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William N. Setzer[a]
[a] Department of Chemistry, University of Alabama in Huntsville, Huntsville, AL, USA

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A theoretical investigation into the formation of sesquiterpene episulfides

William N. Setzer*

Department of Chemistry, University of Alabama in Huntsville, Huntsville, AL, USA

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A theoretical investigation using both density functional theory and post-Hartree–Fock *ab initio* methods has been carried out on the episulfidation of the sesquiterpenes germacrene D, β-caryophyllene, and α-humulene. The calculations show that formation of the sesquiterpene episulfides mintsulfide, caryophyllene-6,7-episulfide, caryophyllene-3,6-episulfide, humulene-6,7-episulfide, and humulene-9, 10-episulfide, by reaction with elemental sulfur, are all exothermic, with formation of mintsulfide the most exothermic. Of the caryophyllene episulfides, caryophyllene-3,6-episulfide is more stable than caryophyllene-6,7-episulfide, consistent with experimental observations. Formation of humulene-6, 7-episulfide involves a lower energy diradical intermediate than formation of humulene-9,10-episulfide, consistent with the early preferential formation of humulene-6,7-episulfide observed experimentally.

Keywords: mintsulfide; caryophyllene-6,7-episulfide; caryophyllene-3,6-sulfide; humulene-6,7-episulfide; humulene-9,10-episulfide; *ab initio*

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1. Introduction

Mintsulfide (**1**) was first isolated from peppermint oil (*1*), but has been detected in minor amounts in a number of essential oils from other plants (*2–14*), as well as mushrooms (*15*). Biosynthesis of mintsulfide in peppermint has been suggested to arise from reaction of germacrene D with elemental sulfur (*16*, *17*), and it has been prepared in the laboratory by photochemical reaction of germacrene D with sulfur (*1*, *18*, *19*). Similarly, heating β-caryophyllene with elemental sulfur at 120° forms caryophyllene-6,7-episulfide as well as caryophyllene-3,6-episulfide, while α-humulene forms humulene-6,7-episulfide, then humulene-9,10-episulfide (*20–22*). This report presents a theoretical investigation of the energetics of the formation of these sesquiterpene sulfides using both density functional theory (DFT) and post-Hartree–Fock *ab initio* molecular orbital theory.

2. Computational methods

All calculations were carried out using SPARTAN '06 for Windows (*23*). The hybrid B3LYP functional (*24*, *25*) and the 6-31G* basis set (*26*) were used for the optimization of all stationary

*Email: wsetzer@chemistry.uah.edu

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points in the gas phase. Single-point Hartree–Fock *ab initio* energies were calculated using the DFT geometries (above) at the 6-31G** (*26*) level, followed by a correlation energy calculation using the second-order Møller–Plesset model (MP2) (*26*). Frequency calculations were used to characterize stationary points as minima. All enthalpies reported are zero-point corrected with unscaled frequencies, but with no thermal corrections; they are, therefore, $H_{(0K)}$. It has been demonstrated that Hartree–Fock (HF) and post-HF methods (*e.g.* MP2) suffer from spin contamination problems and therefore both geometries and energies are unreliable (*27–29*). DFT methods, on the other hand, do not suffer from the effects of spin contamination to the extent that MP2 does. DFT/B3LYP was used, therefore, to calculate the geometries and energies of triplet diradical intermediates for the episulfidation reactions. Evaluations of the spin operators, $\langle S^2 \rangle$,

Table 1. B3LYP (MP2 in parentheses) relative reaction enthalpies, kcal/mol, for formation of sesquiterpene episulfides.

Sesquiterpene episulfide formation	Sesquiterpene + (1/8)S_8	Sesquiterpene + $^3S_1$	Diradical intermediate	Sesquiterpene episulfide	ΔH_r
Mintsulfide	20.0 (42.0)	75.2	65.7	0.0 (0.0)	−20.0 (−42.0)
cis-caryophyllene-6,7-episulfide	25.1 (42.4)	80.5	67.3	22.7 (31.3)	−2.3 (−11.1)
trans-caryophyllene-6,7-episulfide	25.3 (42.9)	80.3	67.0	22.5 (27.7)	−2.8 (−15.2)
(3*R*,6*S*)-caryophyllene-3,6-episulfide	25.1 (42.4)	80.3	67.3	16.3 (19.1)	−8.8 (−23.3)
(3*S*,6*R*)-caryophyllene-3,6-episulfide	25.3 (42.9)	80.5	67.0	16.5 (19.9)	−8.8 (−22.9)
(6*R*,7*R*)-humulene-6,7-episulfide	19.8 (40.1)	75.0	63.4	16.8 (25.5)	−3.0 (−14.6)
(6*S*,7*S*)-humulene-6,7-episulfide	19.9 (40.6)	75.1	64.7	18.9 (28.3)	−0.9 (−12.3)
(9*S*,10*S*)-humulene-9,10-episulfide	19.8 (40.1)	75.0	65.3	16.7 (26.1)	−3.1 (−14.0)
(9*R*,10*R*)-humulene-9,10-episulfide	19.9 (40.6)	75.1	66.0	17.7 (27.1)	−2.2 (−13.5)
(2*S*,3*S*)-humulene-2,3-episulfide	19.8 (40.1)	75.0	68.1	21.6 (30.3)	1.8 (−9.8)

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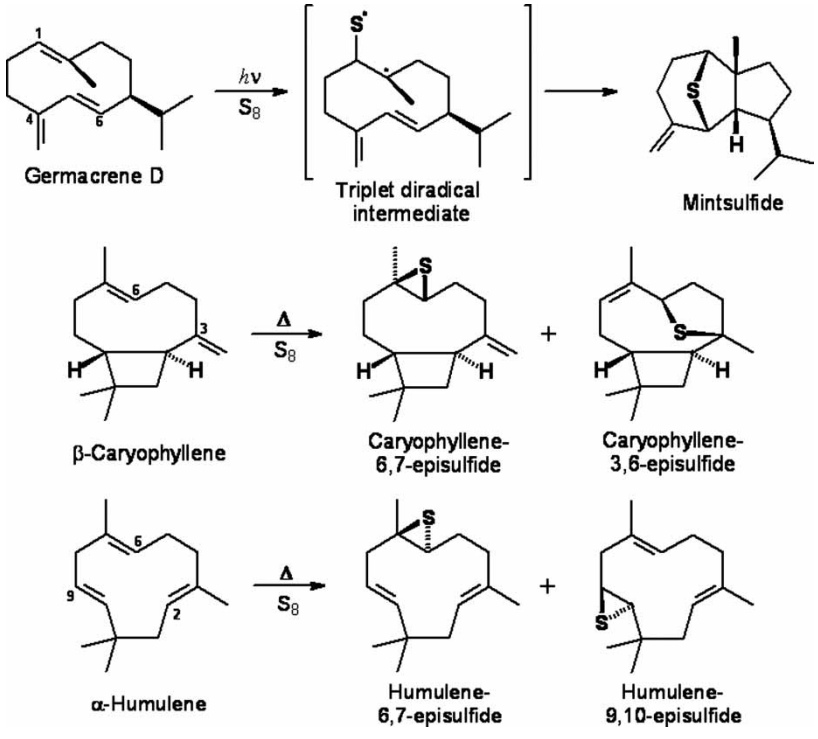

Figure 1. Formation of sesquiterpene episulfides by direct reaction with sulfur.

were carried out to verify that there was minimal spin contamination. The $\langle S^2 \rangle$ for all triplet diradical intermediates ranged from 2.0051 to 2.0085, confirming the negligible spin contamination using the DFT method.

3. Results and discussion

The formation of sesquiterpene sulfides from the sesquiterpenes and elemental sulfur was modeled using both density functional (B3LYP/6-31G*) and post Hartree–Fock *ab initio* (MP2/6-31G**) methods in the gas phase (Table 1). The reaction profiles represent the enthalpy of atomization of cyclooctasulfur (S_8) to triplet sulfur atoms, formation of diradical intermediates from addition of sulfur, and ring closure to give the sesquiterpene sulfide products (see Figure 1). All episulfidation reactions (reactions of sesquiterpene hydrocarbons with elemental sulfur) are shown to be exothermic, with formation of mintsulfide the most exothermic ($\Delta H_r = -20$ kcal/mol). The triplet is the ground state electronic structure of the sulfur atom, and addition of $^3S_1$ to simple alkenes proceeds by way of diradical intermediates (*30*, *31*). The post-HF (MP2/6-31G**) calculations generally show more exothermic enthalpies of reaction for the episulfidation reactions than the DFT (B3LYP/6-31G*) calculations. Zoller *et al.* (*32*) had found analogous differences between B3LYP and MP3 calculations on episulfidation of arenes, although those reactions were endothermic. Note, also, that the B3LYP method has been shown to overestimate the enthalpy of formation of thiirane (*33*), while MP2 underestimates ΔH_f of thiirane (*34*).

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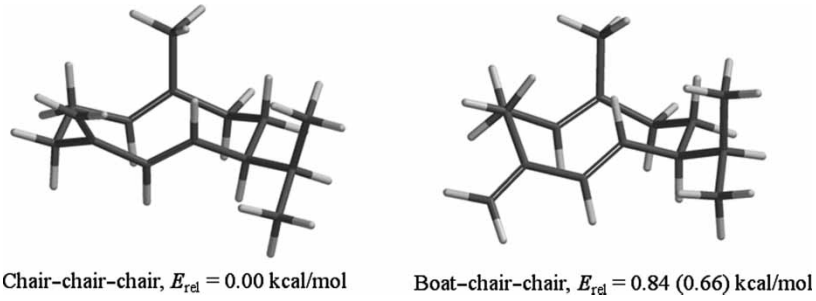

Figure 2. DFT low-energy conformations of germacrene D (MP2 energies in parentheses).

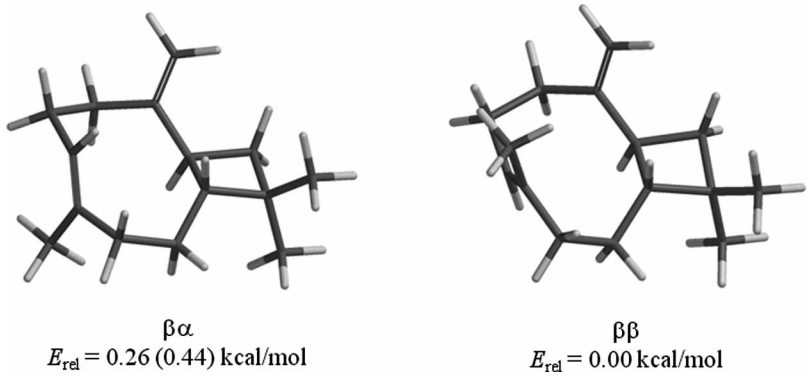

Figure 3. DFT low-energy conformations of β-caryophyllene (MP2 energies in parentheses).

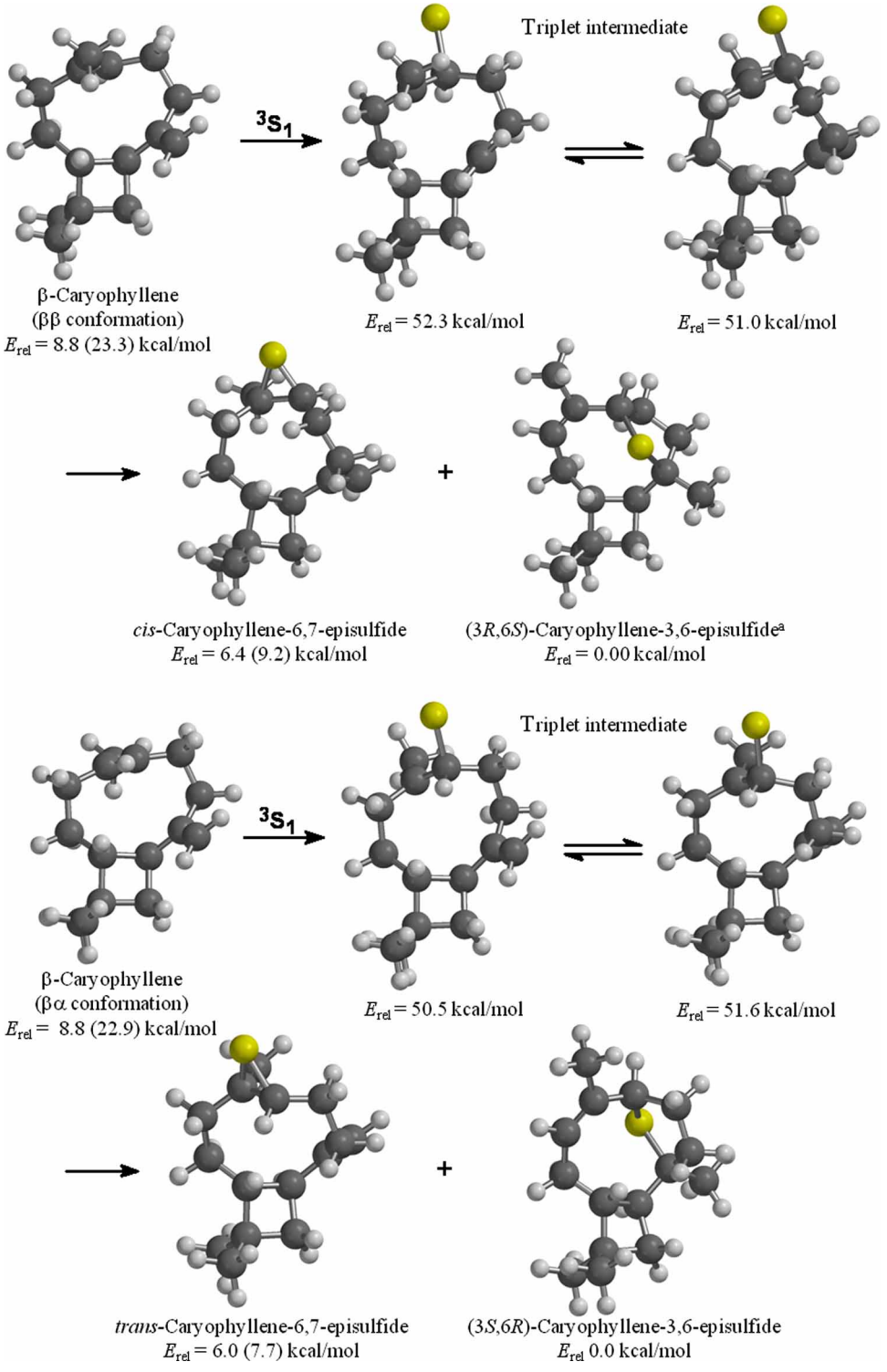

Figure 4. Episulfidation of β-caryophyllene. The energies, DFT (MP2 in parentheses), are relative to the respective products for each transformation.[1]

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In order to model the reaction, it was necessary to determine the most stable conformations of the starting sesquiterpenes as well as the intermediates and products. A conformational analysis of germacrene D reveals the chair–chair–chair conformation to be slightly more stable than the alternative boat–chair–chair (see (*19*)) by less than 1 kcal/mol (DFT, 0.83 kcal/mol; MP2, 0.66 kcal/mol) (Figure 2), and this conformation was used for subsequent calculations for the formation of mintsulfide. Reaction of triplet sulfur atom ($^3S_1$) with germacrene D is predicted to proceed by way of attack at C(1) of germacrene D, with subsequent transannular ring closure to give mintsulfide (Figure 1).

Molecular mechanics calculations had shown two low-energy conformations (designated $\beta\alpha$ and $\beta\beta$, Figure 3) for β-caryophyllene, but discrepancies as to which is lower in energy depends on the force field used (*35*). In this study, *ab initio* calculations using both DFT and MP2 methods show that the $\beta\beta$ conformer is slightly lower in energy (DFT, 0.26 kcal/mol; MP2, 0.28 kcal/mol) than the $\beta\alpha$. Addition of $^3S_1$ to C(6) of β-caryophyllene in the $\beta\beta$ conformation would be expected to lead to a conformationally mobile diradical intermediate with the *S* configuration at C(6) (Figure 4). The lowest-energy conformation (*cis* orientation of the C(6) hydrogen and C(7) methyl) of this diradical intermediate, then, leads to *cis*-caryophyllene-6,7-episulfide. Alternative ring closure of the *trans* intermediate would give a *trans*-fused episulfide, (6*S*,7*S*)-caryophyllene-6, 7-episulfide, but this product is higher in energy than the *cis* (DFT, 2.5 kcal/mol; MP2, 3.0 kcal/mol), and is predicted to be less important. Ashitani and co-workers (*21*, *22*) had observed that episulfidation of β-caryophyllene proceeds with initial formation of *trans*-caryophyllene-6,7-episulfide, but longer reaction times resulted in the formation of caryophyllene-3,6-episulfide with concomitant decline in caryophyllene-6,7-episulfide. These observations are consistent with the *ab initio* calculations: caryophyllene-3,6-episulfide is thermodynamically more stable

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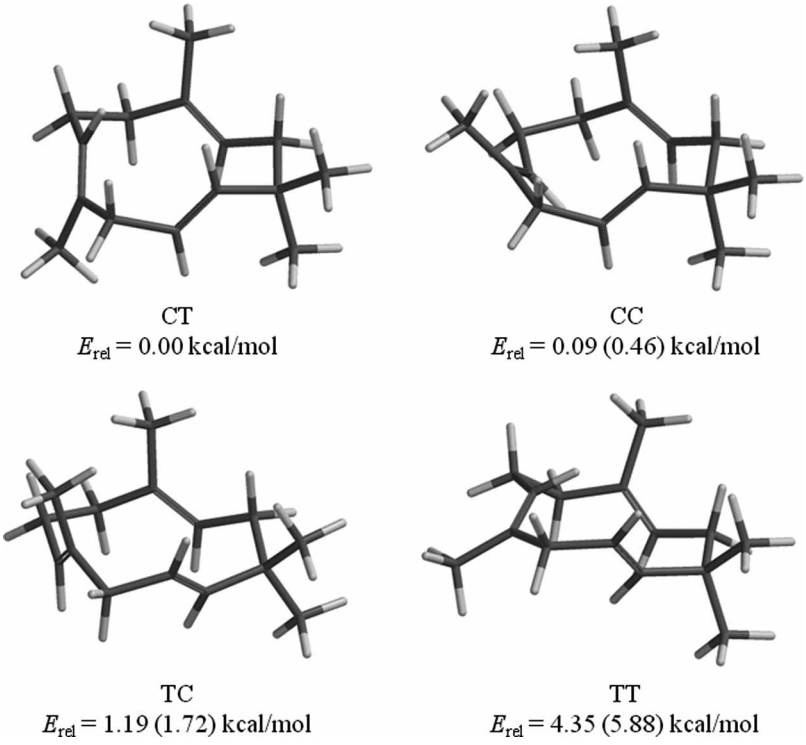

Figure 5. DFT low-energy conformations of α-humulene (MP2 energies in parentheses).

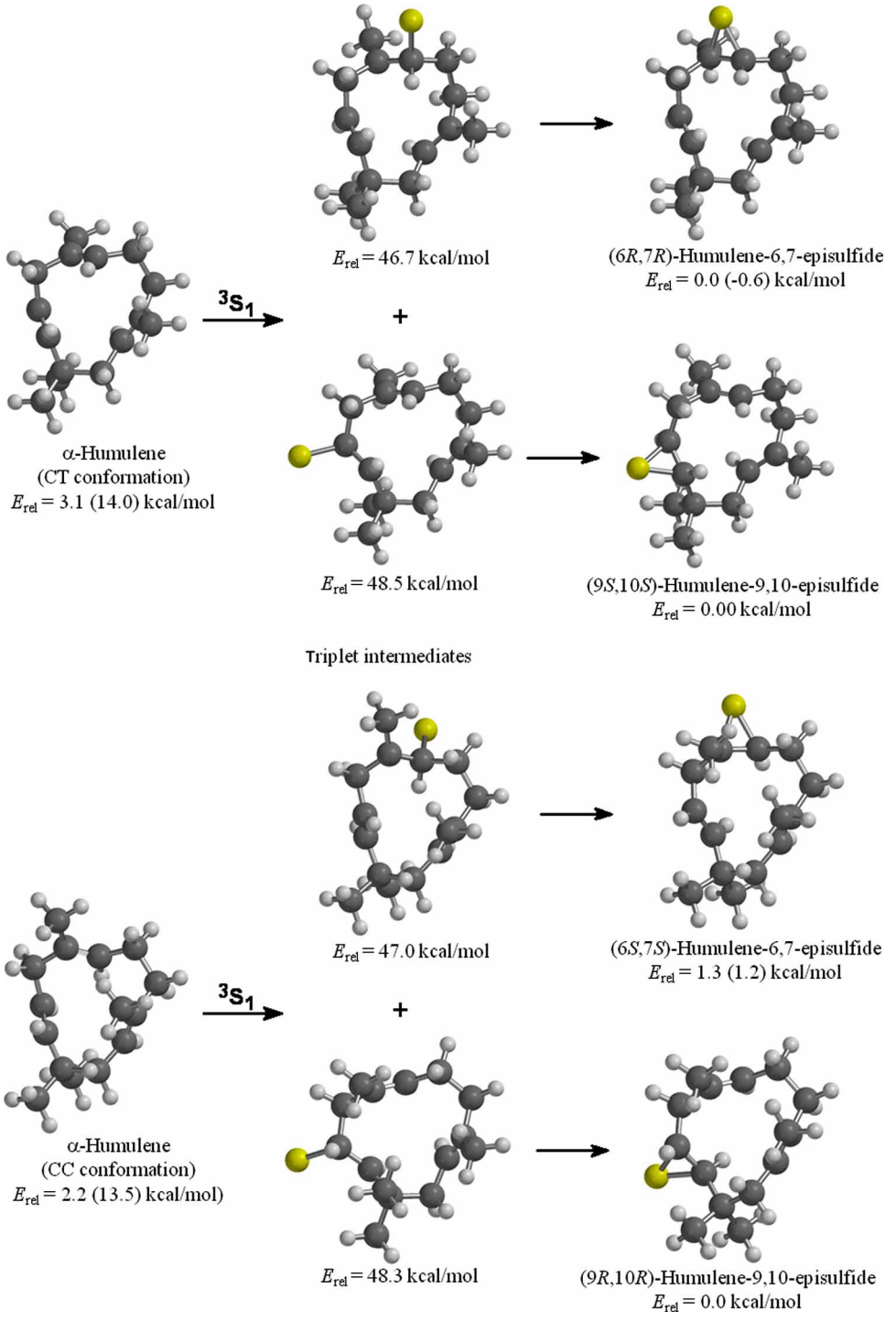

Figure 6. Episulfidation of α-humulene to form humulene-6,7-episulfide and humulene-9,10-episulfide. The energies, DFT (MP2 in parentheses), are relative to the respective products for each transformation.

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than either *cis*- or *trans*-caryophyllene-6,7-episulfide (DFT, 6.4 and 6.2 kcal/mol, respectively; MP2, 9.2 and 8.5 kcal/mol, respectively). Addition of $^3S_1$ to the $\beta\alpha$ conformation of β-caryophyllene leads to the alternative triplet diradical intermediate, *R* configuration at C(6), and the lowest-energy conformation of the triplet intermediate would lead to *trans*-(6*R*,7*R*)-caryophyllene-6,7-episulfide, which is slightly lower in energy than the *cis*-diastereomer (DFT, 0.18 kcal/mol; MP2, 0.70 kcal/mol). This *trans*-caryophyllene-6,7-episulfide (Figure 4) is the stereoisomer suggested by Ashitani and co-workers (*21*, *22*) to arise from direct episulfidation of β-caryophyllene. Transannular ring closure of the triplet intermediate derived from the $\beta\alpha$ conformation of β-caryophyllene would lead to the alternative, higher-energy (3*S*,6*R*)-caryophyllene-3,6-episulfide stereoisomer (see Figure 4). However, this isomer is not the stereoisomer suggested by Ashitani *et al.* (*22*).

Previous molecular mechanics conformational analysis of α-humulene indicated four low-energy conformations (designated CT, CC, TT, and TC, Figure 5), with the CT predicted to be lowest in energy (*36*). *Ab initio* calculations show the CT conformation to be the lowest energy conformation for α-humulene as well as the intermediates and episulfide products. There are two potential diradical intermediates in the addition of a sulfur atom to α-humulene leading to humulene-9,10-episulfide; addition of sulfur atom to C(9) or to C(10). The calculations indicate attack of sulfur at C(9) to be the lower-energy pathway. Both DFT and MP2 calculations indicate humulene-6,7-episulfide and humulene-9,10-episulfide to be nearly equal in energy. The B3LYP calculations show humulene-9,10-episulfide 0.03 kcal/mol more stable than humulene-6,7-episulfide, while the MP2 calculations are reversed, with humulene-6,7-episulfide 0.63 kcal/mol more stable than humulene-9,10-episulfide. Experimentally, direct episulfidation of α-humulene with elemental sulfur slightly favors humulene-6,7-episulfide at relatively short reaction times, but humulene-9,10-episulfide with longer reaction times (*21*, *22*). These data would suggest humulene-6,7-episulfide to be the kinetically controlled product while humulene-9,10-episulfide the thermodynamically controlled product. The diradical intermediate formed by addition of $^3S_1$ to C(6) of α-humulene is lower in energy (1.9 kcal/mol) than the diradical intermediate by addition of $^3S_1$ to C(9), consistent with early preferential formation of humulene-6,7-episulfide. Episulfidation of the CT (lowest-energy) conformation of α-humulene is predicted to lead to (6*R*,7*R*)-humulene-6,7-episulfide and (9*S*,10*S*)-humulene-9,10-episulfide by way of the 6*R* and 9*R* triplet intermediates, respectively (Figure 6). Episulfidation of the TT conformation would lead to the same products, but the TT conformation is relatively high in energy. Alternatively, episulfidation of either the CC or the TC conformations of α-humulene should give rise to 6*S* and 9*S* triplet intermediates, leading to (6*S*,7*S*)-humulene-6,7-episulfide and (9*R*,10*R*)-humulene-9,10-episulfide, respectively. The episulfide products derived from the CT or TT conformations

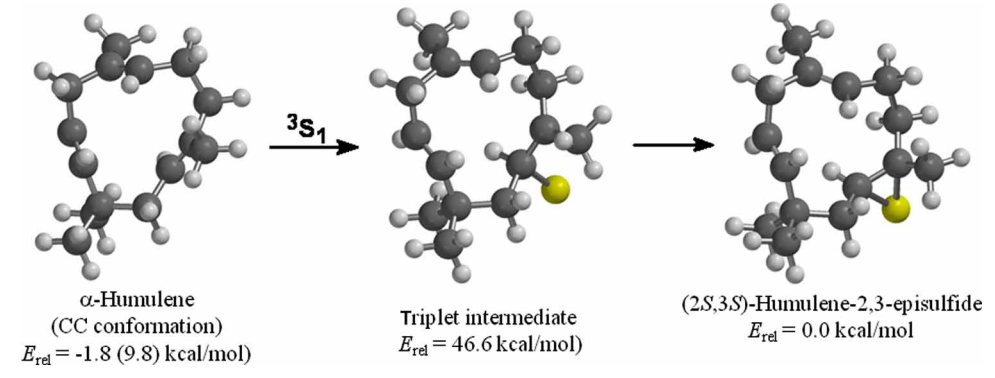

Figure 7. Episulfidation of α-humulene to form humulene-2,3-episulfide. The energies, DFT (MP2 in parentheses), are relative to the product.

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of α-humulene, (6*R*,7*R*)-humulene-6,7-episulfide and (9*S*,10*S*)-humulene-9,10-episulfide, are both lower in energy than those derived from the CC or TC conformations. Given that the starting conformation, the CT conformation, is lowest in energy, the triplet intermediates are lower in energy, and the products are lower in energy, episulfidation of α-humulene is predicted to lead to (6*R*,7*R*)-humulene-6,7-episulfide and (9*S*,10*S*)-humulene-9,10-episulfide (Figure 6).

At first glance, it is unclear why elemental sulfur does not react with α-humulene to form humulene-2,3-episulfide (see Figure 7). This reaction has been modeled and the results are consistent with experiment (*21*, *22*); humulene-2,3-episulfide is higher in energy than formation of either humulene-6,7-episulfide or humulene-9,10-episulfide. In fact, the DFT calculations predict formation of humulene-2,3-episulfide to be endothermic.

4. Summary

Ab initio calculations show that formation of the sesquiterpene episulfides mintsulfide, caryophyllene-6,7-episulfide, caryophyllene-3,6-episulfide, humulene-6,7-episulfide, and humulene-9,10-episulfide, by reaction of the corresponding sesquiterpene hydrocarbon and elemental sulfur, are all exothermic, with formation of mintsulfide the most exothermic. Of the caryophyllene episulfides, caryophyllene-3,6-episulfide is more stable than caryophyllene-6, 7-episulfide, consistent with experimental observations. Formation of humulene-6,7-episulfide involves a lower energy diradical intermediate than formation of humulene-9,10-episulfide, consistent with early preferential formation of humulene-6,7-episulfide observed experimentally. Formation of humulene-2,3-episulfide, which has not been observed experimentally, is the least exothermic (actually endothermic by DFT), consistent with the experiment.

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Note

1. This is the caryophyllene-3,6-episulfide stereoisomer suggested by Ashitani *et al.* (*22*).

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