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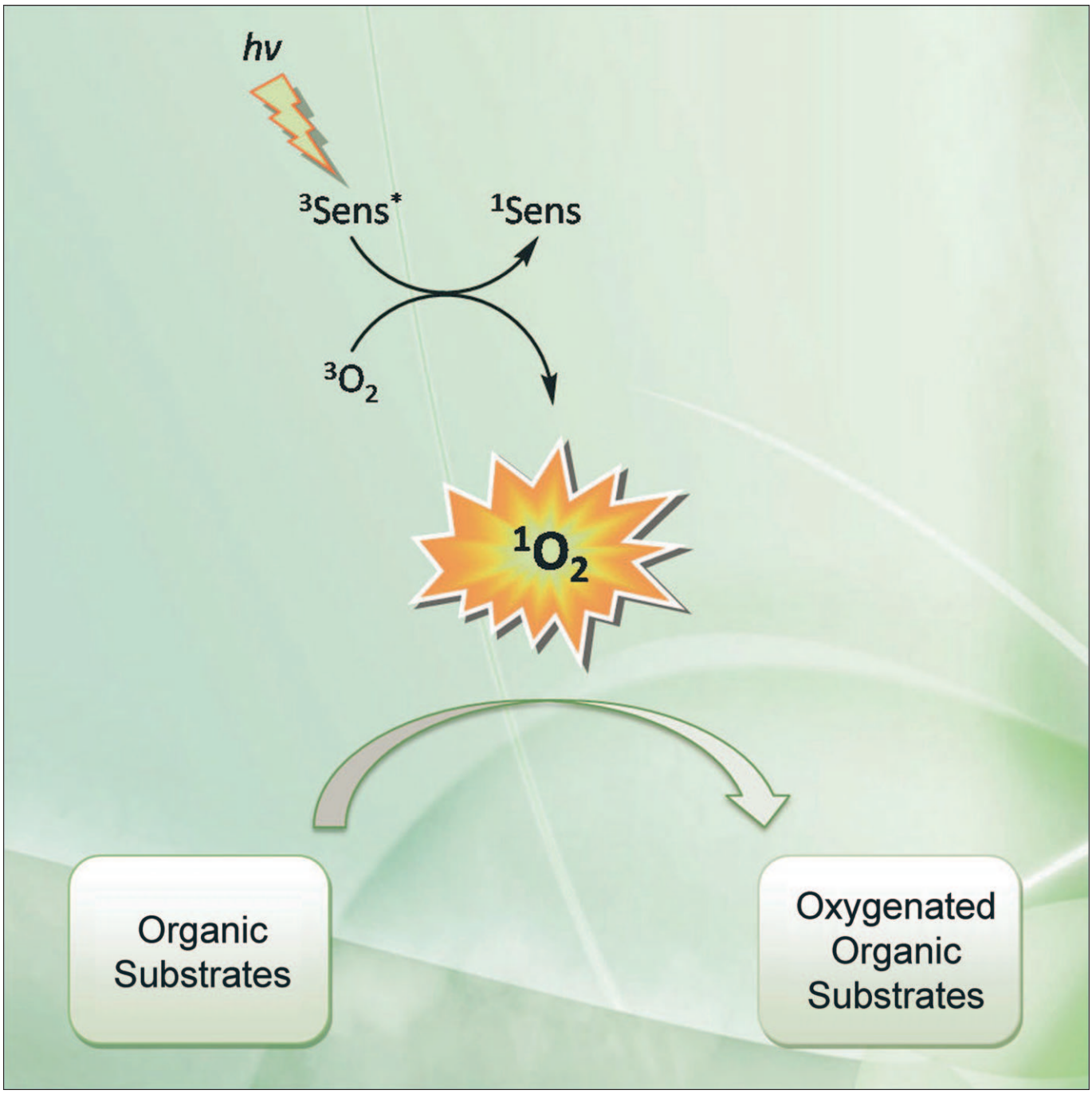
Unraveling the Mechanism of the Singlet Oxygen Ene Reaction: Recent Computational and Experimental Approaches

Mariza N. Alberti and Michael Orfanopoulos*[a]



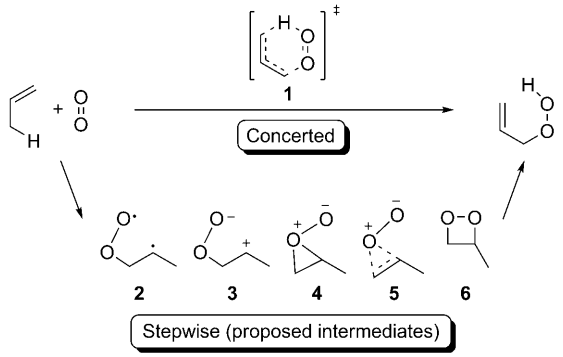
Abstract: The mechanism of the singlet oxygen ene reaction has been a subject of renewed interest within the last few years. The main question being whether this reaction proceeds through a concerted mechanism or if it involves discrete intermediates. In general, the majority of experimental and computational studies support a traditional stepwise mechanism involving a perepoxide-like intermediate. In this minireview we highlight the most prominent and recent theoretical, as well as experimental results relating to the challenging mechanism of the singlet oxygen ene oxyfunctionalization.

Keywords: computational chemistry · cyclopropyl probes · reaction mechanisms · singlet oxygen · stereoselectivity

Introduction

Singlet molecular oxygen $^1O_2$ ($^1\Delta_g$, the lowest excited electronic state)[1] plays a growing role in many natural photochemical,[2] photobiological,[3] and therapeutic processes.[4] This reactive molecular oxygen has a unique chemistry and its use as a reagent in organic synthesis has been of keen interest.[5] Among the various types of $^1O_2$ reactions, the so-called ene or Schenck reaction[6] has inevitably drawn the most extensive either experimental, or theoretical attention.[7] It is noteworthy that the $^1O_2$-mediated allylic oxidation was used as an essential step in the synthesis of natural products[5c,8] or their synthetic analogues.[9] Although this reaction has been studied for many years, its mechanistic details are still a matter of debate either by theoretical or experimental results.[10] The main issue being whether the $^1O_2$ ene reaction is concerted or stepwise. A concerted mechanism in which the characteristic bond shifts take place through a six-membered ring transition state (**1**, Scheme 1) could occur.[11] Alternatively, a range of stepwise processes involving several intermediates could also take place. The proposed intermediates include an open biradical/dipolar (**2** or **3** respectively),[12] a perepoxide (**4**),[13] an exciplex intermediate (**5**, an excited state charge-transfer complex),[14] a 1,2-dioxetane (**6**),[15] as well as gradations between all of these possibilities. Generally, in the $^1O_2$ addition to *simple* alkenes, the formation of the perepoxide (PE) intermediate becomes more likely. On the other hand, in the photooxidation of electron-rich alkenes there is a correlation between PE and open dipolar intermediates.[16]

[a] Dr. M. N. Alberti, Prof. Dr. M. Orfanopoulos
Department of Chemistry, University of Crete
71003 Voutes Campus, Heraklion, Crete (Greece)
Fax: (+30) 2810-545001
E-mail: orfanop@chemistry.uoc.gr

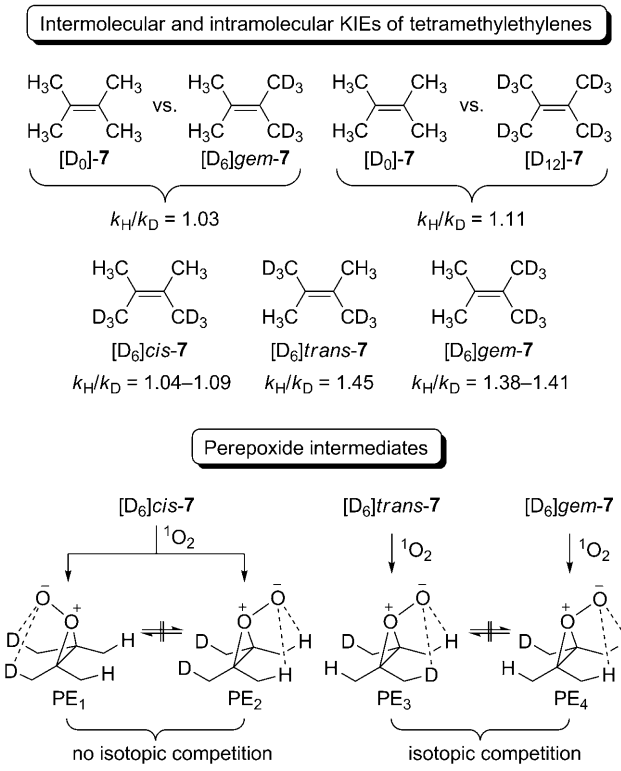


Scheme 1. Concerted and stepwise mechanisms for the $^1O_2$ ene reaction.

Initial Theoretical and Experimental Discoveries

It is generally recognized that the theoretical studies, carried out up to the early 1980s,[17] were rather insufficient to precisely distinguish the mechanistic possibilities of the $^1O_2$ ene reaction. Notably, these studies were performed in a time when only a limited amount of computational resources were available. Despite these limitations, it is important to appreciate the pioneers in that field who laid the foundations of our current knowledge. More recently, among the various computational studies in this field, three of them are briefly mentioned here. In the early 1990s, a PM3 study of the $^1O_2$ addition to propene indicated that both concerted and stepwise pathways (via a strained perepoxide **4** intermediate) are likely to be feasible.[18] In 1996, ab initio molecular orbital studies suggested that the $^1O_2$ addition to allylic olefins and enol ethers (which have abstractable allylic hydrogens) proceeds through a concerted mechanism with a PE-like transition state.[19] In 2001, a highly asynchronous concerted mechanism was reported, when McKee and Sevin investigated the $^1O_2$ addition to 1,3-cyclohexadiene at the DFT(B3LYP) and CASPT2 levels.[20]

The most direct experimental evidence for the mechanism of the $^1O_2$ ene reaction has come from kinetic isotope effects (KIEs) measurements on deuterium-labeled tetramethylethylenes (TMEs). In general, KIE studies are one of the most powerful tools to probe the reaction mechanism. It is instructive to note that an isotopic substitution greatly modifies the reaction rate when this replacement is in a chemical bond that is broken or formed in the rate-limiting step (primary isotope effect). For a KIE measurement to be informative, the competing isotopes (most commonly H and D) must be sterically, stereochemically, and electronically equivalent. Subsequently, negligible or small intermolecular[21] and substantial intramolecular[13] KIEs are strong evidence for the formation of an intermediate in the rate-determining step of the $^1O_2$ addition to TMEs (Scheme 2). Particularly, a negligible intermolecular KIE ($k_H/k_D = 1.03$) for the $^1O_2$ ene reaction of [D_0]-**7** versus [D_6]*gem*-**7** was reported.[21a] Similarly, a small intermolecular KIE ($k_H/k_D = 1.11$) between



Scheme 2. KIE measurements and perepoxide (PE) intermediates for the $^1O_2$ addition to tetramethylethylenes.

[D_0]-**7** and [D_{12}]-**7** was also measured.[21b] Studies of the intramolecular KIEs revealed additional and important key features on the nature of the reaction intermediate.[13] Specifically, a negligible or small intramolecular KIE (k_H/k_D = 1.04–1.09, no isotopic competition) was found in the $^1O_2$ ene reaction with *trans*-related methyl and deuteriomethyl groups in compound [D_6]*cis*-**7**, whereas substantial intramolecular KIEs (k_H/k_D = 1.38–1.45, H/D isotopic competition) were observed with *cis*-related methyl and deuteriomethyl groups in substrates [D_6]*trans*-**7** and [D_6]*gem*-**7**. These intramolecular KIEs were best rationalized by the formation of PE_1-PE_4 intermediates (Scheme 2) in the rate-determining step of this reaction. Furthermore, because all of the methyl groups of TME are symmetrically equivalent, similar isotopic competition would have been expected for [D_6]*cis*-**7**, [D_6]*trans*-**7**, and [D_6]*gem*-**7** in a concerted mechanism; however this was found not to be the case. On this basis, a one-step mechanism was excluded. Additionally, the aforementioned KIE measurements eliminate open biradical/dipolar intermediates from general consideration. If the formation of an open biradical/dipolar intermediate was the case, then: 1) substantial and essentially identical KIEs would be expected from the $^1O_2$ addition to [D_6]*cis*-**7** and [D_6]*trans*-**7**, and 2) no KIE should be observed for the $^1O_2$ addition to [D_6]*gem*-**7**. These assumptions were obviously inconsistent with the experimental results.

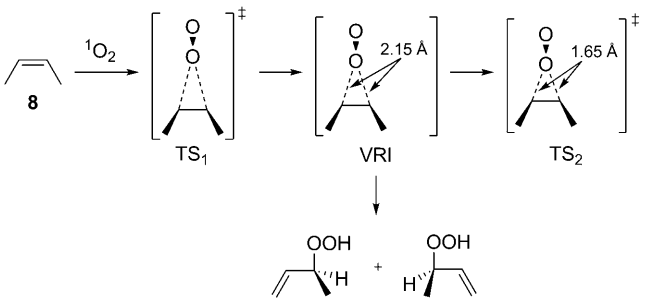
At this point, it is worth mentioning that similar KIEs of the $^1O_2$ ene reaction were measured for trisubstituted[22] and *cis*-disubstituted[23] alkenes. Last, but not least, consistent with the intermediacy of a PE intermediate in the title reaction are: 1) trapping experiments,[24] 2) the lack of Markovnikov-type directing effects,[1a,25] and 3) the observed diastereoselectivities[26] and regioselectivities.[27]

Recent Theoretical Discoveries

One of most important and recent contributions toward understanding the $^1O_2$ ene reaction mechanism is the collaborative effort by the Singleton, Houk, and Foote groups.[28] According to high level ab initio calculations and ^{13}C or ^2H isotope effects,[28,29] the $^1O_2$ addition to *simple* alkenes proceeds through two transition states without an intervening intermediate. This mechanism is defined as a "two-step no-intermediate" process. In particular, for the reaction of $^1O_2$ with *cis*-2-butene or tetramethylethylene, high-level CCSD(T) single-point energies were computed on a grid of B3LYP geometries. The predicted CCSD(T)//B3LYP surface, which is supported by its almost accurate predictions of the intermolecular ^{13}C or ^2H isotope effects and of the reaction barrier, revealed that there are two adjacent saddle points or transition states without the intervention of a minimum or an intermediate. A plausible mechanism for the $^1O_2$ attack on *cis*-2-butene (**8**) is shown in Scheme 3. Accordingly, the first saddle point (TS_1) is a C_s-symmetric rate-limiting transition state with the symmetry of the PE. Notably, TS_1

Mariza N. Alberti was born in Athens, Greece in 1978. She received her BSc degree (1st Class Honors) in 2001 from the University of Crete. She obtained her MSc degree in 2004 and her PhD in 2007 from the University of Crete under the direction of Professor M. Orfanopoulos. She is currently pursuing postdoctoral studies at the same University. Her research activity has been mainly carried out in the field of the mechanistic elucidation of electrophilic addition reactions and the study of photocatalytic processes.

Michael Orfanopoulos received his BSc from the University of Patras, MSc from the University of Toledo, and PhD from Case Western Reserve University in 1979. He was a postdoctoral fellow at Stanford University with Professor H. S. Mosher and at UCLA with Professor C. S. Foote. In 1982 he became a research scientist at the NRC Demokritos, Athens, Greece, and in 1985 he joined the University of Crete, where he is currently Professor of Organic Chemistry. His research focuses on a) chemical and photochemical catalysis involving polyoxometalates and reactive oxygen species, and b) fullerene based carbon nanostructures and photosynthesis of fullerene and heterofullerene derivatives.



Scheme 3. Plausible mechanism for the $^1O_2$ addition to alkene **8**.

does not involve hydrogen abstraction by the trailing oxygen. The second saddle point or transition state (TS_2), also C_s-symmetric, has an elusive PE-like structure and lies near a valley-ridge inflection (VRI) point.[30] At this point, the aforementioned CCSD(T)//B3LYP surface bifurcates[31] and the reaction pathway falls off to one or the other side while abstracting a hydrogen from either terminal methyl group of **8**. A similar mechanism was reported for the $^1O_2$ addition to tetramethylethylene. In Figure 1, a model poten-

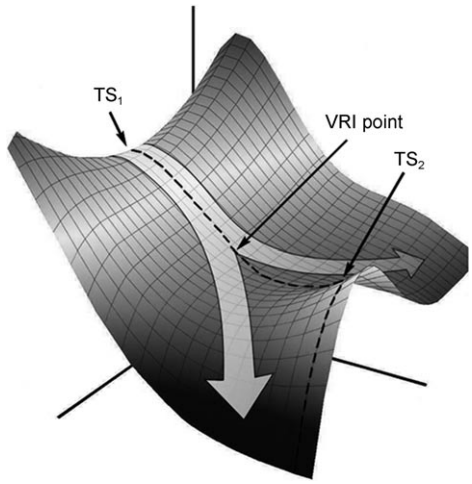


Figure 1. Model potential energy surface with sequential transition states TS_1 and TS_2.

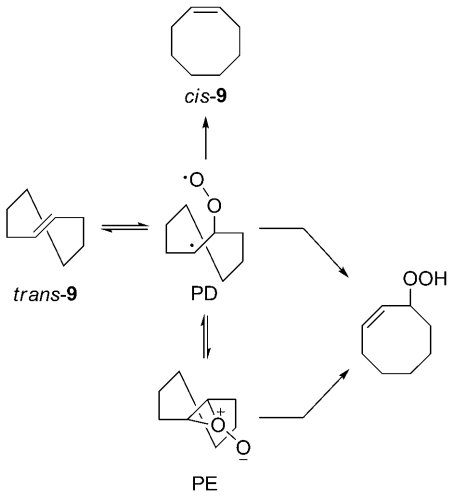
tial-energy surface (PES) with the sequential transition states TS_1 and TS_2 as well as a VRI point is depicted. The most representative reaction pathway is an intrinsic reaction coordinate, which is known as the steepest descent pathway on a PES. This pathway is shown by dotted black line. Additionally, the expected reaction trajectories are indicated by thick arrows. Notably, when a reaction shows this type of surface, the product ratio is governed by the shape of the PES and resulting dynamic effects.[32]

In the early 2000s, Tonachini and co-workers[33] investigated the gas-phase mechanism of the $^1O_2$ ene reaction of propene; the simplest alkene capable in principle of undergoing this reaction. In that study, the possible intermediates or transition states were optimized at the DFT(MPW1K), DFT(B3LYP), and CASSCF levels of theory. These optimizations were followed by multireference perturbative CASPT2 energy calculations. The main result of this theoretical work is that the $^1O_2$ attack on propene is a stepwise process that involves the irreversible formation of a polar biradical intermediate. Another important finding is that a PE is attainable only by passing through a polar biradical intermediate; this perepoxidic structure is located approximately 12 kcal mol^{-1} above (at all the aforementioned levels of theory) the polar biradical intermediate. Furthermore, the calculated energy barrier for the transformation of the polar biradical intermediate to the ene adduct is much lower than the transformation of the polar biradical intermediate to *cis*-methyl perepoxide. Therefore concerning this system, a PE pathway is ruled out. Finally, a concerted pathway was carefully examined and deemed an artifact of restricted DFT calculations.

Later on, Tonachini and co-workers[34] carried out DFT calculations to examine the mechanism of the $^1O_2$ addition to (*E*)-2-methyl-but-2-enal; this substrate was chosen as a simple example model system of an α,β-unsaturated carbonyl compound. In agreement with their above-mentioned results,[33] a stepwise pathway passing through a polar biradical intermediate appears favorable. This mechanism enables interpretation of the relative reactivity of the *s-cis* and *s-trans* conformers of the reactant ((*E*)-2-methyl-but-2-enal), as well as the regioselectivity. Specifically, the higher reactivity of the *s-cis* isomer (with respect to *s-trans*) was attributed to the greater stability of the *s-trans* reactant. Moreover, the observed regioselectivity originated from the different stabilities of the two polar biradical intermediates obtained by the $^1O_2$ attack on the reactant.

In 2008, Houk and co-workers performed B3LYP/6-31G* and CASMP2 calculations to understand the mechanism of the $^1O_2$ ene reaction of tetramethylethylene or *trans*-cyclooctene.[35] Notably, *trans*-cyclooctene has a geometry that prevents the abstraction of an allylic hydrogen. Hence in this case, the PE intermediate is expected to have a longer lifetime than in *normal* alkenes (such as tetramethylethylene).[36] Concerning the computational results, the $^1O_2$ addition to tetramethylethylene proceeds through a "two-step no-intermediate" mechanism; this observation is in accordance with their previously mentioned findings with this system.[28] In contrast, the $^1O_2$ attack on *trans*-cyclooctene was predicted to occur by a stepwise mechanism involving a PE intermediate. A plausible mechanism that could account for the $^1O_2$ ene reaction of *trans*-cyclooctene (*trans*-**9**) is presented in Scheme 4. The PE intermediate is formed via a polarized biradical (PD) intermediate. The latter intermediate can lead to the isomerization of *trans*-cyclooctene. It was also assumed that the change in the photooxidation mechanism of tetramethylethylene and *trans*-cyclooctene presumably occurs because the latter reactant (*trans*-**9**) imposes a large strain in the transition state for hydrogen abstraction.

Despite these seemingly promising results, the majority of calculations carried out so far on the $^1O_2$ ene reaction have several weak points that cannot be ignored. Two of the

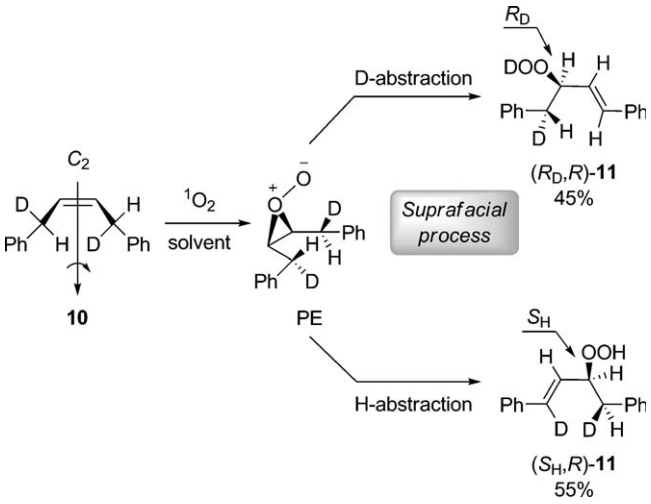


Scheme 4. Plausible mechanism for the $^1O_2$ addition to alkene *trans*-**9**.

major drawbacks are the use of relatively poor basis sets (that may result in an incorrect description of the PES), as well as neglecting any solvent effect. Nevertheless, a computational report by Acevedo and Sheppard provided valuable and updated information regarding the mechanistic details of the title reaction.[37] In this study, the $^1O_2$ addition to tetramethylethylene was investigated by using novel three-dimensional potentials of mean force (3D PMF) coupled to multidimensional mixed quantum and molecular mechanics (QM/MM) simulations, in three different explicit solvents (water, DMSO, and cyclohexane). Notably, these calculations provided an alternative free-energy surface that appears to be consistent with a traditional stepwise mechanism, as opposed to the previously reported "two-step no-intermediate" mechanism.[28] Moreover, the predicted mechanism was found to have two transition states and a symmetric charge-separated PE intermediate, which is in accordance with most of the earlier experimental findings.[13,21–27] It is important to point out that, by reducing the number of simultaneous reaction coordinates, the current 3D PMF derived PES can be downgraded into a two-dimensional (2D) PES. This surface is similar to that reported by the Singleton, Houk, and Foote groups.[28] As a consequence of this, the reported two-step no-intermediate mechanism seems to be an artifact. Finally, and not of least importance, the computational study conducted by Acevedo and Sheppard provided insight into the effect of solvent on the $^1O_2$-mediated allylic oxidation. More specifically, it was suggested that the PE intermediate is sensitive toward solvent polarity and hydrogen bonding. Accordingly, increasing the solvent polarity increases the stability of the PE, as well as the relative energy barrier for product formation. The latter observation solidifies the PE's role as an intermediate and not as a transition state.

Recent Experimental Discoveries

Among the more noteworthy contributions toward identifying the dominant mechanism of the $^1O_2$-mediated allylic oxidation are a recent stereochemical study and the use of hypersensitive probes. Concerning the stereochemical investigation of this classical reaction, a preliminary study has been reported by Stephenson and co-workers.[38] In particular, a stereoisomeric–isotopic relationship was observed for the $^1O_2$ addition to (*R*)-*cis*-5-methyl-3-hexene-2-*d*. This observation is inconsistent with a conventional picture of biradical or dipolar mechanisms. In a recent study, the stereochemistry of the title reaction was examined in more detail.[39] Specifically, the $^1O_2$-mediated allylic oxidation of symmetrical and optically active alkene **10** (Scheme 5) pro-



Scheme 5. Plausible mechanism for the $^1O_2$ addition to chiral alkene **10**.

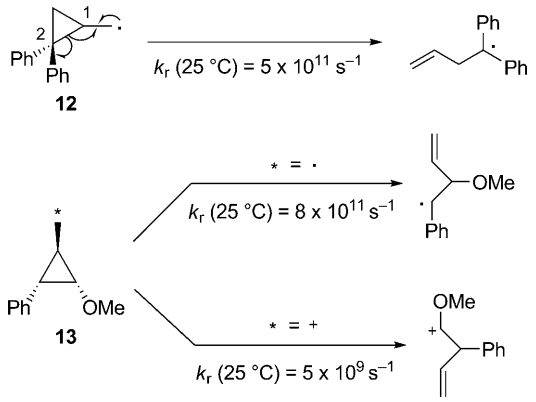
vides important mechanistic insights. It is noteworthy that this chiral alkene has different groups at both ends of the double bond; hence, the ene adducts will contain a new stereogenic center. Moreover, olefin **10** has a C_2 symmetry axis such that the two faces of the double bond are equivalent. The photooxidations of **10** were run in $CHCl_3$, $(CH_3)_2CO$, CH_3CN, and MeOH. In all cases, *trans*[23a] allylic hydroperoxides of type **11** (Scheme 5) were obtained quantitatively. In alkene **10**, as already mentioned above, the two faces (top and bottom) of the double bond are equivalent. For convenience, we present here the mechanistic possibilities considering only the top face. Therefore, approach of $^1O_2$ from this face would abstract either a deuterium atom (D) forming a new *R* stereogenic center, or a hydrogen atom (H) forming a new *S* stereogenic center. These stereogenic centers are defined as R_D and S_H, respectively. In analogous fashion, the observed diastereomeric ene adducts are labeled as (R_D,*R*)-**11** and (S_H,*R*)-**11**.

In the photooxidation of **10** in $CHCl_3$, the (S_H,*R*)-**11**/(R_D,*R*)-**11** ratio, which is proportional to the primary intramolecular isotope effect, was found to be equal to $k_H/k_D =$

1.20 ± 0.05; this ratio was determined by integration of the vinylic signals of the ene products in the ^{1}H NMR spectrum. Additionally, the ratio of the newly formed stereogenic centers, which was determined by integration of the diastereotopic benzylic protons of the ene products in the ^{1}H NMR spectrum, was equal to $S_H/R_D = 1.23 \pm 0.05$. At this point, it is important to emphasize the correspondence of the isotopic k_H/k_D ratio of 1.20 with the diastereomeric ratio $(S_H,R)/(R_D,R)$ of 1.23. Notably, similar isotopic and diastereomeric ratios were found when $(CH_3)_2CO$, CH_3CN, or MeOH was used as the photooxidation solvent.

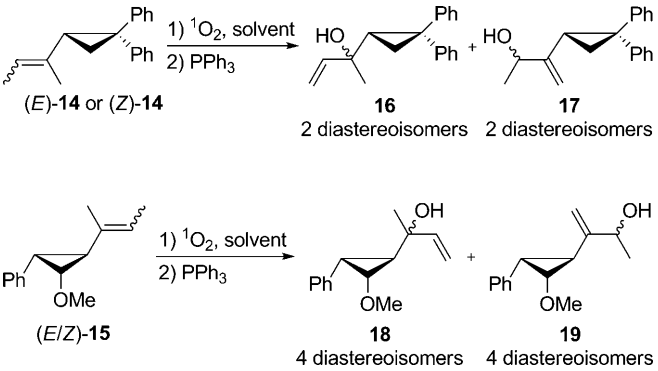
The aforementioned results are better rationalized in terms of a PE-like intermediate (PE, Scheme 5). From this intermediate, the D-abstraction leads to the formation of ene adduct (R_D,R)-**11** that contains a new R_D stereogenic center whereas the H-abstraction leads to the formation of ene adduct (S_H,R)-**11** that contains a new S_H stereogenic center. Furthermore, the observation of an isotope effect that matches exactly with the stereogenic ratio and the absence of crossover products (namely (R_H,R)-**11** and (S_D,R)-**11**) clearly excludes the involvement of an open biradical/dipolar intermediate in the title reaction. Ultimately, these findings confirm that the $^1O_2$ allylic oxidation of *simple* olefins is a highly stereospecific suprafacial process, independent of solvent polarity.

As a part of ongoing research to get further information on the $^1O_2$ ene reaction mechanism, we have recently designed and assayed informative unsaturated substrates that contain cyclopropyl groups as mechanistic probes.[40] It is instructive to note that cyclopropyl groups have been frequently used as traps for radical intermediates,[41] since they involve the rapid rearrangement of the cyclopropylcarbinyl radical to the homoallyl radical. In the early 1990s, Newcomb and co-workers reported that the addition of two phenyl groups at C2 in the cyclopropyl ring results in radicals (such as **12**, Scheme 6) that their ring opens exceedingly fast with a lifetime greater than 2×10^{-12} s; the rate constant of 2,2-diphenylcyclopropyl carbinyl radical ring opening was determined to be 5×10^{11} s^{-1} at room temperature.[42] Later on, a second-generation probe (**13**, Scheme 6), that maintains its hypersensitive reactivity and is capable of distinguishing between a radical and a carbocation intermediate, was reported by Newcomb and co-workers.[43] In the ring opening of **13**, the phenyl group stabilizes an incipient radical more effectively than the methoxy group, whereas the methoxy group favors an incipient carbocation.



Scheme 6. Cyclopropylcarbinyl radical/carbocation ring openings.

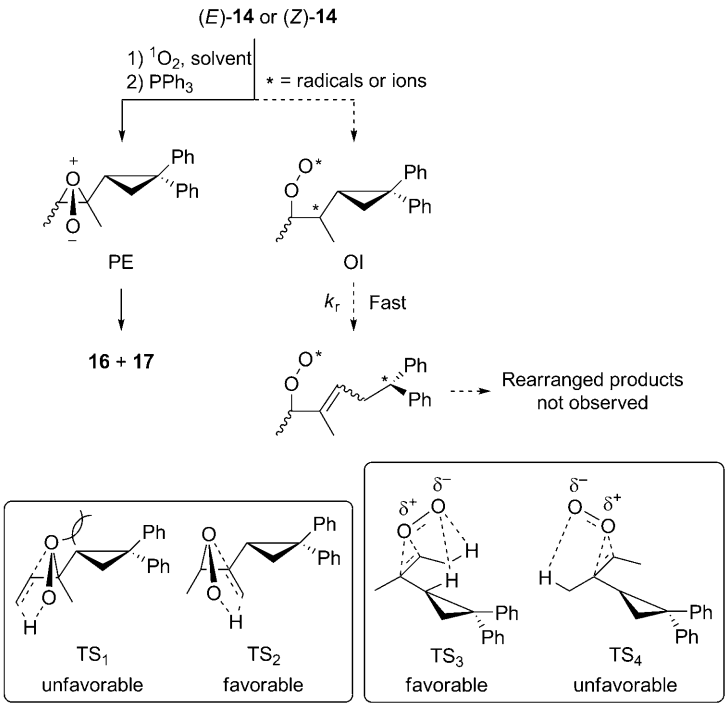
Taking into account the studies conducted by Newcomb and co-workers,[42,43] we examined the photooxidations of (*E*)-**14**, (*Z*)-**14**, and (*E*,*Z*)-**15** in several solvents, such as $CHCl_3$, $(CH_3)_2CO$, CH_3CN, and MeOH (Scheme 7). In all



Scheme 7. $^1O_2$ ene reaction of cyclopropyl substituted alkenes (*E*)-**14**, (*Z*)-**14**, and (*E*,*Z*)-**15**.

cases and after reduction with PPh_3, isomeric allylic alcohols **16–19** containing an intact cyclopropyl group were formed exclusively (the structural assignment of these oxygenated products was carried out by using ^{1}H NMR spectroscopy). Even in MeOH, unlike the triazolinedione addition to cyclopropyl substituted alkenes,[44] no rearranged methanol-trapping products were detected. It should also be mentioned that in the $^1O_2$ ene reaction of alkene (*E*)-**14** there is a substantial preference for hydrogen abstraction from the methyl group *geminal* to the 2,2-diphenylcyclopropyl substituent of the double bond (**16**/**17** = 23:77, in all the solvents studied). This trend in regioselectivity is attributed to the "large group nonbonding effect".[45] In the case of (*Z*)-**14**, the more substituted side of the double bond was found to be the more reactive (**16**/**17** = 70:30, in all the solvents studied). This product site selectivity is in accordance with the well-established "*cis* effect".[46] As expected,[47] the aforementioned regioselections were independent of solvent polarity.

The proposed mechanism that could account for alkenes (*E*)-**14** and (*Z*)-**14** is shown in Scheme 8. The $^1O_2$ addition to these unsaturated substrates should lead to distinctly different products depending on the adopted mechanistic pathway. For instance, when a PE intermediate is involved, ene adducts with cyclopropyl groups intact may be formed. Alternatively, the existence of an open biradical/dipolar intermediate (OI, Scheme 8) could yield rearranged products. Specifically, if an OI intermediate with a lifetime greater than 10^{-11}–10^{-12} s[42,48] had been formed, the ring-opened products should have been detected. At this point, it is pru-



Scheme 8. Plausible mechanism for the $^1O_2$ addition to (*E*)-**14** or (*Z*)-**14**.

dent to suggest that the absence of rearranged products in combination with the observed regioselection can be explained by the intervention of a PE intermediate. In analogous fashion, the formation of allylic alcohols **18** and **19** can be rationalized by a mechanism similar to that proposed for alkenes (*E*)-**14** and (*Z*)-**14**.

Notably, the observed regioselectivity for alkene (*E*)-**14** is explained by examining the possible transition states (TS_1 and TS_2, Scheme 8) leading to ene adducts. In TS_1, which leads to the minor product, the repulsive 1,3-nonbonding interactions between the oxygen atom and the 2,2-diphenylcyclopropyl substituent are larger than those of TS_2. Thus, TS_2 is expected to have lower energy than TS_1. In the case of alkene (*Z*)-**14**, the existence of an interaction between the incoming $^1O_2$ and the two allylic hydrogen atoms highly stabilizes the transition state TS_3, versus TS_4, of the PE formation (Scheme 8).

Summary and Outlook

The last decade has seen an increase in studies investigating the mechanism of the $^1O_2$-mediated allylic oxidation. Despite earlier experimental studies that gave substantial support to the intervention of a perepoxide-like intermediate, recent computational studies, by Singleton[28] and Tonachini[33,34] and their co-workers, have caused doubts on this mechanistic issue. Nevertheless, more recent theoretical as well as experimental efforts (contributed by the Acevedo[37] and Orfanopoulos[39,40] groups, respectively) provided fruitful insights into this photooxidation mechanism. Taking into account both earlier and more recent findings, it seems justifiable to assume that the perepoxide is a viable intermediate in the $^1O_2$ addition to *simple* alkenes. In this minireview, we briefly highlighted the classical and most recent studies relevant to this mechanistic puzzle. Ultimately, we undoubtedly believe that $^1O_2$ will continue to fascinate researchers in chemistry, physics, biology, and medicine.

Acknowledgements

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