.49	0.34	1050	2.75
7	1.67	-0.31	-8.37	0.26	810	3.84
8	3.38	-0.31	-8.42	0.28	850	3.54
9	7.44	1.59	-8.57	0.29	1030	2.94
10	0.34	-0.42	-8.36	0.27	900	3.96
11	1.51	-0.99	-8.43	0.27	870	3.73
12a	5.15	0.84	-8.56	0.11	960	2.83
12b	4.84	0.85	-8.57	0.11	970	2.99
13a	6.51	2.00	-8.58	0.13	1050	2.46
13b	6.25	2.01	-8.58	0.13	1030	2.63
14a	7.09	2.00	-8.59	0.12	1040	2.71
15a	7.01	1.19	-8.61	0.10	1050	2.49
15b	7.02	1.20	-8.62	0.10	1030	2.66
16a	10.91	3.13	-8.74	0.12	1200	1.60
16b	10.52	3.11	-8.74	0.12	1240	1.48
17	-5.80	-4.67	-7.98	-0.10	780	4.55
18	-4.56	-3.87	-7.97	-0.35	750	4.39
19	1.30	2.50	-8.44	0.10	870	2.62
20	3.29	3.23	-8.41	-0.35	920	2.75
21	8.21	2.86	-8.71	0.26	-	2.64

^{a)} AM1 Semi-empirical calculations.

^{b)} Enthalpy for the isodesmic *Reaction 5* in kcal/mol.

^{c)} Enthalpy for the isodesmic *Reaction 7* in kcal/mol.

^{d)} Energy of the HOMO in eV.

^{e)} Energy of the LUMO in eV.

^{f)} Peak oxidation potential [mV] measured by cyclic voltammetry in acetonitrile vs. SCE, taken from references [7–9].

^{g)} Second-order rate constant of *Reaction 4* [$\text{M}^{-1} \text{s}^{-1}$] measured in EtOH by stopped-flow spectrophotometry, and taken from [7–9].

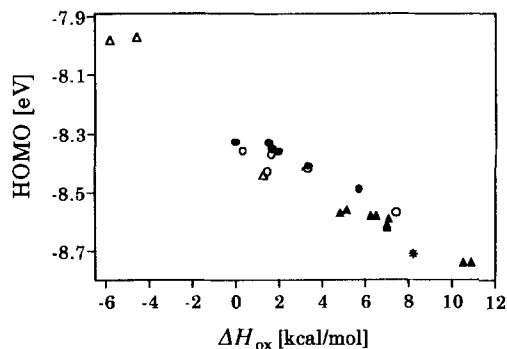


Fig. 3. Correlation (Eqn. 11) between HOMO energy and relative adiabatic ionization potential (ΔH_{ox}). (●): Compounds 1–6; (○): compounds 7–8; (▲): compounds 12a–16b; (△): compounds 17–20; (*): compound 21.

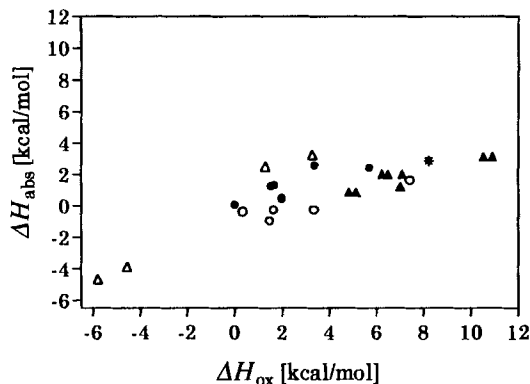


Fig. 4. Correlation ($r^2 = 0.67$) between relative bond dissociation enthalpy (ΔH_{abs}) and the relative adiabatic ionization potential (ΔH_{ox}). (●): Compounds 1–6; (○): compounds 7–9; (▲): compounds 12a–16b; (△): compounds 17–20; (*): compound 21.

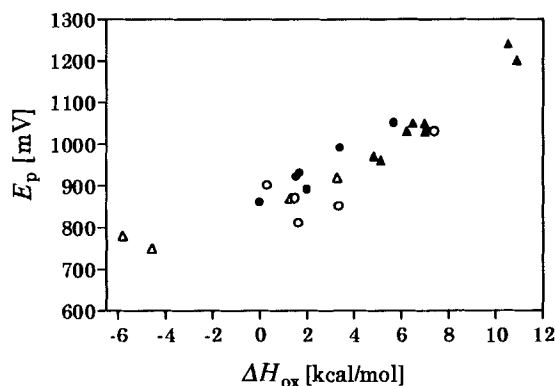


Fig. 5. Correlation (Eqn. 12) between experimental oxidation potential (E_p) and relative adiabatic ionization potential (ΔH_{ox}). (●): Compounds 1–6; (○): compounds 7–9; (▲): compounds 12a–16b; (△): compounds 17–20.

correlation observed in Eqn. 12 and Fig. 5 is consistent with this electro-oxidation mechanism of α -tocopherol and confirms the formation of a radical cation in the first oxidation step.

The correlation between the experimental oxidation potential E_p and the HOMO energy is less satisfactory than the previous one but still fair (Table 7: $r = -0.868$ accounting for 75% of the total variance), indicating that E_p decreases with increasing HOMO energy. This difference in statistical significance is explained by the fact that electronic reorganization after one-electron abstraction is neglected when calculating the HOMO energy (in agreement with Koopmans' theorem), but not when calculating ΔH_{ox} . Presumably the electronic rearrangement of radical cations plays a non-negligible role in the antioxidant process, explaining the better correlation of E_p with the relative adiabatic ionization potential (Table 7; $r = 0.925$) than with the vertical ionization potential ($r = -0.868$), even though the high degree of correlation between HOMO and ΔH_{ox} for this set of compounds ($r = -0.969$) does not allow a univocal conclusion.

Table 7. Correlation Matrix for Semiempirically and Experimentally Derived Parameters

	HOMO	ΔH_{ox}	ΔH_{abs}	E_p	$\log k_s$
HOMO	1				
ΔH_{os}	-0.969	1			
ΔH_{abs}	-0.812	0.808	1		
E_p	-0.868	0.925	0.753	1	
$\log k_s$	0.893	-0.917	-0.867	-0.918	1

In conclusion, ΔH_{ox} appears to be the best among the parameters here investigated to predict the oxidation potential in aprotic solvents (Eqn. 12 and Fig. 5).

4.2.3. *Relations between Theoretical Parameters and Experimental Rate Constants.* The experimental second-order rate constant of the oxidation of tocopherol derivatives mediated by the phenoxyl radical (Reaction 4) [7–9] has been found to be fairly well correlated with their relative bond dissociation energies (ΔH_{abs} ; Fig. 6; $r^2 = 0.75$).

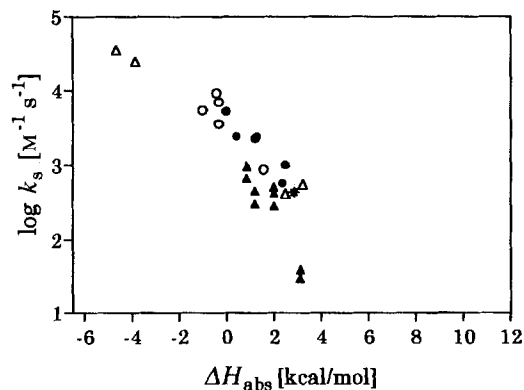


Fig. 6. Correlation ($r^2 = 0.75$) between the logarithm of the second-order rate constant of Reaction 4 ($\log k_s$), and relative bond dissociation enthalpy (ΔH_{abs}). (●): Compounds 1–6; (○): compounds 7–9; (▲): compounds 12a–16b; (△): compounds 17–20; (*) : compound 21.

The relation shows that the smaller ΔH_{abs} , the easier the homolytic cleavage of the phenolic O–H, hence ΔH_{abs} is expected to be well related to the overall H-atom abstraction reaction (e.g., Reaction 4).

The small differences in stabilization observed between six-membered and five-membered tocopherol analogs (Table 6 and Fig. 6) suggest that the overlap between the p-type lone pair orbital on the O-atom *para* to the phenolic O–H and the aromatic π electron system is not the main radical-stabilizing factor, as hypothesized by Mukai and coworkers [5] [6].

An even more significant correlation has been observed between $\log k_s$ and ΔH_{ox} for all compounds (1–21), except 19 and 20 which are able to form an intramolecular H-bond (Eqn. 13 and Fig. 7):

$$\log k_s = -0.17 (\pm 0.02) \cdot \Delta H_{ox} + 3.70 (\pm 0.09) \quad (13)$$

$n = 25; r^2 = 0.83; S = 0.31; F = 116$

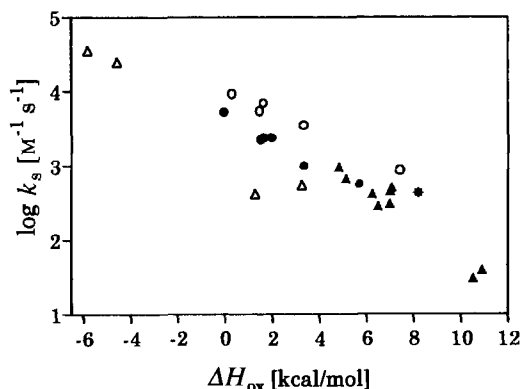


Fig. 7. Correlation (Eqn. 13) between the logarithm of the second-order rate constant of Reaction 4 ($\log k_s$), and relative adiabatic ionization potential (ΔH_{ox}). (●): Compounds 1–6; (○): compounds 7–9; (▲): compounds 12a–16b; (△): compounds 17–20; (*) : compound 21.

This correlation strongly suggests that electron transfer should play an important role at least in the first step of the free radical scavenging process.

The correlation between $\log k_s$ and ΔH_{ox} is better than that between $\log k_s$ and ΔH_{abs} (see Table 7). One possible explanation is that the range of ΔH_{abs} values covered by the vitamin E analogs (nearly 8 kcal/mol) is smaller than their range of ΔH_{ox} values (nearly 17 kcal/mol). As a consequence, the same error in energy affects more the correlation between $\log k_s$ and ΔH_{abs} than that between $\log k_s$ and ΔH_{ox} .

5. Conclusion. – A practical conclusion to this work is that the AM1 semi-empirical method gives satisfactory results compared with the much more time-consuming *ab initio* (3-21G) calculations.

Among the theoretical parameters investigated, some have been found to be useful to identify the most promising antioxidants in a series of analogs. But because of the complexity of the antioxidant process, theoretical parameters alone cannot indicate with certainty whether a compound will be a good antioxidant – they can only evaluate if it possesses some of the required characteristics. In the case of vitamin E and analogs, the most useful theoretical parameters were the HOMO energy, ΔH_{ox} and ΔH_{abs} , which were correlated with antioxidant activities measured as peaks of oxidation potential (E_p) and as rate constants of the reaction with a free radical ($\log k_s$). The parameter ΔH_{ox} appears as the best correlation with the antioxidant activity of vitamin E analogs.

In this series of compounds, the theoretical parameters were not only fairly well correlated with experimental antioxidant activities, they were also highly intercorrelated. This is taken to suggest that vitamin E analogs might act as antioxidants by a dual mechanism of SET and direct H-atom abstraction. Under some conditions, one mechanism can predominate over the other depending on the reactive species and on the medium [4] [18].

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