Communications to the Editor

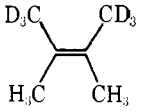
Stereochemical Dependence of Isotope Effects in the Singlet Oxygen–Olefin Reaction

Sir:

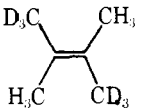
The key question in the mechanism of the reaction of singlet oxygen with olefins concerns the possibility that the reaction might proceed via an intermediate.[1] In this communication we show that the magnitude of the primary isotope effect in this reaction is dependent on the relative stereochemistry of the competing groups. In our view the results are incompatible with any single-step reaction and thus require an intermediate.

Several groups have reported isotope effects in the singlet oxygen reaction, particularly those of Kopecky[2] and Nickon.[3] These effects have been small, in the range k_H/k_D = 1.05–1.80, and have frequently been used to support the view that oxygen removal of H occurs relatively late in the reaction. Unfortunately, this early work, including our own,[4] was difficult to interpret with precision. Commonly, it was not possible to clearly distinguish secondary from primary isotope effects, and in some key substrates the stereochemistry was undefined.

We have studied the singlet oxygenation of *cis*- and *trans*-tetramethylethylene-d_6 (*cis*-**1** and *trans*-**1**, respectively) prepared in isomerically pure form by known chemical reactions.[5]



cis-1, k_H/k_D = 1.04–1.09



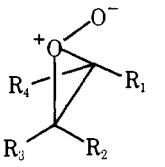
trans-1, k_H/k_D = 1.38–1.41

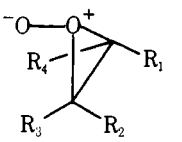
Both substrates react smoothly with singlet oxygen generated by sun lamp irradiation of Rose Bengal in acetone-d_6 at −10 °C under an atmosphere of oxygen. The products of hydrogen or deuterium abstraction are easily distinguished by ^{1}H NMR, and product mixtures are assayed by repeated integration using the integration of the perprotio material as a means of instrument calibration. This NMR analysis was performed directly on the hydroperoxides from the reaction and subsequently on the alcohols derived from triphenylphosphine or dimethyl sulfide reduction.

From *cis*-**1** a very small isotope effect (k_H/k_D = 1.04–1.09) is obtained. From *trans*-**1** a significant effect is observed (k_H/k_D = 1.38–1.41). Both ranges are the result of duplicate runs and multiple integrations. Because of the symmetrical nature of the deuterium substitution, the isotope ratios must derive from competition in the hydrogen abstraction step and not from differences due to rehybridization at the C–O bond site, or other secondary effects. These primary isotope effects require a mechanism in which groups cis to each other are competitive in the singlet oxygen reaction, while geminal or trans dispositions are only weakly so, if at all.

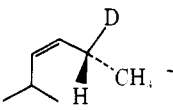
In our view any single-step reaction mechanism would carry with it the requirement that all symmetry equivalent hydrogens in an olefin compete equivalently in this reaction. This is not so in the present case.

A number of intermediates have been proposed for this reaction.[1,8] Of those intermediates presently in contention for rationalizing this reaction, the perepoxide[9] most completely accommodates the present data. If one presumes (a) that perepoxide is formed irreversibly and (b) that pyramidal inversion is slow relative to hydrogen abstraction, then isotope effects should be observed if H and D are able to compete with each other (i.e., in *trans*-**1**), but should be unobserved in *cis*-**1**, where all of the deuterium atoms are on the same side and all of the hydrogen atoms on the opposite side. The slightly positive isotope effect observed for *cis*-**1** ($k_H/k_D \sim 1.05$) could be the result of breakdown of either assumption a or b above or could be the result of a mechanism with requirements structurally similar to the perepoxide, but which allows for limited competition *across* the double bond.





These observations allow one to discuss more clearly the earlier observations of isotope effects. In our initial work in this area,[4] olefin **2**, again in acetone, was found to give largely



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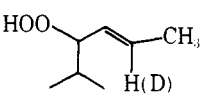
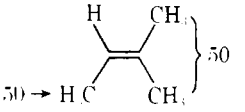


3, k_H/k_D = 1.00–1.08

trans-allylic hydroperoxide **3**. Obtaining only the trans isomer requires that the deuterium be available only on the top face of the olefin and hydrogen be available only on the bottom face. It is probably reasonable that any mechanism that does not allow substituents trans to each other to compete would also allow competition of top and bottom olefin faces. Again a perepoxide or a structural relative easily accommodates the observation of a very small isotope effect.

Finally we note that the isotope effects measured here are transferable to other systems. Using as isotope ratios the approximations that k_H/k_D (cis) = 1.4, k_H/k_D (trans or geminal) = 1, k_H/k_D (top/bottom) = 1, one can predict new product ratios with high accuracy. In compounds **4** and **5**, for example, little change is noted in the ratio of tertiary to secondary hydroperoxides derived from singlet oxygenation. This, we would claim, is due to the fact that the remote CH_3 in **4** is not competitive with the two *cis*-CH_3 groups; substitution of this remote CH_3 in **4** by CD_3 in **5** thus has little effect. On the



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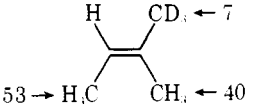

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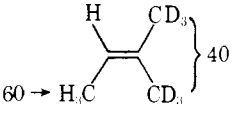

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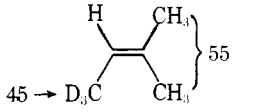

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other hand, in compounds **6** and **7** CD_3 has been substituted for one of the two competitive *cis*-methyls, and larger effects are noted. Significantly, these results can be predicted quantitatively by biasing the inherent reactivities of the three po-

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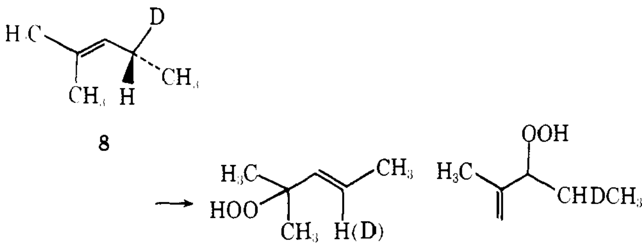
sitions as revealed in **5** by the isotope ratios for cis and trans competition.

Perhaps most intriguing is the finding of an isotope effect in **8** below. Again we have a case where D is presented to the



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$k_H/k_D = 1.2$

top face of the olefin, H to the bottom face. Here, however, in contrast to the transformation **2** → **3** the adjacent *cis*-CH_3 group is equally as reactive as the chiral methylene unit. Thus the top face leads to an isotope effect of 1.4 (a cis competition) and the bottom face a normal product ratio since isotopes are not competing. With our earlier contention that top and bottom faces are equally reactive and noncompetitive, this neatly explains the ratio $k_H/k_D = 1.2$, which is an average of 1.4 (top) with 1.0 (bottom).

Were it not for the recent compelling calculations of Goddard and Harding,[10] which conclude that perepoxides are energetically inaccessible in the reaction, we could claim support here for this intermediate. Our results do, at a minimum, provide strong evidence for some intermediate in the reaction, an intermediate with structural requirements not dissimilar to those of the unknown perepoxides.

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References and Notes

(1) C. S. Foote, *Acc. Chem. Res.*, **1**, 104 (1968).
(2) K. R. Kopecky and J. H. Van de Sande, *Can. J. Chem.*, **50**, 4034 (1972).
(3) A. Nickon et. al., *J. Am. Chem. Soc.*, **94**, 5517 (1972).
(4) L. M. Stephenson, D. E. McClure, and P. K. Sysak, *J. Am. Chem. Soc.*, **95**, 7888, (1973).
(5) Typically esters were reduced to allylic alcohols by $LiAlD_4$. The resulting alcohols are converted to chlorides by Corey's[6] method. These chlorides are stable and show no allylic or cis–trans isomerization by NMR. Conversion to hydrocarbon proceeded smoothly in $LiAlD_4$/diglyme. Here again no allylic rearrangement was found. An independent assessment of cis–trans purity has not yet proven to be possible. In similar systems (e.g., trimethylethylenes-d_3 and -d_6 and the 2-butenes) isomeric purity was completely maintained. In the present case the substantial dissimilarity of the isotope effects also suggests that isomeric purity is also maintained.[7]
(6) J. E. Corey, C. U. Kim, and Makoto Kakeda, *Tetrahedron Lett.*, 4339 (1972).
(7) A complete description of this method is in press: M. Bellarmine Grdina, Michael Orfanopoulos, and L. M. Stephenson, *J. Org. Chem.*
(8) (a) L. B. Harding and W. A. Goddard III, *Tetrahedron Lett.*, 747 (1978); (b) M. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **97**, 3978 (1975); (c) M. A. Frimer, P. D. Bartlett, A. F. Boschung, and J. G. Jewett, *ibid.*, **99**, 7977 (1977).
(9) Although widely attributed to Sharp (D. B. Sharp, Abstracts of the 139th National Meeting of the American Chemical Society, New York, Sept 1960, p 79P), an earlier proposal for such a species has been located by R. E. McCluney of Texas Christian University in H. Staudinger, "Die Ketene", Ferdinand Enke, Stuttgart, 1912, p 55.
(10) L. B. Harding and W. A. Goddard III, *J. Am. Chem. Soc.*, **99**, 4520 (1977).
(11) Address correspondence to the Department of Chemistry, University of Southern California, Los Angeles.

Sr. Bellarmine Grdina, Michael Orfanopoulos
L. M. Stephenson*[11]
Department of Chemistry, Case Western Reserve University
Cleveland, Ohio 44106
and Department of Chemistry
University of Southern California
Los Angeles, California 90007
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Kinetics of Disulfide Cleavage by Methylmercury. Evidence for a Concomitant Electrophilic and Nucleophilic Mechanism

Sir:

The realization that methylmercury is produced in living systems from a variety of organic and inorganic mercury compounds has greatly increased the interest in its chemistry. Rapid ligand exchange reactions play a key role in the bioavailability of CH_3Hg^{II} derivatives which are bound almost exclusively to sulfhydryl ligands.[1,2] Mercaptide anion exchange in RHgSR′–RHgSR″ systems is also surprisingly rapid and provides yet another pathway for the migration of organomercurials in nature.[2] Since the disulfide linkage of cystine is probably the only covalent cross-linkage in most proteins and peptides, the reaction of the -SS- moiety with CH_3Hg^{II} could have a profound effect on the tertiary structure of a large variety of natural products.

The most commonly encountered electrophiles in -SS- bond cleavage are H^+ and metal ions with a high affinity for sulfur, such as Ag^+ and Hg^{2+}.[3] For example, silver ion has been used to good advantage by Davis[4a] in the synthesis of sulfenamides from disulfides and mercury catalysis has been employed in peptide synthesis.[4b] We found no reports of a systematic mechanistic study of metal catalysis of disulfide cleavage.[5] The dual objective of this study is to establish the role of CH_3Hg^{II} in reactions with the ubiquitous disulfide linkage and to provide kinetic evidence for a metal-assisted concomitant cleavage of this functional group.

There are two fundamental mechanistic pathways for heterolytic cleavage of the disulfide bond.[6,7] The first involves attack at sulfur by a nucleophile with displacement of RS^- (eq 1) and the second results from the combined catalysis of both an electrophile and a nucleophile (eq 2).

$$RSSR + Nu^- \longrightarrow RSNu + RS^- \qquad (1)$$

$$RSSR + E^+ \rightleftharpoons RS\overset{+}{S}(E)R \xrightarrow{Nu^-} RSNu + RSE \qquad (2)$$

In a definitive study involving base-catalyzed isotopic exchange between thiol and disulfide, Fava[10a] found that simple S_N2 displacement at sulfenyl sulfur exhibited a second-order rate expression of the form rate = $k_2[RSSR][RS^-]$. The isotopic exchange was also catalyzed by HX ($I^- > Br^- > Cl^-$) but not by the more acidic, but weakly nucleophilic, perchloric acid.[6a] Thorough kinetic studies by Kice on sulfur–sulfur bond scission have firmly established the existence of an acid-catalyzed concomitant -SS- bond rupture involving protonation of one sulfur and nucleophilic displacement at the other (eq 2).[6b,c,11]

There are relatively few analytical methods available that provide accurate rate measurements for disulfide cleavage.[6d] As reported[11a] in a recent kinetic study of the acid-catalyzed disproportionation of an unsymmetrical disulfide, the continuous monitoring of the relative intensity of NMR signals failed to give high quality kinetic data. We experienced similar difficulties but were able to circumvent the problem by monitoring the intensity of the recorder output signal of the NMR with an electronic integrator of the type that is typically used to measure peak areas in gas chromatograms.[12]

Our objectives were realized by examining the cleavage of dimethyl disulfide by the action of methylmercury acetate and triethyl phosphite.[13] The rate of -SS- bond scission was followed in the NMR by continuously measuring the loss of CH_3SSCH_3 (137 Hz) and the formation of CH_3HgSCH_3 (136 Hz) (eq 3). A second mole of CH_3Hg^+ is consumed in a second rapid reaction (eq 4).[14] Our results for -SS- bond breakage under both pseudo-first- and pseudo-second-order conditions are listed in Table I.

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