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Type I and II Photosensitized Oxidation Reactions: Guidelines and Mechanistic Pathways†

Maurício da Silva Baptista[1], **Jean Cadet**[2], **Paolo Di Mascio**[1], **Ashwini A. Ghogare**[3,4], **Alexander Greer**[3,4], **Michael R. Hamblin**[5,6,7], **Carolina Lorente**[8], **Silvia Cristina Nunez**[9], **Martha Simões Ribeiro**[10], **Andrés H. Thomas**[8], **Mariana Vignoni**[8], and **Tania Mateus Yoshimura**[10]

[1]Instituto de Química, Universidade de São Paulo, São Paulo 05508-070, Brazil

[2]Département de Médecine Nucléaire et de Radiobiologie, Université de Sherbrooke, Sherbrooke, Québec JIH 5N4, Canada

[3]Department of Chemistry, Brooklyn College, 2900 Bedford Avenue, Brooklyn, New York 11210, United States

[4]Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, 365 Fifth Avenue, New York, New York 10016, United States

[5]Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA 02114, United States

[6]Department of Dermatology, Harvard Medical School, Boston, MA 02115, United States

[7]Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139, United States

[8]Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata (UNLP), CCT La Plata-CONICET, Diagonal 113 y 64, 1900 La Plata, Argentina

[9]Bioengineering Department, Unicastelo, Sao Paulo, Brazil 08230-030

[10]Centro de Lasers e Aplicações, Instituto de Pesquisas Energéticas e Nucleares, IPEN-CNEN/SP, Av. Lineu Prestes, 2242, 05508-000, São Paulo, Brazil

Abstract

Here, ten guidelines are presented for a standardized definition of type I and II photosensitized oxidation reactions. Because of varied notions of reactions mediated by photosensitizers, a checklist of recommendations is provided for their definitions. Type I and type II photoreactions are oxygen-dependent and involve unstable species such as the initial formation of radical cation or neutral radicals from the substrates and/or singlet oxygen ($^1O_2$ $^1\Delta_g$) by energy transfer to molecular oxygen. In addition, superoxide anion radical ($O_2^{\bullet-}$) can be generated by a charge transfer reaction involving O_2 or more likely indirectly as the result of O_2-mediated oxidation of the radical anion of type I photosensitizers. In subsequent reactions, $O_2^{\bullet-}$ may add and/or reduce a

*Corresponding authors' jean.cadet@usherbrooke.ca (Jean Cadet) and agreer@brooklyn.cuny.edu (Alexander Greer).
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few highly oxidizing radicals that arise from the deprotonation of the radical cations of key biological targets. $O_2^{\bullet-}$ can also undergo dismutation into H_2O_2, the precursor of the highly reactive hydroxyl radical (•OH) that may induce delayed oxidation reactions in cells. In the second part several examples of type I and type II photosensitized oxidation reactions are provided to illustrate the complexity and the diversity of the degradation pathways of mostly relevant biomolecules upon one-electron oxidation and singlet oxygen reactions.

INTRODUCTION

Sensitized photooxidation reactions of key biomolecules including unsaturated lipids, proteins and nucleic acids that trigger the so-called "photodynamic effects" have been shown to be mostly implicated in the deleterious biological effects of UVA radiation through the involvement of endogenous photosensitizers (1–3). Anthropogenic exogenous photosensitizers such as methylene blue, phthalocyanin and hematoporphyrin derivatives are widely used either in the photodynamic therapy (PDT) of skin diseases and malignant cells (4,5) or the inactivation of bacteria and fungi (6–8). Because researchers often do not define photosensitized reactions the same way, the purpose of this paper is to provide a definition of type I and type II photosensitized oxidation reactions, and describe how they are distinct from each other (Scheme 1). The main oxidant that can be generated is $^1O_2$ together with poorly reactive $O_2^{\bullet-}$ and $HO_2^{\bullet}$ as mostly side-products of type I reaction. Other oxidants that can form in subsequent steps include peroxyl radicals (ROO·), alkoxyl radicals (RO·), hydrogen peroxide (H_2O_2) and hydroxyl radical ($^{\bullet}OH$). It should be pointed out that type I reactions produce highly reactive radical cation and neutral radicals issued from suitable substrates and the efficiency of the photosensitized degradation pathways depend on O_2 concentration, nature and concentration of sensitizer, and reactivity of substrate or solvent. Such reactions that in most cases give rise to either photooxygenation or photooxidation products are able to elicit deleterious biological responses in cells. We note that C. S. Foote had made major contributions with the proposed definition of type I and type II (9).

Type I and type II photosensitized oxidation reactions

Why do definitions matter in the context of photosensitized oxidation research?

Over the past 20 years, the literature has revealed differences in the vocabulary on type I and II photosensitized oxidation reactions. We believe that communication among photoscientists is less than optimal and unintentionally vague. Overcoming this language barrier is crucial for more consistent and precise mechanistic interpretations of photosensitized oxidation reactions. It should be mentioned that type III and type IV photosensitization reactions that only applied to oxygen independent photoreactions have been also proposed in the literature. We do not examine the premises on which type III and type IV reactions have been reported; they are not part of the paradigm since there are low levels of consistencies among these reaction types in the literature.

Our approach

Our approach was an open discussion at a mini-symposium on singlet oxygen in Cambury, Brazil in 2014, which included photoscientists from different fields. Participants felt that a consensus could be reached in defining type I and II photosensitized oxidation. Thus, a questionnaire was circulated following the meeting. Over a year, subsequent discussions took place and the participants were given the opportunity to revise answers. At the end of the process, the following recommendations arose for a consensus on the definitions of type I and II photosensitization mechanisms. One potential drawback of this exercise was the lack of representation of $^1O_2$ researchers outside of the mini-symposium. Below are ten rules for defining type I and type II photosensitized reactions. These are practical rules for ascribing the two classifications.

Superoxide anion radical

The literature shows that the formation of $O_2^{\bullet-}$ through a charge transfer reaction is at best a minor process as also emphasized in the manuscript (10–12). The formation of $O_2\cdot$ was proposed initially by C. S. Foote by charge transfer involving O_2 (type II) and indirectly by reaction of the radical anion of the photosensitizer (type I) with oxygen (9). That is a slight modification from the initial definition has however the merit to allow a clear distinction between radical oxidation reactions and $^1O_2$ oxidation. $O_2^{\bullet-}$ can also arise via a sensitizer radical anion formed by one-electron oxidation. The generation of $O_2^{\bullet-}$ that is in equilibrium with $HO_2^{\bullet}$, as a side-product of type I photosensitization is a more prevalent process (12,13). Reactions of $O_2^{\bullet-}$ can occur with highly oxidizing radicals (addition, reduction) or when there is not an appropriate substrate for its conversion into H_2O_2 by dismutation (spontaneous or mediated by superoxide dismutase in cells), the precursor of highly reactive •OH. We note the rate of oxygenated product formation can also vary widely, for example, the rate constant for the reaction of methionine (Met) with ^1O is ~60 million-fold greater than with $O^{\bullet-}$ (14).

Photosensitized oxidative degradation pathways of biomolecules

During the last two decades, major progress has been made in the identification of type I and type II photosensitized oxidation reactions of key biomolecules including amino acids of proteins and nucleobases, mostly guanine of nucleic acids. Below, we provide examples of type I and II photosensitized oxidation reactions involving biomolecules (Schemes 2–7).

(a) Type I photosensitized oxidation reactions

The radical cation produced by one-electron oxidation from suitable DNA base targets is able to undergo deprotonation and hydration in aqueous solutions (15). This was shown to occur in cellular DNA from the measurement by HPLC-ESI-MS/MS of the specific final guanine, cytosine and thymine oxidation products upon photoionization (16,17). The same neutral radicals intermediates that are generated by the latter processes are produced by •OH addition and/or •OH-mediated hydrogen atom abstraction.

Type I reaction with addition of O_2—Scheme 2 shows the one-electron oxidation reaction of thymidine (dThd) through type I mechanism that gives rise to a thymine radical cation (16,17). Hydration of thymine radical cation (path a) then selectively produces 6-hydroxy-5,6-dihydrothymidin-5-yl radical after which O_2 efficiently adds giving rise to oxidation products including 4 diastereomers of 5,6-dihydroxy-5,6-dihydrothymidine (dThdGly) through transient 6-hydroxy-5-hydroperoxyl-5,6-dihydropyrimidine radicals. Another major pathway was the efficient deprotonation reaction of the pyrimidine base radical cations from the methyl group of either thymidine or 5-methyl-2'-deoxycytidine (16,17,20). Oxygen addition to the resulting neutral 5-(uracyl)methyl and 5-(cytosyl)methyl radicals respectively gives rise to related peroxyl radicals. Final oxidation products include 5-(hydroxymethyl)-2'-deoxyuridine (5-HmdUrd) and 5-formyl-2'-deoxyuridine (5-FodUrd) that arise from further reactions of the reactive peroxyl radicals and/or reduction and dehydration of related hydroperoxides as shown for thymidine (Scheme 2, path b). The efficient addition of O_2 to transiently generated carbon centered radicals upon the conversion of initially formed radical cations is the most prevalent key pathway of type I photosensitized reactions giving rise essentially to oxygenation products.

Type I reaction with oxidation by O_2—Scheme 3 shows a second example in which hydration reaction of the guanine radical cation ($Gua^{\bullet+}$) gives rise to 8-hydroxy-7,8-dihydroguan-7-yl radical that may be also produced by •OH addition at C8 (15–19). Molecular oxygen becomes involved by its ability to one-electron oxidize the radical into 8-oxo-7,8-dihydroguanine (8-oxoGua). A competitive reaction that is efficient in cells due to the presence of thiols is the reduction of the guanyl radical with subsequent formation through the opening of the imidazole ring of 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua) (19). It may be noted that FapyGua shows the same oxidation state as the guanine precursor. Further examples of type I photosensitized reactions that involve nucleophilic addition to $Gua^{\bullet+}$ followed by O_2-mediated one-electron oxidation include the formation of DNA-protein crosslinks and DNA intrastrand crosslinks (16,17).

Type I reaction involving addition of superoxide anion radical to highly oxidizing radicals—These are less common reactions that have been shown to be involved with the highly radicals arising from the deprotonation of the radical cation of guanine, tyrosine and tryptophan (16,21–27). Highly oxidizing oxyl radicals that may exist under different tautomeric forms including carbon-centered radicals are thus generated for guanine (Scheme 3) and tyrosine (Scheme 4). Interestingly, oxygen does not show any detectable reactivity with the highly oxidizing guanine radical also called Gua(-H)• (28–30). However $O_2{\cdot}$ is able to add to Gua(-H)• giving rise after protonation to transient hydroperoxides (24). In subsequent steps the hydroperoxides are converted through a rather complicate reaction pathway, including decarboxylation and hydration and rearrangement steps to an oxazolone compound (Scheme 5) (24) that has been detected in cellular DNA (25). $O_2^{\bullet-}$ has also been shown to competitively reduce Gua(-H)•, thus leading to the restoration of the guanine moiety (30). Another efficient reaction of Gua(-H)• in aerated aqueous solutions of 2'-deoxyguanosine is the one-electron oxidation of 8-oxoGua moiety as soon it is generated in aerated aqueous addition (26). Similarly tyrosine peroxide is generated by addition of $O_2{\cdot}$ to the oxidizing tyrosine radical rising from deprotonation of the related radical cation precursor. Reduction of the tyrosine hydroperoxide thus formed, explains the formation of 3-hydroxytyrosine (Scheme 4).

(b) Type II photosensitized oxidation reactions

Singlet oxygen ($^1O_2$, refers to the $^1\Delta$ state) is the predominant, type II reactive oxygen species that is able to reactwith nucleic acids (exclusively guanine), unsaturated lipids, and amino acids such as Trp, His and Met. Biological $^1O_2$ reactions often lead to endoperoxides from [2 + 4] cycloadditions, dioxetanes from [2 + 2] cycloadditions, hydroperoxides from 'ene' reactions or phenol oxidations, and sulfoxides from sulfides (31,32).

Endoperoxide ([2 + 4] cycloaddition)—Scheme 6 shows an example of the type II reaction with a porphyrin–sensitized photooxidation of a 8-methylguanosine derivative according to a [2 + 4] reaction that leads to the singlet oxygen product endoperoxide (33). The *tert*-butyldimethylsilyl (TBDMS) groups provided solubility to 8-methylguanosine in CD_2Cl_2 at low temperature, where two diastereomeric endoperoxides form. Unstable peroxide products from $^1O_2$ reactions with guanine and imidazoles have been suitably detected by low-temperature NMR spectroscopy thanks to their isotopic labeling with ^{13}C and ^{15}N atoms (34,35).

Dioxetane ([2 + 2] cycloaddition)—Scheme 7 shows an example of the type II reaction with tryptophan in a $^1O_2$-mediated [2 + 2] reaction giving rise to dioxetane, which readily cleaves to carbonyl fragments (36,37). This reaction also leads to an 'ene' reaction to reach tryptophan hydroperoxide diastereomers based on evidence from mass spectrometry and the use of ^{18}O-labeled singlet oxygen.

A number of papers have examined the $^1O_2$ reaction with other amino acids, such as Met (38–40). Many papers have also been published on $^1O_2$ oxidations of other biomolecules such as ascorbic acid and bilirubin (41–44). Some biological singlet oxygen reactions are known, such as with amine where charge-transfer physical quenching ($^1O_2 \rightarrow {}^3O_2$) is the main reaction instead of oxidation. Energy-transfer physical quenching such as that between Sens* and carotenoids that have low lying excited states (45) can also occur, although biological examples such as these are rare.

Caveats—The ten-guideline checklist is meant to be precise. However, secondary reactions may arise downstream from the type I and type II reactions. That is, we do not account for species formed in type I and II reactions as interim products, which lack high enough stability downstream as quantifiable end points. One example is photogenerated hydroperoxides (46,47) that can subsequently react and produce $^1O_2$ in the dark via Russell rearrangements. Superoxide can also dismutate biologically to form H_2O_2 and $^1O_2$ in a secondary reaction.

In conclusion, irradiation of $Sens_0$ causes Sens* to undergo two types of photosensitized reactions called type I and II. The above checklist arranges the boundaries between type I and II photosensitization reactions and is used to help untangle their definitions. The recommended ten guidelines may be plain, but provide a more precise approach. It is important to conclude that there is a consensus with most of the previous proposed definitions made by C. S. Foote (9).

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Biographies

Mauricio S. Baptista graduated in Pharmacy and Biochemistry, University of São Paulo in 1990, obtained a Master in Biological Sciences (Biochemistry) at the University of São Paulo in 1992 and a Ph.D. in Chemistry at Marquette University, USA in 1996. He was a post-doctorate fellow at UW-Madison School of Pharmacy, USA in 1997 and was a visiting professor at the Université Joseph Fourier (Grenoble-France) in 2006. Has been a faculty in the Department of Biochemistry, University of São Paulo since 1998, where he is currently full professor of Biochemistry, working mainly in photochemistry/photobiology, membranes and mechanisms of cell death.

Jean CADET has been the head of the Laboratory "*Lésions des Acides Nucléiques*" at the French Atomic Energy Institute in Grenoble, France. He is currently Professor at University of Sherbrooke, Canada. His main research interests deal with the elucidation of molecular effects of solar radiation and biologically relevant oxidants on nucleic acids. He is co-author of 615 peer-reviewed articles and book chapters and his h-index is 78. His editorial activities include being the Editor-in-chief of *Photochemistry & Photobiology* and Executive Editor of the *Journal of Innovation & Research in Health Sciences and Biotechnology*.

Paolo Di Mascio is full professor of biochemistry at São Paulo University, Brazil. His research focused on the chemical sources and the noxious behaviors of molecular oxygen/nitrogen-derived free radicals in biological systems. Studies have focused on identifying the mechanism by which singlet molecular oxygen and other reactive oxygen/nitrogen species play their physiological and pathological roles. Considering the complexity of biological systems and the great variety of free radicals and/or oxidation processes generated by photochemical reactions, he has devoted efforts to develop suitable $^1O_2$ generators based on the thermolysis of ^{16}O or ^{18}O-labeled endoperoxides.

Ashwini A. Ghogare received a M.S. degree in organic chemistry from the Institute of Science at Mumbai University and a Ph.D. degree in organic chemistry with Prof. Alexander Greer at Brooklyn College of the City University of New York (CUNY). Her research interests are in organic synthesis, photoreleasing drugs and photodynamic therapy.

Alexander Greer is a professor of chemistry at Brooklyn College of City University of New York and the Graduate Center of CUNY. For his doctoral and postdoctoral studies he worked in the laboratories of Edward L. Clennan and Christopher S. Foote, respectively. He is an Associate Editor of *Photochemistry & Photobiology*, and has edited virtual and special issues and symposia-in-print on oxygen and sulfur chemistry. His research interests are in photochemistry, singlet oxygen reactors, heterogeneous sensitizers, and photodynamic therapy.

Michael R. Hamblin, Ph.D. is a Principal Investigator at the Wellman Center for Photomedicine, Massachusetts General Hospital, and an Associate Professor of Dermatology, Harvard Medical School. He directs a laboratory of around a dozen scientists who work in photodynamic therapy and low-level light therapy. He has published 348 peer-reviewed articles, an h-index of 76 and over 21,000 citations. He is Associate Editor for 10 journals and serves on NIH Study-Sections. He has edited 11 proceedings volumes together with eight other major textbooks on PDT and photomedicine. In 2011, Dr. Hamblin was honored by election as a Fellow of SPIE.

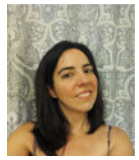
Carolina Lorente was born in La Plata, Argentina, in 1968. She obtained a degree in Biochemistry and a Ph.D. in Science at the *Universidad Nacional de La Plata* (UNLP). She held a postdoctoral position at the *Universidad de Buenos Aires* (UBA). She currently works at the *Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas* (INIFTA) as Independent Researcher of CONICET. Her research interest is the study of photosensitized reactions and their biological implications.

Silvia Cristina Nunez is a DDS with a Master degree in Lasers in Dentistry from the IPEN/FOUPS-SP, Brazil, a PhD in Sciences from the University of São Paulo and spent her postdoctoral fellowship at IPEN-SP. She is currently a Professor at the University Camilo Castelo Branco – Brazil and a collaborator researcher at IPEN. Her research interests include phototherapy, dental applications of phototherapy, photodynamic effects, photodynamic therapy, photochemistry and photobiology.

Martha S. Ribeiro was born in Brazil. She obtained her BSc degree in Physics from the University of Campinas in 1987 and her PhD in Sciences from the University of São Paulo in 2000. She is currently a Senior Researcher at IPEN-CNEN/SP working with Biomedical Optics (Biophotonics) with emphasis in optical therapy and nanomaterials. Her research interests include tissue optics, photobiomodulation and photodynamic effects.

Andrés H. Thomas was born in La Plata, Argentina, in 1968. He studied at the National University of La Plata (UNLP) and was awarded a Ph.D. degree in 2001. After a postdoctoral fellowship at the University of Buenos Aires, he joined the Argentinean

National Research Council (CONICET) as Assistant Researcher. Currently, he is Professor of the Faculty of Science of UNLP and he works at the Institute of Theoretical and Applied Research on Physical Chemistry (INIFTA) as Principal Researcher of CONICET. His research interests include photophysics and photochemistry of biomolecules and photosensitized processes of biological and medical interest.



Mariana Vignoni obtained her degree in Biochemistry at the National University of La Plata (UNLP), Argentina in 2007. She did her PhD in the group of Dr. Andres Thomas at INIFTA (Research Institute of Theoretical and Applied Physical Chemistry) from the UNLP. She did a postdoctoral fellowship at the University of Ottawa in Prof. Scaiano's group. She started as an Assistant Researcher in Prof. Thomas's group at INIFTA in 2013. Her main research activities deal with photosensitization of lipid membranes.

Tania M. Yoshimura is a PhD student of the Nuclear Technology Postgraduate Program at University of São Paulo. Over the last five years she has published seven peer-reviewed articles, one book chapter and has been congratulated with one scientific award. Her main research areas comprise photobiomodulation and antimicrobial phototherapy.

Ten tips for defining Type I and II photosensitized oxidation reactions

Photosensitized reactions involving oxygen are framed as either as type I or type II.

Type I and II photosensitized oxidation reactions require oxygen as a reagent.

The type I and II photosensitized mechanisms apply to photoreactions including initial electron or hydrogen atom abstraction as an oxidizing step. In most cases O_2 participates directly or indirectly as one-electron oxidant or generated $O_2{\cdot}^-$ to the formation of final oxidation products.

Type I and II photosensitized reactions include biomolecule degradation upon one-electron oxidation and $^1O_2$ reactions.

Type I sensitizers undergo photoinduced electron transfer. For example, carbonyl compounds such as benzophenone are photosensitizers, where photoexcited benzophenone has also been shown to act by hydrogen atom abstraction.

Type I leads to the formation of $O_2^{\bullet-}$ and $HO_2^{\bullet}$.

Superoxide anion radical. $O_2{\cdot}^-$ is formed after $Sens{\cdot}^-$ donates an electron to O_2 or by charge transfer to O_2.

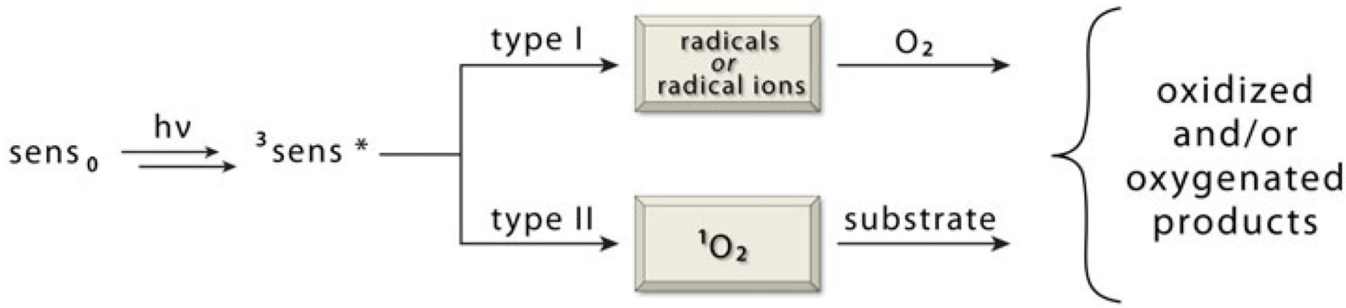
Type II is framed as the sensitized formation of $^1O_2$. The definition is narrow and involves the production of $^1O_2$.

Type II is a sensitizer energy transfer process to oxygen.

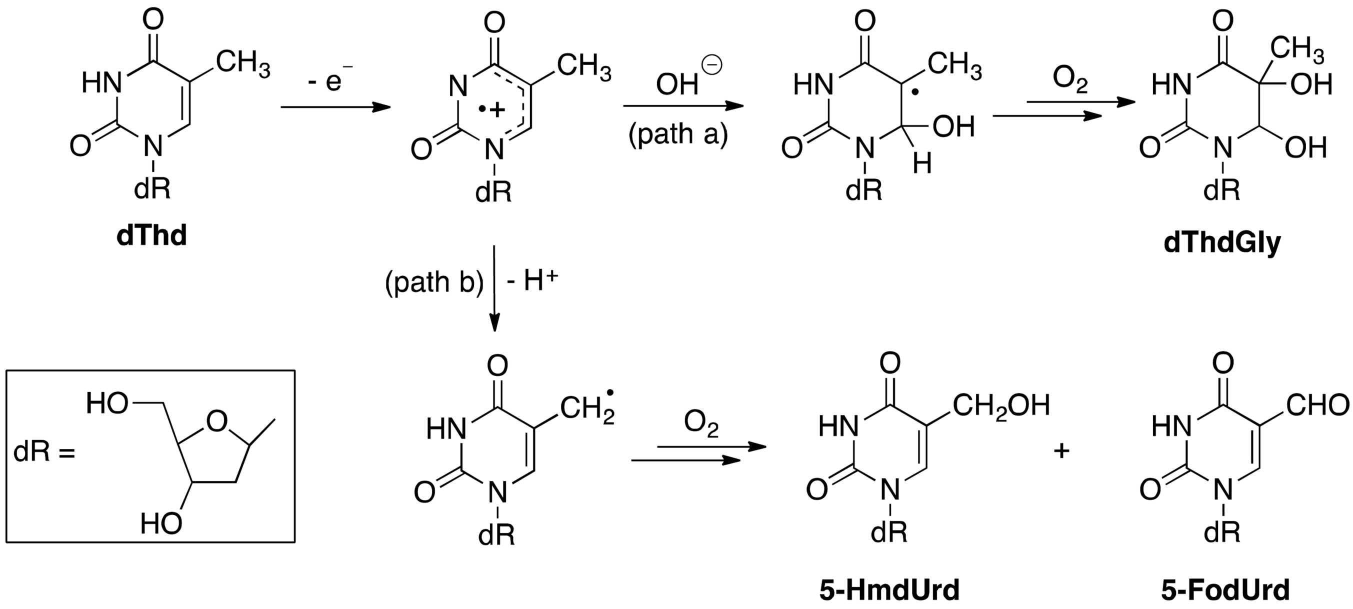
Type II does not refer energy transfer excluding oxygen, such as that between Sens* and carotenoids.

Photosensitized oxidation applies to molecules and living matter.

Photodynamic action is killing via type I or II. It is rational for being oxygen-dependent. The term “oxygen-independent photodynamic action” should not be used.

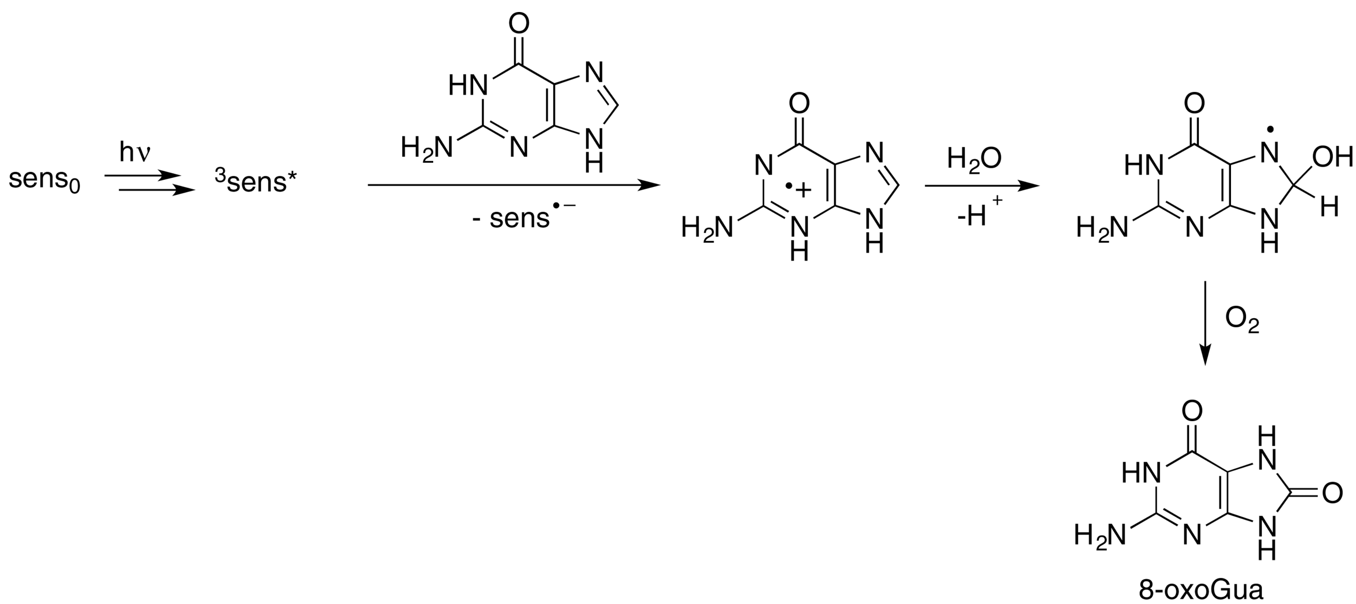

type I
radicals
or
radical ions
O_2
sens 0
hν
^{3}sens *
type II
$^1O_2$
substrate
oxidized
and/or
oxygenated
products

Scheme 1.

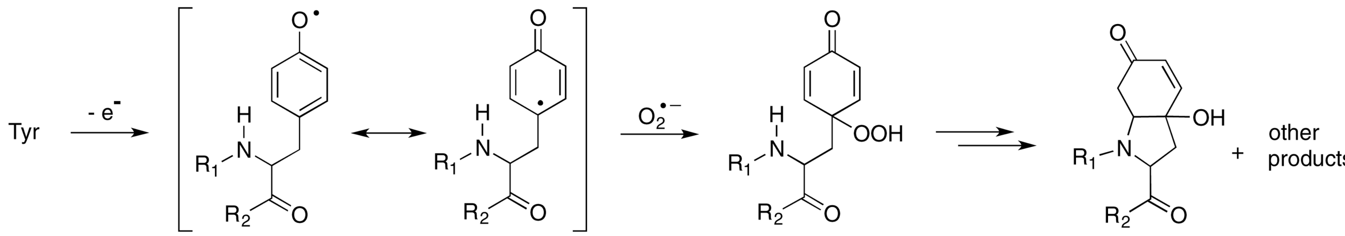


O
HN
CH3
O
N
dR
dThd
- e−
•+
OH⊖
(path a)
OH
H
O2
dThdGly
(path b)
- H+
dR =
HO
CH2•
CH2OH
+
CHO
5-HmdUrd
5-FodUrd

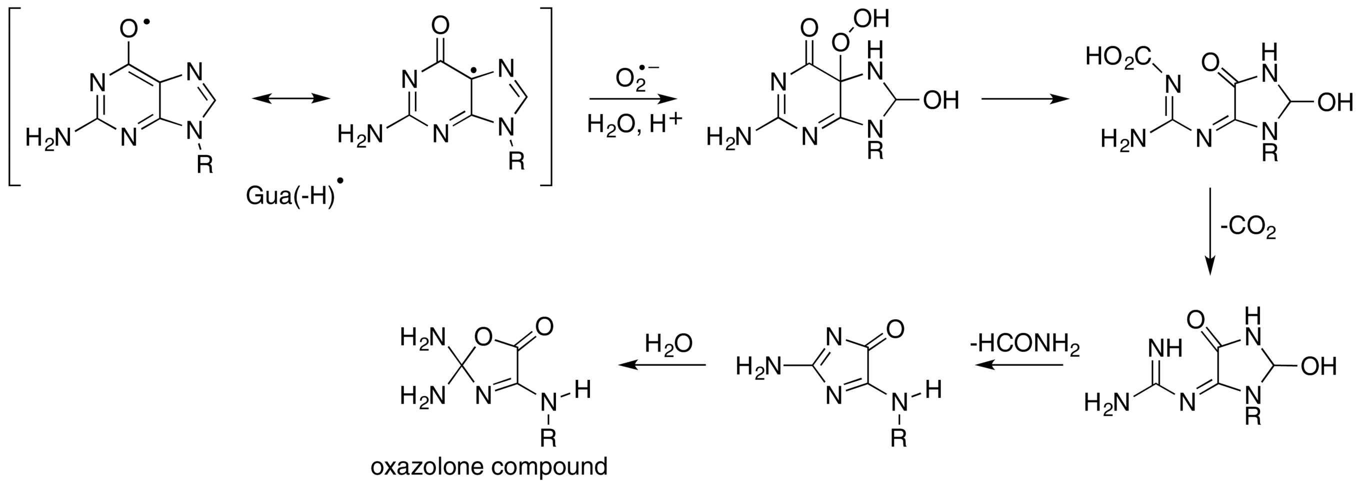
Scheme 2.



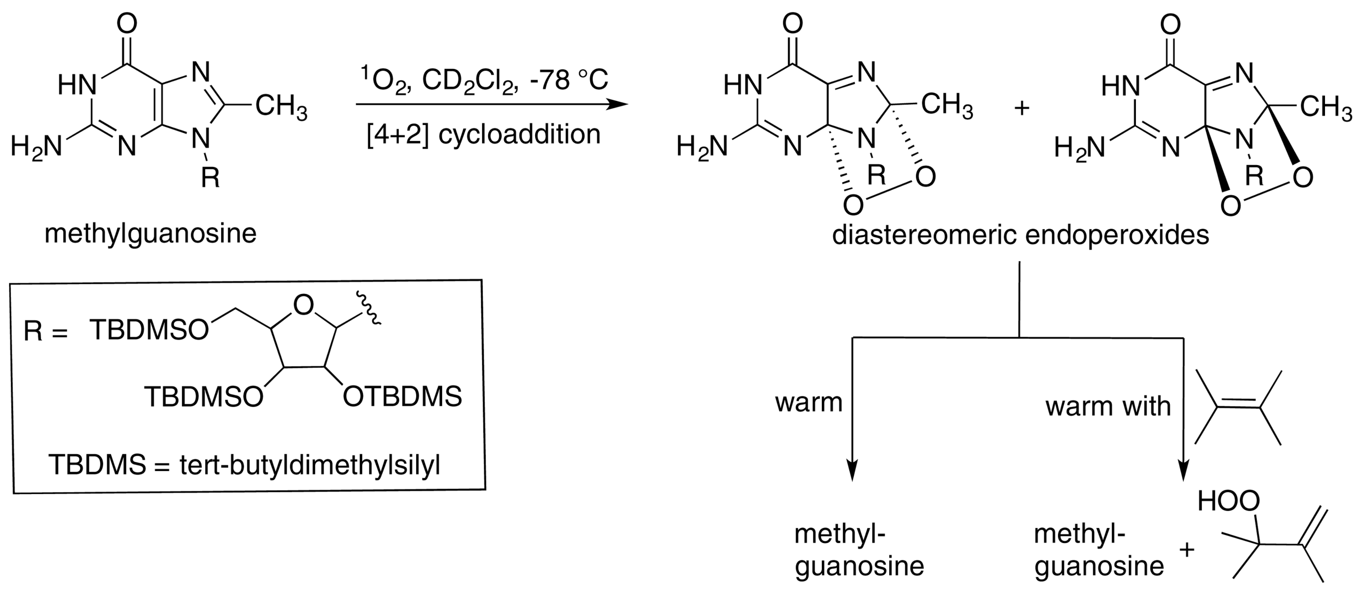
Scheme 3.



Scheme 4.

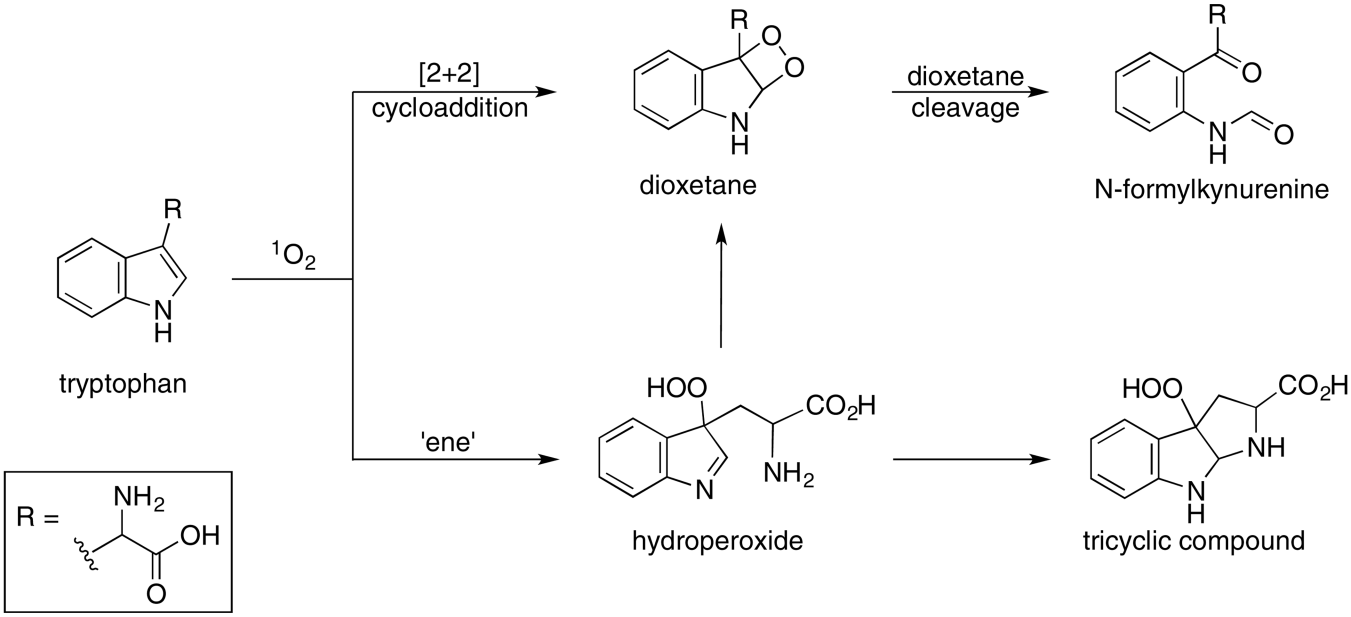


Scheme 5.



$^1O_2$, CD_2Cl_2, -78 °C
[4+2] cycloaddition
methylguanosine
diastereomeric endoperoxides
R = TBDMSO
TBDMSO
OTBDMS
TBDMS = tert-butyldimethylsilyl
warm
warm with
methyl-guanosine
methyl-guanosine
HOO

Scheme 6.


[2+2]
cycloaddition
dioxetane
cleavage
dioxetane
N-formylkynurenine
R
N
H
tryptophan
$^1O_2$
'ene'
HOO
CO_2H
NH_2
hydroperoxide
tricyclic compound
NH
R =
OH
O

Scheme 7.