# Photosensitized Oxygenations and the Role of Singlet Oxygen[1]

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The chemistry of singlet molecular oxygen, generated by the reaction of hydrogen peroxide with metal hypochlorites, has been studied. In all cases, the chemistry is identical with that of the reactive intermediate in the dye-photosensitized oxygenation of olefins and dienes. The techniques used for comparison of the two reactions include detailed studies of stereoselectivity with a variety of acceptors, determination of the ratio of the rates of reaction and decay for the intermediate, relative reactivities of acceptors, and substituent effects on product and reaction rate. From the results of these studies, it is concluded that the reactive intermediate in both the photosensitized and chemical oxygenation is O_2 $(^1\Delta_g)$. The reaction with olefins appears to be a concerted cycloaddition, and there is little polar or diradical character developed at the transition state.
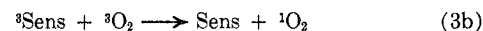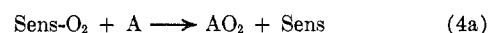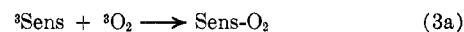
The dye-sensitized photooxygenation of organic compounds has been studied extensively by many workers and represents a very smooth method for introducing oxygen in a highly specific fashion into organic compounds.[3] There are two principal classes of reaction. The first is the oxygenation of cyclic dienes, polycyclic aromatic compounds, and many heterocycles to give cyclic peroxides analogous to the adducts formed with dienophiles in the Diels–Alder reaction. The second class is the oxygenation of olefins containing allylic hydrogen atoms to give allylic hydroperoxides in which the double bond has shifted position. This reaction is analogous to the "ene" reaction. Among the best sensitizers are fluorescein derivatives, methylene blue, certain porphyrins, and polycyclic aromatic hydrocarbons; with most sensitizers, the reaction proceeds best with visible light.

The reaction should be distinguished from the familiar radical oxidation which can be initiated by sensitizers (such as benzophenone) which abstract hydrogen and which may also give allylic hydroperoxides, as shown below. As an example of the difference between the two types of oxidation, isopropyl alcohol is a very reactive acceptor (A) for radical oxidation but is inert in the dye-sensitized photooxygenations.[4]

$$R\cdot + AH \longrightarrow RH + A\cdot$$
$$A\cdot + O_2 \longrightarrow AO_2\cdot$$
$$AO_2\cdot + RH \longrightarrow R\cdot + AO_2H$$
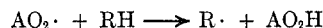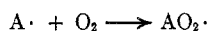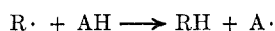
Two of the mechanisms which have been suggested for the photooxygenation are consistent with the kinetic studies which have been carried out.[3b,c,5] Both begin with excitation of the sensitizer to the singlet state, followed by intersystem crossing to the triplet state (steps 1 and 2). The first mechanism, which was originally suggested by Schönberg[6] and has been advocated by Schenck and others,[3,5a] was generally accepted until recently; in this mechanism, the triplet sensitizer reacts with triplet oxygen to give a sensitizer–oxygen complex (step 3a). This complex then reacts with acceptor (A) to give the product peroxide (AO_2) and regenerate sensitizer (step 4a). The other mechanism was originally proposed by Kautsky in 1931.[7] In this mechanism energy is transferred from triplet sensitizer to oxygen to give excited singlet molecular oxygen (step 3b). The singlet oxygen then reacts with acceptor to give the peroxide (step 4b). Kautsky's mechanism was largely ignored after 1940, although it was occasionally discussed as a possibility.

$$\text{Sens} \xrightarrow{h\nu} {}^1\text{Sens} \tag{1}$$
$${}^1\text{Sens} \longrightarrow {}^3\text{Sens} \tag{2}$$
$${}^3\text{Sens} + {}^3O_2 \longrightarrow \text{Sens-}O_2 \tag{3a}$$
$$\text{Sens-}O_2 + A \longrightarrow AO_2 + \text{Sens} \tag{4a}$$
$${}^3\text{Sens} + {}^3O_2 \longrightarrow \text{Sens} + {}^1O_2 \tag{3b}$$
$${}^1O_2 + A \longrightarrow AO_2 \tag{4b}$$

Energy transfer from triplet sensitizer to triplet oxygen to give singlet oxygen is a spin-allowed process. The lowest states of oxygen are shown below, with the electron distribution in the highest occupied (degenerate) orbitals.[8] The $^1\Delta_g$ state has an energy only 22 kcal above that of the ground state; both electrons are paired in a single orbital, leaving the other vacant.

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(2) Alfred P. Sloan Research Fellow, 1965-1967; Guggenheim Fellow, 1967-1968.

(3) (a) K. Gollnick and G. O. Schenck in "1,4 Cycloaddition Reactions," J. Hamer, Ed., Academic Press Inc., New York, N. Y., 1967, p 255; (b) K. Gollnick and G. O. Schenck, *Pure Appl. Chem.*, **9**, 507 (1964); (c) E. J. Bowen, *Advan. Photochem.*, **1**, 23 (1963); (d) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); (e) K. Gollnick, *Advan. Photochem.*, **5**, in press.

(4) (a) G. O. Schenck, H.-D. Becker, K.-H Schulte-Elte, and C. H. Krauch, *Ber.*, **96**, 509 (1963); (b) C. S. Foote and R. Higgins, unpublished.

(5) (a) R. Livingston and V. Subba Rao, *J. Phys. Chem.*, **63**, 794 (1959); (b) T. Wilson, *J. Am. Chem. Soc.*, **88**, 2898 (1966).

(6) A. Schönberg, *Ann.*, **518**, 299 (1935).

(7) (a) H. Kautsky and H. de Bruijn, *Naturwissenschaften*, **19**, 1043 (1931); (b) H. Kautsky, *Biochem. Z.*, **291**, 271 (1937), and intervening papers.

(8) G. Herzberg, "Molecular Spectra and Molecular Structure. I. Spectra of Diatomic Molecules," 2nd ed, D. Van Nostrand Co., New York, N. Y., 1950, p 560.

This state might be expected to undergo two-electron reactions; it resembles ethylene electronically, but should be more electrophilic. The higher singlet state ($^1\Sigma_g^+$) resembles ground-state oxygen electronically and might be expected to undergo one-electron free-radical reactions. Both states have been identified spectroscopically as products of electrodeless discharge and of the chemiluminescent reaction of sodium hypochlorite and hydrogen peroxide,[9] and at least one of the states is produced in certain other reactions.[10] The $^1\Delta_g$ state has a much longer lifetime than the $^1\Sigma_g^+$, and is the major product of the hypochlorite–hydrogen peroxide reaction.[9]

States of the oxygen molecule	Occupancy of highest orbitals	Energy above ground state
Second excited state ($^1\Sigma_g^+$)	⤉ ⤉	37 kcal
First excited state ($^1\Delta_g$)	⤉⤈ —	22 kcal
Ground state ($^3\Sigma_g^-$)	⤉ ⤉	

Reactions with Singlet Oxygen. In order to test the possibility that singlet oxygen is intermediate in the dye-sensitized photooxygenation, the reactions of chemically generated singlet oxygen were studied.[11] Typical acceptors for the photooxygenation were dissolved in alcohol with hydrogen peroxide, and sodium hypochlorite was added. Products identical with those of the photooxygenation were formed in each case. Some of the acceptors and the products formed on chemical oxygenation are shown in Table I.

Other studies have shown that singlet oxygen generated by electrodeless discharge in the gas phase can oxygenate similar acceptors, although only inefficiently.[12] In addition, similar oxygenations can be carried out with other singlet oxygen sources.[10]

Product Distributions. In order to obtain a more detailed comparison of the reactive intermediate in the photooxygenation, reactions which give more than one product were investigated.[13] Comparative photosensitized and chemical oxygenations were carried out, and the product peroxides were reduced for gas chromatographic analysis. The results of some of these product studies are summarized in Table II. As can be seen, the two reactions give product distributions which are identical, within experimental error. Furthermore, as has already been pointed out in the case of photooxygenation, secondary and tertiary products are formed in nearly equal amounts in the absence of

(9) (a) J. S. Arnold, R. J. Browne, and E. A. Ogryzlo, *Photochem. Photobiol.*, **4**, 963 (1965), and references therein; (b) A. U. Khan and M. Kasha, *J. Am. Chem. Soc.*, **88**, 1574 (1966), and references therein.

(10) (a) E. McKeown and W. A. Waters, *Nature*, **203**, 1063; (b) *J. Chem. Soc., Sect. B*, 1040 (1966); (c) H. H. Wasserman and J. R. Scheffer, *J. Am. Chem. Soc.*, **89**, 3073 (1967).

(11) (a) C. S. Foote and S. Wexler, *ibid.*, **86**, 3879, 3880 (1964); (b) C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *ibid.*, **90**, 975 (1968).

(12) E. J. Corey and W. C. Taylor, *ibid.*, **86**, 3881 (1964).

(13) C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Letters*, 4111 (1965).

Table I

Chemical Oxygenations of Typical Photooxygenation Substrates

Compound   Product

[a] Reference 11.   [b] Unstable product.   [c] Unreactive acceptor, very low yield.   [d] Methanol adduct of unstable endoperoxide.   [e] Presumably formed by loss of CO from intermediate peroxide.   [f] Reference 11b.

Table II

Products of Olefin Oxygenations[a]

Olefin	Alcohol A	Alcohol B	Photooxygenation % A	Photooxygenation % B	OCl⁻/H₂O₂ % A	OCl⁻/H₂O₂ % B
			40	60	39	61
			49	51	51	49
			48	52	49	51
			44, 20	36	44, 20	36
			96	4	94	6

[a] After reduction of the peroxides to the corresponding alcohols; mean of four or more analyses.

steric influences.[3b,e,14] That is, there is no Markovnikov-type directing effect. In addition, in the oxygenation of methylcyclohexenes, the predominant products have the double bond exocyclic, and formation of endocyclic products is unfavorable.[3b,e,14] Products which involve shift of the tertiary hydrogen atom from an isopropyl group to oxygen are formed only in minor amounts, probably because the most favorable conformation for the isopropyl hydrogen is in the plane of the double bond.[3b,e,14] The conformation most favorable for reaction in the photooxygenation is perpendicular to the double bond, which favors overlap of the C–H orbital with the p orbital of the double

(14) G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann.*, **674**, 93 (1964).

bond.[3b,e,14,15] As can be seen, exactly similar factors influence the product distribution in the chemical oxygenation.

The oxygenation of limonene (1) provides a particularly sensitive fingerprint for the reactive intermediate. This substrate contains two double bonds, one disubstituted and one trisubstituted. Photooxygenation yields all six possible products (2–7) of attack at the trisubstituted double bond; no products with unshifted double bond are formed, and the disubstituted double bond is inert under the conditions.[14]
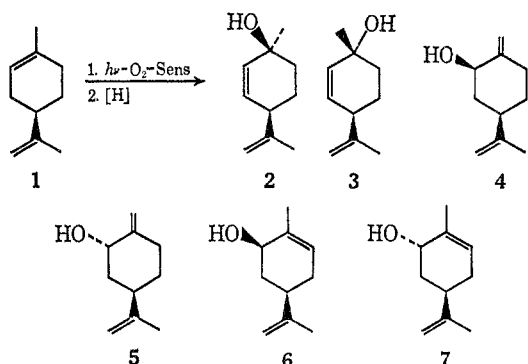
Oxygenation of limonene with OCl⁻–H₂O₂ gives a product mixture which is identical with that of photooxygenation, within experimental error; the results are summarized in Table III.[13]

Table III
Product Distributions in Photosensitized and Chemical Oxygenation of Limonene (1)[a]

Product	Photooxygenation, %	OCl⁻/H₂O₂, %
2	34	34
3	10	10
4	23	21
5	19	18
6	4	7
7	9	10

[a] Average of at least three runs in each case. Results of photooxygenation are nearly identical with those of ref 14.

Alcohol 7 is optically pure when produced by either photooxygenation or chemical oxygenation of optically active limonene. This evidence (together with the consistent absence of any products with unshifted double bond) rules out the intermediacy of allylic free radicals in either the photosensitized[14] or the chemical oxygenation,[13] as the allylic radical (8) leading to 7 would be racemic.

8

The product distribution is the same when the oxygenation is photosensitized by rose bengal in methanol, by riboflavin in aqueous t-butyl alcohol, or by zinc tetraphenylporphine in benzene,[4b,16] so that neither the sensitizer nor the solvent affects the product distribution.

In addition, the product distribution from either type of oxygenation of limonene is very different from that of free-radical autoxidation.[17] Products with the double bond exocyclic to the six-membered ring (i.e., 4 and 5) make up a large fraction of the mixture from photosensitized and chemical oxygenation but are present only as minor products of radical oxygenation,[17] as might be expected since primary hydrogens are more difficult to abstract than secondary or tertiary. A clear demonstration of these effects is provided by the oxygenation of 1,2-dimethylcyclohexene.[18,19] Product distributions (summarized in Table IV) for photosensi-

Table IV
Products from 1,2-Dimethylcyclohexene

Product	Photooxygenation, %	OCl⁻/H₂O₂, %	Radical autoxidn, %
9	89	91	6
10	11	9	39
11	0	0	54

tized and chemical oxygenation are identical; the major product (9) again is the one with an exocyclic double bond. Radical autoxidation gives the product with an unshifted (tetrasubstituted) double bond (11) as the major product; this product is absent from the other oxygenation mixtures.[18]

Photooxygenation of α-pinene (12) yields 13 as the major product.[3b,20] α-Pinene is an extremely unreactive acceptor in the photooxygenation, and this unreactivity is also shown in chemical oxygenation.[13] Most of the oxygen escapes from the solution, and only traces of oxygenated products are found. If the reaction is carried out at room temperature, in the absence of radical inhibitors, a product mixture closely resembling that of radical oxygenation is obtained.[3b,13] At lower temperatures and in the presence of inhibitors the

(15) (a) A. Nickon and J. F. Bagli, J. Am. Chem. Soc., 83, 1498 (1961); (b) A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, J. Org. Chem., 30, 1711 (1965); (c) A. Nickon and W. L. Mendelson, Can. J. Chem., 43, 1419 (1965); (d) A. Nickon and W. L. Mendelson, J. Am. Chem. Soc., 87, 3921 (1965).

(16) The values in Table III are for rose bengal in methanol.
(17) G. O. Schenck, O.-A. Neumüller, G. Ohloff, and S. Schroeter, Ann., 687, 26 (1965).
(18) C. S. Foote and S. Wexler, unpublished; S. Wexler, Ph.D. Thesis, University of California at Los Angeles, 1966.
(19) Photosensitized oxygenation of 1,2-dimethylcyclohexene has also been reported by K.-H. Schulte-Elte, Dissertation, Göttingen, 1961, with somewhat different results from those reported here.
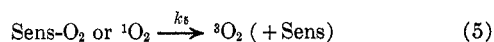(20) G. O. Schenck, H. Eggert, and W. Denk, Ann., 584, 177 (1953).

free-radical products are suppressed, and a product distribution similar to that of photooxygenation is obtained.[13]
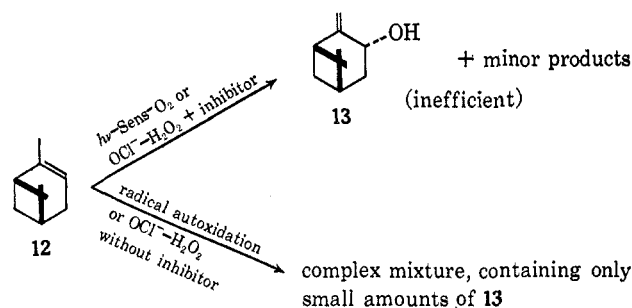
The product distribution studies show that photosensitized and chemical oxygenations produce identical product distributions. The sensitizers used are very bulky and would be expected to exert a strong influence on the stereoselectivity of the reactive intermediate if they were present at the transition state, but no such effect is observed.

Kinetics and Reactivity Considerations. The kinetics of the photooxygenation have been described by the Schenck group and other workers in the field.[3,5,21] There are two competing reactions of the reactive intermediate (singlet oxygen and Sens-O_2 are kinetically equivalent). The first is decay to give ground-state oxygen, and the second is reaction with acceptor to give the product peroxide.

$$\text{Sens-O}_2 \text{ or } {}^1\text{O}_2 \xrightarrow{k_5} {}^3\text{O}_2 \ (+\text{Sens}) \qquad (5)$$

$$\text{Sens-O}_2 \text{ or } {}^1\text{O}_2 + \text{A} \xrightarrow{k_6} \text{AO}_2 \ (+\text{Sens}) \qquad (6)$$

For this scheme, steady-state treatment gives the result

$$\Phi = K \frac{k_6[\text{A}]}{k_5 + k_6[\text{A}]}$$

where Φ is the quantum yield of product formation and K is the quantum yield for formation of the reactive intermediate and depends only on sensitizer at sufficiently high oxygen pressure. It is apparent that if $k_6[\text{A}] \gg k_5$, the reaction is zero order in [A], and $\Phi = K$; when $k_6[\text{A}] \ll k_5$, the reaction is first order in [A], and $\Phi \ll K$. The values of k_6 vary widely for different acceptors and cannot be determined absolutely. However, k_5/k_6 (called β) for a given acceptor is conveniently determined from the dependence of Φ on [A] and is equal to the concentration of acceptor at which half the reactive intermediate is trapped and half decays.

A kinetic scheme exactly analogous to the one above holds also for chemical oxygenation.[21] The dependence of the yield of product (based on hypochlorite added) varies in the same way with acceptor concentration. For example, for 2-methyl-2-pentene in

Table V
Relative Reactivities of Acceptors[a]

Acceptor	Photooxygenation k_6(rel)	β, M[b]	Hypochlorite/H_2O_2 k_8(rel)	β, M[b]
2,5-Dimethylfuran[c]	2.4	0.001	3.8	0.001
Cyclopentadiene[c]	1.2	0.002	1.1	0.003
2,3-Dimethyl-2-butene[d]	(1.00)	0.0027	(1.00)	0.0030
1,3-Cyclohexadiene[c]	0.08[e]	0.03[e]	0.3	0.01
1 Methylcyclopentene[c]	0.05	0.05	0.03	0.1
trans-3-Methyl-2-pentene[c]	0.04	0.07	0.03	0.1
cis-3-Methyl-2-pentene[c]	0.03	0.1	0.03	0.1
2-Methyl-2-butene[d]	0.024	0.11	0.028	0.11
2-Methyl-2-pentene[d]	0.019	(0.14)	0.022	(0.14)
1-Methylcyclohexene[d]	0.0041	0.67	0.0056	0.55
cis-4-Methyl-2-pentene[d]	0.00026	10	0.00024	13
Cyclohexene[d]	0.000048	55	f	
trans 4-Methyl-2-pentene[d]	0.000047	57	0.000044	70

[a] From ref 21. [b] Calculated, based on an average value for photosensitized and chemical oxygenation for 2-methyl-2-pentene of 0.14 M. [c] By acceptor disappearance, usually ±30%. [d] By product appearance, usually ±10%. [e] Result of a single determination. [f] Insufficiently reactive for determination.

methanol–t-butyl alcohol (50:50), the value of β for photooxygenation is 0.13 ± 0.02 M, whereas the value for chemical oxygenation is 0.16 ± 0.04 M. This result is extremely significant, because it means that the ratio of the rate constant for decay to that for reaction with acceptor is identical for the reactive intermediates in photosensitized and chemical oxygenation.

By means of competition experiments, it is possible to determine relative reactivities of different acceptors in the two reactions, and thus relative values of k_6.[21,22] Since k_5 does not change for a given system, values of β for each acceptor can be calculated from these data. Relative reactivities of a variety of acceptors for the two reactions are listed in Table V. The relative reactivities cover a span of five powers of ten, and the values for a given acceptor are identical in the two reactions within experimental error.[21] Alkyl substitution on an olefin increases its reactivity greatly, but cyclohexene derivatives are less reactive than acyclic olefins or cyclopentenes.[3b,e,21,22] The reason for the low reactivity of cyclohexenes (which has been noted by previous workers[3b,22]) is not certain, but it is probably related to the fact that formation of products with

(21) R. Higgins, C. S. Foote, and H. Cheng, International Oxidation Symposium, San Francisco, Calif., 1967; Advances in Chemistry Series, American Chemical Society, Washington, D. C., in press.

(22) K. R. Kopecky and H. J. Reich, Can. J. Chem., 43, 2265 (1965).

endocyclic cyclohexene double bonds is unfavorable. Conformational and steric factors are very important in these reactions[3b,15] and are probably responsible for these effects. The low reactivities of the 4-methyl-2-pentenes are probably due to steric hindrance by the bulky isopropyl group combined with the conformational inaccessibility of the tertiary hydrogen.

Substituent Effects. In order to attempt a separation of steric and electronic effects on the two reactions, the effects of different substituents (Y) on the phenyl group of trimethylstyrene (**14**) were studied.[23] Product distributions from photooxygenation and from chemical oxygenation with a variety of *meta* and *para* substituents ranging from methoxyl to cyano were determined. The average ratio of product **15** to product **16** in the mixture was 2.70 in both reactions and was the same, within the experimental error, for all substituents.
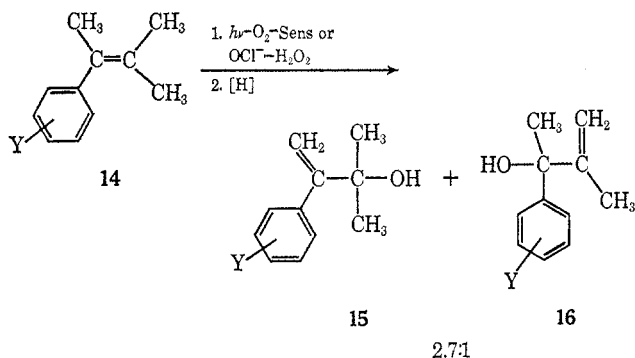
Although no effect of substituent on product distribution was observed, electron-donating substituents increase the reaction rate substantially in this system. The Hammett parameter ρ is -0.93 for rose bengal sensitized photooxygenation and -0.91 for the chemical oxygenation.[23] Good correlation with σ is observed, which means the reaction responds to substituents in nearly the same way as does the ionization of benzoic acids, in contrast to reactions in which the transition state is more subject to resonance effects, which are better correlated with σ^+.

Because the trimethylstyrenes are bulky, it is likely that the double bond is not completely coplanar with the ring, which might invalidate this test for the importance of conjugative effects. For calibration of these olefins as models, the epoxidation with perbenzoic acid in benzene was carried out. For this quite electrophilic reagent the ρ value is -0.9, and a blend of roughly 50% σ^+ produces a better fit than use of the pure σ constant. These results are very similar to those for epoxidation of substituted styrenes, both in the magnitude of ρ and the amount of σ^+ required,[24] so that the trimethylstyrenes behave normally. The substituent

Table VI

Solvent Effect on β (k_5/k_6) for Photosensitized Oxygenation of 2-Methyl-2-pentene

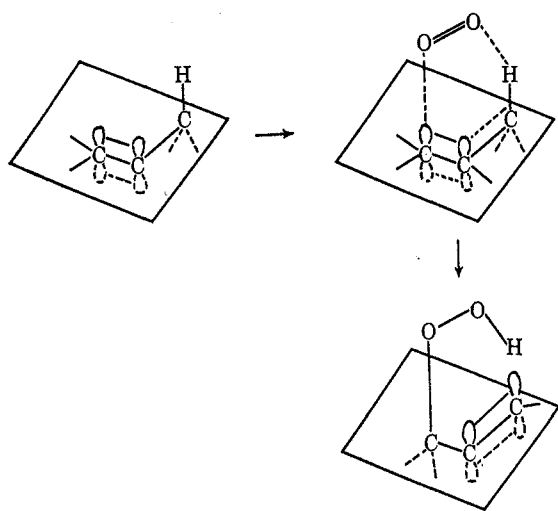| Solvent	β, M^a
Ethyl acetate[b]	0.04
t-Butyl alcohol	0.05
Bromobenzene[c]	0.06
Cyclohexanol[b]	0.075
Acetone[b]	0.08
Dimethyl sulfoxide[b]	0.08
Carbon disulfide[c]	0.09
Benzene[c]	0.10
Iodoethane	0.11
Methanol-*t*-butyl alcohol (50:50)[b]	0.14
Methanol[b]	0.17

[a] Determined by plot of $1/\phi$ vs. $1/[A]$ (see ref 21), maximum probable error around $\pm 30\%$. [b] Rose bengal sensitizer. [c] Zinc tetraphenylporphine sensitizer.

effect studies indicate that the transition state for the reaction is stabilized by electron-donating substituents, but little charge is localized; again, both photosensitized and chemical oxygenation behave identically.

Solvent Effects. Solvent effects on reaction rate provide a further test for charge separation at the transition state. Since k_6 cannot be determined absolutely, the solvent effect on β (k_5/k_6) was determined, and the results are listed in Table VI.[23] No trend in the results with polarity is observed, solvents as different as methanol and benzene giving β values which differ only slightly. Furthermore, no effect of viscosity is observed, as the value for the viscous solvent cyclohexanol is not noticeably different from that for much less viscous solvents. Surprisingly, no detectable effect of heavy atoms on β has been observed; β in bromobenzene (0.06) or in iodoethane (0.11) might have been expected to be considerably larger than that in benzene (0.10) if the decay rate (k_5) were increased by the effect of the heavy bromine or iodine atoms.

Nature of the Transition State. Both Schenck and Nickon have concluded solely on stereochemical grounds that the transition state for photosensitized oxygenation of olefins is cyclic.[3b,14,15] Thus the oxygen is introduced on the same side as the hydrogen is removed, the double bond always shifts, and reaction is most favorable when the hydrogen which is removed can be coplanar with the p lobes of the double bond (which is the geometry required for formation of the incipient double bond). Schenck has written a cyclic transition state with sensitizer attached to the oxygen,[3b,14] whereas Nickon (who also advocates a cyclic mechanism) has remained noncommittal as to whether the oxygen is free or complexed.[15]
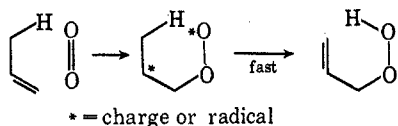
The evidence described above shows that the reactive intermediates in the photosensitized and chemical oxygenations are identical in stereoselectivity of attack, electrophilicity, reaction rate relative to lifetime, and response to substituents. A bulky sensitizer would be expected to alter the stereoselectivity and rate of attack and should also alter the electron demand of the oxygen.

(23) C. S. Foote and R. Denny, unpublished.

(24) Y. Ishii and Y. Inamoto, *J. Chem. Soc. Japan, Ind. Chem. Sec.*, **63**, 765 (1960); *Chem. Abstr.*, **58**, 4393 (1963); see also Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, **32**, 965, 971 (1959), for details of this type of treatment.

There is thus good reason to believe that the oxygen is free of sensitizer at the transition state.[13,21]

Additional evidence on this point comes from the old experiments of Kautsky,[7] in which it was demonstrated that photooxygenation could take place even if sensitizer and acceptor were physically separated, so that the reactive intermediate must be readily diffusible. Similar results have been reported more recently by two groups.[25]

The stereochemical criteria listed above do not distinguish between a concerted cycloaddition and addition followed by rapid hydrogen transfer. However, the product distributions (Table II) show no Markovnikov-type directing effects (secondary and tertiary products are produced in nearly equal amounts in the absence of steric effects). This fact, along with the lack of a substituent effect on product distribution, and the lack of a solvent effect on β make a two-step reaction involving either ionic or diradical intermediates unlikely, since any localized ionic or radical character should be strongly stabilized by alkyl groups and affected by substituents on aryl groups. An ionic transition state would be greatly stabilized by polar solvents.

* = charge or radical

Similar arguments, particularly the lack of a solvent effect, militate against an intermediate "perepoxide" (17), suggested by Sharp[26] and by Kopecky[22] on the basis of the fact that the reaction rate is increased by
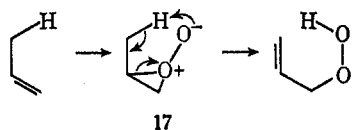
17

electron-donating substituents. This mechanism is difficult to rule out rigorously, however.

A mechanism which is in accord with all criteria is a concerted cycloaddition of singlet oxygen to the olefin, exactly analogous to the mechanism discussed for the "ene" reaction.[27] Singlet oxygen can thus be visualized as a reactive dienophile, analogous to maleic anhydride, which can undergo the Diels–Alder reaction with suitable dienes and the "ene" reaction with suitable olefins. The electrophilic nature of the reagent is consistent with expectation for an electronegative molecule such as oxygen.[28]

Although from its electronic state (which resembles ethylene), $^1\Delta_g$ O_2 is the most likely candidate for the reactive intermediate in these reactions, vibrationally excited ground-state oxygen and $^1\Sigma_g^+$ O_2 should also be considered. Both of these latter species are shorter lived than the reactive intermediate,[29] which has a lifetime of at least 10^{-6} sec in solution, and probably several orders of magnitude longer than this.[11b] In addition, both $^1\Sigma_g^+$ and vibrationally excited ground-state oxygen should resemble ground-state oxygen in their reactivity, since their electron distributions are similar, and would not be expected to undergo concerted reactions, but should be excellent hydrogen atom abstractors.[11b] Kearns has recently provided evidence that a short-lived, hydrogen atom abstracting species is produced with sensitizers of sufficiently high triplet energy.[30] This species is probably $^1\Sigma_g^+$ O_2. Further theoretical arguments supporting these conclusions were recently presented by Khan and Kearns.[30d] Quantum yield and kinetic arguments lead to the conclusion that $^1\Sigma_g^+$ O_2 decays nearly quantitatively to $^1\Delta_g$ oxygen before reacting with substrates which are not powerful hydrogen atom donors;[21] even with this class of substrate,[30] reaction of $^1\Sigma_g^+$ O_2 is very inefficient, probably because of the extremely short lifetime of this species in solution.

1,2-Cycloaddition? Many dienophiles can be made to undergo 1,2-cycloaddition reactions with certain

(25) (a) J. L. Rosenberg and D. J. Shombert, *J. Am. Chem. Soc.*, 82, 3257 (1960); (b) J. Bourdon and B. Schnuriger, *Photochem. Photobiol.*, 5, 507 (1969).

(26) D. B. Sharp, Abstracts, 139th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960, p 79P. The intermediacy of singlet oxygen was also suggested by this author.

(27) (a) J. A. Berson, R. G. Wall, and H. D. Perlmutter, *J. Am. Chem. Soc.*, 88, 187 (1966); (b) R. T. Arnold and J. F. Dowdall, *ibid.*, 70, 2590 (1948); (c) R. K. Hill and M. Rabinovitz, *ibid.*, 86, 965 (1964).

(28) Similar conclusions as to the concerted cyclic nature of the reaction were recently reached by K. Gollnick and by A. Litt and F. Nickon in papers at the International Symposium on Oxidation, San Francisco, Calif., 1967 (Advances in Chemistry Series, American Chemical Society, Washington, D. C., in press). However, Litt and Nickon reported a very small difference in isotope effect between sensitizers in the photooxygenation and in the hypochlorite–hydrogen peroxide oxygenation. These results, if proven correct, cast doubt on the freedom of the oxygen.

(29) Ogryzlo recently reported that $^1\Sigma_g^+O_2$ is quenched by water (and organic solvents) in about ten collisions (International Oxidation Symposium, San Francisco, Calif., Aug 1967; Advances in Chemistry Series, American Chemical Society, Washington, D. C. in press).

(30) (a) K. Kawaoka, A. U. Khan, and D. R. Kearns, *J. Chem. Phys.*, 46, 1842 (1967); (b) D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers, and P. Radlick, *J. Am. Chem. Soc.*, 89, 5455 (1967); (c) D. R. Kearns, R. A. Hollins, A. U. Khan, and P. Radlick, *ibid.*, 89, 5456 (1967) (we are indebted to Professor Kearns for prepublication copies of his manuscripts); (d) A. U. Khan and D. R. Kearns, International Oxidation Symposium, San Francisco, Calif., Aug 1967 (Advances in Chemistry Series, American Chemical Society, Washington, D. C., in press).

olefins. For example, benzyne adds to enamines to give aminobenzocyclobutenes (18).[31]

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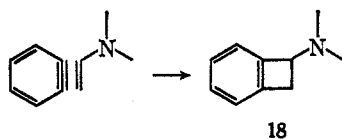
Singlet oxygen (from photosensitized oxygenation) also reacts with enamines; the result is a smooth cleavage to a carbonyl compound and an amide.[32] For example, photosensitized oxygenation of 1-phenyl-2-piperidinoethylene (19) proceeds smoothly to give N-formylpiperidine and benzaldehyde.[32a] Since this enamine has no allylic hydrogens, formation of an allylic hydroperoxide is precluded. A possible mechanism would be a 1,2-cycloaddition (probably nonconcerted) to give a dioxetane intermediate (20) which would cleave to the observed products, although more complicated mechanisms are not ruled out.

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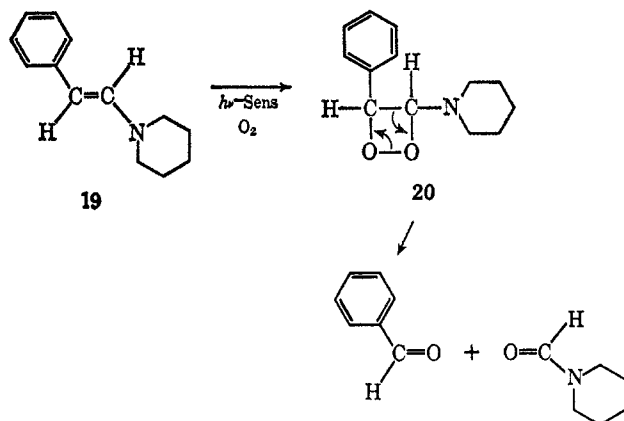
Synthetic Utility of Chemical Oxygenation. As discussed in the section on kinetics, with unreactive substrates high concentrations of acceptors are necessary in order for a significant fraction of the reactive intermediate to be trapped. Large excesses of hypochlorite must be added to compensate for the reactive intermediate which decays and escapes from the solution.

As a reasonable criterion,[11b] the β value of a substrate should not exceed ~0.2 M to allow practical use of chemical oxygenation as a synthetic reaction (see Table V). Thus, for example, 2-methyl-2-butene, cyclohexadiene, or dimethylfuran could be oxygenated practically, whereas 1-methylcyclohexene or any less reactive acceptor would be difficult to oxygenate in high yield.

In methanol, a yield of singlet oxygen (based on hypochlorite) of 70% is obtained.[11b] High yields are also obtained in methanol-t-butyl alcohol and in ethanol. Unfortunately, in other water-miscible solvents the yield is usually below 10%.[11b] The reason for this effect is not yet certain, but it represents a severe limitation to the preparative use of chemical oxygenation. Photosensitized oxygenation is not subject to these effects, which seem to be on the production of singlet oxygen rather than on its reaction.

Biological Implication. The finding that singlet oxygen is the reactive intermediate in photosensitized oxygenations of olefins and dienes has important biological implications. These will be discussed in more detail in a forthcoming publication, but it should be noted that photosensitizing dyes also sensitize the oxidative destruction of nucleic acids and enzymes and can produce skin cancer.[33] In addition, many of the carcinogenic polycyclic aromatic hydrocarbons are known to be good photosensitizers.[33b,34] Furthermore, several classes of oxygenases produce oxygenation with a chemistry which (at least formally) resembles that of singlet oxygen.[35] It seems possible that an enzyme-bound (perhaps metal-bound) form of singlet oxygen is the reactive species. These are only a few of the possible directions for future research in this area.

(31) (a) M. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962); (b) M. Kuehne and J. Kitagawa, *J. Org. Chem.*, **29**, 1270 (1964); (c) see also H. H. Wasserman and J. Solodar, *J. Am. Chem. Soc.*, **87**, 4002 (1965).

(32) (a) C. S. Foote, M. Brenner, and J. Lin, unpublished; (b) similar reactions have been found by Dr. J. Huber (private communication).

(33) (a) H. Blum, "Photodynamic Action and Diseases Caused by Light," Reinhold Publishing Corp., New York, N. Y., 1941; (b) J. D. Spikes and B. W. Glad, *Photochem. Photobiol.*, **3**, 471 (1964).

(34) (a) G. O. Schenck, *Naturwissenschaften*, **43**, 71 (1956); (b) S. S. Epstein and M. Burroughs, *Nature*, **193**, 337 (1962).

(35) (a) B. Samuelsson, *J. Am. Chem. Soc.*, **87**, 3011 (1965); (b) O. Hayaishi, "Oxygen in the Animal Organism," The Macmillan Co., New York, N. Y., 1964, p 151; (c) P. Feigelson, Y. Ishimura, and O. Hayaishi, *Biochem. Biophys. Acta*, **96**, 283 (1965); (d) G. A. Blondin, B. D. Kulkarni, and W. R. Nes, *J. Am. Chem. Soc.*, **86**, 2528 (1964).