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Invited Review

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

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ABSTRACT

Here, 10 guidelines are presented for a standardized definition of type I and type 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 ($O_2^{\cdot-}$) 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, $O_2^{\cdot-}$ may add and/or reduce a few highly oxidizing radicals that arise from the deprotonation of the radical cations of key biological targets. $O_2^{\cdot-}$ can also undergo dismutation into H_2O_2, the precursor of the highly reactive hydroxyl radical ($^{\cdot}OH$) 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, phthalocyanine and hematoporphyrin derivatives are widely used either in the photodynamic therapy (PDT) of skin diseases and malignant cells (4,5) or in 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 $O_2^{\cdot-}$ and $HO_2^{\cdot}$ as mostly side products of type I reaction. Other oxidants that can form in subsequent steps include peroxyl radicals ($ROO^{\cdot}$), alkoxyl radicals ($RO^{\cdot}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($^{\cdot}OH$). 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 depends 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 photosensitization mechanisms (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 type II photosensitized oxidation

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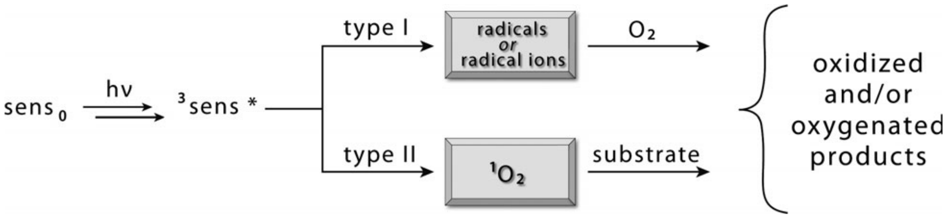


Scheme 1.

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 as 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 type II photosensitized oxidation reactions. 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 type 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 10 rules for defining type I and type II photosensitized reactions. These are practical rules for ascribing the two classifications.

Ten tips for defining type I and type II photosensitized oxidation reactions

- Photosensitized reactions involving oxygen are framed as either as type I or type II.
- Type I and type II photosensitized oxidation reactions require oxygen as a reagent. The type I and type 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 type 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 $O_2^{\cdot-}$ and $HO_2^{\cdot}$.
- 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.

Superoxide anion radical

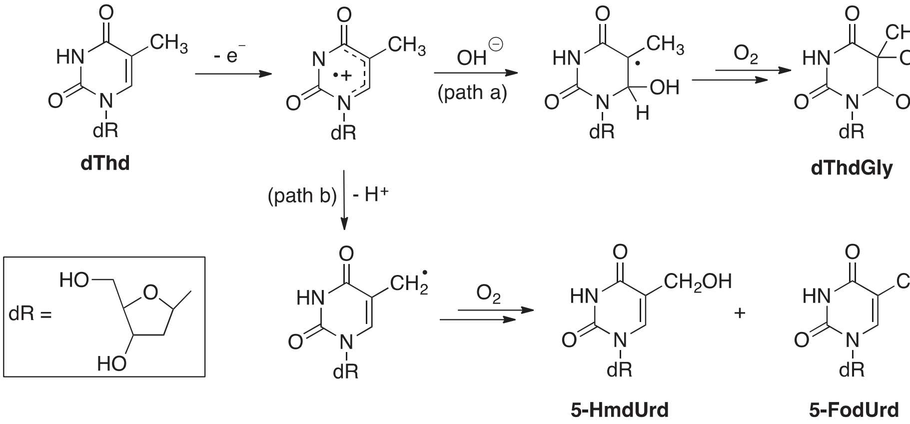
The literature shows that the formation of $O_2^{\cdot-}$ through a charge-transfer reaction is at best a minor process as also emphasized in the manuscript (10–12). The formation of $O_2^{\cdot-}$ was proposed initially by C. S. Foote by charge transfer involving O_2 (type II) and indirectly by reaction 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. $O_2^{\cdot-}$ can also arise via a sensitizer radical anion formed by one-electron oxidation. The generation of $O_2^{\cdot-}$ that is in equilibrium with $HO_2^{\cdot}$, as a side product of type I photosensitization, is a more prevalent process (12,13). Reactions of $O_2^{\cdot-}$ 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 $^{\cdot}OH$. We note the rate of oxygenated product formation can also vary widely; for example, the rate constant for the reaction of methionine (Met) with $^1O_2$ is ~60 million-fold greater than with $O_2^{\cdot-}$ (14).

PHOTOSENSITIZED OXIDATIVE DEGRADATION PATHWAYS OF BIOMOLECULES

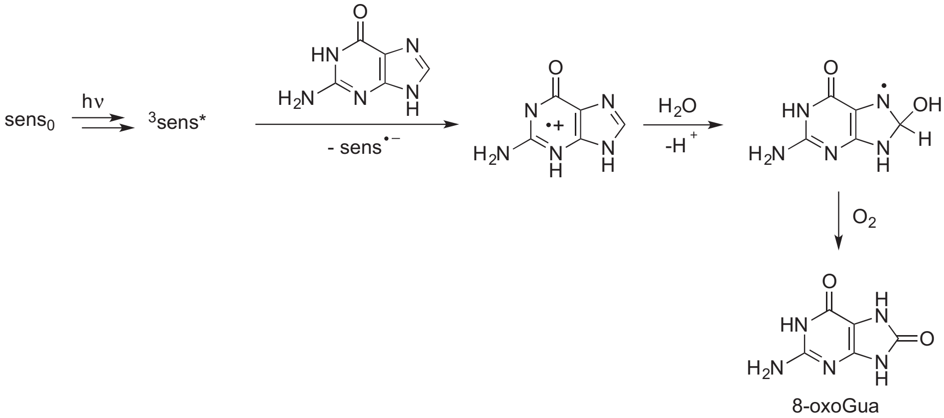
During the last two decades, major progress has been made in the identification of type I and type II photosensitized oxidation reactions of key biomolecules including amino acids of proteins and nucleobases, mostly guanine of nucleic acids. Below, we provide examples of type I and type II photosensitized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

Type I photosensitized oxidation reactions

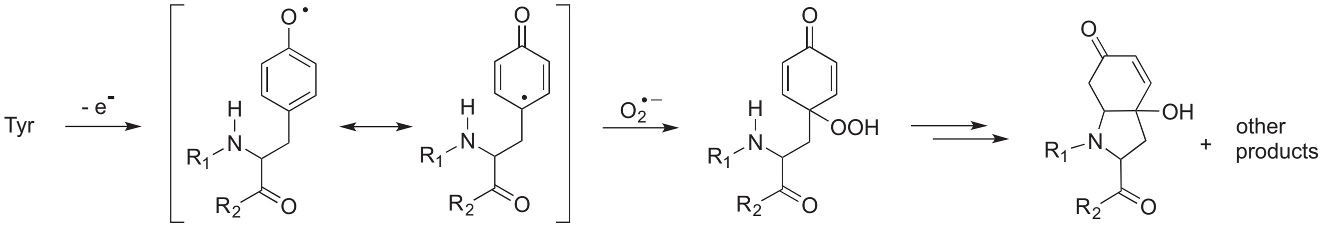
The radical cation produced by one-electron oxidation from suitable DNA base targets is able to undergo deprotonation and hydration in aqueous solutions (15). This was shown to occur in cellular DNA from the measurement by high performance liquid chromatography associated with electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS) of the specific final guanine, cytosine and thymine oxidation products upon photoionization (16,17). The same neutral radicals intermediates that



Scheme 2.



Scheme 3.

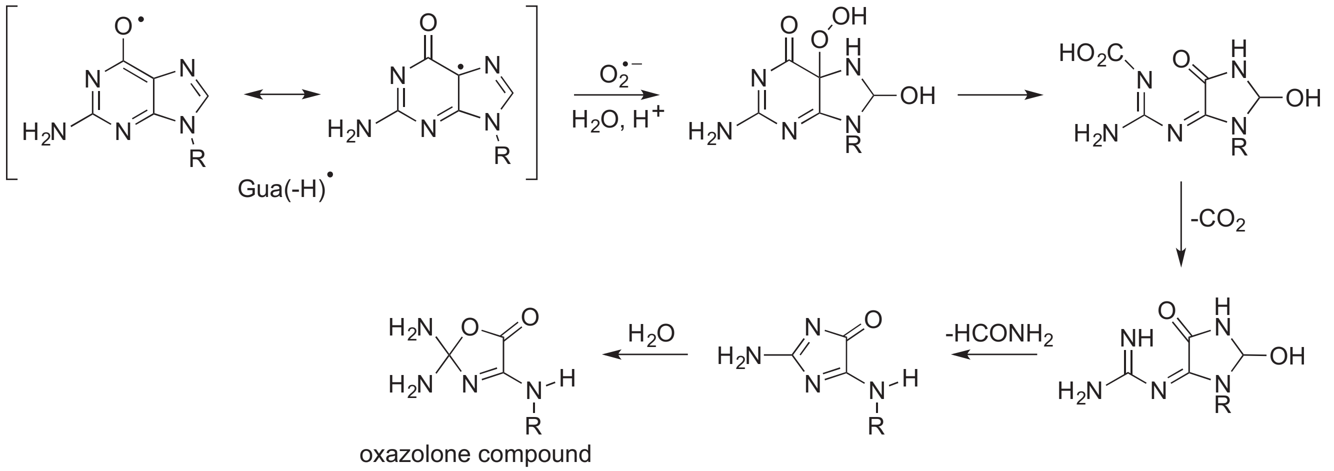


Scheme 4.

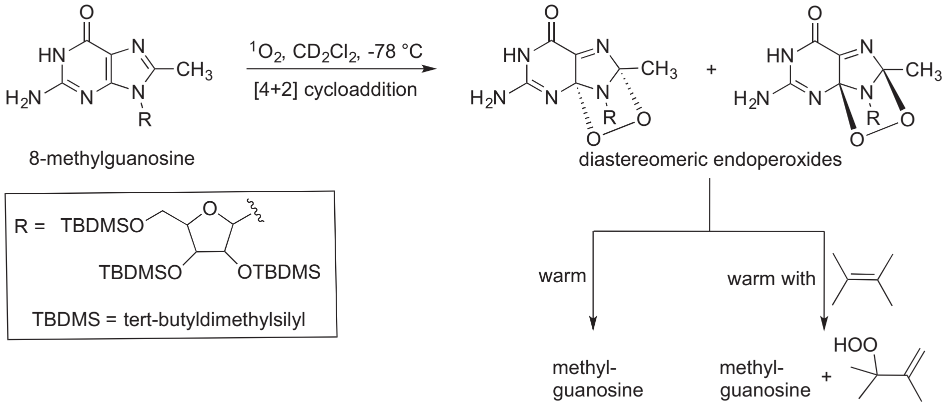
are generated by the latter processes are produced by $^{\cdot}$OH addition and/or $^{\cdot}$OH-mediated hydrogen atom abstraction.

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 (16–18). 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.

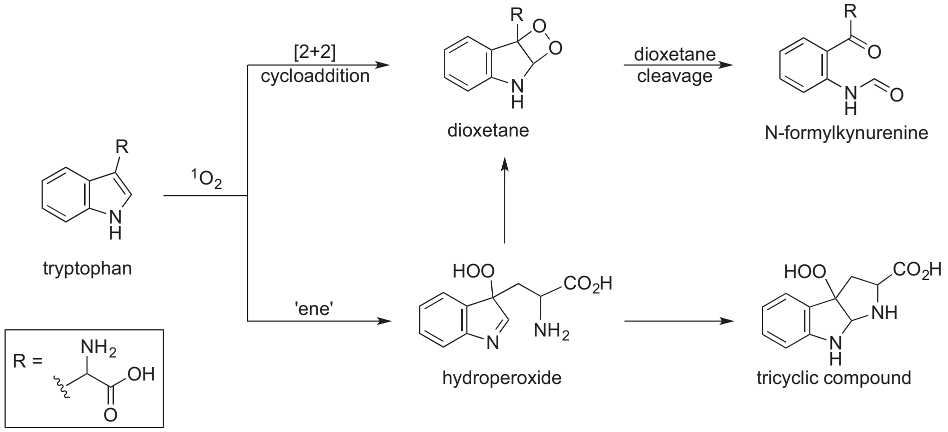
Type I reaction with oxidation by O_2. Scheme 3 shows a second example in which hydration reaction of the guanine radical cation ($Gua^{\cdot +}$) gives rise to 8-hydroxy-7,8-dihydroguan-7-yl radical that may be also produced by $^{\cdot}$OH addition at C8 (15–17,19,20).



Scheme 5.



Scheme 6.



Scheme 7.

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) (20). 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 $Gua^{\cdot +}$ followed by O_2-mediated one-electron oxidation include the formation of DNA-protein cross-links and DNA intrastrand cross-links (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 (16,21–24). 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)$^{\cdot}$ (25–27). However, $O_2^{\cdot -}$ is able to add to Gua (-H)$^{\cdot}$ giving rise after protonation to transient hydroperoxides (24,27). 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 (28). $O_2^{\cdot -}$ has also been shown to competitively reduce Gua (-H)$^{\cdot}$, thus leading to the restoration of the guanine moiety (29). Another efficient reaction of Gua (-H)$^{\cdot}$ 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 (29). Similarly, tyrosine peroxide is generated by the 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).

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 react with 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 (30,31).

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 (32). 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 (33,34).

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 (35,36). 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 (37–39). Many papers have also been published on $^1O_2$ oxidations of other biomolecules such as ascorbic acid and bilirubin (40–43). 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 (44) can also occur, although biological examples such as these are rare.

Caveats. The 10-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 type II reactions as interim products, which lack high enough stability downstream as quantifiable end points. One example is photogenerated hydroperoxides (45,46) 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 type II. The above checklist arranges the boundaries between type I and type II photosensitization reactions and is used to help untangle their definitions. The recommended 10 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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