(except from single-crystal measurements utilizing polarized X-rays[34]). Furthermore, EXAFS diminishes rapidly beyond the first and second coordination shells (typically $r \lesssim 4$ Å) except in cases where atoms are nearly collinear. In such cases, EXAFS from atoms as far as 6 Å can be observed due to amplitude enhancement called focusing effect. In fact, both amplitude and phase of the EXAFS of a more distant neighbor are significantly affected by the intervening atom(s) for bond angle > 120°. For these systems, one must therefore take into account multiple scattering processes involving the intervening atom(s). Recently, a new multiple scattering formalism has been developed[35] which enables bond angle determinations with an accuracy of 5% or ca. 5°.

Nevertheless, the structural content of EXAFS is unparalleled by other spectroscopic techniques when one considers that the few most important bonds in a complex system can be probed within minutes. The future of EXAFS spectroscopy is as bright as the future synchrotron radiation sources. Dedicated synchrotron radiations with energy ranging from UV to hard X-rays are now available.[36] These highly intense light sources will undoubtedly open up a new era in exciting chemical, biological, and material research.

I am indebted to my collaborators Drs. P. Lee, P. Eisenberger, R. Shulman, B. Kincaid, J. Reed, R. Bau, S. Lippard, J. Barton, and A. Simons, for their invaluable participation in various stages of the work reviewed in this Account. I thank Drs. L. F. Dahl, C. Chu, D. Patel, A. P. Ginsberg, Mrs. P. S. Robinson, the referees, and the editors for many helpful comments.

(35) B. K. Teo, submitted for publication.

(36) Four major facilities are being planned in the United States: an expanded SSRL at Stanford, CHESS at Cornell, Aladdin at Wisconsin, and National Synchrotron Light Source at Brookhaven National Laboratory.

Mechanism of the Ene Reaction between Singlet Oxygen and Olefins

L. M. STEPHENSON*

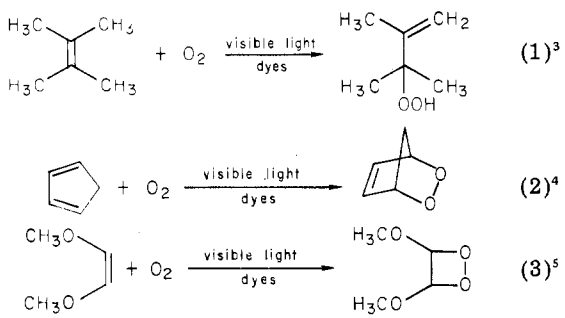
Department of Chemistry and Hydrocarbon Research Institute, University of Southern California, Los Angeles, California 90007

MARY JO GRDINA and MICHAEL ORFANOPOULOS

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44107

Received December 21, 1979 (Revised Manuscript Received August 15, 1980)

Singlet molecular oxygen has been studied since the 1930s,[1] and photosensitized oxygenations of olefins have been synthetically useful for some time.[2] Representative examples of these transformations are given in eq 1–3.[3]



L. M. Stephenson is a native of North Carolina and a graduate of the University of North Carolina at Chapel Hill. Following graduate work at Caltech and a postdoctoral year at Harvard, he embarked on a nomadic career which includes stops at Stanford and Case Western Reserve University. He is presently Professor of Chemistry and Director of the Hydrocarbon Research Institute at USC.

Mary Jo Grdina was born and educated in Cleveland. She received a bachelor's degree from Notre Dame College of Ohio, and a doctorate from Case Western Reserve University in 1979. She taught for a number of years at Notre Dame College, and recently joined the faculty at Oberlin College.

Michael G. Orfanopoulos was born in Athens, Greece. He received his bachelor's degree from the University of Patras, followed by an M.S. from Toledo and a Ph.D. from Case Western Reserve University in 1979. He is presently a postdoctoral fellow at Stanford.

In the last 40 years these reactions have been extensively studied both to determine synthetic utility[6] and to elucidate mechanisms.[6b,7] These oxygenations represent one of the most important hydrocarbon functionalization reactions available to the synthetic organic chemist. This chemistry has also been related both speculatively and rigorously to such diverse areas as air pollution,[8] photocarcinogenicity,[9] and chemiluminescence.[10] Remarkably, however, no agreement exists either informally or in the literature on the mechanisms of these transformations.

It would be difficult to find a more appropriate vehicle for illustrating reaction mechanism methodology than photosensitized oxygenation; virtually every mechanistic technique has been applied to the study of these reactions. The identification of the reactive intermediate in these systems involved spectral tests,[11]

(1) Childs, W. H. J.; Mecke, R. Z. *Physik* **1974**, *68*, 334.
(2) Schenck, G. O. German Patent 933925, **1943**.
(3) Schenck, G. O.; Schulte-Elte, K. *Liebigs Ann. Chem.*, **1958**, *618*, 185.
(4) Schenck, G. O.; Ziegler, K. *Naturwissenschaften* **1945**, *32*, 157.
(5) Bartlett, P. D.; Schaap, A. P. *J. Am. Chem. Soc.* **1970**, *92*, 3223, 6055.
(6) (a) Denny, R. W.; Nickon, A. *Org. React.* **1973**, *20*, 133. (b) Gollnick, K.; Kuhn, H. J. In "Singlet Oxygen"; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979, p 287.
(7) (a) Foote, C. S. *Acc. Chem. Res.* **1968**, *1*, 104. (b) Ranby, B., Rabek, J. F., Eds. "Singlet Oxygen Reactions with Organic Compounds and Polymers", Wiley: New York, 1978.
(8) Pitts, J. N., Jr., *Ann. N.Y. Acad. Sci.* **1970**, *171*, 239.
(9) Khan, A. U.; Kasha, M. *Ann. N.Y. Acad. Sci.* **1970**, *171*, 24.
(10) Kearns, D. R. *Chem. Rev.* **1971**, *71*, 395, 424.

0001-4842/80/0113-0419$01.00/0 © 1980 American Chemical Society

photochemical tests,[7a,b] and a variety of more classical chemical tests.[7a] The intermediate, now known to be an excited state of O_2, is short-lived, but can be identified with certainty through the use of specific excited-state quenchers[12] and from studies of the dependence of the lifetime on solvent properties.[13] In the photosensitized oxygenations themselves, various standard techniques have been applied, including kinetic/substituent effect relationships,[7a,14] isotope effects,[15] stereochemistry,[16] and solvent dependence.[17] Finally, most available theoretical models have been used to analyze these reactions, ranging from frontier molecular orbital concepts[18] to the most sophisticated ab initio methods.[19]

It is the purpose of this Account to summarize the key features of this area, concentrating mainly on the mechanism of the ene reaction, eq 1. By emphasizing recent data from our laboratory, we shall demonstrate that a number of mechanistic possibilities can now be eliminated and that only a limited, related set of possibilities remain to be considered.

The Involvement of $O_2(^1\Delta_g) \equiv {}^1O_2$. Most photosensitized oxygenations are now well established to involve an excited singlet state of molecular oxygen[7a] ($^1\Sigma_g^+$, 37.51 kcal/mol; $^1\Delta_g$, 22.54 kcal/mol; $^3\Sigma_g^-$, 0 kcal/mol). Two such states are of sufficiently low energy to be accessible in an ordinary photochemical reaction. Of these two states, only the Δ state has a sufficiently long solution lifetime (milli- to microsecond) to be responsible for chemical reactions.

Although a number of chemical systems exist for generating singlet oxygen, only dye photosensitization is commonly employed (eq 4–6). This scheme and the

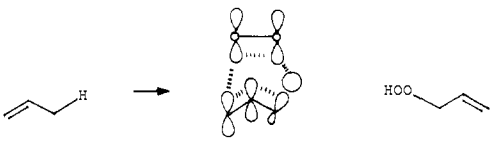
$$\text{dye} \xrightarrow[\text{light}]{\text{visible}} \text{dye}^{*1} \rightarrow \text{dye}^{*3} \quad (4)$$

$$\text{dye}^* + O_2 \rightarrow \text{dye} + {}^1O_2 \quad (5)$$

$${}^1O_2 + \text{substrate} \rightarrow \text{substrate}\cdot O_2 \quad (6)$$

demonstration that singlet oxygen was the key reactive intermediate rest primarily with the early work of Foote.[7a] More recent work has revealed a number of complications including the involvement of electron transfer[20] and radical chain pathways.[21] Generally speaking, these interesting complexities can be avoided in most cases. The systems examined in this Account are all thought to conform to the simple scheme above.

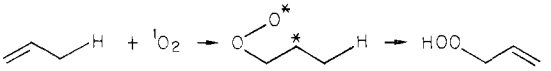
Potential Mechanisms. Over the years a rather large number of mechanisms have been proposed for these photooxygenations, with the ene-like reactions receiving the greatest attention. For the ene reaction, most authors have favored a concerted transformation with simultaneous C–O bond formation and allylic C–H bond breaking. The absence of a substantial solvent



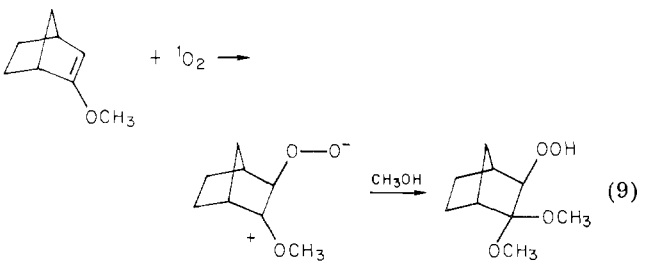
(7)

effect and the well-established requirement[22] for properly aligned C–H bonds in conformationally fixed cyclohexyl systems strengthen this theoretically attractive mechanism.

Diradical (eq 8) and dipolar intermediates (eq 9) are shown. Support for dipolar intermediates derives



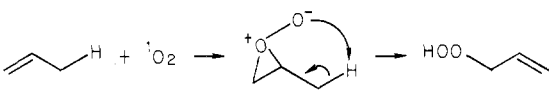
(8)



(9)

primarily from studies of Jefford,[23] particularly work demonstrating solvent incorporation in methoxynorbornene. Recent theoretical work by Goddard and Harding,[19] based on experiments from Conia's lab,[24] favors a diradical formulation.

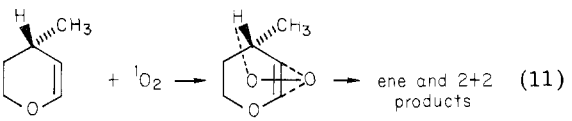
Several other two-step mechanisms have been discussed. Perhaps the most persistent suggestion is the perepoxide advocated some time ago by Sharp[25] (eq 10).



(10)

Several theoretical calculations[26] and low isotope effects are cited in favor of this intermediate.

Recently, several groups have made proposals for more loosely oriented complexes, for example, the Frimer/Bartlett criss-cross interaction,[27] shown in eq 11.

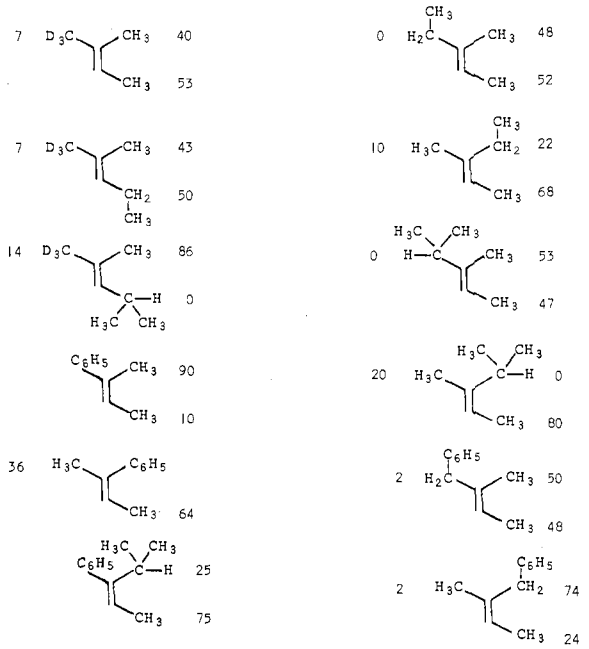


(11)

Regiospecificity. Singlet oxygen has been used in a number of synthetic schemes, including the com-

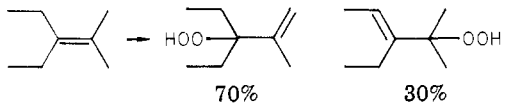
(11) Kasha, M.; Khan, A. U. *Ann. N.Y. Acad. Sci.* **1970**, *171*, 5.
(12) Young, R. H.; Brewer, D. R., ref 7b, p 36. Garner, A.; Wilkinson, F., ref 7b, p 48; Bellus, D., ref 7b, p 61.
(13) Wilkinson, F., ref 7b.
(14) Foote, C. S. *Pure Appl. Chem.* **1971**, *27*, 635.
(15) (a) Kopecky, K. R.; Van de Sande, J. H. *Can. J. Chem.* **1972**, *50*, 4034. (b) Nickon, A.; Chuang, V. T.; Daniels, P. J. L.; Denny, R. W.; DiGiorgio, J. B.; Tsunetsugu, J.; Vilhuber H. G.; Werstink, E. *J. Am. Chem. Soc.* 1972, *94*, 5517.
(16) (a) Foote, C. S.; Wexler, S.; Ando, W. *Tetrahedron Lett.* **1965**, 4111. (b) Litt, F. A.; Nickon, A. *Adv. Chem. Ser.* **1968**, *No. 77*, 118.
(17) (a) Gollnick, K.; Schenck, G. O. *Pure Appl. Chem.* **1964**, *9*, 507. (b) Foote, C. S. *Science* **1968**, *162*, 963. (c) Gollnick, K. *Adv. Chem. Ser.* **1968**, *No. 77*, 78. (d) Gollnick, K. *Adv. Photochem.* **1968**, *6*, 1.
(18) Kearns, D. R.; Fenical, W.; Radlick, P. *Ann. N.Y. Acad. Sci.* **1970**, *171*, 34.
(19) (a) Harding, L. B.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1977**, *99*, 4520. (b) Harding, L. B.; Goddard, W. A., III. *Tetrahedron Lett.* **1978**, 747. (c) Harding, L. B.; Goddard, W. A., III. *J. Am. Chem. Soc.*, **1980**, *102*, 439.
(20) Foote, C. S., in ref 7b.
(21) Foote, C. S., in ref 7a.
(22) Litt, F. A.; Nickon, A. *Adv. Chem. Ser.* **1968**, *No. 77*, 118.
(23) (a) Jefford, C. W. *Tetrahedron Lett.* **1979**, 985. (b) Jefford, C. W.; Rimbault, C. G. *J. Am. Chem. Soc.* **1978**, *100*, 295. (c) Jefford, C. W.; Laffer, M. H.; Boschung, A. F. *Ibid.* **1972**, *94*, 8904. (d) Jefford, C. W.; Rimbault, C. G. *J. Org. Chem.* **1978**, *43*, 1908. (e) Jefford, C. W.; Boschung, A. F. *Helv. Chim. Acta* **1974**, *57*, 2242.
(24) Rousseau, G.; LaPerchec, P.; Conia, J. M. *Tetrahedron Lett.* **1977**, 2517.
(25) Sharp, D. B., "Abstracts of Papers", 138th National Meeting, American Chemical Society: Washington, DC, 1960; p 79p.
(26) (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1975**, *97*, 3978. (b) Dewar, M. J. S.; Thiel, W. *Ibid.* **1977**, *99*, 2338. (c) Dewar, M. J. S.; Griffin, A. C.; Thiel, W.; Turchi, I. J. *J. Am. Chem. Soc.* **1975**, *97*, 4339.
(27) Frimer, A. A.; Bartlett, P. D.; Boschung, A. F.; Jewett, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4339.

Table I
Regiospecificity in Trisubstituted Olefin Singlet Oxygenation



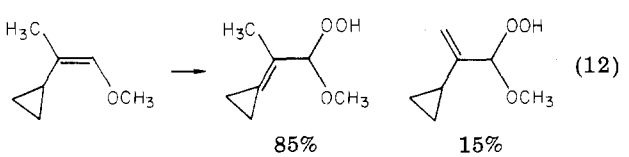
mercial synthesis of perfume intermediates. The regiospecificity of this process is of obvious interest to the preparative chemist.

Early work revealed that abstraction of hydrogen from methyl and methylene positions was about equally probable, methyl being preferred by factors of 2–4. An illustrative example from recent work in our lab[28] is shown below.



Methine hydrogens, however, are notably unreactive and are significantly involved in this reaction only in special cases. Several entries[29] in Table I illustrate this point. Presumably, steric constraints against placing C–H bonds in proper orientations for abstraction account for this low reactivity.

Recently, several laboratories have recognized more subtle aspects of regioselectivity in these reactions. The groups of Conia[24] and Foote[30] provided the first examples of this new specificity with the finding that methoxy groups led to anomalously high reactivities for substituents located cis to the OCH_3. This is dramatically illustrated by the example in eq 12 in which a

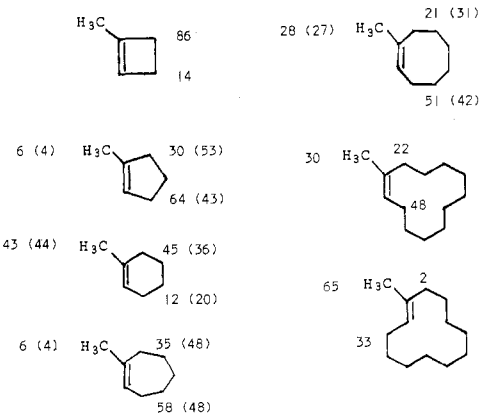


(12)

normally inert cyclopropyl C–H is significantly involved in the ene reaction. Shortly thereafter, and independently, two groups reported that these effects were not

(28) Orfanopoulos, M. G. Ph.D. Thesis, 1979, Case Western Reserve University.
(29) Orfanopoulos, M. G.; Grdina, M. B.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 275.
(30) Lerdal, D.; Foote, C. S. *Tetrahedron Lett.* **1978**, 3227.

Table II
Regiospecificity in the Reaction of Cyclic Trisubstituted Olefins[33]

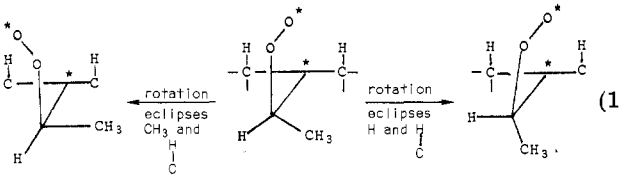


limited to alkoxy substituents but were much more general.[29,31,32] Thus, in trisubstituted olefins anomalous reactivity on the more crowded *side* of the system is invariable. This is demonstrated clearly in Table I, which shows representative data for trisubstituted olefins.

Even cyclic systems obey this generalization, 1-methylcyclohexene representing a modest exception. Here, internal C–H is relatively unreactive, almost surely due to the unfavorable C–H orientation demanded by the cyclohexene conformation. The data in Table II were collected from the literature and analyzed recently by Schulte-Elte and Rautenstrauch.[33]

This same preference for the crowded side exhibits itself in disubstituted olefins where cis isomers are typically about ten times as reactive as their trans counterparts.[7a]

The mechanistic implications of this result have been probed by a number of groups. Early suggestions that anomeric effects might be determinative in the methoxy cases[19] did not survive the recognition that the result was general to other substituents. Recently, Jefford made a novel proposal (eq 13) to deal with this result,



(13)

to wit, that in a difunctional intermediate, rotations favorable to H abstraction on the crowded side are lowest in energy. The model is appropriate to either a diradical or zwitterion; Jefford chooses the latter. Other data, however, make it difficult to accept this interpretation (vide infra).

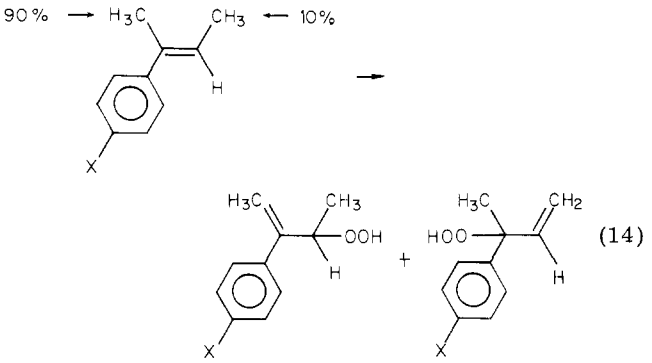
In any case it is clear that an acceptable mechanism for this process must contain within it an appropriate explanation for this very general regiospecificity.

Kinetic Effects. The short solution lifetimes of singlet oxygen require that all chemical reactions of this species have very high bimolecular rate constants.

(31) Schulte-Elte, K. H.; Muller, B. L.; Rautenstrauch, V. *Helv. Chim. Acta* **1978**, *61*, 2777.
(32) Schulte-Elte, K. H.; Muller, B. L.; Pamingle, H. *Helv. Chim. Acta* **1979**, *62*, 816.
(33) Schulte-Elte, K. H.; Rautenstrauch, V. *J. Am. Chem. Soc.* in press.

These vary from 10^3 M^{-1} s^{-1} to values approaching within a few powers of ten of the diffusion limit. Within this range, impressive substrate selectivity can be observed. In fact, $^1O_2$ is a very electrophilic reagent whose reactivity and selectivity are closely paralleled by those of peroxidizing reagents.[34]

Curiously, these large rate differences are not commonly reflected in product ratios. In an early study, Foote and Denny[7a] showed that the ratio of the two products derived from trimethylstyrenes did not vary with *p*-phenyl substituent, while the rate variations displayed a Hammett ρ value comparable to that found for perbenzoic acid expoxidation. This may well have been the first experiment in this field that carried with it the implication that the product and rate-controlling steps in this reaction could be separate. A variation of this experiment was performed recently in our laboratory with comparable results.[28] Large rate variations in reaction 14 (X = $OCH_3 \gg H > CF_3$) are not reflected



(14)

in product ratios which are constant at 9:1 in favor of α-methyl C–H abstraction.

Recent work by Paquette[35] strengthens the argument that electron-donating ability by the olefin largely determines reactivity. Paquette's correlation of reaction rate with ionization potential and HOMO energy levels make this point with particular clarity.

Solvent Effects. Solvent effects provide insight into the singlet oxygen reaction remarkably similar to that brought out in the previous section. The rates of the singlet oxygen ene reaction with olefins show a substantial solvent sensitivity. Recent studies by Gollnick and Hartmann[36] demonstrate that ene reaction rates increase in polar solvents and that the rate constants correlate well with $(\epsilon - 1)/(2\epsilon + 1)$, the Kirkwood–Laidler–Eyring polarity parameter. This model leads to a calculated transition-state dipole moment of 5.6 ± 0.02 D, virtually identical with that calculated by Harding and Goddard[19] for the perepoxide.

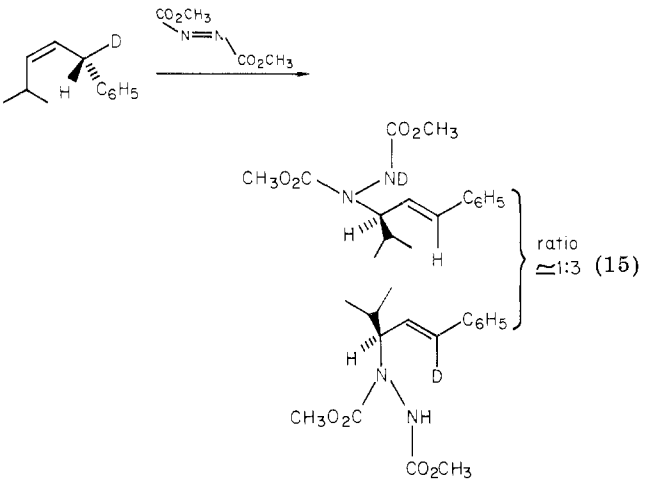
In constrast to this large kinetic effect, no example of a change in ene product distribution in response to solvent changes has been observed. Such a change was sought in our laboratory with particular care for the cis/trans olefin pair 3-methyl-2-pentene, but the product ratios (see Table I) show no sensitivity to solvent changes from benzene to methanol. These results also clearly suggest that rate- and product-determining steps are not identical in this reaction.

(34) Kopecky, K. R.; Reich, H. H. *Can J. Chem.* **1965**, *43*, 2265.
(35) Paquette, L. A.; Liotta, D. C.; Baker, A. D. *Tetrahedron Lett.* **1976**, 2681.
(36) Gollnick, K.; Hartmann, H. Conference Abstracts, International Conference on Oxygen and Oxy-Radicals in Chemistry and Biology; University of Texas: Austin, Texas, May 25–29, 1980.

Recent work by the Bartlett group[27] has been concerned with competitive (2 + 2) and ene reactions. In these cases the 2 + 2 reaction is favored as more polar solvents are employed. It is attractive here to postulate zwitterionic intermediates leading to dioxetane formation (2 + 2 cycloaddition) since the zwitterion is calculated[19] to very polar $\mu \simeq 11$ D.

Similar results are documented in other systems. While a number of possible explanations might be put forth for this result, Bartlett and co-workers favor a common intermediate which partitions to two pathways. If this is correct, then the dioxetane-forming path is obviously the more polar of the two and might involve dipolar intermediates.

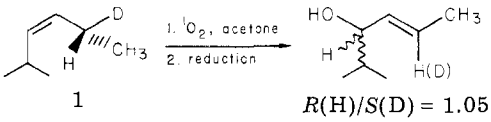
Reaction Stereospecificity. Most modern tests of mechanisms have involved a rigorous examination of reaction stereochemistry. In the case of the ene-type reactions, we have shown that acyclic olefins, which are made chiral by deuterium substitution at a reactive position, provide satisfactory tests. For a genuinely concerted ene reaction,[37] such as that shown in eq 15,



(15)

two distinguishable events can be identified. Attack from the top removes D and produces the *R* stereoisomer at the site of the new C–N bond, while bottom approach leaves D in the olefin and produces the *S* isomer. Because this system is sterically unbiased with top and bottom faces equally accessible, a measure of the isotope effect in the reaction is also available. In the case of this azo–ene reaction, the isotope effect of 3, coupled with the complete stereospecificity of the reaction, strongly supports a picture of a classically concerted transformation with C–H(D) bond breakage coupled to C–N bond formation.

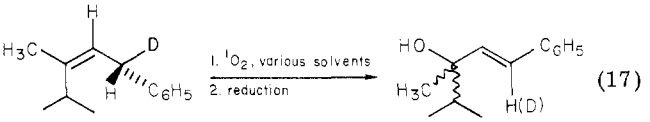
This same test has been applied to the singlet oxygen reaction with two similar acyclic olefins, **1** and **2** (eq 16 and 17) Although the reactivities of these two olefins



(16)

1

$R(H)/S(D) = 1.05$



(17)

2

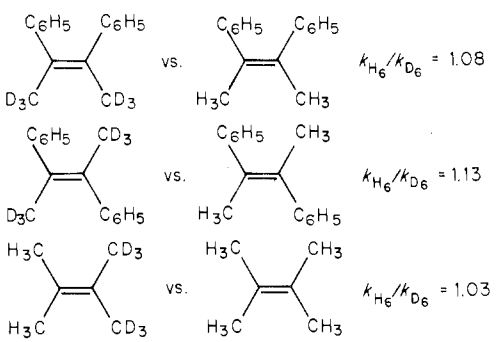
$R(H)/S(D) = 1.04$

(37) Stephenson, L. M.; Mattern, D. L. *J. Org. Chem.* **1976**, *41*, 3614.

differ substantially, the mechanistic conclusions are identical.[38a,b] The reaction is completely stereospecific, and only the anticipated products can be detected (in both cases the *R* stereoisomer has H remaining at the olefin site with *S* isomer having D left behind). In an earlier report,[38] we noted that a high isotope effect ($k_H/k_D \simeq 3$) and low enantiomeric excess ($R/S \simeq 1$) could be found for the disubstituted olefin in methanol solvent. This same effect can be noted in the recent experiments with the more reactive trisubstituted system, but only if one omits addition of the radical scavenger galvinoxyl. Thus, we believe that the earlier result can be accounted for by the intrusion of a radical chain oxidation in a slow singlet oxygen reaction. That this unusual pathway could be found in methanol and apparently not in acetone is consistent with the short lifetime known for singlet oxygen in CH_3OH. This short lifetime would, of course, maximize the opportunities of annoying side reactions.

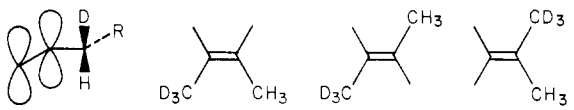
The *E* isomer of **2** also reacts stereospecifically. Here, however, a significant isotope effect can be measured ($k_H/k_D \simeq 1.2$), in contrast to the negligible effects noted for the other two cases.

Isotope Effects. A primary isotope effect is a measurement of the differences in the rates of making or breaking bonds to an atom which can be isotopically varied. In order for such a measurement to be informative, the isotopes which are competing (most commonly, H and D, or H and T) must be in sterically, stereochemically, and electronically equivalent sites. Using this reasoning, many mechanistic chemists have compared intra- and intermolecular isotope effects for given chemical reactions. Intra- and intermolecular effects which are large (>2) and identical are usually the strongest possible mechanistic data pointing to intimate involvement of a hydrogen atom in the rate-limiting step of the reaction. Likewise, high intramolecular and low intermolecular isotope effects are usually taken to be strong evidence favoring a reaction intermediate. Several such comparisons have been made in the singlet oxygen olefin reaction. Kopecky[39] has found low intermolecular isotope effects in comparing d_6 vs. d_0 dimethylstilbenes. Our own measurement[40] which allowed tetramethylethylene-d_6 to compete against tetramethylethylene-d_0 has also revealed a small intermolecular effect. Recent work by Gollnick and Hartmann[36] employing d_{12} vs. d_0 tetramethylethylene shows the effect $k_{H_{12}}/k_{D_{12}} = 1.11$.



All of these measurements are difficult to interpret since it is not clear how one should factor secondary isotope effects out of these numbers. In any case it is significant that intramolecular effects, where genuine competitions are established (see below), are all larger than these intermolecular effects. This again points to a separation of kinetic and product-determining steps.

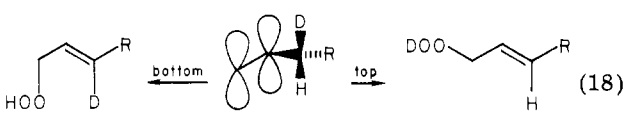
Our studies[41] of the intramolecular effect have revealed additional subtle features of this system, since a number of distinct types of competition can be defined. For reactions at an allylic C–H bond, four types of isotope competitions can be distinguished stereochemically.



top/bottom cis trans geminal

Independent measurements of these isotope effects can, in principle, provide structural information about reaction pathways.

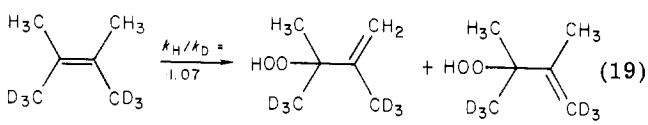
Top/Bottom Competition. Usually the singlet oxygen ene reaction can be depended upon to produce only trans allylic hydroperoxide. Thus, it is possible to design molecules which allow one to test the degree to which the top side of an allyl unit competes with the bottom (eq 18). The two sites are stereochemically and



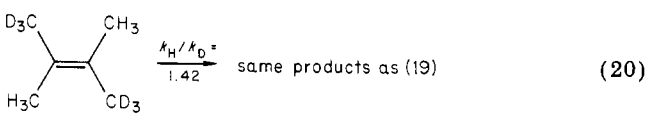
(18)

electronically equivalent and, a priori, might be expected to display a normal isotope effect. Such is not the case. Reactions 16 and 17 clearly imply that the reaction process possesses a stereochemical constraint which does not allow the two allyl faces to compete freely with each other.

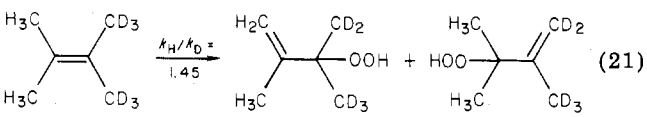
Cis, Trans, and Geminal Competition. These three types of isotope competition can be arranged to occur in reactions of tetramethylethylene, as shown in eq 19, 20, and 21. The behavior of the three labeled olefins



3 (19)



4 (20)



5 (21)

3, **4** and **5** demonstrate that these competitions are far from equivalent. Analysis of these three experiments suggest that only groups which are cis to each other are competitive ($k_H/k_D \simeq 1.4$), and that other stereochem-

(38) (a) Stephenson, L. M.; McClure, D. E.; Sysak, P. K. *J. Am. Chem. Soc.* **1973**, *95*, 7888. (b) Orfanopoulos, M. G.; Stephenson, L. M. *Ibid.* **1980**, *102*, 1417.

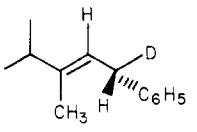
(39) Kopecky, K. R.; Van de Sande, J. H. *Can. J. Chem.* **1972**, *50*, 4034.

(40) Grdina, M. B. Ph.D. Thesis, 1979, Case Western Reserve University.

(41) Grdina, M. B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 3111.

ical relationships, trans, geminal, and top/bottom, are prevented from displaying a primary kinetic isotope effect ($k_H/k_D \simeq 1$).

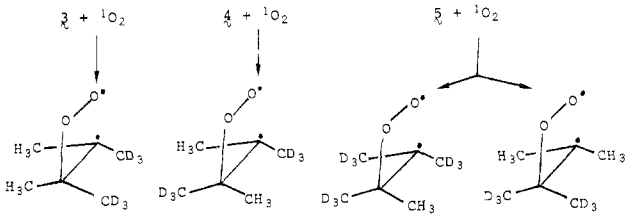
With this understanding, other more subtle competitions are easily interpreted. Perhaps most interesting are mixed competitions such as that inherent in **6**.



6

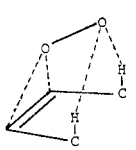
Here, the methyl and CHD units are about equally reactive. One would anticipate no top/bottom competition at the chiral center, but on the top face a cis competition (CH_3 vs. C–D) should be observed. We anticipate, and find, an isotope effect for reaction at the CHD site which is the average of 1.4 (top cis competition) and 1.0 (bottom face, no isotope competition, CH_3 vs. C–H), or k_H/k_D = 1.2. Several additional compounds with this same structural feature have been studied in our laboratories.[28] These show k_H/k_D values ranging from 1.17 to 1.20.

This unusual isotope effect variation, dependent on the stereochemistry of the competing groups, has clear mechanistic significance. The result eliminates from consideration a classical one-step concerted reaction. In a molecule like tetramethylethylene one would anticipate that all 12 hydrogens would be equally competitive. That is, any conceivable isotope competition should give the same result, in contrast to experiment. Equally important, the result eliminates diradicals and dipolar species from general consideration. Pictured below are diradicals expected from the three key labeled tetramethylethylenes **3**, **4** and **5**. One would anticipate



substantial and essentially identical isotope effects from the intermediates formed from **3** and **4**, in contrast to experiment. If the two structures expected from **5** were formed to equal extents (e.g., if there were no secondary isotope effect), then no apparent isotope effect would be found, again in contrast to experiment.

The specific isotope competition requires that the oxygen responsible for the hydrogen abstraction interact competitively only with cis groupings of C–H bonds. Interactions of the type suggested in structure **7**,



7

whether or not such interactions lead to perepoxide, provide a rationalization of this result. If these interactions are formed irreversibly, one would not expect trans, geminal, or top/bottom competition and would anticipate negligibly small intermolecular effects as well. This picture is developed in more detail below.

One should also take account of the low absolute values of the isotope effects found in this reaction. Traditional arguments would claim that hydrogen abstraction occurs "late" on the reaction surface. In terms of a concerted model for the reaction, this would imply diradical (or dipolar) character. In the perepoxide formulation, one would suggest substantial cleavage of one of the three-membered ring C–O bonds preceding O–H bond formation. Both of these traditional formulations carry with them the suggestion, particularly in the styrene systems noted previously, that product ratio variations should accompany substituent changes.

We suggest that the low isotope effects are simply the result of a reaction with a negligibly small activation enthalpy. Both the concerted ene reaction[37] and models for the decomposition of the perepoxide[42] show high isotope effects ($k_H/k_D \simeq 3$–4) in systems with higher activation energies. Thus the low isotope effect cannot be taken to argue for or against either alternative. The isotope effects do, however, imply a *symmetry* for this reaction which matches that of the perepoxide.

Theoretical Work. Various theoretical models have been applied to this reaction with several different predictions arising. In early work, Kearns[43] analyzed the reaction using orbital correlations and concluded that a perepoxide was preferred. In discussions of the correlations between reactivity and ionization potential, Paquette[35] used a HOMO–LUMO analysis and assumed a perepoxide geometry. Fukui,[44] using CNDO/2 with some configuration interaction, favors the perepoxide, but not as a true minimum potential-energy intermediate. Dewar and Thiel,[26] using MINDO/3, describe the perepoxide as a genuine intermediate. In contrast, the results of Goddard and Harding[19] place the diradical in the most favored position, with the perepoxide at least 8 kcal/mol above the known activation enthalpies. The relevance of any of the calculations to the solution phase work reported here can be seriously questioned. The solvent effect work of Gollnick and Hartmann[36] clearly points to the key role played by polar media. Thus, experimentalists should feel obligated to study a number of key systems in the gas phase, and theorists should more explicitly include solvation effects before additional comparisons of experimental data and computational results are made.

Conclusion. The reactions of singlet oxygen are very rapid. Indeed, most of the reactions described proceed with activation enthalpies below 5 kcal/mol. Thus, many traditional ideas concerning mechanism may be difficult to apply. Nonetheless, the data now lead us to several mechanistic generalizations. These generalizations provide a rationalization for the following key features of this reaction:

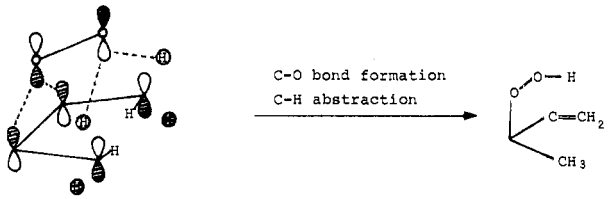
The mechanism must acknowledge the isotope effect data which appear to demand initial interactions of C_s symmetry which only allow cis competition.

(42) Seymour, C. A.; Greene, F. D. *J. Am. Chem. Soc.*, in press, and personal communication. These authors have employed tetramethylethylenes-D_6 **3** and **4** to study the ene reactions of reactive, sterically unhindered triazolinediones. They find a low isotope effect with cis isomer **3** (k_H/k_D = 1.1) and a normal isotope effect ($k_H/k_D \sim 3.8$) with trans isomer **4**. These reactions, while fast, require significantly greater $\Delta H^{\ddagger}$ than comparable $^1O_2$ reactions.

(43) Kearns, D. R.; Fenical, W.; Radlick, P. *Ann. N.Y. Acad. Sci.* **1970**, *171*, 34.

(44) (a) Inagaki, S.; Fujimoto, H.; Fukui, K. *Chem. Lett.* **1976**, 749. (b) Inagaki, S.; Fukui, K. *J. Am. Chem. Soc.* **1975**, *97*, 7480.

Scheme I



The reaction mechanism must predict high stereospecificity.

The reaction mechanism should account for the electron demand displayed by $^1O_2$.

The sequence must be capable of explaining high solvent sensitivity in reaction rates and in the partitioning between ene and 2 + 2 pathways, but little or no solvent effect in the ene reaction competitions.

Finally, perhaps the most difficult point, the mechanism should provide a rationale of the trisubstituted olefin regiospecificity. The high reactivity on the crowded side is nonintuitive and thus highly informative.

For convenience, we prefer to analyze this system in two stages, the first involving initial interactions of the charge transfer type, the second comprising the bond-making and -breaking steps.

The regiospecificity and the exclusive cis competition suggest a specific orientation between $^1O_2$ and olefin. We believe that the frontier molecular orbital theory provides useful insight into the origins of this orientation.

If one considers this to be a reaction between an electron donor (olefin) and an electron acceptor ($^1O_2$), then HOMO → LUMO interactions provide a suitable model for understanding the initial interactions. Examination of detailed calculations for a system like 2-butene reveals that the olefin HOMO is largely π-bonding, with small but significant C–H bonding orbitals mixed in, as shown in Scheme I. Interaction of this HOMO with a π^*-like LUMO on an approaching $^1O_2$ molecule provides a reasonable starting point for the motions which follow. This analysis provides several key explanations. Most important, oxygen should prefer the crowded side of di- and trisubstituted olefins where O--H--C bonding interactions are maximized, and should prefer axially disposed C–H bonds in cyclic systems. Obviously, the exclusive cis competitons, demonstrated by the isotope experiments, are accommodated by this picture. The LUMO–HOMO analysis provides an excellent starting point for a more detailed accounting of the correlation between olefin electron donor ability and reactivity, a point already made by Paquette. This pictue also accommodates another series of isotope effect measurements from Bartlett's lab.[27] Frimer, Bartlett, et al.[27] proposed a criss-cross olefin/O_2 complex to deal with the results. Our present proposal is an extension and modification of their idea and of previous work from our laboratory.[45]

As this argument suggests, these initial orbital interactions determine all of the important reactivity and product-determining features of this reaction. They represent, in a sense, a complete mechanistic description. As a result, the detailed characteristics of the bond-making and bond-breaking steps which follow are difficult to address with clean experimental tests. This must be due, in large part, to the low enthalpy requirements for this reaction. Arguments based on the magnitude of isotope effects or the sensitivity to substituent variation all lose meaning for such rapid reactions. Photochemical 2 + 2 cycloadditions also exhibit this same property. Caldwell and Creed,[46] in particular, have pointed out the importance of initial interactions in determining the nature of 2 + 2 reaction products. Indeed, this may be a characteristic of most reactions that are this rapid.

No evidence or compelling argument of which we are aware demands that the initial interactions in this reaction lead to perepoxides. The absence of positive evidence leads us to favor the most economical explanation available, namely, that these frontier orbital interactions lead the system directly into a concerted ene reaction. Ordinarily, the demonstrated uncoupling of kinetic and product-determining steps in a reaction would lead to the postulation of an intermediate. In this reaction our data clearly lead us to propose a distinctly non-least-motion pathway to product. This pathway itself provides for the fact that the initial (rate determining) interactions are separate from product determining steps.

Additional experiments and theoretical developments may address this remaining point of uncertainty. It will be particularly valuable, for example, to repeat many of the experimental tests outlined in this Account in systems which are unreactive and possess activation enthalpies significantly larger than zero. Equally informative will be experiments in the gas phase allowing a meaningful comparison with theory. We have little doubt that the unusual characteristics of singlet oxygen will continue to make reactions of this species a favored area for the development of new ideas and methods.

We acknowledge, in particular, the efforts of two talented co-workers in this research. David E. McClure and P. Kevin Sysak have contributed both experimentally and intellectually to this problem. Special thanks are due Professor Chris Foote, who has contributed sharp criticism and friendly encouragement, in roughly equal measures, over the past 10 years. The National Science Foundation provided the bulk of the financial support of these investigations.

(45) McClure, D. E. Ph.D. Thesis, 1973, Stanford University.
(46) Caldwell, R. A.; Creed, D. *Acc. Chem. Res.* **1980**, *13*, 45–50.