ELSEVIER

Journal of Molecular Structure (Theochem) 637 (2003) 11–26

THEO CHEM

www.elsevier.com/locate/theochem

Vitamin E models. Shortened sidechain models of α, β, γ and δ tocopherol and tocotrienol—a density functional study

David H. Setiadi[a,*], Gregory A. Chass[a], Ladislaus L. Torday[b], Andras Varro[b], Julius Gy. Papp[b,c]

[a]*Global Institute of Computational Molecular and Materials Science, 210 Dundas Street W., Suite 810, Toronto, Ont., Canada M5G 2E8*
[b]*Department of Pharmacology and Pharmacotherapy, Szeged University, Dom ter12, Szeged 6701, Hungary*
[c]*Division of Cardiovascular Pharmacology, Hungarian Academy of Sciences and Szeged University, Dom ter12, Szeged 6701, Hungary*

Received 23 June 2002; accepted 7 August 2002

Abstract

Model compounds of α-, β-, γ-, and δ-tocopherol and Tocotrienol, as well as their sulphur and selenium congeners, were subjected to density functional analysis. The mono methyl substitution either stabilized or destabilized the ring structures to a small extent as assessed in terms of isodesmic reactions. In general, multiple methyl substitutions destabilized the ring. Dimethyl *para*-substitution results in electronic stabilization and steric repulsion being nearly additive. This was not the case for *ortho*-dimethyl derivatives, whereby steric repulsions dominate; the *meta*-substituted models reflect the same trend to a lesser degree. Structurally, the phenolic hydroxyl orientation was approximately planar, with the hydroxyl proton oriented away from the adjacent Me group whenever the structure permitted such an orientation.

Keywords: Tocopherol; Tocotrienol; Density functional theory; Methyl substitution; Orientation of phenolic OH

1. Preamble

The term 'Vitamin E' was introduced in 1922 [1]. Vitamin E includes two families of compounds: tocopherols and tocotrienols (Fig. 1). Both families consist of a chroman [benzpyrane] ring structure and an isoprenoid sidechain, which is typical of terpenes. The tocopherol family has saturated sidechains, whereas the same sidechain in the tocotrienol family has three non-conjugated double bonds. For both families, the ring carbon atom that carries the sidechain is a stereocentre of *R* configuration. The sidechain of the tocopherols has two additional stereocentres at the branching points, both of which are of *R* configuration.

Each of these families has four homologous members (see Table 1), labelled as α, β, γ, and δ. They differ from each other in the extent of the methyl substitution in the aromatic ring. The natural abundance of the components of the Vitamin E family varies from plant to plant [2].

The most important component of the Vitamin E family is α-tocopherol. It is commercially available in its synthetic form, which comes as an enantiomeric mixture. The effectiveness of the synthetic racemic mixture has traditionally been questioned, without any explanation at the molecular level. Presently, we

* Corresponding author.
E-mail address: dsetiadi@fixy.org (D.H. Setiadi).

0166-1280/03/$ - see front matter © 2003 Published by Elsevier B.V.
doi:10.1016/S0166-1280(02)00597-3

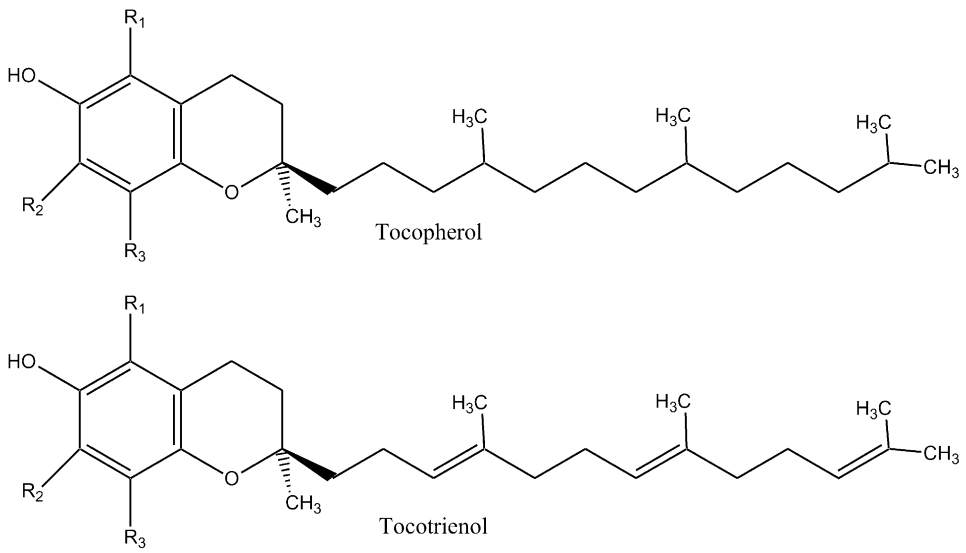

Fig. 1. General molecular structures of tocopherol and tocotrienol. aromatic substituents (R_1, R_2, and R_3) are specified in Table 1.

Table 1
Extent of methyl substitutions of the tocopherol and tocotrienol families

	R_1	R_2	R_3
α	Me	Me	Me
β	Me	H	Me
γ	H	Me	Me
δ	H	H	Me

have more precise data to support this traditional assumption [3].

Recently, the selenium analogue of α-tocopherol (Fig. 2) has been suggested [4] as an alternative congener which may be an effective antioxidant. For this reason we wish to study the structure of the chroman ring comparatively with its S and Se congeners.

2. Introduction

2.1. Oxidative stress and Vitamin E

Oxidative stress may be the cause of aging as well as of the origin of numerous degenerative diseases of the human body [5]. About 5% of the inhaled oxygen escapes the redox reactions associated with metabolism [6]. These by-products include the superoxide anion (O_2^-), the hydroperoxyl radical (·OOH), hydrogen peroxide (H_2O_2) and the hydroxyl radical (·OH). These 'reactive oxygen species' (ROS) are all very reactive and therefore short-lived in the body. Normally, there are natural mechanisms defending against free radicals [7], which may be enzymatic or non-enzymatic. If for some reason, these defense mechanisms become weakened then the free radicals can react with cellular structures such as DNA and

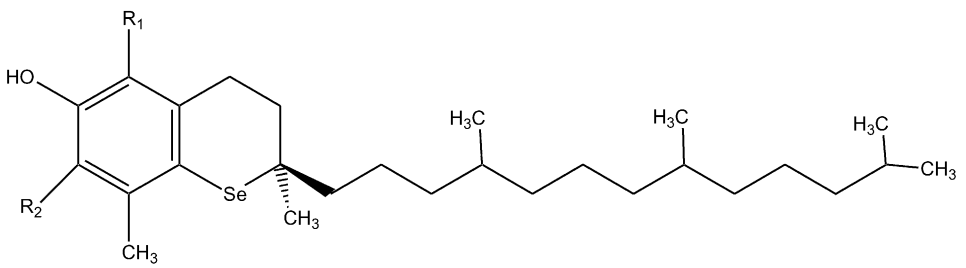

Fig. 2. A general structure of seleno-tocopherol.

proteins, or even destroy membranes through lipid peroxidation [8–10]. It is generally believed that aging and other age-related degenerative diseases such as cardiovascular disorders and cancer can be induced through these pathways [1]. Furthermore, oxidation of a methionine residue has been implicated recently [11] in Alzheimer's disease as a result of oxidative stress.

The potent antioxidant Vitamin E helps to prevent cancer by blocking lipid peroxidation and subsequently reduces the conversion of polyunsaturated fats into free radicals. Lipid peroxidation is a potential initiator not only of cardiovascular diseases but also all forms of cancers, especially of the breast and colon.

Vitamin E works synergistically with Vitamin C and with the mineral selenium, with which it has a special affinity. Selenium and Vitamin E combined constitute a double defense against cancer. As it is not possible to obtain optimally protective quantities of Vitamin E from diet alone, supplements of 400–1600 international units (IU) are recommended daily. Note that 1 mg α-tocopherol = 1.49 IU.

2.2. Structural background

Since it is generally believed that the tail end of tocopherols are only needed to enhance fat solubility [12] it is appropriate to initially concentrate on the fused ring systems (**II**, **III**, **IV**). Compound **III** and **IV** are the sulphur and selenium containing congeners respectively of chroman (**II**).

In a previous paper [13] the geometry of the chroman ring (**II**) as well as its S and Se containing congeners were studied. In the present paper, the effect of the methyl groups introduced to the aromatic ring will be reported. In a subsequent paper [14] the effect of the substituents in α-position of the heteroatom, namely methyl and ethyl, were examined using isodesmic reactions. In the same paper, the energetics of the aromatic hydroxation were also investigated.

3. Method

Molecular orbital computations were carried out, using the GAUSSIAN98 program package [15], on three families of compounds: chromane (**II**), thiochroman (**III**), and selenochroman (**IV**). Tetralin (**I**) is discussed in previous works [13,14] is omitted here.

Eight structures, the unsubstituted and seven methyl substituted ring structures, were considered for oxygen (**II**), sulphur (**III**), and selenium (**IV**) heteroatoms in the ring. Thus, a total of $3 \times 8 = 24$ structures are reported in the present paper. Of the seven substituted structures four are Vitamin E models (α, β, γ, δ) while the remaining three (E, E*, F), two single and one double methylated ring, respectively, have no relation to Vitamin E.

The definition of the spatial orientation, as well as the numbering of the constituent atomic nuclei, are shown in Fig. 3. The input files were numerically generated, whereby visualization tool was used for this purpose.

Two methods and 2 split-valence basis sets were used, mainly the RHF/3-21G, RHF/6-31G(d) and the B3LYP/6-31G(d) levels of theory. Convergence criteria of 3.0×10^{-4}, 4.5×10^{-4}, 1.2×10^{-3}, and 1.8×10^{-3} were used for the gradients of the root mean square (RMS) Force, Maximum Force, RMS Displacement and Maximum Displacement vectors, respectively. However, only the B3LYP/6-31G(d) results are reported in the present paper.

The stabilization or destabilization exerted by the methyl groups attached to the aromatic ring were studied through isodesmic reactions in which the Me group was transferred from toluene to the aromatic ring of the chroman skeleton, as well as its sulphur and selenium congeners. These isodesmic reactions are shown in Fig. 4. The following B3LYP/6-31G(d) energy values were used for toluene and benzene: (−271.56662) and (−232.248659) hartrees respectively.

4. Results and discussion

4.1. Molecular geometries

A total of twenty-four compounds were subjected to geometry optimizations. Of that total each of the oxygen, sulphur, and selenium containing rings had 8 homologues containing 0, 1, 2 and 3 methyl groups attached to the aromatic ring.

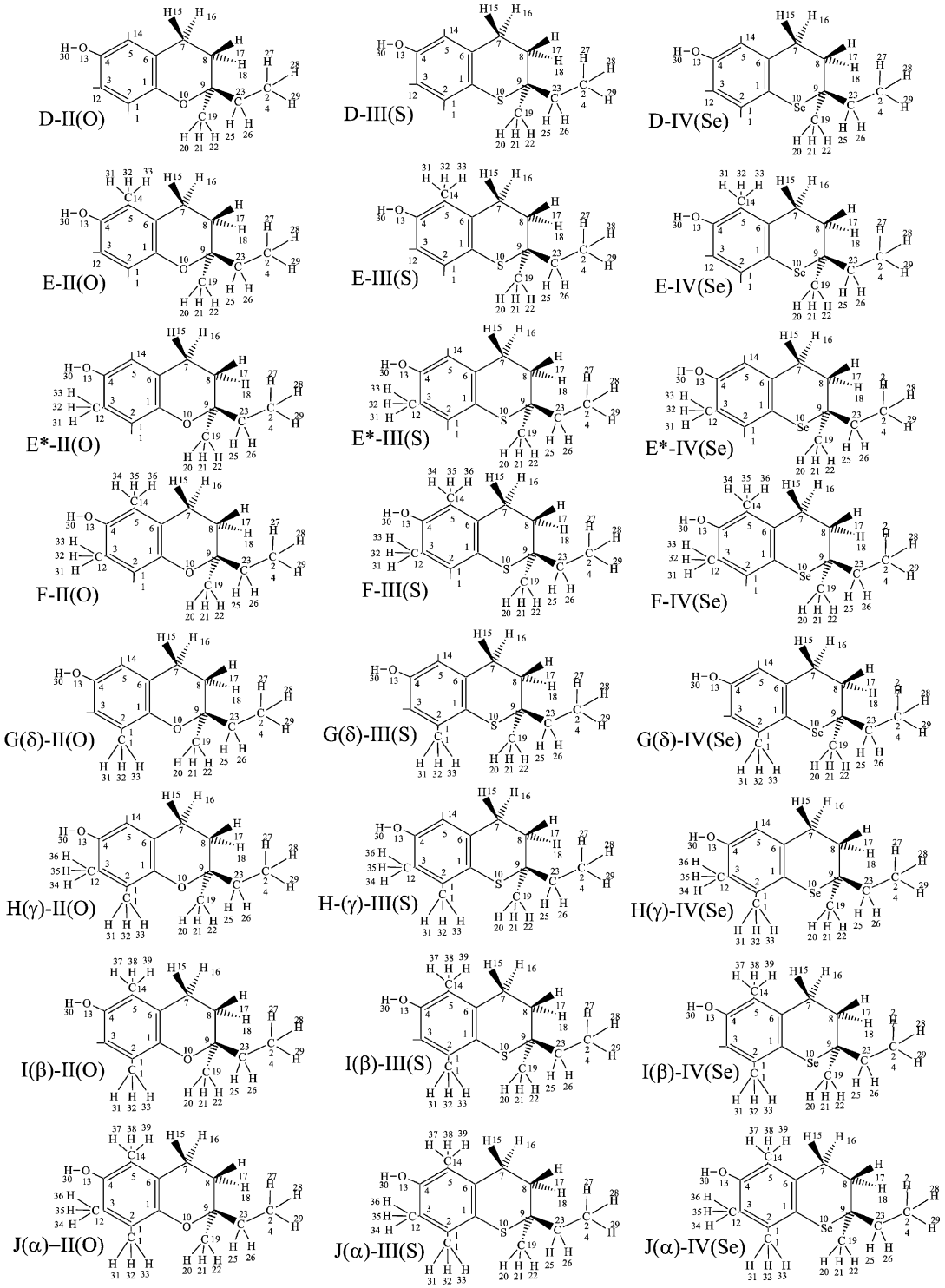

Fig. 3. Structures of the $3 \times 8 = 24$ molecules studied.

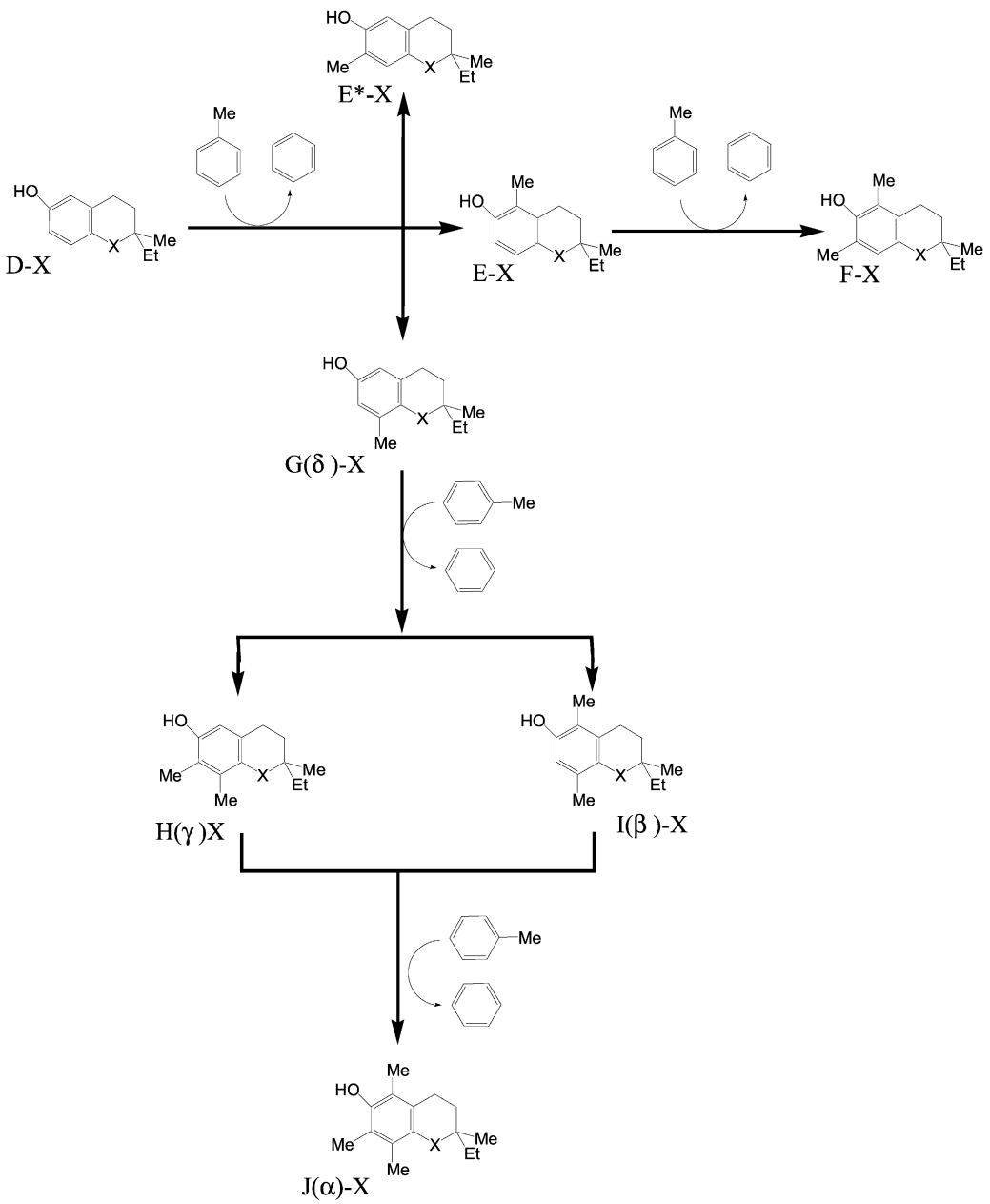

Fig. 4. Isodesmic reactions for the incorporation of aromatic methyl substituents.

These twenty-four structures are shown in Fig. 3 together with their atomic numbering system.

For the tabulation of the optimized geometrical parameters the bond lengths, bond angles, and dihedral angles, for X = O, S and Se are shown in Fig. 4. These parameters are summarized in Tables 2–4, respectively.

The structures of the triple methylated aromatic ring (α-homologues) for the O, S and Se congeners are shown in Fig. 5. The hydroxyl group (OH) was

Table 2
Optimized bond lengths of the 24 structures studied

Model	X	R2	R3	R4	R5	R6	R7	R8	R9	R(9–10)	R10
D	II(O)	1.402	1.388	1.400	1.393	1.402	1.513	1.533	1.541	1.451	1.375
D	III(S)	1.406	1.387	1.399	1.393	1.404	1.518	1.532	1.542	1.862	1.790
D	IV(Se)	1.404	1.387	1.399	1.393	1.404	1.521	1.535	1.540	2.002	1.922
E	II(O)	1.397	1.389	1.397	**1.402**	**1.410**	1.514	1.533	1.539	1.450	1.376
E	III(S)	1.401	1.387	1.396	**1.403**	**1.413**	1.519	1.533	1.540	1.859	1.791
E	IV(Se)	1.399	1.388	1.396	**1.403**	**1.414**	1.522	1.536	1.538	1.997	1.923
E*	II(O)	1.402	1.392	1.408	1.391	1.402	1.512	1.534	1.541	1.450	1.376
E*	III(S)	1.406	1.391	1.407	1.391	1.404	1.518	1.533	1.542	1.862	1.790
E*	IV(Se)	1.404	1.391	1.407	1.391	1.404	1.521	1.535	1.540	2.002	1.922
F	II(O)	1.397	1.393	1.407	**1.401**	**1.410**	1.514	1.534	1.538	1.450	1.376
F	III(S)	1.401	1.391	1.405	**1.401**	**1.413**	1.519	1.534	1.540	1.861	1.792
F	IV(Se)	1.399	1.391	1.405	**1.401**	**1.414**	1.522	1.536	1.538	2.002	1.924
G(δ)	II(O)	**1.411**	1.392	1.400	1.391	1.403	1.513	1.533	1.539	1.449	1.378
G(δ)	III(S)	**1.418**	1.393	1.397	1.391	1.403	1.519	1.531	1.540	1.859	1.795
G(δ)	IV(Se)	**1.415**	1.392	1.397	1.391	1.403	1.522	1.533	1.538	1.997	1.926
H(γ)	II(O)	**1.411**	**1.404**	1.406	1.391	1.398	1.513	1.532	1.540	1.449	1.380
H(γ)	III(S)	**1.418**	**1.405**	1.406	1.390	1.399	1.518	1.530	1.539	1.861	1.797
H(γ)	IV(Se)	**1.415**	**1.404**	1.406	1.390	1.399	1.521	1.533	1.537	2.001	1.928
I(β)	II(O)	**1.406**	1.393	1.398	**1.400**	**1.410**	1.514	1.533	1.537	1.449	1.378
I(β)	III(S)	**1.413**	1.393	1.394	**1.400**	**1.413**	1.520	1.531	1.538	1.858	1.796
I(β)	IV(Se)	**1.409**	1.392	1.394	**1.401**	**1.414**	1.523	1.534	1.536	1.997	1.927
J(α)	II(O)	**1.409**	**1.404**	1.406	**1.398**	**1.406**	1.515	1.532	1.537	1.448	1.381
J(α)	III(S)	**1.414**	**1.404**	1.407	**1.398**	**1.411**	1.523	1.533	1.535	1.857	1.932
J(α)	IV(Se)	**1.414**	**1.404**	1.407	**1.398**	**1.411**	1.523	1.533	1.535	1.997	1.932

Model	X	R11	R12	R13	R14	R15	R16	R17	R18	R19	R30
D	II(O)	1.086	1.085	1.374	1.090	1.097	1.099	1.097	1.096	1.529	0.969
D	III(S)	1.087	1.085	1.370	1.090	1.098	1.099	1.097	1.099	1.537	0.970
D	IV(Se)	1.087	1.085	1.370	1.090	1.098	1.099	1.101	1.096	1.534	0.970
E	II(O)	1.085	1.089	1.379	1.511	1.097	1.100	1.097	1.096	1.529	0.969
E	III(S)	1.087	1.089	1.375	1.512	1.097	1.100	1.096	1.100	1.536	O.969
E	IV(Se)	1.087	1.089	1.375	1.512	1.097	1.100	1.096	1.101	1.534	0.969
E*	II(O)	1.087	1.507	1.377	1.091	1.097	1.099	1.097	1.096	1.530	0.969
E*	III(S)	1.088	1.507	1.373	1.091	1.098	1.099	1.096	1.100	1.537	0.970
E*	IV(Se)	1.088	1.507	1.373	1.091	1.098	1.099	1.096	1.101	1.534	0.970
F	II(O)	1.086	1.511	1.380	1.511	1.097	1.100	1.097	1.097	1.529	0.968
F	III(S)	1.087	1.511	1.377	1.512	1.097	1.100	1.100	1.096	1.536	0.968
F	IV(Se)	1.088	1.511	1.377	1.512	1.097	1.100	1.101	1.096	1.534	0.968
G(δ)	II(O)	1.508	1.086	1.374	1.090	1.097	1.099	1.097	1.096	1.530	0.969
G(δ)	III(S)	1.510	1.086	1.371	1.090	1.097	1.099	1.097	1.100	1.537	0.970
G(δ)	IV(Se)	1.509	1.086	1.370	1.090	1.098	1.099	1.096	1.101	1.534	0.970
H(γ)	II(O)	1.511	1.510	1.378	1.090	1.097	1.099	1.097	1.096	1.530	0.969
H(γ)	III(S)	1.513	1.514	1.376	1.090	1.098	1.099	1.097	1.100	1.537	0.969
H(γ)	IV(Se)	1.511	1.513	1.375	1.090	1.098	1.099	1.096	1.101	1.534	0.969
I(β)	II(O)	1.507	1.090	1.379	1.511	1.097	1.100	1.097	1.096	1.530	0.969
I(β)	III(S)	1.510	1.090	1.376	1.512	1.097	1.100	1.096	1.100	1.537	0.969
I(β)	IV(Se)	1.509	1.090	1.375	1.512	1.097	1.100	1.096	1.101	1.534	0.969
J(α)	II(O)	1.514	1.514	1.380	1.511	1.097	1.100	1.097	1.097	1.529	0.968
J(α)	III(S)	1.513	1.515	1.378	1.512	1.097	1.100	1.096	1.101	1.534	0.968
J(α)	IV(Se)	1.513	1.515	1.378	1.512	1.097	1.100	1.096	1.101	1.534	0.968

Table 3
Optimized bond angles of the 24 structures studied

Model	X	A3	A4	A5	A6	A(5–6–1)	A(6–1–2)	A7	A(7–6–1)	A8	A9	A(10–9–8)	A(1–10–9)	A10
D	II(O)	120.81	119.65	119.53	121.40	118.57	120.02	121.32	120.10	110.79	112.20	109.02	118.45	123.68
D	III(S)	121.58	119.28	119.47	121.78	118.52	119.34	118.16	123.29	115.36	114.99	107.95	102.74	124.56
D	IV(Se)	121.71	119.11	119.49	121.87	118.37	119.44	117.11	124.50	117.39	115.86	106.39	98.87	123.95
E	II(O)	120.00	120.18	120.60	119.11	119.80	120.28	120.75	119.44	111.47	112.42	108.70	118.63	123.83
E	III(S)	120.76	119.77	120.72	119.33	119.66	119.72	117.91	122.41	116.45	115.32	107.20	102.47	124.87
E	IV(Se)	120.79	119.62	120.79	119.33	119.51	119.91	117.09	123.38	118.36	116.24	105.79	98.81	124.40
E*	II(O)	121.90	117.71	120.58	121.59	117.97	120.25	121.72	120.31	110.63	112.21	109.08	118.37	123.67
E*	III(S)	122.70	117.34	120.54	121.97	117.93	119.53	118.40	123.65	115.38	114.92	107.85	102.43	124.41
E*	IV(Se)	122.80	117.19	120.54	122.04	117.81	119.62	117.42	124.75	117.23	115.80	106.54	98.86	123.89
F	II(O)	121.07	118.30	121.52	119.35	118.79	121.09	121.15	120.15	111.45	112.33	108.95	118.75	123.77
F	III(S)	121.83	117.90	121.62	119.57	118.95	120.11	118.23	123.68	116.37	115.24	108.13	103.36	124.78
F	IV(Se)	122.00	117.75	121.65	119.59	118.68	120.30	117.34	124.73	118.23	116.25	106.76	99.14	124.34
G(δ)	II(O)	118.72	120.91	119.67	120.80	119.22	120.51	121.05	119.63	110.91	112.00	108.56	118.28	123.37
G(δ)	III(S)	119.39	120.81	119.49	121.24	119.10	119.94	117.35	122.65	115.63	114.58	107.15	102.27	123.70
G(δ)	IV(Se)	119.62	120.48	119.55	121.35	119.02	119.97	116.57	123.63	117.51	115.57	105.78	98.65	123.50
H(γ)	II(O)	119.83	118.86	120.63	121.22	118.36	121.08	121.00	120.63	111.02	111.81	108.88	119.03	122.51
H(γ)	III(S)	120.51	118.27	120.85	121.65	118.18	120.54	117.61	124.20	115.50	114.38	108.21	103.51	123.17
H(γ)	IV(Se)	120.70	118.01	120.88	121.73	117.91	120.75	116.95	125.12	117.26	115.45	107.07	99.80	123.04
I(β)	II(O)	117.93	121.41	120.74	118.54	120.00	121.34	120.50	119.49	111.65	112.12	108.47	118.77	123.48
I(β)	III(S)	118.65	121.29	120.70	118.82	120.11	120.38	117.15	122.73	116.65	114.87	107.34	103.10	124.05
I(β)	IV(Se)	118.77	121.00	120.83	118.84	119.83	120.70	116.51	123.64	118.56	115.92	106.04	99.15	123.88
J(α)	II(O)	118.70	119.44	121.92	118.68	119.65	121.56	120.30	120.04	111.89	111.94	108.34	119.03	122.45
J(α)	III(S)	119.42	118.52	122.45	118.95	119.39	121.20	116.52	123.42	118.64	115.67	107.35	103.43	123.00
J(α)	IV(Se)	119.43	118.52	122.46	118.95	119.13	121.46	116.52	124.34	118.64	115.66	106.07	99.41	122.99

(*continued on next page*)

Model	X	A11	A12	A13	A14	A15	A16	A17	A18	A19	A23	A24	A30
D	II(O)	118.36	121.14	117.51	119.76	110.07	110.08	109.37	110.67	110.26	111.66	115.16	108.66
D	III(S)	119.15	121.30	117.59	119.50	108.88	108.84	109.65	108.55	109.16	111.17	116.34	108.81
D	IV(Se)	119.18	121.38	117.62	119.35	108.43	108.27	109.65	107.71	109.70	112.27	115.88	108.80
E	II(O)	118.81	119.87	121.52	120.03	110.18	110.05	109.27	110.54	110.32	111.66	115.15	108.30
E	III(S)	119.59	120.09	121.38	119.42	109.09	108.76	109.61	108.23	109.36	111.17	116.38	108.44
E	IV(Se)	119.69	120.17	121.33	119.24	108.63	108.31	109.58	107.41	109.83	112.24	115.89	108.42
E*	II(O)	118.01	122.11	116.82	119.53	110.14	110.23	109.33	110.71	110.24	111.63	115.12	108.56
E*	III(S)	118.80	122.31	116.89	119.28	108.95	108.90	109.67	108.56	109.24	111.14	116.32	108.73
E*	IV(Se)	118.85	122.36	116.91	119.19	108.48	108.43	109.65	107.77	109.70	112.17	115.93	108.74
F	II(O)	118.37	121.11	121.16	120.00	110.17	110.15	109.35	110.54	110.43	111.68	115.16	108.80
F	III(S)	119.21	121.35	121.01	119.39	109.12	108.79	109.68	108.24	109.42	111.18	116.36	108.87
F	IV(Se)	119.20	121.42	120.96	119.20	108.70	108.36	109.56	107.46	109.80	112.23	115.90	108.85
G(δ)	II(O)	119.83	120.36	117.32	120.09	109.94	110.11	109.39	110.74	110.32	111.60	115.27	108.55
G(δ)	III(S)	121.18	120.39	117.49	119.84	108.64	108.86	109.71	108.64	109.31	111.20	116.30	108.70
G(δ)	IV(Se)	120.48	120.60	117.50	119.68	108.25	108.33	109.72	107.79	109.73	112.24	115.90	108.71
H(γ)	II(O)	120.08	120.92	117.77	119.73	109.95	110.10	109.49	110.77	110.25	111.61	115.31	108.26
H(γ)	III(S)	119.12	122.45	117.85	119.44	108.64	109.01	109.77	108.74	109.32	111.13	116.39	108.37
H(γ)	IV(Se)	118.54	122.45	117.82	119.31	108.23	108.57	109.69	107.87	109.70	112.18	115.90	108.39
I(β)	II(O)	120.33	119.09	121.27	120.37	110.04	110.11	109.41	110.57	110.49	111.62	115.29	108.27
I(β)	III(S)	121.73	119.16	121.23	119.56	108.83	108.84	109.72	108.35	109.48	111.22	116.38	108.37
I(β)	IV(Se)	121.16	119.36	121.16	119.39	108.43	108.32	109.68	107.47	109.87	112.27	115.84	108.36
J(α)	II(O)	119.78	122.02	121.04	120.26	110.00	109.97	109.46	110.62	110.39	111.71	115.29	108.89
J(α)	III(S)	118.09	124.06	120.79	119.43	108.38	108.32	109.73	107.56	109.91	112.32	115.84	109.15
J(α)	IV(Se)	118.10	124.06	120.79	119.43	108.37	108.32	109.73	107.55	109.92	112.32	115.84	109.14

Table 4
Optimized dihedral angles of the 24 structures studied

Model	X	D(3–2–1–6)	D4	D5	D6	D(1–6–5-4)	D7	D(10–1–2–3)	D(8–7–6–1)	D9	D(10–9–8–7)	D(1–10–9–8)	D(6–1–10–9)	D8
D	II(O)	0.17	0.17	−0.37	0.20	0.14	−179.77	178.49	−16.77	44.81	−58.22	43.10	−15.77	163.13
D	III(S)	−0.91	0.94	−0.29	−0.41	0.44	178.74	176.78	−19.56	53.48	−65.15	42.74	−17.02	162.22
D	IV(Se)	−0.81	0.55	−0.03	−0.24	−0.03	178.40	178.13	−16.03	53.45	−67.51	45.10	−17.53	165.64
E	II(O)	−0.10	0.80	−0.53	−0.48	1.17	−178.87	178.47	−15.30	43.78	−57.92	43.83	−16.35	164.73
E	III(S)	−0.49	1.07	−1.00	−1.05	1.62	179.99	177.75	−15.35	50.75	−65.58	45.17	−17.71	166.32
E	IV(Se)	−1.04	1.30	−0.33	−1.00	1.15	179.94	178.43	−12.73	51.44	−67.59	46.35	−18.22	168.53
E*	II(O)	0.38	0.08	−0.39	0.25	0.20	−179.56	178.67	−16.61	44.77	−58.31	43.01	−15.49	163.15
E*	III(S)	−0.21	0.33	−0.11	−0.24	0.36	178.69	177.60	−17.97	52.32	−65.61	44.02	−16.87	163.79
E*	IV(Se)	−0.79	0.58	−0.07	−0.22	0.04	178.48	178.29	−16.09	53.53	−67.46	44.84	−17.11	165.57
F	II(O)	0.69	0.56	−0.52	−0.42	0.22	−178.68	179.09	−16.62	43.10	−58.35	42.93	−15.08	165.85
F	III(S)	0.30	0.95	−0.26	−1.03	0.35	−180.03	178.22	−19.38	50.19	−64.89	42.12	−14.49	167.12
F	IV(Se)	−0.09	0.88	−0.14	−0.90	0.04	−180.08	178.78	−16.85	51.02	−67.04	43.94	−15.94	168.99
G(δ)	II(O)	0.33	−0.08	−0.46	0.38	1.30	−179.50	179.01	−14.12	45.05	−58.50	45.09	−17.08	163.09
G(δ)	III(S)	−0.38	0.14	−0.35	0.09	1.60	178.98	178.06	−14.57	53.76	−65.86	45.82	−18.11	162.05
G(δ)	IV(Se)	−0.67	0.16	−0.14	0.03	1.05	178.67	178.77	−12.18	54.26	−67.72	46.69	−18.45	164.61
H(γ)	II(O)	0.05	0.48	−0.65	0.28	0.25	180.41	178.22	−16.57	44.67	−16.57	−58.43	−16.36	163.26
H(γ)	III(S)	0.71	0.01	−0.50	0.29	0.43	179.21	178.45	−19.39	53.90	−19.39	−65.01	−14.11	161.91
H(γ)	IV(Se)	−0.31	0.59	−0.47	0.06	0.23	178.96	178.19	−18.59	55.51	−18.59	−66.50	−14.59	162.77
I(β)	II(O)	1.16	0.02	−0.58	−0.04	1.19	−178.64	179.67	−14.51	43.76	−14.51	−58.48	−16.11	165.31
I(β)	III(S)	0.63	0.55	−0.62	−0.52	1.68	−179.42	179.22	−15.13	51.42	−15.13	−65.61	−15.66	165.98
I(β)	IV(Se)	0.06	0.64	−0.44	−0.47	1.15	−179.83	179.62	−12.71	51.81	−12.71	−67.40	−16.87	168.31
J(α)	II(O)	−0.26	1.35	−1.06	−0.40	1.46	−178.76	178.32	−14.04	42.84	−58.47	46.24	−18.20	166.18
J(α)	III(S)	−0.94	1.97	−1.59	−0.38	2.70	−179.14	177.16	−15.07	51.46	−65.31	45.20	−16.77	168.67
J(α)	IV(Se)	−0.48	1.99	−1.61	−0.36	1.89	−179.17	178.71	−12.44	51.45	−67.32	46.16	−17.08	168.67

Model	X	D(9–10–1–2)	D10	D12	D13	D14	D15	D16	D17	D18	D19	D23	D24	D30
D	II(O)	165.98	−178.52	−179.93	−179.82	−179.44	41.49	−74.76	−74.70	167.57	−172.28	62.36	−179.94	179.79
D	III(S)	166.43	−177.28	−179.61	179.65	179.88	39.98	−74.40	−68.87	174.83	−179.41	57.01	173.70	179.88
D	IV(Se)	163.59	−178.32	−179.82	179.86	179.78	43.17	−70.37	−69.27	174.92	178.89	53.19	179.19	−179.82
E	II(O)	165.14	−179.35	−179.71	−179.60	179.83	43.30	−72.49	−75.67	166.76	−171.84	62.75	−179.11	−1.63
E	III(S)	164.16	−178.92	−179.73	179.46	179.15	44.27	−69.54	−71.63	172.37	−179.73	56.47	174.30	−0.63
E	IV(Se)	162.34	−179.63	−179.62	179.46	179.13	46.26	−66.81	−71.40	173.10	−178.90	53.19	−179.30	−0.47
E*	II(O)	166.28	−178.67	−179.99	179.86	−179.35	41.62	−74.73	−74.67	167.55	−172.35	62.34	−179.90	179.76
E*	III(S)	165.45	−177.75	−179.85	179.86	179.99	41.53	−72.83	−69.93	173.72	−179.85	56.53	173.63	−179.93
E*	IV(Se)	163.85	−178.55	−179.72	179.85	179.81	43.17	−70.48	−69.22	174.95	178.93	53.33	179.01	−179.85
F	II(O)	166.57	−179.84	−179.78	179.77	179.93	44.41	−71.50	−76.25	166.11	−172.39	62.11	−179.41	−3.06
F	III(S)	167.67	−179.20	−179.64	179.57	179.13	44.99	−68.86	−72.13	171.81	180.00	56.17	174.40	−1.40

(*continued on next page*)

Table 4
(*Continued*)

Model	X	D(9–10–1–2)	D10	D12	D13	D14	D15	D16	D17	D18	D19	D23	D24	D30
F	IV(Se)	165.25	−179.71	−179.69	179.62	179.16	46.73	−66.40	−71.74	172.72	178.69	53.03	−179.45	−0.36
G(δ)	II(O)	164.28	−179.03	−180.06	179.84	−179.25	41.46	−74.71	−74.37	167.76	−172.40	62.19	178.27	179.74
G(δ)	III(S)	163.54	−178.30	−179.92	179.84	−179.68	39.83	−74.35	−68.50	175.09	−179.08	57.30	173.42	179.77
G(δ)	IV(Se)	162.15	−178.79	−179.91	179.96	−179.92	42.18	−71.30	−68.50	175.65	179.19	53.56	178.89	179.94
H(γ)	II(O)	165.49	−178.47	−179.61	179.61	−179.33	41.54	−74.59	−74.60	167.41	−172.34	62.38	179.68	178.99
H(γ)	III(S)	168.23	−178.49	−179.82	179.82	−179.40	39.74	−74.51	−68.25	175.20	−179.24	57.21	173.05	179.45
H(γ)	IV(Se)	166.95	−178.50	−179.40	179.77	−179.72	40.48	−73.11	−67.30	176.82	179.67	54.24	178.54	179.35
I(β)	II(O)	165.42	−180.17	−180.08	179.68	−179.75	43.82	−71.90	−75.56	166.73	−172.39	62.10	179.14	−1.60
I(β)	III(S)	165.80	−180.23	−179.84	179.49	−179.62	43.99	−69.68	−70.82	173.03	−179.73	56.41	173.96	−1.14
I(β)	IV(Se)	163.58	−180.49	−179.81	179.62	179.53	46.04	−66.88	−71.00	173.44	178.82	53.12	−179.66	−0.89
J(α)	II(O)	163.22	−179.67	−179.00	179.51	179.96	44.54	−71.00	−76.30	165.89	−172.23	62.30	−179.68	−6.33
J(α)	III(S)	165.17	−180.62	−177.73	179.13	179.91	46.34	−66.60	−71.23	173.13	179.00	53.14	179.90	−6.16
J(α)	IV(Se)	163.74	−180.62	−177.74	179.10	179.88	46.34	−66.56	−71.23	173.13	179.01	53.16	179.89	−6.30

almost always coplanar with the aromatic ring (within ± 3 degrees), deviating at most up to ± 7 degrees as a result of the steric 'congestion' arising from the six-fold substitution on the benzene ring. The orientation of the OH was such that it pointed away from the adjacent CH_3 group, whenever the structure would permit. Table 4 shows this in column D30, with an optimized *anti*-orientation for the OH in models D, E*, G(δ) and H(γ) and a *syn*-orientation in models E, F, I(β) and J(α), irrespective of the starting orientation.

The variables in Tables 2 and 3 also show structural trends, whereby the C–C bonds adjacent to the C carrying the Me substitution are lengthened, irrespective of heteroatom substitution. In contrast, the bond angles change with heteroatom substitution, irrespective of Me substitution; summarized in Table 3. Several other structural trends of smaller magnitude are also apparent but not elaborated upon here.

4.2. Molecular energetics

The computed total energies are summarized in Table 5. The energies of stabilization calculated according to the scheme given in Fig. 6 are tabulated in Table 6. The graphical representation of these results is shown in Fig. 7.

A comparison of the relative activity of z-tocopherols ($z = \alpha, \beta, \gamma, \delta$) as measured by $\ln\{[A_z]/[A_\alpha]\}$ may be calculated using the calculated energy of stabilization (ΔE_z).

$$\ln\{[A_z]/[A_\alpha]\} = F(\Delta E_z)$$

The numerical values are given in Table 7. Such a plot, shown in Fig. 8, suggests that there may be an exponential relationship interconnecting either one, or both, of the paths shown below:

$$\delta \rightarrow \gamma \rightarrow \alpha$$

$$\delta \rightarrow \beta \rightarrow \alpha$$

For this reason the relationship is converted to the following form:

$$y = 1.0 - \ln\{[A_z]/[A_\alpha]\} = f(\Delta\Delta E_z) = f(x)$$

where $x = \Delta\Delta E_z = \Delta E_\alpha - \Delta E_z$

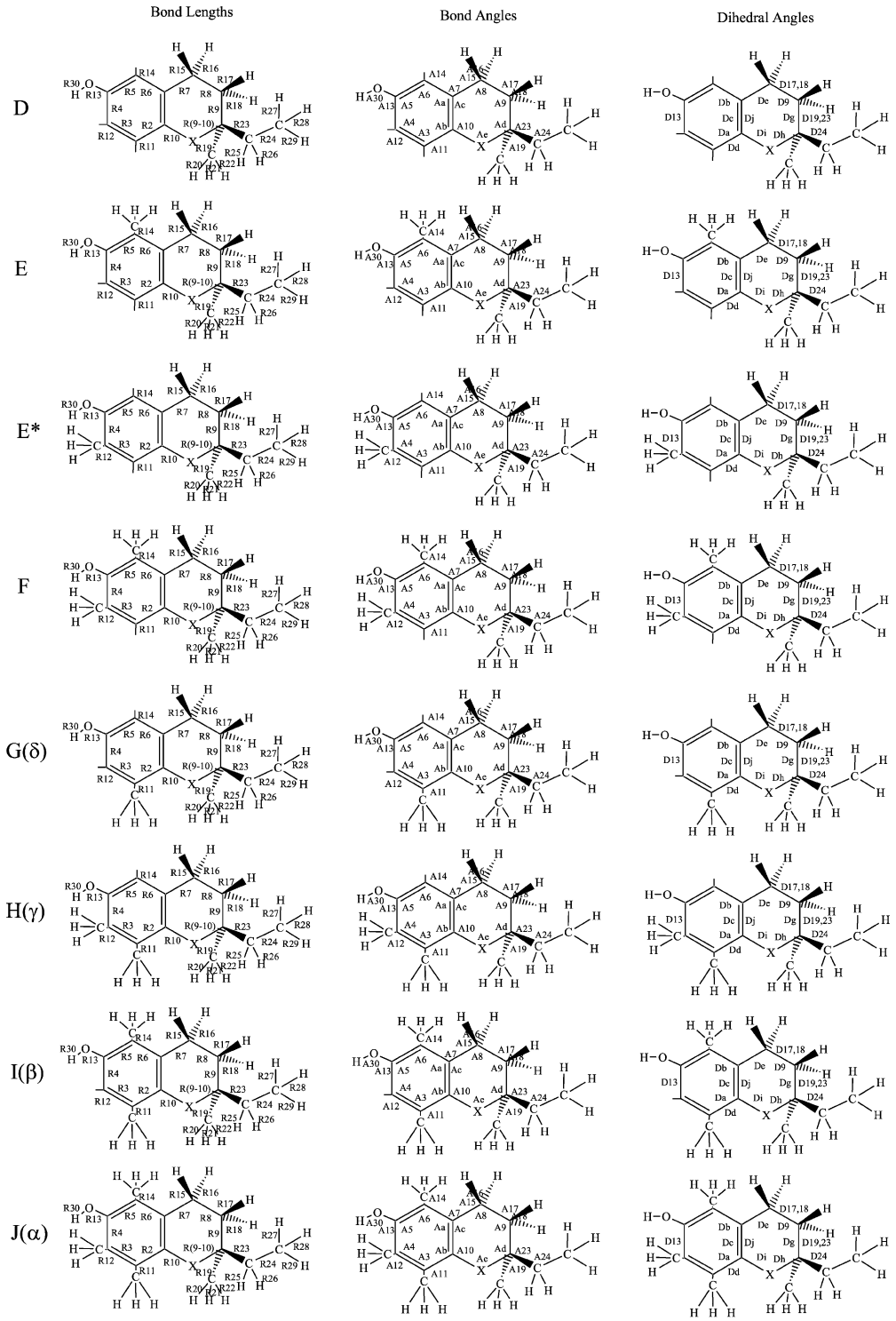

Fig. 5. Numbering of bond lengths, bond angles and dihedral angles for the eight structures investigated. X may be O, S or Se.

Table 5
Total energies (hartrees) computed for the 24 optimized structures

	II(O)	III(S)	IV(Se)
D	−617.36422	−940.33278	−2941.52972
E	−656.68052	−979.64832	−2980.84517
E*	−656.68287	−979.65164	−2980.84873
F	−695.99823	−1018.96614	−3020.16312
G(δ)	−656.68269	−979.65015	−2980.84932
H(γ)	−695.99754	−1018.96431	−3020.16386
I(β)	−695.99890	−1018.96543	−3020.16461
J(α)	−735.31221	−1058.27721	−3059.47685

The exponential function obtained for the first (δ → γ → α) of these two paths is shown in Fig. 9. While the fit shown in Fig. 9 was fairly good ($R^2 = 0.99$), the other path (δ → β → α) did not allow a fit to a reasonably good exponential function. With respect to the exponential fit obtained for the δ → γ → α, it seemed that β was estimated to be less stable by 1.750 kcal mol^{-1}.

While we have no explicit structured explanation for this derivation, it should be pointed out that the two methyl groups in the β form are in *para*-position with respect to each other. This would suggest that any electronic effects the Me-groups might exert on the aromatic ring would be cancelled, or nearly cancelled, by vectorial addition. For this reason, we collected all the computed dipole moments in Table 8, which is hoped to reveal the polarity of the various forms.

This data reveals that homologous E, F, β, and α have dipole moments less than 1 Debye due to partial cancellation of electronic effects while homologous D, E*, δ and γ have dipoles over 2 Debye. This is the case for all three congeners.

The question of arithmetical additivity in the stabilization or destabilization effects of these Me-groups on the chroman ring and its congeners has to be examined at least in passing. The results are shown in Table 9.

It appears that the stabilization energies are not additive, indicating that in addition to the electronic effects, steric 'congestion' occurs when the methyl groups are proximally introduced. Such an observation has been noted by Hammett [16] in studying chemical reactivity. When the substituents were far away from the reaction site, good correlation was observed between reactivity and structure. Alternatively, when substituents were placed in an *ortho*-position, the points scattered randomly and did not correlate at all. Thus, the Hammett's linear free-energy relationship is valid only when the substituents are far away from the reaction site.

For the I(β) isomers, where the two Me-groups are in *para*-position with respect to each other,

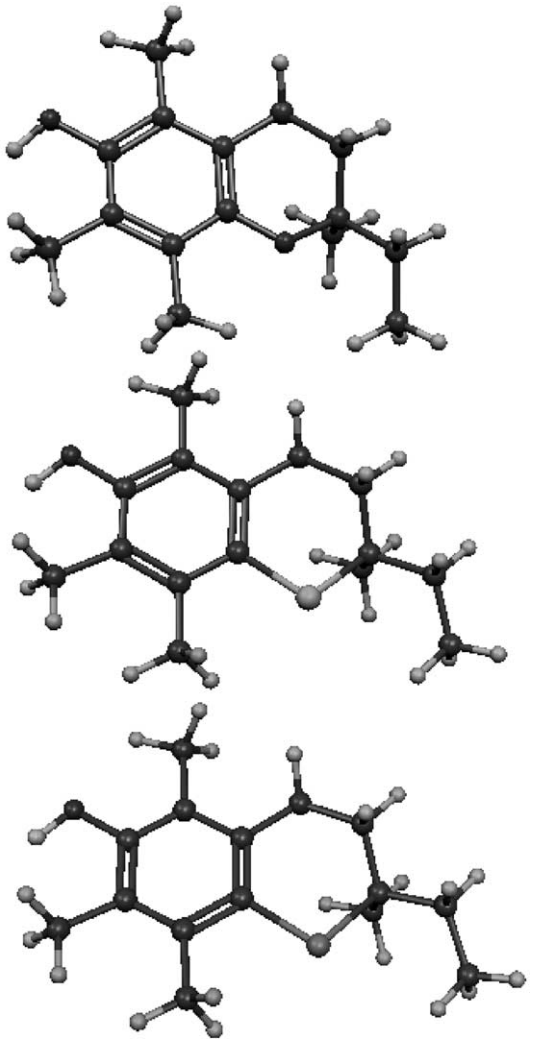

Fig. 6. Three optimized structures of the shortened sidechain model of the α-tocopherol.

Table 6
Energy of stabilization associated with single or multiple methyl group transfers

	II(X = O)		III(X = S)		IV(X = Se)	
	Single step	Accumulated steps	Single step	Accumulated steps	Single step	Accumulated steps
XD → XE	1.043	1.043	1.520	1.520	1.576	1.576
XD → XE*	−0.430	−0.430	−0.562	−0.562	−0.658	−0.658
XE → XF	0.161	1.204	0.090	1.610	0.007	1.583
XD → XG(δ)	−0.320	−0.320	0.372	0.372	−1.028	−1.028
XG(δ) → XH(γ)	1.952	1.633	2.386	2.759	2.147	1.118
XG(δ) → XI(β)	1.100	0.781	1.684	2.056	1.676	0.648
XI(β) → XJ(α)	2.918	3.699	3.879	5.934	3.587	4.235

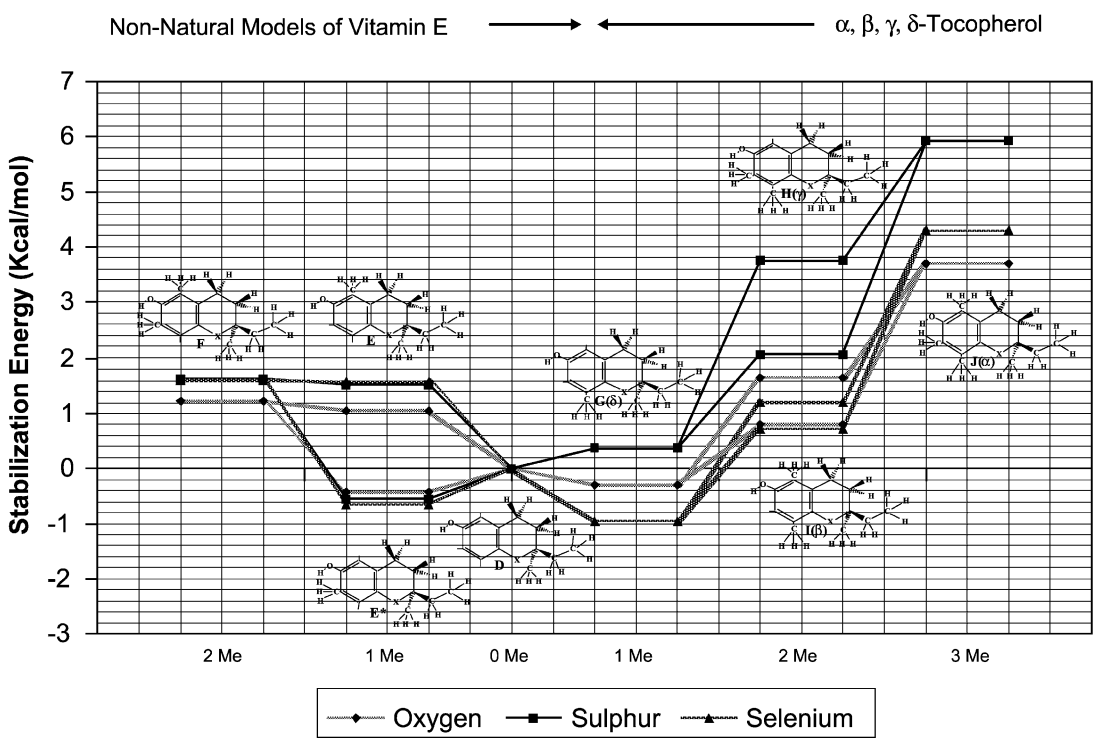

Fig. 7. Computed stabilization energies.

Table 7
Relative biological activity of tocopherols and computed stabilization energy values of model compounds

Relative activity[a]				Computed stabilization energy	
z-tocopherol	$[A_z]/[A_\alpha]$	$\ln\{[A_z]/[A_\alpha]\}$	$1\text{-}\ln\{[A_z]/[A_\alpha]\}$	ΔE_z	$\Delta\Delta E_z = \Delta E_\alpha - \Delta E_z$
α	1.000	0.000	0.000	3.698	0.000
β	0.570	−0.562	1.562	0.780	2.918
γ	0.370	−0.994	1.994	1.634	2.054
δ	0.014	−4.269	5.269	−0.318	4.016

[a] Activities were taken from Ref. [3], also quoted in Table 3 of Ref. [13].

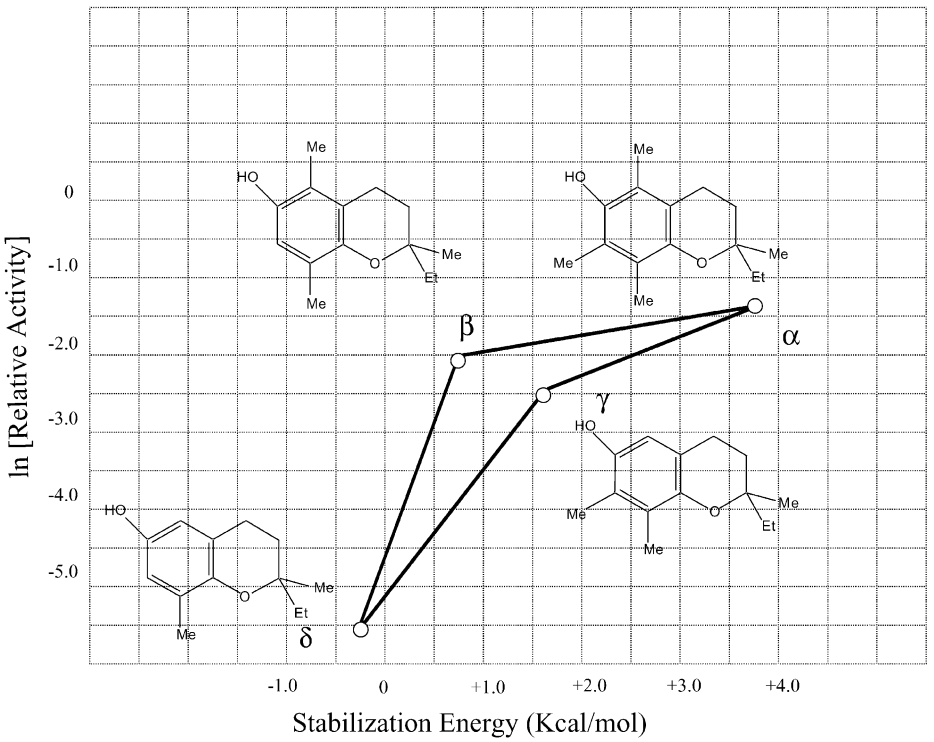

Fig. 8. Relative activity of tocopherol vs stabilization energies of tocopherol model.

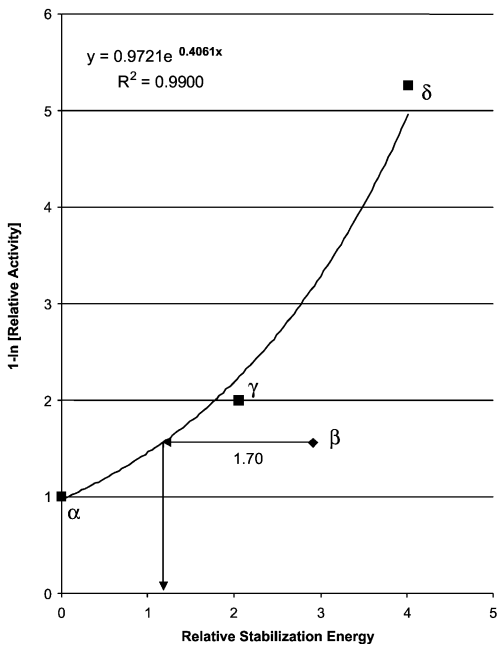

Fig. 9. Modified relative activity of tocopherol vs relative stabilization energies of tocopherol model.

the discrepancy is within 0.2 kcal mol^{-1}. For the F isomers, where the Me groups are in *meta*-position with respect to each other, the discrepancy is within 0.7 kcal mol^{-1}. In these two cases the Me groups are virtually independent of each other. However, when two Me groups are in an *ortho*-orientation, the discrepancy is 4.3 kcal mol^{-1}, indicating that steric destabilizing congestion dominates over electronic stabilizing effects.

Table 8
Dipole moments of optimized structures

Homologue	II(O) $\|\mu\|$ (Debye)	III(S) $\|\mu\|$ (Debye)	IV(Se) $\|\mu\|$ (Debye)
D	2.7878	3.0528	2.9677
E	0.5764	0.8893	0.8484
E*	2.4686	2.8062	2.7313
F	0.436	0.8416	0.8323
G(δ)	2.6586	2.7262	2.6327
H(γ)	2.3264	2.4493	2.3562
I(β)	0.7322	0.5561	0.5327
J(α)	0.6622	0.6971	0.6876

Table 9
Energies of stabilizations calculated as a sum of components or through direct computations

	II(X = O)		III(X = S)		IV(X = Se)	
	Sum of Components	Directly Calculated	Sum of Components	Directly Calculated	Sum of Components	Directly Calculated
XE + XE* → XF	0.613	1.205	0.958	1.613	0.918	1.581
XG(δ) + XE* → XH(γ)	−0.750	1.634	−0.190	3.758	−1.094	1.183
XG(δ) + XE → XI(β)	0.723	0.780	1.892	2.055	0.548	0.712
XI(β) + XE* → XJ(α)	0.350	3.698	1.494	5.933	−0.010	4.301

5. Conclusions

Both Me and heteroatom substitution change the molecular structure of Vitamin E, in terms of bond lengths, bond angles and dihedral angles. The effect of Me substitution was observed predominantly in the case of adjacent bond lengths, while heteroatom substitution influenced bond angles and dihedral angles.

With the exception of the model of β-tocopherol, where the 2 introduced Me groups (*para*-oreintation) nearly cancel their electronic contribution and provide little steric congestion, a general trend was observed with increasing substitution in the following sequence δ → γ → α. The structural contribution is measured by the relative stabilities in kcal mol^{-1} units, with δ being the most stable and α being the least stable. This trend correlated with the logarithmic relative activity of the Vitamin E homologues δ, γ and α, respectively.

This clearly indicates that there is a structural basis for the differing biological activity of the naturally occurring Tocopherol homologues.

Acknowledgements

The authors thank Michelle A. Sahai, Jacqueline M.S. Law, Christopher N.J. Marai and Tania A. Pecora for helpful discussions, and preparation of tables and figures and Graydon Hoare for database management, network support and software and distributive processing development. A special thanks is extended to Andrew M. Chasse for his development of novel scripting and coding techniques, which facilitate a reduction in the number of CPU cycles needed. The pioneering advances of Kenneth P. Chasse, in all composite computer-cluster software and hardware architectures, are also acknowledged. David C.L. Gilbert and Adam A. Heaney are also thanked for CPU time.

References

[1] M. Evans, K.S. Bishop, Science 55 (1922) 650.
[2] J.B. Bauernfeind, Vitamin E: a comprehensive treatise, Marcel Dekker, New York, 1980, pp. 99–167.
[3] B. Weimann, H. Weiser, Am. Clin. Nutr. 53 (1991) 1056S–1060S.
[4] N. Al-Maharik, L. Engman, J. Malmstrom, C. Schiesser, Intramolecular homolytic substitution at selenium: synthesis of novel selenium-containing Vitamin E analogues, J. Org Chem. 66 (2001) 6286–6290.
[5] A.D.N.G. de Grey, The Mitochondrial Free Radical Theory of Aging, R.G. Landes Company, Austin, Teas, 1999.
[6] B. Chance, H. Sies, A. Boveris, Physiological Review 59 (1979) 527.
[7] B.N. Ames, M.K. Shigenaga, in: J.G. Scandalios (Ed.), Molecular Biology of Free Radical Scavenging Systems, Cold Spring Harbor Laboratory Press, New York, 1992, p. 1.
[8] S. Steenken, Chem. Rev. 89 (1979) 503.
[9] K.L. Fong, P.B. McCay, J.L. Poyer, B.H. Misra, B. Keele, J. Biol. Chem. 248 (1973) 7792.
[10] T.I. Mak, W.B. Weglicki, J. Clin. Invst. 75 (1985) 58.
[11] S. Varadarajan, J. Kanski, M. Aksenova, C. Lauderback, D.A. Butterfield, J. Am. Chem. Soc. 123 (2001) 5625.
[12] G.W. Burton, K.U. Ingold, Acc. Chem. Res. 19 (1986) 194.
[13] D.H. Setiadi, G.A. Chass, L.L. Torday, A. Varro, J.Gy. Papp, THEOCHEM (2002) in press.
[14] D.H. Setiadi, G.A. Chass, L.L. Torday, A. Varro, J.Gy. Papp, I.G. Csizmadia, Eur. Phys. J. D (2002) in press.
[15] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam,

A.D. Daniels, K.N. Kudin, M.C. Strain, Ö. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, Gaussian Inc., Pittsburgh PA, 1998.

[16] L.P. Hammtt, J. Am. Chem. Soc. 59 (1937) 96.