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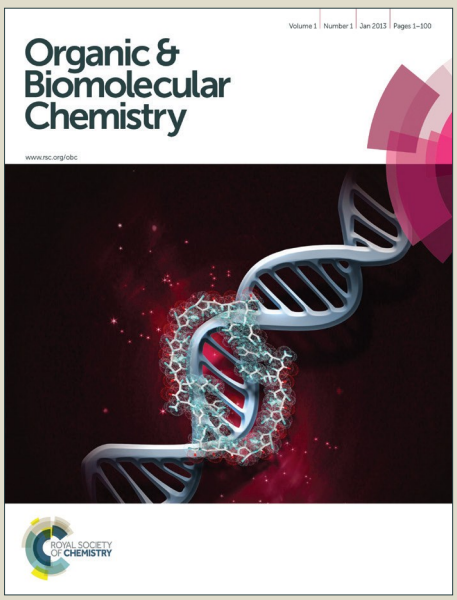

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Investigation into 9(*S*)-HPODE-derived allene oxide to cyclopentenone cyclization mechanism via diradical oxyallyl intermediates

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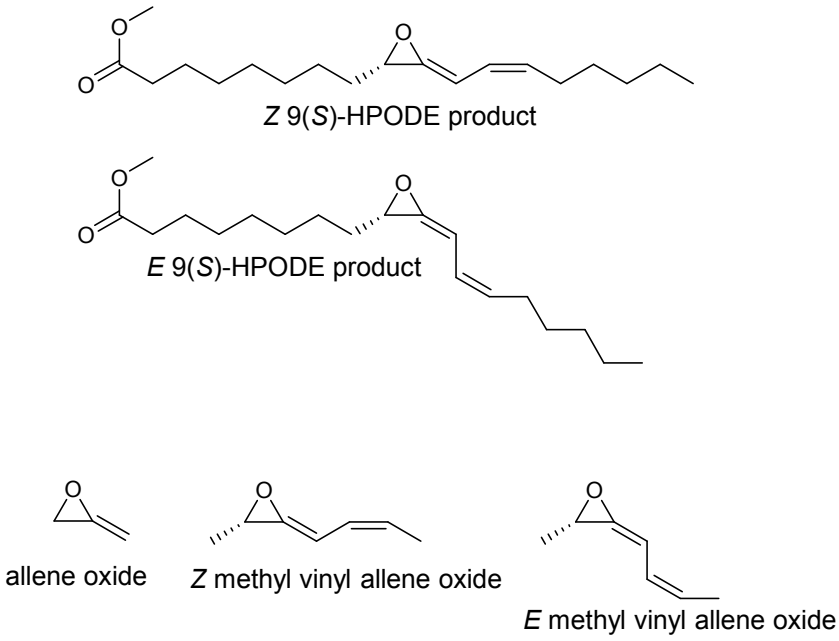
Abstract

The cyclopentane core is ubiquitous among a large number of biologically relevant natural products. Cyclopentenones have been shown to be versatile intermediates for the stereoselective preparation of highly substituted cyclopentane derivatives. Allene oxides are oxygenated fatty acids which are involved in the pathways of cyclopentenone biosynthesis in plants and marine invertebrates; however, their cyclization behavior is not well understood. Recent work by Brash and co-workers (*J. Biol. Chem.* **2013**, *288*, 20797) revealed an unusual cyclization property of the 9(*S*)-HPODE-derived allene oxides: the previously unreported 10Z-isomer cyclizes to a *cis*-dialkylcyclopentenone in hexane/isopropyl alcohol (100:3,v/v), but the known 10*E*-isomer does not yield *cis*-cyclopentenone under the same conditions. The mechanism for cyclization has been investigated for unsubstituted and methyl substituted vinyl allene oxide using a variety of methods including CASSCF, ωB97xD, and CCSD(T) and basis sets up to cc-pVTZ. The lowest energy pathway proceeds via homolytic cleavage of the epoxide ring, formation of an oxyallyl diradical, which closes readily to a cyclopropanone intermediate. The cyclopropanone opens to the requisite oxyallyl which closes to the experimentally observed product, *cis*-cyclopentenone. The calculations show that the open shell, diradical pathway is lower in energy than the closed shell reactions of allene oxide to cyclopropanone, and cyclopropanone to cyclopentenone.

Introduction

There is growing interest regarding the mechanistic pathway of allene oxide rearrangement to cyclopentenones, both in experimental biology[1-10] and in computational theory[11-16]. Among the downstream cyclic products arising from biosynthetic pathways containing key allene oxide intermediates are jasmonic acid in plants[17] and clavulones in marine invertebrates.[18] The natural allene oxides are produced by a formal dehydration of unsaturated fatty acid hydroperoxides catalyzed by specialized cytochromes P450 or catalase-related hemoproteins.[19-20] In an aqueous environment the half-life of the allene oxide products is estimated as only 30 - 40 s at pH 7.4 and 0°C.[21-22] Nonetheless, rapid extraction and processing under cold conditions has permitted NMR analysis of the methyl ester derivatives.[23] The consistent appearance of the olefinic signals in the proton NMR reveals that, with one exception,[1] the natural allene oxides share a common geometry of the unsaturated epoxyene moiety[23-25] with the double bond impinging on the epoxide in the *E* configuration (**Scheme 1**).[1, 26] The exception was uncovered recently with the discovery that cytochrome P450 CYP74C3 forms two allene oxide stereoisomers from its substrate 9*S*-hydroperoxy-octadeca-10*E*,12*Z*-dienoic acid (9*S*-HPODE), and a mixture of 9,10-epoxy allene oxide methyl esters of the 10*E* and 10*Z* configuration were characterized by NMR (**Scheme 1**).[1] Significantly, after chromatographic separation of the *E* and *Z* isomers at -15°C and subsequent exposure to room temperature in the hexane/isopropyl alcohol (100:3, v/v) solvent, the *Z* isomer forms cyclopentenone spontaneously, whereas the *E* isomer degrades by reaction with solvent but does not cyclize.[1]



Scheme 1. The allene oxides from 9(*S*)-hydroperoxylinoleic acid and the unsubstituted and substituted allene oxides used in the calculations

Theoretical studies of the reactions of allene oxides have focused on simplified substituted and unsubstituted allene oxides (**Scheme 1**).[11-16] Isomerization of the parent allene oxide is believed to proceed via ring opening to an oxyallyl intermediate which can close to cyclopropanone.[6, 27-28] An experimental investigation into the thermal stereomutation of enantiomerically enriched *trans* di *tert*-butyl cyclopropanone via an oxyallyl intermediate found little solvent effect[29-30] ($\Delta G^{\ddagger}$ = 27 – 29 kcal/mol for solvents ranging from acetonitrile to isooctane), suggesting the intermediate is a diradical rather than a zwitterion. A recent crystallographic study has provided further evidence of an oxyallyl diradical intermediate.[31] Early calculations on the ring opening of unsubstituted allene oxide at the CASSCF(4,4)/6-31G(d)

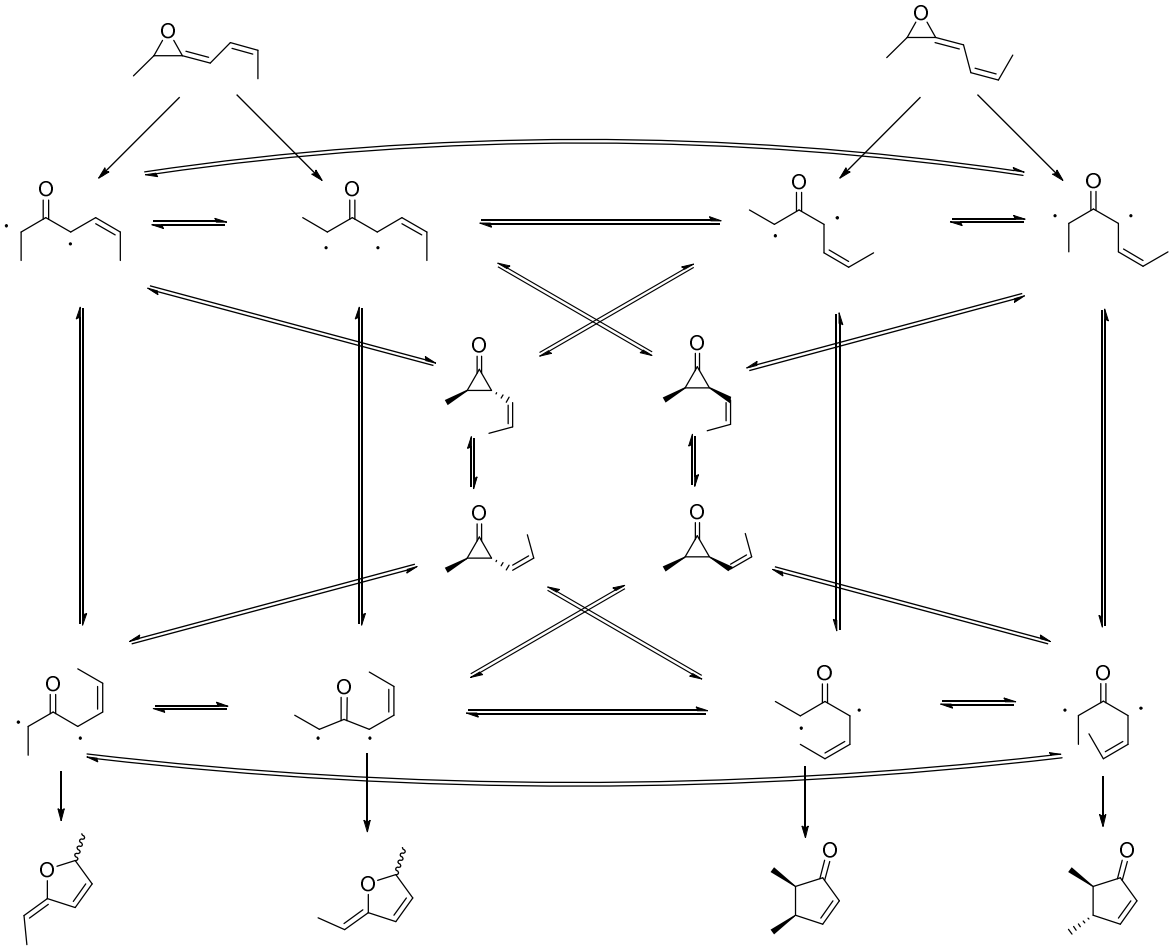
level of theory likewise found that the oxyallyl intermediate was a diradical and showed that it had a very small barrier for ring closing to cyclopropanone.[29] The CASPT2 calculations yield a free energy of 28 kcal/mol for the ring opening barrier of cyclopropanone to oxyallyl diradical,[13] in good agreement with the experimental value of 27 – 29 kcal/mol for racemization of *trans* di *tert*-butyl cyclopropanone.[30] Later studies showed that spin unrestricted B3LYP density functional and QCISD(T) calculations also gave good values for the relative energies of allene oxide, oxyallyl and cyclopropanone.[13] The singlet and triplet states of oxyallyl diradical have been observed directly by photoelectron spectroscopy and the singlet oxyallyl diradical was found to be 1.3 kcal/mol lower in energy than the triplet.[28, 32] Large basis set CASPT2 and EOM-SP-CCSD(dT) calculations agree with this experimental observation.[10, 28, 32]

Until recently, studies of the rearrangement of substituted allene oxide to cyclopentenone have assumed *E* stereochemistry for the double bond in allene oxide. Density functional calculations on vinyl substituted *E* allene oxide with the UB3LYP/6-31G(d) level of theory found that the stepwise pathway for the formation of cyclopentenone via an oxyallyl intermediate was competitive with the concerted reaction.[11, 15] Recent calculations with closed shell density functional theory at the B3LYP/6-311++G(3df,3pd) level found that the stepwise pathway for the vinyl substituted *E* allene oxide via a cyclopropanone intermediate to cyclopentenone was lower in energy than the concerted pathway,[13-14] but this study did not examine the stepwise mechanism for the *Z* isomer. De Lera, Lopez and coworkers have carried out a detailed investigation of methyl substituted vinyl *E* allene oxide[11, 16] and *Z* allene[12] oxide using ωB97XD density functional theory with a 6-311++G(3df,2p) basis set and PCM solvation. The stepwise pathways were found to be comparable in energy for the *E* and *Z* isomers. The

concerted pathway is possible only for the *E* isomer but not for the *Z* isomer, and is about 3 kcal/mol higher in energy than the stepwise path. With spin restricted ωB97XD, the ring opening of allene oxide proceeded directly to vinyl cyclopropanone without a local minimum for oxyallyl. However, with spin unrestricted ωB97XD, an oxyallyl intermediate could be characterized.[16] De Lera and co-workers[12] proposed that cyclopentenone was then formed from vinyl cyclopropanone by a concerted [1,3] sigmatropic rearrangement. The lowest energy pathways led from methyl substituted *Z* vinyl allene oxide to *cis* dimethylcyclopentenone and from the *E* isomer to *trans* dimethylcyclopentenone.

Recent investigation of the reaction of substituted allene oxide used density functional theory and found closed shell pathways for cyclization to cyclopentenone.[12] Because experimental and theoretical studies point to the importance of diradical intermediates, we have re-examined the pathways for the cyclization of methyl vinyl substituted allene oxide to cyclopentenone using theoretical methods such as CASSCF, spin unrestricted CCSD(T) and spin unrestricted density functional theory that are suitable for diradicals. As in previous theoretical studies,[11-16] the present work uses methyl substituted vinyl allene oxide (hereafter simply termed methyl vinyl allene oxide) to model the reactions of the *Z* and *E* 9(*S*)-HPODE products (**Scheme 1**). These simpler models retain all of the important stereochemical features of the full system. **Scheme 2** outlines the possible reaction pathways for the stepwise ring opening of *Z* and *E* methyl vinyl allene oxide to an oxyallyl species, which can adopt a number of conformations / configurations. Oxyallyl can close to vinyl substituted cyclopropanone which, after rotation of the vinyl group, can open to other conformations / configurations of oxyallyl that are able to cyclize to cyclopentenone or dihydrofuran. Cyclopropanone can also rearrange

directly to cyclopentenone in a concerted fashion. First, we investigated the reaction of unsubstituted allene oxide to explore the levels of theory needed to study the system, and then we examined the mechanism for methyl vinyl allene oxide.



Scheme 2. Pathways for the conversion of *Z*- and *E*-methyl vinyl allene oxide to cyclopentenone and dihydrofuran via oxyallyl diradical and cyclopropanone intermediates.

Method

Calculations were performed with the Gaussian 09 series of programs[33] using complete active space SCF (CASSCF), restricted active space SCF (RASSCF[34]), density functional theory (DFT), coupled cluster (CCSD(T)[35-36]) and Brueckner-Doubles (BD(T)[37]) methods. Spin unrestricted methods were used to calculate diradical states with the DFT, CCSD(T) and BD(T) levels of theory. Optimized gas-phase geometries and vibrational frequencies for the unsubstituted allene oxide pathway were calculated using CASSCF with an active space of 4-electron, 4-orbital (4,4) and the 6-31++G(d,p)[38-41] basis set, and RASSCF with a 20 electron, 19 orbital active space (20,19) and the cc-pVTZ basis set, and DFT with the ωB97xD functional and the cc-pVTZ[42] basis set. For the RASSCF calculations, the RAS1 space consisted of 7 occupied orbitals and up to 2 holes, the RAS2 space was defined as 6 electrons in 6 orbitals, and the RAS3 space consisted of 6 virtual orbitals with up to 2 electrons. Single point energy calculations were performed with the B3LYP[43-46] and ωB97xD[47] DFT functionals, CASSCF with (4,4), (12,12), and (12,11) active spaces, CASMP2[48] with a (4,4) active space, RASSCF(20,19), and CCSD(T) and BD(T) with cc-pVTZ and aug-cc-pVTZ[49] basis sets using the CASSCF(4,4)/6-311++G(d,p) and UωB97xD/cc-pVTZ gas phase optimized geometries. For the methyl vinyl substituted allene oxide pathways, gas phase optimized geometries, vibrational frequencies and thermal contributions to the enthalpy were calculated using CASSCF(10,8)/6-31++G(d,p) and UωB97xD/cc-pVTZ. Single point energies were calculated with the B3LYP and ωB97XD functionals and with CASSCF and CCSD(T) methods with the cc-pVTZ and aug-cc-pVTZ basis sets using the CASSCF(10,8)/6-31++G(d,p) and UωB97xD/cc-pVTZ optimized geometries. Intrinsic reaction coordinate (IRC) calculations were performed to confirm the nature of the transition

states. IRCmax[50] calculations were performed on UωB97xD/cc-pVTZ optimized transition states with UCCSD(T)/cc-pVTZ energies to find an approximate energy of the transition state along the UCCSD(T) surface. For the lowest energy pathways for methyl vinyl allene oxide, the structures were then optimized in solution using the ωB97XD/cc-pVTZ level of theory and the SMD polarizable continuum model[51] for solvation using isopropyl alcohol.

Results and Discussion

Unsubstituted Allene Oxide

To calibrate the computational methods for the study of the conversion of methyl vinyl substituted allene oxide to cyclopentenone, we first consider the potential energy surface for the ring opening of the unsubstituted allene oxide shown in **Figure 1**. This system involves an oxyallyl intermediate and has been studied experimentally[28, 32] and by a variety of high level theoretical methods.[10, 28, 32] We have used CASSCF, CASMP2, RASSCF, DFT, CCSD(T), and BD(T) with a number of different basis sets. The (4,4) active space for the CASSCF and CASMP2 calculations of the unsubstituted oxyallyl intermediate includes the carbonyl π and π* orbitals and the in- and out-of-phase p-orbitals having diradical character, as illustrated in **Figure 2**. To further probe the effects of dynamic correlation, the energies were also calculated with CASSCF(12,11) and CASSCF(12,12). The (12,11) active space included the C-C and C-O sigma bonding and antibonding orbitals associated with the **1** to **3** rearrangement and the (12,12) active space included orbitals that were primarily C-H bonding and antibonding. The orbitals in these two active spaces were combined for the RAS(20,19) calculations. Two holes were allowed in the RAS1 space, which contained all of the C-C, C-H, and C-O bonding orbitals that

were not included in the (6,6) RAS2 space, as well the oxygen lone pairs. Two excitations were allowed into the RAS3 space, which contained all relevant antibonding orbitals. The active orbitals are shown in **Figure S1**.

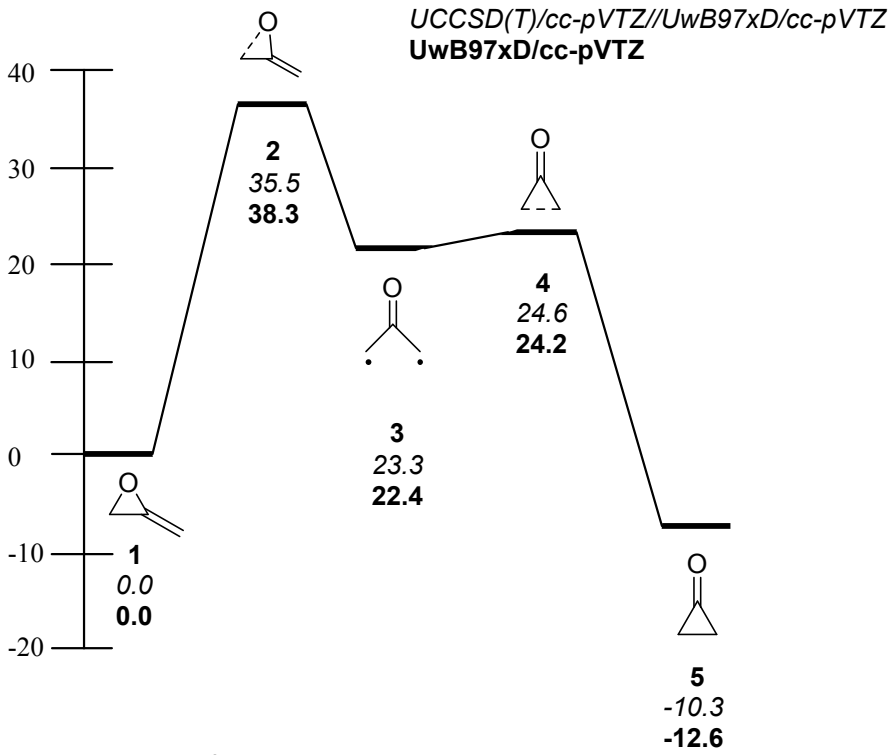


Figure 1. Cyclization pathway of unsubstituted allene oxide to cyclopropanone via oxyallyl intermediate. Energies given in kcal/mol using cc-pVTZ basis set with UωB97xD/cc-pVTZ optimized geometries.

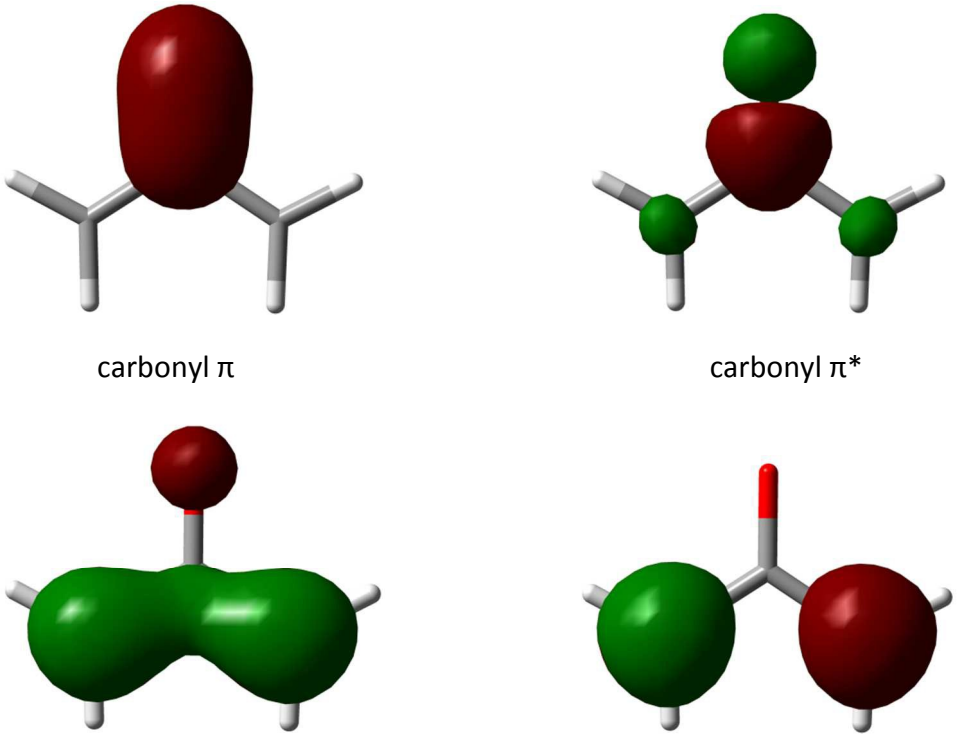


Figure 2. Orbitals selected for the (4,4) active space used for CASSCF and CASMP2 calculations of unsubstituted allene oxide.

The CASSCF and DFT calculations indicate that the oxyallyl intermediate and associated transition states have substantial amounts of diradical character. CAS(4,4) calculations have been used in the past to obtain good optimized geometries for these diradicals. **Table 1** shows that the various methods yield a wide range of energies for these structures relative to allene oxide. CAS(4,4)/aug-cc-pVTZ//CAS(4,4)/6-311++G(d,p) calculations give 31.8 kcal/mol for the allene oxide ring opening barrier and 13.3 kcal/mol for the energy of oxyallyl relative to allene oxide. The CAS(12,11) and CAS(12,12) calculations represent two different active spaces, and increase the barrier by ca. 4 kcal/mol and the oxyallyl energy by 1 – 7 kcal/mol, indicating the importance of including additional dynamic correlation. When the two orbital spaces are combined in the RAS(20,19) calculations, the singlet oxyallyl and the ring opening transition

state are both 4 kcal/mol higher than with CAS(4,4) using the same basis set and geometry. Optimization at the RAS(20,19)/cc-pVDZ level of theory lowers the ring opening barrier by 3 kcal/mol and yields a geometry intermediate between the CAS and DFT optimized geometries. RAS optimization has negligible effect on the other energies. The CASMP2 calculations yield results that are much higher than our best estimates (see below) and can be dismissed. Density functional and CCSD(T) calculations should provide good estimates of dynamic electron correlation. The ring opening barriers calculated by UωB97xD are in good agreement with the UCCSD(T) values at the same geometry, but the UB3LYP density functional typically yields barriers that are ca. 5 kcal/mol too low.[52] UωB97xD and UCCSD(T) calculations place oxyallyl 22 – 24 kcal/mol above allene oxide. The UCCSD(T) ring opening barrier depends on the geometry used for the transition state. By finding a maximum in the UCCSD(T) energy along the UωB97xD reaction path using the IRCMax approach[50], the ring opening barrier is estimated to be 40 kcal/mol. In principle, UBD(T) calculations should be even better for these systems than UCCDS(T). The barriers and relative energies change by only 0 – 1 kcal/mol comparing UBD(T) and UCCSD(T). Because the CCSD(T) calculations agree very well with BD(T) but are less costly, they are used to explore the reactions of substituted allene oxide. While spin unrestricted calculations are appropriate for diradicals, some caution is necessary because of spin contamination ($<S^2>$ = 0.7 – 1.0, see **Table S3**). The closed shell spin restricted calculations in **Table 1** are generally 6 – 15 kcal/mol higher than their open shell unrestricted counterparts, indicating they are unsuitable for these systems with diradical character. The notable exceptions are the RCCSD(T) and RBD(T) calculations. The large perturbative triplets corrections bring the ring opening and oxyallyl energies close to the UCCSD(T) and UBD(T)

values. However, such large triples contributions should be viewed with caution. While there is considerable variation in the allene oxide ring opening barrier, all of the calculations agree that the barrier for ring closing of oxyallyl to cyclopropanone is less than 2 kcal/mol.

Table 1. Relative energies (in kcal/mol) of structures along allene oxide cyclization pathway[a]

Method	Basis set	**1**	**2**	**3**	**4**	**5**
CASSCF(4,4)[b]	aug-cc-pVDZ	0.0	29.5	10.9	11.0	-12.4
CASSCF(4,4)[b]	cc-pVTZ	0.0	31.5	13.4	13.5	-11.5
CASSCF(4,4)[b]	aug-cc-pvTZ	0.0	31.8	13.3	13.3	-11.3
CASSCF(12,11)[b]	cc-pVTZ	0.0	35.1	14.4	14.9	-12.5
CASSCF(12,12)[b]	cc-pVTZ	0.0	35.0	20.9	20.7	-7.6
RASSCF(20,19)[b]	cc-pVTZ	0.0	36.2	16.5	16.0	-13.1
RASSCF(20,19)[b]	cc-pVDZ	0.0	33.4	15.0	14.6	-14.9
RASSCF(20,19)[c]	cc-pVDZ	0.0	31.4	14.8	14.6[b]	-15.0
RASSCF(20,19)[d]	cc-pVDZ	0.0	30.5	14.2	12.8	-15.1
CASMP2(4,4)[b]	aug-cc-pVTZ	0.0	46.9	28.4	28.1	-5.8
UCCSD[b]	aug-cc-pVTZ	0.0	37.2	21.3	22.3	-10.0
UCCSD(T)[b]	aug-cc-pVTZ	0.0	38.3	24.0	24.8	-9.4
UCCSD(T)[d]	cc-pVTZ	0.0	35.5	23.3	24.6	-10.3
UCCSD(T)[e]	cc-pVTZ		40.1		24.9	
UBD[b]	aug-cc-pVTZ	0.0	37.8	21.4	22.5	-10.1
UBD(T)[b]	aug-cc-pVTZ	0.0	37.0	23.9	24.6	-9.4
UB3LYP[b]	aug-cc-pVTZ	0.0	31.6	19.4	19.9	-9.4
UωB97XD[b]	cc-pVTZ	0.0	37.7	22.5	23.3	-11.0
UωB97XD[b]	aug-cc-pVTZ	0.0	37.1	22.3	23.0	-10.7
UωB97XD[d]	cc-pVTZ	0.0	38.3	22.4	24.2	-10.7
RCCSD[b]	aug-cc-pVTZ	0.0	46.7	33.8	31.6	-10.0
RCCSD(T)[b]	aug-cc-pVTZ	0.0	33.9	25.4	24.2	-9.4
RBD[b]	aug-cc-pVTZ	0.0	48.9	34.1	32.0	-10.1
RBD(T)[b]	aug-cc-pVTZ	0.0	38.0	25.8	24.2	-9.4
RB3LYP[b]	aug-cc-pVTZ	0.0	37.8	30.6	28.0	-9.4
RwB97XD[b]	aug-cc-pVTZ	0.0	46.5	37.4	35.0	-10.7

[a] See **Figure 1** for structure numbers; relative energies without ZPE or thermal corrections[f], [b] CASSCF(4,4)/6-311++G(d,p) gas phase optimized geometry, [c] RASSCF(20,19)/cc-pVDZ gas phase optimized geometry, [d] UωB97XD/cc-pVTZ gas phase optimized geometry, [e] UCCSD(T)/cc-pVTZ IRCmax energies along the UωB97XD/cc-pVTZ IRC, [f] CASSCF(4,4)/6-311++G(d,p) ZPE for **1** – **5**: 40.2, 37.2, 37.5 ,37.5, 40.3 kcal/mol and $\Delta H_{0\text{-}298}$ for **1** – **5**: 2.5, 2.6, 3.2, 2.6, 2.4 kcal/mol; UωB97XD/cc-pVTZ ZPE for **1** – **5**: 39.1, 35.6, 36.0, 36.2, 38.4 kcal/mol and $\Delta H_{0\text{-}298}$ for **1** – **5**: 2.4, 2.6, 3.1, 2.5, 2.6 kcal/mol

While singlet oxyallyl diradical is difficult to compute because of issues such as spin contamination and multireference character, an accurate description of triplet oxyallyl diradical should be easy to obtain with single reference spin unrestricted calculations. **Table 2** lists the energies of the singlet and triplet oxyallyl diradicals relative to allene oxide for a variety of levels of theory. The UCCSD(T)/aug-cc-pVTZ and UBD(T)/aug-cc-pVTZ energies for triplets should be the most reliable and are used as reference values. The CASSCF(4,4) energies of triplet oxyallyl diradical are 12 – 13 kcal/mol lower than the UCCSD(T) energies with the same basis set. This is likely due to the lack of dynamic correlation inherent in the CASSCF method. Use of (12,11) and (12,12) active spaces give energies that are lower than CCSD(T) by 7.9 and 5.5 kcal/mol, respectively. RASSCF(20,19)/cc-pVTZ single point energies give better agreement with CCSD(T), but are still 4 kcal/mol too low. The CASMP2 calculations for the triplet are 3 – 6 kcal/mol higher than the UCCSD(T) energies. The UB3LYP energies are about 4 – 5 kcal/mol lower than UCCSD(T) with the same basis set, but the UωB97XD relative energies of triplet oxyallyl diradical are in good agreement with UCCSD(T). This suggests that the UωB97XD calculations give reliable relative energies for triplet species.

Table 2. Energies (in kcal/mol) of singlet and triplet spin states of oxyallyl diradical, **3**, relative to allene oxide, **1**.

Method	Basis Set	Singlet	Triplet	Singlet-Triplet[f]
CASSCF(4,4)	6-31G(d)	12.5	7.5	5.0
	6-311++G(d,p)	11.3	7.6	3.7
	cc-pVDZ	11.3	6.6	4.7
	cc-pVTZ	13.4	9.8	3.6
	aug-cc-pVTZ[b]	13.3	10.2	3.1
RASSCF(20,19)	cc-pVDZ[b]	15.0	15.4	-0.4
RASSCF(20,19)	cc-pVDZ[c]	14.2	15.5	-1.3
RASSCF(20,19)	cc-pVDZ	14.8	15.5	-0.7
CASMP2(4,4)	6-31G(d)[b]	26.0	22.4	3.6

	6-311++G(d,p)[b]	24.4	24.1	0.3
	aug-cc-pVTZ[b]	28.4	29.1	-0.7
UCCSD(T)	6-31G(d)[b]	22.3	19.8	2.5
	6-311++G(d,p)[b]	21.4	20.1	1.3
	cc-pVTZ[c]	23.3	22.6	0.7
	cc-pVTZ[b]	24.0	23.3	0.7
	aug-cc-pVTZ[b]	24.0	23.1	0.9
BD(T)	6-31G(d)[b]	22.3	19.7	2.6
	6-311++G(d,p)[b]	21.4	19.9	1.5
	aug-cc-pVTZ[b]	23.9	23.0	0.9
UB3LYP	6-31G(d)	18.8	17.4	1.4
	6-311++G(d,p)	18.1	17.5	0.6
	aug-cc-pVTZ[b]	19.4	18.9	0.5
UωB97XD	6-31G(d)	21.8	19.8	2.0
	6-311++G(d,p)	21.0	19.7	1.3
	cc-pVDZ	21.2	19.3	1.9
	aug-cc-pVTZ[b]	22.3	21.2	1.1
	aug-cc-pVTZ[c]	22.1	21.4	0.7
CASPT2[d]	cc-pVTZ			-0.9
EOM-SF-CCSD(dT)[e]	aug-cc-pVTZ			-1.5
Experiment[d]				-1.3

[a]optimized with specified method unless otherwise stated; energies are without ZPE or thermal corrections [b]CASSCF(4,4)/6-311++G(d,p) gas phase optimized geometry [c]UωB97XD/aug-cc-pVTZ gas phase optimized geometry [d]ref[28] [e]ref[10] [f]ZPE(singlet)-ZPE(triplet) = 0.1 kcal/mol at CASSCF(4,4)/6-311++G(d,p) and UωB97xD/cc-pVTZ

In a series of experiments using photoelectron spectroscopy, Lineberger and coworkers found that the $^1A_1$ state of oxyallyl diradical was 1.3 kcal/mol lower than the $^3B_2$ state.[28] The best calculations in the literature (CASPT2 and EOM spin flip CCSD(dT)) find the $^1A_1$ state 0.9 kcal/mol and 1.5 kcal/mol lower than $^3B_2$ state.[10, 28] With the present CAS(4,4) calculations, the $^1A_1$ state is 3.1 kcal/mol higher than the $^3B_2$ state. When dynamic correlation is included by CASMP2 and RAS(20,19) at the CAS(4,4) geometries, the singlet state is lower than the triplet state by 0.7 and 2.2 kcal/mol, respectively. Optimization with RAS(20,19)/cc-pVDZ decreases the singlet-triplet gap to 0.7 kcal/mol. The DFT and CCSD(T) calculations place the $^1A_1$ state 0.5

– 0.9 kcal/mol above the $^3B_2$ state. Since the CCSD(T) calculations should be quite reliable for the triplet oxyallyl, this suggests that the CCSD(T) energy of the singlet is about 2 kcal/mol too high, yielding 22 kcal/mol as our best estimate for the energy of singlet oxyallyl diradical relative to allene oxide.

The calculations on the unsubstituted allene oxide ring opening indicate CAS(4,4) and UωB97xD yield good geometries, but that large basis sets calculations with UωB97xD and UCCSD(T) are needed for reliable energies. However, preliminary calculations on methyl vinyl allene oxide indicated that CCSD(T) calculations with the aug-cc-pVTZ basis set would be too costly for exploring the reaction mechanism shown in **Scheme 2**. To obtain a more affordable level of theory, we tried (a) reducing the basis set from aug-cc-pVTZ to aug-cc-pVDZ and (b) removing the extra diffuse function from aug-cc-pVTZ to give cc-pVTZ. **Table 3** shows that the aug-cc-pVDZ basis is not suitable since the energies differ by 2 – 7 kcal/mol when compared to aug-cc-pVTZ. The energies with the cc-pVTZ basis are within 0.2 kcal/mol of the larger basis and calculations with this basis are used for the methyl vinyl substituted allene oxide system.

Table 3. Comparison of basis sets for the energy of singlet diradical oxyallyl, **3**, relative to allene oxide, **1** (in kcal/mol)[a]

	aug-cc-pVDZ	cc-pVTZ	aug-cc-pVTZ
CASSCF(4,4)	10.9	13.4	13.3
CASMP2(4,4)	21.6	28.4	28.4
UB3LYP	17.6	19.6	19.4
UωB97XD	20.5	22.5	22.3
UCCSD(T)	19.2	24.0	24.0

[a]CASSCF(4,4)/6-311++G(d,p) gas phase optimized geometry

Methyl Vinyl Allene Oxide

The reaction mechanism for the cyclization of methyl vinyl allene oxide shown in **Scheme 2**. The relative energetics of the numerous pathways were first examined using CASSCF, CCSD(T) and DFT calculations in the gas phase. The geometries and energies were then recalculated in solution using DFT and the SMD polarizable continuum solvation model. The lowest energy profiles for the closed shell and diradical pathways are shown in **Figure 3**.

The reaction starts with ring opening to give a substituted oxyallyl intermediate. Since the vinyl group is in conjugation with the oxyallyl group, the π orbitals of the diradical intermediate are delocalized and a larger active space is required for the CASSCF calculations. The 10 electron, 8 orbital active space, shown in **Figure 4**, consists of the carbonyl π and π^* orbitals, the in- and out-of-phase oxyallyl p-orbitals having diradical character, the vinyl π and π^*, and two in-plane orbitals having oxygen lone pair character (LP1 and LP2). Some structures could only be obtained with a smaller 8 electron, 7 orbital active space (omitting LP2). For structures where both the CAS(10,8) and CAS(8,7) calculations converged, the differences in relative energies were below 0.5 kcal/mol. As **Figure 4** shows, there is strong conjugation between the vinyl group and the diradical, yielding orbitals that resemble allyl radical.

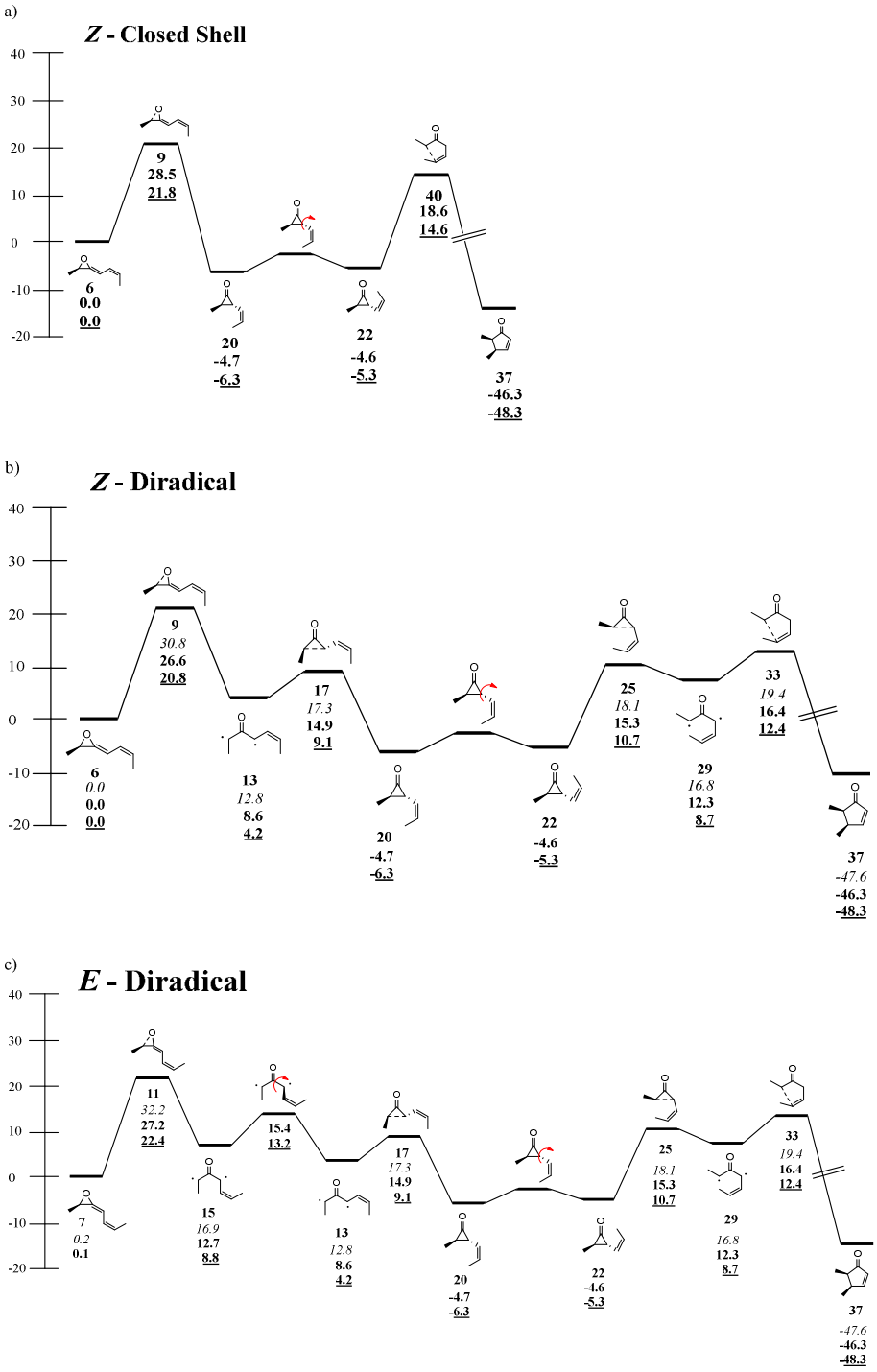
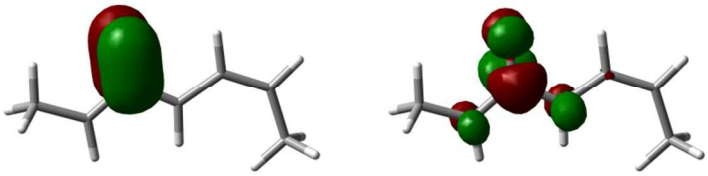
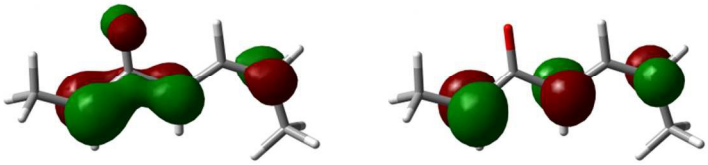


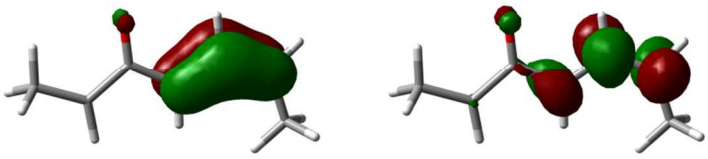
Figure 3 Lowest enthalpy cyclization pathways of methyl vinyl substituted allene oxide to *cis*-dimethylcyclopentenone: (a) closed shell pathway for *Z*-isomer, (b) open shell diradical pathway for *Z*-isomer, (c) open shell diradical pathway for *E*-isomer in kcal/mol; CCSD(T)/cc-pVTZ//ωB97xD/cc-pVTZ (italics); ωB97xD/cc-pVTZ gas phase (bold); ωB97xD/cc-pVTZ solution (bold underlined).



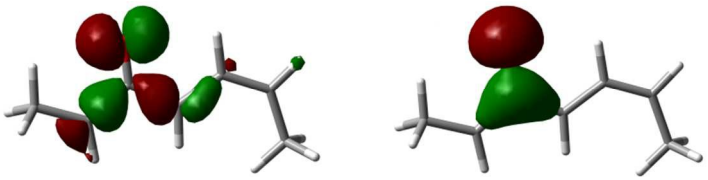
carbonyl π carbonyl π*



In-phase p-type orbital out-of-phase p-type orbital



vinyl π vinyl π*



oxygen lone pair (LP1) oxygen lone pair (LP2)

Figure 4. Orbitals selected for the (10,8) active space for CASSCF and CASMP2 calculations for methyl vinyl allene oxide system. LP2 was dropped for the (8,7) active space calculations.

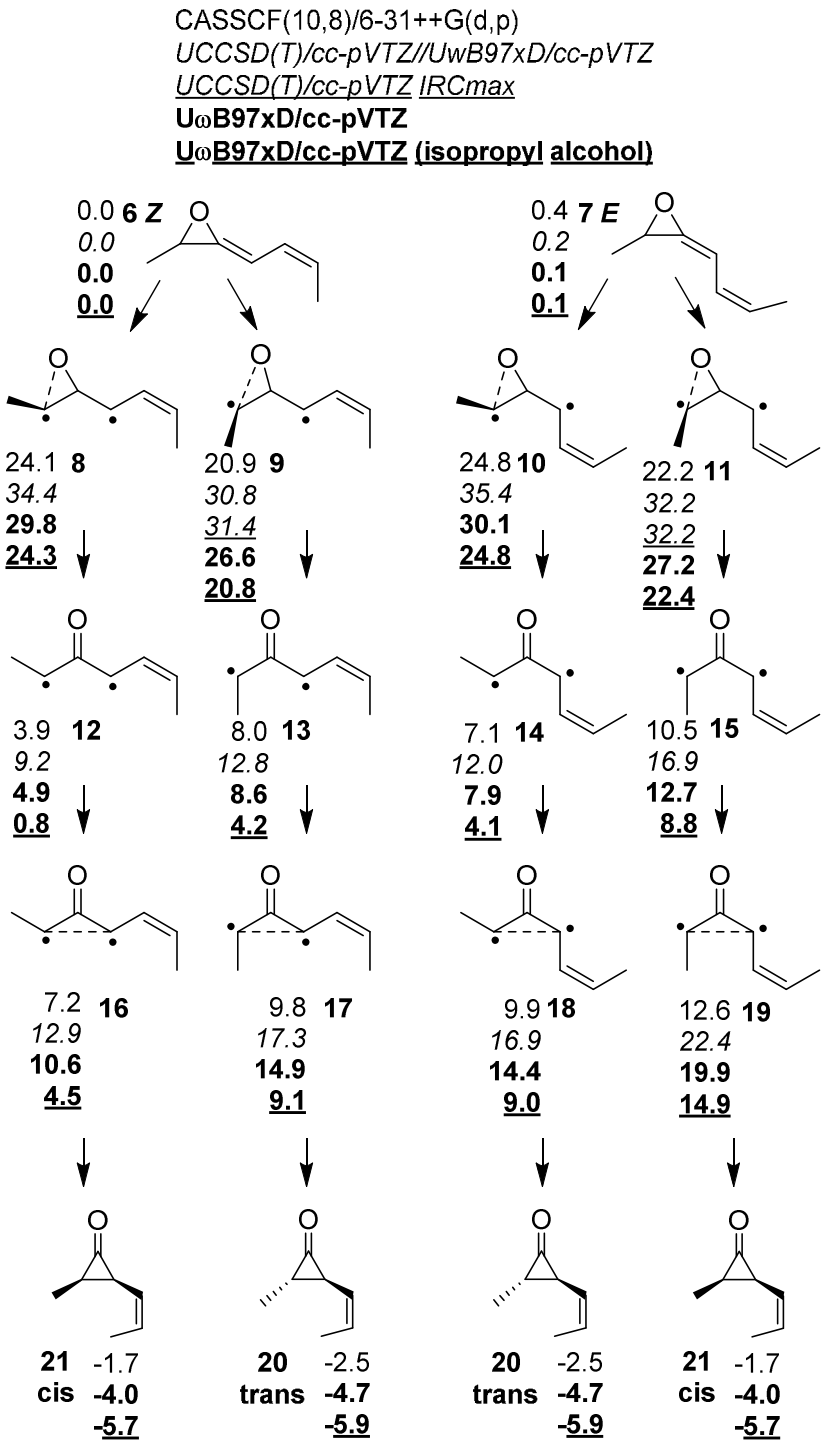
Scheme 3 outlines the ring opening of methyl vinyl substituted allene oxide to oxyallyl and subsequent closing to cyclopropanone. **Table 4** and **5** list the relative enthalpies for various levels of theory at the CAS and ωB97xD optimized geometries (optimization with CCSD(T) is not feasible). For minima, CAS and DFT give very similar geometries, and the UCCSD(T) energies differ by less than 1.5 kcal/mol between these geometries. For the transition states, the geometries can differ by 0.1 Å for bonds formed or broken, and the UCCSD(T) estimates of the

barrier heights can differ by 1 – 4 kcal/mol depending on whether the CAS or DFT optimized transition state geometry is used. For the critical allene oxide ring opening steps, more reliable estimates of the UCCSD(T) barriers were obtained by using the IRCMax method to find the maximum in the UCCSD(T) energy along the UωB97xD reaction path.

Table 4. Enthalpies of methyl vinyl allene oxide and transition states for ring opening (in kcal/mol)[a]

Method	Basis Set	**6**	**7**	**8**	**9**	**10**	**11**
CASSCF(10,8)[b]	6-31++G(d,p)	0.0	0.4	24.1	20.9	24.8	22.2
UCCSD[c]	cc-pVTZ	0.0	0.3	36.1	33.1	36.3	33.6
UCCSD(T)[c]	cc-pVTZ	0.0	0.2	34.4	30.8	35.4	32.2
UCCSD(T)[c,d]	cc-pVTZ	0.0			31.4		32.2
UωB97XD[c]	cc-pVTZ	0.0	0.1	29.8	26.6	30.1	27.2
UωB97XD[e]	cc-pVTZ	0.0	0.1	24.3	20.8	24.8	22.4
UωB97XD[f]	cc-pVTZ	0.0			17.9		18.6
RωB97XD[g]	cc-pVTZ	0.0	0.1	31.7	28.5	32.6	31.1
RωB97XD[h]	cc-pVTZ	0.0			21.8		

[a] see Scheme 3 for structure numbers [b] CASSCF(10,8)/6-31++G(d,p) gas phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$ [c] UωB97XD/cc-pVTZ gas phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$ [d] UCCSD(T)/cc-pVTZ IRCmax energies along the gas phase UωB97XD/cc-pVTZ IRC [e] UωB97XD/cc-pVTZ solution phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$ [f] UωB97XD/cc-pVTZ geometries, ZPE and $\Delta H_{0\text{-}298}$ optimized with two isopropyl alcohols hydrogen bonded to the allene oxide [g] RωB97XD/cc-pVTZ gas phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$ [h] RωB97XD/cc-pVTZ solution phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$

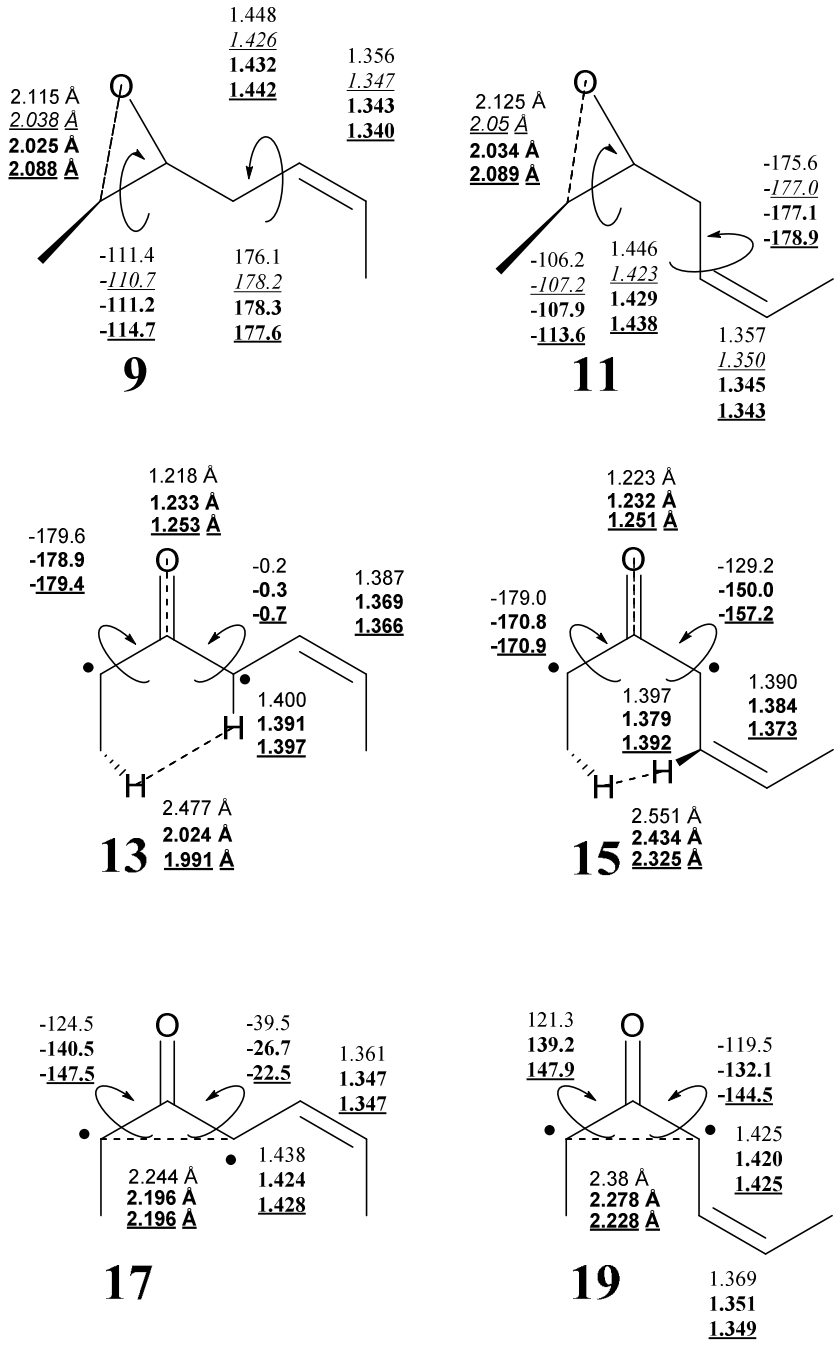


Scheme 3. *Z*- and *E*-methyl vinyl allene oxide (**6** and **7**), transition states for ring epoxide ring opening (**8** – **11**) to form methyl vinyl oxyallyl diradicals (**12** – **15**) and transition states for ring closure (**16** – **19**) to form *trans* and *cis* methyl vinyl cyclopropanones (**20** and **21**). Enthalpies in

kcal/mol calculated at CASSCF(10,8)/6-31++G(d,p) (plain), CCSD(T)/cc-pVTZ//UωB97xD/cc-pVTZ (italics), CCSD(T)/cc-pVTZ IRCmax values (italics, underlined), gas phase UωB97xD/cc-pVTZ (bold) and solution UωB97xD/cc-pVTZ (bold, underlined).

The *Z*- and *E*-isomers (structures **6** and **7**, resp.) are nearly equal in energy. Each of the isomers can open in two different ways (transition structures **8** – **11**) yielding four diradical intermediates (**12** – **15**). Conjugation with the vinyl substituent is expected to stabilize formation of the diradical. The ring opening barriers for the substituted allene oxides **8** – **11** are 7 – 10 kcal/mol lower than the corresponding calculations for the unsubstituted case, **2**. For the CASSCF and spin unrestricted DFT calculations, the epoxide opening transition states for the methyl group rotating away from the oxygen (**9** and **11**) are 2 – 3 kcal/mol lower than for the methyl group rotating toward the oxygen (**8** and **10**) due to steric interaction. The lowest transition state for ring opening of the *Z*-isomer (**9**) is 0.7 – 1.2 kcal/mol lower than for the *E*-isomer (**11**) by CAS and DFT. For the UCCSD(T) level of theory, the IRCMax method provides a more reliable estimates of the barriers than using the CAS or DFT optimized geometry, and gives 0.9 kcal/mol for the difference in the barriers for ring opening of *E*- and *Z*-allene oxide. The CCSD(T) IRCMax and gas phase UωB97XD optimizations result in transition structures that are earlier along the reaction path than the CASSCF and solution UωB97XD optimized geometry, as judged by the C-O distance shown in **Scheme 4**. Optimization of the transition states with closed shell RωB97XD/aug-cc-pVTZ produced barriers that are about 1 – 3 kcal/mol higher than the corresponding open shell structures and have restricted to unrestricted instabilities, indicating that the lowest energy epoxide ring opening transition states have some diradical character.

The ring opening barriers calculated by UωB97XD and UCCSD(T) in the gas phase range from 27 to 36 kcal/mol, considerably higher than expected for a reaction that occurs rapidly at room temperature. When two explicit molecules of isopropyl alcohol are hydrogen bonded to the oxygen, the barriers were reduced to 17.9 and 18.6 kcal/mol for the *Z* and *E* isomers, respectively, for the UωB97XD calculations. A more practical method of estimating the solvation energy that can be applied to the entire rearrangement mechanism is the implicit solvation approach which uses a polarizable continuum to represent the solvent. With UωB97XD and SMD implicit solvation calculations using isopropyl alcohol, the barriers were 20.8 and 22.4 kcal/mol for the *Z* and *E* isomers, respectively. This is commensurate with the rapid rearrangement of *Z*-allene oxide at room temperature observed experimentally.



Scheme 4. Comparison of geometries of methyl vinyl substituted oxyallyl intermediates and associated transition states optimized at CASSCF(10,8)/6-31++G(d,p) (plain), CCSD(T) from IRCmax (italics, underlined) levels of theory, gas phase UωB97XD/cc-pVTZ (bold) and solution UωB97XD/cc-pVTZ (bold undelined).

The results of IRC calculations for the conversion of methyl vinyl allene oxide to cyclopropanone are shown in **Figure 5**. The closed shell, spin restricted RωB97xD IRC has no oxyallyl minimum, in agreement with the findings of de Lera and co-workers.[12] By contrast, the open shell, spin unrestricted UωB97xD IRCs for both the *Z*- and *E*-isomers show clear minima for the oxyallyl diradicals and barriers of 6 – 8 kcal/mol for closure of oxyallyl to cyclopropanone in agreement with the work of Lopez et al.[16, 53] Since the UωB97xD calculations are in good agreement with higher level calculations for the unsubstituted oxyallyl intermediate and transition states, they should also be reliable for the methyl vinyl substituted oxyallyl intermediates and transition states and give a better representation of the potential energy surface for the reaction than spin restricted RωB97xD calculations used by de Lera and co-workers.

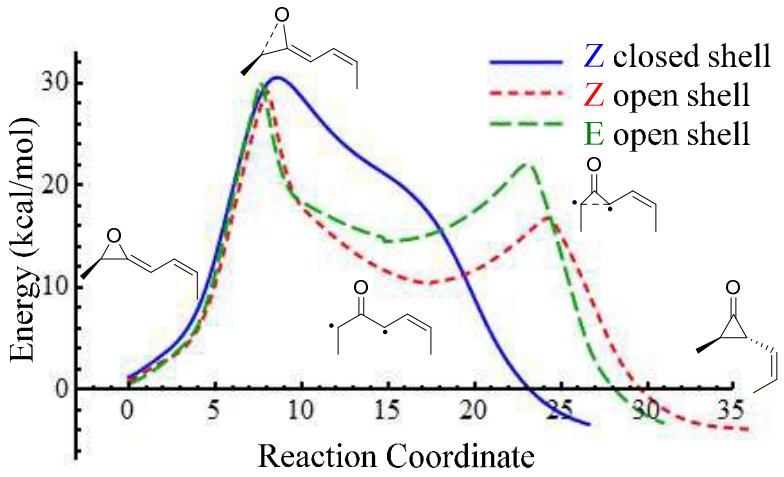


Figure 5. Intrinsic reaction coordinate for the conversion of methyl vinyl allene oxide to cyclopropanone via oxyallyl diradical in the gas phase calculated by RωB97xD/cc-pVTZ for the *Z*-isomer (solid blue line), UωB97xD/cc-pVTZ for the *Z*-isomer (short dashed red line) and the *E*-isomer (long dashed green line).

Relative to allene oxide, the methyl vinyl-substituted oxyallyl intermediates are about 5 – 10 kcal/mol more stable than unsubstituted oxyallyl because the diradical is stabilized by strong conjugation with the vinyl group. In **13** and **15**, the CC bond length between the radical center and the vinyl group is nearly equal to the CC bond length within the vinyl group (**Scheme 4**, ca. 1.39 Å in the CAS structures), indicating that it should be regarded as an allyl radical. Structures **13** and **15** are slightly less stable than **12** and **14** because of steric interactions between the hydrogens of the methyl and vinyl groups, as shown in **Scheme 4**. Solvation stabilizes the singlet diradicals by 3 – 6 kcal/mol depending on structure. The triplet methyl vinyl oxyallyl radicals are nearly spin pure but the singlets have S^2 of 0.8 – 1.0. Similar to the unsubstituted case, the singlet-triplet energy differences for the substituted oxyallyl diradical are small (2 kcal/mol or less), and removal of the spin contamination should lower the energy by only a small amount.

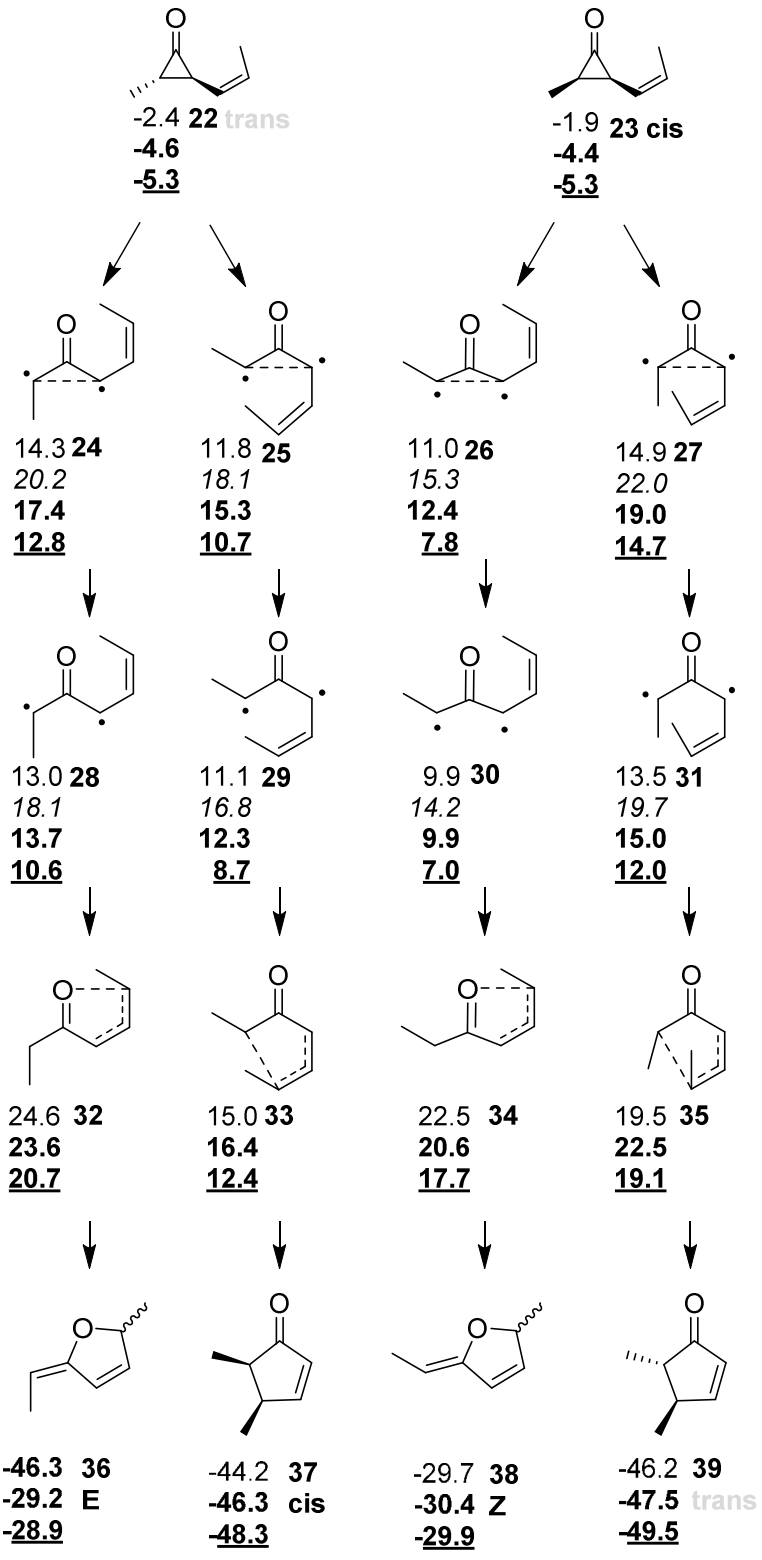
The oxyallyl diradical readily cyclizes in a disrotatory fashion to produce a cyclopropanone. For the *Z*-isomer, the lowest transition state for allene oxide ring opening yields oxyallyl **13** which cyclizes via transition state **17** to *trans*-cyclopropanone, **20**. Correspondingly, ring opening of the *E*-isomer of substituted allene oxide produces oxyallyl **15** which cyclizes via **19** to the *cis*-cyclopropanone **21**. The barriers for ring closure of the substituted oxyallyl diradicals are small (4 – 9 kcal/mol, **Table 5**) but are significantly larger than for the unsubstituted case (0 – 2 kcal/mol, **Table 1**). Again, this can be attributed to the stabilizing effect that the vinyl group has on the diradical structure.

Table 5. Relative enthalpies of methyl vinyl substituted oxyallyl, cyclopropanone, and 5-membered ring intermediates and transition states[a]

	CASSCF	UCCSD(T)[d]	ωB97xD[d]	ωB97xD[e]
12	3.9[b]	9.2	4.9	0.8
13	8.0[b]	12.8	8.6	4.2
14	7.1[c]	12.0	7.9	4.1
15	10.5[b]	16.9	12.7	8.8
16	7.2[c]	12.9	10.6	4.5
17	9.8[c]	17.3	14.9	9.1
18	9.9[c]	16.9	14.4	9.0
19	12.6[b]	22.4	19.9	14.9
20	-2.5[c]		-4.7	-6.3
21	-1.7[c]		-4.0	-5.8
22	-2.4[c]		-4.6	-5.3
23	-1.9[c]		-4.4	-5.3
24	14.3[c]	20.2	17.4	12.8
25	11.8[b]	18.1	15.3	10.7
26	11.0[c]	15.3	12.4	7.8
27	14.9[b]	22.0	19.0	14.7
28	13.0[b]	18.1	13.7	10.6
29	11.1[b]	16.8	12.3	8.7
30	9.9[b]	14.2	9.9	7.0
31	13.5[b]	19.7	15.0	12.0
32	24.6[b]		23.6	20.7
33	15.0[b]	19.4	16.4	12.4
34	22.5[b]		20.6	17.7
35	19.5[b]		22.5	19.1
36	-28.2[b]		-29.2	-28.9
37	-44.2[b]	-47.6	-46.3	-48.3
38	-29.7[b]		-30.4	-29.9
39	-46.2[b]		-47.5	-49.5
40			18.6	14.6
41			29.5	25.0

[a] see Schemes 3, 5 and 6 for the structure numbers; enthalpies relative to *Z*-methyl vinyl allene oxide, **6** at the corresponding level of theory,
[b] CASSCF(10,8)/6-31++G(d,p) enthalpies using CASSCF(10,8)/6-31++G(d,p) gas phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$, [c] CASSCF(8,7)/6-31++G(d,p) enthalpies using CASSCF(8,7)/6-31++G(d,p) gas phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$, [d] enthalpies calculated with the cc-pVTZ basis set using ωB97xD/cc-pVTZ gas phase optimized geometries, ZPE and $\Delta H_{0\text{-}298}$ [e] enthalpies calculated with the cc-pVTZ basis set using ωB97xD/cc-pVTZ solution optimized geometries, ZPE and $\Delta H_{0\text{-}298}$

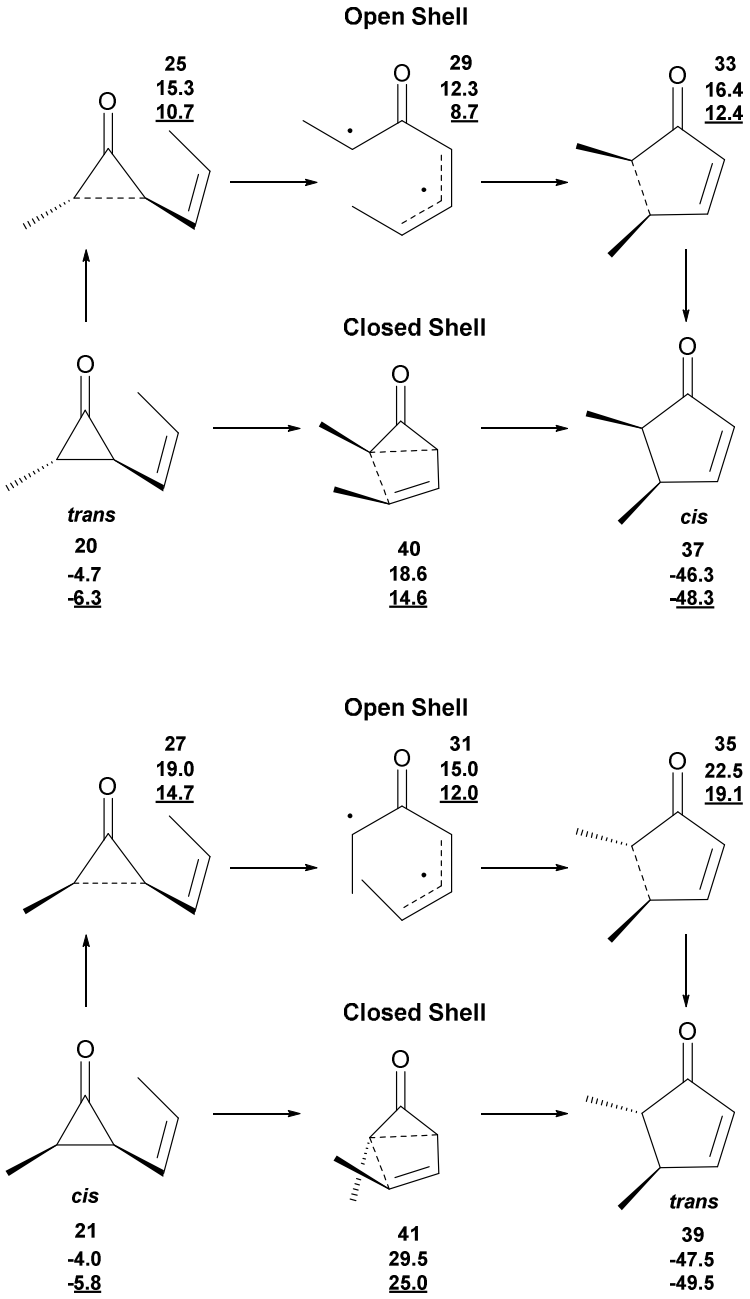
CASSCF(10,8)/6-31++G(d,p)
UCCSD(T)/cc-pVTZ//UwB97xD/cc-pVTZ
UωB97xD/cc-pVTZ
UωB97xD/cc-pVTZ (isopropyl alcohol)



Scheme 5. Conversion of *trans* and *cis* methyl vinyl cyclopropanone (**22** and **23**) to *cis* and *trans* dimethyl cyclopentenone (**37** and **39**) and *E*- and *Z*-dihydrofuran (**36** and **38**) via methyl vinyl oxyallyl diradicals (**28** – **31**). Enthalpies given at CASSCF(10,8)/6-31++G(d,p) (plain), CCSD(T)/cc-pVTZ//UωB97xD/cc-pVTZ (italics), gas phase UωB97xD/cc-pVTZ (bold) and solution UωB97xD/cc-pVTZ (bold underlined).

Scheme 5 shows the ring opening of the appropriate rotamers of cyclopropanone to configurational isomers of oxyallyl diradical that can close to 5-membered ring products. The barriers for rotation of the vinyl group in the substituted cyclopropanones are small, ~1 kcal/mol optimized at ωB97XD/cc-pVTZ for both *cis*- and *trans*-cyclopropanone. Since most CC bond rotational barriers for oxyallyl diradical are higher (as discussed below), cyclopropanone acts as a low energy intermediate for the interconversion of the various conformational/configurational isomers of oxyallyl diradical. After rotation of the vinyl group, *cis*- and *trans*-cyclopropanone can each open to two different oxyallyl diradicals, one of which can close to a cyclopentenone, while the other can close to a dihydrofuran. For *trans*-cyclopropanone **22**, the lower energy transition state **25** leads to oxyallyl **29** which has a low barrier (ca 4 kcal/mol) for closing to *cis*-cyclopentenone **37**. The other cyclopropanone ring opening transition state **24** is ca 3 kcal/mol higher and leads to **28,** which has a barrier of about 10 kcal/mol for closing to *E*-dihydrofuran **36**. By contrast, the lower energy transition state for opening *cis*-cyclopropanone **23** leads via oxyallyl **30** to *Z*-dihydrofuran **38**, and the higher energy transition state leads via **31** to *trans*-cyclopentenone **39**. The lowest energy transition states for oxyallyl intermediates **28**-**31** closing to a 5-membered ring yields the observed *cis*-cyclopentenone **37**.

In addition to a stepwise diradical pathway, the rearrangement of cyclopropanone to cyclopentenone could occur via a closed shell concerted path[12], as shown in **Scheme 6**. For *trans*-cyclopropanone, the relative energy of the closed shell concerted transition state optimized at the RωB97XD/aug-cc-pVTZ level of theory is 2 kcal/mol higher than the barrier for the diradical pathway. Considering that removal of spin contamination is expected to lower the calculated energy of the open shell transition states, diradical ring opening is still favored over closed shell concerted. For *cis*-cyclopropanone, the closed shell transition state **41** is 6 kcal/mol higher than the diradical transition state **35**. This indicates that the diradical stepwise pathway is preferred over the closed shell concerted pathway for 5-membered ring formation.



Scheme 6. Enthalpies (in kcal/mol) for the conversion of *trans* and *cis* methyl vinyl cyclopropanone to cyclopentenone via stepwise diradical and closed shell concerted pathways at ωB97XD/aug-cc-pVTZ optimized in the gas phase (bold) and in solution (bold, underlined).

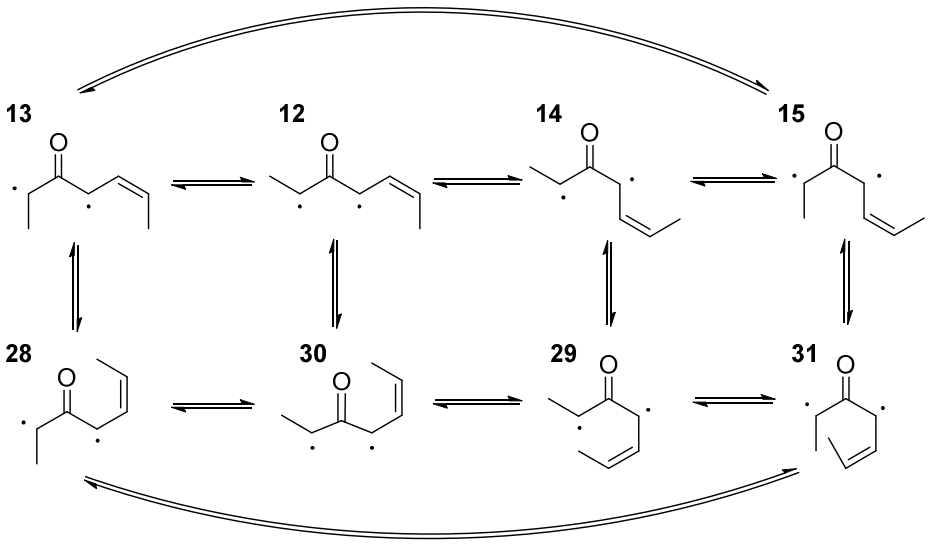
The oxyallyl diradical may be able to convert to different conformers / configurational isomers if the barriers for CC bond rotation are lower than the barriers for cyclization. The

possible transitions are shown in **Scheme 7** and the barriers are listed in **Table 6**. The barriers for rotation about the CC bond next to the vinyl group (**12** **30** and **14** **29**) are higher than ring closure to cyclopropanone because of the strong conjugation between the vinyl group and the diradical. The lowest rotational barriers are for **28** **31**, **29** **30**.

Table 6. Barriers (in kcal/mol) for CC rotation in oxyallyl diradicals[a]

	UB3LYP	UωB97XD	CASSCF(10,8)
12 **13**	15.2/10.5	14.1/10.4	9.2/4.7
12 **14**	12.4/8.5	10.6/7.4	7.4/4.2
12 **30**	15.8/10.1	14.3/9.2	11.9/6.0
13 **15**	9.1/3.5	7.8/3.2	4.2/1.1
14 **15**	11.3/4.9	10.5/5.4	5.8/1.4
14 **29**	13.4/7.2	11.9/6.8	9.9/5.3
28 **31**	4.1/1.0	2.4/0.8	0.9/0.2
29 **30**	4.1/8.5	3.0/6.2	1.7/3.6

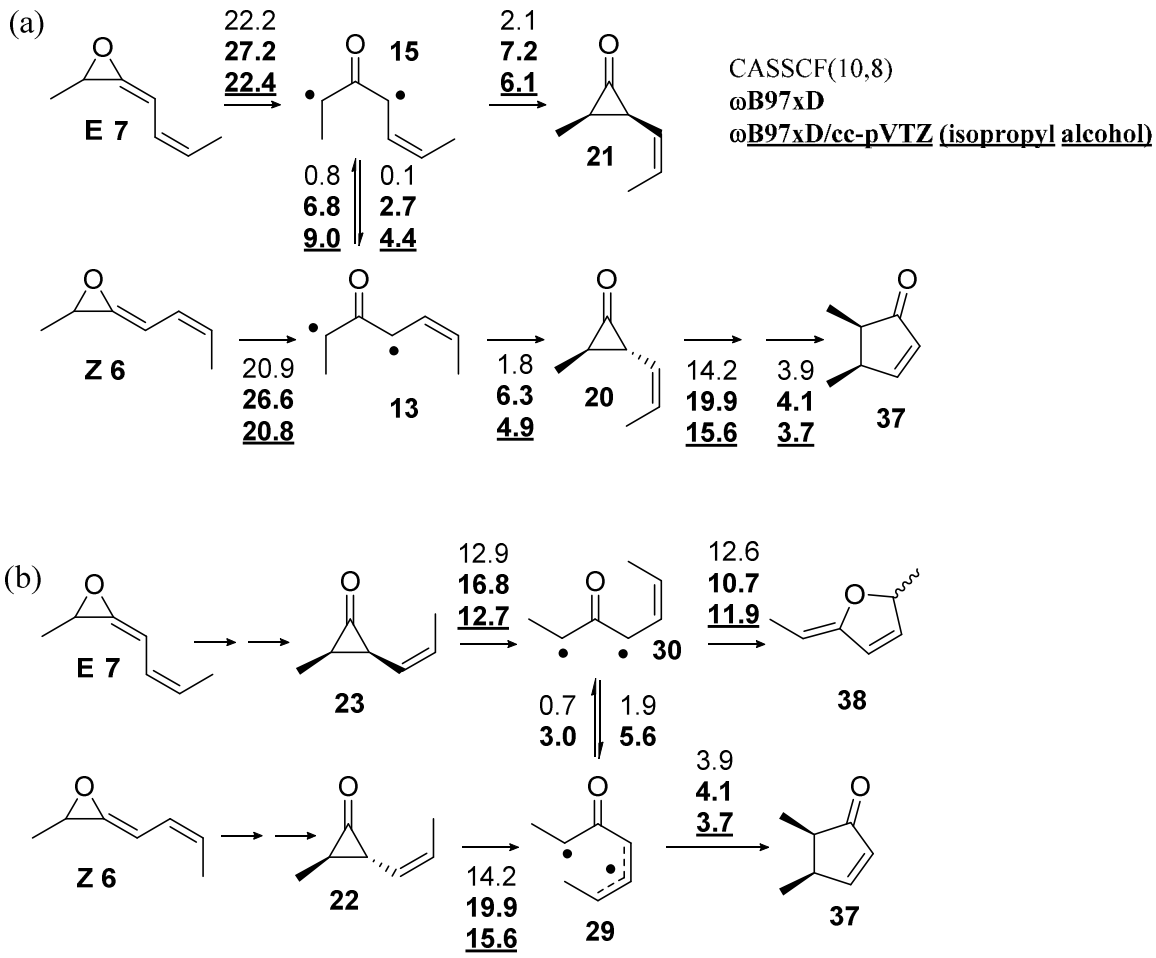
[a]Energy barriers (gas phase, without ZPE or thermal corrections) for forward / reverse reactions calculated with the cc-pVTZ basis set using CASSCF(10,8)/6-31++G(d,p) optimized geometries (transition states not found for **28** **30**, **29** **31**, **13** **28**, **15** **31**)



Scheme 7. Interconversion of conformers of methyl vinyl oxyallyl diradicals via CC bond rotations.

Bond rotations in **12** - **15** can interconvert oxyallyl diradicals originating from *Z*- and *E*-allene oxides, potentially making the initial stereochemistry irrelevant. Conversion from **12** – **15** to **28** – **31** is needed for ring closure to the products, and interchange among **28** - **31** can determine the nature of the final cyclization product. The barriers for converting **12** – **15** to **28** – **31** directly by bond rotation are 5 – 8 kcal/mol higher than the barriers for ring closure to cyclopropanone. Thus interconversion via cyclopropanone is a potential pathway for establishing an equilibrium between the oxyallyl species **12** - **15** and **28** – **31**. The nature of the final product would then be determined by the lowest barrier for ring closing to cyclopentenone, dihydrofuran or allene oxide. Since transition state **33** is 4 – 10 kcal/mol lower than transition states **32**, **34** and **35** and 10 – 15 kcal/mol lower than transition states **8** – **11**, the final product for both *E*- and *Z*-allene oxide cyclization is *cis*-cyclopentenone. The same result can be reached by examining the mechanism one step at a time. Ring opening of *Z*-allene

oxide **6** and *E*-allene oxide **7** form different oxyallyl diradicals, **13** and **15** respectively, but only **15** has bond rotation barriers lower than for cyclopropanone ring closing. In particular, the rotation barrier for converting **15** to **13** (3 kcal/mol for DFT, 1 kcal/mol for CASSCF) is lower than the barrier for cyclization of **15** via **19** to *cis*-cyclopropanone **21** (7 – 8 kcal/mol for DFT and 3 kcal/mol for CASSCF). This would allow ring opening of *E*-allene oxide **7** to form *trans*-cyclopropanone by conversion of **15** to **13**, as shown in **Scheme 8**, and generate the same *cis*-cyclopentenone product as obtained from *Z*-allene oxide **6**. This pathway is shown in Figure 3(c) for the rearrangement of *E*-allene oxide to *cis*-cyclopentenone. A similar crossover between the *E*- and *Z*-diradical pathways is possible after cyclopropane ring opening. The barrier for CC bond rotation in **30** to give **29** is about 10 kcal/mol lower than the barrier for cyclization of **30** to dihydrofuran **38**. Transition state **33** for the conversion of oxyallyl to *cis*-cyclopentanone **37** is lower in energy than the transition states producing other 5-membered ring products (**32**, **34**, **35**) and lower than the transition states for return to allene oxide (**8** – **11**). Consequently, the various pathways converge to produce the same final product, *cis*-cyclopentanone **37**.



Scheme 8. Convergence of the pathways for cyclization of *E*- and *Z*-methyl vinyl allene oxide. Values indicate the barriers calculated from enthalpies using geometries optimized with CASSCF(10,8)/6-31++G(d,p) (plain) and ωB97XD/cc-pVTZ ind the gas phase (bold) and in solution (bold, underlined).

Summary

The energy profiles for stepwise pathways for the conversion of methyl vinyl allene oxide to *cis*-cyclopentenone have been summarized in **Figure 3**. The closed shell stepwise pathway for the rearrangement of methyl vinyl allene oxide to *cis*-cyclopentenone via cyclopropanone was found to be higher in energy than the corresponding open shell pathways.

Open shell calculations indicate that allene oxide opens to oxyallyl diradical which can close to cyclopropanone. Rotation of the vinyl group and opening of cyclopropanone yields a different set of oxyallyl structures. Different conformers / configurational isomers of oxyallyl can also be interconverted by various CC bond rotations. This yields a number of points where *E*- and *Z*-pathways can interconvert (**Scheme 8**). Appropriate oxyallyl diradicals can close to 5-membered ring products, and the lowest energy transition state is for the formation of *cis*-cyclopentenone. The differences in the barriers for the opening of *Z*- and *E*-methyl vinyl allene oxide to oxyallyl diradical are small and alone do not account for the observed difference in the cyclization behavior of the *Z*- and *E*-isomers. Experimentally, the *cis*-cyclopentenone is found to an enantiomeric excess of 61:39. Since the diradical pathway going through an achiral oxyallyl radical would lead to a racemic mixture of *cis*-cyclopentenone, a small portion of the cyclization has to proceed via a pathway that can transfer the chirality of the starting vinyl allene oxide. To explore this alternative, Lopez and coworkers have examined the possible effects of molecular dynamics on the formation of chiral products.[16]

In addition to the formation of cyclopentenone, vinyl substituted allene oxide can react with nucleophiles to produce ring opened products. As a result, the cyclization behavior may depend on the reaction conditions. Grechkin and co-workers were able to observe cyclization of the *E*-isomer to *cis*-cyclopentenone on prolonged storage in hexane.[54] By contrast, in hexane/isopropyl alcohol (100:3, v/v) Brash and co-workers found nearly equal amounts of isopropyl alcohol adduct and cyclization product for the *Z*-isomer, but only the isopropyl alcohol adduct for the *E*-isomer.[1] A small increase in the barrier for ring opening can significantly alter the branching ratio when there is competition between cyclization and adduct formation. If the

barrier for ring opening of the *E*-isomer is 1 -2 kcal/mol higher than for the *Z*-isomer, and if the barrier for the formation of the isopropyl alcohol adduct is a little lower for the *E*-isomer than the *Z*-isomer, the rate of formation of the adduct will be more favorable than ring opening, and little or no cyclization product will be seen for *E*-isomer. This explanation may reconcile the differing behaviors of cyclization observed by Brash et al.[1] and by Grechkin et al.[54] The formation of isopropyl alcohol adducts will be the subject of a future study.

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