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ARTICLES

Christopher Foote's Discovery of the Role of Singlet Oxygen [$^1\text{O}_2$ ($^1\Delta_g$)] in Photosensitized Oxidation Reactions

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ABSTRACT

The chemistry of singlet molecular oxygen [$^1\text{O}_2$ ($^1\Delta_g$)], its importance in atmospheric, biological, and therapeutic processes, and its use as a reagent in organic synthesis have been of considerable interest. Many aspects of singlet oxygen chemistry have emanated from the work of Christopher S. Foote and co-workers. Singlet oxygen is a historically interesting molecule with an unusual story connected with its discovery. Foote and Wexler conducted experiments in the 1960s where evidence was obtained supporting $^1\text{O}_2$ generation via two independent routes: (1) a photochemical reaction (dye-sensitized photooxidation) and (2) a chemical reaction (NaOCl with H_2O_2). An important factor in the discovery of $^1\text{O}_2$ as the critical reaction intermediate in dye-sensitized photooxygenations was Foote's reassessment of the chemical literature of the 1930s, when $^1\text{O}_2$ was suggested to be a viable intermediate in dye-sensitized photooxidation reactions. Experiments that used silica gel beads provided evidence for a volatile diffusible oxidant such as $^1\text{O}_2$. However, a contemporaneous quarrel surrounded this early work, and the possible existence of solution-phase $^1\text{O}_2$ was ignored for over 2 decades. Not long after Foote's initial studies were published in 1964, the idea of singlet oxygen as an intermediate in photooxidation chemistry gained increasing recognition and verification in organic, gas phase, and biological processes. There are many documented impacts that $^1\text{O}_2$ has had and continues to have on biology and medicine, for example, photodynamic therapy and plant defenses.

Introduction

Christopher S. Foote (June 5, 1935–June 13, 2005) was a leading authority on chemical reactions involving singlet

molecular oxygen [$^1\text{O}_2$ ($^1\Delta_g$)]. I was mentored by Foote in 1997–1999 as a postdoctoral fellow in chemistry at UCLA. This Account is presented in his memory and represents a tribute to his research efforts. It describes how his early work shaped current thinking in oxidation chemistry and photochemistry.^{1–5} Two ground-breaking papers were published in the *Journal of the American Chemical Society* in 1964 by Foote and Wexler^{6,7} based on work conducted in the Department of Chemistry and Biochemistry at UCLA. The work was soon followed by a classic paper that appeared in *Accounts of Chemical Research* in 1968.⁸ These papers reported that the oxidation of organic molecules by NaOCl and H_2O_2 yielded near identical product distributions from those generated independently in dye-sensitized photooxidations. A total of 42 years ago, the following comments were made “*the weight of evidence favors the intermediacy of singlet oxygen. Further experiments are in progress.*”⁷ Foote's suggestion for the intermediacy of $^1\text{O}_2$ is now widely accepted. Subsequent developments led to interest in other $^1\text{O}_2$ -mediated processes in organic and biological reactions.

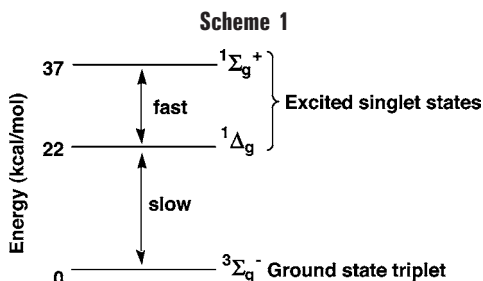
History of Photooxidation Research

The history of research on photooxidation processes dates back to the 19th century. In the late 1800s, biologists discovered that dyes, oxygen, and light are toxic to

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organisms such as paramecia. Photochemical reactions involving oxygen were found to result in oxygenation of biological material via an unknown photooxidation mechanism. At the time, little was known about the viability of reactive intermediates, the mechanism of oxygen uptake in biological systems, and the chemistry underlying the toxicity. Even knowledge of the spin-state properties of molecular oxygen was lacking. In 1924, G. N. Lewis proposed that ground-state molecular oxygen was a triplet diradical species.⁹ Molecular orbital descriptions of triplet ground-state O₂ and excited singlet delta (¹Δ) and excited singlet sigma (¹Σ) O₂ were provided by Mulliken in the late 1920s (Scheme 1).^{10,11}

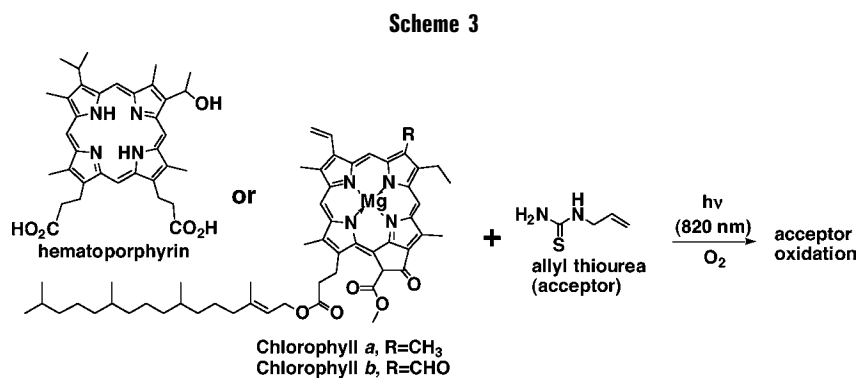
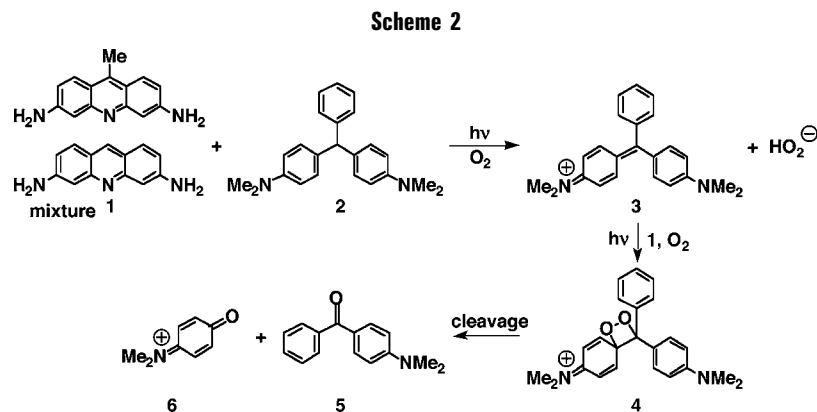


Spectroscopic techniques to detect short-lived intermediates were not available at that time, and a mechanistic explanation of the photooxidation chemistry of organic and biological materials floundered in the early 20th century. However, in 1931, Kautsky and de Bruijn conducted a brilliant series of experiments at the University of Heidelberg.¹² A dye (tryptaflavine, **1**) and an oxygen-acceptor compound (leucomalachite green, **2**) were ad-

sorbed separately on SiO₂ gel beads that were 1.2 and 0.23 mm in size, respectively. These were then mixed and irradiated in the presence of O₂ (Scheme 2).^{12,13} Oxidation of **2** took place to give malachite green (**3**) and **5** and **6**, presumably by the pathway shown in Scheme 2. The chemistry was found not to be due to diffusion of **1** or **2**, which remained attached to the original beads. The oxygen source was found not to be H₂O. Because **1** and **2** were separated by several millimeters and the compounds were not adsorbed on the same gel granules, Kautsky's "three-phase test" suggested the formation of a diffusible O₂ species, assumed to be in the ¹Σ_g⁺ state.¹²⁻¹⁴ Kautsky was challenged almost immediately about his mechanistic interpretation involving ¹O₂.

Contemporary skepticism about the notion of a singlet oxygen intermediate was widespread. In 1935, Gaffron reported that infrared irradiation (820 nm) of bacteriochlorophyll or hematoporphyrin in the presence of O₂ resulted in the oxidation of a thiosinamine (allyl thio-urea) acceptor (Scheme 3).¹⁵ He argued that the ¹Σ_g⁺ state (37 kcal/mol) could not possibly form by energy transfer from a dye emitting at 820 nm, corresponding to 35 kcal/mol.¹⁶ Terenin and others made similar arguments, noting that the intermediacy of singlet oxygen (¹Σ_g⁺) in Kautsky's experiment could be ruled out based on energetics, given insufficient energy associated with emission at 820 nm.¹⁷

Kautsky published a rebuttal indicating that the singlet delta state, ¹O₂ (¹Δ_g), was estimated to be 22 kcal/mol above the ground state.¹⁸ His polemic against Gaffron suggested that the quenching of chlorophyll luminescence by O₂ in plants could lead to ¹O₂ (¹Δ_g) but not



configurations	state of molecular oxygen
$[\pi_x \uparrow \pi_y \downarrow] - [\pi_x \downarrow \pi_y \uparrow]$	${}^1\text{O}_2 ({}^1\Sigma_g^+)$ 2 nd excited state
$[\pi_x \uparrow \pi_y \uparrow] - [\pi_x \downarrow \pi_y \downarrow]$	${}^1\text{O}_2 ({}^1\Delta_g)$ 1 st excited state
$[\pi_x \uparrow \pi_y \uparrow] + [\pi_x \downarrow \pi_y \downarrow]$ $[\pi_x \downarrow \pi_y \downarrow] + [\pi_x \uparrow \pi_y \uparrow]$	${}^3\text{O}_2 ({}^3\Sigma_g^-)$ ground state

FIGURE 1. Spin-orbital diagrams for the ground and first two excited states of O_2 .²⁰

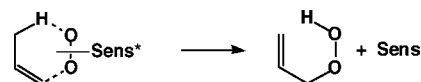
${}^1\text{O}_2 ({}^1\Sigma_g^+)$.¹⁹ (The distribution of the two electrons in the highest orbitals for the ${}^1\Sigma$, ${}^1\Delta$, and ${}^3\Sigma$ states are shown in Figure 1.)²⁰ The caveat was that the energy of the ${}^1\Delta$ state had not been characterized with certainty. Kautsky was perhaps the only scientist at the time to hold this view.

Noticeably absent from the literature of that period are references to Kautsky's rebuttal, published in a biochemical journal.¹⁸ Three possible reasons are the following: (i) the dilemma about the accuracy of the energetics measured for the ${}^1\Delta_g$ state; (ii) the onset of World War II may have diverted attention from the topic; and (iii) at the time, there was a vigorous debate about the nature of biological oxidations, which concerned mechanisms of oxidation versus dehydrogenation. One of the protagonists was Otto Warburg. In the 1930s, progress was made with Warburg's discovery of "yellow enzyme" containing what is now known as flavin adenine dinucleotide (FAD).^{21,22} A few years later, diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN), now known as NAD and NADP, were discovered, and slowly, the biochemical mechanisms began to be unraveled. It is possible that Kautsky's work was overshadowed by major controversies about mechanisms of "natural" biological oxidations.²³

Opinions in the papers on photooxidation in the following 2 decades (~1940–1963) were one-sided. The paradigm in vogue at the time attributed O_2 uptake in photooxidation reactions to an excited sensitizer–oxygen adduct.^{24–26} Individuals working in this field, many of whom were highly opinionated, discounted the contribution of ${}^1\text{O}_2 ({}^1\Delta_g)$. Blum surveyed the literature in a selective manner and concluded that a sensitizer–oxygen complex is the key reactive intermediate.²⁷ Bowen²⁸ and Livingston²⁹ conducted work in the area and considered various mechanisms, but their papers usually suggested the involvement of a "sensitizer oxygen complex". The thought that ${}^1\text{O}_2 ({}^1\Delta_g)$ had been ruled out as an intermediate persisted into the 1960s. In 1964, fully 23 years after Kautsky, Gollnick and Schenck³⁰ reported a moloxide version ('Sens–OO') of the ${}^1\text{O}_2$ "ene" reaction of alkenes to give allylic hydroperoxides, where the double bond has shifted (Scheme 4).

In 1963–1964, the contributions of Michael Kasha and independently Elmer A. Ogryzlo advanced the field in a very important way. Kasha and Khan detected the red

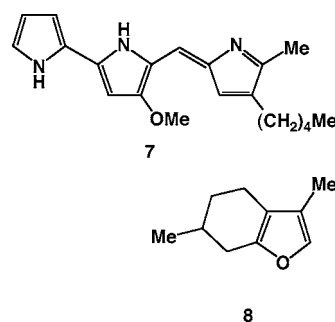
Scheme 4



chemiluminescence of ${}^1\text{O}_2$ in $\text{NaOCl-H}_2\text{O}_2$ solutions and attributed this to the emission of pairs of ${}^1\text{O}_2$ molecules.^{31–33} Ogryzlo and co-workers found evidence for dimol complexes [$2 {}^1\text{O}_2 ({}^1\Delta_g)$] in electric discharge (gas phase) reactions of molecular oxygen.^{34–36} Singlet oxygen luminescence was established in the gas and condensed phases. Pathways where ${}^1\text{O}_2$ decays to ${}^3\text{O}_2 + h\nu$ [1268 nm (22 kcal/mol)] and where two unbound singlet oxygen molecules ($2 {}^1\text{O}_2$) decay to $2 {}^3\text{O}_2 + h\nu$ [634 nm (44 kcal/mol) and 701 nm] were reported.^{37,38}

Early Research Efforts of Christopher Foote

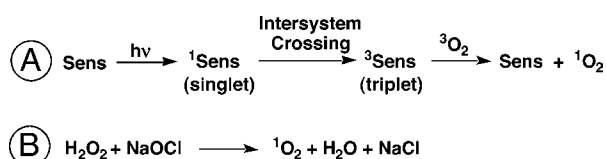
Christopher Foote was an undergraduate at Yale University about the time that many advances in photooxidations of organic compounds were being made. While an undergraduate, Foote worked with Harry H. Wasserman and carried out preparation of the red pigment prodigiosin (**7**) from cultures of *Serratia marcescens*. Wasserman was interested in the photooxidation of pyrroles, such as those present in this pigment.³⁹ In 1957, Foote received a Fulbright scholarship and spent a year at the University of Göttingen with G. O. Schenck. There, Foote investigated the rose bengal-sensitized photooxidation of menthofuran (**8**) in methanol solvent.⁴⁰ The work carried out with Wasserman and Schenck gave Foote an early involvement and understanding of photooxidations, and this later developed to his independent research on the mechanism of dye-sensitized photooxidations.



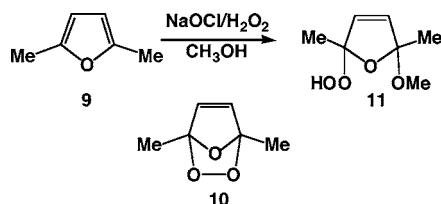
Contributions from Foote's Laboratory at UCLA

After an interlude at Harvard with R. B. Woodward, receiving his Ph.D. for Diels–Alder reactions, Foote began his independent career at UCLA. In the 1960s, new techniques were required to study the mechanisms of photooxidation reactions. Kautsky's idea of a dye-sensitized photochemical route to ${}^1\text{O}_2 ({}^1\Delta_g)$ languished until experiments were conducted by Foote and Wexler.^{6,7} Their evidence supported ${}^1\text{O}_2$ generation via two independent routes: (1) a photochemical reaction (dye-sensitized photooxidation, Scheme 5A), and (2) a chemical reaction (NaOCl with H_2O_2 , Scheme 5B). For example, in methanol, 2,5-dimethylfuran (**9**) gave 2,5-dimethyl-2-hydroperoxy-5-methoxydihydrofuran (**11**) in 84% yield by reaction with

Scheme 5



Scheme 6

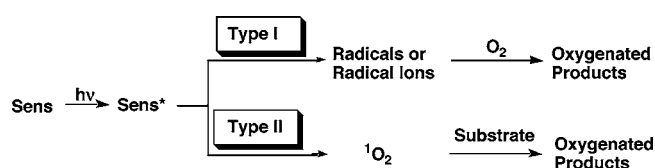


NaOCl (1.0 M) and H_2O_2 (0.18 M), while 74% was obtained from photooxidation (Scheme 6). The oxidant in the dye-sensitized photooxidation reaction in dilute homogeneous solution was essentially indistinguishable from that in the reaction of NaOCl with H_2O_2 , known at the time to yield ${}^1\text{O}_2$.^{31,32}

In the 1960s, energy transfer was a hot topic, mainly because of the pioneering work by George Hammond and his co-workers at Caltech. Foote shared an interest in this subject and proposed that energy transfer takes place between triplet sensitizers and ground-state molecular oxygen (${}^3\text{O}_2$), to yield the ground-state of the sensitizer and ${}^1\text{O}_2$ (${}^1\Delta_g$). Reactions of other hydrocarbon acceptors (e.g., 2,3-dimethyl-2-butene, 1,3-cyclohexadiene, $\Delta^9,10$ -octalin, and tetraphenylcyclopentadienone, all of which react with ${}^1\text{O}_2$ at double bonds) confirmed the parallel between reactions (1) and (2).^{6,41} Foote's classic paper in the first volume of *Accounts of Chemical Research* in 1968 emphasized this parallelism and summarized the results of oxygenation of a variety of alkenes and dienes.⁸ Foote described ${}^1\text{O}_2$ as "biologically important". Stereoselectivity and substituent effects on product distributions and reaction rates in singlet oxygen reactions were assessed. For the first time, the reactivity of ${}^1\text{O}_2$ could be judged against that of other reactive oxygen species. Hydroxyl radicals were found to be far more reactive than ${}^1\text{O}_2$, while nitric oxide (NO) was found to be far less reactive; the selectivity of the latter was found to be sufficiently high to enable reactions with other radical species. Superoxide was found to be of very low reactivity compared to ${}^1\text{O}_2$. Prior to this time, no practical method was available for comparing the chemistry and reactivity of ${}^1\text{O}_2$ with other reactive oxygen species.

The work of Foote constitutes an important milestone in the history of singlet oxygen chemistry. In 1964, Kautsky was near the end of his life, and Foote never had the opportunity to present to Kautsky the data concerning the relationship between $\text{NaOCl}-\text{H}_2\text{O}_2$ and dye-sensitized photooxidation, which supported ${}^1\text{O}_2$ generation by two completely different routes. Foote was strongly influenced by Kautsky's work, but these two did not have an opportunity to meet and discuss the subject. In addition, it is not likely that Kautsky was aware of Foote's new results prior to his death. A critical factor that was important in guiding Foote's work was his reading of Kautsky's papers

Scheme 7

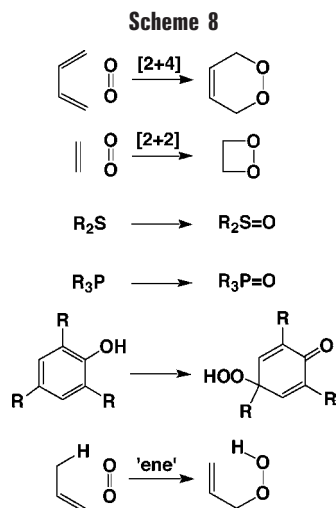


and his realization that it was ignored in subsequent reviews and monographs. This led to Foote's reassessment that singlet oxygen had not been ruled out as the critical reaction intermediate and that it was most likely the key intermediate in photosensitized oxidations. An even more direct link with Kautsky is apparent in the work of Foote published in the *Journal of the American Chemical Society* in 1978.⁴² In this paper, Wolf, Foote, and Rebek reported a heterogeneous trapping study of ${}^1\text{O}_2$, which was similar to the Kautsky three-phase test but used polymer-attached rose bengal as the sensitizer and a ${}^1\text{O}_2$ acceptor, 6-methyl-5-heptenoate, attached to a separate polymer bead.⁴²

The response to the work of Foote and Wexler resulted in contributions of other researchers to the understanding of oxidation of organic molecules by ${}^1\text{O}_2$. One such example is a paper by Corey and Taylor that was published back-to-back with Foote and Wexler's paper.^{7,43} The Corey paper was submitted soon after (June 25) Foote and Wexler's work (June 1). A method of ${}^1\text{O}_2$ production via electric discharge was applied by Corey and Taylor. In 1956, Foner and Hudson had discovered that electric discharges promoted the formation of ${}^1\text{O}_2$.⁴⁴ Molecular oxygen was passed through an electric discharge and bubbled into a solution where oxidation of acceptor molecules could take place to form products similar to those from $\text{NaOCl}-\text{H}_2\text{O}_2$ and dye-sensitized photooxidation.⁴³

Interestingly, the work of Foote and Wexler also generated skepticism. One of the most eminent scientists in the field, G. O. Schenck, whom Foote had worked for, was not persuaded that the sensitizer-oxygen intermediate should be discarded. For years, Schenck had advocated the moloxide mechanism (Scheme 4). As late as 1970, Schenck continued to suggest a sensitizer-oxygen complex (moloxide) rather than a diffusible ${}^1\text{O}_2$ species: "The complexolytic mechanism of ${}^1\text{O}_2$ formation appears to be internally consistent and free of contradictions to the presently known experimental facts."⁴⁵ Arguments in favor of excited sensitizer-oxygen complexes ceased when (i) Kopecky and Reich found that rates of photooxidation were independent of the sensitizer used⁴⁶ and (ii) Foote, Ando, and Wexler showed that sensitizers exert no steric influence on the oxygen reactivity⁴⁷ and (iii) that radical scavengers do not influence the reaction.⁴⁷ These three results are opposite to what one would expect for a sensitizer-oxygen complex. However, the product distribution was altered because of sensitizer interactions at high concentrations: xanthene and acridine dyes can abstract a hydrogen atom from the substrate, which leads to the production of radicals.⁴⁵

An appreciation for two types of photosensitized oxidation, named type I and type II, soon emerged in the field (Scheme 7).⁴⁸ Both reactions involve the absorption of light by a sensitizer (Sens) to produce an excited-state sensitizer

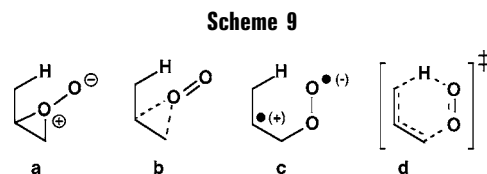


(Sens^{*}). However, type I photooxidation is a reaction where radicals or radical ions lead to the production of oxygenated compounds. Ideal sensitizer properties and experimental conditions that favor the singlet oxygen (type II) pathway include (i) a low sensitizer and O₂ concentration, (ii) a high intersystem crossing yield of the sensitizer, (iii) a low chemical reactivity of the sensitizer triplet state, and (iv) a small singlet–triplet splitting of the sensitizer. Competition between type I and II photooxidation chemistry is inevitable upon the formation of an excited sensitizer in the presence of ³O₂. Thermal processes to generate ¹O₂ represent alternatives to photosensitized oxidation. Decomposition of triphenylphosphite ozonide,⁴⁹ photoperoxides [9,10-diphenylanthracene endoperoxide, 1,4-dimethylnaphthalene endoperoxide, and 3,3'-(1,4-naphthalene)dipropionate endoperoxide],^{50–55} heterocycle–O₃ adducts (pyrroles, oxazoles, and imidazoles),⁵⁶ and a sodium molybdate (Na₂MoO₄)–hydrogen peroxide system⁵⁷ have come to be widely applied as thermal sources of ¹O₂.

Singlet Oxygen Unveiled as a Synthetic and Biological Agent

The idea that ¹O₂ is an intermediate in organic chemistry and biology signified an important break with the past. Researchers quickly recognized that ¹O₂ reactions had great synthetic utility for generating oxygenated hydrocarbons, such as endoperoxides from [2 + 4] cycloadditions, dioxetanes from [2 + 2] cycloadditions, sulfoxides from sulfide oxidations, phosphine oxides from phosphine oxidations, and hydroperoxides from phenol oxidations and “ene” reactions (Scheme 8).^{4,5,8,58}

A number of papers of Foote and co-workers focused on the reaction of singlet oxygen with phosphines, sulfides, organometallic complexes, and conjugated and nonconjugated olefins.^{59–68} The “ene” reaction of singlet oxygen with olefins was a topic of particular interest. When I was a postdoctoral fellow in Foote's group, I examined how singlet oxygen undergoes “ene” reactions and why there had been such a difficulty in understanding this from an experimental point of view.⁶⁹ Perepoxyde (a), exciplex (b), and diradical and zwitterionic intermediates (c) had been proposed, in addition to a concerted



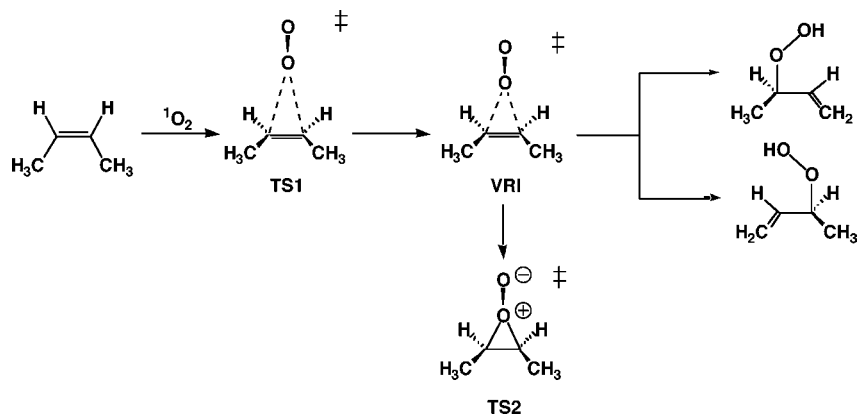
reaction via transition-state d (Scheme 9). The research groups of Foote, Houk, and Singleton came together in this effort to collect computational and experimental data. Measured ¹³C and literature ²H isotope effects were used to gauge the accuracy of the computations. Single-point energy calculations at the CCSD(T) level on a grid of B3LYP-optimized geometries predicted that the ¹O₂ “ene” reaction with *cis*-2-butene contained a valley-ridge inflection (VRI). Two transition states are connected sequentially on a pathway that bifurcates at the VRI point prior to TS2 to give allylic hydroperoxide products (Scheme 10). Previous to this work, there was a struggle to understand the role of the perepoxyde species, i.e., whether or not it was a viable reaction intermediate. The theory suggests that the perepoxyde is not a minimum on the potential energy surface. Important kinetic isotopic selectivity and regioselectivity information was also deduced from the consideration of calculated dynamical effects.^{70–72}

A biological example of the ¹O₂ “ene” reaction is in lipid peroxidation processes, where a shift in the double bond takes place. For example, ¹O₂ adds –OOH to linoleoyl groups at the 9', 10', 12', and 13' positions (Scheme 11).⁷³ Oxygen radical attack, in contrast, yields only the conjugated 9' and 13' hydroperoxides. Thus, the product distribution can be used to distinguish between ¹O₂- and radical-mediated lipid peroxidation.^{73–78}

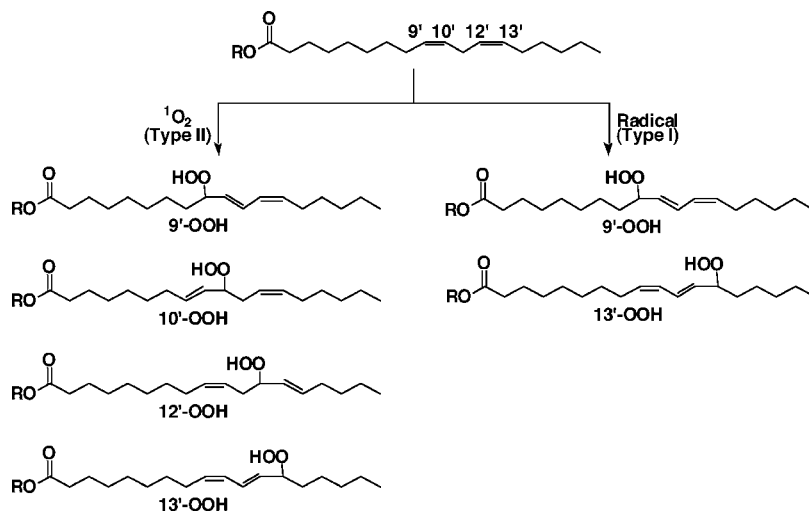
Foote had considerable enthusiasm and excitement about future prospects for singlet oxygen in chemistry and biochemistry. He published many papers to establish mechanisms of biological oxidations, such as the photooxidation of bilirubin and guanosine and ascorbic acid derivatives.^{79–84} The photooxidation of biological-model compounds often provided new mechanistic insights. For example, in 2004, a comprehensive study of the reaction of ¹O₂ with 2',3',5'-tris-(*O*-*tert*-butyldimethylsilyl)guanosine (**12**) was reported (Scheme 12).⁸² Unstable products were detected by low-temperature nuclear magnetic resonance (NMR) and ¹³C-labeling. A mechanism was suggested for the conversion of guanosine **12** to 8-oxoG (**13**). The subsequent photooxidation of **13** yields 5-hydroperoxy-8-oxo-7,8-dihydroguanosine (**14**) at low temperature. Reduction of **14** yields the corresponding alcohol (**15**), which rearranges to a stable final product spirodiimidohydroantoin (**16**).

Fueled by the Foote and Wexler effort, the number of scientists examining ¹O₂ continued to grow.^{85,86} The role of singlet oxygen in photodynamic action was established,^{87–89} it arises from the high reactivity of ¹O₂ with biomolecules (e.g., membranes and lipids), amino acids (e.g., His, Trp, and Met), and nucleic acids (e.g., guanosine). Anthropogenic sensitizers (dyes, pharmaceuticals, and cosmetics) can serve as oxygen-dependent photodynamic agents and produce singlet oxygen. A number of natural products can also “sensitize” organisms to pho-

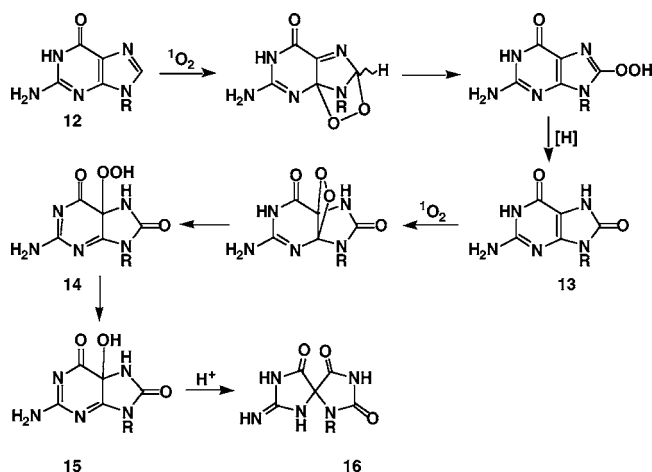
Scheme 10



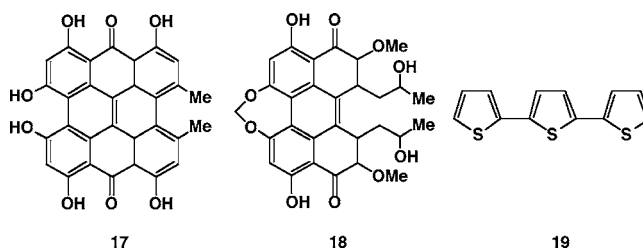
Scheme 11



Scheme 12



Scheme 13



presence of light and oxygen, compounds 17–19 give singlet oxygen in high yield.

Conclusion

A total of 42 years after its publication, Foote's work has possessed considerable significance. Not long after Foote's initial studies were published in 1964, the idea of singlet molecular oxygen as a critical intermediate in photooxidation chemistry gained increasing recognition and subsequent verification for organic, gas phase, and biological processes. The importance of $^1\text{O}_2$ is now fully realized along with proof of its existence in a variety of oxidation reactions. Today, little of the moloxide mechanism remains except for situations involving high sensitizer concentrations, where radical or electron-transfer oxidation (type I) processes can take place. The chemistry of

tochemical damage by oxygen (e.g., chlorophyll, non-iron porphyrins, flavins, polyacetylenes, other plant pigments, and mold toxins).^{90–93} Hypericin (St. John's Wort, 17) represents a natural photooxidation photosensitizer with antitumor and anti-HIV activity; it is sold over the counter and touted to be an antidepressant agent (Scheme 13). Other examples include cercosporin (18), which is a photodynamic mold toxin, and α -terthienyl (19), which is a photodynamic insecticide from marigolds. In the

singlet oxygen remains a focus of exciting and cutting-edge research in chemistry, biology, and medicine.

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References

- (1) (a) Adam, W. The Singlet Oxygen Story. *Chem. Unserer Zeit* **1981**, *15*, 190–196. (b) Ranby, B. The History of Singlet Oxygen. An Introduction. *Kem. Tidskr.* **1981**, *93*, 36–37.
- (2) *Benchmark Papers in Organic Chemistry, Vol. 5: Singlet Molecular Oxygen*; Schaap, A. P., Ed.; Halsted Press: Stroudsburg, PA, 1976.
- (3) Foote, C. S. An Ancient Problem. *CHEMTECH* **1976**, *6*, 612–613.
- (4) *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press, Inc.: New York, 1979.
- (5) *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 1.
- (6) Foote, C. S.; Wexler, S. Olefin Oxidations with Excited Singlet Molecular Oxygen. *J. Am. Chem. Soc.* **1964**, *86*, 3879–3880.
- (7) Foote, C. S.; Wexler, S. Singlet Oxygen. A Probable Intermediate in Photosensitized Autoxidations. *J. Am. Chem. Soc.* **1964**, *86*, 3880–3881.
- (8) Foote, C. S. Photosensitized Oxygenations and the Role of Singlet Oxygen. *Acc. Chem. Res.* **1968**, *1*, 104–110.
- (9) Lewis, G. N. The Magnetochemical Theory. *Chem. Rev.* **1924**, *1*, 231–248.
- (10) Mulliken, R. S. Interpretation of the Atmospheric Oxygen Bands: Electronic Levels of the Oxygen Molecule. *Nature* **1928**, *122*, 505–505.
- (11) Mulliken, R. S. The Interpretation of Band Spectra: Part III. Electron Quantum Numbers and States of Molecules and Their Atoms. *Rev. Mod. Phys.* **1932**, *4*, 54–56.
- (12) Kautsky, H.; de Bruijn, H. The Explanation of the Inhibition of Photoluminescence of Fluorescent Systems by Oxygen: The Formation of Active, Diffusing Oxygen Molecules by Sensitization. *Naturwissenschaften* **1931**, *19*, 1043–1043.
- (13) Kautsky, H.; de Bruijn, H.; Neuwirth, R.; Baumeister, W. Energy Transfers at Surfaces. VII. Photosensitized Oxidation Mediated by a Reactive, Metastable State of the Oxygen Molecule. *Ber.* **1933**, *66B*, 1588–1600.
- (14) Kautsky, H.; Hirsch, A.; Flesch, W. Energy Transformations on Boundary Surfaces. VIII. The Significance of the Metastable State in Photosensitized Oxidations. *Ber.* **1935**, *68B*, 152–162.
- (15) Gaffron, H. The Mechanism of Oxygen Activation by Illuminated Dyes. II. Photooxidation in the Near Infrared. *Ber.* **1935**, *68B*, 1409–1411.
- (16) Gaffron, H. Metastable Oxygen and Carbon Dioxide Assimilation. *Biochem. Z.* **1936**, *287*, 130–139.
- (17) Terenin, A. N. The Nature of the Photochemical Action in Sensitized Oxygen Oxidation Reactions and Hydroperoxide Breakdown Reactions. *Akad. Nauk S.S.S.R.* **1955**, 85–91.
- (18) Kautsky, H. Reciprocal Action between Sensitizers and Oxygen in Light. *Biochem. Z.* **1937**, *291*, 271–284.
- (19) Kautsky, H. Quenching of Luminescence by Oxygen. *Trans. Faraday Soc.* **1939**, *35*, 216–219.
- (20) (a) Kasha, M. Singlet Oxygen Electronic Structure and Energy Transfer. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 1, pp 1–12. (b) Levine, I. N. *Quantum Chemistry*, 5th ed.; Prentice Hall: Upper Saddle River, NJ, 2000; pp 402–407.
- (21) Warburg, O.; Christian, W. The Yellow Oxidation Enzyme. *Biochem. Z.* **1933**, *258*, 496–498.
- (22) Warburg, O.; Christian, W. Pyridine, the Hydrogen-Transferring Component of the Fermentation Enzymes. (Pyridine Nucleotide). *Biochem. Z.* **1936**, *287*, 291–328.
- (23) A good historical account of biological oxidation, including Warburg's work, is the following: *Molecules and Life. Historical Essays on the Interplay of Chemistry and Biology*; Fruton, J. S., Ed.; Wiley-Interscience: New York, 1972. There is no mention of Kautsky's work in this book.
- (24) Schönberg, v. A. Notiz über die Photochemische Bildung von Biradikalen. *Liebigs Ann. Chem.* **1935**, *518*, 299–302.
- (25) Schenck, G. O. Photosensitized Reactions with Molecular Oxygen. *Naturwissenschaften* **1948**, *35*, 28–29.
- (26) One exception appeared, suggesting that photooxidation reactions resulted from a vibrationally (not electronically) excited form of O₂. Rosenberg, J. L.; Shombert, D. J. The Reaction of Oxygen with Electronically Excited Acriflavine. *J. Am. Chem. Soc.* **1960**, *82*, 3257–3260.
- (27) Blum, H. F. Physiological Effects of Sunlight on Man. *Physiol. Rev.* **1945**, *25*, 483–530.
- (28) Bowen, E. J. Photochemistry of Anthracene. II. The Photooxidation of Anthracenes in Solution. *Discuss. Faraday Soc.* **1953**, *14*, 143–146.
- (29) Livingston, R. S. Chemical Changes Produced by Radiation. *Conf. Biol. Antioxid., Trans.* **1950**, *5*, 17–40.
- (30) Gollnick, K.; Schenck, G. O. Mechanism and Stereoselectivity of Photosensitized Oxygen Transfer Reactions. *Pure Appl. Chem.* **1964**, *9*, 507–525. The formation of the hydroperoxide is stereospecific, where the new C–O bond bears a *cis* relationship to the C–H bond that is broken. Nickon, A.; Bagli, J. F. Photosensitized Oxygenation of Mono-olefins. *J. Am. Chem. Soc.* **1959**, *81*, 6330–6330.
- (31) Khan, A. U.; Kasha, M. Red Chemiluminescence of Molecular Oxygen in Aqueous Solution. *J. Chem. Phys.* **1963**, *39*, 2105–2106.
- (32) Khan, A. U.; Kasha, M. Rotational Structure in the Chemiluminescence Spectrum of Molecular Oxygen in Aqueous Systems. *Nature* **1964**, *204*, 241–243.
- (33) Khan, A. U.; Kasha, M. Chemiluminescence Arising from Simultaneous Transitions in Pairs of Singlet Oxygen Molecules. *J. Am. Chem. Soc.* **1970**, *92*, 3293–3300.
- (34) Arnold, S. J.; Ogryzlo, E. A.; Witzke, H. Some New Emission Bands of Molecular Oxygen. *J. Chem. Phys.* **1964**, *40*, 1769–1770.
- (35) Bader, L. W.; Ogryzlo, E. A. Reactions of ¹O₂ (¹Δ_g) and ¹O₂ (¹Σ_g⁺). *Discuss. Faraday Soc.* **1964**, 46–56.
- (36) Arnold, J. S.; Browne, R. J.; Ogryzlo, E. A. The Red Emission Bands of Molecular Oxygen. *Photochem. Photobiol.* **1965**, *4*, 963–969.
- (37) Infrared detection and the use of lasers that can produce short pulses with nanosecond time resolution provided evidence for the luminescence (1268 nm) of ¹O₂ (¹Δ_g → ³Σ_g⁻). Direct evidence showed that ¹O₂ (¹Δ_g) can be formed by energy transfer from an excited sensitizer and ³O₂ in solution. (a) Krasnovskii, A. A., Jr. Photosensitized Luminescence of Singlet Oxygen in Solution. *Biofizika* **1976**, *21*, 748–749. (b) Khan, A. U.; Kasha, M. Direct Spectroscopic Observation of Singlet Oxygen Emission at 1268 nm Excited by Sensitizing Dyes of Biological Interest in Liquid Solution. *Proc. Nat. Acad. Sci. U.S.A.* **1979**, *76*, 6047–6049. (c) Hurst, J. R.; McDonald, J. D.; Schuster, G. B. Lifetime of Singlet Oxygen in Solution Directly Determined by Laser Spectroscopy. *J. Am. Chem. Soc.* **1982**, *104*, 2065–2067. (d) Ogilby, P. R.; Foote, C. S. Chemistry of Singlet Oxygen. 36. Singlet Molecular Oxygen (¹Δ_g) Luminescence in Solution Following Pulsed Laser Excitation. Solvent Deuterium Isotope Effects on the Lifetime of Singlet Oxygen. *J. Am. Chem. Soc.* **1982**, *104*, 2069–2070.
- (38) Singlet oxygen (¹Δ_g) was also detected in the gas-phase by EPR. (a) Wasserman, E.; Murray, R. W.; Kaplan, H. L.; Yager, Y. A. Electron Paramagnetic Resonance of ¹Δ Oxygen from a Phosphite–Ozone Complex. *J. Am. Chem. Soc.* **1968**, *90*, 4160–4161. (b) Kearns, D. R.; Khan, A. U.; Duncan, C. K.; Maki, A. H. Detection of the Naphthalene-Photosensitized Generation of Singlet ¹Δ Oxygen by Paramagnetic Resonance Spectroscopy. *J. Am. Chem. Soc.* **1969**, *91*, 1039–1040. (c) Wasserman, E.; Kuck, V. J.; Delavan, W. M.; Yager, Y. A. Electron Paramagnetic Resonance of ¹Δ Oxygen Produced by Gas-Phase Photosensitization with Naphthalene Derivatives. *J. Am. Chem. Soc.* **1969**, *91*, 1040–1041.
- (39) Wasserman, H. H.; Liberles, A. Formation of Epoxides in the Pyrrole and Furan Series by Photooxidation. *J. Am. Chem. Soc.* **1960**, *82*, 2086.
- (40) Schenck, G. O.; Foote, C. S. Über die Photosensibilisierte Autoxydation von Menthofuran. *Angew. Chem.* **1958**, *70*, 505.
- (41) Foote, C. S.; Wexler, S.; Ando, W.; Higgins, R. Chemistry of Singlet Oxygen. IV. Oxygenations with Hypochlorite–Hydrogen Peroxide. *J. Am. Chem. Soc.* **1968**, *90*, 975–981.
- (42) Wolf, S.; Foote, C. S.; Rebeck, J., Jr. Chemistry of Singlet Oxygen. 29. Three-Phase “Kautsky Test” for Singlet Oxygen. *J. Am. Chem. Soc.* **1978**, *100*, 7770–7771. Other studies that are reminiscent of the Kautsky experiments include Midden, W. R.; Wang, S. Y. Singlet Oxygen Generation for Solution Kinetics: Clean and Simple. *J. Am. Chem. Soc.* **1983**, *105*, 4129–4135 and Eisenberg, W. C.; Taylor, K.; Murray, R. W. Gas-Phase Kinetics of the Reaction of Singlet Oxygen with Olefins at Atmospheric Pressure. *J. Phys. Chem.* **1986**, *90*, 1945–1948.

- (43) Corey, E. J.; Taylor, W. C. A Study of the Peroxidation of Organic Compounds by Externally Generated Singlet Oxygen Molecules. *J. Am. Chem. Soc.* **1964**, *86*, 3881–3882.
- (44) Foner, S. N.; Hudson, R. L. Metastable Oxygen Molecules Produced by Electrical Discharge. *J. Chem. Phys.* **1956**, *25*, 601–602.
- (45) Schenck, G. O. Mechanism of Formation of Singlet Oxygen in Photosensitized Oxygenation. *Ann. N. Y. Acad. Sci.* **1970**, *171*, 67–78.
- (46) Kopecky, K. R.; Reich, H. J. Reactivities in Photosensitized Olefin Oxidations. *Can. J. Chem.* **1965**, *43*, 2265–2270.
- (47) Foote, C. S.; Wexler, S.; Ando, W. Chemistry of Singlet Oxygen. III. Product Selectivity. *Tetrahedron Lett.* **1965**, *46*, 4111–4118.
- (48) Foote, C. S. in *Free Radicals in Biology*; Pryor, W. A., Ed.; Academic Press: New York, 1976; pp 85–133.
- (49) Bartlett, P. D.; Mendenhall, G. D. Evidence for a Duality of Mechanism in the Oxidation Reactions of Triphenyl Phosphite Ozonide. *J. Am. Chem. Soc.* **1970**, *92*, 210–211.
- (50) Wasserman, H. H.; Scheffer, J. R. Singlet Oxygen Reactions from Photoperoxides. *J. Am. Chem. Soc.* **1967**, *89*, 3073–3075.
- (51) Stevens, B. Kinetics of Photoperoxidation in Solution. *Acc. Chem. Res.* **1973**, *6*, 90–96.
- (52) Wasserman, H. H.; Scheffer, J. R.; Cooper, J. C. Singlet Oxygen Reactions with 9,10-Diphenyl Peroxide. *J. Am. Chem. Soc.* **1972**, *94*, 4991–4996.
- (53) Wasserman, H. H.; Larsen, D. L. Formation of 1,4-Endoperoxides from the Dye-Sensitized Photooxygenation of Alkyl-naphthalenes. *Chem. Commun.* **1972**, 253–254.
- (54) Saito, I.; Matsuura, T.; Inoue, K. Formation of Superoxide Ion from Singlet Oxygen. On the Use of a Water Soluble Singlet Oxygen Source. *J. Am. Chem. Soc.* **1981**, *103*, 188–190.
- (55) Di Mascio, P.; Sies, H. Quantification of Singlet Oxygen Generated by Thermolysis of 3,3'-(1,4-Naphthylene)dipropionate Endoperoxide. Monomol and Dimol Photoemission and the Effects of 1,4-Diazabicyclo[2.2.2]octane. *J. Am. Chem. Soc.* **1989**, *111*, 2909–2914.
- (56) Wasserman, H. H.; Yoo, J. U.; DeSimone, R. W. Singlet Oxygen Reactions from the Adducts of Ozone with Heterocycle Substrates. *J. Am. Chem. Soc.* **1995**, *117*, 9772–9773.
- (57) Aubry, J.-M.; Bouttemy, S. Preparative Oxidation of Organic Compounds in Microemulsions with Singlet Oxygen Generated Chemically by the Sodium Molybdate/Hydrogen Peroxide System. *J. Am. Chem. Soc.* **1997**, *119*, 5286–5294.
- (58) *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 2–4.
- (59) An abbreviated list of Foote's publications is provided.^{60–69}
- (60) Foote, C. S.; Denny, R. W. Chemistry of Singlet Oxygen. XIII. Solvent Effects on the Reaction with Olefins. *J. Am. Chem. Soc.* **1971**, *93*, 5168–5171.
- (61) Manning, L. E.; Kanner, R. C.; Foote, C. S. Chemistry of Singlet Oxygen. 43. Quenching by Conjugated Olefins. *J. Am. Chem. Soc.* **1983**, *105*, 4707–4710.
- (62) Liang, J. J.; Gu, C. L.; Kacher, M. L.; Foote, C. S. Chemistry of Singlet Oxygen. 45. Mechanism of the Photooxidation of Sulfides. *J. Am. Chem. Soc.* **1983**, *105*, 4717–4721.
- (63) Jensen, F.; Foote, C. S. Chemistry of Singlet Oxygen. 48. Isolation and Characterization of the Primary Photoproducts from Photooxidation of Catechols. *Photochem. Photobiol.* **1983**, *46*, 325–330.
- (64) Orfanopoulos, M.; Foote, C. S. Intermediate in the Ene Reaction of Singlet Oxygen with 1,4-Diphenyl-*cis*-2-butene and 2-Butene. *J. Am. Chem. Soc.* **1988**, *110*, 6583–6584.
- (65) O'Shea, K. E.; Foote, C. S. Chemistry of Singlet Oxygen. 51. Zwitterionic Intermediates from 2,4-Hexadienes. *J. Am. Chem. Soc.* **1988**, *110*, 7167–7170.
- (66) Selke, M.; Foote, C. S. Reactions of Organometallic Complexes with Singlet Oxygen. Photooxidation of Vaska's Complex. *J. Am. Chem. Soc.* **1993**, *115*, 1166–1167.
- (67) Nahm, K.; Li, Y.; Evanseck, J. D.; Houk, K. N.; Foote, C. S. Structures and Energies of Intermediates in the Reactions of Singlet Oxygen with Organic Phosphines and Sulfides. *J. Am. Chem. Soc.* **1993**, *115*, 4879–4884.
- (68) The photophysics and photochemistry of fullerenes was also studied, e.g., Arbogast, J. W.; Darmanyan, A. P.; Foote, C. S.; Diederich, F. N.; Whetten, R. L.; Rubin, Y.; Alvarez, M. M.; Anz, S. J. Photophysical Properties of Sixty Atom Carbon Molecule (C₆₀). *J. Phys. Chem.* **1991**, *95*, 11–12.
- (69) Singleton, D. A.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. Mechanism of Ene Reactions of Singlet Oxygen. A Two-Step No-Intermediate Mechanism. *J. Am. Chem. Soc.* **2003**, *125*, 1319–1328.
- (70) Singleton, D. A.; Hang, C.; Szymanski, M. J.; Greenwald, E. E. A New Form of Kinetic Isotope Effect. Dynamic Effects on Isotopic Selectivity and Regioselectivity. *J. Am. Chem. Soc.* **2003**, *125*, 1176–1177.
- (71) Doubleday, C.; Suhrada, C. P.; Houk, K. N. Dynamics of the Degenerate Rearrangement of Bicyclo[3.1.0]hex-2-ene. *J. Am. Chem. Soc.* **2006**, *128*, 90–94.
- (72) Carpenter, B. K. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Jr., Eds.; Wiley: Hoboken, NJ, 2004; pp 925–960.
- (73) Stratton, S. P.; Liebler, D. C. Determination of Singlet Oxygen-Specific versus Radical-Mediated Lipid Peroxidation in Photosensitized Oxidation of Lipid Bilayers: Effect of β -Carotene and α -Tocopherol. *Biochemistry* **1997**, *36*, 12911–12920. See also refs 74–78.
- (74) Thomas, M. J.; Shirley, P. S.; Hedrick, C. C.; DeChatelet, L. R. Role of Free Radical Processes in Stimulated Human Polymorphonuclear Leukocytes. *Biochemistry* **1986**, *25*, 8042–8048.
- (75) Schafer, F. Q.; Buettner, G. R. Singlet Oxygen Toxicity Is Cell Line-Dependent: A Study of Lipid Peroxidation in Nine Leukemia Cell Lines. *Photochem. Photobiol.* **1999**, *70*, 858–867.
- (76) Girotti, A. W. Photosensitized Oxidation of Membrane Lipids: Reaction Pathways, Cytotoxic Effects, and Cytoprotective Mechanisms. *J. Photochem. Photobiol., B* **2001**, *63*, 103–113.
- (77) Niziolek, M.; Korytowski, W.; Girotti, A. W. Self-Sensitized Photodegradation of Membrane-Bound Protoporphyrin Mediated by Chain Lipid Peroxidation: Inhibition by Nitric Oxide with Sustained Singlet Oxygen Damage. *Photochem. Photobiol.* **2005**, *81*, 299–305.
- (78) Nelson, M. J.; Seitz, S. P. The Mechanism of Lipoyxygenases. In *Active Oxygen in Biochemistry*; Valentine, J. S., Foote, C. S., Greenberg, A., Liebman, J. L., Eds.; Blackie Academic and Professional: New York, 1995; Vol. 3, pp 276–312.
- (79) Foote, C. S. Photooxidation of Biological Model Compounds. *Oxygen Oxy-Radicals Chem. Biol.* **1981**, 425–440.
- (80) Hickerson, R. P.; Prat, F.; Muller, J. G.; Foote, C. S.; Burrows, C. J. Sequence and Stacking Dependence of 8-Oxoguanine Oxidation: Comparison of One-Electron vs Singlet Oxygen Mechanisms. *J. Am. Chem. Soc.* **1999**, *121*, 9423–9428.
- (81) Bernstein, R.; Prat, F.; Foote, C. S. On the Mechanism of DNA Cleavage by Fullerenes Investigated in Model Systems: Electron Transfer from Guanosine and 8-Oxo-guanosine Derivatives to C₆₀. *J. Am. Chem. Soc.* **1999**, *121*, 464–465.
- (82) McCallum, J. E. B.; Kuniyoshi, C. Y.; Foote, C. S. Characterization of 5-Hydroxy-8-oxo-7,8-dihydroguanosine in the Photosensitized Oxidation of 8-Oxo-7,8-dihydroguanosine and Its Rearrangement to Spiroiminodihydantoin. *J. Am. Chem. Soc.* **2004**, *126*, 16777–16782.
- (83) Kwon, B. M.; Foote, C. S.; Khan, S. I. Photooxygenation of Ascorbic Acid Derivatives and Model Compounds. *J. Am. Chem. Soc.* **1989**, *111*, 1854–1860.
- (84) Foote, C. S.; Ching, T.-Y. Chemistry of Singlet Oxygen. XXI. Kinetics of Bilirubin Photooxygenation. *J. Am. Chem. Soc.* **1975**, *97*, 6209–6214.
- (85) Pryor, W. A.; Houk, K. N.; Foote, C. S.; Fukuto, J. M.; Ignarro, L. J.; Squadrito, G.; Davies, K. J. A. Free Radical Biology and Medicine: It's a Gas Man! *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2006**, *291*, R491–R511.
- (86) Recent success has led to the detection of ¹O₂ in single cells. Snyder, J. W.; Skovsen, E.; Lambert, J. D. C.; Ogilby, P. R. Subcellular, Time-Resolved Studies of Singlet Oxygen in Single Cells. *J. Am. Chem. Soc.* **2005**, *127*, 14558–14559.
- (87) Straight, R. C.; Spikes, J. D. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 85–144.
- (88) *Porphyrin Photosensitization*; Kessel, D., Dougherty, T. J., Eds.; Plenum Press: London, U.K., 1983.
- (89) Foote, C. S. Photooxidation and Toxicity. *Mol. Basis Environ. Toxic.* **1980**, 37–50.
- (90) Daub, M. E.; Hangarter, R. P. Light-Induced Production of Singlet Oxygen and Superoxide by the Fungal Toxin, Cercosporin. *Plant Physiol.* **1983**, *73*, 855–857.
- (91) Youngman, R. J.; Schieberle, P.; Schnabl, H.; Grosch, W.; Elstner, E. F. The Photodynamic Generation of Singlet Molecular Oxygen by the Fungal Phytotoxin, Cercosporin. *Photobiochem. Photobiophys.* **1983**, *6*, 109–119.
- (92) Trevithick-Sutton, C. C.; Chin, K. K.; Contos, S. D. Lens α -Crystallin and Hypericin: A Photophysical Mechanism Explains Observed Lens Damage. *Photochem. Photobiol.* **2004**, *80*, 444–449.
- (93) Flors, C.; Nonell, S. Light and Singlet Oxygen in Plant Defense Against Pathogens: Phototoxic Phenalenone Phytoalexins. *Acc. Chem. Res.* **2006**, *39*, 293–300.

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