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Stereochemistry of the Singlet Oxygenation of Simple Alkenes: A Stereospecific Transformation†

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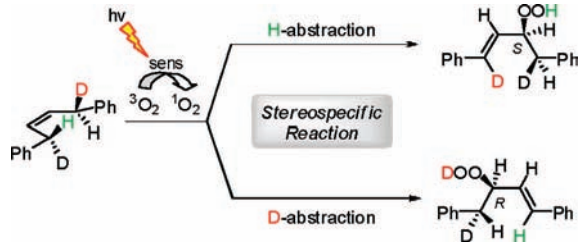
ABSTRACT



The stereochemistry of the allylic oxidation (ene reaction) mediated by singlet oxygen ($^1O_2$), using the optically active alkene (*S,S*)-*cis*-1,4-diphenyl-2-butene-1,4-d_2, in MeOH and aprotic solvents was investigated. Our findings indicate that the title reaction is a highly stereospecific suprafacial process, independent of solvent polarity. The observation of an isotope effect, which matches the stereogenic ratio exactly, rules out biradical or open dipolar intermediates.

Recent years have seen a burgeoning in research interest directed toward unraveling the chemistry of singlet oxygen ($^1O_2$, $^1\Delta_g$).[1,2] This increased attention has been motivated by singlet oxygen's environmental[3] and biological[4] importance as well as its powerful synthetic potential.[5] Among the reactions of $^1O_2$ with unsaturated substrates,[6] the ene or Schenk reaction[7] has received the most extensive experimental and theoretical attention. Several mechanisms have been postulated for this reaction. Although recent theoretical

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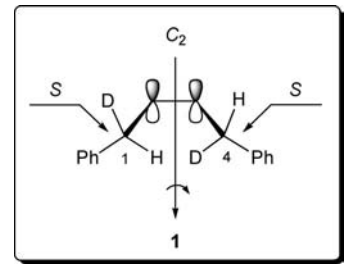
calculations support a *two-step no-intermediate* mechanism,[8] it is generally accepted that the ene reaction proceeds through an intermediate. In particular, previous isotopic studies of teramethylethylenes-d_6 (TME-d_6)[9a] and trapping experiments[9b,c] have already excluded the possibility of a concerted mechanism. Additionally, biradicals,[10] open dipolar intermediates,[10] perepoxides,[9,11] and gradations between all of these possibilities have found both experimental and theoretical support.

Studies on the stereoselectivity[12] and regioselectivity[13] of the $^1O_2$ ene reaction with nonfunctionalized alkenes have also attracted considerable attention. It is generally recognized that $^1O_2$ adds to trisubstituted alkenes with *syn* selectivity (*cis effect*)[14] and to nonsymmetrical *cis*-1,2-dialkylsubstituted alkenes with regioselective double-bond formation next to the large group (*nonbonding large group effect*).[15] Moreover, the addition of $^1O_2$ to alkylsubstituted alkenes shows a general preference for hydrogen abstraction from the group that is geminal to the larger substituent of the double bond.[16]

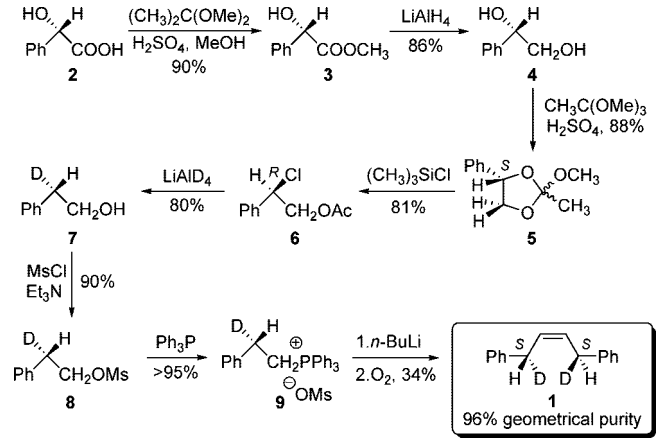
In this paper, we report details regarding the stereochemistry of the $^1O_2$ ene reaction with simple nonfunctionalized alkenes. To the best of our knowledge, this is the first example for the photooxygenation of a symmetrical and optically active alkene bearing equivalent double bond faces. The results presented may have important implications regarding the precise mechanism of this classical ene reaction.

The photooxygenation of (*S*,*S*)-*cis*-1,4-diphenyl-2-butene-*1,4-d*$_2$ (**1**) was examined. This olefin has three distinctive characteristics: (a) chirality at the two reactive allylic carbons C1 and C4, by virtue of stereospecific deuteration, (b) different groups at both ends of the double bond such that the ene adducts will contain a new stereogenic center, and (c) a C_2 symmetry axis such that the two faces of the double bond are equal.



The key intermediate for the synthesis of (*S*,*S*)-*cis*-1,4-diphenyl-2-butene-*1,4-d*$_2$ (**1**) is the optically active (by virtue deuterium labeling) alcohol **7**, whose chiro-optical properties are known[17] (Scheme 1). Esterification of (*S*)-(+)-mandelic acid (**2**) afforded (*S*)-(+)-methyl mandelate (**3**) which was reduced with $LiAlH_4$ to (*S*)-(+)-phenylethylene glycol (**4**). Reaction of **4** with trimethyl orthoacetate by the method of Newman[18] afforded a mixture of two diastereomers (2*S*,4*S*)- and (2*R*,4*S*)-2-methoxy-2-methyl-4-phenyl-1,3-dioxolane (**5**). Subsequent treatment with trimethylsilyl chloride afforded (*R*)-2-chloro-2-phenylethyl acetate (**6**).[17] Reduction of **6** with $LiAlD_4$ to the corresponding alcohol (**7**), followed by mesylation and subsequent reaction with PPh_3 of the resultant mesylate **8**, afforded the phosphonium salt **9**. Finally, the

Scheme 1. Synthesis of (*S*,*S*)-*cis*-1,4-Diphenyl-2-butene-*1,4-d*$_2$ from (*S*)-(+)-Mandelic Acid (**2**)



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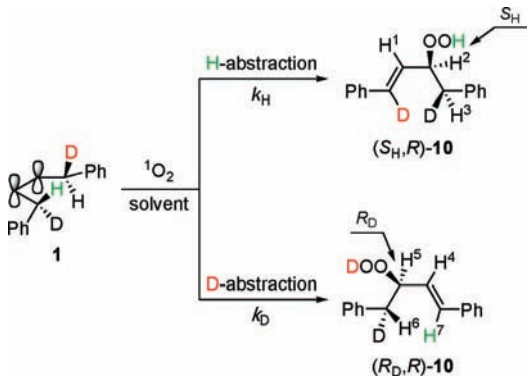
preparation of the optically active olefin **1** was accomplished through a Wittig reaction with ylide **9** in the presence of molecular oxygen. Olefin **1** was synthesized in 96% geometrical purity.

Olefin **1** reacted smoothly with singlet oxygen that had been generated in situ using irradiation of a TPP containing solution (10^{-4} M in $CHCl_3$) at 0 °C, with oxygen being bubbled through by a 300 W xenon lamp. A catalytic amount of galvinoxyl radical (2×10^{-4} M) was also added to the reaction mixture as a free radical scavenger in order to avoid the formation of any products unrelated to singlet oxygen's action. The photooxygenation reactions of **1** were also run in $(CH_3)_2CO$, CH_3CN, and MeOH. In all cases, products of type **10** were obtained in high yield (Scheme 2). As expected,

Scheme 2. Allylic Oxidation of Olefin **1**



only the *trans* allylic hydroperoxides were found in the reaction mixture.[11a] For convenience, we have presented the mechanistic possibilities here considering the approach of $^1O_2$ from only one of the two equivalent faces of the double bond. Approach of $^1O_2$ from the top face will form the new *S*-stereogenic center and produce the *trans* allylic hydroperoxide on abstraction of H, whereas formation of the *R*-stereogenic center will occur following D abstraction (Scheme 2). We define the new stereogenic centers as S_H or R_D indicating H or D abstraction from the allylic position of alkene **1**, and these two diastereomeric products are labeled (S_H,R)-**10** and (R_D,R)-**10**. With this mechanistic possibility (via perepoxide formation), one could obtain crossover products (R_H,R)-**10** and (S_D,R)-**10** only to the extent that the opposite enantiomer (*R*,*R*)-*cis*-1,4-diphenyl-2-butene-*1,4-d*$_2$ is present in the starting material.

The ratio of products (S_H,R)-**10**:(R_D,R)-**10**, which is the result of competition for abstraction at the two allylic centers of the olefin, is proportional to the primary kinetic isotope effect k_H/k_D. In the photooxygenations of **1** (in $CHCl_3$), integration of the vinylic signal at 6.64 ppm (H^7) of (R_D,R)-**10** and the overlapping vinylic signals at 6.17 ppm (H^1 and H^4) of (S_H,R)-**10** and (R_D,R)-**10** isomers was used to determine the primary isotope effect $k_H/k_D = 1.20 \pm 0.05$ (Figure 1A). The same isotopic ratio was found when $(CH_3)_2CO$, CH_3CN, or MeOH was used as the reaction solvent.

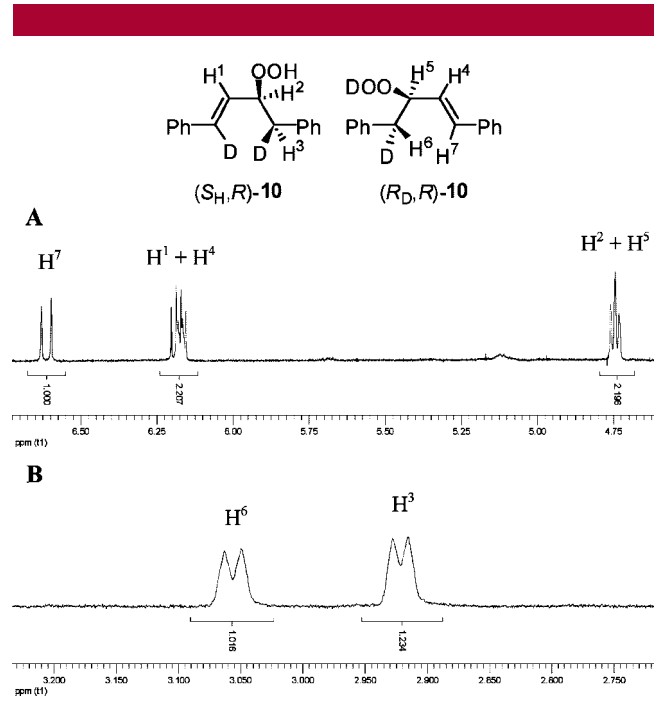


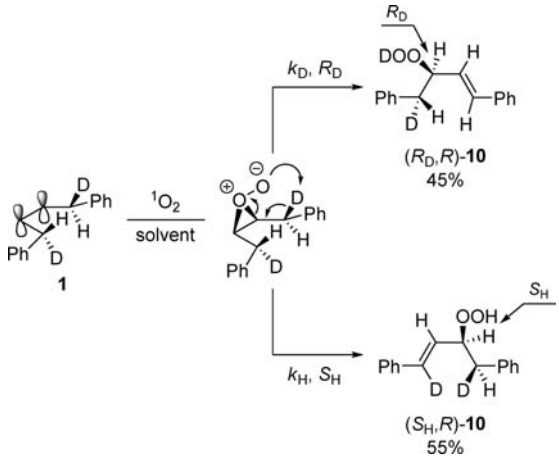
Figure 1. Portions of the ^1H NMR spectra of allylic hydroperoxides (S_H,R)-**10** and (R_D,R)-**10**.

In order to determine the chirality of the new stereogenic centers *S*/*R* of **10** and to correlate the *S*/*R* and k_H/k_D ratios of the ene products of **1**, a detailed ^1H NMR analysis was conducted. Fortunately, examination of the diastereotopic benzylic protons, H^3 and H^6, of **10** by NMR reveals that both are measurably separated, even in the absence of any chiral shift reagent. Thus, the benzylic proton H^3 resonates as a doublet at a higher magnetic field than the diastereomeric benzylic proton H^6 (Figure 1B). It is worth mentioning here that the coupling constant of H^3 is slightly different than that of H^6, because of the *syn* and *anti* relationship with the neighboring H^2 and H^5 respectively. In addition, it is simple to demonstrate that one isomer of product **10** has only H at the crucial vinylic position, while the other has only D. Integration of H^3 and H^6 signals determines the ratio of the newly formed stereogenic centers $S_H/R_D = 1.23 \pm 0.05$. The unequal formation of these stereogenic centers (10% *ee* of the *S* enantiomer) is due to the competition for abstraction at the chiral allylic centers of the olefin **1**. It is important to emphasize here the correspondence of the diastereomeric ratio (S_H,R)-**10**:(R_D,R)-**10** of 1.23 with the isotopic k_H/k_D ratio of 1.20.

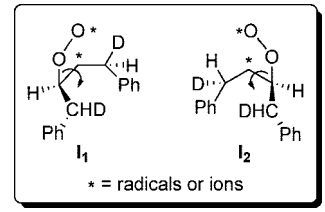
Identical diastereomeric ratios are found when $(CH_3)_2CO$, CH_3CN, or MeOH is used as the solvent in the photooxygenation of **1**, under similar reaction conditions. In all cases, the ratio of the two diastereomeric allylic hydroperoxides is equal to the primary isotope effect.

These results are best rationalized by involving the formation of a perepoxide (PE) as intermediate. An *exciplex*[19] between the olefin and oxygen with similar stereochemical requirements to that of a PE might also accommodate the results. In Scheme 3, a PE intermediate is used for illustrative purposes. From this intermediate, abstraction of deuterium

Scheme 3. Proposed Mechanism of the Sensitized Photooxygenation of Olefin **1**



(D), and subsequent C−O bond formation, leads to the R_D stereogenic center with hydrogen (H) remaining in the product double bond, while abstraction of H leads to the formation of the S_H stereogenic center. These results clearly indicate that the $^1O_2$ allylic oxidation is a highly stereospecific suprafacial process. Had the crossover products (R_H,*R*-**10** and S_D,*R*-**10**) been formed, the ^{1}H NMR would have been more complicated. The observation of an isotope effect, which matches exactly the stereogenic ratio, makes it difficult to argue that the reaction proceeds through a biradical or an open dipolar intermediate. For a stepwise biradical or open dipolar mechanism, intermediates I_1 and I_2 are expected to be formed in equal amounts. This implies that neither (R_H,*R*)-**10** nor (S_D,*R*)-**10** products would be preferentially formed, and because of free rotation around the previous carbon−carbon double bond, a nonstereospecific reaction would occur leading to racemic products.



In conclusion, our results provide strong evidence of a stereospecific suprafacial mechanism for the $^1O_2$ ene reaction of simple olefins. Taking also into consideration that the majority of previously reported studies[9−11] precluded the possibility of a concerted mechanism, we strongly suggest that the $^1O_2$ ene reaction with simple alkenes proceeds via the irreversible formation of a perepoxide or an exciplex intermediate.

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Supporting Information Available: Detailed experimental procedures and spectral data. ^{1}H NMR, ^{13}C NMR, and HMQC spectra for compound **1**. ^{1}H and ^{13}C NMR spectra of compounds **3**−**8**. ^{1}H NMR spectra of compound **9**. ^{1}H NMR spectra for the measurement of primary isotope effect and diastereomeric ratio of (S_H,*R*)-**10** and (R_D,*R*)-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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