

## Vitamin E models

### The effect of heteroatom substitution in 2-ethyl-2-methyl chroman and 2-ethyl-2-methyl-6-hydroxychroman

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**Abstract.** The molecular conformations of shortened molecular models of vitamin E (tocopherol and tocotrienol) and their sulfur and selenium congeners were studied computationally at the DFT level of theory [B3LYP/6-31G(d)]. The sequence of stabilization by the various heteroatoms was found to be the following: O ~ Se > S. On the basis of the present structural results it seems that the seleno-congener of vitamin E is a distinct possibility.

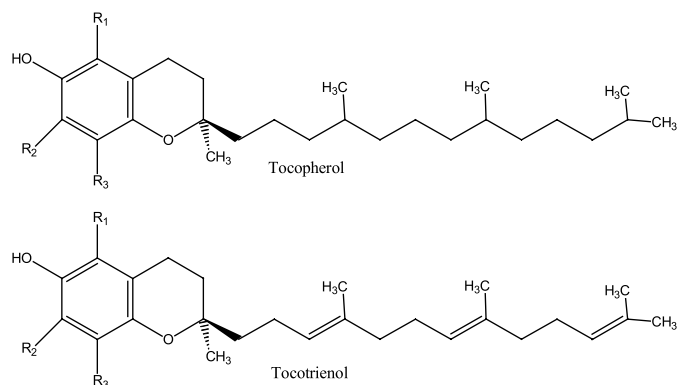
**PACS.** 31.15.Ar Ab initio calculations

## 1 Introduction

It is in human nature to wonder if “Mother Nature” always did the best possible structural arrangement for bioactive molecules, or whether we can improve upon it. The question has been asked in general about antioxidants, and in particular about vitamin E [1,2].

### 1.1 Vitamin E structures

Vitamin E, a term introduced in 1922 [3], does not represent a single compound but includes two families of compounds: tocopherols and tocotrienols. Both families consist of a chroman [benzopyrane] ring structure and a sidechain. The sidechain contains an isoprenoid skeleton, typical of terpenes. Members of the tocopherol family have saturated sidechains, but the same sidechain in the tocotrienol family has three non-conjugated double bonds. For both families, the carbon atom that carries the sidechain is a stereo centre of the *R* configuration. However, the sidechains of tocopherols have two additional



**Fig. 1.** Structures of tocopherols and tocotrienols. Substituents R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are hydrogens or methyl groups.

stereo-centres at their branching points, both of which are of *R* configuration. The structural variations of the two families are shown in Figure 1.

Each of these families has four homologous members, labeled as  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . They differ from each other in the extent of methyl substitution in the aromatic ring. Thus, these are two (2) families of compounds (tocopherol and tocotrienol) and each may come in four (4) homologous forms [4].

Of these  $2 \times 4 = 8$  species, it is  $\alpha$ -tocopherol which is most frequently used, partly because of its commercial

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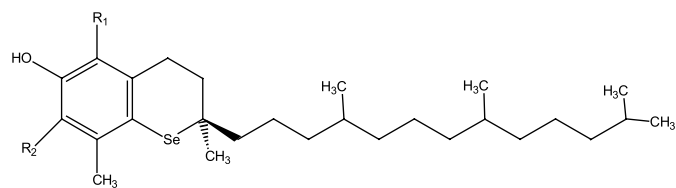


Fig. 2. Seleno-congener of  $\alpha$ -tocopherol.

availability in synthetic form. Of course, the synthetic form is not a pure enantiomer. The effectiveness of the synthetic form has been questioned, without an explanation at the molecular level even though the primary function of vitamin E is an antioxidant rather than taking part in an oxidation reaction. Presently, we have more precise data to support the earlier assumption [5] that the different stereoisomers exhibit different effectiveness of biological activity.

It has recently been suggested [6] that the selenium congener of  $\alpha$ -tocopherol [Fig. 2] may be a very effective antioxidant. Thus, one may ask if the sulphur (S) and selenium (Se) congeners of vitamin E might be more efficient antioxidants than vitamin E itself. The answer to such a question may be decided by studying the redox mechanism of the three congeners containing O, S and Se.

## 1.2 Conformational background

One of the structural problems of vitamin E is associated with the saturated ring fused to the benzene ring. This ring cannot be considered to be cyclohexane, nor any of its heterocyclic analogues in the chair conformation, because it has, at least formally, one carbon-carbon double bond. The so-called “half-chair” conformation had been considered to be the most likely structure and was confirmed by experiment [7–13].

Of the four  $\text{CH}_2$  groups found in tetralin, the two allylic  $\text{CH}_2$  exhibit quasiaxial or pseudoaxial ( $a'$ ) and quasi-equatorial or pseudo-equatorial ( $e'$ ) orientation. The orientation of the central  $\text{CH}_2\text{-CH}_2$  moiety is expected to be close to non-cyclic molecules such as ethane or butane. Thus, the further one moves away from the double bond, the closer one comes to the ideal planar situation. Estimated dihedral angles ( $D_i$ ) are shown in Figure 3.

The ring is expected to exist in two inter-convertible enantiomeric forms, with the transition state for such a ring-flip expected to show some molecular symmetry; interconnecting the two non-super-imposable mirror image (enantiomer) minima on either side. It is tempting to consider the planar structure to be a good candidate for the transition state, but such a conformation could be a higher order critical point. It is more likely that the transition state is a boat conformation. The ring-inversion has been studied computationally in the case of tetralin as well as its oxygen, sulfur and selenium congeners [14].

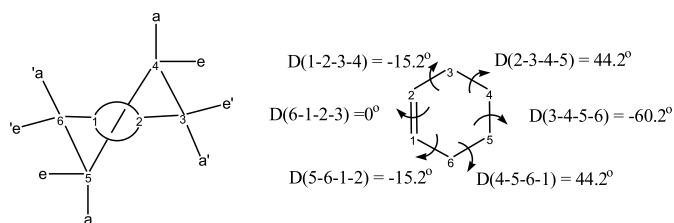


Fig. 3. Previously reported conformation and dihedral angles of cyclohexene.

## 2 Method

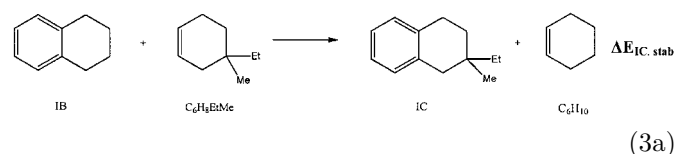
Since it is generally believed that the hydrocarbon tails of tocopherols are only necessary to enhance fat solubility [15] or “affinity” for hydrophobic environs, it is appropriate to concentrate an “activity”-related investigation (antioxidative character) on the fused ring systems, without the tail end.

Molecular orbital computations were carried out using the Gaussian 98 program package [16]. All computations were carried out at the B3LYP/6-31G(d) level of theory. Convergence criteria of  $3.0 \times 10^{-4}$ ,  $4.5 \times 10^{-4}$ ,  $1.2 \times 10^{-3}$  and  $1.8 \times 10^{-3}$  were used for the gradients of the RMS (root mean square) Force, Maximum Force, RMS Displacement and Maximum Displacement vectors, respectively.

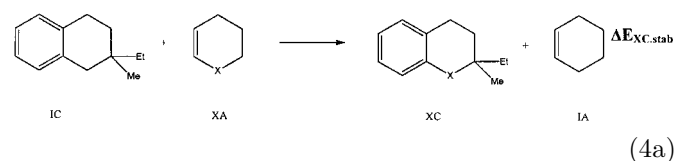
Four families (A, B, C, D) of the four compounds (I, II, III, IV) were studied as shown in Figure 4. All together, sixteen compounds were studied. Compound III and IV are sulfur and selenium congeners of II.

The definition of the spatial orientation of the constituent atomic nuclei shown in Figure 4 was used in numerically generating the input files. No visualization tool was used for any purpose for this work. It should be noted that there are two extra hydrogen atoms in the carbon congeners (*i.e.*  $\text{X} = \text{CH}_2$ ) of IA, IB, IC and ID. The position of these two hydrogen atoms were optimized but omitted from the tabulated data. Key torsional angles are defined in Figure 5.

In order to compare the relative stabilities of the  $\text{X} = \text{O}$ , S and Se congeners, the following three isodesmic reactions were applied.



$$\Delta E_{\text{IC.stab}} = [E(\text{IC}) + E(\text{C}_6\text{H}_{10})] - [E(\text{IB}) + E(\text{C}_6\text{H}_8\text{EtMe})] \quad (3b)$$



$$\Delta E_{\text{XC.stab}} = [E(\text{XC}) + E(\text{IA})] - [E(\text{IC}) + E(\text{XA})] \quad (4b)$$

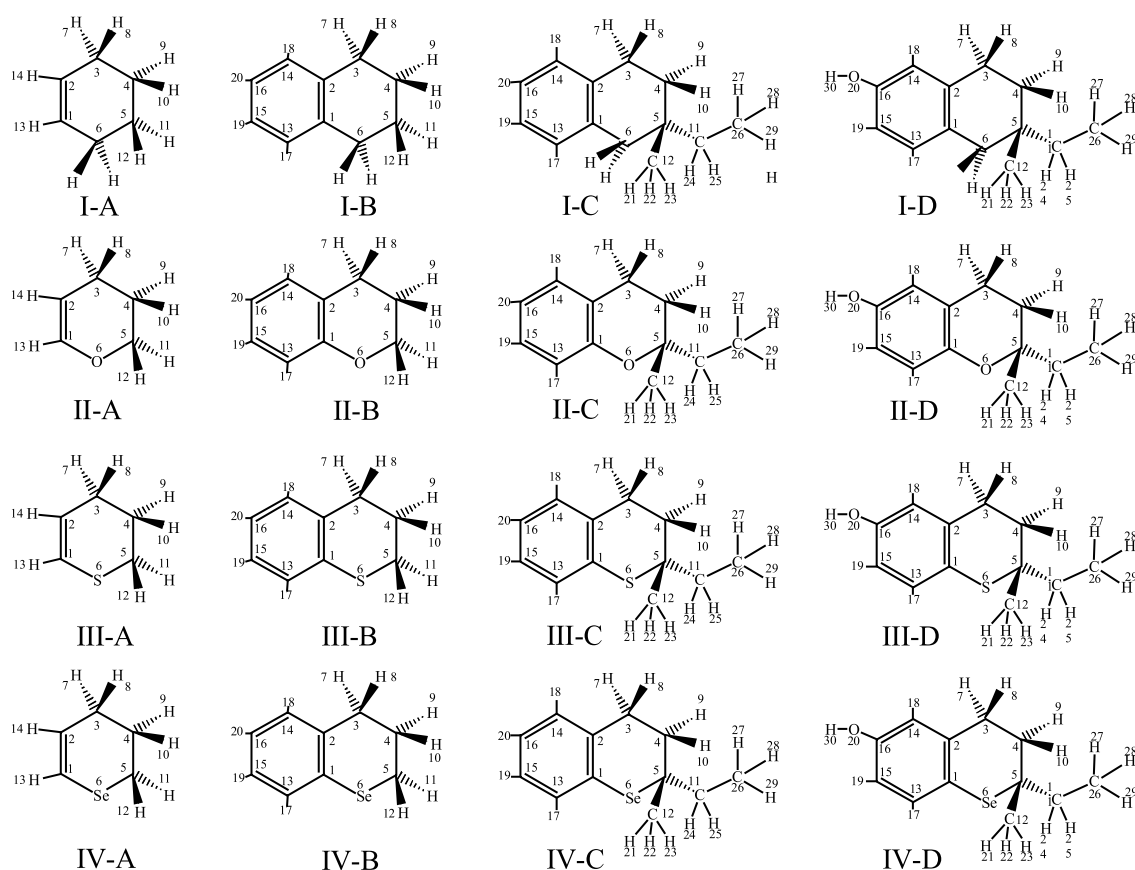
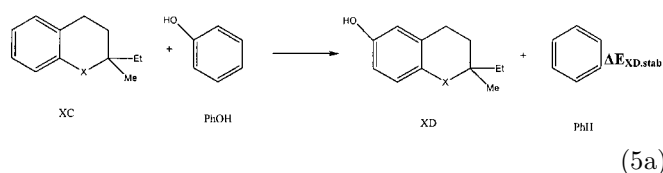


Fig. 4. Atomic numbering of the sixteen compounds studied.

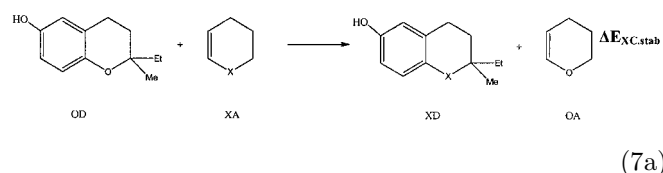


$$\Delta E_{\text{XD.stab}} = [E(\text{XD}) + E(\text{PhH})] - [E(\text{XC}) + E(\text{PhOH})] \quad (5b)$$

The overall stabilization energy is the sum of the two individual stabilization energies

$$\Delta E_{\text{Total.stab}} = \Delta E_{\text{XD.stab}} + \Delta E_{\text{XC.stab}} \quad (6)$$

Replacing oxygen (O) to sulfur (X = S) or selenium (X = Se). We may also obtain isodesmic energies as listed below in equations (7a, 7b)



$$\Delta E_{\text{O} \rightarrow \text{X}} = [E(\text{XD}) + E(\text{OA})] - [E(\text{OD}) + E(\text{XA})] \quad (7b)$$

Where X = S or Se

For the sake of convenience, the variations of geometrical and energetic parameters from O to S to Se were fitted to

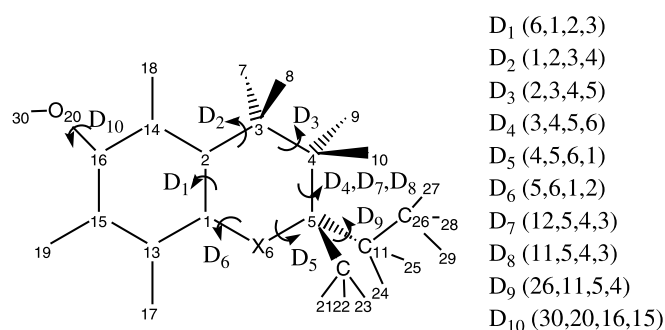


Fig. 5. Definition of key dihedral angles.

quadratic functions, even though no quadratic relationships are assumed to be operative. For such graphical presentation the optimized parameters were plotted against the covalent atomic radii: O = 0.745 Å, S = 1.040 Å and Se = 1.163 Å [8,9].

### 3 Results and discussion

Although computations have been carried out at several levels of theory, only the results obtained at the highest level [B3LYP/6-31G(d)] are reported in this work.

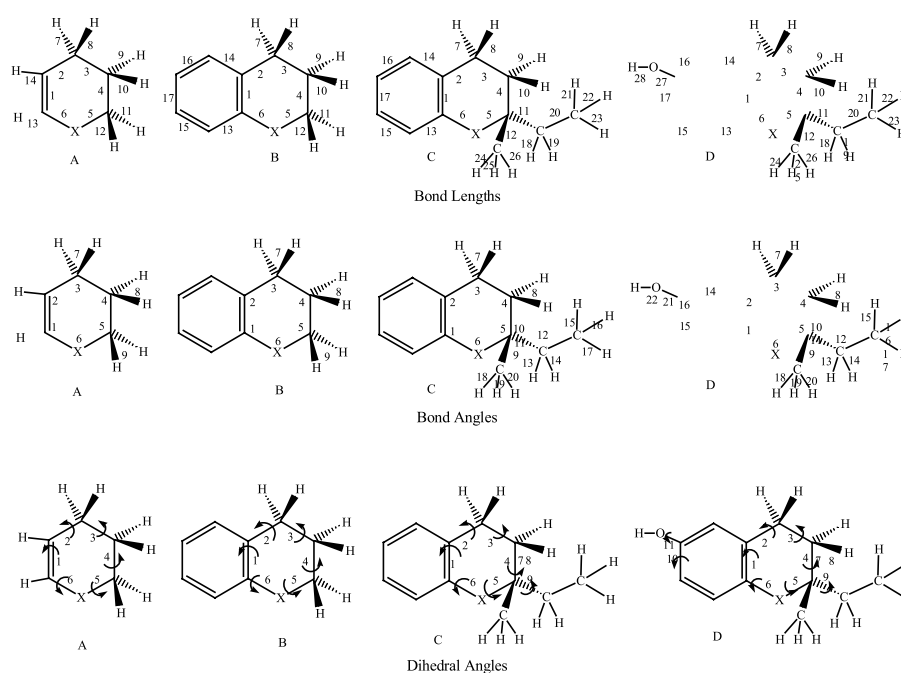


Fig. 6. Labeling of bonds, angles, and dihedrals.

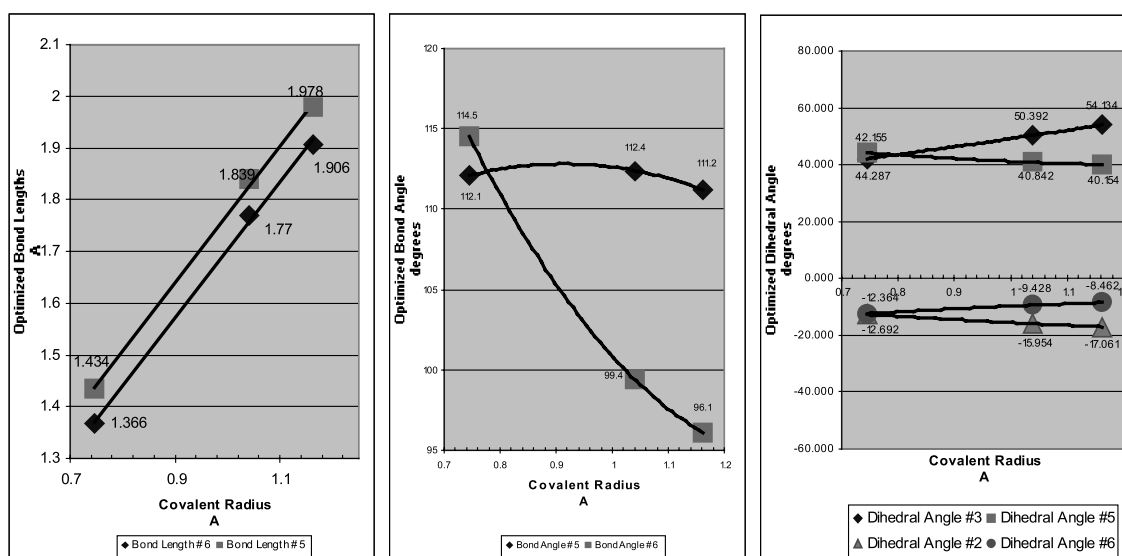


Fig. 7. Geometrical variation in cyclohexene as a result of oxygen, sulfur and selenium substitution. Atomic radii in angstrom on horizontal axis.

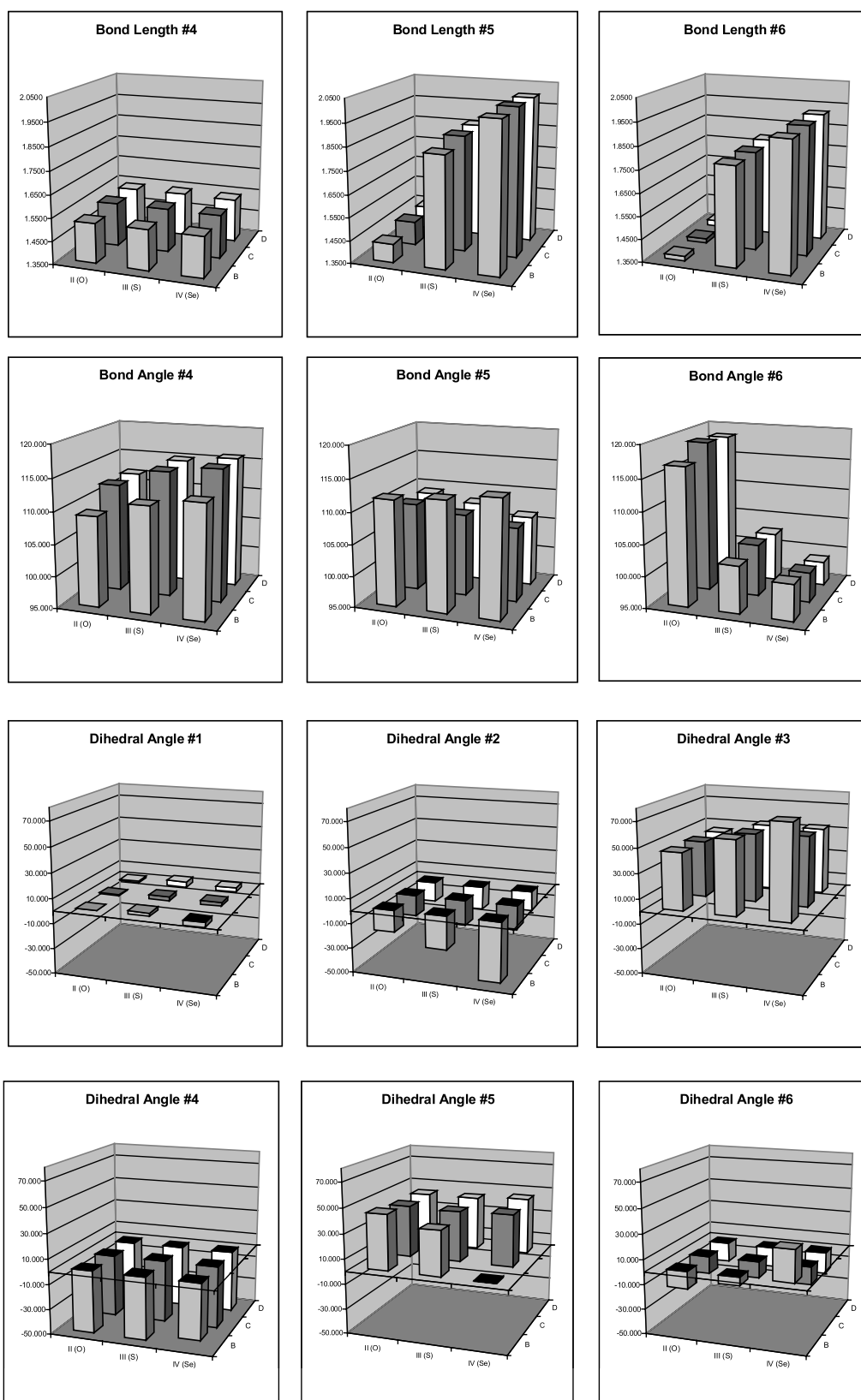
### 3.1 Molecular geometry of stable structures

The labeling of the bond lengths, bond angles and dihedral angles are given in Figure 6. The corresponding optimized parameters are summarized in Tables 1, 2 and 3, respectively.

The optimized dihedral angles of cyclohexene compare favourably to those reported earlier as shown in Table 4; the geometry changes with heteroatom substitution. The increasing atomic size created by the progression from oxygen to sulfur, then to selenium makes a noticeable difference, as is illustrated in Figure 7 for selected bond length, bond angles and dihedral angles.

When both substitutions by the heteroatoms within the ring, as well as alkyl and hydroxyl substitution on tetralin are considered, the changes are quite complex. Some of the tabulated results are shown in the form of a 3D-bar diagram in Figure 8.

Changes in C–C bond lengths and bond angles about a carbon atom are influenced slightly by the nearby O, S or Se. However, the changes are not large and their change is not necessarily monotonic, as one would expect on the basis of the periodic table (O→S→Se). Very often the parameter in question for sulfur is either smaller or larger



**Fig. 8.** Variation of selected bond lengths, bond angles and dihedral angles as a function of heteroatom type and ring substitution.

**Table 1.** Optimized bond lengths for the stable conformers ( $\lambda = 0$ ) of the sixteen compounds studied at B3LYP/6-31G(d) level of theory.

Length	X		A	B	C	D
1	CH2	I	1.3370	1.4066	1.4061	1.4043
	O	II	1.3383	1.4054	1.4049	1.4015
	S	III	1.3388	1.4072	1.4065	1.4042
	Se	IV	1.3369	1.4053	1.4043	1.4022
2	CH2	I	1.5098	1.5203	1.5184	1.5181
	O	II	1.5087	1.5163	1.5128	1.5126
	S	III	1.5082	1.5182	1.5177	1.5178
	Se	IV	1.5093	1.5101	1.5205	1.5214
3	CH2	I	1.5373	1.5338	1.5351	1.5347
	O	II	1.5380	1.5338	1.5331	1.5332
	S	III	1.5363	1.5321	1.5318	1.5321
	Se	IV	1.5369	1.5421	1.5343	1.5347
4	CH2	I	1.5352	1.5327	1.5476	1.5477
	O	II	1.5277	1.5245	1.5399	1.5407
	S	III	1.5313	1.5272	1.5418	1.5423
	Se	IV	1.5282	1.5261	1.5392	1.5395
5	CH2	I	1.5373	1.5339	1.5460	1.5462
	O	II	1.4336	1.4306	1.4533	1.4509
	S	III	1.8391	1.8364	1.8635	1.8622
	Se	IV	1.9779	1.9970	2.0032	2.0017
6	CH2	I	1.5099	1.5203	1.5195	1.5191
	O	II	1.3658	1.3717	1.3702	1.3748
	S	III	1.7704	1.7884	1.7878	1.7901
	Se	IV	1.9057	1.9150	1.9205	1.9222
7	CH2	I	1.0990	1.1011	1.0995	1.0996
	O	II	1.0984	1.1002	1.0991	1.0992
	S	III	1.0987	1.1011	1.0992	1.0993
	Se	IV	1.0987	1.1009	1.0993	1.0993
8	CH2	I	1.1020	1.0977	1.0979	1.0980
	O	II	1.1008	1.0969	1.0971	1.0973
	S	III	1.1017	1.0967	1.0973	1.0975
	Se	IV	1.1020	1.0956	1.0974	1.0977
9	CH2	I	1.0970	1.0993	1.0983	1.0983
	O	II	1.0965	1.0971	1.0963	1.0963
	S	III	1.0977	1.0967	1.0994	1.0995
	Se	IV	1.0986	1.0963	1.1009	1.1009
10	CH2	I	1.0990	1.0968	1.0992	1.0991
	O	II	1.0969	1.0963	1.0972	1.0971
	S	III	1.0964	1.0977	1.0966	1.0965
	Se	IV	1.0964	1.0982	1.0965	1.0962
11	CH2	I	1.0990	1.0968	1.5389	1.5533
	O	II	1.1003	1.0932	1.5464	1.5467
	S	III	1.0954	1.0942	1.5484	1.5480
	Se	IV	1.0930	1.0921	1.5433	1.5429
12	CH2	I	1.0970	1.0993	1.5534	1.5391
	O	II	1.0933	1.1009	1.5293	1.5294
	S	III	1.0940	1.0955	1.5364	1.5365
	Se	IV	1.0928	1.0924	1.5342	1.5341
13	CH2	I	1.0897	1.4027	1.4028	1.4038
	O	II	1.0862	1.4004	1.4017	1.4017
	S	III	1.0870	1.4044	1.4056	1.4061
	Se	IV	1.0865	1.3998	1.4038	1.4045
14	CH2	I	1.0897	1.4026	1.4024	1.4020
	O	II	1.0860	1.4005	1.4007	1.4022
	S	III	1.0891	1.4024	1.4033	1.4035
	Se	IV	1.0901	1.3996	1.4041	1.4042
15	CH2	I		1.3920	1.3922	1.3891
	O	II		1.3908	1.3905	1.3882
	S	III		1.3907	1.3901	1.3872
	Se	IV		1.3935	1.3905	1.3874

Length	X		A	B	C	D
16	CH2	I		1.3920	1.3921	1.3939
	O	II		1.3930	1.3927	1.3933
	S	III		1.3920	1.3913	1.3930
	Se	IV		1.3945	1.3913	1.3929
17	CH2	I		1.3970	1.3970	1.3991
	O	II		1.3984	1.3986	1.4001
	S	III		1.3965	1.3972	1.3992
	Se	IV		1.3956	1.3967	1.3989
18	CH2	I			1.0965	1.0966
	O	II			1.0962	1.0962
	S	III			1.0954	1.0957
	Se	IV			1.0954	1.0955
19	CH2	I			1.0999	1.1000
	O	II			1.0989	1.0989
	S	III			1.1014	1.1014
	Se	IV			1.1022	1.1022
20	CH2	I			1.5347	1.5346
	O	II			1.5328	1.5327
	S	III			1.5322	1.5322
	Se	IV			1.5318	1.5318
21	CH2	I			1.0960	1.0960
	O	II			1.0956	1.0956
	S	III			1.0953	1.0953
	Se	IV			1.0954	1.0954
22	CH2	I			1.0953	1.0953
	O	II			1.0952	1.0953
	S	III			1.0950	1.0950
	Se	IV			1.0954	1.0954
23	CH2	I			1.0961	1.0960
	O	II			1.0945	1.0945
	S	III			1.0957	1.0957
	Se	IV			1.0951	1.0950
24	CH2	I			1.0957	1.0957
	O	II			1.0933	1.0933
	S	III			1.0945	1.0945
	Se	IV			1.0947	1.0948
25	CH2	I			1.0975	1.0975
	O	II			1.0957	1.0958
	S	III			1.0976	1.0976
	Se	IV			1.0985	1.0984
26	CH2	I			1.0970	1.0970
	O	II			1.0947	1.0947
	S	III			1.0944	1.0945
	Se	IV			1.0946	1.0948
27	CH2	I				1.3704
	O	II				1.3736
	S	III				1.3701
	Se	IV				1.3697
28	CH2	I				0.9698
	O	II				0.9694
	S	III				0.9697
	Se	IV				0.9697
29	CH2	I	1.1020	1.1010	1.0961	1.0974
	O	II	-	-	-	-
	S	III	-	-	-	-
	Se	IV	-	-	-	-
30	CH2	I	1.0990	1.0977	1.1012	1.1014
	O	II	-	-	-	-
	S	III	-	-	-	-
	Se	IV	-	-	-	-

than that for the oxygen and selenium-containing compound.

Take for example bond angle 9 in Model D.

$$112.1^\circ \rightarrow 111.6^\circ \rightarrow 112.4^\circ$$

$$\text{O} \rightarrow \text{S} \rightarrow \text{Se}. \quad (8)$$

Of the geometrical parameters, noting the dihedral angles,  $D_1$  is close to  $0^\circ$  and  $D_4$  is close to  $60^\circ$ ; which would not commonly be expected.  $D_2$ ,  $D_3$ ,  $D_5$  and  $D_6$  values were

plotted against the covalent radii of the heteroatoms O, S and Se in Figure 9.

On going from the single heterocyclic ring (A) to the next larger system where a benzene ring is fused to the heterocycle (B) a large amplification in dihedral angles were noticed. This amplification was followed by two consecutive attenuations on going from B to C and subsequently from C to D. Thus, the final system (D) did not differ much from the original (A) ring structure.

**Table 2.** Optimized bond angles for the stable conformers ( $\lambda = 0$ ) of the sixteen compounds studied at B3LYP/6-31G(d) level of theory.

Angle	X		A	B	C	D
1	CH2	I	123.551	121.478	121.403	121.656
	O	II	125.660	<b>123.140</b>	<b>123.513</b>	<b>123.685</b>
	S	III	126.839	<b>124.430</b>	<b>124.472</b>	<b>124.568</b>
	Se	IV	126.352	<b>121.524</b>	<b>123.923</b>	<b>123.950</b>
2	CH2	I	123.549	121.474	121.208	121.146
	O	II	121.987	<b>120.367</b>	<b>120.085</b>	<b>120.099</b>
	S	III	125.694	<b>123.008</b>	<b>123.250</b>	<b>123.290</b>
	Se	IV	126.717	<b>120.500</b>	<b>124.359</b>	<b>124.497</b>
3	CH2	I	112.032	113.377	113.683	113.516
	O	II	109.598	<b>110.734</b>	<b>110.770</b>	<b>110.799</b>
	S	III	113.681	<b>114.512</b>	<b>115.197</b>	<b>115.362</b>
	Se	IV	114.923	<b>111.714</b>	<b>117.150</b>	<b>117.394</b>
4	CH2	I	110.975	110.288	113.362	113.422
	O	II	109.817	<b>109.179</b>	<b>112.098</b>	<b>112.208</b>
	S	III	112.563	<b>111.518</b>	<b>114.838</b>	<b>114.991</b>
	Se	IV	113.271	<b>112.709</b>	<b>115.859</b>	<b>115.864</b>
5	CH2	I	110.968	110.291	106.822	106.868
	O	II	112.052	<b>111.805</b>	<b>109.102</b>	<b>109.018</b>
	S	III	112.355	<b>112.445</b>	<b>108.124</b>	<b>107.948</b>
	Se	IV	111.242	<b>113.499</b>	<b>106.813</b>	<b>106.393</b>
6	CH2	I	112.024	113.385	114.651	114.549
	O	II	114.478	<b>116.747</b>	<b>118.922</b>	<b>118.457</b>
	S	III	99.425	<b>102.512</b>	<b>103.294</b>	<b>102.744</b>
	Se	IV	96.134	<b>100.694</b>	<b>99.749</b>	<b>98.873</b>
7	CH2	I	105.362	105.707	105.339	105.408
	O	II	105.785	<b>106.132</b>	<b>105.771</b>	<b>105.798</b>
	S	III	105.316	<b>105.813</b>	<b>105.294</b>	<b>105.325</b>
	Se	IV	105.189	<b>106.843</b>	<b>105.075</b>	<b>105.107</b>
8	CH2	I	106.709	106.735	106.446	106.473
	O	II	107.415	<b>107.498</b>	<b>107.101</b>	<b>107.121</b>
	S	III	107.040	<b>107.232</b>	<b>106.776</b>	<b>106.779</b>
	Se	IV	107.117	<b>107.001</b>	<b>106.719</b>	<b>106.747</b>
9	CH2	I	106.710	106.735	110.462	110.424
	O	II	108.513	<b>108.246</b>	<b>112.169</b>	<b>112.128</b>
	S	III	108.019	<b>107.869</b>	<b>111.628</b>	<b>111.632</b>
	Se	IV	108.847	<b>108.920</b>	<b>112.294</b>	<b>112.364</b>
10	CH2	I			109.748	109.730
	O	II			<b>111.681</b>	<b>111.662</b>
	S	III			<b>111.107</b>	<b>111.171</b>
	Se	IV			<b>112.215</b>	<b>112.277</b>
11	CH2	I			108.711	108.644
	O	II			<b>110.37</b>	<b>110.262</b>
	S	III			<b>109.296</b>	<b>109.164</b>
	Se	IV			<b>109.707</b>	<b>109.700</b>
12	CH2	I			116.585	116.607
	O	II			<b>115.236</b>	<b>115.165</b>
	S	III			<b>116.430</b>	<b>116.344</b>
	Se	IV			<b>115.952</b>	<b>115.887</b>

Angle	X		A	B	C	D
13	CH2	I			108.968	109.023
	O	II			<b>108.397</b>	<b>108.428</b>
	S	III			<b>108.782</b>	<b>108.811</b>
	Se	IV			<b>108.944</b>	<b>108.882</b>
14	CH2	I			107.908	107.917
	O	II			<b>108.011</b>	<b>108.073</b>
	S	III			<b>107.148</b>	<b>107.196</b>
	Se	IV			<b>107.435</b>	<b>107.519</b>
15	CH2	I			112.074	112.049
	O	II			<b>110.795</b>	<b>110.304</b>
	S	III			<b>112.170</b>	<b>112.143</b>
	Se	IV			<b>110.351</b>	<b>110.388</b>
16	CH2	I			110.081	110.074
	O	II			<b>112.234</b>	<b>112.230</b>
	S	III			<b>111.157</b>	<b>111.085</b>
	Se	IV			<b>112.237</b>	<b>112.266</b>
17	CH2	I			112.212	112.248
	O	II			<b>110.274</b>	<b>110.759</b>
	S	III			<b>110.016</b>	<b>110.055</b>
	Se	IV			<b>110.019</b>	<b>109.883</b>
18	CH2	I			111.928	111.924
	O	II			<b>110.977</b>	<b>110.941</b>
	S	III			<b>112.195</b>	<b>112.167</b>
	Se	IV			<b>112.213</b>	<b>112.198</b>
19	CH2	I			111.049	111.066
	O	II			<b>110.510</b>	<b>110.552</b>
	S	III			<b>109.607</b>	<b>109.662</b>
	Se	IV			<b>109.931</b>	<b>109.920</b>
20	CH2	I			110.779	110.792
	O	II			<b>110.246</b>	<b>110.246</b>
	S	III			<b>110.862</b>	<b>110.878</b>
	Se	IV			<b>110.856</b>	<b>110.906</b>
21	CH2	I				117.565
	O	II				<b>117.510</b>
	S	III				<b>117.594</b>
	Se	IV				<b>117.622</b>
22	CH2	I				108.699
	O	II				<b>108.663</b>
	S	III				<b>108.817</b>
	Se	IV				<b>108.804</b>
23	CH2	I	105.363	105.716	106.084	105.277
	O	II	-	-	-	-
	S	III	-	-	-	-
	Se	IV	-	-	-	-

### 3.2 Molecular energetics

The computed total energies are summarized in Table 5. These energy values are not comparable since each of the sixteen molecular systems has a different number of electrons. In order to make an energetic comparison of the sixteen molecular structures some isodesmic reaction energy calculation should be made in order to determine the relative stabilization or destabilization exerted by the substituents on the basic structures. The calculations were carried out according to equations (3–6). Stabilization energies are summarized in Table 6.

The stabilization energies reveal that oxygen and selenium substitutions stabilize the ring system more or less to the same extent. However, sulfur destabilizes (by 6 kcal/mole) the same ring system. This is particularly clear from the last column of Table 6.

### 4 Conclusions

The present work shows that O and Se stabilize the fused ring system of tocopherols more or less to the same extent, while S destabilizes it slightly.

**Table 3.** Optimized dihedral angles for the stable conformers ( $\lambda = 0$ ) of the sixteen compounds studied obtained at B3LYP/6-31G(d) level of theory.

Dihedral	X		A	B	C	D
1	CH2	I	-1.606	3.264	4.190	4.550
	O	II	-3.886	<b>0.228</b>	<b>0.838</b>	<b>1.395</b>
	S	III	-2.443	<b>2.654</b>	<b>3.225</b>	<b>4.521</b>
	Se	IV	-2.553	<b>-3.888</b>	<b>3.088</b>	<b>3.371</b>
2	CH2	I	-13.867	-18.123	-14.180	-14.817
	O	II	-12.692	<b>-17.573</b>	<b>-17.223</b>	<b>-16.775</b>
	S	III	-15.954	<b>-27.094</b>	<b>-20.504</b>	<b>-19.562</b>
	Se	IV	-17.061	<b>-47.917</b>	<b>-19.002</b>	<b>-16.029</b>
3	CH2	I	44.106	47.228	43.767	44.242
	O	II	42.155	<b>45.834</b>	<b>45.396</b>	<b>44.816</b>
	S	III	50.392	<b>59.079</b>	<b>54.894</b>	<b>53.486</b>
	Se	IV	54.134	<b>75.163</b>	<b>56.036</b>	<b>53.455</b>
4	CH2	I	-60.472	-62.512	-60.748	-60.783
	O	II	-60.193	<b>-61.223</b>	<b>-57.953</b>	<b>-58.221</b>
	S	III	-64.744	<b>-64.009</b>	<b>-64.757</b>	<b>-65.148</b>
	Se	IV	-66.598	<b>-44.710</b>	<b>-66.422</b>	<b>-67.513</b>
5	CH2	I	44.138	47.172	49.425	49.000
	O	II	44.287	<b>44.939</b>	<b>41.987</b>	<b>43.101</b>
	S	III	40.842	<b>36.080</b>	<b>40.796</b>	<b>42.738</b>
	Se	IV	40.154	<b>-0.484</b>	<b>41.883</b>	<b>45.098</b>
6	CH2	I	-13.904	-18.068	-23.282	-23.087
	O	II	-12.364	<b>-14.149</b>	<b>-14.361</b>	<b>-15.770</b>
	S	III	-9.428	<b>-6.740</b>	<b>-13.425</b>	<b>-16.018</b>
	Se	IV	-8.462	<b>25.773</b>	<b>-14.412</b>	<b>-17.532</b>
7	CH2	I			-178.664	-178.716
	O	II			<b>-172.048</b>	<b>-172.281</b>
	S	III			<b>-179.108</b>	<b>-179.407</b>
	Se	IV			<b>179.959</b>	<b>178.890</b>
8	CH2	I			60.422	60.469
	O	II			<b>62.447</b>	<b>62.363</b>
	S	III			<b>57.268</b>	<b>57.012</b>
	Se	IV			<b>54.400</b>	<b>53.199</b>
9	CH2	I			174.334	174.240
	O	II			<b>-179.929</b>	<b>-179.936</b>
	S	III			<b>173.611</b>	<b>173.703</b>
	Se	IV			<b>178.813</b>	<b>179.196</b>
10	CH2	I				-179.778
	O	II				<b>179.822</b>
	S	III				<b>179.651</b>
	Se	IV				<b>179.867</b>
11	CH2	I				-179.884
	O	II				<b>179.794</b>
	S	III				<b>179.884</b>
	Se	IV				<b>-179.818</b>

**Table 4.** Previously reported and present optimized dihedral angles of cyclohexene.

	Previously reported*	Present optimized**
D1	0.00	-1.61
D2	-15.20	-13.87
D3	44.20	44.11
D4	-60.20	-60.47
D5	44.20	44.14
D6	-15.20	-13.90

\*Reference [8], \*\* B3LYP/6-31G(d).

The stabilization and relative stabilization are of the following order:

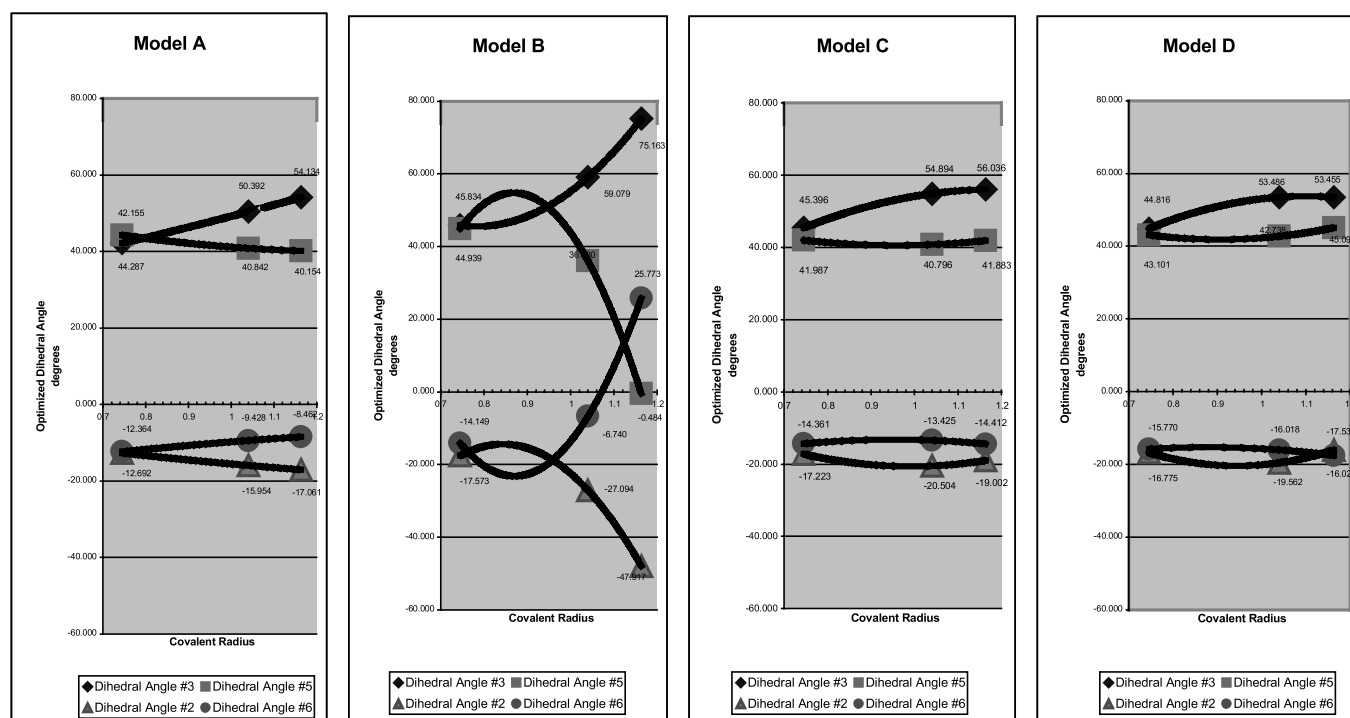
$$\begin{array}{ccccccc}
 \text{O} & \sim & \text{Se} & \gg & \text{S} & & \\
 -4.82 & & -4.73 & & +1.19 & (\text{kcal mol}^{-1}) & \\
 0.00 & & +0.09 & & +6.01 & (\text{kcal mol}^{-1}). & 
 \end{array}$$

On the basis of the present structural results it seems that the seleno congener of vitamin E is a distinct possibility.

It remains to be seen if the energies of the red-ox reaction mechanism follow the same sequence.

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**Fig. 9.** Variation of selected bond lengths, bond angles and dihedral angles as a function of the heteroatom site and ring substitution.

**Table 5.** Optimized total energies of the sixteen compounds studied.

		Total energy (Hartree)			
X		A	B	C	D
CH <sub>2</sub>	I	-234.6482949	-388.3063939	-506.2415280	-581.4572576
O	II	-270.5443727	-424.2034064	-542.1505510	-617.3642250
S	III	-593.52225062	-747.1778850	-865.1177830	-940.3327840
Se	IV	-2594.7100207	-2748.3683314	-2866.3144144	-2941.5297229

**Table 6.** Stabilization energies exerted by oxygen, sulfur and selenium ring substitution as well as aromatic hydroxylation.

		Stabilization energy (kcal/mol) <sup>a</sup>				
X		IB→IC (Eq. (3))	IC→XC (Eq. (4))	XC→XD (Eq. (5))	Total (Eq. (6))	O→X (Eq. (7))
CH <sub>2</sub>	I	0.344	–	–	–	–
O	II	–	-6.412	1.592	-4.820	0.000
S	III	–	0.428	0.759	1.188	6.008
Se	IV	–	-5.293	0.566	-4.726	0.094

<sup>a</sup> The following component energy values were used:  $E(\text{Ph-H}) = -232.2486592$ ,  $E(\text{Ph-OH}) = -307.4648704$ ,  $E(\text{C}_6\text{H}_{10}) = -234.6482949$ ,  $E(\text{C}_6\text{H}_8\text{EtMe}) = -352.5867031$ .

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## References

1. J.S. Wright, E.R. Johnson, G.A. DiLabio, *J. Am. Chem. Soc.* **123**, 1173 (2001)
2. M. Evans, K.S. Bishop, *Science* **55**, 650 (1922)
3. C.H. Schiesser, *From Marco Polo to chiral stannanes - radical chemistry for the new millennium* (Arkivoc, 2001)
4. J.B. Bauernfeind, in: *Vitamin E: a comprehensive treatise* (Marcel Dekker, New York, 1980)
5. B. Weimann, H. Weiser, *Am. Clin. Nutr.* **53**, 10565 (1991)
6. N. Al-Maharik, L. Engman, J. Malmstrom, C.J. Schiesser, *Org Chem.* **66**, 6286 (2001)
7. F.A.L. Anet, D.J. O'Leary, *Tetrahedron Lett.* **30**, 1059 (1989)
8. W. Auf der Heyde, W. Luttkke, *Chem. Ber.* **111**, 2384 (1978)
9. J.F. Chiang, S.H. Bauer, *J. Am. Chem. Soc.* **91**, 1898 (1969)
10. H.J. Geise, H.R. Buys, *Recl. Trav. Chim. Pays-Bas* **89**, 1147 (1970)
11. V.A. Naumov, V.G. Dashevskii, N.M. Zaripov, *J. Struct., Chem. USSR* **11**, 793 (1970)
12. T. Ogata, K. Kozima, *Bull. Chem. Soc. Jpn.* **42**, 1263 (1969)
13. L.H. Scharpen, J.E. Wollrab, D.P. Ames, *J. Chem. Phys.* **49**, 2368 (1986)
14. D.H. Setiadi, G.A. Chass, L.L. Torday, A. Varro, J.Gy. Papp, *Theochem* (2002) in press
15. G.W. Burton, K.U. Ingold, *Acc. Chem. Res.* **19** 194 (1986)
16. 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. 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*, Gaussian Inc., Pittsburgh PA, 1998
17. C. Glidwell, *Inorg. Chim. Acta.* **20**, 113 (1976)
18. C. Glidwell, *Inorg. Chim. Acta.* **36**, 135 (1979)