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Thermodynamics of competing oxidation reactions of allyl methyl disulfide by hydrogen peroxide: a first principle molecular computational study on the conformations of allyl methyl disulfide and its oxidized products[†]

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Allyl methyl disulfide, a peroxide scavenger, was studied together with three isomeric (two sulfoxides and one epoxide) forms of its mono-oxidized products. After a full conformational study of the reactant and three isomeric oxidized forms, the geometries were optimized at B3LYP/6-31G (d) level of theory. The epoxide form turned and to be more stable than either one of the two isomeric sulfoxides. Changes for Thermodynamic functions of oxidation reactions were calculated and from the $\Delta G_{\mathrm{reaction}}$ values the equilibrium constant for the interconversions of the oxidized products were estimated. Bader-type AIM analyses were performed on the electron density, computed at the B3LYP/6-311++G (d,p) level of theory. In several of the sulfoxide conformations C—H···O═S< secondary interactions were observed. Copyright © 2008 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: oxidation of disulfide; allyl methyl disulfide; *ab initio* and density functional study; disulfide component of garlic

INTRODUCTION

Garlic contains many organic sulfur compounds. Some of them have a single sulfur atom while some of them have several. Also, some of the sulfur atoms have low oxidation state as —S— or —S—S— while some of them have sulfur of a higher oxidation state (>S═O). Typical examples[1] are shown in Fig. 1.

Many of the health benefits of garlic are attributed to its sulfur-containing organic compounds.[2–8] Particularly the antioxidant ability of ally methyl sulfide is of great importance.[9–11]

Oxidative stress of biological systems originates from the fact that 1 of every 20 oxygen molecules (i.e. 5% of the O_2 inhaled and retained by the body) escapes complete reduction to water:

$$O_2 \xrightarrow{+e^-} \cdot O_2^- \xrightarrow{H^+} HO-O\cdot \xrightarrow{+e^-} HO-O^- \xrightarrow{H^+} HO-OH \rightarrow HO\cdot \rightarrow - \rightarrow H_2O$$

If the hydrogen peroxide is not eliminated enzymatically (e.g. by glutathione peroxidase), then it may accumulate and can cause biological damage. Sulfur-containing compounds found in garlic, such as allyl methyl disulfide, may also act as a peroxide scavenger. During this process, allyl methyl disulfide is oxidized.

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[†] *This paper is dedicated to Professor Arpad Kucsman on the occasion of his 80th birthday.*

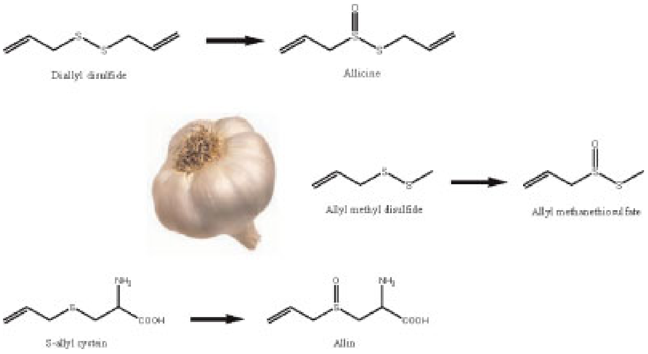


Figure 1. Selected low and higher oxidation state sulfur compounds found in garlic

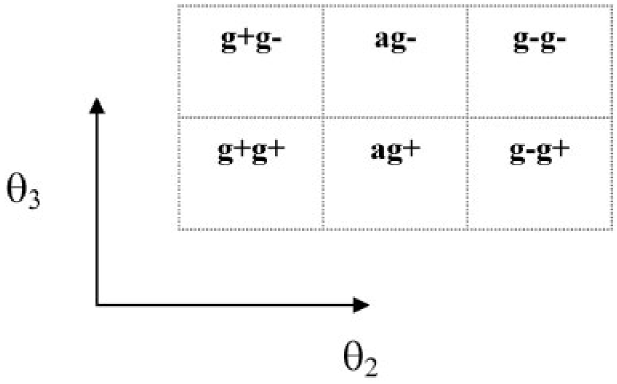


Figure 2. Topology of the potential energy surfaces of compounds (**1**)–(**4**)

The present paper, a thermodynamical study preceding to any kinetic consideration of the problem, focuses attention on three different oxidized forms of allyl methyl sulfide, (Scheme 1) their structures and their thermodynamic stabilities.

METHOD

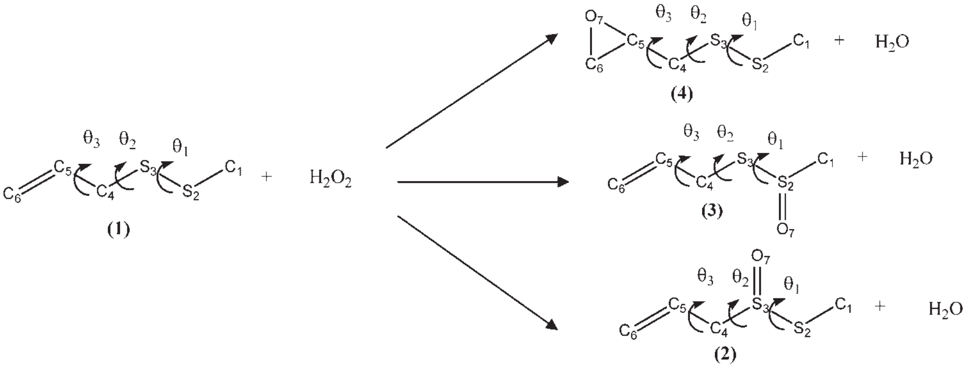
If we define dihedral angles: θ_1 (C_1S_2—S_3C_4), θ_2 (S_2S_3—C_4C_5) and θ_3 (S_3C_4—C_5C_6), by keeping $\theta_1 = 90^\circ$, *ab initio* potential energy surfaces (PESs) of the type:

$$E = f(\theta_2, \theta_3) \tag{1}$$

were generated at HF/6-31G(d) level of theory for (**1**)–(**4**), in accordance with previously published methodology.[1] The surfaces for compounds (**1**), (**2**) and (**4**) exhibited six stable conformations corresponding to the pattern shown in Fig. 2, but compound (**3**) had only four minima.

Using Gaussian 03,[12] these geometries of each of the four species (from (**1**) to (**4**)) were subjected to geometry optimization and frequency calculation at the B3LYP/6-31G(d)[13,14] level of theory. The optimized conformations of each of the four compounds were computed at G3MP2B3 level of theory[15–17] for the generation of reliable thermodynamic functions.

The $4 + (2 \times 6) = 16$ conformers of compounds **2**–**4**, previously geometry optimized at the B3LYP/6-31G(d) level of theory, were



Scheme 1. Allyl methyl disulfide (**1**) and its possible oxidized products ((**2**)–(**4**)) generated by hydrogen peroxide

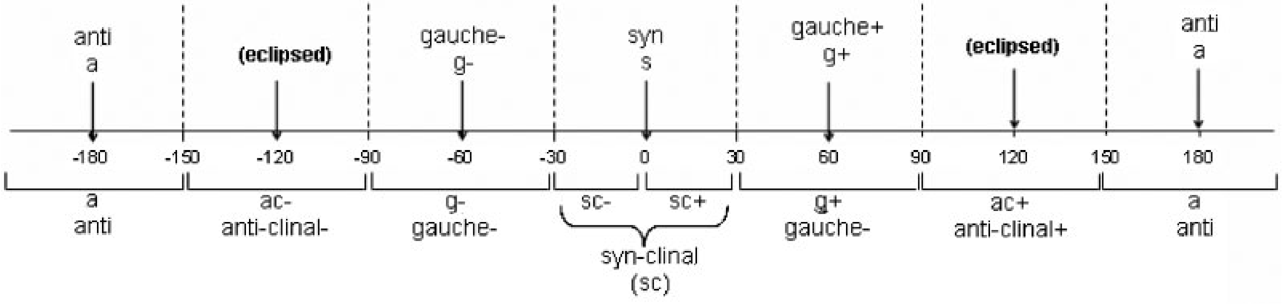


Figure 3. Conformational assignment used to designate optimized structures

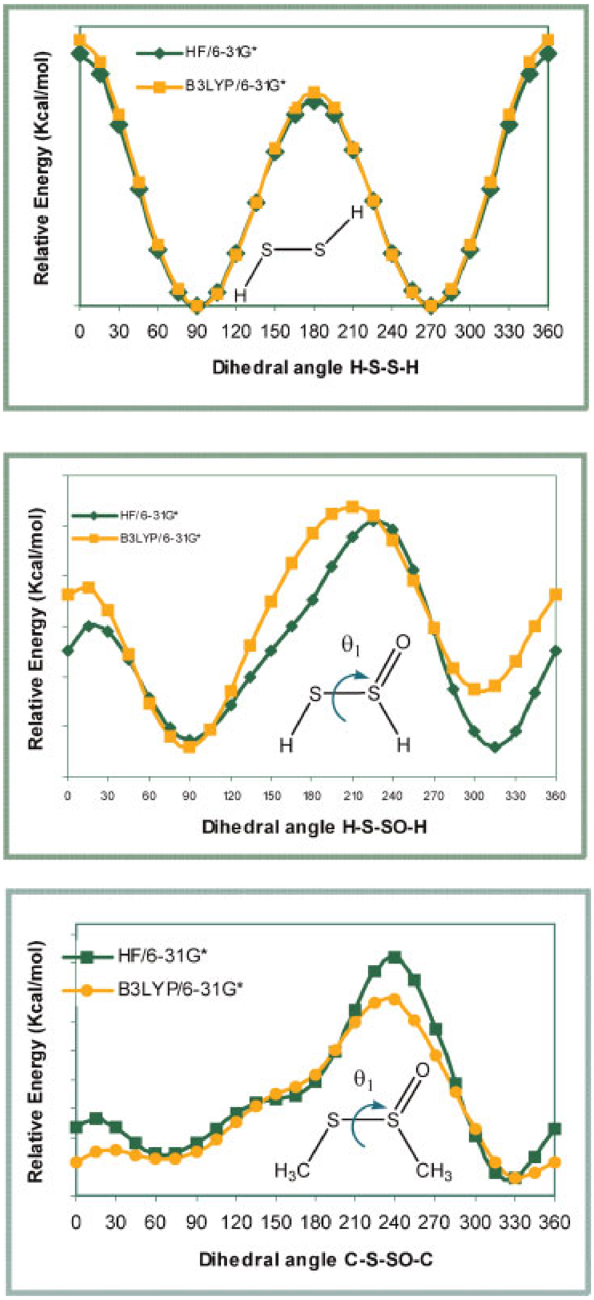


Figure 4. Rotation about the S–S bond of three model compounds: HS–SH; HS–S(O)H, $H_3CS–S(O)CH_3$ and associated potential energy curves computed at two levels of theory

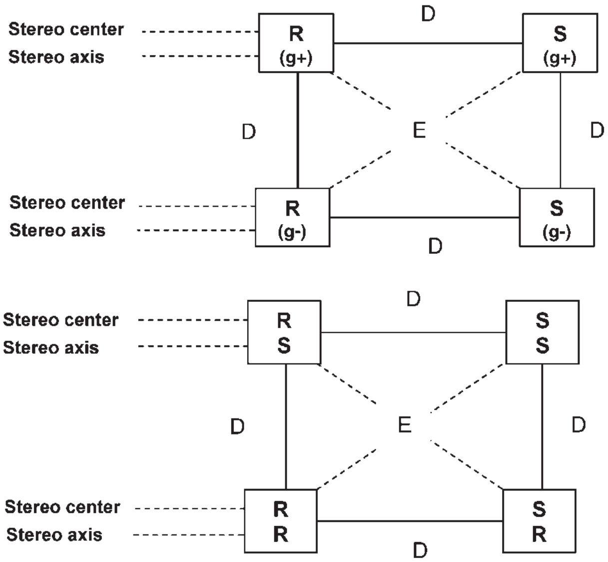


Figure 5. A schematic illustration of the emergence of enantiomeric and diastereotopic relationship upon the combination of point chirality (α stereo-centre) and axis chirality(atropism)

subsequently submitted to Bader's Atoms in Molecules (AIM) analysis[18,19] using AIM2000 program package.[20] The AIM analysis has been carried out at B3LYP/6-311++G(d,p) level of theory. Result of this mathematical analysis reveals the exact identification of primary and secondary interactions via the localization of the critical points of the electron density and the subsequent calculation of electron density at the bond critical point (ρ_b). The primary interactions are genuine chemical bonds and the secondary interactions would be hydrogen bonds or donor–acceptor complexations.The conformational assignments, used in this paper, are summarized in Fig. 3.

RESULTS AND DISCUSSION

For modelling the rotation about the S—S bond, dihydrogen-disulfide [HS—SH], sulfinothioic S-acid [HS—S(O)H] and S-methyl methanesulfinothioate [MeS—S(O)Me] were used in a preliminary study. Due to the chirality of the tricoordinated sulfur, the last two of these potential energy curves (PECs) turned out to asymmetric (Fig. 4), showing definite minima at $\theta_1 = 90^\circ$.

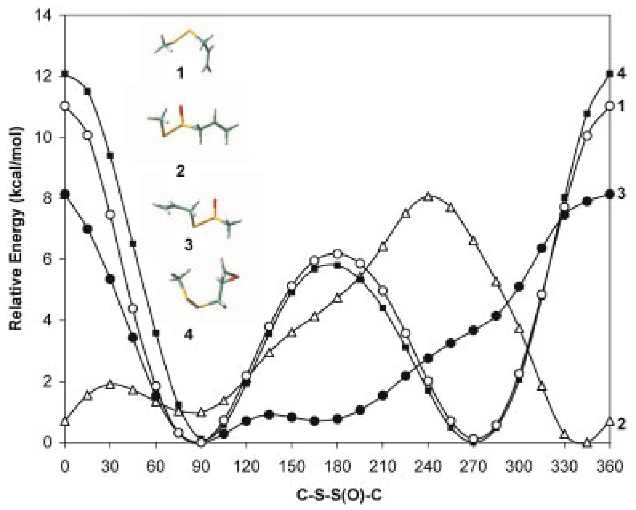


Figure 6. Potential energy curves of four compounds computed at B3LYP/6-31G(d) level of theory. Compounds **1**–**4** are defined in Scheme 1. This figure is available in colour online at www.interscience.wiley.com/journal/poc

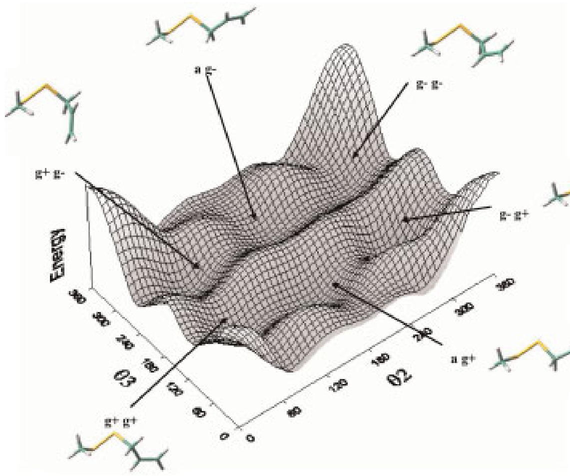


Figure 7. PES of compound (**1**) generated at HF/3-21G level of theory ($\theta_1 = 90^\circ$)

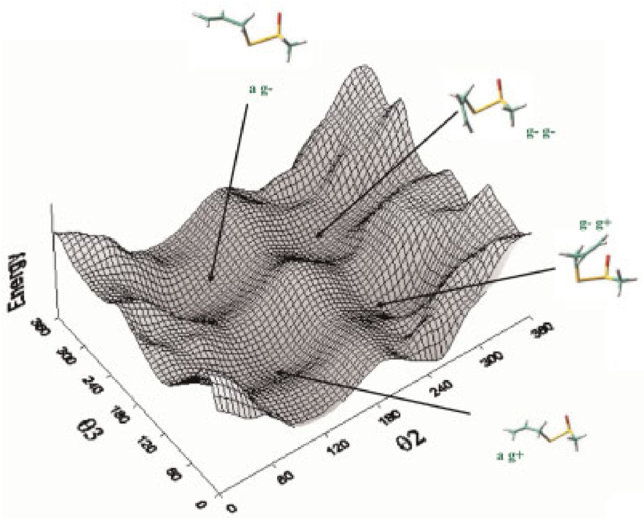


Figure 9. PES of compound (**3**) generated at HF/3-21G level of theory ($\theta_1 = 90^\circ$)

Such a phenomenon is frequently related to ‘Atropisomerism’ or axis chirality. It is due to the fact that rotation itself, about an axis, by virtue of the fact that it may be clockwise or counterclockwise, represents chirality. Thus, g(+) and g(−) conformers in H—S—S—H are enantiomeric and therefore energetically degenerate. The equivalence between R and S stereoisomers as well as rotating in the plus (P) direction and that of the minus (M) direction is given below:

$$\begin{aligned}(+)\,&\text{i.e. P} \rightarrow \text{S}\\ (-)\,&\text{i.e. M} \rightarrow \text{R}\end{aligned} \qquad (2)$$

When the axis chirality (+, i.e. P and −, i.e. M), resulting from internal rotation, and point chirality (R and S) originating from the pyramidal structure of the sulfoxide >S═O, are occurring together then enantiomeric (E) and diastereomeric (D) relationships emerge (Fig. 5).

Turning to the four compounds (**1**–**4**) investigated, compound (**1**) has been studied extensively previously.[1,21,22] Its PEC (**1**) is shown in comparison to those of its oxidation products (**2**–**4**) in Fig. 6. Note that all the products posses of R absolute configuration. However, compounds **2** and **3** show very asymmetric rotation potential (Fig. 6) with respect to rotation about the S—S bond. Most of the strong asymmetry shown in the PECs of compounds (**2**) and (**3**) is due to the fact that the chiral sulfur centre is part of the rotation about the S—S bond. The asymmetry of the PEC is hardly noticeable in the case of

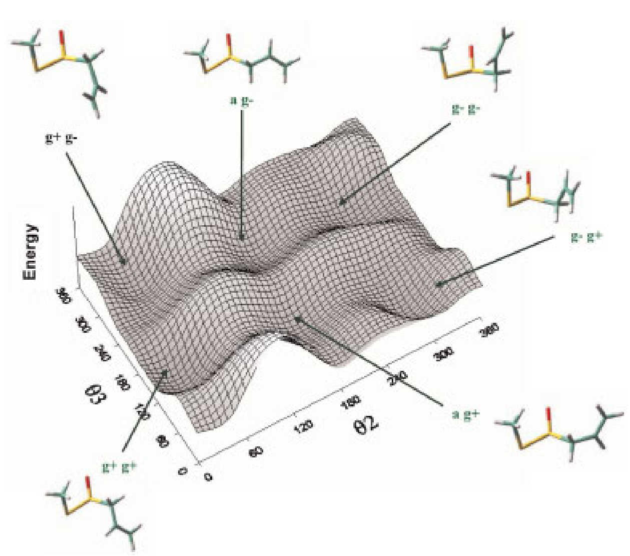


Figure 8. PES of compound (**2**) generated at HF/3-21G level of theory ($\theta_1 = 90^\circ$)

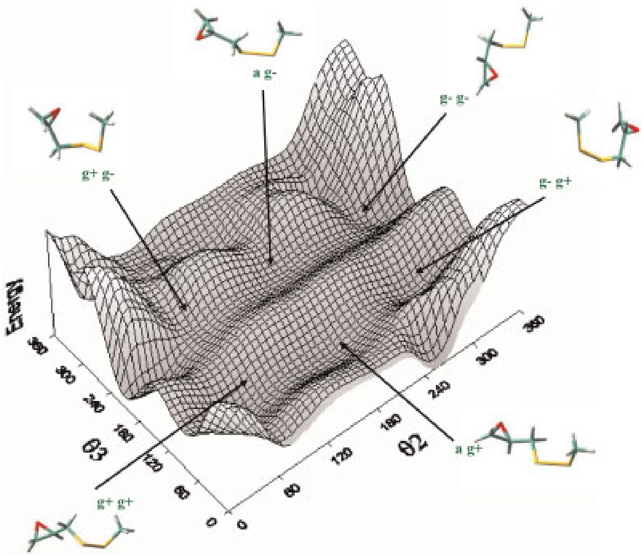


Figure 10. PES of compound (**4**) generated at HF/3-21G level of theory ($\theta_1 = 90^\circ$)

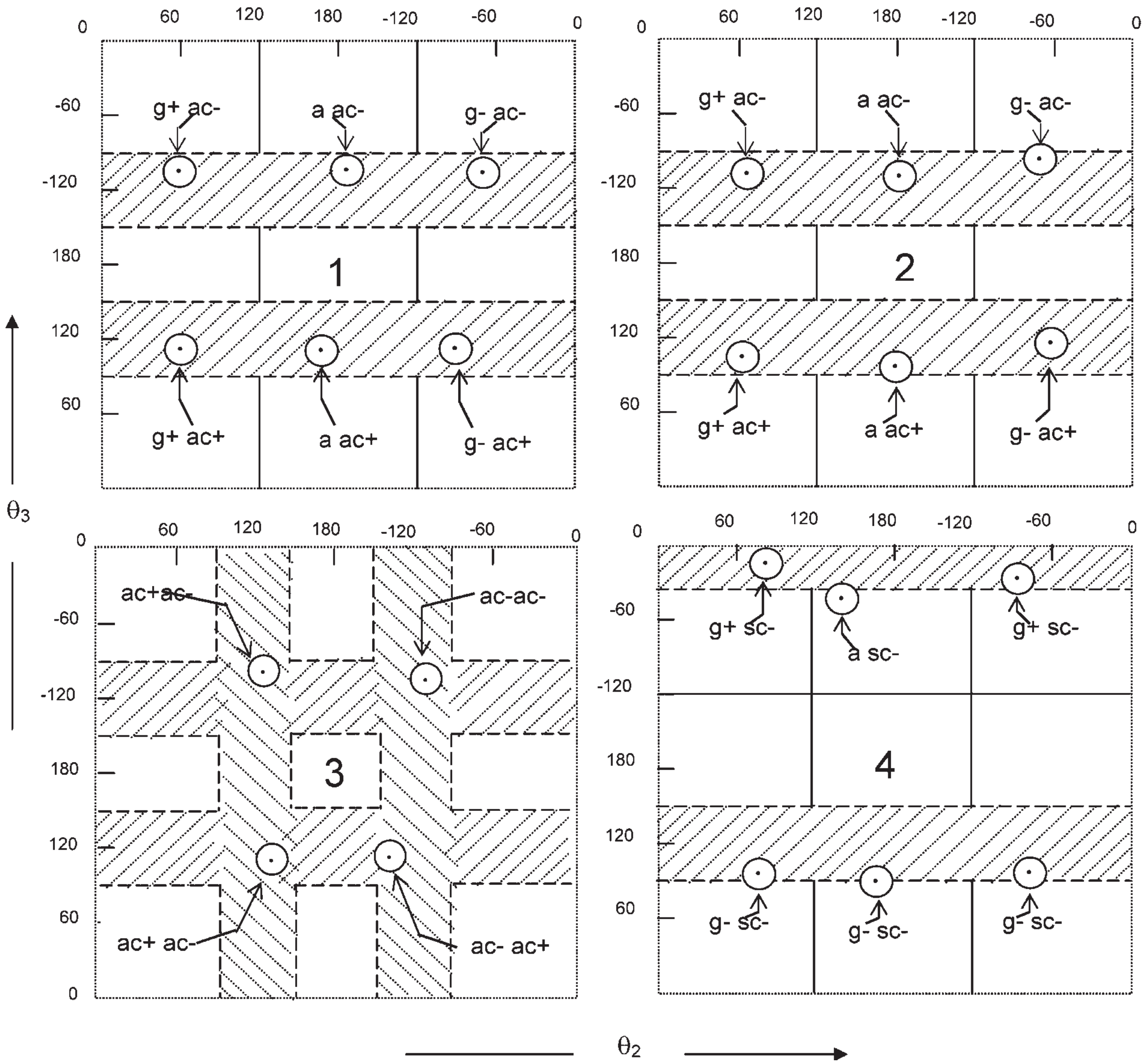


Figure 11. Topological pattern of optimized geometries for compound (**1**)–(**4**)

compound (**4**) since the point chiral carbon atom is some distance away from the rotation about the S—S bond.

The four PESs of the type (1) for compounds (**1**)–(**4**) are shown in Figs 7–10, respectively. The surfaces of compounds (**1**), (**2**) and (**4**) exhibit rather similar topological patterns as illustrated schematically by Fig. 2. The lack of symmetry of these molecules is manifested in asymmetric shapes of the PESs. The topological pattern of the PESs is shown in Fig. 11. These surfaces (Figs 7–11) are like Ramachandran maps, used in the conformational analysis of peptides. In Fig. 11, the circles designate the minimum energy conformations and the shaded areas are specifying the structural change of the eclipsing or near eclipsing conformations. Their optimized stable geometries are shown with their characteristic θ_1, θ_2 and θ_3 dihedral angles in Table 1.The thermodynamic functions for those structures computed at B3LYP/6-31G(d) and G3MP2B3/6-31G(d) levels of theory are tabulated in Tables 2 and 3, respectively. Compounds (**2**)–(**4**) are structural isomers therefore the numerical values of their thermodynamic functions are comparable. Compounds (**2**) and (**3**) are almost isoenergetic differing from each other by about a milihartree while compound (**4**) is the most stable of the three by more then 20 milihartrees.

In order to study the oxidation (Scheme 1) of (**1**) to (**2**), (**3**) and (**4**), the thermodynamic function had to be computed also at two levels of theory for H_2O (Table 4) and H_2O_2 (Table 5). The thermodynamic functions for the oxidation reaction (Scheme 1) were computed at B3LYP/6-31G(d) and G3MP2B3/6-31G(d) levels of theory and the results are tabulated in Tables 6 and 7, respectively. The results of the G3MP2B3/6-31G(d) calculations are graphically shown in Fig. 12. At this level of theory, the difference between (**2**) and (**3**) as well as between (**3**) and (**4**) is 1.72 and 0.62 kcal/mol on the ΔG scale; thus they are quite comparable.

A first approximation of aqueous solvent effect was considered by PCM model using the Gaussian 03 program, considering that

Table 1. Dihedral angles (θ_1, θ_2, θ_3), total and relative energies of compounds **1**–**4** computed at B3LYP/6-31G(d) level of theory

	B3LYP/6-31G(d)				
	θ_1	θ_2	θ_3	ENERGY (Hartree)	ΔE (kcal/mol)
Compound **1**					
g+ [g− ac−]	95.0241	−70.3483	−111.5363	−953.5982717	1.456
g+ [g− ac+]	91.9014	−94.8971	116.7907	−953.6005919	0
g+ [g+ ac−]	88.0553	66.5402	−116.2027	−953.5995861	0.631
g+ [g+ ac+]	87.1427	72.9922	117.1856	−953.5985439	1.285
g+ [a ac−]	88.3596	−166.9459	−108.2024	−953.5991302	0.917
g+ [a ac+]	107.4938	160.5445	109.3553	−953.5993474	0.781
Compound **2**					
g+ [g− ac−]	88.1347	−69.04	−91.8968	−1028.7730512	1.569
g+ [g− ac+]	91.2177	−68.0201	122.643	−1028.7755512	0
g+ [g+ ac−]	82.3629	67.5038	−115.292	−1028.7735578	1.251
g+ [g+ ac+]	82.2585	65.6489	100.9776	−1028.7760197	−0.294
g+ [a ac−]	79.9579	−177.533	−114.741	−1028.7742774	0.799
g+ [a ac+]	83.7035	177.6092	95.7668	−1028.7750509	0.314
Compound **3**					
g+ [ac− ac−]	88.2316	−111.8396	−116.6642	−1028.774565	0.849
g+ [ac− ac+]	89.7940	−91.4306	117.2907	−1028.7759191	0
g+ [ac+ ac−]	93.5336	132.6538	−112.5603	−1028.7729550	1.860
g+ [ac+ ac+]	83.2488	135.1174	116.1036	−1028.7751945	0.455
Compound **4**					
g+ [g− sc−]	91.1404	−93.6576	−22.9697	−1028.7998902	−0.301
g+ [g− ac+]	92.4201	−72.7207	101.3783	−1028.7994105	0
g+ [g+ sc−]	88.4830	83.7559	−18.0098	−1028.7967374	1.677
g+ [g+ ac+]	88.2358	73.4632	94.3472	−1028.7991770	0.147
g+ [a sc−]	86.9299	150.1689	−38.2024	−1028.7960172	2.129
g+ [a ac+]	85.8946	158.9335	87.9344	−1028.7982346	0.738

Table 2. Thermodynamic functions and their relative values of compounds **1**–**4** computed at B3LYP/6-31G(d) level of theory

	B3LYP/6-31G (d)								
	U (Hartree)	ΔU (kcal/mol)	H (Hartree)	ΔH (kcal/mol)	G (Hartree)	ΔG (kcal/mol)	S (cal/molK)	ΔS (cal/molK)	Zero-point correction (Hartree)
Compound **1**									
g+ [g− ac−]	−953.478121	1.41817	−953.477177	1.41817	−953.521348	0.79756	92.967	2.083	0.111569
g+ [g− ac+]	−953.480381	0	−953.479437	0	−953.522619	0	90.884	0	0.111789
g+ [g+ ac−]	−953.479490	0.55911	−953.478545	0.55973	−953.522293	0.20456	92.075	1.191	0.111573
g+ [g+ ac+]	−953.478432	1.22301	−953.477488	1.22301	−953.521402	0.76367	92.424	1.54	0.111554
g+ [a ac−]	−953.478881	0.94126	−953.477936	0.94189	−953.522225	0.24723	93.213	2.329	0.111619
g+ [a ac+]	−953.479100	0.80384	−953.478156	0.80384	−953.522417	0.12675	93.156	2.272	0.111617
Compound **2**									
g+ [g− ac−]	−1028.648124	1.6196020	−1028.64718	1.6196020	−1028.694871	0.1995480	100.374	4.763	0.115145
g+ [g− ac+]	−1028.650705	0	−1028.649761	0	−1028.695189	0	95.611	0	0.115449
g+ [g+ ac−]	−1028.648669	1.2776093	−1028.647725	1.277609	−1028.694744	0.2792417	98.96	3.349	0.115187
g+ [g+ ac+]	−1028.651175	−0.2949294	−1028.650231	−0.294929	−1028.696213	−0.642569	96.778	1.167	0.115356
g+ [a ac−]	−1028.649361	0.8433727	−1028.648417	0.843372	−1028.695599	−0.257278	99.304	3.693	0.115147
g+ [a ac+]	−1028.650266	0.2754766	−1028.649322	0.275476	−1028.695717	−0.331325	97.648	2.037	0.115201
Compound **3**									
g+ [ac− ac−]	−1028.649887	0.82769	−1028.648943	1.6196020	−1028.694704	0.64194	96.313	0.623	0.115278
g+ [ac− ac+]	−1028.651206	0	−1028.650262	0	−1028.695727	0	95.69	0	0.115347
g+ [ac+ ac−]	−1028.648139	1.92457	−1028.647195	0.843372	−1028.693751	1.23995	97.986	2.296	0.115320
g+ [ac+ ac+]	−1028.650384	0.51581	−1028.649440	0.275476	−1028.695292	0.27296	96.505	0.815	0.115405
Compound **4**									
g+ [g− sc−]	−1028.673636	−0.26543652	−1028.672692	−0.265436	−1028.716870	0.3620729	92.980	−2.106	0.117500
g+ [g− ac+]	−1028.673213	0	−1028.672269	0	−1028.717447	0	95.086	0	0.117230
g+ [g+ sc−]	−1028.670634	1.618347	−1028.669689	1.6189745	−1028.714875	1.6139544	95.102	0.016	0.117153
g+ [g+ ac+]	−1028.672957	0.16064243	−1028.670120	1.3485179	−1028.717588	−0.088478	95.921	0.835	0.117197
g+ [a sc−]	−1028.669820	2.12913973	−1028.668876	2.1291397	−1028.714532	1.8291901	95.091	0.005	0.117162
g+ [a ac+]	−1028.671915	0.81450733	−1028.670971	0.8145073	−1028.717008	0.2754766	96.893	1.807	0.117222

Table 3. Thermodynamic functions and their relative values of compounds **1**–**4** computed at G3MP2B3/6-31G(d) level of theory

	G3MP2B3/6-31G (d)								
	U (Hartree)	ΔU (kcal/mol)	*H* (Hartree)	ΔH (kcal/mol)	*G* (Hartree)	ΔG (kcal/mol)	*S* (cal/molK)	ΔS (cal/molK)	Zero-point correction (Hartree)
Compound **1**									
g+ [g− ac−]	−952.426394	1.43009	−952.425450	1.43009	−952.470068	0.80195	93.906	2.106	0.107105
g+ [g− ac+]	−952.428673	0	−952.427729	0	−952.471346	0	91.800	0	0.107318
g+ [g+ ac−]	−952.427879	0.49824	−952.426935	0.49824	−952.471113	0.14621	92.980	1.18	0.107112
g+ [g+ ac+]	−952.426625	1.28513	−952.425681	1.28513	−952.470032	0.82454	93.345	1.545	0.107092
g+ [a ac−]	−952.426286	1.49786	−952.425342	1.49786	−952.470076	0.79693	94.151	2.351	0.107153
g+ [a ac+]	−952.426378	1.44013	−952.425434	1.44013	−952.470139	0.75740	94.090	2.29	0.107151
Compound **2**									
g+ [g− ac−]	−1027.549878	0.10855914	−1027.548934	0.10855914	−1027.595123	−0.04957325	97.213	0.53	0.110764
g+ [g− ac+]	−1027.550051	0	−1027.549107	0	−1027.595044	0	96.683	0	0.110831
g+ [g+ ac−]	−1027.549371	0.42670646	−1027.548427	0.42670646	−1027.595089	−0.02823793	98.208	1.525	0.110662
g+ [g+ ac+]	−1027.550242	−0.11985431	−1027.549298	−0.11985431	−1027.595794	−0.47063213	97.859	1.176	0.110740
g+ [a ac−]	−1027.550017	0.02133532	−1027.549073	0.02133532	−1027.595541	−0.31187222	97.800	1.117	0.110733
g+ [a ac+]	−1027.549133	0.57605372	−1027.548188	0.57668123	−1027.595094	−0.03137548	98.722	2.039	0.110593
Compound **3**									
g+ [ac− ac−]	−1027.550282	−1.46021461	−1027.549338	−1.46021461	−1027.594624	−0.34450272	95.312	3.743	0.110831
g+ [ac− ac+]	−1027.547955	0	−1027.547011	0	−1027.594075	0	99.055	0	0.110707
g+ [ac+ ac−]	−1027.548474	−0.32567743	−1027.547530	−0.32567743	−1027.591823	1.41315139	93.222	5.833	0.110538
g+ [ac+ ac+]	−1027.549974	−1.26694168	−1027.549029	−1.26631417	−1027.595390	−0.82517499	97.575	1.480	0.110788
Compound **4**									
g+ [g− sc−]	−1027.551670	1.96912	−1027.550726	1.96912	−1027.596137	2.12474	95.575	−0.522	0.112459
g+ [g− ac+]	−1027.554808	0	−1027.553864	0	−1027.599523	0	96.097	0	0.112538
g+ [g+ sc−]	−1027.552530	1.42946	−1027.551586	1.42946	−1027.597230	1.43887	96.066	−0.031	0.112472
g+ [g+ ac+]	−1027.553774	0.64884	−1027.552829	0.64947	−1027.598880	0.40348	96.922	0.825	0.112510
g+ [a sc−]	−1027.550017	3.00639	−1027.549073	3.00639	−1027.595015	2.82881	96.693	0.596	0.112518
g+ [a ac+]	−1027.551908	1.81977	−1027.550964	1.81977	−1027.597385	1.34161	97.701	1.604	0.112564

Table 4. Thermodynamic functions of H_2O computed at two levels of theory.

	U (Hartree)	*H* (Hartree)	*G* (Hartree)	*S* (cal/molK)	Zero-point correction (Hartree)
			B3LYP/6-31G (d)		
H_2O	−76.384944	−76.384000	−76.405446	45.135	0.021174
			G3MP2B3/6-31G (d)		
H_2O	−76.342806	−76.341861	−76.363307	45.137	0.021174

Table 5. Thermodynamic functions of H_2O_2 computed at two levels of theory

	U (Hartree)	*H* (Hartree)	*G* (Hartree)	*S* (cal/molK)	Zero-point correction (Hartree)
			B3LYP/6-31G (d)		
H_2O_2	−151.503495	−151.502550	−151.528542	54.704	0.021174
			G3MP2B3/6-31G (d)		
H_2O_2	−151.384872	−151.383927	−151.409932	54.732	0.021174

Table 6. Relative thermodynamic functions of oxidation reactions computed at B3LYP/6-31G(d) level of theory

	B3LYP/6-31G (d)			
	Δ*U* (kcal/mol)	Δ*H* (kcal/mol)	Δ*G* (kcal/mol)	Δ*S* (cal/molK)
	Reaction 1 $(COMP2 + H_2O) - (COMP1 + H_2O_2)$			
g+ [g− ac−]	−30.86844732	−30.86907483	−30.84585698	−0.079
g+ [g− ac+]	−32.48804934	−32.48867685	−31.04540500	−4.842
g+ [g+ ac−]	−31.21044000	−31.21106751	−30.76616328	−1.493
g+ [g+ ac+]	−32.78297881	−32.78360632	−31.68797473	−3.675
g+ [a ac−]	−31.64467658	−31.64530409	−31.30268390	−1.149
g+ [a ac+]	−32.21257267	−32.21320018	−31.37673002	−2.805
	Reaction 2 $(COMP3 + H_2O) - (COMP\ 1 + H_2O_2)$			
g+ [ac− ac−]	−31.97474657	−31.97537408	−30.74106290	−4.140
g+ [ac− ac+]	−32.80243160	−32.80305911	−31.38300511	−4.763
g+ [ac+ ac−]	−30.87785997	−30.87848748	−30.14304634	−2.467
g+ [ac+ ac+]	−32.28661879	−32.28724630	−31.11003848	−3.948
	Reaction 3 $(COMP4 + H_2O) - (COMP1 + H_2O_2)$			
g+ [g− sc−]	−46.87746969	−46.87809720	−44.65043847	−7.473
g+ [g− ac+]	−46.61203317	−46.61266068	−45.01251145	−5.367
g+ [g+ sc−]	−44.99368617	−44.99368617	−43.39855702	−5.351
g+ [g+ ac+]	−46.45139074	−45.26414276	−45.10099029	−4.532
g+ [a sc−]	−44.48289344	−44.48352095	−43.18332126	−5.362
g+ [a ac+]	−45.79752584	−45.79815335	−44.73703478	−3.560

the reactions are supposed to exist in biologic media at B3LYP/6-31G(d) level of theory. Results are shown in Table 8 and graphically shown in Fig. 13. As it can be noted, the two figures are comparable. On the ΔG scale, the difference between (**2**) and (**3**) as well as between (**3**) and (**4**) is 0.305 and 13.718 kcal/mol for the molecule in gas phase and 0.15 and 15.69 kcal/mol in water media.

The equilibrium constants for the isomerization of the oxidized product are illustrated in Fig. 14 and as expected:

$$K_{\mathbf{2}\rightarrow\mathbf{4}} = K_{\mathbf{2}\rightarrow\mathbf{3}} \cdot K_{\mathbf{3}\rightarrow\mathbf{4}} \tag{3}$$

or

$$\Delta G_{\mathbf{2}\rightarrow\mathbf{4}} = \Delta G_{\mathbf{2}\rightarrow\mathbf{3}} + \Delta G_{\mathbf{3}\rightarrow\mathbf{4}} \tag{4}$$

Table 7. Relative thermodynamic functions of oxidation reactions computed at G3MP2B3/6-31G (d) level of theory

	G3MP2B3/6-31G (d)			
	ΔU (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)	ΔS (cal/molK)
	Reaction 1 $(COMP2 + H_2O) - (COMP1 + H_2O_2)$			
g+ [g− ac−]	−49.66047432	−49.66047432	−48.41361294	−4.182
g+ [g− ac+]	−49.76903346	−49.76903346	−48.36403969	−4.712
g+ [g+ ac−]	−49.34232700	−49.34232700	−48.39227762	−3.187
g+ [g+ ac+]	−49.88888778	−49.88888778	−48.83467182	−3.536
g+ [a ac−]	−49.74769814	−49.74769814	−48.67591191	−3.595
g+ [a ac+]	−49.19297974	−49.19235223	−48.39541517	−2.673
	Reaction 2 $(COMP3 + H_2O) - (COMP1 + H_2O_2)$			
g+ [ac− ac−]	−49.91398816	−49.91398816	−48.10048570	−6.083
g+ [ac− ac+]	−48.45377355	−48.45377355	−47.75598299	−2.340
g+ [ac+ ac−]	−48.77945098	−48.77945098	−46.34283159	−8.173
g+ [ac+ ac+]	−49.72071523	−49.72008772	−48.58115798	−3.820
	Reaction 3 $(COMP4 + H_2O) - (COMP1 + H_2O_2)$			
g+ [g− sc−]	−50.78497134	−50.78497134	−49.04990758	−5.820
g+ [g− ac+]	−52.75409616	−52.75409616	−51.17465474	−5.298
g+ [g+ sc−]	−51.32462951	−51.32462951	−49.73577546	−5.329
g+ [g+ ac+]	−52.10525133	−52.10462382	−50.77116614	−4.473
g+ [a sc−]	−49.74769814	−49.74769814	−48.34584192	−4.702
g+ [a ac+]	−50.93431861	−50.93431861	−49.83303943	−3.694

Table 8. Computed energy and Gibbs free energy values obtained at B3LYP/6-31G(d) [scrf = (pcm,solvent = water)] level of theory for compounds **1**–**4**

	SCF done: *E* (RB + HF − LYP)	Total free energy in solution: with all non electrostatic terms (a.u.)
	Compound **1**	
g+ [g− ac−]	−953.604090	−953.592332
g+ [g− ac+]	−953.609394	−953.595420
g+ [g+ ac−]	−953.605871	−953.593777
g+ [g+ ac+]	−953.604670	−953.592621
g+ [a ac−]	−953.605332	−953.593434
g+ [a ac+]	−953.605490	−953.593629
	Compound **2**	
g+ [g− ac−]	−1028.779369	−1028.767177
g+ [g− ac+]	−1028.779274	−1028.768662
g+ [g+ ac−]	−1028.779187	−1028.767166
g+ [g+ ac+]	−1028.785541	−1028.773263
g+ [a ac−]	−1028.781224	−1028.768767
g+ [a ac+]	−1028.780306	−1028.768738
	Compound **3**	
g+ [ac− ac−]	−1028.779363	−1028.767639
g+ [ac− ac+]	−1028.785085	−1028.769172
g+ [ac+ ac−]	−1028.779724	−1028.769172
g+ [ac+ ac+]	−1028.781898	−1028.770166
	Compound **4**	
g+ [g− ac−]	−1028.808257	−1028.798022
g+ [g− ac+]	−1028.807603	−1028.797202
g+ [g+ ac−]	−1028.806300	−1028.794805
g+ [g+ ac+]	−1028.807919	−1028.796168
g+ [a ac−]	−1028.805354	−1028.793957
g+ [a ac+]	−1028.806924	−1028.795477

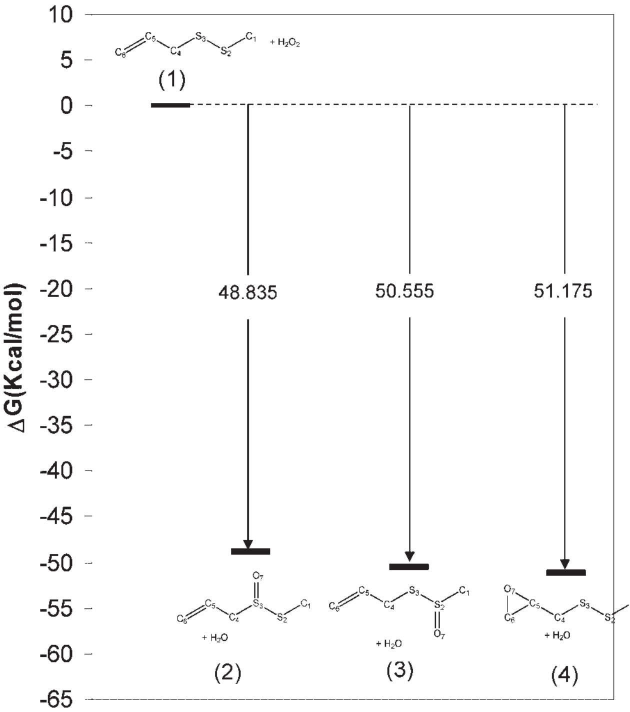


Figure 12. Gibbs free energy levels of oxidation reactions according Scheme 1

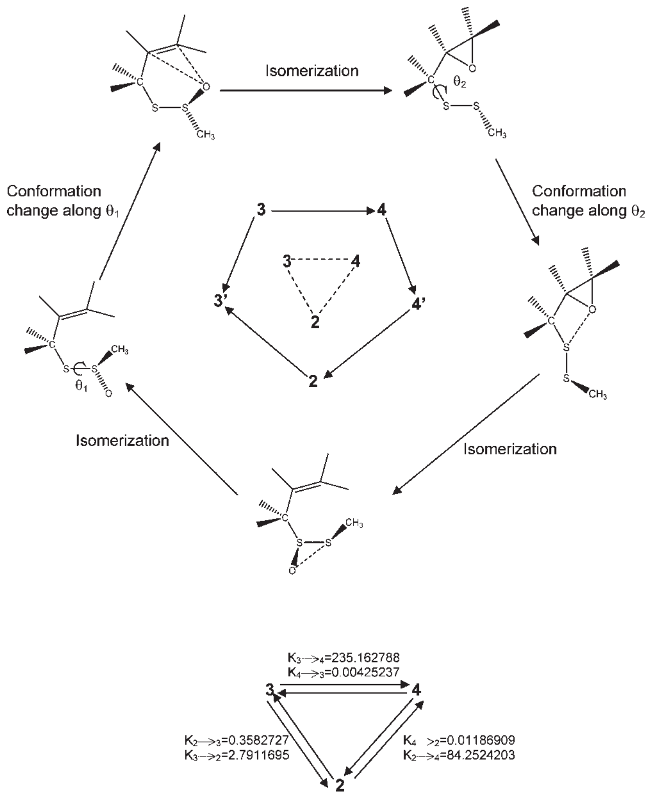


Figure 14. Interconversions and equilibrium constants for isomers **2**–**4**

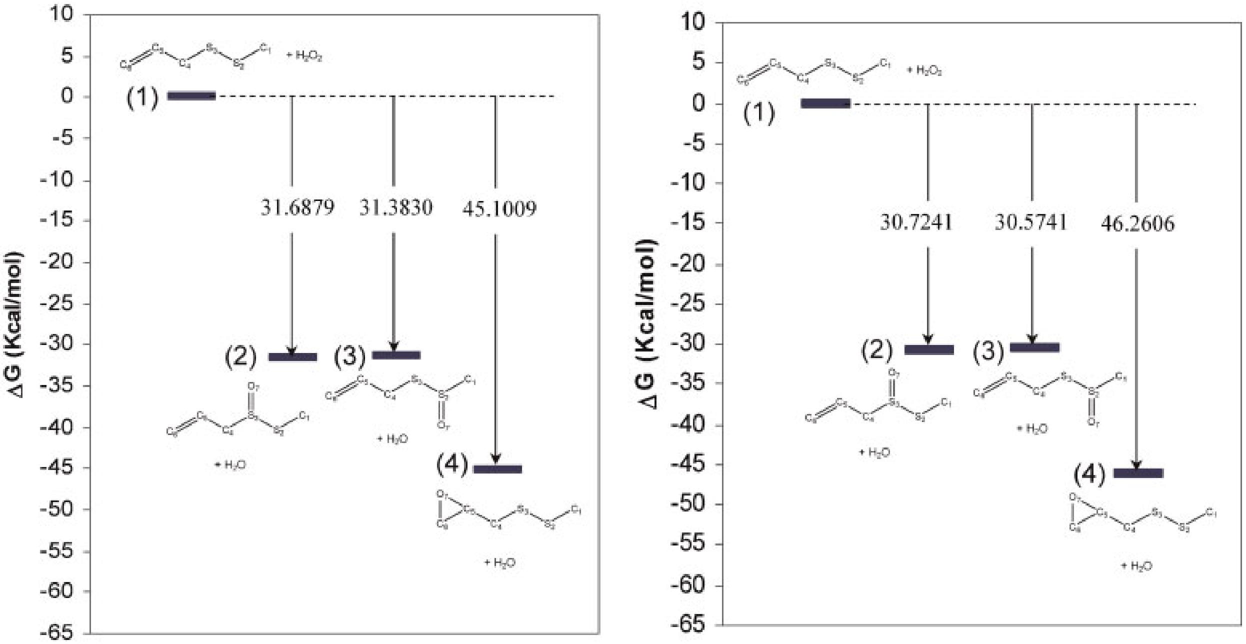


Figure 13. Gibbs free energy levels of oxidation reactions according Scheme 1 at B3LYP/6-31G (d) level of theory: left for molecules in gas phase; right for molecules in aqueous media

SUPPLEMENTARY INFORMATION

In order to see if some secondary interactions such as hydrogen bond,[18] involving C—H protons or donor-acceptor complexation, such as Kucsman-type S. . .O interaction,[23–25] may exist Bader-type AIM analysis were performed on the oxidized products compounds **2**–**4**. The results are shown in Figs S1, S2 and S3, respectively. In all three cases, C—H bonds are involved in the observed secondary interactions. Since such interactions are very weak, they do not influence the relative stability of the various conformers.

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