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The Cyclopropyl Group as a Hypersensitive Probe in the Singlet Oxygen Ene Reaction Mechanism

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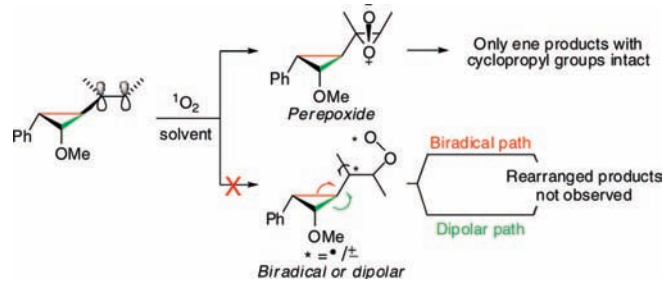
ABSTRACT



Cyclopropyl-substituted olefins are employed as mechanistic probes in the singlet oxygen−alkene ene reaction. In MeOH and aprotic solvents [$CHCl_3$, $(CH_3)_2CO$, CH_3CN], only the allylic hydroperoxides bearing an intact cyclopropyl group are detected. The reaction mechanism is independent of solvent polarity. Our findings, to a certain experimental limit, exclude a biradical or dipolar intermediate.

The chemistry of singlet oxygen ($^1O_2$, $^1\Delta_g$)[1] has received remarkable attention over the last several years due to its synthetic utility[2] and environmental[3] and biomedical significance.[4] Among the various types of reactions involving $^1O_2$,[1,5] the ene or Schenck[6] reaction is the most studied experimentally and computationally. The mechanism of this reaction is the subject of much current controversy, the main question being whether the reaction is concerted or involves intermediates. A concerted mechanism, via a six-membered ring transition state (**a**), has been favored by many researchers (Scheme 1).[7] Biradicals (**b**),[8] zwitterions (**c**),[8b,9] perepoxides (**d**),[10] and a π-complex or exciplex (**e**)[11] have also been proposed as intermediates. Among these, the formation of a perepoxide intermediate (**d**) was the most popular and found

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(2) (a) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308–5317. (b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052–1103, and references cited therein.

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(6) Schenck, G. O.; Eggert, H.; Denk, W. *Liebigs Ann. Chem.* **1953**, *584*, 177–198.

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(10) (a) Stephenson, L. M.; Grdina, S. B.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419–425. (b) Yamaguchi, K.; Yabushita, S.; Fueno, T.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 5043–5046. (c) Hotokka, M.; Roos, B.; Siegbahn, P. *J. Am. Chem. Soc.* **1983**, *105*, 5263–5269.

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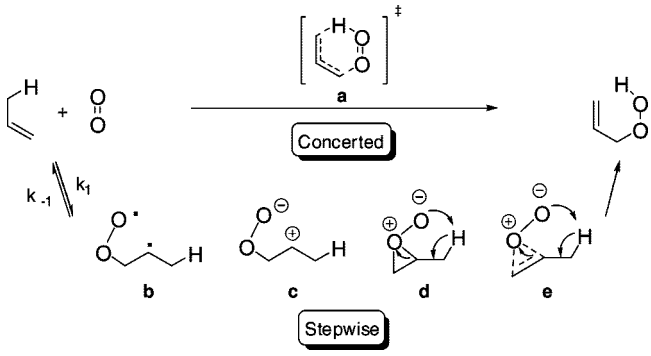
Scheme 1. Proposed Mechanisms for the $^1O_2$ Ene Reaction



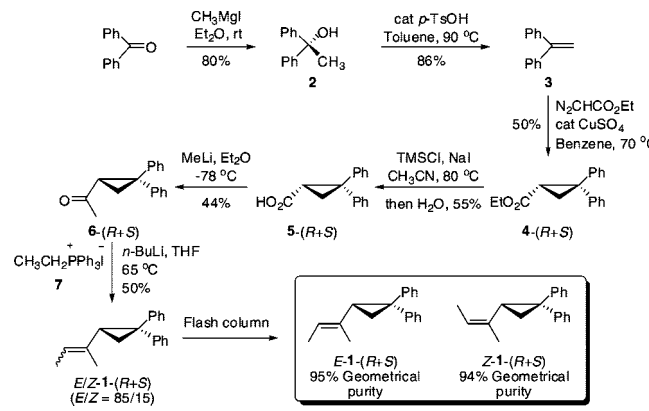
support through trapping experiments,[12] the lack of Markovnikov effects, stereo-[13] and regioselectivities,[14] as well as isotope effect measurements on deuterium-labeled tetramethylethylenes[10a] and 2-butenes.[15]

Previous theoretical calculations for this mechanism are notably contradictory.[16] A perepoxide intermediate was favored by semiempirical MINDO/3[17a] as well as SCF CNDO/2-CI methods.[17b] However, early ab initio calculations (GVB-CI) by Harding and Goddard support a biradical intermediate.[8a] More recently, evidence in the formation of biradical intermediates was derived from CASSCF studies on $^1O_2$-ethylene interaction.[18] In addition, density function levels of theory support a polar biradical intermediate in the interaction of $^1O_2$ with propene, excluding an energetically unfavorable perepoxide intermediate.[8b] In a recent report by Leach and Houk, the $^1O_2$ ene reaction with alkenes was suggested to proceed through a highly asynchronous concerted mechanism, involving regions of the potential surface with both perepoxide and polarized biradical character.[19] Subsequently, Singleton and co-workers, based on high level ab initio calculations and experimental kinetic isotope effects, proposed that $^1O_2$ ene reaction is a concerted *two-step no-intermediate* mechanism.[20] It is useful to note here that in all of the above computational methods, the influence of the reaction solvent is neglected. There is no doubt that the precise mechanism of this reaction remains obscure.

It is obvious that a better experimental approach to probe the nature of the intermediate in the $^1O_2$ ene reaction requires designing a more informative substrate. It was this quest that prompted us to design an alkene that bears the 2,2-diphenylcyclopropyl group as a mechanistic probe capable of distinguishing a biradical or dipolar character of the intermediate.

We have studied the singlet oxygenation of *E*- and *Z*-2-(2′,2′-diphenylcyclopropyl)-2-butene (*E*-**1** and *Z*-**1**), prepared in isomerically pure forms by known chemical reactions (Scheme 2). From this synthetic scheme it is worth mentioning that attempts to saponify cyclopropyl ester **4** were thwarted by the reactivity of the system; only products in which the cyclopropane ring was ruptured were obtained. However, transformation of the ethyl ester into a trimethylsilyl ester with TMSCl/NaI system, followed by hydrolysis,[21] afforded carboxylic acid **5**. Separation of *E*/*Z*-**1** olefins was accomplished by flash column chromatography, using hexane as an eluent. The trans stereochemistry of the newly formed double bond in *E*-**1** was assigned by nuclear Overhauser effect difference experiments (DNOE).

Scheme 2. Synthetic Sequence for the Preparation of Olefins *E*-**1** and *Z*-**1**



Similar probes have been used in the past as traps for other radical intermediates, since they involve the rapid rearrangement of the cyclopropyl carbinyl radical (**8a**) to the homoallyl radical (**9a**) (eq 1).[22] In this work, the addition of two phenyl groups at C2 in the cyclopropyl ring, such as in **8b**, results

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(17) (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1975**, *97*, 3978–3986. (b) Inagaki, S.; Fukui, K. *J. Am. Chem. Soc.* **1975**, *97*, 7480–7484.

(18) (a) Tonachini, G.; Schlegel, H. B.; Bernardi, F.; Robb, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 483–491. (b) Maranzana, A.; Ghigo, G.; Tonachini, G. *J. Am. Chem. Soc.* **2000**, *122*, 1414–1423.

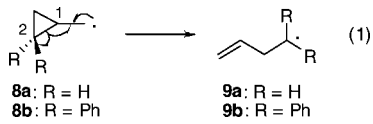
(19) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, 1243–1255.

(20) Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 1319–1328.

(21) For details, see the Supporting Information.

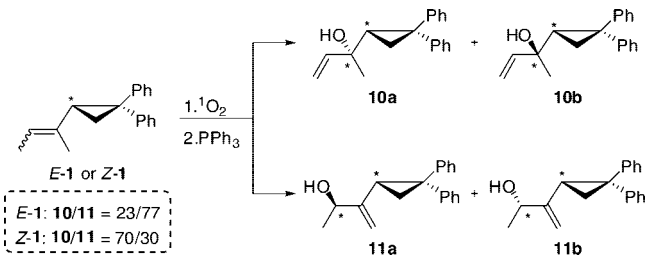
(22) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275–277.

in radicals that ring opens exceedingly fast, with lifetimes of only a few picoseconds, at ambient temperatures.[23]



Both substrates *E*-**1** and *Z*-**1** react smoothly with $^1O_2$, which was generated by 300 W xenon lamp irradiation of TPP in $CHCl_3$, Rose Bengal in $(CH_3)_2CO$ and CH_3CN, or Methylene blue in MeOH at 0 °C or rt. In all cases, isomeric ene allylic hydroperoxides were exclusively formed. Since the ene adducts contain a new stereogenic center (Scheme 3), the reaction mixture consists of two pairs of diastereomeric hydroperoxides (total of eight isomers). Thus, the ^1H NMR analysis was considerably complicated. Fortunately, after the reduction of the reaction mixture with PPh_3, each diastereomer of the two pairs **10a**,**b** and **11a**,**b** (Scheme 3) was separated and well characterized by ^1H NMR spectroscopy. In all cases, the ^1H NMR spectra show the characteristic absorptions of the three cyclopropyl protons between 1.1 and 2.5 ppm.[21] Representative ^1H NMR spectra of the diastereomeric pair **10a**,**b** are shown in Figure 1.

Scheme 3. Photooxygenation and Subsequent Reduction of Olefins *E*-**1** and *Z*-**1**



In nonhydroxylic solvents, the only detected and isolated products were the ene adducts **10** and **11** with intact cyclopropyl ring. Even in MeOH, unlike the corresponding PTAD−cyclopropylalkene ene reaction,[24] apart from the ene adducts **10** and **11**, no rearranged methanol-trapping products were detected. These results also indicate that solvent polarity play an insignificant role in the mechanism of $^1O_2$ ene reaction.

It is worth mentioning that in the $^1O_2$ ene reaction with alkene *E*-**1** there is a substantial preference for hydrogen abstraction from the methyl group geminal to the 2,2-diphenylcyclopropyl substituent of the double bond (**10**/**11** = 23:77, in $CHCl_3$). This regioselection can be attributed to

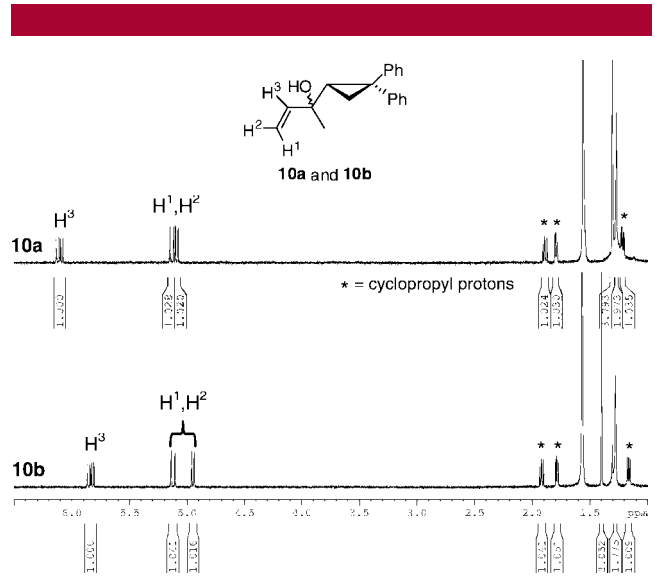


Figure 1. ^1H NMR spectral regions from 1 to 6.5 ppm for allylic alcohols **10a** and **10b**.

previously reported *nonbonding large group effect*.[25] Moreover, in the case of *Z*-**1**, the more substituted side of the double bond was the more reactive (**10**/**11** = 70:30, in $CHCl_3$). This product regioselectivity is in agreement with the well-known *site selectivity* or *cis effect*.[26] These trends in regioselectivity were independent of solvent polarity, consistent with previous studies on reaction rates.[27]

The proposed mechanism that could account for these results is presented in Scheme 4. The $^1O_2$ ene reaction of alkene *E*-**1** should lead to distinctly different products depending on the mechanistic path adopted (Scheme 4). When an intermediate perepoxide is invoked (path I), ene products with cyclopropyl groups intact may be formed. On the other hand, an open intermediate (biradical or dipolar) should result in rearranged products (path II). In particular, if a biradical intermediate with a lifetime greater than 10^{-11}−10^{-12} s (rate of 2,2-diphenylcyclopropyl carbinyl radical ring opening: 5×10^{11} s^{-1})[23b,28] had been formed, the ring-opened products should have been detected. Interestingly, the exclusive formation of the unrearranged products **10a**,**b** and **11a**,**b** in combination with the observed regioselection, can be rationalized by the intermediacy of a perepoxide (path I). Subsequently, in transition state TS_I leading to the minor ene products **10a**,**b**, the nonbonding interactions involving the large diphenylcyclopropyl group, are expected to be stronger than those in TS_{II} where these

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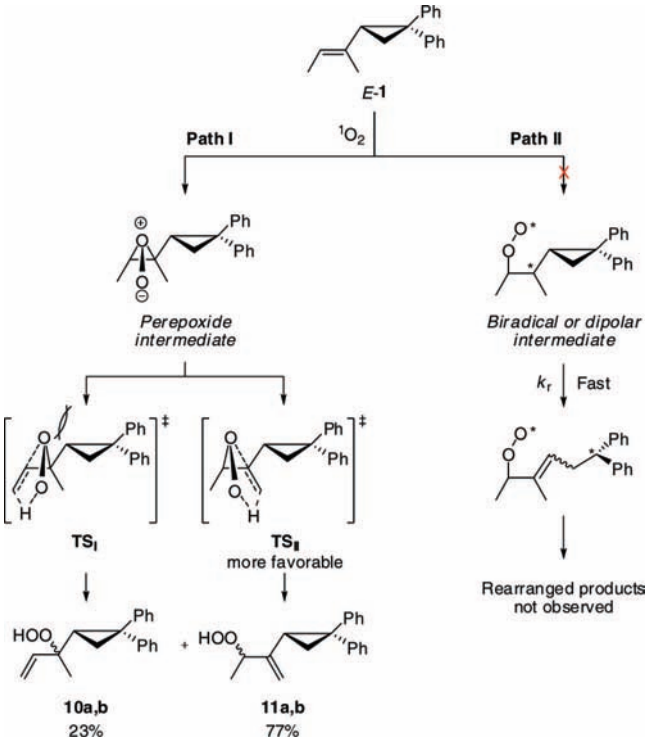
(27) (a) Foote, C. S.; Denny, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5168–5171. (b) Gollnick, K.; Griesbeck, A. *Tetrahedron Lett.* **1984**, *25*, 725–728.

(28) For clocking secondary and tertiary cyclopropyl rearrangements, see: Engel, P. S.; He, S.−L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1997**, *62*, 1210–1214. Choi, S.−Y.; Toy, P. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 8609–8613.

Scheme 4. Proposed Mechanistic Possibilities in the Allylic Oxygenation of *E*-**1**

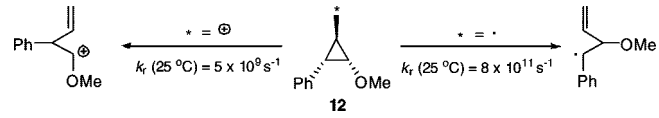


interactions are much less pronounced. A similar mechanism is also suggested for the photooxygenation of isomer *Z*-**1**. Although the present results can also be rationalized by a concerted mechanism, previous isotopic studies of tetramethylethylenes-d_6[10a] and trapping experiments[12] excluded this mechanistic possibility.

In order to further investigate the mechanism of $^1O_2$ ene reaction, we also used the second-generation hypersensitive probe (**12**) which was reported by Newcomb and coworkers.[29] This probe is capable of distinguishing between biradical and dipolar intermediates. Consequently, in ring opening of this cyclopropyl carbinyl system, the phenyl group stabilize an incipient radical more effectively than the methoxy group; whereas the methoxy group favors an incipient carbocation. For example, cyclopropyl carbinyl radical **12** rearranges with regioselectivity 160:1 at ambient temperature to the benzylic radical; while cyclopropyl carbinyl cation **12** opens with even more selectivity >1000:1 to oxonium ion.

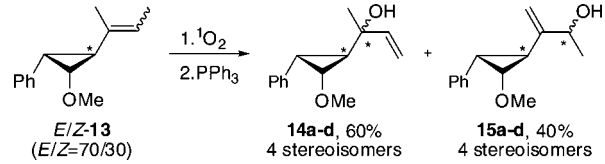
Specifically, we carried out the photooxygenations of *E*/*Z*-**13** in $CHCl_3$, $(CH_3)_2CO$, CH_3CN, and MeOH at 0 °C or rt.

(29) (a) Newcomb, M.; Chestney, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 9753–9754. (b) Le Tadic-Biadatti, M.—H.; Newcomb, M *J. Chem. Soc., Perkin Trans. 2* **1996**, 1467–1473.



In all cases, the ene allylic hydroperoxides were exclusively formed. After the reduction of the complex reaction mixture with PPh_3, we managed to isolate by column chromatography the mixture of allylic alcohols **14a**−**d** and **15a**−**d**. In these products, which are presented in Scheme 5, the cyclopropyl

Scheme 5. Photooxygenation and Subsequent Reduction of Olefin *E*/*Z*-**13**



ring remains intact. Even when MeOH was used as a solvent, no rearranged methanol-trapping derivatives were detected. The exclusive formation of the unrearranged products **14a**−**d** and **15a**−**d** can again be better rationalized by the intermediacy of a perepoxide. Therefore, the proposed mechanism that could account for the formation of the allylic alcohols **14a**−**d** and **15a**−**d**, is similar to that already presented in Scheme 4.

In conclusion, two hypersensitive radical probes were used for the investigation of $^1O_2$-alkene ene reaction in various solvents. In all the reaction conditions used herein, no rearranged products were detected. In light of our findings, it is difficult to argue for a biradical or dipolar mechanism. In our view, modeling of $^1O_2$ ene reaction will continue to provide a relevant and challenging problem. Since experimental work seems to have reached its limits, the challenge now might lead to more accurate computational work for conclusive mechanistic refinements.

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Supporting Information Available: Detailed experimental procedures, spectral data, and ^1H NMR, DNOE, ^{13}C NMR, and HMQC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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